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Clinical Utility of Serologic Testing for Celiac Disease in Asymptomatic Patients

An Evidence-Based Analysis

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List of Abbreviations

AGA	Anti-gliadin antibody
AHRQ	Agency for Health Research and Quality
CD	Celiac disease
CI	Confidence interval(s)
DGP	Deamidated gliadin peptides
ELISA	Enzyme-linked immunosorbent assay
EMA	Endomysial antibody
GFD	Gluten-free diet
HbA1c	Hemoglobin A1c
HR	Hazard ratio
IgA	Immunoglobulin A
IgG	Immunoglobulin G
MAS	Medical Advisory Secretariat
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
RR	Relative risk
SD	Standard deviation
SDS	Standard deviation score
SMR	Standardized mortality ratio
tTG	Tissue transglutaminase

Executive Summary

Objective

The objective of this evidence-based analysis was to evaluate the clinical utility of serologic testing for celiac disease in asymptomatic individuals presenting with one of the non-gastrointestinal conditions evaluated in this report. The clinical utility was based on the effects of a gluten-free diet (GFD) on outcomes specific to each of these conditions. The prevalence of celiac disease in asymptomatic individuals and one of these non-gastrointestinal conditions was also evaluated.

Clinical Need and Target Population

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.

Technology Under Evaluation

Serologic Tests for Celiac Disease

There are a number of serologic tests for celiac disease available. Serologic tests are automated with the exception of the anti-endomysial antibody test, which is more time-consuming and operator-dependent than the other tests.

Research Questions

1. What is the prevalence of asymptomatic celiac disease in patients presenting with one of the non-gastrointestinal conditions evaluated?
2. What is the effect of the gluten-free diet on condition-specific outcomes in patients with asymptomatic celiac disease presenting with one of the non-gastrointestinal conditions evaluated?
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 subjects presenting with one of the non-gastrointestinal conditions evaluated?

Research Methods

Study Population

The study population consisted of individuals with newly diagnosed celiac disease without any symptoms consistent with the disease presenting with one of the non-gastrointestinal conditions evaluated. When evaluating the risk of lymphoma and all-cause mortality, the study population consisted of asymptomatic individuals with a positive celiac disease serologic test and/or small bowel biopsy.

Literature Search

Search Strategy

Literature searches were performed for each disease/condition evaluated between December 2010 and March 2011 using OVID MEDLINE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA). No restrictions for start date of search were used.

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

- Studies, systematic reviews, and meta-analyses that assessed the effects of a GFD in patients with newly diagnosed asymptomatic celiac disease presenting with one of the non-gastrointestinal conditions evaluated. If symptoms were not reported in the study but subjects were identified through screening for celiac disease the study was included.
- Studies, systematic reviews, and meta-analyses that assessed the prevalence of newly diagnosed asymptomatic celiac disease in patients with one of the non-gastrointestinal conditions evaluated. If symptoms were not reported in the study but subjects were identified through screening for celiac disease the study was included.
- Studies, systematic reviews, and meta-analyses that evaluated the risk of all-cause mortality or lymphoma in individuals with asymptomatic celiac disease.
- Sample size ≥ 10.
- Publications in English.

Exclusion Criteria

- Studies that retrospectively assessed the prevalence of asymptomatic celiac disease.
- Studies that reported the prevalence of one of the non-gastrointestinal conditions evaluated in subjects already diagnosed with celiac disease.
- Studies in individuals with one of the non-gastrointestinal conditions evaluated if the condition could be explained by other causes.
- Studies in subjects with celiac disease and symptoms consistent with the disease. If the study included individuals with and without symptoms consistent with celiac disease and their results were analysed separately, the results in individuals without symptoms were included in the analysis.
- Studies in which individuals did not report any symptoms consistent with celiac disease at study start but that either retrospectively reported the presence of such symptoms after following a GFD, or that previously presented with symptoms consistent with celiac disease.
- Study results published in letters to the editor or comments about other studies.
- Studies with a sample size ≥ 10, however, in which less than 10 patients were included in the analysis.

Outcomes of Interest

The effects of a GFD on disease-specific outcomes for each condition evaluated in patients with asymptomatic celiac disease was assessed. The prevalence of asymptomatic celiac disease in patients

presenting with one of the conditions evaluated was also assessed.

Results of Evidence-Based Analysis

Three eligible observational studies evaluated the effects of GFD on growth parameters in subjects with asymptomatic celiac disease and idiopathic short stature. Four eligible observational studies evaluated the effects of GFD on metabolic control in subjects with asymptomatic celiac disease and type 1 diabetes. Five eligible observational studies evaluated the risk of all-cause mortality and five eligible observational studies evaluated the risk of lymphoma in subjects with asymptomatic celiac disease. No eligible studies on the effects of the GFD for the other conditions evaluated were identified. Twenty-three eligible studies measured the prevalence of asymptomatic celiac disease in subjects presenting with one of the 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. 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 patients 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 5 studies that evaluated the risk of all-cause mortality in asymptomatic patients with celiac disease were identified. There were 5 cohort studies, 2 prospective and 3 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 for each serologic tests evaluated based on the GRADE Working Group criteria. 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 Subjects

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 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 patients 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.

Background

Preamble

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. (1) The report concluded that the clinical validity and clinical utility of serologic tests for celiac disease was considered high in this population and that study findings suggest that IgA tTG is the most accurate and most cost-effective serologic test. (1)

The results of the evidence-based analysis performed by MAS (1) and the input from experts and the Citizen's Reference Panel on Health Technology were considered by the Ontario Health Technology Advisory Committee (OHTAC) in making recommendations regarding the use of serologic tests for celiac disease. (2) The recommendations made by OHTAC were specific to gastrointestinal indications, unexplained anemia unresponsive to iron supplementation, and dermatitis herpetiformis (Appendix 1). (2) However since testing in other non-gastrointestinal conditions in individuals without symptoms consistent with celiac disease[1] were raised by the Professional Panel, it was decided that a separate evidence-based analysis of these possible indications would be undertaken by MAS, which is the subject of this report.

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. (2)

Objective of Analysis

The objective of this evidence-based analysis was to evaluate the clinical utility of serologic testing for celiac disease in asymptomatic patients presenting with one of the non-gastrointestinal conditions evaluated in this report. The clinical utility was based on the effects of a gluten-free diet (GFD) on outcomes specific to each of these conditions. The prevalence of celiac disease in individuals without symptoms consistent with the disease presenting with one of these non-gastrointestinal conditions was also evaluated.

Clinical Need and Target Population

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. (3) This results in impaired digestion and absorption of nutrients. (4) The immunological response is triggered by the ingestion of gluten. (3) Treatment consists of strict lifelong adherence to a gluten-free diet (GFD). (3) Symptoms improve with a GFD but recur when gluten-containing foods are restarted. (4)

Celiac disease may have different presentations:

- [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.

- Classic: patients present with gastrointestinal symptoms and the classic features of intestinal malabsorption with fully developed gluten-induced villous atrophy and other classic histologic features. (5)
- Atypical: patients present with little or no gastrointestinal symptoms. Presenting symptoms include iron deficiency anemia among others. Fully developed gluten-induced villous atrophy is present. (5)
- Silent: patients do not present clear gastrointestinal or atypical symptoms but present gluten-induced villous atrophy. (5)
- Latent: patients with a previous diagnosis of celiac disease who responded to a GFD and a normal small bowel mucosa. It may also include subjects with normal small bowel mucosa despite the ingestion of gluten but who may later develop celiac disease. (5)
- Refractory: patients diagnosed with celiac disease who do not respond to a GFD. This may be due to either lack of compliance or inadvertent consumption of gluten. However refractory celiac disease can occur in patients who develop ulcerative-jejunoileitis or enteropathy-associated T-cell lymphoma. (5)

Celiac Disease Diagnosis Guidelines

According to celiac disease guidelines, the diagnosis of celiac disease is established by small bowel biopsy. (6-8) Serologic tests are used to initially detect and to support the presence of celiac disease. (4;6-8) Different serologic tests for celiac disease are available: anti-gliadin antibody (AGA), anti-endomysial antibody (EMA), anti-tissue transglutaminase antibody (tTG), and anti-deamidated gliadin peptides antibody (DGP). (9) The diagnosis of celiac disease is confirmed by the presence of characteristic villous morphology abnormalities in the small bowel mucosa through a histological evaluation of small bowel biopsy specimens. (4;8)

The diagnosis of celiac disease must be performed on a gluten-containing diet since the small bowel abnormalities and the serologic antibody levels may resolve or improve on a GFD. (4)

Prevalence of Celiac Disease

General Population

The prevalence of celiac disease in studies included in the 2004 systematic review conducted by the Agency for Health Research and Quality (AHRQ) varied between 0.14% and 1.87%. (5) A pooled estimate was not calculated due to concerns with heterogeneity across studies, however the median prevalence reported across the studies was 0.47% [interquartile range (IQR) 0.25%, 0.71%]. (5) According to the authors of the 2004 AHRQ review the prevalence did not vary by age group, i.e., adults and children. (5)

Ontario Context

Serologic tests for celiac disease are available in both community and hospital laboratories in Ontario.

Technology under Review

Serologic Tests for Celiac Disease

There are a number of serologic tests for celiac disease available (table 2). Serologic tests are automated with the exception of the anti-endomysial antibody test, which is more time-consuming and operator-dependent than the other tests. (4;7)

For each serologic test, both immunoglobulin A (IgA) or G (IgG) can be measured, however, IgA measurement is the standard antibody measured in celiac disease. (4)

Table 2: Types of Serologic Celiac Disease Tests.

Serologic test	Type of assay
Anti-gliadin antibody (AGA) IgA and IgG	ELISA
Anti-endomysial antibody (EMA) IgA and IgG	Indirect immunofluorescence
Anti- tissue transglutaminase antibody (tTG) IgA and IgG	ELISA
Anti-deamidated gliadin peptides antibody (DGP)	ELISA

ELISA refers to enzyme-linked immunosorbent assay; Ig immunoglobulin

Regulatory Status

Diagnostic kits for the serologic tests for celiac disease listed in table 2 have been licensed by Health Canada. (10)

Evidence-Based Analysis

List of non-gastrointestinal conditions evaluated in this report

Table 3 provides the list of the non-gastrointestinal conditions evaluated in this report. These conditions were evaluated if they were unexplained by other causes. The list is based on the 2009 Clinical Practice Guidelines from The National Institute for Health and Clinical Excellence (NICE) (9) and expert opinion.

Table 3: 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

Research Questions

1. What is the prevalence of asymptomatic celiac disease in individuals presenting with one of the non-gastrointestinal conditions evaluated (see list on table 3)?
2. What is the effect of the gluten-free diet on condition-specific outcomes in patients with asymptomatic celiac disease presenting with one of the non-gastrointestinal conditions evaluated (see list on table 3)?
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?

Research Methods

Study Population

The study population consisted of asymptomatic individuals with newly diagnosed celiac disease presenting with one of the non-gastrointestinal conditions evaluated. When evaluating the risk of lymphoma and all-cause mortality, the study population consisted of asymptomatic individuals with a positive celiac disease serologic test and/or characteristic abnormalities on small bowel biopsy.

Literature Search

Search Strategy

Literature searches were performed for each condition evaluated (table 3) between December 2010 and March 2011 using OVID MEDLINE, the Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA). Search terms and end date for study publications for each search are provided in Appendix 2. No restrictions for start date of search were used.

Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search. Articles with an unknown eligibility were reviewed with a second clinical epidemiologist and then a group of epidemiologists until consensus was established.

Inclusion Criteria

- Studies, systematic reviews, and meta-analyses that assessed the effects of a gluten-free diet in patients with newly diagnosed asymptomatic celiac disease presenting with one of the non-gastrointestinal conditions evaluated. If symptoms were not reported in the study but subjects were identified through screening for celiac disease the study was included.
- Studies, systematic reviews, and meta-analyses that assessed the prevalence of newly diagnosed asymptomatic celiac disease in subjects with one of the non-gastrointestinal conditions evaluated. If symptoms were not reported in the study but subjects were identified through screening for celiac disease the study was included.
- Studies, systematic reviews, and meta-analyses that evaluated the risk of all-cause mortality or lymphoma in individuals with asymptomatic celiac disease.
- Sample size ≥ 10.
- Publications in English.

Exclusion Criteria

- Studies that retrospectively assessed the prevalence of asymptomatic celiac disease.
- Studies that reported the prevalence of one of the non-gastrointestinal conditions evaluated in subjects already diagnosed with celiac disease.
- Studies in individuals with one of the non-gastrointestinal conditions evaluated that if these conditions could be explained by other causes.
- Studies in subjects with celiac disease and symptoms consistent with the disease. If the study included both symptomatic and asymptomatic individuals and their results were analysed separately, the results in individuals without symptoms were included in the analysis.
- Studies in which individuals did not report any symptoms consistent with celiac disease at study start but that either retrospectively reported the presence of such symptoms after following a GFD, or that previously presented with symptoms consistent with celiac disease.
- Study results published in letters to the editor or comments about other studies.
- Studies with an initial sample size ≥ 10, however, in which less than 10 patients were included in the analysis.

Outcomes of Interest

Outcomes specific to each condition included in this report were evaluated when analysing the effects of a GFD in asymptomatic subjects with a positive celiac disease serologic test and/or small bowel biopsy and

one of the conditions evaluated:

- Improvement in fertility
- Reduction of the risk of recurrent spontaneous abortions
- Reduction of the risk of low birth weight infants
- Improvement in epilepsy symptoms
- Improvement in peripheral neuropathy symptoms
- Improvement in ataxia symptoms
- Improvement in growth parameters in pediatric patients diagnosed with idiopathic short stature
- Improvement in bone health parameters in subjects with osteopenia or osteoporosis
- Delayed puberty
- Improvement of amenorrhea
- Reduction of the risk of recurrent aphtous stomatitis
- Improvement of metabolic control (HbA1c, changes in insulin dosage, and changes in the number of hypoglycemic episodes) in patients with type 1 diabetes
- Improvement of alopecia
- Improvement of depression
- Chronic idiopathic thrombocytopenic purpura

The following outcomes were also evaluated:

- Risk of lymphoma in patients with asymptomatic celiac disease
- Risk of all-cause mortality in patients with asymptomatic celiac disease
- Prevalence of newly diagnosed celiac disease in subjects with asymptomatic celiac disease and presenting with one of the non-gastrointestinal conditions evaluated.

Statistical Analysis

Changes in the outcomes listed above once a GFD was introduced and the risk of lymphoma and all-cause mortality in subjects with asymptomatic celiac disease were reported as published in the studies identified.

The pooled estimate of the prevalence of asymptomatic celiac disease in subjects with the conditions evaluated was calculated using the weighted average method. Comparisons in prevalence rates between individuals with one of the conditions evaluated and controls were performed with Review Manager 5 (version 5.0.025, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) using the Mantel Haenszel method.

In all analyses, the highest quality of evidence among the studies identified for each outcome was used. For instance, if both prospective and retrospective studies were identified for the same outcome, the data from prospective studies were used. For prevalence studies, only data from controlled studies were used unless controlled studies were not identified.

Quality of Evidence

The quality of the observational studies identified was determined based on the study design and risk of bias including subject recruitment, patient attrition, exposure and outcome definition, accounting for possible confounding. (11)

The quality of the body of evidence was assessed as high, moderate, low, or very low according to the GRADE Working Group criteria (12) as presented below.

1. Quality refers to the criteria such as the adequacy of allocation concealment, blinding and follow-up.

2. Consistency refers to the similarity of estimates of effect across studies. If there are important and unexplained inconsistencies in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the magnitude of the difference in effect, and the significance of the differences guide the decision about whether important inconsistency exists.

3. Directness refers to the extent to which the interventions and outcome measures are similar to those of interest.

As stated by the GRADE Working Group, the following definitions of quality were used in grading the quality of the evidence:

High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain

Results of Evidence-Based Analysis

Three eligible observational studies evaluated the effects of a GFD on growth parameters in patients with asymptomatic celiac disease and idiopathic short stature. (13-15) Four eligible observational studies evaluated the effects of GFD on metabolic control in patients with asymptomatic celiac disease and type 1 diabetes. (16-19) Five eligible observational studies evaluated the risk of all-cause mortality (20-24) and five eligible observational studies evaluated the risk of lymphoma in patients with asymptomatic celiac disease. (25-29) No eligible studies on the effects of the GFD for the other conditions evaluation were identified. Twenty-three eligible studies measured the prevalence of asymptomatic celiac disease in subjects presenting with the conditions evaluated. (14;30-51)

Table 4: Body of evidence examined according to study design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	
Small RCT	
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	14
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study (Cross-sectional, prevalence studies)	23
Case series	3
Retrospective review, modelling	
Studies presented at an international conference or other sources of grey literature	
Expert opinion	
Total	40

RCT refers to randomized controlled trial.
Study classification based on Goodman et al. (52)

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.

A weighted average of the prevalence of asymptomatic celiac disease both in individuals with the conditions evaluated and in the control group if available was calculated.

Celiac disease was diagnosed through serologic tests in all studies and confirmed by small bowel biopsy in some studies. Given the higher accuracy of the small bowel biopsy and the serologic tests IgA tTG and IgA EMA compared to IgA AGA, (1) only the prevalence results based on IgA tTG, IgA EMA, or small bowel biopsy were included in the analyses.

All studies evaluated the prevalence of asymptomatic celiac disease in a cross-sectional way. Table 5 shows the number of eligible studies identified and the pooled prevalence of asymptomatic celiac disease

for each condition evaluated. Additional details about individual studies are provided in Appendix 3.

No eligible prevalence studies were identified in patients with amenorrhea, delayed puberty, alopecia, and depression.

Table 5: Prevalence of Asymptomatic Celiac Disease in Subjects with one of the Non-Gastrointestinal Conditions Evaluated

Condition	N. Studies Sample size (non-gastrointestinal conditions /controls)	Prevalence of Asymptomatic Gluten Sensitivity (patients with the conditions listed below)	Prevalence of Asymptomatic Gluten Sensitivity (Controls)
Infertility	3 cross-sectional	3.9%	1.0%
	N=297 / 506 (controls)	Not statistically significant vs. controls	
Recurrent spontaneous abortion	3 cross sectional	1.7%	1.0%
	N=131/ 506 (controls)	Not statistically significant vs. controls	
Women with low birth weight infants	1 cross sectional	9.3%	1.3%
	N=150 / 305 (controls)	Not statistically significant vs. controls	
Epilepsy	4 cross-sectional	1.8%	1.0%
	N=1648/6174 (controls)	Not statistically significant vs. controls	
Peripheral Neuropathy	1 cross-sectional	0	No comparative study
Ataxia	1 cross-sectional	3.1%	1.0%
	N=32 / 73 (controls)	Not statistically significant vs. controls	
Short Stature	6 cross-sectional	1.1%	No comparative study
	N=7492		
Osteopenia, Osteoporosis	3 cross-sectional	4.3%	3.0%
	N=318 / 2135 (controls)	Not statistically significant vs. controls	
Recurrent Aphtous Stomatitis	1 cross-sectional	4.8%	0
	N=41 / 49 (controls)	Not statistically significant vs. controls	
Type 1 Diabetes*	3 cross-sectional	8.9%	0.3%
	N=202 / 269 (controls)	**Statistically Significant vs. controls Difference: 9% (95% CI 5%, 14%)**	
Chronic Idiopathic Thrombocytopenia Purpura	1 cross-sectional	2.7%	0.6%
	N=74 / 162 (controls)	Not statistically significant vs. controls	

* Studies published since 2005 were included

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.

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

The effects of a GFD in individuals with one of the conditions evaluated and newly diagnosed asymptomatic celiac disease were examined.

Four eligible studies were identified in subjects with type 1 diabetes, (16-19) and three in subjects with idiopathic short stature. (13-15) No eligible studies were identified in subjects with any of the other

conditions evaluated.

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.

Four eligible studies evaluated the impact of a GFD on metabolic control in subjects with type 1 diabetes and asymptomatic celiac disease. (16-19) All studies had a case-control design, one was prospective, (17) and three were retrospective (16;18;19). All studies were in pediatric patients. (16-19) Subjects with type 1 diabetes being followed at the study clinics were recruited to participate in the studies. In all studies, cases were defined as subjects with type 1 diabetes who had a positive celiac disease serologic test and/or characteristic abnormalities on a small bowel biopsy at the start of the study without symptoms consistent with celiac disease. The diagnosis of celiac disease was made by serologic tests (IgA tTG, IgA EMA, IgA AGA) and confirmed by small bowel biopsy. (16;18;19) Controls were subjects with type 1 diabetes who had a negative serologic test for celiac disease at the start of the study. Controls were matched to cases by age, gender, and diabetes duration in three studies, (16;17;19) and by age and gender in one study. (18) A GFD was introduced in subjects who were diagnosed with celiac disease at the start of the study. The follow-up extended from up to 3 years before the diagnosis of celiac disease until up to 4 years after the diagnosis depending on the study. (16-19)

The sample size in each study ranged from 18 to 49 in cases and 26 to 58 among controls. (16-19) The mean age in the studies varied between 10 and 11 years. (16-19) Fifty-three to sixty-three percent of the subjects were girls, as reported in two studies (17;18), it wasn't reported in the other two studies. (16;19) The participation rate was not reported in the studies. In one study, 4 out of 27 (14.8%) subjects were withdrawn from the analysis due to incomplete medical records or because the celiac disease diagnosis was made before the type 1 diabetes diagnosis. (19) In one study 2 (10%) out of 20 cases were withdrawn due to the presence of other concomitant diagnosis. (16) No withdrawals were reported in two studies. (17;18) Compliance with a GFD was not reported in three studies. (16;18;19) The study by Sun et al. only included patients who complied with the GFD. (17)

The results of the studies are summarized below. Additional details in table 6.

Changes in HbA1c levels

One prospective (17) and three retrospective case-control studies (16;18;19) evaluated the changes in HbA1c levels.

The prospective study observed statistically significantly lower HbA1c levels in 18 cases compared to 26 controls from approximately 3 years before the celiac disease diagnosis until the time of diagnosis, i.e., 8.3% [standard deviation (SD) 1.1] vs. 8.7% (SD 0.9), p 0.02, respectively, at the time of celiac disease diagnosis. (17) The difference in HbA1c levels between cases and controls was not statistically significant at 1 and 2 years after the introduction of the GFD. (17)

Three retrospective case-control studies did not observe statistically significant differences in HbA1c levels between cases and controls either before (0 to 18 months) or after (1 to 4 years) the celiac disease diagnosis and GFD start. (16;18;19)

Number of Hypoglycemia Episodes

One retrospective case-control study compared the number of hypoglycemia episodes between cases and controls from 18 months before the diagnosis of celiac disease to 18 months after the diagnosis. (16) No details were provided with regards to how the hypoglycemia episodes were identified. The severity of

hypoglycemia episodes was not reported in the study. A total of 18 cases and 26 controls were included in the study. (16)

No statistically significant difference in the number of hypoglycemia episodes was observed between cases and controls between 18 and 6 months before the celiac disease diagnosis. (16) During the period ranging from 6 months before the diagnosis until 6 months after the diagnosis of celiac disease, the mean number of episodes was higher in cases (4.5, SD 4.0) compared to controls (2.0, SD 2.2), p=0.01. (16) After 6 months following the diagnosis of celiac disease and the introduction of the GFD, no statistically significant difference between cases and controls was observed. (16)

Additional details in table 6.

Insulin Dosage

Three case-control studies evaluated the changes in insulin dosage in cases and controls before and after the introduction of a GFD, 1 prospective (17) and 2 retrospective. (16;19)

The only prospective case control study did not find a statistically significant difference in insulin dosage between cases and controls either before or after the diagnosis of celiac disease and introduction of the GFD. (17) A retrospective case-control study did not observe a statistically significant difference in insulin dosage between cases and controls either before or after the diagnosis of celiac disease and the start of a GFD. (19) A second retrospective case-control study reported that the insulin dosage was similar between cases and controls 18 months before the diagnosis of celiac disease. (16) Thereafter, the insulin dosage decreased in cases with the lowest dosage at the time of diagnosis of celiac disease, although the difference between cases and controls was not statistically significant, p-value: 0.05. (16) After the diagnosis of celiac disease and introduction of the GFD, there was an increase in the insulin dosage in cases, and it was not statistically significantly different between cases and controls more than 6 months after the celiac disease diagnosis. (16)

Additional details about these studies in table 6.

Summary and Conclusions

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, (17) 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 (16) and since there were inadequate details reported 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. (17)

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.

Table 6: The Effects of a GFD on Type 1 Diabetes Metabolic Control in Patients with Asymptomatic Celiac Disease

Study Country N	Study Design Outcomes Recruitment	Patient Population Symptoms	Celiac Disease diagnosis criteria Withdrawals GFD Compliance	Effects of GFD on HbA1c (GFD duration) N cases/controls	Effects of GFD on Hypoglycemia episodes (GFD duration) N cases/controls	Effects of GFD on insulin dose (GFD duration) N cases/controls
Mohn et al. (16) (2001) Italy N= 20 cases N=26 controls Pediatric	• **Study design** Retrospective case-control Power calculation: not reported Follow-up: 1.5 yrs • **Recruitment** Cases and controls: type 1 diabetes patients followed at hospital clinics. Cases: patients diagnosed with CD Controls: subjects who tested negative for CD serology, matched to cases by age, gender and diabetes duration. • **Exclusion Criteria** - Not reported	• **Celiac Disease Symptoms** 20 (100%) asymptomatic • **Patient Population** <u>Mean Age</u> 11.0 (1.8-21.9) yrs <u>Girls</u> Not reported <u>Mean duration of type 1 diabetes at CD diagnosis</u> 6.3 (1-19) yrs <u>Participation rate</u> Not reported	• **Celiac Disease diagnosis** Serology (IgA EMA, AGA) confirmed by small bowel biopsy • **Withdrawals** 2 (10%) excluded due to other concomitant diagnoses • **GFD Compliance** Not reported	**N=18 (cases) / N=26 (controls)** • **HbA1c (18 mos before CD diagnosis to 18 mos after CD diagnosis)** No difference during f-up between cases and controls	**N=18 (cases) / N=26 (controls)** • **Hypoglycemia episodes** ***18 to 6 mos before CD diagnosis*** No significant difference between cases and controls ***6 mos before CD diagnosis to 6 mos after CD diagnosis*** Cases: 4.5 ± 4 Controls: 2.0 ± 2.2 p .01 ***> 6 mos after CD diagnosis*** Not different between groups > 6 mos after GFD start	**N=18 (cases) / N=26 (controls)** **Insulin requirement (18 mos before CD diagnosis to 18 mos after CD diagnosis)** **<u>Cases vs. controls / before-after</u>** Similar between cases and controls 18 mos before CD diagnosis, decreased progressively thereafter in cases with the lowest point at the time of CD diagnosis (0.6 ± 0.2 vs. 0.9 ± 0.3 in controls, p .05). Increase after start of GFD in cases. Not different between cases and controls > 6 mos after GFD start

Study Country N	Study Design Outcomes Recruitment	Patient Population Symptoms	Celiac Disease diagnosis criteria Withdrawals GFD Compliance	Effects of GFD on HbA1c (GFD duration) N cases/controls	Effects of GFD on Hypoglycemia episodes (GFD duration) N cases/controls	Effects of GFD on insulin dose (GFD duration) N cases/controls
Goh et al. (18) (2010) US N=29 cases N=58 controls Pediatric	• **Study design** Retrospective case-control Power calculation: not reported Follow-up: 1 yr • **Recruitment** Cases and controls: patients with type 1 diabetes retrospectively identified through hospital database Cases: patients diagnosed with CD Controls: negative CD serology matched by age and gender to cases • **Exclusion Criteria** Not reported	• **Celiac Disease Symptoms** Asymptomatic: 28 (100%) • **Patient Population** Mean Age ± SD Cases: 10.2 ± 3.7 yrs Controls: 9.8 ± 3.8 yrs Girls Cases: 17 (60.7%) Controls 31 (53.4%) Mean diabetes duration ± SD Cases: 3.5 ± 3.32 yrs Controls: 4.8 ± 2.5 yrs Participation rate Not reported	• **Celiac Disease diagnosis** Serology (IgA EMA, tTG), confirmed by small bowel biopsy • **Withdrawals** None at 1 yr • **GFD Compliance** Not reported	**N=29 (cases) / N=58 (controls)** • **Effects on HbA1c (1 yr)** No statistically significant difference between cases and controls during the 12 mos before or after GFD	**Not evaluated**	**Not evaluated**

Study Country N	Study Design Outcomes Recruitment	Patient Population Symptoms	Celiac Disease diagnosis criteria Withdrawals GFD Compliance	Effects of GFD on HbA1c (GFD duration) N cases/controls	Effects of GFD on Hypoglycemia episodes (GFD duration) N cases/controls	Effects of GFD on insulin dose (GFD duration) N cases/controls
Sun et al. (17) (2009) UK N=49 cases N=49 controls Pediatric	• **Study design** Case-control Power calculation: not reported Follow-up: 2 yrs • **Recruitment** Caseas and controls: subjects < 16 yrs seen at diabetic clinics with type 1 diabetes Cases: positive CD serology on annual screening. Controls: negative CD serology, matched to cases by age, sex, and diabetes duration. Recruitment not described in detail. • **Exclusion Criteria** - Refusal of biopsy - GFD refusal - Poor GFD compliance (defined by positive serology on GFD)	• **Celiac Disease Symptoms** Asymptomatic: 49 (100%) • **Patient Population** <u>Mean Age ± SD</u> cases: 11.9 ± 3.5 yrs controls: 11.9 ± 3.3 yrs <u>Girls</u> Cases: 31 (63.0%) Controls: 31 (63.0%) <u>Mean age at type 1 diabetes diagnosis ±SD</u> Cases: 6.0 ± 3.7 yrs controls: 6.0 ± 3.8 yrs <u>Mean age at CD diagnosis ±SD</u> Cases: 9.1 ± 3.7 yrs <u>Mean time between diabetes and CD diagnosis ±SD</u> 3.2 ± 2.8 yrs <u>Participation rate</u> Not reported	• **Celiac Disease diagnosis** Serology (IgA EMA, tTG), confirmed by small bowel biopsy • **Withdrawals** None • **GFD Compliance** 100%	**N=49 (cases) / N=49 (controls)** • **Effects on HbA1c, %, ± SD (2 yrs)** ***Controls*:** 8.7% ± 0.9 (mean during f-up) ***Before CD diagnosis (3.0 yrs before CD diagnosis to diagnosis)*** Cases: 8.3% ± 1.1, p .02 vs. controls ***At CD diagnosis*** CD-DM1: 8.4% ± 1.3, p < .001 vs. controls ***After CD diagnosis and start of GFD*** Cases: 8.9% ± 1.5 (1 yr) Cases: 8.7% ± 1.4 (2 yrs) Not significantly different from controls at baseline	**Not evaluated**	**N=49 (cases) / N=49 (controls)** • **Insulin dose, U/kg/day, ± SD (2 yrs)** <u>*Before CD diagnosis (baseline)*</u> cases: 1.0 ± 0.3 controls: 0.9 ± 0.3 NS <u>*After starting GFD*</u> cases: 0.9 ± 0.4 (1 yr) cases: 0.8 ± 0.3 (2 yrs) NS vs. controls at baseline. No comparison among CD patients.

Study Country N	Study Design Outcomes Recruitment	Patient Population Symptoms	Celiac Disease diagnosis criteria Withdrawals GFD Compliance	Effects of GFD on HbA1c (GFD duration) N cases/controls	Effects of GFD on Hypoglycemia episodes (GFD duration) N cases/controls	Effects of GFD on insulin dose (GFD duration) N cases/controls
Valletta et al. (19) (2007) Italy N=23 cases N=43 controls Pediatric	• **Study design** Retrospective case series, controlled Power calculation: not reported Follow-up: up to 4 yrs • **Recruitment** Cases and controls: patients with type 1 diabetes followed at a clinic identified through chart review. Cases: patients diagnosed with CD Controls: patients with negative IgA AGA matched to cases by age, sex, duration of diabetes– Recruitment not described in detail. • **Exclusion Criteria** - CD dx before diabetes - Incomplete medical records	• **Celiac Disease Symptoms** Asymptomatic: 25/27 GI symptoms: 2/27 • **Patient Population (CD diagnosed)** Mean age ± SD at CD diagnosis 12.2 ± 6.1 yrs Mean age at diabetes diagnosis ±SD 8.0 ± 3.3 yrs Girls Not reported Participation rate Not reported	• **Celiac Disease diagnosis** Serology (IgA EMA, tTG, AGA), confirmed by small bowel biopsy • **Withdrawals** 4/27 (14.8%) – incomplete records, celiac disease diagnosed before diabetes etc. • **GFD Compliance** Not reported	**N= 23 (cases)/ N=43 (controls)** • **HbA1c (up to 4 yrs)** No difference between patients and controls both at baseline and f-up According to graph, among cases, it seems that there was no significant difference during f-up.	**Not evaluated**	**N= 23 (cases), N=43 (controls)** • **Insulin dosage (GFD up to 4 yrs)** No difference between cases and controls both at baseline and follow-up.

AGA anti-gliadin antibody; CD celiac disease; EMA endomysial antibody; f-up follow-up; GFD gluten-free diet; mos months; Hb hemoglobin; mos months; NR not reported; NS not statistically significant; SD standard deviation; tTG tissue transglutaminase; U unit; yr year

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. (13-15) 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. (13-15) The sample size in each study ranged from 10 to 29 subjects. (13-15) The patient population consisted of pediatric patients with idiopathic short stature who had been referred to the study site for evaluation of celiac disease. (13-15) The number of patients who refused to participate in the study was not reported in the studies.

Short stature was defined as height < 3rd percentile for age and gender in all three studies. (13-15) The short stature was idiopathic or had no endocrine causes. (13-15) Celiac disease was diagnosed by small bowel biopsy at the start of the study in all studies. (13-15)The outcomes evaluated were changes in growth velocity (cm/year) standard deviation score (13;14) and changes in growth standard deviation score (SDS) according to chronological age. (15)

The mean age of the subjects included in the studies varied between 8.4 and 12.1 years. (13-15) Between 25% and 65.5% of the subjects were female. The duration of follow-up on a GFD varied between 6 months and 3 years in two studies, (14;15) and it wasn't clear in one study. (13)

Most subjects demonstrated an improvement in growth parameters (table 7). Compliance with the GFD was not reported in the studies. In one study, 6 out of 16 subjects (37.5%) were excluded from the analysis as they were not followed after the introduction of the GFD. (14) Withdrawals were not reported in the other two studies. (13;15)

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.

Additional information in table 7.

Table 7: The Effects of a GFD on Idiopathic Short Stature in Patients with Asymptomatic Celiac Disease

Study Country N	Study Design Outcomes Recruitment	Patient Population Symptoms	Celiac Disease diagnosis criteria Short Stature definition	Withdrawals GFD compliance	Effects of GFD
Cacciari et al. (14) (1985) Italy N= 104	• **Study design** Case Series, before-after comparison F-up: 3 to 33 mos • **Recruitment** All children with short stature and CD with positive small bowel biopsy but no GI symptoms who attended the pediatric clinic.	• **Symptoms** No GI symptoms • **Patient Characteristics** Idiopathic short stature: 88/104 (84.6%) Mean age: 9.4 to 13.4 yrs (2.8-16.8) Bone age delay (% of chronologic age): 16.6% - 28.2% • **Participation rate** Not reported	• **Celiac disease diagnosis** Serology (AGA) confirmed by small bowel biopsy • **Short stature definition** < 3rd percentile	• **Withdrawals** 6/16 (37.5%) – not followed after GFD. • **GFD Compliance** Not reported	• **Effect of GFD on height velocity SDS** **N=10** Improvement: 6/10 (60.0%) GFD duration: 6-33 mos Statistical significance of changes not provided Mean Height velocity SDS (range), N=9 Before GFD: -1.81 (-1.2 to 2.4) After GFD: +0.49 (-5.0 to 6.7) GFD duration: 3 to 12 mos*
Bonamico et al. (13)(1992) Italy N=29	• **Study design** Case series, before-after comparison F-up: unclear • **Recruitment** Children with short stature and CD with positive small bowel biopsy and no GI symptoms referred to the endocrinology clinic. No somatic, cardiac, or renal malformations or chromosomal abnormalities	• **Symptoms** No GI symptoms • **Patient Characteristics** Mean age: 8.4 yrs ± 3.1 Growth velocity: from -2 SD below average to 25th percentile Growth delay SD, mean (range): -2.7 SD (-2, 3.7) GH deficiency: 5/14 (36%) • **Participation rate** Not reported	• **Celiac disease diagnosis** Small bowel biopsy • **Short stature definition** Height < 3rd percentile	• **Withdrawals** 0 • **GFD Compliance** Not reported	• **Effect of GFD on growth velocity** **N=29** 29/29 (100%) significant acceleration of growth velocity Growth velocity Before GFD: -2.3 SD Post GFD: + 3.7 SD GFD duration: not clear

Study Country N	Study Design Outcomes Recruitment	Patient Population Symptoms	Celiac Disease diagnosis criteria Short Stature definition	Withdrawals GFD compliance	Effects of GFD
Cacciari et al. (15) (1991) Italy N=11	• **Study design** Case series, before-after comparison F-up: 3 yrs • **Recruitment** Children with short stature diagnosed with CD (positive biopsy and AGA serology) and no GI symptoms.	• **Symptoms** No GI symptoms • **Patient Characteristics** <u>Mean chronological age</u> Male: 12.1 yrs (6.2-19.2) Female: 11.7 yrs (9.6-15) <u>Mean bone age</u> Male: 8.9 yrs (3.8-14) Female: 9.9 yrs (7.5-11.7) • **Participation rate** Not reported	• **Celiac disease diagnosis** Small bowel biopsy • **Short stature definition** Height < 3rd percentile	• **Withdrawals** Not reported • **GFD Compliance** Not reported	• **Effect of GFD on growth, GFD duration: 3 yrs** **N=11** Mean chronological age height SDS ± SD: Baseline: -2.52 ± 0.83 Yr 1: -2.23 ± 0.77 Yr 2: -1.99 ± 0.80 Yr 3: -1.69 ± 0.87 p value not reported

AGA antigliadin antibody; CD celiac disease; f-up follow-up; GFD gluten-free diet; GH growth hormone; GI gastrointestinal; mos months; SD standard deviation; SDS standard deviation score; yr year

* 1st evaluation reported in the publication was used in this table

The Risk of Lymphoma in Patients with Asymptomatic Celiac Disease

Five studies that evaluated the association between lymphoma and asymptomatic celiac disease were identified. (25-29) There was one retrospective cohort study, (26) 3 case-control, (25;27;29) and 1 retrospective case-control study. (28) The retrospective cohort study evaluated the risk of lymphoma in subjects with asymptomatic celiac disease. (26) The case-control studies evaluated the risk of asymptomatic celiac disease in subjects with newly diagnosed lymphoma.

Risk of lymphoma in patients with asymptomatic celiac disease

One retrospective cohort study evaluated the risk of lymphoma in subjects with asymptomatic celiac disease. (26)

A total of 6,849 subjects originally recruited from the general population to participate in a population-based survey conducted between 1978 and 1980 were included in the retrospective cohort by Lohi et al. (26) Celiac disease was diagnosed in 2001 using serologic tests, IgA tTg or IgA EMA using serum stored at the time of recruitment (1978-1980). (26) The outcome, non-Hodgkin's lymphoma (NHL), was identified through a national cancer database during a follow-up of 19 years. (26) The relative risk (RR) of NHL among individuals who tested positive for celiac disease compared to individuals who tested negative was calculated through a Cox regression model adjusted for age and sex. (26) A total of 202 asymptomatic subjects had a positive IgA tTG serologic test and 73 patients had a positive IgA EMA serologic test. (26) The mean age was 59.1 years (SD 14.2) among IgA tTG-positive individuals, 50.6 (SD 13.9) among IgA tTG-negative individuals, 49.3 years (SD 11.9) among IgA EMA-positive individuals, and 50.8 years (SD 14.0) among IgA EMA-negative individuals. (26)

A total of 3 NHL cases were reported among the 202 IgA tTG-identified patients vs. 28 among 6,647 IgA tTG negative individuals, RR 2.76 (95% CI: 0.83, 9.16). (26) A total of 2 NHL cases were reported among 73 IgA EMA-positive individuals, vs. 29 among 6,776 IgA EMA-negative individuals, RR 5.94 (1.41, 25.04). (26) Therefore, during up to 19 years of follow-up, there was no statistically significantly increase in the risk of lymphoma in IgA-tTG-identified individuals, however the risk was statistically significant among IgA-EMA-identified individuals. (26) The total follow-up time was 103,815 patient-years, there were therefore 2.9 lymphoma cases per 100,000 person-years if diagnosed through IgA tTG and 1.9/100,000 if diagnosed through IgA EMA. (26) 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 celiac disease patients assessed by serology. The authors did not comment on the fact that the risk of NHL was higher in subjects with positive IgA EMA serology but not with positive IgA tTG serology compared to subjects with negative celiac disease serology. However, this could be due to imprecision given the very small number of events, i.e., 3 NHL cases among IgA EMA positive subjects, and 2 NHL cases among IgA tTG positive subjects. No information on GFD was provided.

Additional information in table 8.

Table 8: Risk of Lymphoma in Patients with Asymptomatic Celiac Disease

Study N Follow-up	Study Design Statistical Analysis	Patient Population Symptoms	Celiac disease diagnosis Lymphoma diagnosis criteria	RR (95% CI) Lymphoma (celiac disease vs. control)	Site of lymphoma GFD	Participation Rate Withdrawals
Lohi et al. (26) (2009) N= 6,849 202 CD (IgA tTG) 73 CD (IgA EMA) 6,647 controls Period: 1978-1996	• **Study Design** Retrospective cohort F-up: up to 19 yrs • **Recruitment** Sample of general population with positive serologic celiac disease test identified through population-based health survey used. No previous CD or malignancy diagnosis. Controls: subjects from the same cohort with negative serology or positive only to 1st IgA tTG • **Analysis** Cox regression. RR age and sex adjusted	• **Asymptomatic Celiac disease** Mean age ± SD: 59.1 ± 14.2 yrs (tTG) 49.3 ± 11.9 yrs (EMA) Female: 61.4% (tTG) 71.6% (EMA) • **Controls** Mean age ± SD: 50.6 yrs Female: 53.5%	• **CD diagnosis** Serology (positive in 2 tests, either 2 IgA tTG or 1 IgA tTG and IgA EMA) . • **Lymphoma diagnosis** Malignancies extracted from the national cancer registry	• **Risk of NHL** <u>Among IgA tTG positive</u> RR: 2.92 (0.87, 9.74) Events: 3 <u>Among IgA EMA positive</u> RR: 6.43 (1.52, 27.22) Events: 2	• **Lymphoma location:** Groin, low extremities, tonsils, skin, esophagus • **GFD during f-up** Not reported	• 90% agreed to participate • 87% with blood sample • CD or cancer diagnosis beteween 1978-1980 excluded (n=144, 2.1%)

CD celiac disease; CI confidence interval; EMA endomysial antibody; f-up follow-up; GFD gluten-free diet; IgA immunoglobulin A; NHL non-Hodgkin's lymphoma OR odds ratio; SD standard deviation; tTG tissue transglutaminase

Risk of asymptomatic celiac disease in patients with lymphoma

Four case-control studies, (25;27-29) one of which retrospective, (28) evaluated the risk of asymptomatic celiac disease in patients newly diagnosed with lymphoma.

Celiac disease was diagnosed through serologic tests and confirmed by small bowel biopsy in three studies (25;27;29) and small bowel biopsy in one study. (28)

Cases consisted of patients with newly diagnosed lymphoma who were diagnosed with asymptomatic celiac disease at the start of the study. (25;27-29) The control group consisted of a sample of the general population that had a negative serologic test for celiac disease. (25;27-29) In all studies identified, celiac disease was diagnosed at the same time as the lymphoma, therefore the effects of GFD in the development of lymphoma were not evaluated. The studies included only adult patients. (25;27-29)

The studies are described below, additional details in table 9.

In a multicentre case-control study by Mearin et al., adult patients newly diagnosed with NHL at referral centres in Europe between 1998 and 2001 were included. (25) Controls were subjects representing the general population identified either through celiac disease mass screening programs, blood donors, or subjects attending outpatient services, depending on the country and study site. (25) A total of 1,471 cases and 9,676 controls were included. (25) Celiac disease was diagnosed using IgA EMA, and a positive serology was confirmed by small bowel biopsy. (25) The odds ratio of asymptomatic celiac disease in patients with newly diagnosed NHL vs. controls was calculated using unmatched logistic regression adjusted for age and sex. (25) The mean age of cases and controls was 59 and 60 years, respectively. (25) A total of 4 asymptomatic celiac disease cases were identified through screening of NHL cases and 38 in controls, odds ratio (OR) of asymptomatic celiac disease in patients with newly diagnosed NHL was 1.3 (95% CI: 0.6, 2.7). (25) The authors stated that the risk of NHL was not increased in subjects with asymptomatic celiac disease, and that asymptomatic celiac disease is rare in patients with NHL. (25)

In a case-control study by Farre et al., consecutive newly diagnosed patients with lymphoid malignancy were included between 1998 and 2000. (29) Controls were hospitalized subjects matched to cases by age, gender and study site. (29) A total of 298 cases and 251 controls were included. (29) The mean age was 58 years in cases and 55 years in controls. (29) The diagnosis of celiac diseased was performed by serology (IgA tTG, IgA EMA). (29) Subjects with either clinical symptoms or a positive IgA EMA underwent small bowel biopsy to confirm the diagnosis. (29) The OR of celiac disease in patients with lymphoma vs. controls was calculated using logistic regression. (29) Asymptomatic celiac disease was diagnosed in one patient with lymphoma and one control. (29) The results were not stratified according to celiac disease presentation, i.e., asymptomatic or symptomatic, but the authors concluded that there was no increased risk of lymphoma in either asymptomatic or symptomatic lymphoma, OR 0.62 (95% CI: 0.10, 3.79). (29)

Catassi et al. performed a case-control study including consecutive NHL cases newly diagnosed between 1996 and 1990 at the study sites. (27) Controls were selected from two population-based studies on mass celiac disease screening. (27) Celiac disease was diagnosed by serology (IgA EMA) and confirmed by small bowel biopsy. (27) The odds ratio of celiac disease in cases vs. controls was calculated by Mantel Haenszel analysis adjusted by age and gender. (27) There were 653 cases and 5,720 controls. (27) The median age was 57 years in cases (not reported in controls). (27) Celiac disease was diagnosed in 6 cases, 2 of which were diagnosed through screening at the same time as the NHL, which were therefore classified by the authors as asymptomatic. (27) Celiac disease was diagnosed in 24 controls. (27) The authors did not provide separate results by celiac disease presentation, i.e., asymptomatic or not, however they state in a different publication that the rate of NHL in asymptomatic celiac disease, 2/653, was lower

than expected in the overall general population, 1/100-200. (53)

Johnston et al. through a retrospective review of a pathology records database identified cases of lymphoma of the small intestine diagnosed between 1987 and 1996. (28) The pathology records database was also searched to identify small bowel biopsy reports with the diagnosis of celiac disease in the cases of small intestine lymphoma. (28) No information was provided about how the decision to perform a small bowel biopsy was made, i.e., whether all patients with lymphoma were investigated for celiac disease, if it was randomly performed among cases, or if only selected cases were tested for celiac disease. Controls of the general population were used, however no details were provided about how the controls were identified and tested for celiac disease. The OR of asymptomatic celiac disease in cases with small bowel lymphoma vs. controls was calculated, however no details were provided on the methods used for the analysis. (28) There were 138 cases and 1,823 controls. (28) Twelve patients were diagnosed with asymptomatic celiac disease among cases and 15 patients among controls, OR 15.7 (95% CI 9.7, 25.5). (28) The authors concluded that although celiac disease was significantly associated with lymphoma the risk to the patient is low, i.e., approximately 1/1,000 patients over a 10-year period and that the data is not sufficient to confirm the increased risk of small bowel lymphoma in patients with celiac disease. (28) The study does not provide details about the diagnosis of celiac disease in cases, i.e., being a retrospective study it is not clear testing for celiac disease was performed routinely or selectively in small bowel lymphoma cases. This could lead to detection bias if cases of small bowel lymphoma are more thoroughly screened for celiac disease than controls. Similarly, no information is provided about the diagnosis of celiac disease in the control group. Moreover, the baseline characteristics in cases and controls were not provided and the results do not seem to be adjusted for potential confounders, which makes it difficult to interpret their findings.

In conclusion one retrospective cohort study did not show an increase in the risk of lymphoma among subjects with asymptomatic celiac disease. (26) Three prospective case-control studies did not find a significant risk of asymptomatic celiac disease in cases with newly diagnosed lymphoma. (25;27;29)

Table 9: Risk of Asymptomatic Celiac Disease in Patients with Newly Diagnosed Lymphoma

Study N Follow-up	Study Design Statistical Analysis	Patient Population Symptoms	Celiac disease diagnosis Lymphoma diagnosis criteria	OR (95% CI) Risk of celiac disease in lymphoma	Site of lymphoma GFD	Participation Rate Withdrawals
Mearin et al. (25) (2006) N= 1,444 (NHL) N=9,676 (controls)	• **Study Design** Case-Control Multinational Mean f-up: N/A, exposure and outcome measured at the same time • **Recruitment** Cases Newly diagnosed NHL cases from referral centres in 10 European countries. Controls Individuals screened for CD from the general population, blood donors, or hospital controls • **Analysis** Logistic regression adjusted for age and sex (unmatched) Power: 0.92	• **Cases** Mean age: 59 yrs (overall, not only screening-identified) Female: 49% • **Controls** Mean age: 60 yrs	• **CD diagnosis** Serology (IgA EMA) confirmed by biopsy • **Lymphoma diagnosis** Lymphoma was classified according to Revised European-American Lymphoma Classification	• **Celiac disease among NHL** OR: 1.3 (0.6, 2.7) N of asymptomatic CD: 4 (cases), 38 (controls)	• Lymphoma location 2 small bowel, 1 bone marrow, and 1 lymph nodes • **GFD** None in asymptomatic celiac disease	• 87.6% NHL cases agreed to participate • 25 (1.7%) NHL patients did not have a serum sample for screening • 100% participation rate among controls
Catassi et al. (27)(2002) N=653 (NHL) N=5,720 (controls)	• **Study Design** Case-Control F-up: N/A (outcome and exposure measured at the same time) • **Recruitment** Consecutive newly dx NHL of any primary site cases at study sites Controls: Identified from 2 studies on population screening for CD • **Analysis** OR of CD in newly dx NHL calculated by Mantel Haenszel analysis, age and sex-adjusted	• **Cases** Median age: 57 (20-92) Female: 43% • **Controls** NR	• **CD diagnosis** Serology (IgA EMA) confirmed by biopsy • **Lymphoma diagnosis** Lymphoma classified according to site and histology	• **Celiac disease among NHL** 2 asymptomatic CD (diagnosed at the same time as NHL) Authors state in a separate publication that the rate of NHL in screening-identified CD (2/653) was lower than expected in the general population (1/100-200) (53) Results in Symptomatic and Asymptomatic CD: OR: 3.1 (1.3, 7.6) AR: 0.6 (-0.12, 1.37) Events: 6 (0.9%) in CD 24 (0.4%) – controls	• Lymphoma location 1 small bowel and 1 B cell lymphoma of the ileum • **GFD** None in asymptomatic celiac disease	• 47% agreed to participate 53% not included due to lack of consent, missing serum sample, or not meeting inclusion criteria

Study N Follow-up	Study Design Statistical Analysis	Patient Population Symptoms	Celiac disease diagnosis Lymphoma diagnosis criteria	OR (95% CI) Risk of celiac disease in lymphoma	Site of lymphoma GFD	Participation Rate Withdrawals
Johnston et al. (28) (2000) N=69 (lymphoma) N=1,823 (controls)	• **Study Design** Retrospective case-control F-up: N/A (outcome and exposure measured at the same time) • **Recruitment** Cases: Lymphoma and adenocarcinoma cases retrospectively identified through laboratory database Controls: sample of general population (no details on recruitment provided) • **Analysis** OR of celiac disease in cases vs. controls Confounder adjustment not reported	• **Cases** Mean age: 60.2 yrs Female: 21.7% • **Controls** General population (no additional details provided)	• **CD diagnosis** Small bowel biopsy (according to database records) • **Lymphoma diagnosis** Cases of lymphoma of the small bowel identified through lab database	• **CD in small bowel lymphoma** OR: 15.7 (9.7, 25.5) 12 celiac disease diagnosed during 10 years f-up	• Lymphoma location 12 small bowel lymphoma • **GFD** None in silent cases (celiac disease and NHL diagnosed at the same time)	• Not reported
Farre et al. (29) (2004) N=298 cases / 251 controls	• **Study Design** Case-control F-up: N/A (outcome and exposure measured at the same time) • **Recruitment** Cases: consecutively newly diagnosed lymphoid malignancy Controls: hospitalized patients matched for age and sex. • **Analysis** Logistic regression matched by age and sex.	• **Cases** Mean age: 58 yrs Female: 41.9% • **Controls** Mean age: 55 yrs Female: 49.4%	• **CD diagnosis** Serology (IgA tTG and EMA) confirmed by small bowel biopsy • **Lymphoma diagnosis** Lymphoid malignancy diagnosed according to the WHO Classification for Neoplastic Diseases of the Lymphoid Tissues	• **CD in lymphoma** Authors reported that there was no increased risk of lymphoma in asymptomatic or symptomatic cases OR 0.62 (0.10 , 3.79) Number of celiac disease patients Cases: 2 (0.7%), 1 asymptomatic Controls: 3 (1.2%), 1 asymptomatic	Plasma cell myeloma	• 298/345 (86.3%) included

CD celiac disease; CI confidence interval; EMA endomysial antibody; f-up follow-up; GFD gluten-free diet; IgA immunoglobulin A; N/A not applicable; NHL non-Hodgkin's lymphoma OR odds ratio; tTG tissue transglutaminase; WHO World Health Organization

The Risk of All-Cause Mortality in Patients with Asymptomatic Celiac Disease

A total of 5 studies that evaluated the risk of all-cause mortality in asymptomatic patients with celiac disease were identified. (20-24) There were 5 cohort studies, (20-24) 2 prospective (20;24) and 3 retrospective. (21-23)

In most studies, the risk of all-cause mortality in subjects diagnosed with asymptomatic celiac disease recruited from the general population was compared to that of control subjects with a negative serologic celiac disease test recruited from the general population. The percentage of subjects who declined participation ranged between 10% to 29.4% in two studies, (21;24) there was no information from the other studies. Withdrawal rates were reported in two studies, 4.7% (20) and 0.2%. (23)

The studies are described below. Additional details in table 10.

One prospective cohort study evaluated the risk of all-cause mortality in subjects with asymptomatic celiac disease diagnosed between 1962 and 1994. (20) Celiac disease was diagnosed through small bowel biopsy. (20) The patients were followed for a mean of 6 years, during which all-cause mortality was ascertained through the patients' medical records or through municipal death registries. (20) The standardized mortality ratio (SMR) of the observed rate of mortality in subjects with asymptomatic celiac disease was compared to the expected rate in the general population adjusted for age and sex using Poisson regression. (20) A total of 67 asymptomatic subjects were included in the study, which is the focus of our analysis. (20) Subjects older than 18 years were included. (20) Approximately 76% of the sample size was comprised of women. (20) No increased risk in all-cause mortality was observed, i.e., one death occurred among the asymptomatic celiac disease subjects (expected: 0.8), yielding a SMR of 1.2 (95% CI: 0.2, 7.0, p 0.99). (20) The study also evaluated the risk of all-cause mortality in relatives of subjects with celiac disease, 862 parents and 862 siblings. (20) Among the relatives, 123 were diagnosed with asymptomatic celiac disease. (20) No increase in all-cause mortality was observed in the relatives' group, SMR 0.8 (95% CI: 0.3, 1.7) in fathers, SMR 1.1 (95% CI: 0.3, 2.7) in mothers, SMR 1.1 (95% CI 0.2, 3.3) in brothers, and SMR 0.9 (95% CI: 0.3, 2.1) in sisters of celiac disease patients. (20)

A prospective cohort study by Johnston et al., included subjects who had been recruited for a population-based cardiovascular study between 1983 and 1995. (24) Celiac disease was diagnosed through serologic tests. (24) The relative risk (RR) of mortality in asymptomatic celiac disease compared to the expected risk in the general population adjusted for age and calendar year was calculated using Poisson regression. (24) A total of 102 subjects were included in the study, 13 of whom had a positive serologic test for celiac disease. (24) The mean age was 60.1 years and 50 (49.0%) were female. (24) After a mean follow-up of 11.6 years, there was no significant increase in the risk of mortality in asymptomatic celiac disease subjects compared to what is expected in the general population, RR 0.92 (95% CI: 0.5, 1.6). (24)

A retrospective cohort study by Lohi et al. included subjects who had been recruited for a population-based health survey between 1978 and 1980. (21) Celiac disease was diagnosed in asymptomatic subjects if two serologic tests were positive, either 2 IgA tTG tests or both IgA tTG and IgA EMA. (21) Controls were subjects recruited for the same health survey that either had a negative celiac disease serologic test or were only positive to the 1st IgA tTG test. (21) The RR of all-cause mortality in subjects with celiac disease was compared to subjects with a negative serology adjusted for multiple factors using Cox regression. (21) All-cause mortality during a follow-up of up to 28 years was ascertained through a vital records database. Among 6,849 subjects recruited, 204 subjects had two positive IgA tTG tests and 74 had one positive IgA tTG and one positive IgA EMA test, the other subjects were used as controls. (21) These subjects did not present with symptoms consistent with celiac disease. (21) The mean age was 59.1 years (SD 14.2) among subjects who tested positive for IgA tTG and 49.2 years (SD 11.8) for IgA EMA-positive subjects. (21) Females comprised 61.5% of the subjects with a positive IgA tTG test and 72% of subjects with a positive IgA EMA test. (21) There was no significant increase in the risk of mortality

among subjects with celiac disease compared to controls. (21) There were 128 and 2,941 deaths among IgA tTG-positive subjects and their controls, respectively, RR 1.18 (95% CI 0.99, 1.42). (21) There were 23 and 3,046 deaths among IgA EMA-positive subjects and their controls, respectively, RR 0.91 (95% CI: 0.59, 1.38). (21)

A retrospective cohort study by Rubio-Tapia et al. included young men (mean age: 20.5 years, SD 2.5) from a military base recruited for an infectious disease cohort study between 1948 and 1954. (22)Celiac disease was diagnosed through serology, both IgA tTG and IgA EMA-positive. (22) Controls were subjects from the same cohort with a negative serologic test, matched by age, gender, and enlistment status. (22) All-cause mortality during follow-up was ascertained through a vital records database. (22) The hazard ratio (HR) of all-cause mortality in celiac disease compared to patients with a negative serologic test was calculated using Cox proportional hazards analysis. (22) A total of 9,133 subjects were included in the cohort, 14 of which diagnosed with celiac disease. (22) The mean age at recruitment was 20 years. (22) Within a follow-up of 45 years, there were 9 (64.3%) deaths among celiac disease patients, 6 of which of known causes (emphysema, lymphoma, esophageal cancer, cardiovascular disease, 1 not specified), and 2,216 (24.3%) deaths among controls, HR 3.9 (95% CI: 2.0, 7.5). (22) Additionally, information on comorbidities that may be associated with an increased risk of death were not collected or adjusted for in the analysis, which may affect the validity of the study results. The authors believe that the results should be interpreted with caution given the small number of patients diagnosed with celiac disease and the limited adjustment for potential confounders.

A retrospective cohort study by Metzger et al. included subjects recruited for a population-based health survey. (23) Celiac disease was diagnosed through serology, IgA tTG, in asymptomatic subjects. (23) Subjects from the same cohort with a negative serologic test for celiac disease were included as controls. (23) All-cause mortality was ascertained through a vital records database. (23) The HR of all-cause mortality in subjects with asymptomatic celiac disease compared to patients with a negative serologic test was calculated using Cox proportional hazards analysis adjusted for age. (23) A total of 4,663 subjects were included in the cohort, 63 of which were diagnosed with celiac disease. The mean age was 49 years and 49.6% of the subjects were female. (23) There were 15 deaths among subjects with asymptomatic celiac disease and 308 deaths among seronegative subjects during the 8 years of follow-up, HR 2.53 (95% CI: 1.50, 4.25). (23) The authors state that the increased mortality risk should be interpreted with caution as it could be due to false positive serologic test results since confirmation by small bowel biopsy was not performed and more than half of the deaths (8/15) were due to liver disease or heart failure, and there is a possibility of a false positive result in patients with these conditions.

In conclusion, two prospective studies did not show an increased risk of all-cause mortality in subjects with asymptomatic celiac disease.

Table 10: Risk of All-Cause Mortality in Patients with Asymptomatic Celiac Disease

Study N Follow-up	Study Design Statistical Analysis	Patient Population Symptoms	CD diagnosis criteria Outcome and covariates ascertainment	All-Cause Mortality OR, RR, HR, SMR (95% CI) GFD effects	Participation Rate Withdrawals
Corrao et al.(20) (2001) N= 67 asymptomatic CD N= 123 asymptomatic CD (parents and siblings' cohorts) Period: 1962-1998	• **Study Design** Cohort, Multicentre Mean f-up: 6.0 yrs • **Recruitment** CD cases: Consecutive CD diagnosed between 1962-1994 from GI clinics. Relatives' cohorts: subjects diagnosed at gastroenterology clinics. Controls: general population mortality rate used as comparison, age, sex-adjusted • **Analysis** Poisson regression SMR (observed/ expected), age and sex adjusted	• **Celiac disease** > 18 yrs Female: 76% • **Controls** Not applicable	• **CD diagnosis** Small bowel biopsy • **Mortality ascertainment** Mortality and covariates ascertained through patient interviews and review of medical records or city registries. Cause defined according to ICD-9	• **All-cause mortality (asymptomatics)** SMR 1.2 (0.1, 7.0) Events: 1 (expected: 0.8), p .99 **Relatives of CD patients** Fathers SMR: 0.8 (0.3, 1.7) Events 7 (expected 8.4) Similar for mothers, brothers and sisters of CD patients • **GFD effects** Adherence and effects in asymptomatics not reported.	• **Participation Rate** CD cohort: not reported Relatives cohort: 8/873 (0.9%) • **Withdrawals** CD cohort: 50 (4.7%) Relatives' cohorts: not reported
Johnston et al. (24) (1998) N= 13 asymptomatic CD (1983 cohort) Period: 1983-1995	• **Study Design** Cohort Mean f-up: 11.6 yrs • **Recruitment** Patients randomly identified from the general population for a cardiovascular study were used for this study. CD cases: positive serology Controls: expected mortality rate in the general population, adjusted for age and sex • **Analysis** Observed events compared to expected according to age, calendar yr. Poisson distribution	• **Celiac disease** Mean age: 60.1 yrs Female: 52.8% • **Controls** Not applicable	• **CD diagnosis** Serology (IgA AGA, ARA, EMA). Small bowel biopsy performed in 20/102 • **Mortality ascertainment** Outcome information obtained from patient interviews and mortality registry	• **All-cause Mortality in subjects with at least 1 positive serologic test** RR 0.92 (0.5, 1.6) Events: 13 (expected 14.1) • **GFD effects** Not evaluated	• 30/102 (29.4%) did not participate • 52/72 (72.2%) did not do a small bowel biopsy
Lohi et al. (21) (2009) N= 6,849 204 asymptomatic	• **Study Design** Retrospective cohort F-up: up to 28 yrs • **Recruitment** Patients randomly identified from the general population for a	• **Celiac disease** Mean age ± SD: 49.2 ± 11.8 yrs (EMA) 59.1 ± 14.2 yrs (tTG) Female: 72% (EMA)	• **CD diagnosis** Positive serology in 2 tests. • **Mortality ascertainment**	• **All-cause mortality by serologic test** IgA tTG positive RR: 1.18 (0.99, 1.42) Events: 128/204 (CD) 2,941/6,783 (controls)	• 10% did not participate in survey • 87% with blood sample

CD (IgA tTG) 74 asymptomatic CD (IgA EMA) Period: 1978-2005	population-based heart survey were used for this study. CD cases: positive serologic test. Controls: Negative serology or positive only to 1st IgA tTG • **Analysis** Cox regression, RR adjusted for multiple factors	61.5% (tTG) • **Controls** Mean age ± SD: 51.1 ± 14.1 yrs Female: 53.7%	Information obtained from medical records and national mortality registry	IgA EMA positive RR: 0.91 (0.59, 1.38) Events: 23 /74 (CD) 3,46/6,913 (controls) • **GFD effects** Not evaluated	
Rubio-Tapia et al. (22)(2009) Period: 1948-1997 N=9,133	• **Study Design** Retrospective cohort F-up: 45 yrs • **Recruitment** Healthy young men from military base who were part of a cohort study for infectious diseases were used for this study CD cases: positive serologic test Controls: Seronegative for CD Matched for age, gender, enlistment status • **Analysis** Cox proportional hazards adjusted for age, gender, enlistment status	• **Celiac disease** Median age: 20 (14.3-46.4) yrs Female: 0 • **Controls** Not reported	• **CD diagnosis** Serology, both IgA tTG and IgA EMA positive • **Mortality ascertainment** Vital records database	• **All-cause mortality** HR: 3.9 (2.0, 7.5) Events: 9, 6 of known causes: Emphysema (1), lymphoma (1), larynx cancer (1), esophageal cancer (1), CV (1), not specified (1). • **GFD effects** Unknown (authors)	• Not reported
Metzger et al. (23) (2006) N=4,570 CD= 63 (1.4%) Period: 1989-1998	• **Cases** Retrospective cohort Mean f-up: 8.0 (0-8.9) yrs • **Recruitment** Patients randomly identified from the general population for population-based heart survey were used CD cases: positive serologic test for CD Controls: negative serologic test for CD • **Analysis** Cox proportional hazards adjusted for age	• **Celiac disease** <u>Mean age:</u> Men: 57.2 (53.1-61.4) yrs Women: 52.8 (46.5-59.0) yrs <u>Female:</u> 49.6% • **Controls** <u>Mean age:</u> Men: 49.7 (49.2-50.3) yrs Women: 49.2 (48.7-49.8) yrs <u>Female:</u> 49.9%	• **CD diagnosis** Serology IgA tTG • **Mortality ascertainment** Obtained from vital records database. Covariates obtained from medical records	• **All-cause mortality** HR: 2.53 (1.50, 4.25) Events: 15	• N=13 (0.2%) – moved away.

AGA antigliadin antibody; ARA anti-reticulin antibody; CD celiac disease; CI confidence interval; EMA endomysial antibody; f-up follow-up; GFD gluten-free diet; HR hazard ratio; IgA immunoglobulin A; N/A not applicable NHL non-Hodgkin's lymphoma OR odds ratio; RR relative risk; SD standard deviation; SMR standardized mortality ratio; tTG tissue transglutaminase; yr year

Grading of Evidence

The quality of the evidence for each serologic tests evaluated based on the GRADE Working Group criteria. (12)

Overall, the quality of the evidence ranged from low to very low depending on the outcome evaluated. Additional details in tables 11 to 13.

Table 11: GRADE Quality of Evidence: Effects of GFD on Symptoms and Conditions in Subjects with Asymptomatic Celiac Disease

Symptom/Condition	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings	Overall Quality
Type 1 Diabetes Mellitus HbA1c **Pediatric**	1 prospective case-control study	▪ **Subject selection** No serious limitation* ▪ **CD diagnosis** No limitation ▪ **Measure of outcomes** No limitation. ▪ **Intervention (GFD)** No limitation ▪ **Losses to f-up** No serious limitation ▪ **Blinding of outcome measurement** No blinding, however, this may not pose a threat to validity since the outcome was objectively measured	Not applicable (1 study)	▪ **Patient population** No limitations, however it can only be generalized to the pediatric population ▪ **Outcome** No limitations	▪ **Sparse data** No limitation ▪ **Precision** No limitation ▪ **Publication bias** Could not be evaluated	Significantly lower HbA1c in celiac disease patients with type 1 diabetes vs. control before the diagnosis of celiac disease. After the diagnosis, HbA1c levels in subjects with celiac disease and type 1 diabetes rose to a level similar to that of controls.	
	Low →						**Low**
Type 1 Diabetes Mellitus (DM1) Hypoglycemia events **Pediatric**	1 retrospective case-control	▪ **Subject selection** Possible selection bias* ▪ **CD diagnosis** No limitation ▪ **Measure of outcomes (-1)** Retrospectively identified. There were uncertainties on how the events were ascertained and event severity. ▪ **Intervention (GFD)** GFD compliance not provided ▪ **Losses to f-up** No limitation ▪ **Blinding of outcome measurement** No blinding (not applicable, retrospective study)	Not applicable (1 study)	▪ **Patient population** No limitations, however it can only be generalized to the pediatric population ▪ **Outcome** No limitations	▪ **Sparse data** Not considered a serious limitation ▪ **Precision** Not considered a serious limitation ▪ **Publication bias** Could not be evaluated	No statistically significant difference between cases and controls from 18 months to 6 months before the celiac disease diagnosis and GFD introduction and > 6 months after the GFD introduction. Cases had a statistically significantly higher number of hypoglycemic episodes vs. controls in the period ranging from 6 months prior to 6 months after the celiac disease diagnosis. The severity of episodes among cases and controls was not reported. GFD compliance was not reported.	
	Low	**Very Low** →					**Very Low**

Symptom/Condition	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings	Overall Quality
Type 1 Diabetes Mellitus (DM1) Insulin dosage **Pediatric**	1 prospective case-control study	▪ **Subject selection** No serious limitation* ▪ **CD diagnosis** No limitation ▪ **Measure of outcomes** No limitation. ▪ **Intervention (GFD)** No limitation ▪ **Losses to f-up** No serious limitation ▪ **Blinding of outcome measurement** No blinding, however, this may not pose a threat to validity since the outcome was objectively measured	N/A	▪ **Patient population** No limitations, however it can only be generalized to pediatric population ▪ **Outcome** No limitations	▪ **Sparse data** No limitation ▪ **Precision** No limitation ▪ **Publication bias** Could not be evaluated	No significant difference in insulin dosage between cases and controls either before or after the celiac disease diagnosis. No significant difference in insulin dosage before and after the celiac disease diagnosis among cases.	
	Low →						**Low**
Short Stature Growth parameters (growth velocity standard deviation score, height standard deviation score) **Pediatric**	3 Observational studies (Case Series, before-after comparisons)	▪ **Subject selection** Possible selection bias* ▪ **CD diagnosis** No limitation ▪ **Losses to f-up** No limitation ▪ **Measure of outcomes** No limitation ▪ **Intervention (GFD)** GFD compliance not reported. ▪ **Blinding of outcome measurement** No blinding, however, this may not pose a threat to validity since outcomes were objectively measured	No limitation	▪ **Patient population** No limitation ▪ **Outcome** No limitations	▪ **Precision** Not considered a serious limitation ▪ **Sparse data** Not considered a serious limitation ▪ **Publication bias** Could not be evaluated	All studies reported an improvement in growth parameters once a GFD was introduced.	
	Low →						**Low**

CD refers to celiac disease; GFD gluten-free diet; HbA1c hemoglobin A1c
* Participation rate not reported.

Table12: GRADE Quality of Evidence: Risk of Lymphoma in Subjects with Asymptomatic Celiac Disease

Symptom/Condition	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings	Overall Quality
Risk of lymphoma among CD subjects without symptoms consistent with the disease	1 cohort study	▪ **Subject selection** No limitation ▪ **CD diagnosis** No limitation ▪ **Losses to f-up** No limitation ▪ **Measure of outcomes** No limitation. ▪ **Blinding of outcome measurement** No blinding, however, this was not considered a serious limitation.	Not applicable (1 study)	▪ **Patient population** No limitations. ▪ **Outcome** No limitations	▪ **Precision** Wide confidence intervals. ▪ **Sparse data (-1)** Number of events in each analysis was 2 and 3 respectively. ▪ **Publication bias** Not a limitation	A non-significant increased risk of NHL was observed if subjects were diagnosed using IgA tTG (RR 2.92, 95% CI: 0.87, 9.74, events: 3), but the risk was significant if IgA EMA was used to diagnose CD (RR 6.43, 95% CI: 1.52, 27.22, # events: 2) Lack of significant differences or discrepancy between the two analyses could be due to small number of events. Statistical power to detect a difference not provided.	
	Low →			Low	Very Low		**Very Low**
Risk of celiac disease without symptoms consistent with the disease in patients with lymphoma	3 case-control studies	▪ **Subject selection** No limitation ▪ **CD diagnosis** No limitation ▪ **Losses to f-up** No limitation. ▪ **Measure of outcomes** No limitation ▪ **Blinding of outcome measurement** No blinding, however, this may not pose a threat to validity since outcomes were objectively measured	No limitation	▪ **Patient population** No limitations. ▪ **Outcome** No limitations	▪ **Precision** Wide confidence intervals. Not considered a serious limitation ▪ **Sparse data** No limitation ▪ **Publication bias** Not a limitation	There was no evidence of a significant increase in the risk of celiac disease without symptoms consistent with the disease in patients with lymphoma.	
	Low →						**Low**

CD refers to celiac disease; EMA endomysial antibody; NHL non-Hodgkin lymphoma; RR relative risk; tTG tissue transglutaminase

Table 13: GRADE Quality of Evidence: Risk of Mortality in Subjects with Asymptomatic Celiac Disease

Symptom/Condition	Design	Quality	Consistency	Directness	Other Modifying Factors	Summary of Findings	Overall Quality
Risk of Mortality in subjects with celiac disease without symptoms consistent with the disease	2 cohort studies	▪ **Subject selection** No serious limitation ▪ **CD diagnosis** No limitation ▪ **Losses to f-up** No limitation ▪ **Measure of outcomes** No limitation. ▪ **Blinding of outcome measurement** No blinding, however, this may not considered a serious limitation.	No limitation	▪ **Patient population** No limitation. ▪ **Outcome** No limitation	▪ **Precision** Non-statistically significant results in some studies. Statistical power to detect a difference between groups not reported. ▪ **Sparse data** Not a limitation ▪ **Publication bias** Not a limitation	There was no evidence of an increase in all-cause mortality in subjects with celiac disease without symptoms consistent with the disease	
	Low →						**Low**

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

The clinical utility of serologic testing for celiac disease in asymptomatic patients was assessed based on the effects of the GFD on disease-specific outcomes.

Eligible studies that evaluated the effects of a GFD on disease-specific outcomes were only identified for two conditions, 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 testing was demonstrated.

The budget impact in patients with idiopathic short stature without symptoms consistent with celiac disease was calculated by multiplying the number of individuals in Ontario that may be eligible for the test by the cost of the serologic test for celiac disease [$60 for IgA tTG (1)]. The number of individuals eligible for the test was calculated by multiplying the estimated prevalence of idiopathic short stature in the affected age groups by the population in Ontario in those age groups based on the 2006 census data. (54)

The prevalence of short stature was estimated as 1%. According to a publication by Cohen et al., (55) in 60% of the cases, the cause of short stature cannot be identified and it can be considered as idiopathic. Therefore, the prevalence of idiopathic short stature was estimated as 0.6%. It was assumed that children 5 to 14 years old would be most likely to be diagnosed with the disease. Based on the Ontario population of the same age group, it was estimated that approximately 9,200 children with idiopathic short stature in Ontario would be potentially eligible for serologic testing for celiac disease. Assuming a cost per IgA tTG test of $60, (1) the budget impact of testing 9,200 children in Ontario would be C$552,000.

Discussion

With the exception of subjects with type 1 diabetes, a review of the literature did not observe a statistically significant increase in the prevalence of asymptomatic celiac disease in subjects presenting with one of the non-gastrointestinal conditions evaluated.

Eligible studies that evaluated the effects of a GFD on disease-specific outcomes were only identified for two conditions: type 1 diabetes and idiopathic short stature. The effects of a GFD were not demonstrated in patients with concomitant type 1 diabetes and asymptomatic celiac disease. Studies in pediatric patients with concomitant idiopathic short stature and asymptomatic celiac disease showed an acceleration of

growth with the introduction of the GFD. The quality of the evidence for these two analyses was considered low. No published evidence of the effects of a GFD in the other non-gastrointestinal conditions evaluated was identified. Therefore, the clinical utility of serologic testing for celiac disease in asymptomatic patients was only demonstrated in pediatric patients with idiopathic short stature.

The studies identified did not show an increased risk of lymphoma in subjects with asymptomatic celiac disease and vice-versa. Similarly, no increased risk of all-cause mortality was observed in asymptomatic subjects with celiac disease.

Conclusion

- 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.

Appendices

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

OHTAC Recommendations (1)

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: Literature Search Strategies

Searches performed between December 2010 and March 2011

Ovid MEDLINE(R) 1948 to March Week 3 2011

Search terms used:

exp Alopecia/

exp Alopecia Areata/

alopecia.mp.

(alopecia or (follicular adj3 mucinosis)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

baldness.mp.

(aphtous adj3 ulcer$).tw.

(canker adj3 sore$).tw.

(oral adj3 ulcer$).tw.

(aphtous adj3 stomatitis).tw.

(mouth adj3 ulcer$).tw.

exp Oral Ulcer/

exp Stomatitis, Aphthous/

exp Mouth Diseases/ep, et, pa [Epidemiology, Etiology, Pathology]

oral lesions.mp.

exp Mouth Mucosa/pa [Pathology]

lymphoma/ti, ab, de or lymphomas/ti, ab, de or lymphoma!.mp. or hodgkin?/ti, ab, de [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

exp Lymphoma, Non-Hodgkin/ or exp Hodgkin Disease/

malignancy.mp.

cancer.mp. or exp Neoplasms/

exp Mortality/

exp Death/

*Celiac Disease/mo [Mortality]

exp Depression/

exp Depressive Disorder/

depression.mp.

exp Mental Disorders/

exp Diabetes Mellitus, Type 1/

exp Hypoglycemia/

exp Blood Glucose/

exp Diabetes Complications/

exp infertility/

(recurrent adj3 miscarriage).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

exp fertility/

exp pregnancy/

exp pregnancy outcome/

"birth weight"/

exp birth weight/

exp Infant, Low Birth Weight/

exp Motor Neuron Disease/

exp Epilepsy/

Peripheral Nervous System Diseases/

Gluten ataxia.mp

exp Muscle Cramp/

exp Paresthesia/

exp Cerebellar Ataxia/

exp Polyneuropathies/

exp Ataxia/

exp Osteoporosis/

exp Bone Diseases, Metabolic/

osteopenia.mp.

exp Bone Density/

exp Fractures, Bone/

exp Bone Diseases/

exp Growth Disorders/

short stature.mp.

(growth adj3 failure).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

(growth adj3 disorder).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

(growth adj3 retardation).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

(delayed adj3 puberty).tw

Puberty, delayed/

Exp Amenorrhea/

Amenorrhea.mp

exp Purpura, Thrombotic Thrombocytopenic/ or exp Purpura, Thrombocytopenic/ or exp Purpura/ or exp Purpura, Thrombocytopenic, Idiopathic/

exp Celiac Disease/

Appendix 3: Prevalence of Celiac Disease in Asymptomatic Patients Presenting with one of the Non-Gastrointestinal Conditions Evaluated

The results of the eligible studies that evaluated the prevalence of celiac disease in asymptomatic patients and one of the non-gastrointestinal conditions evaluated is presented in the tables below.

Table A1: Prevalence of Celiac Disease in Asymptomatic Patients Presenting with Infertility, Recurrent Spontaneous Abortions, and Women with Low Birth Weight Infants

Study, Country N Follow-up	Study Design Statistical Analysis	Patient Population Symptoms	CD diagnosis criteria	Prevalence of celiac disease among patients with adverse pregnancy outcomes	Participation Rate
Kumar et al. (44) (2011) India N=104 (history of recurrent abortion) N= 230 (infertility) N=150 (women with low birth weight infants) N= 350 (controls)	• **Study Design** Cross-sectional • **Inclusion Criteria** Cases: Consecutive women with recurrent abortion, infertility, low birth weight infants unexplained by another cause who attended the hospital clinic. Controls: women with normal obstetric history who attended the outpatient clinic of the same hospital	• **Mean Age ± SD** Recurrent spontaneous abortion: 26.5 ± 3.8 yrs Women with low birth weight infants: 28.3 ± 4.0 yrs Infertility: 29.7 ± 4.6 yrs Control: 27.8 ± 4.5 yrs • **Symptoms** **Anemia** Recurrent spontaneous abortion: 86 (82.7%) Women with low birth weight infants: 123 (82%) Infertility: 78 (33.9%) Control: 144 (47.2%) *Only CD cases without anemia were included in the analysis*	• **Serology** IgA tTG	**Recurrent Spontaneous abortions** • CD Cases (without anemia) 2/18 (11.1%) **Infertility** • CD Cases (without anemia) 9/152 (5.9%) **Women with Low Birth Weight Infants** • CD Cases (without anemia) 5/27 (18.5%) **Controls** • CD Cases (without anemia) 3/161 (1.9%) p value not provided for subgroup of patients without anemia.	**Participation Rate** 8.7% - 19.2% depending on the study group due to lack of consent of presence of inclusion criteria
Kolho et al. (45)(1999) Finland N= 63 (unexplained recurrent miscarriage) N=47 (unexplained infertility) N= 51 (controls)	• **Study Design** Cross-sectional • **Inclusion criteria** Cases: Women with unexplained recurrent (≥3 consecutive) miscarriages and infertility (unexplained in some) with blood sample available. Controls: hospital personnel without reproductive	• **Median age (range)** Unexplained recurrent miscarriage: 34 (20-44) yrs Unexplained infertility: 36 (27-41) yrs Controls: 35 (25-43) yrs • **Symptoms** None reported	• **Serology** IgA EMA	**Recurrent unexplained miscarriage** • CD Cases 1/63 (1.6%) **Unexplained infertility** • CD Cases 1/47 (2.1%) **Controls** • CD Cases	Not reported.

	problems			1 (2.0%) Difference NS for both outcomes	
Collin et al. (46)(1996) Finland N=98 (unexplained infertility) N=50 (≥ 2 spontaneous abortions) N=150 (control)	• **Study Design** Cross-sectional • **Inclusion criteria** Cases Consecutive cases of infertility and ≥ 2 spontaneous abortions Controls Women with a normal obstetric history who underwent a laparoscopic sterilization	• **Median age (range)** Unexplained infertility: 31 (22-42) yrs Miscarriages: 31 (22-46) yrs Control: 38 (26-45) yrs • **Symptoms (among CD cases)** 2/4 (50%) silent	• **Serology** IgA AGA or ARA, confirmed by biopsy	**≥ 2 miscarriages** • CD Cases 0 **Unexplained infertility** • CD Cases (among asymptomatic women) 2 (2.0%) **Controls** 0 p value not provided	Not reported

AGA anti-gliadin antibody; ARA anti-reticulin antibody; CD celiac disease; EMA endomysial antibody; IgA immunoglobulin A; NR not reported; NS not statistically significant; SD standard deviation; tTG tissue transglutaminase; yr year

Table A2: Prevalence of Celiac Disease in Asymptomatic Patients Presenting with Epilepsy

Study Country N	Study Design Recruitment	Patient Population Participation Rate	% positive serology, biopsy IgA tTG IgG EMA	% positive small bowel biopsy
Antigoni et al. (47) (2007) Greece N=255 idiopathic epilepsy N= 280 controls Pediatric	• **Study design** Cross-sectional • **Recruitment** Cases: Patients being followed at the Neurology outpatient clinic. Controls: healthy children seen at the pediatric outpatient clinic for a routine evaluation	• **Patient characteristics** Cases Mean age: 7.9 (2-14) yrs Girls: 118 (46.3%) Controls Mean age: 7.5 (2-14) yrs Girls: 135 (48.2%) • **Participation rate** Not reported	• **IgA tTG** Epilepsy: 2 (0.8%) Controls: 0 • **IgA EMA** Epilepsy: 0 Controls: 0 p value not provided	• **Small bowel biopsy** 2/255 (0.8%) Controls: not done
Dalgic et al. (48) (2005) Turkey N= 170 idiopathic epilepsy N= 103 controls Children	• **Study design** Cross-sectional • **Recruitment** Cases: Children with idiopathic epilepsy Controls: healthy children seen at the pediatric outpatient clinic for a routine evaluation	• **Patient characteristics** Cases Mean age ± SD: 9.8 ± 4.6 yrs Girls: 75 (44.1%) Controls Mean age ± SD: 9.9 ± 3.6 yrs Girls: 105 (51.7%) • **Participation rate** Not reported	• **IgA tTG** Epilepsy: 8 (4.7%) Controls: 0 p .026	• **Small bowel biopsy** 2/170 (1.2%) Controls: not performed
Pratesi et al. (49) (2003) Brazil N= 255 epilepsy (119 children, 136 adults) N=4,405 controls Adults and children	• **Study design** Cross-sectional • **Recruitment** Cases: Adults and children attending an epilepsy clinic clinic Controls: individuals attending the medical laboratory of the same hospital	• **Patient characteristics** Cases Mean age, children: 8.0 (1-14) yrs Mean age, adults: 30.3 (15-65) yrs Controls Not reported • **Participation rate** Not reported	• **IgA EMA** Children: 1/119 (0.8%) Adults: 1/136 (0.7%) Controls: 15/4405 (0.3%) NS	**Not reported**
Ranua et al. (50) (2005) Finland N=968 epilepsy (not only idiopathic) N=1,386 controls Adults	• **Study design** Cross-sectional • **Recruitment** Cases: Adults treated for epilepsy at the study hospital. Controls: age- and gender matched individuals from the general population	• **Patient characteristics** Cases Mean age±SD: 46.4 ± 15.7 yrs Mean duration of epilepsy: 15.2 ± 11.9 yrs Female: 472 (48.8%) Controls: not reported • **Participation rate** 968 (70%)	• **IgA EMA** 15/853 (1.8%) Controls: 13/574 (2.3%) p=.5 • **IgA tTG** 20/853 (2.3%) Controls: 14/574 (2.4%) p 0.9	**Not reported**

EMA endomysial antibody; IgA immunoglobulin A; NR not reported; NS not statistically significant; SD standard deviation; tTG tissue transglutaminase; yr year

Table A3: Prevalence of Celiac Disease in Asymptomatic Patients Presenting with Peripheral Neuropathy

Study Country N	Study Design Recruitment	Patient Population Symptoms	% positive serology IgA tTG, IgG EMA	% positive small bowel biopsy
Lock et al. (51) (2005) UK N=32 peripheral neuropathy Adults	• **Study design** Cross-sectional • **Recruitment** Recruited at the neurology department	• **Patient characteristics** Mean age: 66 (32-86) yrs • **Participation rate** Not reported	• **IgA tTG** 0	Not evaluated

CD celiac disease; EMA endomysial antibody; IgA immunoglobulin A; NS not statistically significant; tTG tissue trasnglutaminase; yr year

Table A4: Prevalence of Celiac Disease in Asymptomatic Patients Presenting with Ataxia

Study Country N	Study Design Recruitment	Patient Population Symptoms	% positive serology IgA tTG IgA EMA	% positive small bowel biopsy
Abele et al. (43) (2003) Germany N=105 (32 sporadic adult-onset ataxia of unknown origins , 73 controls) Adults	• **Study design** Cross-sectional • **Recruitment** Cases: recruited at the neurology department Controls: age- and gender-matched, recruitment process unclear	• **Patient characteristics** <u>Cases</u> Mean age ± SD: 55 ± 14 yrs Mean disease duration ± SD:11 ± 11 yrs Female: 13 (40.6%) <u>Controls</u> Mean age ± SD: 53 ± 14 yrs Female: 34 (46.6%) • **Participation rate** Not reported	• **IgA EMA** 1/32 (3.1%) Controls: 1/73 (1%) NS	Not evaluated

CD celiac disease; EMA endomysial antibody; IgA immunoglobulin A; NS not statistically significant; SD standard deviation; yr year

Table A5: Prevalence of Celiac Disease in Asymptomatic Patients Presenting with Idiopathic Short Stature

Study Country N	Study Design Recruitment	Patient Population Symptoms	CD diagnosis criteria Short Stature definition	Prevalence of CD
Cacciari et al. (14)(1985) Italy N= 104 short stature	• **Study design** Case Series / Before-after (cross-sectional evaluation of prevalence) F-up: 3 to 33 mos • **Recruitment** All children with short stature and no GI symptoms who attended the pediatric clinic and had a small bowel biopsy done.	• **Patient Characteristics** Idiopathic short stature: 88/104 (84.6%) Mean age: 9.4 to 13.4 (2.8- 16.8) yrs Bone age delay (% of chronologic age): 16.6% - 28.2% • **Participation rate** Not reported	• **CD diagnosis** Serology (AGA) confirmed by small bowel biopsy • **Short stature definition** < 3rd percentile	• **% patients with CD** 16 (15.4%)
Stenhammar et al. (42)(1986) Sweden N=87 short stature	• **Study design** Case series (cross-sectional evaluation of prevalence) • **Recruitment** Children with short stature without GI symptoms.	• **Patient Characteristics** Median age: 9.5 yrs (1.0-16.5) Mean height SD: 2.7 (2.0-5.0) Mean weight SD: 2.5 (1.0-6.0) • **Participation rate** Not reported	• **CD diagnosis** Small bowel biopsy • **Short stature definition** Height > 2 SD below the mean for age and gender	• **% patients with CD** 2/87 (2.3%)
Groll et al. (30)(1980) England N=34 short stature of no endocrine cause	• **Study design** Case Series (cross-sectional evaluation of prevalence) • **Recruitment** Children with short stature and no GI symptoms referred to the gastroenterology clinic	• **Patient Characteristics** Age: 2.5 to 17.0 yrs • **Participation rate** Not reported	• **CD diagnosis** Serology (unclear which) confirmed by biopsy • **Short stature definition** Height 2 SD below mean height for age	• **% patients with CD** 8/34 (23.5%)
Tumer et al. (31)(2001) Turkey N=84 short stature without cause	• **Study design** Cross-sectional • **Recruitment** Children with short stature without GI symptoms.	• **Patient Characteristics** Age: 16 mos to 14 yrs Female: 46 (54.8%) • **Participation rate** Not reported	• **CD diagnosis** IgA EMA confirmed by biopsy • **Short stature definition** Height < 3rd percentile for age	• **% patients with CD** 7 (8.3%)

Study Country N	Study Design Recruitment	Patient Population Symptoms	CD diagnosis criteria Short Stature definition	Prevalence of CD
Rossi et al. (32)(1993) United States N=117 short stature	• **Study design** Cross-sectional • **Recruitment** Children with short stature seen at the endocrinology clinic.	• **Patient Characteristics** Age: 2 to 17 yrs • **Participation rate** Not reported	• **CD diagnosis** IgA EMA confirmed by small bowel biopsy • **Short stature definition** Height < 3rd percentile for age	• **% patients with CD** 2 (1.7%)
Giovenale et al. (33)(2006) Italy N= 7066 short stature	• **Study design** Cross-sectional • **Recruitment** Children with short stature seen at outpatient clinics. • **Exclusion criteria** Excludes subjects with thyroid or adrenal function abnormalities	• **Patient Characteristics** Age: 2 to 14 yrs Female: 2826 (40.0%) • **Participation rate** Not reported	• **CD diagnosis** IgA EMA, tTG confirmed by biopsy • **Short stature definition** Not defined	• **% patients with CD** 44 (0.63%)

AGA refers to anti-gliadin antibody; CD celiac disease; EMA endomysial antibody; f-up follow-up; GFD gluten-free diet;GI gastrointestinal; IgA immunoglobulin A; mos months; NS not statistically significant; SD standard deviation; tTG tissue trasnglutaminase; yr year

Table A6: Prevalence of Asymptomatic Celiac Disease in Patients with Osteopenia or Osteoporosis

Study Country N	Study Design Recruitment	Patient Population Symptoms	CD diagnosis criteria Osteopenia/Osteoporosis definition	Prevalence of Celiac Disease
Armagan et al. (34) (2005) Turkey N=89 premenopausal women with idiopathic low BMD N=76 controls Adults	• **Study Design** Cross-sectional • **Recruitment** No details on recruitment. Premenopausal, idiopathic low BMD, normal calcium levels Control: healthy premenopausal women without osteoporosis • **Exclusion Criteria** - Conditions and medications that affect bone metabolism - Diseases associated with CD - Use of calcium (> 1.5 g/d) or vitamin D (> 800 IU/d) among others	• **Patient Population** Mean Age Low BMD: 36.0 (25-44) Control: 35.0 (25-45) Female: 100% (low BMD and controls) • **Participation rate** Not reported	• **CD diagnosis** Serology (IgA AGA, IgA EMA if AGA positive) • **Low BMD definition** BMD lumbar spine ≥ 2.5 SD below the young adult mean	• **IgA EMA** 9 (10.1%) Control: 0 p value not provided
Gonzalez et al. (35)(2002) Argentina N=127 postmenopausal, osteoporotic women N= 747 controls (not age-matched)	• **Study Design** Cross-sectional • **Recruitment** Consecutive postmenopausal, osteoporotic women Control: from population-based study, not age-matched • **Exclusion Criteria** Not reported	• **Patient Population** Mean age Osteoporosis: 68 (50-82) yrs Control: 29 (16-79) yrs) Female: 100% (osteoporosis and controls) • **Participation rate** Not reported	• **CD diagnosis** Serology (IgA or IgG AGA, IgA EMA if AGA positive) Confirmed by biopsy • **Osteoporosis definition** ≥ 1 nontraumatic fracture and/or femoral neck BMD T-score < 2.5	• **IgA EMA** 1 (0.8%) Control: 6 (0.8%) p value not provided
Vancikova et al. (36) (2002) Czech Republic N=102 osteoporosis N=1,312 controls Adults	• **Study Design** Cross-sectional • **Recruitment** Recruitment method not reported. Patients with primary osteoporosis included. Controls: blood donors • **Exclusion Criteria** Secondary causes of osteoporosis.	• **Patient Population** Mean age Osteoporosis: 64 (45-85) yrs Controls: 35 (18-60) yrs Female Osteoporosis: 97 (95.1%) Control: 523 (39.9%) • **Participation rate** Not reported	• **CD diagnosis** Serology (IgA, IgG AGA, igA tTG, EMA) • **Osteoporosis definition** Not reported	• **IgA tTG** 7 (6.9%) Controls: 92 (7.0%) • **IgA EMA** 1 (1.0%) Controls: 6 (0.5%) p value not provided

AGA refers to anti-gliadin antibody; BMD bone mineral density; CD celiac disease; EMA endomysial antibody; f-up follow-up; IgA immunoglobulin A; mos months; SD standard deviation; tTG tissue trasnglutaminase; yr year

Table A7: Prevalence of Asymptomatic Celiac Disease in Patients with Recurrent Aphtous Stomatitis

Study Country N	Study Design Recruitment	Patient Population Symptoms	CD diagnosis criteria Aphtous Stomatitis definition	Prevalence of CD
Aydemir et al. (37)(2004) Turkey N=41 Recurrent aphtous stomatitis (RAS) N= 49 controls Adults and children	• **Study design** Cross-sectional • **Recruitment** Patients with RAS presenting at the dermatology and family practice clinics. Controls: patients referred to the gastroenterology out-patient clinic for reasons other than RAS • **Exclusion Criteria** Not reported	• **Patient Population** Mean Age ± SD RAS: 40.0 ± 10.8 yrs Controls: 38.0 ± 12.9 yrs Female 23 (56%) • **Participation Rate** Not reported	• **CD diagnosis** Serology (IgA AGA, IgA EMA), confirmed by small bowel biopsy • **Recurrent aphtous stomatitis (RAS) diagnosis** History and physical examination	• **IgA EMA** RAS: 2 (4.8%) Control: 0 • **Small bowel biopsy** RAS: 2 (4.8%) Control: 0 p value not provided

AGA refers to anti-gliadin antibody; CD celiac disease; EMA endomysial antibody; IgA immunoglobulin A; RAS recurrent aphtous stomatitis; SD standard deviation; tTG tissue trasnglutaminase; yr year

Table A8: Prevalence of Asymptomatic Celiac Disease in Patients with Type 1 Diabetes

Study Country N	Study Design Recruitment	Patient Population Symptoms	Celiac Disease (CD) diagnosis criteria	Prevalence of CD
Djuric et al. (38)(2010) Serbia N=121 type 1 diabetes N=125 controls Pediatric	• **Study design** Cross-sectional, controlled • **Recruitment** Patients followed at a hospital clinic Controls: healthy children and adolescents – details on recruitment not reported • **Exclusion Criteria** - Not reported	• **Patient Population** Mean Age Type 1 diabetes: 10.8 (2-18) yrs Controls: 10.4 yrs (2-18) yrs Girls Type 1 diabetes: 70 (57.9%) Controls: 68 (54.4%) Mean diabetes duration ± SD 3.6 ± 3.6 yrs • **Participation Rate** Not reported	• **CD diagnosis** Serology (IgA tTG) confirmed by small bowel biopsy	• **IgA tTG** Type 1 diabetes: 5 (4.1%) – among asymptomatic Controls: 1 (0.8%) P < .05 (***considering 7 pts, 2 symptomatic in type 1 diabetes group***) • **Small bowel biopsy** 5 (4.1%), 2 refused biopsy • **Losses to f-up** 2/9 (22.2%) did not agree to biopsy with positive IgA tTG
Sari et al. (39) (2010) Turkey N=48 type 1 diabetes N=103 controls Pediatric	• **Study design** Cross-sectional, controlled • **Recruitment** Children with type 1 diabetes – recruitment method not reported Controls:, and healthy children and adolescents without type 1 diabetes– details on recruitment not reported • **Exclusion Criteria** Not reported	• **Patient Population** Mean Age Type 1 diabetes: 12.1 (3.5-23) yrs Controls: 12.2 (3.5-17) yrs Girls Type 1 diabetes: 30 (62.5%) Mean diabetes duration ± SD Not reported • **Participation Rate** Not reported	• **CD diagnosis** Serology (IgA tTG) , confirmed by small bowel biopsy	• **IgA tTG** Type 1 diabetes: 10 (20.8%) Healthy controls: 0 p .00005 • **Small bowel biopsy** Type 1 diabetes: 3 (6.3%) – only 8 accepted to do biopsy (5 had normal mucosa) Healthy controls: not performed
Soyucen et al. (40)(2010) Turkey N=33 type 1 diabetes N=41 controls Pediatric	• **Study design** Cross-sectional, controlled • **Recruitment** Children with type 1 diabetes – recruitment method not reported Controls: non-diabetic children– details on recruitment not reported • **Exclusion Criteria** - Other acute or chronic diseases - IgA deficiency	• **Patient Population** Mean Age ± SD Type 1 diabetes: 10.0 ± 3.5 yrs Controls: 9.1 ± 3.1 yrs Girls Type 1 diabetes: 19 (57.6%) Controls: 18 (43.9%) Mean diabetes duration ± SD 2.0 (0.5-7) yrs • **Participation Rate** Not reported	• **CD diagnosis** Serology (IgA EMA)	• **IgA EMA** Type 1 diabetes: 3 (9.1%) Controls: 0 p< .05

CD celiac disease; EMA endomysial antibody; IgA immunoglobulin A; SD standard deviation; tTG tissue transglutaminase;

Table A9: Prevalence of Asymptomatic Celiac Disease in Chronic Idiopathic Thrombocytopenia Purpura

Study Country N	Study Design Recruitment	Patient Population Symptoms	CD diagnosis criteria Short Stature definition	Prevalence of CD
Altintas et al. (41) (1985) Turkey N= 74 chronic idiopathic thrombocytopenic purpura (cITP) N=162 controls Adults	• **Study design** Cross-sectional (prevalence evaluation) • **Recruitment** Patients with cITP were included, no details on recruitment. Controls: age- and sex-matched healthy controls.	**Patient Characteristics** Mean age: cITP: 33.7 (16-83) yrs Controls: 33.2 (18-71) yrs Female cITP: 57 (77%) controls: 123 (76%)	• **CD diagnosis** Serology: IgA and IgG AGA, IgA and IgG EMA • **cITP definition** Not defined	• **IgA EMA** cITP: 2 (2.7%) Controls: 1 (0.6%) NS

AGA refers to anti-gliadin antibody; CD celiac disease; cITP chronic idiopathic thrombocytopenic purpura; EMA endomysial antibody; IgA immunoglobulin A; NS not statistically significant

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