Elevated liver enzymes of newly-diagnosed pediatric celiac patients- a prospective-observational study

Asaf Regev (assafre84@gmail.com)
Tel Aviv Sourasky Medical Center https://orcid.org/0000-0001-5383-3223

Amir Ben-Tov
Tel Aviv Sourasky Medical Center

Anat Yerushalmy - Feler
Tel Aviv Sourasky Medical Center

Yael Weintraub
Tel Aviv Sourasky Medical Center

Hadar Moran Lev
Tel Aviv Sourasky Medical Center

Shlomi Cohen
Tel Aviv Sourasky Medical Center

Achiya Amir
Tel Aviv Sourasky Medical Center

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Abstract

Objectives

Celiac disease clinical presentation is constantly changing. We set to determine the prevalence of elevated transaminases in newly diagnosed celiac patients, and to evaluate this sub-group of patients for associated clinical and laboratory findings and assess their natural course of disease following therapeutic diet initiation.

Methods

We conducted a prospective-observational study of all newly-diagnosed pediatric celiac patients, between August 2016 – April 2018, in a pediatric gastroenterology clinic. Clinical data, anthropometrics and blood test results were recorded at diagnosis and at three, six and twelve months of follow-up. We compared patients with normal and elevated transaminases at diagnosis. ALT threshold was set at 24 U/l.

Results

Of 125 newly-diagnosed celiac patients, 31 (24.8%) had elevated ALT at diagnosis; two (1.6%) with over 3xULN. Patients with elevated ALT at diagnosis were significantly younger (mean age 5.5 (SD- 3.4) vs 7.3 (SD- 3.7) years, $p < 0.01$) and more commonly presented with diarrhea (32.3% vs. 14.9%, $p = 0.03$). 80% of patients with elevated ALT levels, normalized their ALT within 3 months and all within one year. Following gluten free diet initiation, patients with elevated ALT had similar clinical course, growth, serology normalization rate, and laboratory results, compared to patients with normal ALT over a one year follow up. A single patient was simultaneously co-diagnosed with celiac disease and auto-immune hepatitis.

Conclusions

Clinically significant ALT abnormalities are rare among newly diagnosed pediatric celiac patients. Significant elevations failing to normalize on gluten free diet, should raise concern of a concomitant primary liver disease and warrant further investigations.

Introduction

Celiac disease (CD) is an autoimmune disorder, affecting mainly the intestinal mucosa. Inflammation is mediated by auto-antibodies, generated in genetically susceptible individuals, following intestinal exposure to gluten or related proteins abundant in one of the three main cereals used by man: wheat, barley and rye (1). The disorder is common with a prevalence of up to 1 percent in the general population (2–4). CD classical presentation of severe and prolonged diarrhea, weight loss, wasting and abdominal distention is rare nowadays (5). More commonly, celiac patients present with non-specific abdominal symptoms, extra intestinal manifestations and occasionally patients are asymptomatic altogether and are diagnosed following screening (6). Extra-intestinal manifestations may include malabsorption and related disorders, impaired growth and weight gain, fatigue, skin rash and liver involvement (7).

Data regarding the nature of celiac-associated elevated liver enzymes (ELE) in children, occasionally referred to as hypertransaminasemia, is limited. Past studies, using different thresholds of normal alanine-aminotransferase (ALT) levels, reported prevalence ranging between 4 to 40% among newly diagnosed celiac patients. Clinical features, including higher Marsh scores, presence of malabsorption and lower hemoglobin levels, were described in association with ELE; however, without consistency (8–15). Furthermore, little is known about the natural clinical course of patients with ELE at diagnosis. Finally, the clinical significance of ELE in newly diagnosed celiac patients is controversial, specifically, weather liver involvement may advance, independent of gluten exposure, to chronic hepatitis with resultant chronic liver disease complications (16).

In this prospective-observational study, we followed a cohort of newly diagnosed CD patients for one year. We describe the prevalence of ELE, clinical associations and the natural course during the follow-up period; upper-normal transaminase levels were set, as now commonly accepted, according to the thresholds found in the NHANE survey (17, 18). Finally, we review past results in the literature, and discuss comparison to our present findings.

Methods

We conducted a prospective-observational study of children (< 18 years) diagnosed with CD at the Pediatric Gastroenterology Clinic of the Tel Aviv Medical Center, between August 2016 – April 2018. Patients were thereafter followed for one year. Celiac diagnosis was based on the North-American and European Societies for Gastroenterology, Hepatology and Nutrition (ESPGHAN 2012, NASPGHAN 2016) guidelines (19, 20). In short, diagnosis was based on positive anti-tissue transglutaminase (aTTG) serology and histology compatible with CD (Marsh ≥ 2); or alternatively, on suggestive symptoms, highly elevated (> 10xUpper limit of normal (ULN)) aTTG serology, positive anti-endomysial antibody, and clinical improvement following gluten-free diet (GFD) initiation. We collected data including patient demographics, personal and family medical history, anthropometrics, clinical data and blood test results prior to the diagnosis, and at three, six and twelve months of follow-up. We excluded patients diagnosed elsewhere, patients with unavailable pre-diagnostic ALT levels, uncertain CD diagnosis and patients with a second intestinal or a known primary liver disease.

Weight, height and body mass index (BMI) were recorded as percentiles for sex and age according to the Centers of Disease Control and Prevention (CDC) growth charts https://www.cdc.gov/growthcharts/clinical_charts.htm). ULN of ALT was based on the findings of the third American National Health and Nutrition Examination Survey (NHANES) 1999–2006 (17, 18); i.e. male/female average of 24 U/l. ULN of aspartate-aminotransferase (AST)- 40 U/l and gamma-glutamyl-transpeptidase (GGT)- 28 U/l, were based on local laboratory thresholds. aTTG was categorized as normal, elevated and highly-elevated (> 10xULN).

Categorical variables were reported as number and percentage. Continuous variables were evaluated for normal distribution using histogram and Q-Q plot. Normally distributed continuous variables were

reported as mean and standard deviation (SD), and skewed variables were reported as median and interquartile range (IQR). Categorical variables were compared between patients with and without elevated ALT using Chi-square test or Fisher's exact test, and continuous variables were compared using independent sample T-test or Mann Whitney test. Generalized estimating equations (GEE) models were applied for repeated measure analysis. GEE models included age, sex, ALT level at presentation and time. In further analysis we also included the interaction between ALT level at presentation and time. All statistical tests were two sided and $p < 0.05$ was considered as statistically significant. SPSS software was used for all statistical analyses (IBM SPSS Statistics for Windows, Ver. 26; IBM Corp., Armonk, NY, USA, 2019). The study was reviewed and approved by the institutional ethics committee.

Results

Study cohort

During the study period we identified in our clinic 389 patients with a new diagnosis of CD; 125 patients, 73 (57.6%) females, had a biochemical profile including liver enzymes at diagnosis, constituting the main cohort. Mean age at diagnosis was 6.8 (SD − 3.7) years ranging between 1.6–17.4 years. Seven patients (5.6%) had prior medical history of other autoimmune (AI) disorders and four (3.2%) had immune deficiencies (three (2.4%) with IgA deficiency, one (0.8%) with common variable immune deficiency). Family history of AI/inflammatory disorders was recorded in 38 (30.4%) patients, including 27 (21.6%) with family history of CD and five (4%) patients with family history of inflammatory bowel disease (Table 1).

Table 1
Characteristics of 125 patients with celiac disease at presentation

Gender	
Male, n (%)	52 (41.6)
Age(years), mean (SD)	6.8 (3.7)
Additional AI / immune deficiency, n (%)	10 (8)
Family history of AI/Inflammatory disorders, n (%)	38 (30.4)
Family history of celiac disease	27 (21.6)
Signs and symptoms	
Abdominal, n (%)	73 (58.4)
Abdominal pain, n (%)	53 (42.4)
Diarrhea, n (%)	24 (19.2)
Nausea, n (%)	5 (4.0)
Vomiting, n (%)	3 (2.4)
Bloating, n (%)	7 (5.6)
Constitutional symptoms	46 (36.8)
Growth, n (%)	36 (28.8)
Fatigue, n (%)	7 (5.7)
Decreased appetite, n (%)	6 (4.8)
Abnormal laboratory	21 (15.9)
Anemia, n (%)	16 (12.8)
Elevated liver enzymes, n (%)	5 (4.1)
Family screen, n (%)	9 (7.2)
Incidental, n (%)	7(5.6)
Anthropometrics	
Weight percentile, median (IQR)	35(9–64)

AI- autoimmune; SD- standard deviation; IQR- interquartile range; BMI- body mass index; IU- international unit; ALT- alanine aminotransferase; AST- aspartate aminotransferase; GGT- gamma-glutamyl transpeptidase; ALP- alkaline-phosphatase; ULN- upper limit of normal; aTTG- anti-tissue transglutaminase. *Patients with normal aTTG were IgA deficient and were diagnosed using anti-deamidated gliadin protein (aDGP) IgG antibodies.

Gender	
Height percentile, median (IQR)	48(10–80)
BMI percentile, median (IQR)	40(13–77)
Laboratory data	
Hemoglobin (g/dL), mean (SD)	12.3 (1.3)
MCV, mean (SD)	78.3 (6.4)
ALT (IU), median (IQR)	20(15–24)
AST (IU), median (IQR)	33(28–39)
GGT (IU), median (IQR)	11(9–14)
ALP (IU), median (IQR)	229(181–276)
Total Bilirubin, median (IQR)	0.4(0.3–0.5)
Albumin (mg/dL), mean (SD)	4.5 (0.3)
aTTG High-Positive (> 10*ULN), n(%) Positive(> 1–10*ULN), n(%) Normal*, n(%)	 **89 (71.2)** 33 (26.4) 3 (2.4)
Histopathology	
Marsh 2/3 in 2nd part of duodenum, n (%)	106 (87.6)
Marsh 2/3 in duodenal bulb, n(%)	117 (96.7)

AI- autoimmune; SD- standard deviation; IQR- interquartile range; BMI- body mass index; IU- international unit; ALT- alanine aminotransferase; AST- aspartate aminotransferase; GGT- gamma-glutamyl transpeptidase; ALP- alkaline-phosphatase; ULN- upper limit of normal; aTTG- anti-tissue transglutaminase. *Patients with normal aTTG were IgA deficient and were diagnosed using anti-deamidated gliadin protein (aDGP) IgG antibodies.

Abdominal related symptoms dominated the clinical presentation and were found in 73 (58.4%) patients, including abdominal pain in 53 (42.4%) and diarrhea in 24 (19.2%). Sixteen (12.8%) patients were asymptomatic and were diagnosed following family screening or incidentally. None of the patients presented with isolated ELE without additional symptoms. At diagnosis, patients had a median weight, height and BMI percentiles of 35 (IQR 9–64), 48 (IQR 10–80) and 40 (IQR 13–77) for age and sex, respectively (Table 1).

aTTG serology, at diagnosis, was high-positive (> 10 x ULN) in 89 (71.2%) and positive (1–10 X ULN) in 33 (26.4%) patients. Three patients (2.4%) with IgA deficiency had positive serology for anti-deamidated

gliadin protein (aDGP) IgG antibodies. 122 (97.6%) patients were diagnosed endoscopically; the remaining three (2.4%) were diagnosed following typical clinical presentation and high-positive serology. A positive Marsh 2/3 histology, was found in 106 (86.9%) biopsies taken from the 2nd part of the duodenum, and in 117 (96.7%) of duodenal bulbs (Table 1).

Liver enzymes

Thirty-six (28.8%) children had elevated liver enzymes: 31 (24.8%) with elevated ALT levels (> 24 U/l), of whom two had significant elevation of > 3xULN; 19 (22.1%) with elevated AST, and one with elevated GGT (Table 2). Children with elevated ALT at presentation were significantly younger (mean age 5.5 (SD- 3.4) years vs 7.3 (SD- 3.7) years, $p < 0.01$), more commonly presented with diarrhea (32.3% vs. 14.9%, $p = 0.03$) and had higher AST values (41 vs. 33 U/l, $p < 0.01$) at diagnosis. The 19 patients with elevated AST levels were all within 1-2xULN range. Similarly, also the children with elevated AST (> 40 U/l) at diagnosis were younger (mean ages- 4.0 vs. 7.4 years, $p < 0.01$), had diarrhea more often (44.4% vs. 15.9%, $p = 0.02$) and had higher ALT levels (means 32.8 vs. 20.9 U/l, $p < 0.01$). No additional associations between elevated liver enzymes and other clinical and laboratory parameters were found (Table 3). A single patient with elevated GGT level at diagnosis, was in the range of 1-2xULN, and normalized the GGT in the following blood test; no other patients had cholestatic-enzymes abnormalities.

Table 2
Liver enzymes of 125 children with celiac disease at diagnosis

	ALT (n = 125)	AST (n = 86)	GGT (n = 30)
Median (IU)	20	33	11
IQR (IU)	15–24	28–39	9–14
Patients with LE > 1xULN, n(%)	31 (24.8%)	19 (22.1%)	1 (3.3%)
Patients with LE > 2xULN, n(%)	5 (4%)	0	1 (3.3%)
Patients with LE > 3xULN, n(%)	2 (1.6%)	0	0

IU- international units; LE- liver enzymes; ULN- upper limit of normal; ALT- alanine aminotransferase, ULN- 24IU; AST- aspartate aminotransferase, ULN- 40IU; GGT- gamma-glutamyl transpeptidase, ULN- 28IU.

Table 3
Celiac patients with and without elevated ALT or AST at diagnosis.

	Patients ALT > 24 IU (n = 30)	**Patients with normal ALT (n = 95)**	**P**	**Patients AST > 40 IU (n = 19)**	**Patients with normal AST (n = 68)**	**P**
Female gender, n (%)	18 (58.1)	55 (58.5)	0.97	10 (55.6%)	27 (39.1%)	0.29
Other AI / immune deficiency, n (%)	4 (12.9)	6 (6.4)	0.25	2 (11.1%)	7 (10.1%)	1
Family history:	10 (32.3)	28 (29.8)	0.8	4 (22.2%)	15 (21.7%)	0.57
-AI/Inflammatory disorders, n (%)	8 (25.8)	19 (20.2)	0.51	2 (11.1%)	3 (16.7%)	0.75
-celiac disease, n (%)						
Age (years), mean (SD)	**5.6 (3.4)**	**7.3 (3.7)**	**< 0.01**	**4.1 (2.5)**	**7.0 (3.2)**	**0.01**

AI- autoimmune; SD- standard deviation; IQR- interquartile range; Wt- weight; Ht- height; BMI- body mass index; IU- international units; ALT- alanine-aminotransferase, AST- aspartate-aminotransferase; GGT- gamma-glutamyl transpeptidase; ULN- upper limit of normal; aTTG- anti-tissue transglutaminase.

	Patients ALT > 24 IU (n = 30)	Patients with normal ALT (n = 95)	P	Patients AST > 40 IU (n = 19)	Patients with normal AST (n = 68)	P
Presentation:	19 (61.3)	54 (57.4)	0.70	12 (66.7%)	39 (56.5%)	0.59
Abdominal symptoms, n (%)	11 (35.5)	42 (44.7)	0.37	4 (22.2%)	31 (44.9%)	0.1
-abdominal pain, n (%)	**10 (32.3)**	**14 (14.9)**	**0.03**	**8 (44.4%)**	**11 (15.9%)**	**0.02**
-diarrhea, n (%)	0	5 (5.3)	0.49	0	5 (7.2%)	0.58
-nausea, n (%)	1 (3.2)	2 (2.1)	0.73	1 (5.6%)	2 (2.9%)	0.51
-vomiting, n (%)	2 (6.5)	5 (5.3)	0.81	1 (5.6%)	4 (5.8%)	1
-bloating, n (%)	12 (38.7)	34 (36.2)	0.23	6 (33.3%)	25 (36.2%)	1
Constitutional symptoms, n (%)	1 (3.2)	6 (6.4)	0.51	1 (5.6%)	4 (5.9%)	1
-fatigue, n (%)	2 (6.5)	4 (4.3)	0.62	0	2 (2.9%)	1
-decreased appetite, n (%)	9 (29.0)	27 (28.7)	0.97	5 (27.8%)	21 (30.4%)	1
-growth delay, n (%)	5 (16.1)	11 (11.7)	0.52	3 (16.7%)	4 (5.8%)	0.15
Laboratory results	3 (9.7)	2 (2.1)	0.09	3 (17.6%)	1 (1.5%)	0.24
-anemia, n (%)	2 (6.5)	7 (7.4)	0.85	0	6 (8.7%)	0.34
-elevated liver enzymes, n (%)	0	7 (7.4)	0.4	1 (5.6%)	6 (8.8%)	1
Family screening, n (%)						
Incidental, n (%)						

AI- autoimmune; SD- standard deviation; IQR- interquartile range; Wt- weight; Ht- height; BMI- body mass index; IU- international units; ALT- alanine-aminotransferase, AST- aspartate-aminotransferase; GGT- gamma-glutamyl transpeptidase; ULN- upper limit of normal; aTTG- anti-tissue transglutaminase.

	Patients ALT > 24 IU (n = 30)	Patients with normal ALT (n = 95)	P	Patients AST > 40 IU (n = 19)	Patients with normal AST (n = 68)	P
Anthropometrics	44 (21–84)	30 (8–60)	0.25	42 (21–90)	28 (8–57)	0.22
-Wt/age percentile, median (IQR)	45 (12–89)	48 (8–79)	0.90	31 (12–98)	26 (6–68)	0.47
-Ht/age percentile, median (IQR)	41 (4–77)	40 (19–77)	0.49	64 (42–80)	29 (13–76)	0.36
-BMI/age percentile, median (IQR)						
Serology	23 (74.2)	66 (70.2)	0.45	16 (88.9)	44 (63.8)	**0.06**
-aTTG > 10xULN, n (%)						
Laboratory results	12.4 (1.5)	12.2 (1.3)	0.26	12.0 (1.3)	12.5 (1.0)	0.14
-hemoglobin g/dL, mean (SD)	0.4 (0.3–0.7)	0.4 (0.3–0.5)	0.66	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.63
-bilirubin IU/L, median (IQR)	4.5 (0.4)	4.4 (0.2)	0.10	4.4 (0.4)	4.4 (0.3)	0.39
-albumin mg/dL, mean (SD)	-	-	-	32.8 (28–37)	20.9 (15–23)	**0.01**
- ALT IU mg/dL, median (IQR)	**41 (31–49)**	**33 (28–37)**	**< 0.01**	-	-	-
-AST IU, median (IQR)	11 (10–13)	11 (9–12)	0.08	10 (9–10)	12 (9–15)	0.1
-GGT IU, median (IQR)						
Marsh 2/3 histology	27 (87.1)	79 (84.0)	0.68	15 (93.8%)	58 (86.6%)	0.68
-in 2nd part of duodenum, n (%)	27 (87.1)	90 (95.7)	0.09	16 (100%)	64 (95.5%)	1
-in duodenal bulb, n (%)						

AI- autoimmune; SD- standard deviation; IQR- interquartile range; Wt- weight; Ht- height; BMI- body mass index; IU- international units; ALT- alanine-aminotransferase, AST- aspartate-aminotransferase; GGT- gamma-glutamyl transpeptidase; ULN- upper limit of normal; aTTG- anti-tissue transglutaminase.

Natural history of CD patients with ELE

Patients were followed for up to one-year post diagnosis; 60 patients completed a full follow-up of 12 months. All patients experienced clinical improvement following the introduction of GFD. Eighty percent of patients with elevated ALT levels, normalized their ALT within 3 months of follow-up, and all patients within one year (Fig. 1). Liver enzyme decrement was associated with, and paralleled, normalization of aTTG values. AST levels showed a similar trend; however, 3 patients (9.4%) had persistent elevated AST levels. Patients with elevated ALT had similar levels of aTTG at diagnosis and similar decrease rates compared to celiac patients with normal liver enzymes during the follow up period. Likewise, hemoglobin and albumin levels and anthropometrics at one year post-diagnosis were all comparable between the two groups (Fig. 2).

A single patient was simultaneously co-diagnosed with celiac disease and auto-immune hepatitis. Family screening, for celiac diagnosis in a sibling, demonstrated highly elevated liver enzymes and positive celiac serology. Further investigations including auto-immune serology, immunoglobulin levels, gastroscopy and liver biopsy were positive for the final co-diagnoses. None of the other patients with elevated ALT was subsequently diagnosed with a primary liver disease to date.

Discussion

In this prospective-observational study of 125 newly-diagnosed celiac patients, 31 (24.8%) had elevated ALT at diagnosis. However, only two patients had significant elevations of over 3xULN, one of whom was later co-diagnosed with auto-immune hepatitis. Patients with elevated ALT at diagnosis were younger, had associated elevated AST levels (but not cholestatic enzymes), and tended to present more commonly with diarrhea, compared to the remaining of the cohort. Their natural history was similar to that of normal-ALT patients, including clinical improvement rates on GFD, growth, aTTG decrease rate, and basic laboratory results' changes, over one year of follow-up.

Elevated liver enzymes, most notably ALT, were previously described as one of the extra-intestinal manifestations of celiac disease, ranging between 4–40% of newly diagnosed patients (Table 4; 8–15). Studies in children demonstrate a downward trend in the incidence of elevated ALT at celiac diagnosis over time. Recent reports demonstrated relatively low prevalence of 5–15% (13–15), compared to older studies in pediatrics with prevalence of up to ~ 40%; similar to the prevalence in adult CD patients (8–12, 21). In our study, using a relatively low threshold, we found 25% of patients with some degree of ALT elevation. However, considering the commonly used 40 IU threshold, only 5% of patients had ALT elevations; in line with the results of recent studies in children. These temporary changes, we presume, reflect the net effects of increased awareness of celiac disease in the public and among treating physicians, with resultant quicker diagnosis for some, and an overall increase in celiac diagnosis in general, specifically of patients with a less severe phenotype of disease.

Table 4
Elevated liver enzymes in newly diagnosed celiac disease patients- literature review

Authors	Study design	Cohort	Age mean, range (Y)	ALT (IU) ULN	Patients with elevated ALT (%)	significant correlations	associated primary liver diseases
Bonamico et al, 1986[8]	Retrospective	65	3.5, 0.6–18	45	18 (27.7)		
Demir et al, 2000[9]	Retrospective	81	5.9, 0.8–16	n/a	16 (19.8)		Cirrhosis (2)
Farre et al, 2002[10]	Prospective	114	4.5, 0.9–17	n/a	37 (32.0)	Younger age at diagnosis	
Arslan et al, 2005[11]	Prospective	27	6, 1–11	45	7 (25.9)		
Di Biase et al, 2010[12]	Prospective	350	9, 1–16	41	140 (40.0)		AIH (7)
Äärelä el al, 2016[13]	Retrospective	150	median-7.3 IQR-4.3–11.8	30	22 (14.7)	Higher Marsh score; elevated TSH	
Lee et al, 2016[14]	Prospective	185	10, 6.7–14.5	40	28 (15.1)	Younger age at diagnosis	fatty liver disease (1)
Benelli et al, 2019[15]	Retrospective/ Prospective	700	Median-7.4 IQR-0.8–17.9	40	27 (3.9)	Younger age at diagnosis; low Hb; low ferritin	PSC (1)

Y- years, IU- international unit; ALT- alanine aminotransferase; ULN- upper limit of normal; AIH- autoimmune hepatitis;IQR- inter-quartile range; TSH- thyroid stimulating hormone; Hb- hemoglobin; PSC- primary sclerosing cholangitis.

Our finding of association between elevated ALT at presentation and young age at diagnosis was previously described by others: Farre et al., Lee et al., and Benelli et al. (10, 14–15). Other associations however, were less consistent: Benelli et al., described the association of elevated ALT with a complex of symptoms and laboratory findings, designated as "malabsorption", including diarrhea, failure to thrive,

low hemoglobin and ferritin levels at presentation (15). Furthermore, other associations described by others, such as higher Marsh scores, lower hemoglobin, ferritin and thyroid-stimulating-hormone levels at diagnosis, were not significant in our present study (13, 15). Considering these findings together, we postulate that those patients who are diagnosed younger, on the background of overall global trend of increasing age at celiac diagnosis (22, 23), have a more aggressive phenotype of disease resulting in earlier diagnosis, a more "classical" symptomatic gastrointestinal presentation (i.e. diarrhea) and extra intestinal manifestations.

Nevertheless, despite the high number of patients with elevated ALT, the clinical significance of this finding is limited. The vast majority of patients (80%) normalized their ALT once started on GFD within three months, and all by one year of follow-up. Furthermore, the natural history of patients with elevated ALT, including clinical improvement, weight gain, linear growth, and basic laboratory studies, did not differ from the remaining of the cohort (Fig. 2).

A key element affecting the primary endpoint of our study- the prevalence of elevated liver enzymes among newly diagnosed celiac patients, is the threshold beyond which a result is considered abnormal. Most of past studies set the upper limit of norm at ALT values of 30–45 U/l (Table 4). We chose to rely on the cutoff of 24 U/l, an average value for males and females, as was found in the national health and nutritional survey (NHANES, 17,18). This threshold is now widely accepted as the "true" upper limit of normal in lean and healthy children. Setting the bar at a low threshold, increased the sensitivity of our study and therefore increased the prevalence we found; however, most of these abnormal findings were not clinically significant, and ultimately only two patients had substantial elevations. Analyzing AST levels yielded similar results to ALT analysis (data is partially shown); however, the usage of AST in children is hampered by lack of specificity to the liver, especially in the face of the commonly encountered increased AST levels caused by technical problems in blood drawing resulting in hemolysis. Cholestatic enzymes' elevations were not noted in previous reports, and apart from a single patient with a one-time-only GGT elevation, neither did we find such patients. Finally, our ability to assess alkaline-phosphatase in the cohort was hindered by lack of specificity of the enzyme to the liver, and the fact that children have a high bone turn-over rate as part of their natural growth, causing elevated alkaline-phosphatase levels of bone origin.

Overtime, celiac disease is associated with other autoimmune disorders, most notably diabetes mellitus type 1 with a co-prevalence of ~ 10% (24). In our cohort, we found only 7 (6%) patients with other autoimmune diseases, lower than expected. This may reflect the relatively short follow-up that failed to fully appreciate the auto-immune burden in this cohort. On the contrary, 38 (30%) patients had a positive auto-immune and/or inflammatory family history, underscoring the strong genetic background of this disease.

One patient, presenting with significantly elevated ALT, was co-diagnosed with autoimmune hepatitis. It is likely that the hepatitis evident as highly-ELE was driven mainly by specific auto-antibodies targeting hepatic epitopes, rather than the non-specific auto-antibodies milieu produced by the CD pathogenesis.

Nevertheless, it is difficult to assess the true separate contribution of each of the autoimmune processes. Celiac disease prevalence in children with AIH is 3.5%-6.4%, and AIH prevalence in patients with celiac disease 1.4% (25–37); further data describing the temporary relationships and interplay of the co-diagnoses is lacking.

The observational-prospective nature of our study enabled us to collect detailed demographic, anthropometric and clinical data during the diagnostic process of the participants and up to one year of follow up. The majority of patients normalized their ALT levels quickly once the gluten free diet was introduced, and all, within the one-year follow-up timeframe. Therefore, prolonging the follow-up duration was not likely to produce further prognostication results regarding the patients with ELE. The main limitation of our study is the moderate size of the cohort and consequently small number of participants with significant ALT elevations, preventing further sub-group analysis. Patients with significant ALT elevations may very well present a specific disease phenotype; however, our study was not large enough to detect it.

In conclusion, setting a low threshold, ALT abnormalities were common (~ 25%) among newly diagnosed celiac patients and were typically associated with young age at diagnosis; however, significant ALT elevations are uncommon (1.6%). The natural history of celiac patients with elevated ALT is similar to that of patients with normal liver enzymes. While for most newly diagnosed celiac patients the existence of elevated liver enzymes is clinically insignificant, significant elevations (> 3xULN) failing to normalize on gluten free diet, should raise concern of a co-existing primary liver disease, and warrant further investigations.

Abbreviations

aDGP- anti-deamidated gliadin protein; AI- autoimmune; AIH- autoimmune hepatitis; ALP- alkaline-phosphatase; ALT- alanine aminotransferase; AST- aspartate aminotransferase; aTTG- anti-tissue transglutaminase; BMI- body mass index; CD – celiac disease; ELE- elevated liver enzymes; GGT- gamma-glutamyl transpeptidase; GFD- gluten free diet; Hb- hemoglobin; Ht – height; IQR- interquartile range; IU- international unit; PSC- primary sclerosing cholangitis; SD- standard deviation; TSH- thyroid stimulating hormone; ULN- upper limit of normal; Wt – weight; Y- years.

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28. Supplementary

Figures

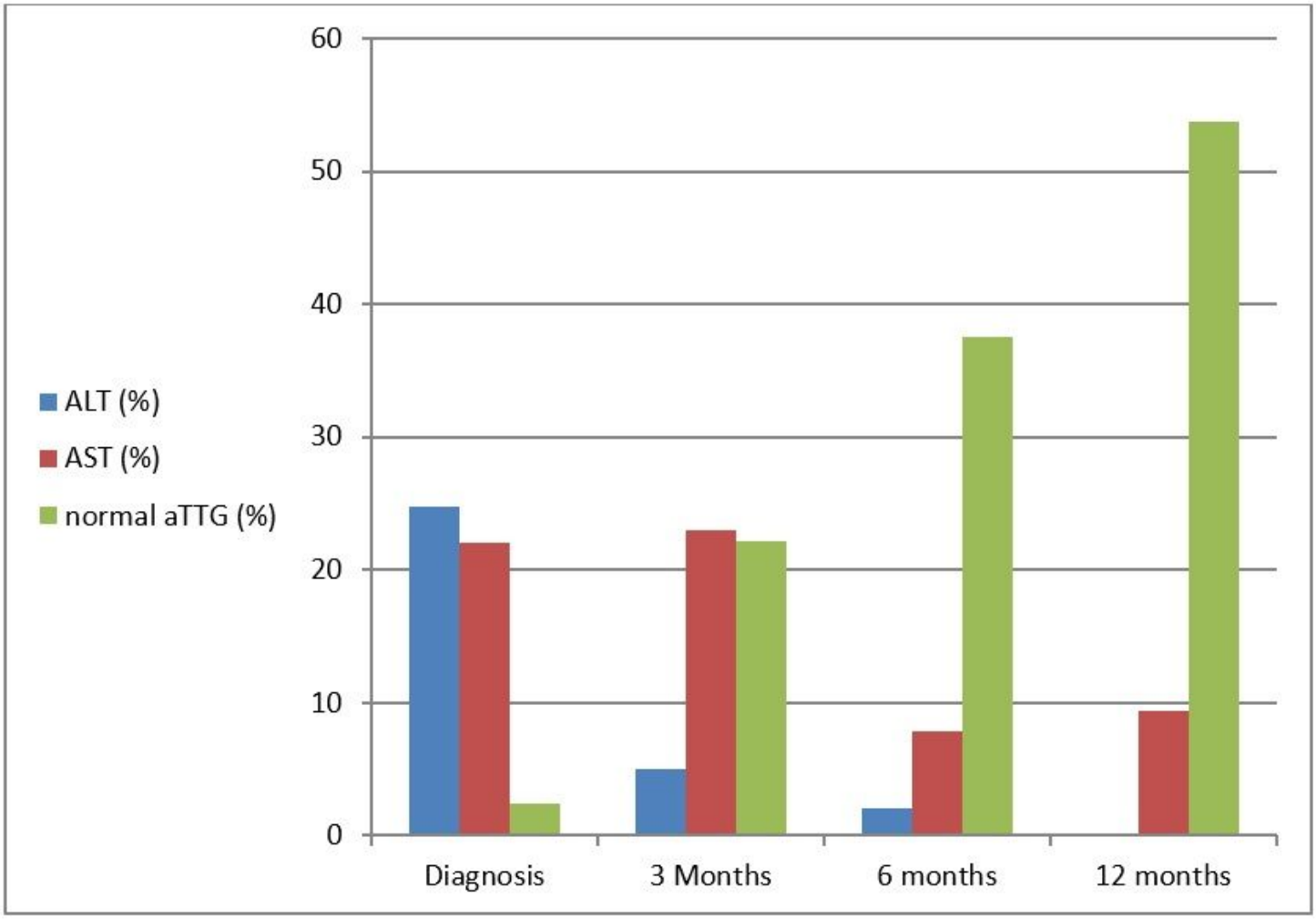

Figure 1

Patients with elevated transaminases and celiac serology during one year of follow-up. Legend: %- percent of patients; ALT- alanine aminotransferase, ULN- 24IU; AST- aspartate aminotransferase, ULN- 40IU; aTTG- anti-tissue transglutaminase, ULN- 7 U/ml.

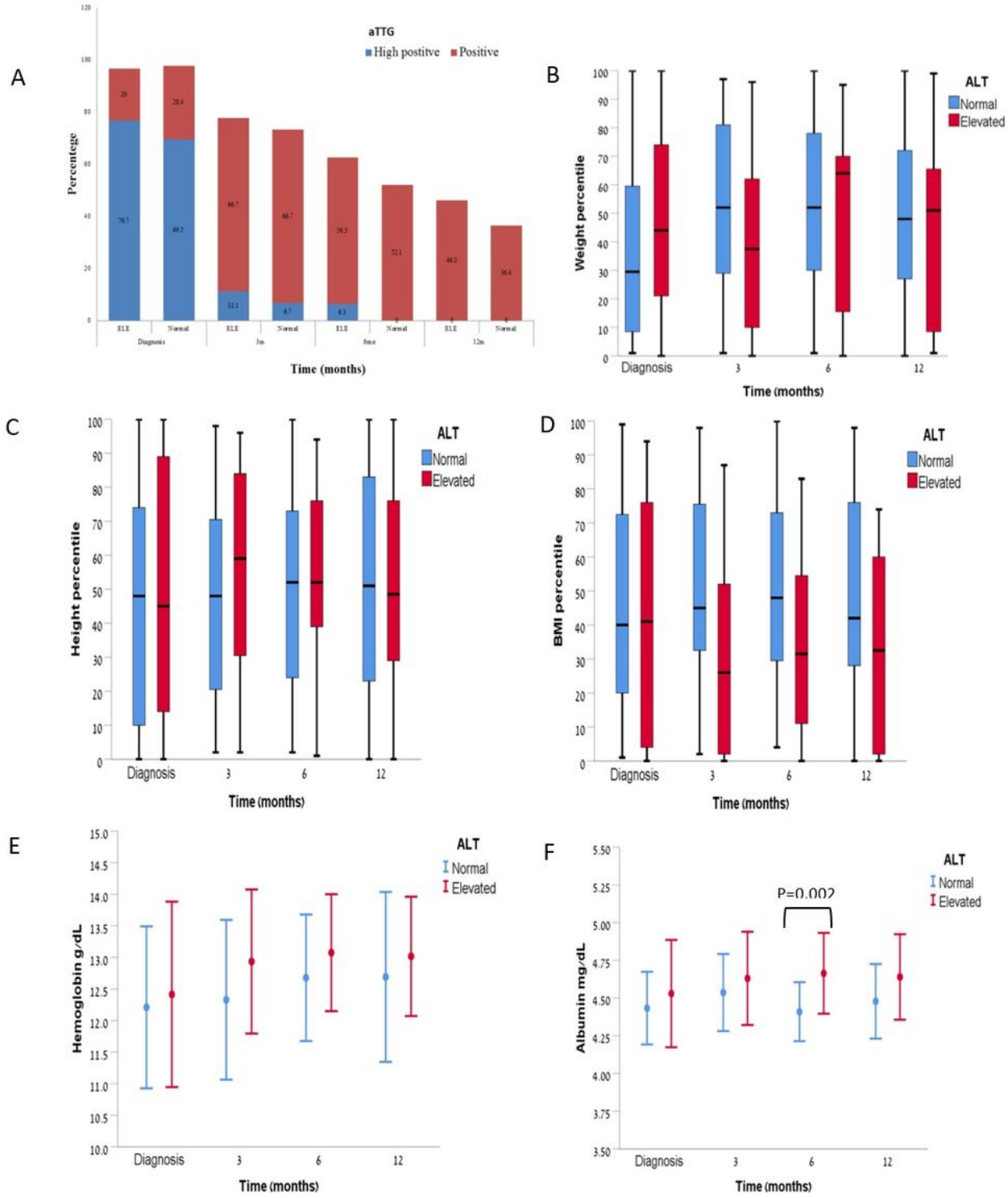

Figure 2

Celiac patients with vs. without elevated ALT at diagnosis during a one year follow up Legend: A: positive and high-positive aTTG levels. B: Height percentiles for age and sex (median, IQR). C: Weight percentiles for age and sex (median, IQR). D: BMI percentiles for age and sex (median, IQR). E: Hemoglobin levels (mean, SD). F: Albumin levels (mean, SD). aTTG- anti-tissue transglutaminase; ELE- elevated liver enzymes; ALT- alanine-aminotransferase; SD- standard deviation; IQR- interquartile range.