OHTAC Recommendation

Clinical Utility of Serologic Testing for Celiac Disease in Asymptomatic Patients

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Background

Celiac Disease

Celiac disease is an autoimmune disease characterized by a chronic inflammatory state of the proximal small bowel mucosa, accompanied by structural and functional changes. (1) The immunological response is triggered by ingestion of gluten. (1) Treatment consists of strict lifelong adherence to a gluten-free diet (GFD). (1)

Published systematic literature reviews reported that the prevalence of celiac disease in the general population varied between 0.14% and 1.87% (median across studies: 0.47%, interquartile range: 0.25%, 0.71%) based on studies that used small bowel biopsy to confirm the diagnosis. (2;3)

Celiac Disease Diagnosis

According to celiac disease guidelines, the diagnosis of celiac disease is established by small bowel biopsy. (4-6) Serologic tests are used to initially detect and support the presence of celiac disease. (4-7)

Serologic Testing for Celiac Disease

There are a number of serologic tests used for the diagnosis of celiac disease including anti-gliadin antibody (AGA), anti-tissue transglutaminase antibody (tTG), anti-endomysial antibody (EMA), and anti-deamidated gliadin peptides antibody (DGP). For each serologic test, both immunoglobulin A (IgA) or IgG can be measured, however, IgA measurement is the standard antibody measured in celiac disease. (7)

An evidence-based analysis published in December 2010 by the Medical Advisory Secretariat (MAS) evaluated the clinical utility of different serologic tests used in the diagnosis of celiac disease in individuals with symptoms consistent with this disease. (8) The clinical validity and clinical utility of serologic tests for celiac disease was considered high in individuals with symptoms consistent with this disease. (8) The study findings suggest that IgA tTG is the most accurate and most cost-effective serologic test. (8)

The results of the evidence-based analysis performed by MAS (8) and the input from both a Professional Panel and a Citizen's Reference Panel on Health Technology were considered by the Ontario Health Technology Advisory Committee (OHTAC) in making recommendations in December 2010 regarding the use of serologic tests for celiac disease in subjects with symptoms consistent with the disease (Appendix 1). (9) However since testing in asymptomatic individuals presenting with other non-gastrointestinal conditions was raised by the Professional Panel, it was decided that a separate evidence-based analysis of these possible indications would be undertaken by MAS.

The present recommendations are based on the results of the MAS evidence-based analysis on the clinical utility of serologic testing for celiac disease in asymptomatic patients presenting with non-gastrointestinal conditions (listed in Appendix 2).

Throughout the report, when "asymptomatic" celiac disease is mentioned, it refers to individuals with a positive serologic celiac disease test and/or characteristic abnormalities on a small bowel biopsy who never had symptoms consistent with celiac disease[1]. (9)

- [1] * In Adults: chronic diarrhea especially in the presence of weight loss, abdominal pain, and/or unexplained iron-deficiency anemia unresponsive to iron supplementation.
- In Pediatrics: Chronic diarrhea especially in the presence of failure to thrive or weight loss; severe constipation especially with poor weight gain.
- In Adults and Pediatrics: Unexplained iron deficiency anemia unresponsive to iron supplementation, or subjects with dermatitis herpetiformis.

OHTAC Findings

The research questions of the Medical Advisory Secretariat (MAS) evaluation were:

1. What is the prevalence of asymptomatic celiac disease in individuals presenting with one of the non-gastrointestinal conditions evaluated (list in appendix 2)?

2. What is the effect of the GFD on condition-specific outcomes in patients with asymptomatic celiac disease presenting with one of the non-gastrointestinal conditions evaluated (list in appendix 2)?

3. What is the clinical utility of serologic testing for celiac disease in asymptomatic patients presenting with one of the non-gastrointestinal conditions evaluated? The clinical utility was defined as the impact of the GFD on disease specific outcomes.

4. What is the risk of all-cause mortality and lymphoma in individuals with asymptomatic celiac disease?

5. What is the budget impact of serologic testing for celiac disease in asymptomatic patients presenting with one of the non-gastrointestinal conditions evaluated?

Prevalence of Celiac Disease in Asymptomatic Patients

The prevalence of celiac disease in asymptomatic patients presenting with one of the conditions evaluated was analysed. Most studies also included a control group that generally consisted of individuals randomly selected from the general population.

Although there was a trend to a higher prevalence of asymptomatic celiac disease in individuals with the conditions evaluated compared to the controls, it only reached statistical significance in type 1 diabetes, weighted average 8.9% vs. 0.3%, respectively (difference: 9%, 95% confidence interval: 5%, 14%). No eligible prevalence studies were identified in patients with amenorrhea, delayed puberty, alopecia, and depression.

The Effects of a Gluten-Free Diet on Disease-Specific Outcomes in Patients with Asymptomatic Celiac Disease

The effects of GFD on metabolic control in patients with asymptomatic celiac disease and Type 1 Diabetes

The effects of a GFD on metabolic control (HbA1c, number of hypoglycemic episodes, and changes in insulin dosage) in subjects with asymptomatic celiac disease and type 1 diabetes were evaluated.

One prospective case-control study reported an increase in HbA1c levels in cases with type 1 diabetes and asymptomatic celiac disease after the introduction of a GFD, however, the clinical significance of this change is unclear.

Only one eligible retrospective case-control study evaluated the effects of a GFD on hypoglycemia episodes and since there were inadequate details in the study about both the ascertainment and severity of hypoglycemia episodes in both cases and controls, it is not possible to draw conclusions regarding the effects of a GFD on hypoglycemia episodes based on this study.

One prospective case-control study did not show a statistically significant change in insulin dosage between cases with type 1 diabetes and asymptomatic celiac disease and controls with type 1 diabetes either before or after the introduction of a GFD.

No eligible studies that evaluated the effects of a GFD on the long-term outcomes of type 1 diabetes such as cardiovascular or renal events in patients with asymptomatic celiac disease were identified.

The effects of a gluten-free diet in patients with idiopathic short stature and asymptomatic celiac disease

A total of 3 eligible studies were identified. All studies consisted of case series that compared growth parameters in subjects with asymptomatic celiac disease and idiopathic short stature before and after the celiac disease was diagnosed and the GFD was instituted.

Most subjects included in the studies demonstrated an improvement in growth parameters. Compliance with the GFD was not reported in the studies. The results of the studies suggest an increase in growth velocity in pediatric patients with asymptomatic celiac disease and idiopathic short stature once a GFD is introduced.

Risk of lymphoma in patients with asymptomatic celiac disease

One retrospective cohort study evaluated the risk of lymphoma in subjects with asymptomatic celiac disease. The authors concluded that the number of events identified was low during the long follow-up period and that the risk of overall malignancies was not increased among patients with asymptomatic celiac disease.

Risk of asymptomatic celiac disease in patients with lymphoma

Four case-control studies, one of which retrospective, evaluated the risk of asymptomatic celiac disease in patients newly diagnosed with lymphoma. One retrospective cohort study did not show an increase in the risk of lymphoma among subjects with asymptomatic celiac disease. Three prospective case-control studies did not find a statistically significant risk of asymptomatic celiac disease in patients with newly diagnosed lymphoma.

Risk of All-Cause Mortality in patients with Asymptomatic Celiac Disease

A total of five studies that evaluated the risk of all-cause mortality in asymptomatic patients with celiac disease were identified. There were five cohort studies, two prospective and three retrospective. The two prospective studies did not show an increased risk of all-cause mortality in subjects with asymptomatic celiac disease.

Grading of Evidence

The quality of the evidence was evaluated using the GRADE Working Group criteria. (10) Overall, the quality of the evidence ranged from low to very low depending on the outcome evaluated.

The Clinical Utility of Serologic Testing for Celiac Disease in Asymptomatic Patients

Eligible studies that evaluated the effects of a GFD on disease-specific outcomes were only identified for two of the conditions evaluated, type 1 diabetes and idiopathic short stature.

The clinical utility of serologic testing for celiac disease in patients with type 1 diabetes without symptoms consistent with celiac disease was not demonstrated since the studies identified did not provide evidence of the impact of the GFD on either metabolic control or long-term outcomes in these patients.

The clinical utility of serologic testing for celiac disease in patients with idiopathic short stature without symptoms consistent with celiac disease was demonstrated since the studies identified showed an acceleration in growth once the diagnosis of celiac disease was made and a GFD was introduced.

The Budget Impact of Serologic Testing for Celiac Disease in Asymptomatic Patients

The budget impact of serologic testing for celiac disease in asymptomatic patients was calculated for the conditions for which clinical utility for serologic testing was demonstrated. The budget impact in patients with idiopathic short stature without symptoms consistent with celiac disease was estimated as C$552,000 as calculated by multiplying the estimated number of individuals in Ontario with idiopathic short stature that may be eligible for the test by the cost of the serologic test for celiac disease.

Conclusions

- Based on a review of the literature, there is an increased risk of asymptomatic celiac disease in subjects with type 1 diabetes.
- Based on low quality evidence, in patients with idiopathic short stature and asymptomatic celiac disease there is an acceleration in growth once a gluten-free diet is introduced.
- With the exception of idiopathic short stature, there was no published evidence of clinical utility of celiac disease testing in asymptomatic patients with respect to a gluten-free diet intervention in the other conditions evaluated.
- Based on low to very low quality evidence, asymptomatic celiac disease does not confer an increased risk of lymphoma or mortality.
- Similarly, in patients with lymphoma there is no increased risk of asymptomatic celiac disease.

Decision Determinants

OHTAC has developed a decision-making framework that consists of seven guiding principles for decision making and a decision-making tool, called the Decision Determinants (DD) tool. The evaluation of the four explicit main criteria (overall clinical benefit, value for money, feasibility of adoption into health system, and consistency with expected societal & ethical values). For more information on the Decision-Making Framework and the meaning of the symbols below, please refer to the Decision Determinants Guidance Document or visit: http://www.health.gov.on.ca/english/providers/program/ohtac/decision_frame.html

	Technology
Overall clinical benefit	The clinical utility of serological testing in asymptomatic patients with idiopathic short stature was demonstrated based on low quality evidence of growth improvement after the start of a gluten-free diet.
Consistency with expected societal and ethical values	Not evaluated.
Value for money	The budget impact of serological testing for celiac disease in asymptomatic patients with idiopathic short stature was considered relatively low.
Feasibility of adoption into the health system	The additional volume of tests in asymptomatic patients with idiopathic short stature is expected to be relatively low.

OHTAC Recommendations

1. For children and adolescents with idiopathic short stature OHTAC recommends that serologic testing for celiac disease (IgA tTG¶) be made available to guide a decision to introduce a gluten-free diet and evaluate its effect on growth. This is based on low quality evidence of improved growth on a gluten-free diet in pediatric patients with idiopathic short stature and celiac disease without symptoms consistent with this disease.

2. Given the lack of demonstrated clinical utility, OHTAC does not recommend routine serologic testing in other conditions associated with a higher prevalence of celiac disease unless symptoms consistent with celiac disease (see * below) develop.

* In Adults: chronic diarrhea especially in the presence of weight loss, abdominal pain, and/or unexplained iron-deficiency anemia unresponsive to iron supplementation.
In Pediatrics: Chronic diarrhea especially in the presence of failure to thrive or weight loss; severe constipation especially with poor weight gain.
In Adults and Pediatrics: Unexplained iron deficiency anemia unresponsive to iron supplementation, or subjects with dermatitis herpetiformis.

¶ IgA tTG refers to the immunoglobulin A (IgA) anti-tissue transglutaminase antibody serologic test.

Appendix 1: OHTAC Recommendations on Serologic Testing for Celiac Disease in Individuals with Symptoms Consistent with this Disease

The following recommendations on serologic testing for celiac disease in individuals with symptoms consistent with the disease were published by OHTAC in December 2010. (9)

OHTAC Recommendations
The following recommendations are being made in regards to gastrointestinal indications, unexplained anemia unresponsive to iron supplementation, and dermatitis herpetiformis. OHTAC will make recommendations regarding IgA tTG testing for possible non-gastrointestinal indications and for asymptomatic high risk individuals once the evidence-based analysis for these indications is provided for its consideration.

1. Based on moderate quality evidence for IgA tTG¶, OHTAC supports the use of this serologic test in the diagnosis of celiac disease in subjects with suspicion of celiac disease (see * below),

2. Patients with a negative IgA tTG serologic test with strong suspicion of celiac disease (see * below) with or without IgA deficiency should be referred to a gastroenterologist for consideration of a small bowel biopsy.

3. Individuals with type 1 diabetes mellitus, autoimmune thyroid disease, and first degree relatives of individuals with celiac disease are reported to be at a higher risk of developing celiac disease and there should be a heightened awareness in testing for celiac disease if they meet the criteria listed at * below.

4. In people with a positive serologic test for celiac disease it is recommended that a confirmatory small bowel biopsy be performed.

5. Repeat serologic testing for patients diagnosed with celiac disease is reasonable for those patients who remain symptomatic despite strict adherence to a gluten-free diet. In this case, serologic testing for celiac disease should not be repeated more that once a year for each patient.

* In Adults: chronic diarrhea especially in the presence of weight loss, abdominal pain, and/or unexplained iron-deficiency anemia unresponsive to iron supplementation.
In Pediatrics: Chronic diarrhea especially in the presence of failure to thrive or weight loss; severe constipation especially with poor weight gain.
In Adults and Pediatrics: Unexplained iron deficiency anemia unresponsive to iron supplementation, or subjects with dermatitis herpetiformis.
¶ IgA tTG refers to the immunoglobulin A (IgA) anti-tissue transglutaminase antibody serologic test.

Appendix 2:

List of non-gastrointestinal conditions evaluated

Table 3 provides the list of the non-gastrointestinal conditions evaluated in this report. This list is based on the 2009 Clinical Practice Guidelines from The National Institute for Health and Clinical Excellence (NICE) (3) and expert opinion.

Table: List of Conditions Evaluated in this Report

Conditions	Conditions continued
Unexplained amenorrhea	Unexplained short stature
Unexplained aphtous stomatitis	Unexplained infertility
Unexplained alopecia	Unexplained osteopenia or osteoporosis
Unexplained ataxia	Unexplained peripheral neuropathy
Unexplained chronic thrombocytopenia purpura	Unexplained recurrent miscarriages
Unexplained delayed puberty	Type 1 diabetes
Unexplained depression	Women with low birth weight infants unexplained by other causes

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