Original Article

Correlation of elevated transaminases and histological findings in children with celiac disease: a retrospective cross-sectional study

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Background: Celiac disease (CD) is a common chronic immune-mediated enteropathy, with 1% prevalence in North America. Initial screening for CD with serum tissue transglutaminase (tTG) immunoglobulin A (IgA) levels is the current recommendation by most consensus authorities, although, this value does not correlate with the extent of luminal or extra-luminal disease severity. Hypertransaminasemia is commonly reported in CD and despite this well recognized finding, the association and correlation of elevated transaminases with disease severity has not been determined. Our study aimed to determine whether elevated transaminases can be used as a surrogate marker to predict the severity of histologic disease in paediatric patients.

Methods: We performed a retrospective cross-sectional chart review of all children ages 6 months to 17 years referred for suspected CD to the Paediatric Gastroenterology and Hepatology Division at Children's Hospital, London Health Sciences Centre from June 1, 2008 to June 28, 2016. Age at diagnosis, transaminases measured within 6 months, CD histological confirmation, and no other causes of liver injury were included. A total of 347 children were identified, and 44 (mean age: 10.4 years) were included after the exclusion criteria was applied. Bivariate analysis was applied using Kruskal-Wallis and Chi-square tests for continuous and categorical variables, respectively. Logistic regression and Spearman correlations were also applied to the data to determine the strength of our hypothesized association.

Results: Our study demonstrated no statistical significance between any of the serum transaminase levels and histologic severity of disease. These corresponded to alanine aminotransferase (ALT) (P=0.503), aspartate aminotransferase (AST) (P=0.291), gamma-glutamyl transferase (GGT) (P=0.379) and alkaline phosphatase (ALP) (P=0.095). However, our results may suggest a trend toward more advanced disease or longer standing protein-losing enteropathy at presentation as shown by a lower IgG value (P=0.021). Our study also supported the correlation between histological disease severity and patients who experienced diarrhea as a presenting symptom (P=0.002).

Conclusions: Although elevated transaminases and CD is well recognized, our study did not show an association between histological disease severity and degree of elevated transaminases.

Keywords: Hypertransaminasemia; celiac disease (CD); elevated transaminases; disease severity

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Introduction

Background

Celiac disease (CD) is a common chronic immune-mediated enteropathy, with 1% prevalence in North America (1). It is caused by an autoimmune reaction to gliadin, which causes enterocyte injury and villous blunting in the small intestines (2). Those with symptomatic disease may present with diarrhea, fatigue, abdominal pain and nutritional deficiencies. In children, failure to thrive, short stature, lack of weight gain and/or weight loss can also be seen (2). CD has been associated with several autoimmune conditions such as thyroid disease and diabetes (2). Primary immune-mediated liver diseases have also been associated with CD, such as primary biliary cholangitis, primary sclerosing cholangitis and autoimmune hepatitis (AIH) (3).

Rationale and knowledge gap

Initial screening for CD with serum tissue transglutaminase (tTG) immunoglobulin A (IgA) levels is the current recommendation by most consensus authorities (4-6). Additionally, current international guidelines suggest that together with anti-tTG IgA antibodies, a total IgA serum level must also be measured to exclude an IgA deficiency that could cause a false-negative anti-tTG IgA result (7). Although having a positive tTG IgA level is both sensitive (99%) and specific (75%) for CD, the precise tTG IgA value does not correlate with the extent of luminal or extra-luminal disease severity according to the published literature (5). The gold standard for identifying disease severity is endoscopy with duodenal biopsy, which is both invasive and costly. Timely access to endoscopy also represents a challenge in readily confirming a CD diagnosis. If there is a delay in a child receiving an endoscopy, symptoms may persist causing discomfort for the child as guidelines recommend treatment only after a diagnosis has been confirmed (4). Treatment for CD involves a strict adherence to a gluten-free diet for life, and patients with CD who are still ingesting gluten for long periods of time may be at risk for many health concerns (2,4).

Early identification and treatment of children with CD is important. Those with CD are at increased risk of osteoporosis/osteopenia, infertility and impaired growth (2,8,9). Treatment with a gluten-free diet without histological confirmation is not ideal as histological diagnosis may not be reliable post treatment (10). The European Society of Pediatric Gastroenterology, Hepatology & Nutrition (ESPGHAN) 2012 guidelines have suggested that the need for endoscopy is not as strongly recommended in symptomatic patients with a tTG IgA level >10 times the upper limit of normal and confirmation of either human leukocyte antigen (HLA) DQ2 and/or DQ8 genetic haplotype consistent with CD (11). Similarly, the latest guidelines from the American College of Gastroenterology recommended a combination of high tTG IgA level >10 times the upper limit with a positive endomysial antibody (EMA) in a separate blood draw as a reliable test for diagnosis without a biopsy in paediatric patients (12). However, those who do not fulfill these criteria are often left undiagnosed, and thus unwell, while they wait confirmatory testing or start a gluten-free diet without confirmation of diagnosis. Therefore, other indicators of disease severity in those not meeting these criteria are needed in order to prescribe timely treatment. Determining other criteria that correlate with severity of CD that could be easily assessed by primary health care providers could assist in developing a triaging system of those who require more prompt endoscopic confirmation of their CD. Liver enzyme abnormalities may be a potential

Highlight box

Key findings

- There is no statistical significance between serum transaminase levels and histologic severity of celiac disease (CD) in paediatric subjects.
- Our results support the correlation between histological disease severity and patients who experienced diarrhea, as well as a trend toward more advanced disease or longer standing protein-losing enteropathy at presentation as shown by a lower IgG value.

What is known and what is new?

- Initial screening for CD includes serum tissue transglutaminase (tTG) immunoglobulin A (IgA) levels, although this value does not correlate with the extent of disease severity. Additionally, the most reported hepatic manifestation in CD is an isolated elevation in liver enzymes, which at this time, no study has demonstrated whether elevated liver enzymes are correlated with CD disease severity.
- We determined that there is no association between histological disease severity and degree of elevated liver enzymes.

What is the implication, and what should change now?

- Current work up for children suspected of CD should include serum liver transaminases, and future studies are needed to determine better predictors of histological severity.

surrogate marker of CD severity (5,6,10).

Objective

While the small bowel is primarily affected in this disease, CD is a systemic disorder that can be associated with diseases throughout the body such as in the liver, skin, pancreas, and bone (13). The most reported hepatic manifestation is an isolated elevation in liver enzymes referred to as hypertransaminasemia (10). The mechanisms underlying the elevation in enzymes is poorly understood, although the prevalence of hypertransaminasemia in patients with CD is frequent with a range of 32–59% reported in the literature (14). This discovery paired with the knowledge that current diagnostic tests are unable to predict the severity of disease, leads to the question of whether elevated transaminases may be a missing piece in CD diagnosis.

Furthermore, despite this well-recognized association between elevated transaminases and CD (5), the association and correlation of elevated transaminases with disease severity has not yet been determined (5,6). Our study aimed to determine whether elevated transaminases can be used as a surrogate predictive marker of the severity of histologic disease, potentially aiding in making a timely diagnosis and, when needed, expediting access to endoscopy. We present this article in accordance with the STROBE reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-22-58/rc).

Methods

Participants

We performed a retrospective cross-sectional chart review of all children ages 6 months to 17 years referred to the Paediatric Gastroenterology and Hepatology Division at Children's Hospital, London Health Sciences Centre from June 1, 2008 to June 28, 2016, which corresponds to the start of the online booking system at our institution. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Western University research ethics board of London Ontario (REB# 108211) and individual consent for this retrospective analysis was waived.

To explore the correlation between liver transaminases and CD histological severity our inclusion criteria were based on 4 different requirements; (I) age at diagnosis, (II) alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) measured within 6 months of diagnosis, (III) CD histologic confirmation, and (IV) no other identified causes of liver injury, specifically: sepsis, fatty liver disease, viral hepatitis, drug induced liver injury or primary liver disease. Patients with other causes of liver injury were excluded to limit potential confounders that can increase liver enzymes independently of CD.

Variables

Patient variables collected included age, sex, body mass index (BMI), symptoms and signs at presentation (abdominal pain, vomiting, diarrhea/loose stool, anemia, fatigue, poor weight gain/weight loss, poor growth velocity defined as <6 cm/year), serum serology [leukocytes, hemoglobin, thrombocytes, tTG-IgA, immunoglobulin G (IgG) level, baseline IgA level, iron, calcium, 25-OH vitamin D], liver enzymes (ALT, AST, ALP, GGT), associated diseases (thyroid disease, diabetes, IgA deficiency), and a family history of CD. Although anti-actin IgA antibody levels have been used as a serological marker of villous atrophy in a previous study (15), our institution does not currently check for anti-actin IgA antibodies for patients suspected of CD and therefore could not be included as a data variable. One investigator collected and assembled all the data for this study (MH).

Reference standard

Histologic assessment of CD severity was measured using the Marsh-Oberhuber criteria (16). This criterion assesses intraepithelial lymphocytosis (IEL) and the morphology of the intestinal villi and crypts to provide the "Marsh Type" (MT) of the specimen. Histologic sections were graded between MT 0 and 4 (0 meaning no histologic evidence of CD, and 4 as severe villous blunting with crypt hyperplasia and IEL) (10). All sections were graded into either 0, 1, 2, 3a, 3b, 3c or 4; with each increasing classification corresponding to an increase in crypt hyperplasia and atrophy of the villi. Patients were then stratified based on MT classification to determine which variables correlated with higher disease severity. In order to ensure consistent grading of biopsy results, a single gastrointestinal pathologist (JCW) graded all biopsies and confirmed there were no cases of giardia in any of the samples, which could have led to a false positive diagnosis of CD.

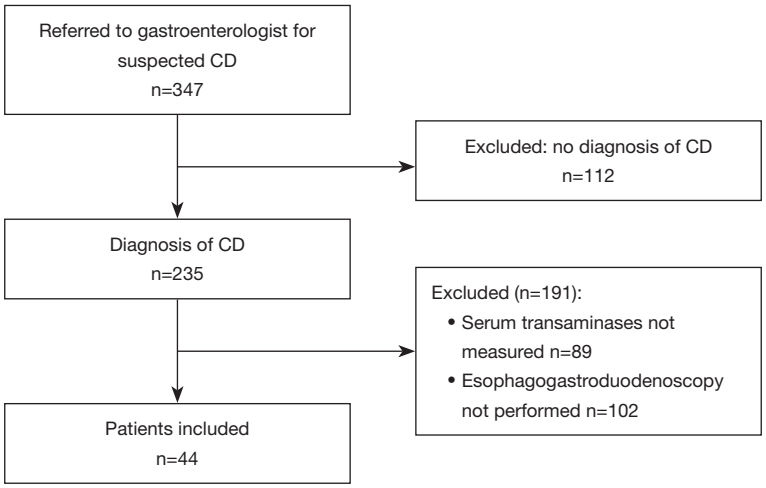

Figure 1 Flow diagram for study population selection. CD, celiac disease.

In the literature, normal ranges for ALT, AST and ALP are 11–35 U/L, 15–35 U/L and 180–1,200 for children, respectively (14). The normal range for GGT is reported as 3–25 U/L (14). These standards were used to classify whether the subjects had elevated levels of transaminases for this study.

Statistical analysis

Continuous variables were summarized using means and standard deviations (or medians and interquartile ranges for non-normal distributions), and comparisons were examined using Spearman correlations and Kruskal-Wallis tests. Categorical variables were summarized using frequencies and percentages, and comparisons were examined using Pearson chi-square tests. Multinomial logistic regression analyses were conducted to determine whether a degree of liver enzyme abnormality could predict more advanced histologic luminal disease. P values of <0.05 were considered statistically significant. All analyses were conducted in SPSS v.24 (IBM Corp., Armonk, NY, USA).

Results

The retrospective chart review identified 347 patients who had been referred for assessment of possible CD within the defined timeframe. Two hundred and thirty-five patients were diagnosed by a gastroenterologist with CD, of which 44 fit all inclusion criteria. Reasons for exclusion are shown in *Figure 1*.

Demographics

Demographics of patients included in the study are shown in *Table 1*. The most common gastrointestinal manifestations were abdominal pain (80%), diarrhea (48%), and weight loss/no weight gain (45%). Specific comorbidities included IgA deficiency (2%), type 1 diabetes (11%), and thyroid disease (9%). Eighteen percent of children had a first-degree relative with CD. Two of 44 patients (4.5%) were graded at MT 1, 2/44 (4.5%) at MT 2, 6/44 (14%) at MT 3a, 19/44 (43%) at MT 3b, and 15/44 (34%) at MT 3c. There were no cases of MT 4. At presentation, mean ALT, AST, GGT and ALP levels were normal at 21 (range, 10–49 U/L), 27.6 (range, 16–52 U/L), 12.1 (range, 5–29 U/L), and 178.5 (range, 56–399 U/L), respectively. Out of our sample of 44 patients, only 12 had at least one liver enzyme identified as elevated at presentation.

Bivariate analysis

We conducted a bivariate analysis between histologic grading of disease and other collected variables as shown in *Table 2*. Histologic disease severity did not significantly correlate with any of the liver enzyme levels; ALT (P=0.503), AST (P=0.291), GGT (P=0.379) or ALP (P=0.095). Interestingly, weight (P=0.050) and baseline IgG (P=0.030) and IgA levels (P=0.013) each showed a statistically significant association with MT severity. The only categorical variable with statistical significance to histologic severity was the presence of diarrhea (P=0.002).

Table 1 Baseline characteristics of patient population

Baseline variable measured	Value
N	44
Sex, n [%]	
Female	28 [64]
Male	16 [36]
Age (years), mean (range)	10.4 (1, 17)
BMI (kg/m^2), median (range)	17.95 (13.5, 25.8)
BMI Z-score, median (range)	−0.055 (−2.69, −1.98)
Clinical manifestations, n [%]	
Fatigue	17 [39]
Poor weight gain	20 [45]
Poor growth	11 [25]
Abdominal pain	35 [80]
Diarrhea	21 [48]
Anemia	2 [5]
Asymptomatic	5 [11]
Liver enzymes, median (range)	
ALT (U/L)	18 (10, 49)
AST (U/L)	25 (16, 52)
GGT (U/L)	12 (5, 29)
ALP (U/L)	165 (56, 399)
Associated disease, n [%]	
Thyroid disease	4 [9]
Type 1 diabetes	5 [11]
IgA deficiency	1 [2]
Family history of celiac disease	8 [18]
Duodenal histology Marsh-Oberhuber type, n [%]	
0	0 [0]
1	2 [4.5]
2	2 [4.5]
3a	6 [14]
3b	19 [43]
3c	15 [34]
4	0 [0]

N, number (patient population); BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; IgA, immunoglobulin A.

Spearman correlation

We ran a Spearman correlation between liver enzymes (ALT, AST, GGT and ALP) and Marsh-Oberhuber type (*Table 3*). There was a strong negative correlation (indicated by an r value between −0.4 to −0.6) between MT and ALP level, whereby lower ALP was strongly associated with severity of luminal disease (r=−0.43, P<0.05). There was also a very strong positive relationship (indicated by an r value between 0.61–0.8) between ALT and AST levels (r=0.71, P<0.01).

Multinominal logistic regression model

Based on the results of our bivariate analysis, we performed a separate multinomial logistic regression model (*Table 4*) for all statistically significant continuous variables at P<0.05 (tTG IgA, baseline IgG and IgA levels and weight). The overall model for tTG IgA highlighted that children with MT 3b were likely to have a lower tTG IgA than those with an MT score of 3c [odds ratio (OR) =0.99; 95% confidence interval (CI): 0.98–1.00; P=0.020]. When comparing MT groups and baseline IgG levels at presentation, we found that MT 3b had a higher IgG level than MT 3c (OR =1.63; 95% CI: 1.08–2.48, P=0.021). In fact, in 30/44 (68%) patients the IgG level ranges from 2.6 to 21.7 g/L. Of note, this multinomial logistic regression was performed with MT 3a, 3b and 3c only. Out of the included 44 patients, only 4 had a grading of either MT 1 or 2. After removing these 4 patients, there was a significant association between MT grading and tTG-IgA level as shown in *Table 4*. When including all gradings of MT separately (1, 2, 3a, 3b, and 3c) there was no statistically significant association with tTG IgA (not shown).

Discussion

Key findings

To our knowledge, the present study is the first to assess the potential correlation between histological severity of CD and elevation of serum transaminases, in addition to investigating other possible variables associated with disease severity. In children with CD, hypertransaminasemia is a phenomenon that is well recognized with an incidence of 36% (8). Furthermore, 4–9% of paediatric patients with isolated elevated liver enzymes are found to have asymptomatic CD (9,17). Treatment of CD has been shown to reverse the hypertransaminasemia in most patients (18),

Table 2 Factors associated with histological disease severity by Marsh-Oberhuber type

Variable	Marsh-Oberhuber type				P value
	1&2 (n=4)	3a (n=6)	3b (n=19)	3c (n=15)	
Age at diagnosis (years), median (IQR)	10.5 (5.8, 13.8)	13.5 (3.5, 15.5)	13.0 (6.0, 15.0)	7.0 (4.0, 14.0)	0.387
Female sex, n [%]	3 [75]	4 [67]	11 [58]	10 [67]	0.931
Weight (kg), median (IQR)	42.1 (27.4, 61.0)	54.6 (13.0, 57.7)	51.1 (25.7, 54.4)	22.6 (15.1, 43.3)	0.050*
BMI (kg/m^2), median (IQR)	18.9 (18.0, 20.7)	19.7 (14.8, 21.2)	18.0 (15.0, 20.6)	16.3 (14.7, 18.3)	0.273
BMI Z-score, median (IQR)	1.1 (0.3, 1.7)	–0.2 (–1.3, 0.6)	–0.1 (–1.5, 0.7)	–0.6 (–1.1, 0.2)	0.173
Leukocytes (10^9/L), median (IQR)	5.5 (3.7, 9.4)	5.7 (4.1, 9.5)	6.2 (5.0, 7.9)	6.7 (5.7, 9.5)	0.712
Hemoglobin (g/L), median (IQR)	128.5 (121.0, 136.0)	137.5 (118.3, 145.8)	132.5 (124.8, 139.2)	128.0 (123.0, 139.0)	0.700
Thrombocytes (10^9/L), median (IQR)	238.0 (179.0, 324.0)	289.5 (231.0, 339.0)	271.5 (243.5, 329.8)	285.0 (251.0, 369.0)	0.619
tTG-IgA (RU/mL), median (IQR)	146.2 (24.6, 200.0)	196.6 (99.2, 200.0)	90.8 (44.0, 200.0)	200.0 (186.4, 200.0)	0.103
IgG (g/L), median (IQR)	9.0 (n/a)	6.8 (5.2, 10.7)	10.3 (9.2, 13.8)	6.4 (4.4, 9.6)	0.030*
IgA (g/L), median (IQR)	1.0 (n/a)	0.7 (0.5, 0.7)	1.5 (0.9, 2.4)	1.3 (0.9, 1.8)	0.013*
Iron (µmol/L), median (IQR)	24.2 (n/a)	–	20.6 (n/a)	10.0 (8.0, 20.5)	0.119
Calcium (mmol/L), median (IQR)	2.4 (n/a)	–	2.3 (n/a)	2.2 (2.1, 2.5)	0.543
25-OH vitamin D (nmol/L), median (IQR)	53.0 (n/a)	108.0 (n/a)	89.0 (67.3, 119.0)	57.5 (n/a)	0.399
Albumin (g/L), median (IQR)	46.0 (46.0, 46.8)	48.0 (44.5, 50.5)	45.0 (43.0, 48.0)	43.5 (37.0, 48.0)	0.248
ALT (U/L), median (IQR)	17.5 (11.5, 19.8)	20.0 (13.8, 33.5)	15.5 (13.0, 27.5)	23.0 (16.8, 26.5)	0.503
AST (U/L), median (IQR)	26.0 (19.5, 34.0)	34.5 (19.8, 40.5)	25.0 (17.5, 26.0)	24.5 (21.5, 39.8)	0.291
GGT (U/L), median (IQR)	11.5 (9.5, 14.3)	12.0 (n/a)	13.0 (8.5, 26.0)	9.5 (5.0, 12.0)	0.379
ALP (U/L), median (IQR)	305.0 (143.3, 391.8)	183.0 (81.0, 246.0)	190.0 (139.0, 245.5)	127.0 (103.5, 176.8)	0.095
Fatigue, n [%]	1 [25]	1 [17]	7 [37]	8 [53]	0.458
Poor weight gain, n [%]	1 [25]	3 [50]	8 [42]	8 [53]	0.807
Poor growth, n [%]	1 [25]	2 [33]	4 [21]	4 [27]	0.950
Abdominal pain, n [%]	3 [75]	5 [83]	14 [74]	13 [87]	0.858
Diarrhea, n [%]	0 [0]	6 [100]	6 [32]	9 [60]	0.002*
Anemia, n [%]	0 [0]	1 [17]	0 [0]	1 [7]	0.397
Asymptomatic, n [%]	1 [25]	0 [0]	2 [11]	2 [13]	0.764

*, statistically significant finding with a P value set at P<0.05. IQR, interquartile range; BMI, body mass index; tTG-IgA, tissue transglutaminase immunoglobulin A; IgG, immunoglobulin G; n/a, not applicable; IgA, immunoglobulin A; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

with one study documenting normalization of transaminase levels in 63–90% of patients after a year of treatment (gluten avoidance) (5) and other studies highlighting a small proportion of patients going on to develop an overlap with AIH (18-20).

The reported incidence of hypertransaminasemia ranges from 32–59% of patients with a diagnosis of CD in the literature (17). This represents a much higher percentage than that seen within our included patient cohort. This might be attributed to the small number of patients within our study sample who had liver enzymes measured in their initial work-up, which gave us an incomplete sample to draw conclusions from as shown in *Figure 1*. It is also likely a contributing factor to the reason our study

Table 3 Spearman's rho correlations

Variable	ALT	AST	GGT	ALP
Marsh-Oberhuber type	0.18	0.05	–0.31	–0.43*
ALT	–	0.71**	–0.22	0.12
AST	–	–	–0.20	0.02
GGT	–	–	–	0.36

Asterisks highlight the strength of correlation. *, moderate correlation (0.4–0.6); **, strong correlation (0.61–0.8). ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase.

Table 4 Summary of the multinominal logistic regression analyses with Marsh-Oberhuber type 3a, 3b, or 3c as the outcome

Predictor	Marsh type 3c reference	OR	95% CI	P value
Weight	3a	1.05	0.99, 1.12	0.082
Weight	3b	1.05	1.01, 1.10	0.024*
tTG-IgA	3a	1.00	0.98, 1.01	0.633
tTG-IgA	3b	0.99	0.98, 1.00	0.020*
IgG	3a	1.16	0.78, 1.71	0.463
IgG	3b	1.63	1.08, 2.48	0.021*
IgA	3a	0.00	0.00, 2.34	0.072
IgA	3b	1.40	0.48, 4.07	0.541

The overall model test for each analysis had P<0.05. *, statistically significant finding. OR, odds ratio; CI, confidence interval; tTG-IgA, tissue transglutaminase immunoglobulin A; IgG, immunoglobulin G; IgA, immunoglobulin A.

did not demonstrate statistical significance between the different MT groups and liver enzyme abnormalities at presentation. Common practice between 2008–2016 at our institution did not include measuring liver enzymes for patients suspected of CD, and as such has encouraged a practice change moving forward. Although this data is missing from this study, the resulting realization has now provided a change in the work-up for these patients and will be used in further studies exploring this relationship. Despite this, our results may suggest a trend toward more advanced disease or longer standing protein-losing enteropathy at presentation as shown by a mildly lower albumin level and a lower IgG value (P=0.030, shown in *Table 2*) as the MT score increases.

Our study supported the correlation between histological disease severity and patients who experienced diarrhea. These patients also presented with a lower baseline IgG level (P=0.021), when compared to those with less severe MT scores as shown in *Table 4*. This would also support the association seen in our Spearman correlation (*Table 3*) where a lower ALP was more strongly associated with severity of luminal disease. Rather than being a surrogate marker of biliary involvement, ALP is likely a marker of bone health in this patient population (21). ALP is recognized as a marker of bone formation, with lower serum total ALP indicative of less bone formation and osteoblast activity (22). Many studies have found reduced bone mineralization in children with CD at diagnosis which resolves completely when treated with a gluten free diet (23,24). This supports our finding that lower ALP was more strongly associated with severity of luminal disease. CD causes a wide variety of consequences such as maldigestion and malabsorption which can result in features of malnutrition; such as reduced calcium and vitamin D absorption (25). It makes sense that with more luminal disease and less absorption that markers such as ALP will be reduced with this population. Although we did not find a significant association for all liver enzymes and disease severity, it is of note that markers of bone health such as ALP may be used to assess the severity of disease in future studies.

Additionally, we found that MT 3b had a higher IgG level than MT 3c; (OR =1.63; 95% CI: 1.08–2.48; P=0.021)

and 68% of patients in this study presented with IgG levels ranging from 2.6 to 21.7 g/L, suggesting a more autoimmune prone milieu in those patients. This is inferred from the diagnostic criteria for AIH which includes an IgG level >1.10 times the normal limit (26).

Strengths and limitations

Both the retrospective nature, the size of the patient population, and the missing information due to variation in investigative practice at time of diagnosis amongst the clinician group limited our ability to compare certain variables of interest to histological severity. As this is a retrospective study, the authors discovered that investigative practices in the past did not routinely check for transaminase values when patients were suspected of CD, and as such current practice has changed to include measuring all liver enzymes at presentation for all patients moving forward. Additionally, it may be of value to screen patients suspected of CD with elevated liver enzymes for autoimmune liver disease as well.

Increasing the sample size to include patients with a working diagnosis of CD without histological confirmation would risk including falsely diagnosed patients. Furthermore, the authors also investigated the liver enzyme profiles of those subjects that were excluded for a reason of "no CD" diagnosis and revealed a limited number of patients having enzyme levels recorded either by the referring health care provider or consultant at time of presentation. As such, in order to avoid introducing further selection bias it is difficult to comment on how our particular population of patients would compare to previous studies if all liver enzymes had been measured at time of presentation for a child referred for confirming a diagnosis of CD.

For future studies, a prospective design would allow for a more comprehensive data collection at the time of diagnosis. Although, this is the only study to date that the authors are aware of that investigated the potential correlation between serum transaminase levels and histological severity of disease in CD, adding to current knowledge on the diagnosis of the disease. Our hope is that these findings will contribute to further investigations on histological disease severity markers, as well as current practice guidelines.

Comparison with similar research and explanation of findings

Hypertransaminasemia and disease onset

There are many studies that have tried to explain the association between hypertransaminasemia and CD onset. Hypertransaminasemia is reported as an early manifestation of CD throughout the literature (21,27-30). One study that reported a paediatric hypertransaminasemia incidence rate of 32% suggested that rather than being a consequence of CD specifically, elevated transaminases may be involved in highlighting the start of the disease development (17). Farre *et al.* also discovered that in some paediatric patients, elevated transaminases were the only manifestation of CD, and higher frequencies of hypertransaminasemia were found in younger subjects. In support of this idea, an additional study reported a case where the sole manifestation of silent CD was hypertransaminasemia of unknown origin (31). It is possible that elevated transaminases could be an early indicator of disease that fades with progression of disease, thus explaining why there is no strong correlation with disease severity, and is found in differing percentages of patients in various studies.

Some literature has postulated that chronic liver damage leading to elevated liver enzymes is probably minimal or extremely slow in its development in patients with CD (32-34). It may be possible that patients with longstanding undiagnosed CD present with elevated transaminases and those with early detection of the disease do not. Although opposing the prior theories, this idea also points to the disease progression as the main influencer of liver enzyme levels. Similar to other studies, our study could not highlight symptom duration prior to diagnosis or disease onset, an especially hard task for asymptomatic patients. Overall, the manifestation of elevated liver enzymes in CD remains controversial in terms of either having a greater role at disease onset or being slowly developed over time with longstanding disease. Future studies could track the progression of liver enzyme involvement over the course of the disease, as well as disease onset, to determine if timing of diagnosis is the key to understanding liver involvement in CD.

Intestinal permeability and its role in liver enzyme elevation

There are many theories in the literature for why elevated

liver enzymes are seen in patients with CD. Another highly reported reason for this manifestation is the increased permeability of the intestines that occurs in autoimmune diseases (17,21,28,35,36). This permeability causes more toxins to enter the liver and, thus, cause injury and elevated liver enzymes (17,21,27). Previous research has reported that patients with CD and hypertransaminasemia show significant increases in permeability of the intestines compared to those individuals who present with normal liver tests (33). Since our study was unable to demonstrate a relationship between elevated transaminases and disease severity in CD, it may be due to the lack of patients in our cohort who would be classified as having more severe disease (MT4); therefore, we were unable to successfully stratify our patients in the way that we had hoped for in our study design. It seems that although intestinal damage and hypertransaminasemia are common in CD, no definitive relationship between the degree of each can be drawn currently. In order to determine if this explanation is plausible, future studies are needed to investigate the degree of permeability between individuals with CD and whether that degree of permeability correlates with elevated transaminases.

Implications and actions needed

Diagnosis and treatment of CD, even in asymptomatic patients, is vital since those with undiagnosed CD have a four-fold increase in all-cause mortality compared to those with known CD (37). Early predictors of CD severity, such as lower weight and diarrhea identified in our study, are imperative, as early treatment of CD is important in both symptom management and prevention of complications.

Future studies are encouraged to look prospectively for a more comprehensive collection of data to discover additional less invasive diagnostic methods to determine disease severity. Researchers may also look at collecting anti-actin IgA antibodies as part of the work up for patients suspected of CD as a recommendation for future routine practice.

Conclusions

Although elevated transaminases in CD is well recognized, our study did not show an association between histological disease severity and degree of elevated transaminases. Based on our findings, we are limited in drawing a firm conclusion as to the potential association between CD histologic severity and the degree of liver enzyme elevation. There is a noted trend towards more severe liver enzyme abnormalities that correlate with more severe disease when observing ALP values specifically. However, this observation will require validation with prospective database collection to ensure more complete data and establish the strength of this association before proposing the need to prioritize endoscopic confirmation over other patients with the same diagnostic question. Based on this, current work-up for children suspected of CD presenting with abdominal pain and loose stools should still include testing for a full set of liver enzymes (ALT, AST, GGT and ALP), but elevated values may not be indicative of CD severity and would still require further investigation to rule out primary liver disease. Further, larger prospective studies are needed to assess whether weight and baseline IgG levels correlate with MT scores as better predictors of histological severity and whether these factors should potentially prompt sooner endoscopic assessment and treatment with a gluten-free diet.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

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