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Interpreting positive celiac serology in children with new-onset type 1 diabetes

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Abstract

Objectives: The association of celiac disease (CD) in type 1 diabetes mellitus (T1DM) is well-established, yet variation exists in screening practices. This study measures the accuracy of early screening with tissue transglutaminase immunoglobulin A (TTG-IgA) and endomysial antibody (EMA) in newly diagnosed T1DM.

Methods: This is a retrospective study of children with T1DM between 2013 and 2019 with early CD screening and follow-up. Data elements included anthropometrics, serologies, blood pH, bicarbonate, and Hemoglobin A1c. Celiac serologies were analyzed using chi-square and receiver operating characteristic curves to calculate optimal levels for predicting CD.

Results: A total of 1,292 children met inclusion criteria with 142 having positive celiac serologies; 47 (33.1 %) of whom were subsequently diagnosed with CD – an incidence of 3.6 %. All subjects with positive EMA and TTG-IgA ≥8 times upper limit of normal were diagnosed with CD. Gastrointestinal symptoms, BMI, and thyroid disease were not statistically significant variables in this cohort, although there was a trend toward CD in lower BMI patients and higher TTG IgA in those with markedly elevated $HgbA_{1c}$.

Conclusions: Early celiac screening in T1DM is reliable and promotes timely CD diagnosis and treatment. Although transient positive celiac serologies were noted, the degree of TTG-IgA elevation and EMA positivity are strong predictors of coexisting CD. Larger prospective studies using these assays will further define the risk stratification algorithm that is needed for our T1DM community.

Introduction

Type 1 diabetes mellitus (T1DM) and celiac disease (CD) are associated conditions with an overlap in genetics (HLA-DQ genotyping), immune dysregulation (T-cell mediated autoimmune disorders), and environmental triggers (infectious agents, microbiome, diet). Given this connection, it is not surprising that CD in individuals with T1DM is markedly higher with an estimated prevalence of 8 % compared to the 1 % of CD cases found worldwide [1, 2]. Children with T1DM and undetected CD have an increased risk of diabetic retinopathy, nephropathy, iron deficiency anemia [3], as well as an increased susceptibility to other autoimmune conditions such as Hashimoto's thyroiditis [4, 5]. From a gastrointestinal standpoint, delays in the diagnosis of CD can lead to decreased growth, nutritional deficiencies, bone disease, and prolonged enteropathy that increase mortality risk [6].

Tissue transglutaminase immunoglobulin A (TTG IgA) antibody is universally accepted as the first-line screening test for CD [7]. Given its low cost, ease of testing, and high sensitivity, this has been endorsed by both pediatric and adult gastroenterology societies. Nonetheless, false positive results can occur, particularly in those with other autoimmune conditions [8]. Additional serologies such as endomysial antibody (EMA) utilize indirect immunofluorescence and have a high specificity and are particularly relevant in serology-based diagnosis of CD. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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(ESPGHAN) 2020 guidelines deem an elevated TTG IgA greater than 10 times the upper limit of normal and a positive EMA on a second sample as adequate for diagnosis without biopsy [9]. Currently, the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) continues to recommend endoscopy and duodenal biopsy as the standard for diagnosis with characteristic histologic findings defined by increased intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy [10, 11].

Presently, there is no consensus on the timing and frequency of serologic testing for CD in children with T1DM [1]. The International Society for Pediatric and Adolescent Diabetes recommends that children with T1DM be screened at the time of diagnosis and every 1–2 years thereafter, with the frequency of assessment increasing if clinically indicated or if the patient has a first-degree relative with CD [12]. Conversely, the American Diabetes Association recommends screening for CD "soon after the T1DM diagnosis" and again in those who have clinical symptoms that suggest CD [13]. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends all patients with T1DM be screened for CD but does not specify any repeat testing without clinical indications [9, 14]. As CD may be asymptomatic or present with atypical manifestations, establishing timely and effective screening practice in T1DM patients is needed [15].

This study aims to assess the reliability and diagnostic accuracy of early celiac serologic testing with TTG IgA and EMA screening in children with newly diagnosed T1DM. We also sought to risk stratify the T1DM population for coexisting CD on the basis of demographics, anthropometrics, metabolic disturbances, and other coexisting autoimmune disorders.

Methods

This is a single-center retrospective cohort study performed at the Children's Hospital of Philadelphia (CHOP) with approval of the hospital's Institutional Review Board. Patient charts were accessed through the hospital's electronic medical records. The study population included subjects aged 0–18 years with a new diagnosis of T1DM at CHOP between 2013 and 2019 with a minimum 1-year follow-up data available after diagnosis. Subjects were identified using ICD-9 or ICD-10 diagnosis codes of T1DM.

Inclusion criteria require CD screening serologies – total Immunoglobulin A level, TTG-IgA, and EMA – all be collected within 72 h following T1DM diagnosis for consistency with CHOP's inpatient screening protocol of newly diagnosed patients. EliaA CeliKey assay (Thermo Fisher Scientific) was used to measure TTG-IgA and NOVA Lite indirect immunofluorescence of endomysial antibodies for EMA (Inova Diagnostics). With regards to positive celiac serologies in the T1DM cohort, positive predictive value (PPV) was calculated according to EMA titers 1:5 to 1:648 and how many times each subject's TTG IgA value were above the upper limit of normal reference range (ULN). Groups were created at intervals from 1.00–1.99×, 2.00–2.99×, 3.00–3.99× all the way up to >10× ULN concentration. For subjects with positive CD serologies at the time of T1DM diagnosis, subsequent serologies and pathology reports were extracted if available. Diagnostic criteria for CD in this cohort comprised of positive celiac antibody and intestinal damage as seen on duodenal biopsy. Biopsy criteria to confirm CD diagnosis included classic duodenal pathology of intraepithelial lymphocytosis, crypt hyperplasia, and/or villous atrophy. Serology-only diagnosis was also accepted if strong clinical suspicion (e.g., positive symptoms and/or family history) and no available endoscopy. Additional tests analyzed included pH, bicarbonate, and hemoglobin A_{1C} (HbA_{1c}) levels to assess the degree of metabolic disturbances in the cohort. Gastrointestinal manifestations such as abdominal pain, nausea, vomiting, and weight loss were similarly noted along with comorbidities (e.g., autoimmune thyroiditis), anthropometrics (weight, height, BMI percentiles), and demographics (race, gender, ethnicity, age at T1DM diagnosis).

Descriptive statistics (mean±standard deviation, median, and interquartile range (IQR)) were used to characterize the study cohort. Microsoft Excel and R studio statistical software were used to perform data analysis. Primary analysis measured positive predictive values of celiac serology to stratify risk of CD. Chi-squared tests were used to assess statistical significance across different groups within the T1DM cohort, and receiver operating characteristic (ROC) curves were used to assess sensitivity and specificity of serologies. Frequency distribution tables were also created to compare anthropometric data across the T1DM cohort with 95 % confidence intervals calculated where appropriate to determine significance.

Results

Initial data collated 2,376 patients, with 1,084 subsequently excluded due to not meeting criteria: incorrect diagnosis (141), T1DM diagnosis outside the institution (546), study timeframe (207), age at onset [16], or lack of celiac serologic testing at time of T1DM diagnosis (168). This resulted in a final study cohort of 1,292 pediatric subjects with a new diagnosis of T1DM and early CD screening as seen in Figure 1. The median age of our cohort at T1DM diagnosis was 10.6

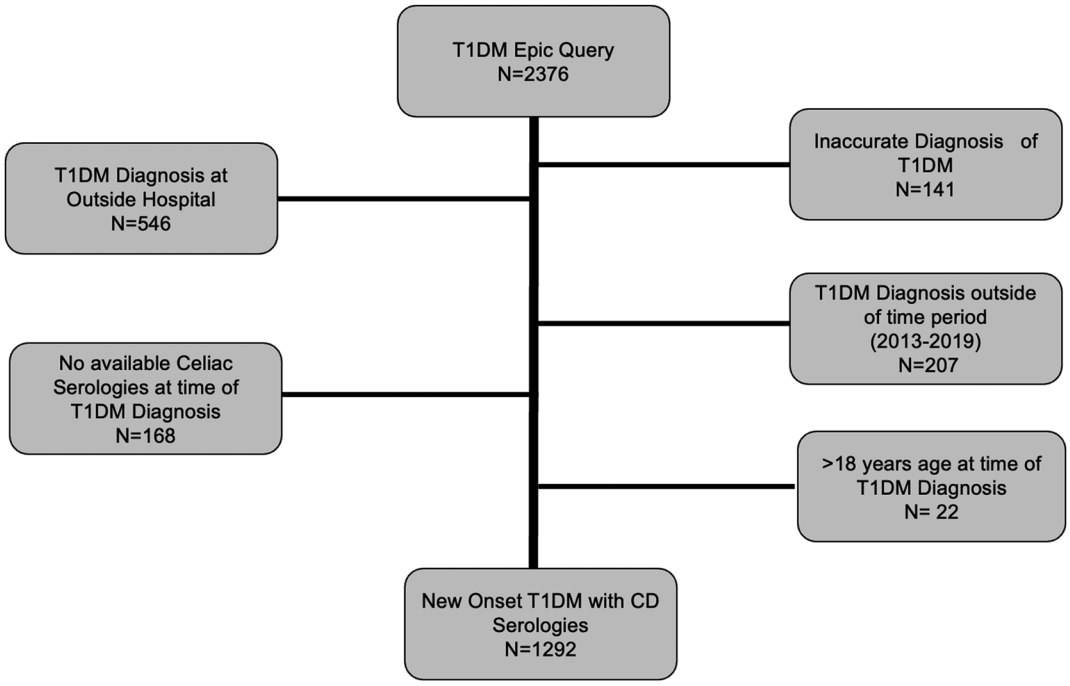

Figure 1: Flowchart of our study cohort of pediatric patients with newly diagnosed type 1 diabetes, filtered through selection process based on inclusion and exclusion criteria.

years with an interquartile range of 6.4 years and longitudinal follow-up of 3.1 years duration (range 1–6.6 years). There were 47.7 % female subjects, 70.8 % non-Hispanic white, 15.5 % non-Hispanic Black, 1.4 % Asian, 1.9 % multiple races, 6.8 % non-Hispanic other, and 6.4 % Hispanic or Latino.

Celiac screening at T1DM diagnosis identified 142 subjects with positive TTG IgA and/or EMA. Of those with positive screen, 137 had positive TTG IgA levels ranging from 2 to 10× ULN, while 93 had positive EMA. It should be noted that nine subjects that screened negative had low total IgA levels (<20). Based on chart review and subsequent follow-up, subjects with positive TTG IgA were divided into two groups as shown in Table 1. Group A (n=47) comprised those with an initial positive celiac screen and subsequent CD diagnosis. Forty-two subjects had serology plus histologic confirmation ultimately on endoscopy, while five were diagnosed on serology alone due to family declining endoscopy and preceding with CD due to symptoms or a strong family history. Group B (n=95) comprised of those with potential CD-positive celiac screen and no active CD by the end of the follow-up period. This group included subjects with transient celiac autoimmunity, seroconversion, and those with positive serologies and negative endoscopy; this latter group included 12 subjects as described in Table 2.

The ROC curve as shown in Figure 2 evaluates sensitivity and specificity of TTG IgA and an optimal cutoff for TTG IgA levels above the ULN. The ROC curve predicted a cutoff value

Table 1: Demographics & clinical presentation of pediatric cohort of newly diagnosed type 1 diabetes mellitus (T1DM).

	Total T1DM cohort (n=1292)	**T1DM + CD serology–(n=1150)**	**T1DM and celiac disease Dx (n=47)**	**T1DM and potential celiac disease (serology+, but no celiac Dx to date) (n=95)**
Female gender, n (%)	568 (47.7 %)	486 (42.2 %)	28 (59.6 %)	54 (56.8 %)
White, n (%)	918 (71.1 %)	799 (69.4 %)	41 (91.5 %)	76 (80.0 %)
Hispanic or Latino, n (%)	83 (6.4 %)	74 (6.4 %)	3 (6.4 %)	6 (6.3 %)
Median age at T1DM diagnosis, years (range)	9.5 (0–18)	9.4 (0–18)	10.3 (3–16)	9.9 (1–17)
Diabetic ketoacidosis at T1DM diagnosis, n (%)	590 (45.7 %)	520 (45.2 %)	25 (53.1 %)	45 (47.4 %)
HbA_{1c}>13.5 % at diagnosis, n (%)	256 (19.8 %)	215 (18.7 %)	12 (24.4 %)	29 (30.5)
Celiac serology positivity at T1DM diagnosis, %	TTG IgA (10.6 %) Endomysial (7.2 %)	N/A	TTG IgA (100 %) Endomysial (85.1 %)	TTG IgA (96.8 %) Endomysial (55.8 %)

Table 2: Follow-up of potential celiac disease cases with endoscopy.

Cases	Age at T1DM Dx and screening, sex, race/ethnicity	Initial TTG IgA (times ULN)	Endomysial AB (titer)	Initial endoscopy results	Follow-up period
Subject ID #1	10 yo female (White, Not-Hispanic/Latino)	Positive (1× ULN)	Positive (1:20)	Normal	CD serologies never normalized; developed active CD × 1 year at repeat scope
Subject ID #2	5 yo male (White, Not-Hispanic/Latino)	Positive (1× ULN)	Positive (1:5)	Normal	CD serologies increased; EGD × 2 negative
Subject ID #3	6 yo female (White, Not-Hispanic/Latino)	Positive (2× ULN)	Positive (no titer)	Normal	TTG IgA seroconversion at 5 years (EMA normal at 4 years); EGD × 2 negative
Subject ID #4	9 yo female (White, Not-Hispanic/Latino)	Positive (2× ULN)	Positive (1:20)	Normal	CD serologies normalized in 4 months
Subject ID #5	9 yo male (White, Not-Hispanic/Latino)	Positive (1× ULN)	Negative	Normal	CD serologies normalized in 3 months
Subject ID #6	8 yo female (White, Not-Hispanic/Latino)	Positive (2× ULN)	Negative	Normal	CD serologies normalized in 5 months
Subject ID #7	12 yo female (Black, Hispanic/Latino)	Positive (3× ULN)	Negative	Normal	CD serologies downtrend, never normalized × 3 years
Subject ID #8	9 yo female (White, Not-Hispanic/Latino)	Positive (3× ULN)	Positive (1:80)	Normal	CD serologies never normalized × 4 years
Subject ID #9	12 yo Male (White, Not-Hispanic/Latino)	Positive (1× ULN)	Negative	Normal	CD serologies normalized × 5 years
Subject ID #10	8 yo female (White, Not-Hispanic/Latino)	Positive (7× ULN)	Negative	Normal duodenum, +Eosinophilic Esophagitis	CD serologies downtrend, never normalized × 2 years
Subject ID #11	11 yo female (White, Not-Hispanic/Latino)	Positive (3× ULN)	Negative	Normal	CD serologies increased, developed active CD × 2 years at repeat scope
Subject ID #12	17 yo Male (White, Not-Hispanic/Latino)	Positive (2× ULN)	Positive (1:80)	Normal	CD serologies normalized in 11 months, transiently positive thereafter

of 5× ULN to be optimal, with a corresponding sensitivity of 77.8 % and specificity of 79.8 % for CD diagnosis. PPV analysis of TTG IgA showed that ≥9X ULN is 100 % diagnostic of CD. Combining positive EMA with TTG IgA levels found a lower cutoff as ≥8× ULN showed 100 % predictive value with all 11 cases diagnosed with CD – 10 with histologic confirmation and one by serology only due to subject declining endoscopy.

We also compared the positive EMA titers and ROC to determine an ideal cutoff given its positive titer (≥1:5). From this curve, an optimal cutoff for EMA titer was determined to

TTG IgA Upper Limit of Normal`	Positive Predictive Value
1.00-1.99x	0.063
2.00-2.99x	0.167
3.00-3.99x	0.11
4.00-4.99x	0.375
5.00-5.99x	0.6
6.00-6.99x	0.44
7.00-7.99x	0.59
8.00-8.99x	0.667
9.00-9.99x	1
>10x	1

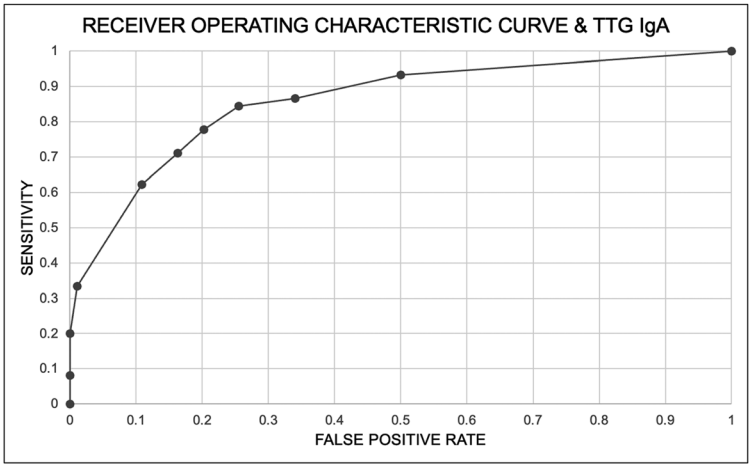

Figure 2: This Figure displays the positive predictive values for positive TTG IgA (at increments 1–10× ULN) in T1DM, alongside the receiver operating characteristics analysis of TTG IgA for predicting celiac disease. The curve demonstrates TTG 5× the ULN is the optimal cutoff value for anticipating celiac disease at T1DM diagnosis.

be 5× or 1:80, with a corresponding sensitivity of 85 % and specificity of 67.4 %. On comparison, the study population had no significant difference in demographics such as age (p=0.43), gender (p=0.96), or race (p=0.61) regardless of celiac positivity.

Gastrointestinal symptoms were found in less than half of patients with positive screen and subsequent CD diagnosis. No significant difference (p=0.79) in these manifestations was identified from serologies with similar proportions: 45 % in confirmed celiac (positive serology, positive histology) vs. 42.5 % in potential CD (positive serology, negative histology).

The incidence of low BMI at time of T1DM diagnosis (defined as less than the 5th percentile on Centers for Disease Control growth curves) demonstrated no statistically significant difference (p=0.98) between those with suspected CD and the rest of the cohort. Of the 1,226 subjects with available BMI values at T1DM diagnosis, group A had 9 of 47 (19.2 %) subjects with low BMI, group B had 11 of 95 (11.6 %) subjects with low BMI, and the overall cohort had 176 of 1,226 (14.4 %) of subjects with low BMI. Weight and height percentiles showed similar data trends.

Diabetic ketoacidosis (DKA) is defined by low pH (<7.30) and bicarbonate levels (<15 mmol/L) per the American Diabetes Association [17]. As seen in Table 1, DKA was present in 590 subjects or 45.7 % of the total study cohort. Of 70 subjects with a positive celiac screen in DKA, 53.3 % were confirmed to have CD vs. 47.4 % had a positive TTG IgA serology without subsequent CD. Subjects in DKA showed a higher predominance of positive (49.3 %) vs. negative (45.2 %) celiac serologies, which suggests association with the level of metabolic disturbance and susceptibility of coexisting autoimmune disease, although this was not statically significant (p=0.82).

Our study also observed a higher HbA_{1c} concentration in those subjects with positive TTG IgA. Furthermore, comparison of positive celiac serology vs. active CD diagnosis showed a rise in TTG IgA values as $HgbA_{1C}$ increased as depicted in Figure 3, but particularly so in those with active CD and $HgbA_{1c}$ levels>13.5 %.

Finally, coexisting thyroid conditions (e.g., autoimmune thyroiditis, chronic lymphocytic thyroiditis, hypothyroidism) were analyzed in the total cohort, as well as separately for groups A and B. Eight of 47 subjects (17.0 %) in group A had coexisting thyroid disease compared with 22 of 95 subjects (23.2 %) in group B. This difference was not statistically significant (p=0.5) (Figure 4).

Discussion

This is one of the first studies to evaluate both TTG IgA and EMA screening at the time of T1DM diagnosis and in North American cohort. Consistent with epidemiologic studies, a strong association between CD and T1DM was identified with 3.6 % (47/1,292) incidence of CD in our T1DM cohort, affirming the need for celiac screening [18]. Since demographics and age at diagnosis did not statistically modify the risk of celiac susceptibility in our cohort, CD screening at T1DM diagnosis appears to be both an appropriate and timely practice. This approach allows for earlier detection and management of coexisting autoimmune conditions, nutritional deficiencies, and long-term complications that can develop from persistent enteropathy.

Spontaneous normalization of celiac serology and fluctuating celiac serologies was also frequently identified

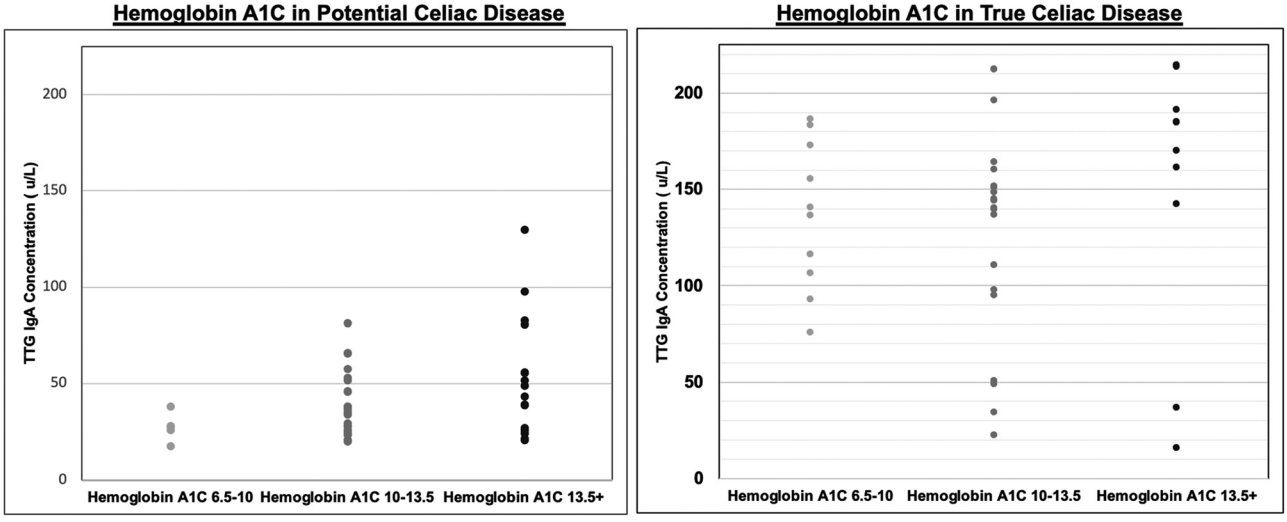

Figure 3: Association between TTG IgA levels and $HgbA_{1c}$ at T1DM diagnosis. Among those with TTG IgA seropositivity, scatter plots show a wider range of TTG IgA levels in those with true celiac disease. Furthermore, TTG IgA levels were generally higher, particularly in the highest $HgbA_{1c}$ group (13.5+).

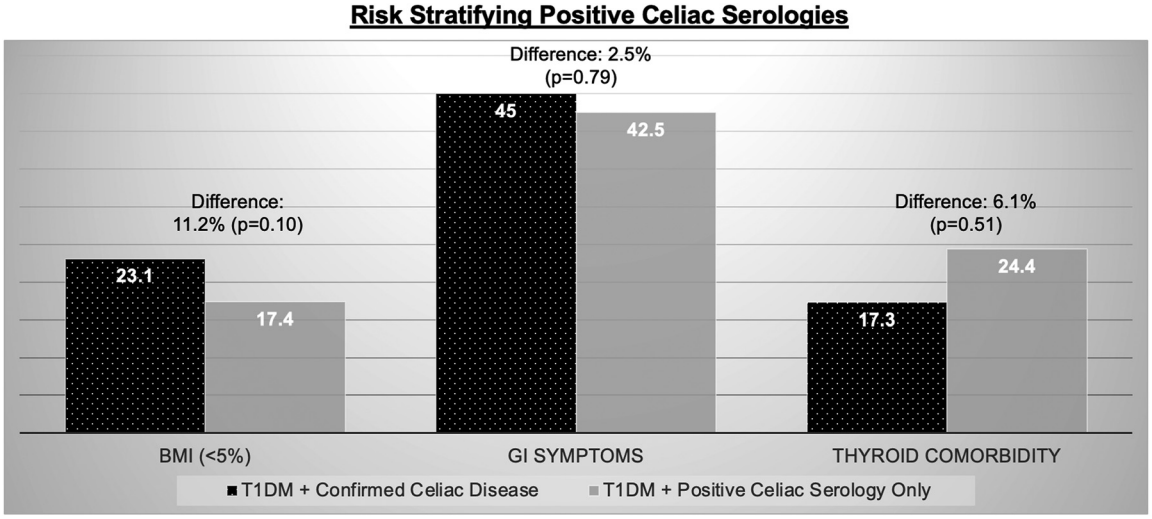

Figure 4: Comparing BMI, gastrointestinal symptoms, and thyroid conditions in those with positive serology (TTG-IgA, EMA) vs. true celiac disease at T1DM diagnosis. A trend toward low BMI was seen in those with celiac, although none of these variables were statistically significant to a risk stratification strategy on the likelihood of celiac disease.

in our cohort – a phenomenon not entirely understood but corroborated in previous European and Asian studies [19–21]. The reported accuracy of EMA was lower than established sensitivity and specificity, which have been historically studied in homogenous populations. It does lead to questions if a different set of normalized predictive values would apply to diverse racial and ethnic communities and those with coexisting autoimmune conditions. Nevertheless, crossing a threshold of TTG IgA (5× ULN) and EMA titers (4× or 1:40) increased our predictive value of active CD as the ROC complements the PPV analysis. This use of TTG IgA and EMA as predictors for CD needs to continue to be refined to guide diagnostic evaluation with other ongoing studies [16, 22].

This work also provides corroborative data on the potential of serology-based CD diagnosis using ESPGHAN guidelines with high TTG IgA positivity as well as positive EMA. This is particularly valuable given the limited data on serologic diagnosis in T1DM cohorts and new information to consider as NASPGHAN CD guidelines are revised. Although it is notable that one of the 11 subjects declined endoscopy, all other cases with a TTG IgA ≥8× ULN and positive EMA had biopsy confirmed CD.

This study validates previous reports that T1DM subjects who develop coexisting CD often present with silent or atypical manifestations, rather than overt GI symptoms [23]. Anthropometrics were of particular interest given the association of CD and T1DM with poor growth, weight loss, and failure to thrive, but anthropometric measures also failed to provide significant distinction in risk-stratification.

The observed association between TTG IgA and severity of metabolic disturbances in T1DM (based on $HgbA_{1C}$ levels or occurrence of DKA) needs to be further explored as does the practical discussion of managing two severe autoimmune conditions simultaneously while optimizing management of T1DM. In light of the known association between elevated HbA_{1c} and DKA, we could be observing an epiphenomenon based upon the assertion that celiac positivity begets a higher HbA_{1c}, which is in turn related to the occurrence of DKA or *vice versa*.

There are notable limitations to this study, including its retrospective nature, limited follow-up after CD screening, and variation in clinical practice patterns for referral to endoscopy. False negatives could also be present given that majority of subjects with positive CD serology did not have endoscopy performed. Lack of geographical and racial diversity is also a limitation that may impact generalizability, although its large sample size allows us to extrapolate the predictive value of two validated celiac serologic screening tools: TTG IgA and EMA. However, future iterations of a multicenter study would benefit from a more geographically and racially diverse diabetes population, potentially using different celiac lab assays and HLA-DQ genotyping as well to further refine a risk assessment strategy.

This longitudinal study demonstrates the utility of early screening for CD in the emergency room or inpatient setting for children with newly diagnosed T1DM. With minimal literature available on CD serologies at the onset of T1DM and variable practice recommendations, this study provides new data to formalize a screening pathway in the diabetes community using comprehensive celiac serologic screening

and develop a clinical algorithm for clinicians to make informed decisions with a positive serology and when to proceed with endoscopy for coexisting CD.

Research ethics: The local Institutional Review Board deemed the study exempt from review.
Informed consent: Not applicable.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission. Dr. Arunjot Singh and Lydia Ramharack conceptualized and designed the study, coordinated, and supervise data collection, drafted the initial manuscript, and reviewed as well as revised the manuscript. Dr. Colin Hawkes and Dr. Steven Willi conceptualized and designed the study, assisted with statistical analysis, and revised the manuscript as well as critically reviewed it for important intellectual content. Paige Coughlin coordinated data collection and analysis, drafted the initial manuscript, and reviewed as well as revised the manuscript. Lionola Juste conceptualized and designed the study, coordinated and supervised data collection, and reviewed and revised the manuscript. Dr. Sando Ojukwu coordinated and supervised data collection, and reviewed and revised the manuscript.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: It should be noted that Lionola Juste serves as a consultant for Fulcrum Therapeutics, although this had no effect in her work for this study. All other authors state no conflict of interest or financial disclosures.
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Data availability: Not applicable.

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