Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review

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abstract

BACKGROUND AND OBJECTIVES: Prevalence rates of type 1 diabetes (T1D) and celiac disease (CD) vary from 1.6% to 16.4% worldwide. Screening guidelines are variable and not evidence based. Our aim was to conduct a systematic review of CD in T1D.

METHODS: Medline, Embase, and the Cochrane Library were searched. Studies were limited to those in English and in humans. We selected longitudinal cohort studies screening for CD in T1D with at least 5 years of follow-up. Screening rates, characteristics, and prevalence of biopsy-proven CD in people with T1D were extracted.

RESULTS: We identified 457 nonduplicate citations; 48 were selected for full-text review. Nine longitudinal cohort studies in 11 157 children and adolescents with 587 cases of biopsy-proven CD met the inclusion criteria. Median follow-up was 10 years (range: 5–18 years). The weighted pooled prevalence of CD was 5.1% (95% confidence interval: 3.1–7.4%). After excluding 41 cases with CD onset before T1D, CD was diagnosed in 218 of 546 (40%) subjects within 1 year, in 55% within 2 years, and in 79% within 5 years of diabetes duration. Two studies (478 cases) reported higher rates of CD in children aged <5 years at T1D diagnosis. The duration of follow-up varied across the included studies. CD screening frequency progressively decreased with increased T1D duration.

CONCLUSIONS: Because most cases of CD are diagnosed within 5 years of T1D diagnosis, screening should be considered at T1D diagnosis and within 2 and 5 years thereafter. CD screening should be considered at other times in patients with symptoms suggestive of CD. More research is required to determine the screening frequency beyond 5 years of diabetes duration.

The association between type 1 diabetes (T1D) and celiac disease (CD) is well documented in young people, although reported rates vary. Prevalence rates from both cross-sectional and longitudinal studies range from 1.6% to 16.4% worldwide,[1–5] with the majority of studies only including children and adolescents. In contrast, CD prevalence is 0.3% to 1.0% in the general population of all ages.[6] A greater risk is conferred by female gender,[1,7] younger age, and, in type 1 diabetes, younger age at diabetes diagnosis.[7,8]

Recognized adverse effects of untreated CD include iron deficiency, anemia, growth retardation, and osteoporosis.[9] In T1D, undiagnosed CD may be associated with unstable blood glucose levels, a greater risk of hypoglycemia,[10] and increased risk of retinopathy.[11] In those with confirmed CD and T1D, nonadherence to a gluten-free diet (GFD) is associated with early elevation of albumin excretion rate,[12] whereas CD duration >10 years, irrespective of GFD adherence, is a risk factor for the development of diabetic retinopathy.[13] Other clinical improvements associated with GFD compliance, including weight z scores, hemoglobin, and serum ferritin, have been reported,[14] as well as height z scores and the reversal of iron-deficiency anemia.[15] In contrast, noncompliance with a GFD was associated with lower total bone mineral density, lower volumetric lumbar spine z score, higher bone turnover, lower vitamin D, and lower ferritin.[16] The rationale for CD screening is to prevent these adverse effects and complications, and to maximize growth. Because seroconversion from negative to positive CD autoantibodies can occur beyond 10 years of diabetes duration,[17] repeated screening for CD is necessary.

Despite the well-recognized increased risk of CD in T1D and the potential for increased morbidity, there are no systematic reviews examining the incidence of CD or optimal screening frequency for CD in T1D. Contemporary guidelines for T1D recommend screening by measurement of tissue transglutaminase (TTG) or anti-endomysial antibodies (EMAs).[18–20] Recommendations for screening frequency are variable and not evidence based. The International Society for Pediatric and Adolescent Diabetes recommends screening at the time of diagnosis and every 1 to 2 years thereafter, with more frequent assessment if clinically indicated or if there is a first-degree relative with CD,[18] whereas the American Diabetes Association recommends considering CD screening soon after diabetes diagnosis and in those with clinical symptoms suggestive of CD.[20] In view of these variable recommendations, we systematically reviewed the epidemiology of CD in people with T1D to inform screening guidelines.

METHODS

Study Aims

There are 2 specific aims of this review. First, we systematically reviewed the epidemiology of biopsy-proven CD in people with T1D, with subgroup analysis by age, gender, and duration of diabetes. Our second specific aim was to examine the risk of CD in people with T1D, at diagnosis and at specific time intervals after diagnosis, to determine the optimal frequency of screening.

Study Selection

Inclusion criteria were longitudinal cohort studies that screened for CD by using either EMAs and/or TTG in children, adolescents, or adults with T1D at least twice. Only studies in humans and reported in the English language were included. Exclusion criteria were studies other than longitudinal cohort studies, not in

individuals with T1D, and no reports of screening frequency. The diagnosis of T1D was based American Diabetes Association criteria,[21] and CD was confirmed by small bowel biopsy.

Data Sources and Searches

Two reviewers (A.P.-S. and H.P.) independently searched Medline, Embase, and the Cochrane Library from 1946 to November 30, 2014, for studies of celiac autoimmunity and biopsy-proven CD in people with T1D. Search terms were as follows: "Diabetes Mellitus, type 1/or diabetes mellitus, type 1.mp," "celiac disease or celiac disease.mp," "celiac sprue or celiac sprue.mp," "celiacs or coeliacs.mp," "silent celiac or silent celiac.mp," "asymptomatic celiac or asymptomatic celiac.mp," "subclinical celiac or subclinical celiac.mp," "gluten sensitive enteropathy.mp or exp celiac disease," "reticulin.mp or exp Reticulin," "gliadin.mp or exp Gliadin," "endomysial or endomysium.mp," "tissue transglutaminase.mp," "antireticulin.mp," "antigliadin.mp," "antiendomysial.mp," and "antiendomysium.mp." We also performed manual searches through article reference lists.

Data Extraction and Quality Assessment

Two reviewers independently extracted data from the included studies. For each individual study, data were collected regarding study design, country, population and size, duration of follow-up, age at CD diagnosis, age at diabetes diagnosis, gender, diagnostic test(s) performed, frequency of screening, small bowel biopsy results, and prevalence rates. Reports of CD-related symptoms around the time of CD diagnosis were also collated. Study quality was assessed by using the Newcastle-Ottawa quality assessment scale for cohort studies.[22] This scale evaluates 3 areas, selection, comparability (confounding factors), and outcome (assessor blinding and follow-up), giving a possible total score of 9, with

a score of >7 indicating good methodologic quality. Corresponding authors of included studies were contacted to request additional data when applicable.

Data Synthesis and Analysis

Meta-analysis of prevalence rates for CD was conducted by using a quality-effects model, which takes into account differences in study quality in the estimation of weighted pooled prevalence.[23] Incidence density, which provides an estimate of incident cases of CD during a specified time period, was calculated as the total number of diagnosed cases divided by the number of patients screened during follow up (n = 4839, 8789, and 20 299 at 1, 2, and 5 years, respectively). Incidence is reported per 1000 patient-years, with 95% confidence intervals estimated assuming a Poisson distribution. Statistical analyses were performed by using Stata, version 13 (StataCorp, College Station, TS), and meta-analysis of prevalence was conducted by using MetaXL (Epigear, Brisbane Australia).[23]

RESULTS

The initial search returned a total of 605 citations. After review of abstracts and full texts, 596 studies were excluded (Fig 1), leaving 9 cohort studies that met the inclusion criteria.[1,7,8,17,24–28] The studies were from Europe (n = 7) and Australia (n = 2). Study characteristics are summarized in Table 1. They included a total of 11 157 young people diagnosed with T1D ≤21 years of age (range: 0.6–21.0 years). The overall methodologic quality of the studies was fair, with 4 of 9 studies (44%) scoring ≥7 on the Newcastle-Ottawa Scale.[8,24,26,27] No adult studies were identified. There were a total of 587 cases of coexisting biopsy-proven CD and T1D, and of these, 41 were diagnosed before T1D. Median follow-up after diabetes diagnosis was 10 years (range: 5–18 years).
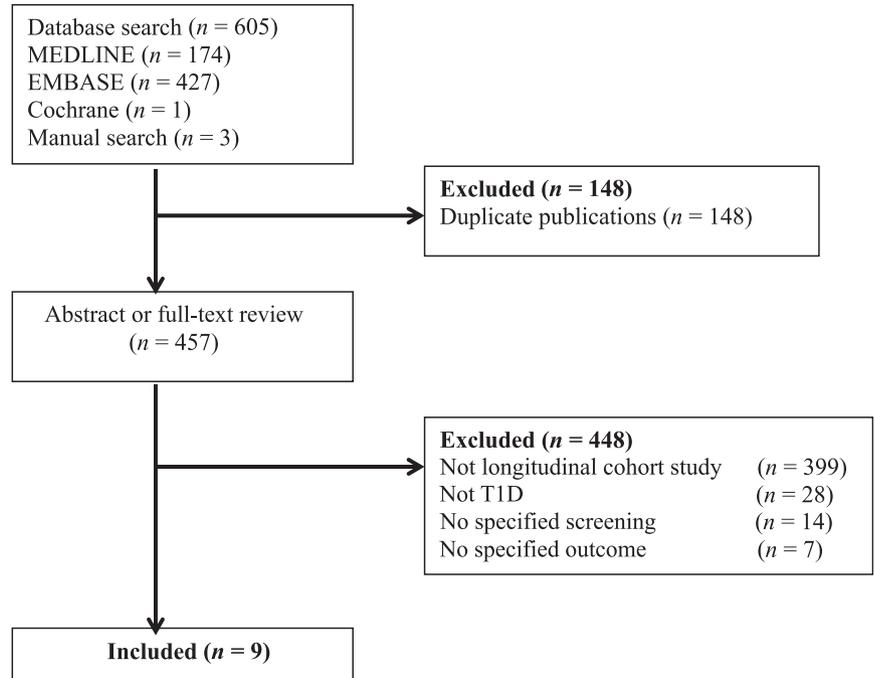

FIGURE 1
Flowchart showing the number of citations retrieved by individual searches and number of studies included in the review.

Definition of T1D

Three studies provided a definition of T1D[8,17,28] or reported the presence of islet autoantibodies.[8,17]

Prevalence of Biopsy-Proven CD

Prevalence was reported by all studies and varied from 1.6% to 9.7% (Fig 2). CD was reported in 587 of 11 157 children and adolescents with T1D; a meta-analysis of prevalence using the quality-effects model was 5.1% (95% confidence interval: 3.1–7.4%). CD was diagnosed in 41 cases before diabetes diagnosis (7% of all CD cases), and these cases were excluded from further analysis.

Incidence and Incidence Density

Two Australian studies[8,17] reported the incidence of biopsy-proven CD per 1000 person-years, with similar rates: 7.2 (1990–1996)[17] and 7.7 (1990–2009).[8] For 6 studies,[7,8,24–27] the number of patients screened per year of diabetes duration was available, enabling incidence density to be calculated (Table 2). Incidence density was 43.4 per 1000 patient-

years at 1 year, 32.8 at 2 years, and 20.1 at 5 years (Table 3). This finding indicates that the rate of CD was highest within the first year after diagnosis of T1D. The incidence density rates decreased significantly between the 3 time points: year 2 compared with year 1 (P = .002) and year 5 compared with year 2 (P < .001).

Seroconversion

Five studies reported seroconversion to positive EMAs and/or TTG after diabetes diagnosis[1,17,24,25,27]; time to seroconversion ranged from 2 years[1] to 10.2 years.[17] The other 4 studies reported time between CD and T1D diagnosis, without providing information on seroconversion.

Association Between CD, Gender, and Age

Seven studies reported CD prevalence by gender,[1,7,8,17,25,26,28] and of these, the prevalence was higher in girls in 2 studies (67% and 61%),[1,7] higher in boys in 3 studies (range: 64–69%),[25,26,28] and not different in

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TABLE 1 Characteristics of Included Studies Screening for CD in T1D

First Author, Year	Country	Study Design	Number Screened	CD Prevalence, %	Follow-up, y	Age at CD Diagnosis,[a] y	Age at Diabetes Diagnosis, y	Screening Test	Screening Frequency	Newcastle-Ottowa Scale
Barera, 2002[24]	Italy	Prospective	274	6.2	6	NR	8.3 ± 4.6	EMA IgA; if IgA deficient, IgG EMAs and AGAs	At diagnosis and annually	7
Cerutti, 2004[7]	Italy	Retrospective	4322	6.8	10	7.2 ± 4.3	5.5 ± 3.7	IgA/IgG AGAs and/or EMAs	Annually	6
Crone, 2003[25]	Austria	Longitudinal	157	5.1	8	NR	NR	EMAs	2–3 times yearly	5
Glastras, 2005[17]	Australia	Prospective	173	4.6	13	NR	NR	EMAs and/or AGAs	At diagnosis, 1–3 times yearly thereafter	6
Larsson, 2008[26]	Sweden	Prospective	300	9.7	5	11.1	6.5	IgA EMAs	At diagnosis, then annually	8
Pham-Short, 2012[8]	Australia	Prospective	4379	4.2	≥10	9.6 ± 3.7	6.6 ± 4.0	IgA EMAs and/or IgA TTG	At diagnosis 1–2 times yearly thereafter	8
Poulain, 2007[1]	France	Retrospective	950	1.6	>10	9.4 ± 4.8	6.0 ± 4.2	EMA and or TTG	NR	6
Salardi, 2008[27]	Italy	Prospective	331	6.6	18	NR	NR	EMA	At diagnosis and then every 6–12 mo	8
Uibo, 2010[28]	Estonia	Prospective	271	4.1	6	9.9 (range: 3.1–16.2)	NR	IgA EMA and IgA TTG	NR	6

AGA, anti-gliadin antibody; NR. not reported.

[a]Data are presented as means ± SDs or medians (range)NR not reported

2 studies[8,17] Six studies reported CD prevalence by age at diabetes diagnosis,[7,8,17,24,26,28] 2 studies reported an association between younger age (<5 years) at T1D diagnosis and development of CD,[7,8] with 1 study noting a tendency toward younger age at diabetes diagnosis, although the relationship was not statistically significant.[26]

Three studies reported no relationship with age at diabetes diagnosis.[17,24,28]

Association Between CD and Diabetes Duration

Of the 546 CD cases diagnosed after diabetes, 40% were within 1 year of diabetes, 55% within 2 years, and 79% within 5 years of diabetes

diagnosis. The proportion of patients screened decreased from 50% at the end of year 1, to 35% ($P < .001$) at the end of year 5, and 12% at the end of year 10.

Symptomatology

Five studies reported data on CD-related symptoms and signs (gastrointestinal, short stature, anemia, or asymptomatic; $n = 308$),[1,7,25,28,29] with 85% of cases asymptomatic at the time of CD diagnosis.

Recommendations for Screening

The majority of studies (7 of 9) recommended screening for CD at least once in people with T1D.[1,7,8,17,24–26] Four studies recommended screening at diabetes onset,[1,8,24,26] whereas follow-up screening recommendations were variable in frequency and duration, ranging from annually for at least 2 years[26] up to an unspecified duration of diabetes (described as several years).[1,17,24]

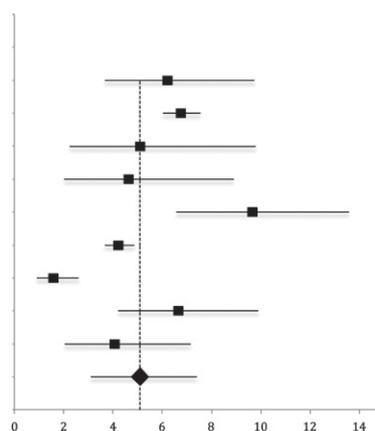| Study ID	Number screened	Prevalence % (95% CI)
Barera et al, 2002[24]	274	6.2 (3.7–9.8)
Cerutti et al, 2004[7]	4322	6.8 (6.0–7.6)
Crone et al, 2003[25]	157	5.1 (2.2–9.8)
Glastras et al, 2005[17]	173	4.6 (2.0–8.9)
Larsson et al, 2008[26]	300	9.7 (6.6–13.6)
Pham-Short et al, 2012[8]	4379	4.2 (3.7–4.9)
Poulain et al, 2007[1]	950	1.6 (0.1–2.6)
Salardi et al, 2008[27]	331	6.7 (4.2–9.9)
Uibo et al, 2010[28]	271	4.1 (2.0–7.2)
Weighted Pooled Prevalence 5.1 (3.1–7.4)		

FIGURE 2

Prevalence of CD in T1D. The forest plot shows unadjusted prevalence estimates (boxes) and pooled prevalence (diamond) with 95% confidence intervals (bars).

TABLE 2 Number of New CD Cases Diagnosed in Relation to T1D Duration

	Number	Proportion, %
Total CD cases in study	587	
Before diabetes diagnosis	41	7
Within 1 year of diabetes diagnosis	220	37
Within 1–2 years of diabetes diagnosis	78	13
2 to <5 years after diabetes diagnosis	135	24
5–10 years after diabetes diagnosis	89	15
More than 10 years after diabetes diagnosis	25	4

DISCUSSION

In this systematic review of 9 longitudinal cohort studies involving 11 157 children and adolescents with T1D, of whom 587 had biopsy-proven CD, the prevalence of CD varied from 1.6% to 9.7%, with a weighted pooled prevalence of 5.1%. Incidence density at 1, 2, and 5 years of diabetes duration was 43.4, 32.8, and 20.1 per 1000 patients-years, respectively, indicating that the risk of CD is highest within the first year of diabetes duration. Because 55% of cases were diagnosed within 2 years and 79% within 5 years of diabetes duration, screening should be considered at diabetes diagnosis and within 2 and 5 years after diagnosis. Because of limited evidence from long-term studies, it is not possible to recommend the screening frequency beyond 5 years of diabetes duration. However, among the studies with longer follow-up, 16% of CD cases were diagnosed between 5 and 10 years of diabetes duration and 5% were diagnosed after >10 years. CD should be considered at any time in patients with symptoms suggestive of CD.

Prevalence of CD in T1D

There was considerable variation in the prevalence of CD across the 9 included studies. Possible explanations for this heterogeneity include ethnic differences across the study populations, which is likely to reflect the greater risk of CD among individuals with high-risk HLA antigen genotypes,[30] as well as the varying impact of environmental influences across different countries.[31] Our finding of the highest prevalence rate in Sweden (9.7%) is in keeping with the The Environmental Determinants of Diabetes in the Young (TEDDY) study, which recently reported a higher risk of CD in Swedish children compared with those in the United States, Finland, and Germany.[31] The variation in prevalence rates may also be related to differences in study design, including retrospective versus prospective, the frequency of screening, and duration of follow-up. To address this issue, we chose to use a quality-effects model in the meta-analysis of prevalence,[23] which accounts for study quality in the estimation of pooled prevalence.

Clinical Importance of CD Screening in T1D

It is notable that 85% of cases presented asymptomatically in this review. Although the merits of early diagnosis may be argued,[32] especially in those with a milder disease phenotype,[33] compliance to a GFD in those with biopsy-proven CD may improve clinical variables such as weight and serum ferritin.[14] Improvements in quality of life and depression scores have been reported 1 year after CD diagnosis.[34] In contrast, nonadherence to a GFD has been associated with elevated albumin excretion rate,[12] lower bone mineral density, lower vitamin D, and lower ferritin[14] in youth with coexisting CD and T1D. These clinical and psychological improvements support routine CD screening in T1D and highlight the importance of adherence to a GFD to prevent complications of untreated CD.

Strengths and Weaknesses

This is the first systematic review, to our knowledge, to examine screening for CD in T1D to determine the optimal screening frequency. The strengths of this review are the large sample size and long observation period, providing representative data on the epidemiology in T1D across different countries. Our analysis is limited by the variable follow-up periods across the studies, as well as missing data on the number of patients screened throughout each year of diabetes duration. The frequency of antibody screening for CD progressively decreased with increased duration of diabetes, which is likely to have led to an underestimate of incidence and prevalence.

There are various factors associated with the systematic review process that may influence our findings. Although predetermined selection criteria were implemented to ensure an unbiased selection, we sought to minimize this bias by placing no limitations on the basis of age; however, the lack of adult studies identified may influence the generalizability of our results beyond the pediatric age range. Another potential weakness is that the populations of the included studies were predominantly of European descent, whereas no studies from other regions such as North America and the Middle East met the eligibility

TABLE 3 Pooled Incidence Density of CD in Young People With T1D

	Population Screened	Biopsy-Proven CD Cases	Incidence per 1000 Patient-Years (95% CI)
Year 1	4839	210	43.4 (37.8–49.5)
Year 2	8789	288	32.8 (29.2–36.7)
Year 5	20 299	407	20.1 (18.2–22.1)

Incidence was calculated from available data in 6 publications.[7,8,24–27] Year 2 versus year 1, P = .002; year 5 versus year 2, P < .001. CI, confidence interval.

criteria. The reduced screening frequency between years 2 and 5 coincided with reduced prevalence and incidence rates; however, we estimate that this would not have significantly influenced case detection rates had the screening rate been maintained at 50% between 2 and 5 years. Furthermore, some studies did not provide sufficient information to be able to calculate incidence density,[1,17,28] and thus our reported values are conservative.

Screening in Adults

No longitudinal adult studies examining the screening frequency of CD in T1D were identified. However, a retrospective study in 118 adults with T1D and CD[35] found that 48% of those diagnosed with T1D after age 18 years reported CD symptoms for >5 years before CD diagnosis, in contrast to the group whose diabetes was diagnosed in childhood, with a majority (59%) reporting CD-related symptoms for <6 months before CD diagnosis. Prospective studies are required in adults to determine the optimal frequency of screening.

Implications for Clinical Practice

On the basis of our systematic review of data from cohort studies, more than half of CD cases were diagnosed within 2 years of diabetes duration, with most cases diagnosed within the first 5 years after diabetes diagnosis. The contemporaneous diagnosis of both conditions most likely describes the diagnosis of preexisting CD not previously recognized and may reflect the high background risk of the population studied.[30] Although CD can be diagnosed beyond 10 years after diabetes diagnosis, more research is required to establish the optimal screening frequency beyond 5 years of diabetes duration as well as the optimal screening frequency in adults with T1D. The impact of gender, age at diabetes diagnosis, and diabetes duration on CD development is unclear. In patients with clinical symptoms such as growth failure, weight loss, and frequent unexplained hypoglycemia, or those with a first-degree relative with CD, screening for CD should be considered irrespective of diabetes duration.[18,36] Although not examined in this review, it should be noted that screening for immunoglobulin (Ig) A deficiency (prevalence: 1:500) is recommended in recent guidelines[18] due to the risk of a false-negative TTG result, and if present, then IgG-specific antibody tests (TTG or EMA IgG or both) should be performed.[18,19]

Future Directions

This systematic review shows an elevated risk of CD in people with T1D, particularly in the early course of disease. We were unable to examine the effect of gender and age at diabetes diagnosis on CD development, highlighting the need for prospective cohort studies beyond 5 years of diabetes duration as well as those that report on the impact of annual CD screening and with the inclusion of adults to further quantify the frequency of CD screening in T1D.

ABBREVIATIONS

CD: celiac disease
EMA: anti-endomysial antibody
GFD: gluten-free diet
Ig: immunoglobulin
T1D: type 1 diabetes
TTG: tissue transglutaminase

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