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ORIGINAL ARTICLE

Gastroenterology: Celiac Disease

Long-term laboratory follow-up is essential in pediatric patients with celiac

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Abstract

Objectives: Celiac disease (CeD) requires long-term follow. The role of laboratory testing other than celiac serology during follow up is unclear. We aimed to determine which laboratory tests are required during follow up based on the prevalence of abnormal tests and timing of abnormalities appearance.

Methods: Retrospective chart-review of children diagnosed with CeD between 1999 and 2018 was conducted. Demographic, clinical and laboratory data were recorded from diagnosis and during follow-up.

Results: The cohort included 500 children with CeD [59.8% females, median (IQR) age at diagnosis 5.7(3.7–8.9) years]. Mean follow-up time was 5.5 years (range 1.5–16.2). The most frequently abnormal laboratory tests at time of diagnosis were low ferritin (64.3%), vitamin D (33.6%), zinc (29.9%), hemoglobin (29.2%), and folate (14.7%). In 74 (14.8%) patients, anemia developed only during follow up, while in another 46 patients, anemia resolved after diagnosis and reappeared later (after a mean ± SD 2.8 ± 2.1 years from CeD diagnosis, for the entire group). Abnormal values that developed during follow up were low folate in 40 patients (3.9 ± 2.6 years), and abnormal liver enzymes in 18 patients (3.1 ± 2.7 years). Elevated TSH during follow-up was observed in 14/280 (5%) patients, after a mean ± SD of 2.2 ± 1.6 years from diagnosis. Patients diagnosed as teenagers (12–18 years) had shorter intervals to reappearance of anemia and folate deficiency.

Conclusions: Multiple laboratory abnormalities may occur in pediatric patients with CeD, both at diagnosis and during long-term follow-up. We suggest continued monitoring of hemoglobin, ferritin, folate, liver, and thyroid function in addition to celiac serology during follow-up of CeD.

KEYWORDS

follow up, laboratory measures, micronutrients, nutrition

1 | INTRODUCTION

Celiac disease(CeD) is one of most common autoimmune disorders in childhood, with an estimated overall prevalence of 1%–3%, worldwide.[1,2] Small bowel mucosal damage in susceptible individuals is mediated via CD4 + T cells immunoreaction to gluten peptides. Both gastrointestinal and extra-intestinal manifestations may be present at diagnosis and during follow-up, including abdominal pain, diarrhea,

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vomiting, abdominal distention, fatigue, micronutrient deficiencies, weight loss and impaired growth, which usually are age dependent.[3–7] Pediatric patients with CeD, especially those diagnosed at younger age, can present with anemia, hypoalbuminemia, elevated liver enzymes and deficiencies of iron, folic acid and vitamin D.[7]

Long-term laboratory follow-up for CeD is mainly based on local clinical practices with paucity of evidence-based recommendations. Thus, some studies have reported high rates of anemia, vitamin D deficiency and elevated transaminases during follow-up,[8–10] while others suggested low yield of routine laboratory investigations.[11,12] The ESPGHAN position paper on management and follow-up of children and adolescents with CeD[13] recommend comprehensive laboratory evaluation at time of diagnosis (complete blood cell count; micronutrients status and liver function tests); however, omitted the necessity of routine laboratory investigations during follow-up in patients with a stable clinical course and good adherence to gluten-free diet, other than the correction of iron stores and consideration of thyroid function monitoring.[13]

In this study, we aimed to evaluate the yield of long-term laboratory follow-up in pediatric patients with CeD, in a large cohort at a tertiary referral center.

What is Known

- Celiac disease (CeD) is an immune-mediated condition characterized by small bowel damage, triggered by gluten exposure in individuals with a genetic predisposition.
- Long-term laboratory follow-up of patients with CeD is largely based on local and opinion-based clinical practices with paucity of evidence-based recommendations.

What is New

- In pediatric CeD, laboratory abnormalities such as anemia, hypoferritinemia, and nutritional and vitamin deficiencies can persist during follow-up or can emerge during the disease course, despite adherence to a gluten-free diet.
- Continued monitoring of hemoglobin, ferritin, folate, liver and thyroid function in addition to celiac serology during follow-up of CeD is suggested.

2 | METHODS

2.1 | Study design and population

The study was performed at the Institute of Gastroenterology, Nutrition and Liver Diseases at Schneider Children's Medical Center of Israel, which serves as a tertiary referral center for pediatric patients across the country. The study population included all pediatric patients (up to 18 years) diagnosed with CeD, between the years 1999 and 2018. A retrospective review of electronic medical records was conducted. Case retrieval was achieved using the search terms 'celiac disease' and 'gluten-sensitive enteropathy' ($n = 910$), which are embedded in the records. Patients were excluded if their follow-up was shorter than 18 months ($n = 362$) or had a concomitant endocrine disease at diagnosis, $n = 48$, (including type 1 diabetes mellitus ($n = 33$) and hypothyroidism ($n = 15$)).

2.2 | Ethics Statement

The study was approved by the institution ethical review board of the Rabin Medical Center (RMC 0642–15).

2.3 | Data collection and study variables

The data extracted from medical records included: gender, age at diagnosis, frequency of follow-up visits, and self-reported gluten-free diet (GFD) adherence according to the number of transgressions patients committed per month. The frequency of follow-up visits was calculated from the end of the first year after CeD diagnosis. Lost to follow-up was defined as the absence of visits for more than 3 years. Patients were classified to four age groups according to age at CeD diagnosis: group 1: 0–3 years; group 2: 3–6 years; group 3: 6–12 years; and group 4: 12–18 years.

Baseline laboratory characteristics at diagnosis and follow-up were evaluated including celiac serology (anti-tissue transglutaminase (TTG) and anti-endomysium antibodies (EMA)), hemoglobin, albumin, ferritin, vitamin D, zinc, aspartate aminotransferase (AST), alanine aminotransferase (ALT), folic acid, vitamin B12, thyroid stimulating hormone (TSH), thyroxine (T4).

2.4 | Definitions

TTG was expressed as multiples of the upper limit of normal(ULN). EMA titer of 1:5 and above was considered positive. In cases of selective IgA deficiency, CeD diagnosis was based on intestinal biopsies.[14] Anemia was defined according to WHO[15,16] as

hemoglobin (Hb) < 11 gr/dL for children ≤5years old, <11.5 gr/dL for children 5–11 years old, <12 gr/dL for children 12–14 years old and <13 gr/dL for boys and < 12 gr/dL for girls older 15 years. Iron deficiency was defined as ferritin <12 ng/ml for patients ≤ 5 years old and a ferritin <15 ng/ml in older children.[16] Hypoalbuminemia was defined as albumin <3.5 gr/dL.[17] Folic acid deficiency was defined as <10 nmol/L,[18] vitamin B12 deficiency was defined as <150 pmol/L[18] and vitamin D deficiency was defined as <50 nmol/L.[19,20] Zinc deficiency was defined as <70 μg/dL.[21] Elevated AST and ALT were defined as levels x2 above upper limit of normal (ULN) for age. Elevated TSH was defined as level x1.5 above ULN for age.

2.5 | Adherence to gluten free diet

In our clinical practice and in accordance with the professional guidelines, all children diagnosed with CeD are promptly advised to adopt a strict GFD. To ensure proper dietary guidance and adherence, a comprehensive consultation with a pediatric dietitian is scheduled shortly after the diagnosis. In this study, adherence to GFD was self-reported by patients and/or caregivers during each clinical visit and stratified to: good adherence, partial adherence (defined as ≤ 1 lapses/month) and poor adherence (> 1 lapses/month).

2.6 | Statistical analysis

Categorical variables were described as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and reported as mean and standard deviation (SD) or as median and interquartile range. Chi-square test and Fisher's exact test were used to compare categorical variables. ANOVA, independent samples *t*-test and Mann-Whitney test were used to study the association between continuous variables and categorical variables. Spearman correlation coefficient was applied to study the association between continuous variables. Repeated measures ANOVA and paired *t*-test were used for repeated measures analysis. Kaplan Meier curve was used to describe events during the follow-up period and Log-Rank test and univariate cox regression were applied to compare categorical and continuous variables, respectively. All statistical tests were two sided and $p < 0.05$ was considered as statistically significant. Statistical analysis was performed using the SPSS statistical software (IBM SPSS Statistics for Windows, version 28, IBM Corp., Armonk, NY, USA, 2021).

3 | RESULTS

3.1 | Cohort characteristics

The study included 500 patients (59.8% females) diagnosed with CeD. The median age at diagnosis was 5.7 years (IQR 3.7–8.9) and the median age at last follow-up was 11.8 years (IQR 8.6–15.7). The median duration of follow-up was 5.1 years (IQR 3.1–7.3), with a range between 1.5 and 16.2 years. The mean(± SD) time between follow-up visits was 10.2(± 4.4) months, and 33.4% were lost to follow-up.

Adherence to GFD was reported as good in the majority (82.7%) of patients. Normalization of TTG was observed in 417/500 (83.4%) patients, within a median duration of 0.87 years (range: 2 month–6.8 years) from diagnosis (Table 1).

TABLE 1 General characteristics of 500 children with CeD at diagnosis.

Characteristics	*N* = 500
Gender: females, *n* (%)	299 (59.8)
Median age at diagnosis, years (IQR)	5.7 (3.7–8.9)
Median duration of follow up, years (IQR)	5.1 (3.1–7.3)
Mean time between visits, months (± SD)	10.2 (± 4.4)
Age groups	
0–3 years, *n* (%)	87 (17.4)
3–6 years, *n* (%)	186 (37.2)
6–12 years, *n* (%)	166 (33.2)
12–18 years, *n* (%)	61 (12.2)
Reported compliance with GFD	
Good, %	82.7
Partial, %	15.4
Poor, %	1.9
TTG levels, x ULN	
< x 3, %	17.1
x 3–5, %	22.3
x 5–10, %	23.9
> x 10, %	36.7
TTG normalization	
TTG normalization, *n* (%)	417 (83.4)
Median time to TTG normalization, years (IQR)	0.87 (0.58–1.35)

Abbreviations: GFD, gluten free diet; TTG, tissue trans glutaminase; ULN, upper limits of normal.

3.2 | Laboratory results

Anemia at diagnosis was observed in 133/456(29.2%) patients, resolving in 125/133(94%) of them (Table 2). No significant associations were found between age group or TTG levels at diagnosis and time to resolution of anemia. During follow-up, anemia occurred in 120/448(26.8%) patients: in 74/323 (22.9%) patients that presented with normal Hb at diagnosis, and in 46/125 (36.8%) that normalized anemia after diagnosis in whom anemia reoccurred (Table 3). Patients in the oldest age group (group 4) had a shorter time to the first appearance of anemia, mean(±SD) 2.4(±0.4) years, compared to other age groups, $p = 0.023$ (Figure 1). Patients who self-reported incomplete adherence to GFD had a non-significant trend towards shorter time to first appearance of anemia compared to others. A second event of anemia was observed in 41/456(9%) patients (with available Hb at diagnosis), after a mean(±SD) 4.6(±2.2) years from the diagnosis, with patients from age group 4 and those with poor adherence to GFD having significantly shorter time to second event of anemia, 4.7(±0.5) years, $p < 0.001$ and 3.1(±1.3) years, $p < 0.01$, respectively). No difference in the time to first and second Reoccurrence of anemia was observed between genders.

Hypoferritinemia at diagnosis was present in 225/350(64.3%) patients, resolving in 193/225(85.8%) of them (Table 2). No significant associations were found between gender, age group or TTG levels at diagnosis and time to ferritin normalization. During follow-up, hypoferritinemia occurred in 133(38%) patients (Table 3). Patients with hypoferritinemia at diagnosis experienced a faster reoccurrence compared to those with normal ferritin (3.2±0.5 vs. 12.9±3.5 years, $p < 0.001$). No significant associations were found between gender, age groups at diagnosis or adherence to GFD and time to hypoferritinemia reoccurrence. A second event of hypoferritinemia was observed after a mean(±SD) 4.4(±2.2) years from the diagnosis in 79/345(22.9%) patients with available ferritin at diagnosis. Patients from age-group 4 had shorter time to second event of hypoferritinemia mean(±SD) 4(±0.7) years compared to other age groups, $p = 0.05$. No significant associations were found between adherence to GFD or gender and second event of hypoferritinemia.

Hypoalbuminemia at diagnosis was observed in 15/382(3.9%) patients, resolving in all of them. (Table 2). Hypoalbuminemia occurred in only three cases during follow-up.

TABLE 2 Laboratory abnormalities at the time of celiac disease diagnosis.

	n/N (%)	Mean ± SD time to normalization, years
Anemia	133/456 (29.2)	1.2 ± 1.4
Hypoferritinemia	225/350 (64.3)	1.9 ± 1.8
Hypoalbuminemia	15/382 (3.9)	0.4 ± 0.3
Vitamin D deficiency	39/116 (33.6)	1.5 ± 1.7
Zinc deficiency	26/87 (29.9)	1.2 ± 0.9
AST elevation	51/401(12.7)	0.8 ± 1.1
ALT elevation	22/414 (5.3)	0.4 ± 0.3
Folic acid deficiency	24/163 (14.7)	1.4 ± 1.6
Vitamin B12 deficiency	2/189 (1.1)	NA
TSH elevation	2/282 (0.7)	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; *N*, number of patients with available laboratory variable at diagnosis; SD, standard deviation; TSH, thyroid stimulating hormone.

TABLE 3 Laboratory abnormalities occurrence during follow up.

	n/Total at diagnosis (%)	First occurrence during follow-up *n/N* (%)	Reoccurrence during follow-up[a] *n/N* (%)	Mean ± SD time from diagnosis, years
Anemia	120 (26.8)	74/323 (22.9)	46/125 (36.8)	2.8 ± 2.1
Hypoferritinemia	133 (38)	40/125 (32)	93/225 (41.3)	3.1 ± 2.3
Vitamin D deficiency	30 (25.9)	19/77 (24.7)	11/39 (28.2)	3.4 ± 2.4
Zinc deficiency	10 (11.5)	7/61 (11.5)	3/26 (11.5)	2 ± 2
Elevated ALT	21 (5.1)	18/392 (4.6)	3/22 (13.6)	3.1 ± 2.7
Folic acid deficiency	48 (29.4)	40/139 (28.8)	8/24 (33.3)	3.9 ± 2.6
Vitamin B12 deficiency	4 (2.1)	4/187 (2.1)	0	NA
Elevated TSH	14 (5)	14/280 (5)	0	2.2 ± 1.6

Abbreviations: ALT, alanine aminotransferase; SD, standard deviation; TSH, thyroid stimulating hormone.

[a]Reoccurrence among patients with abnormal value at diagnosis.

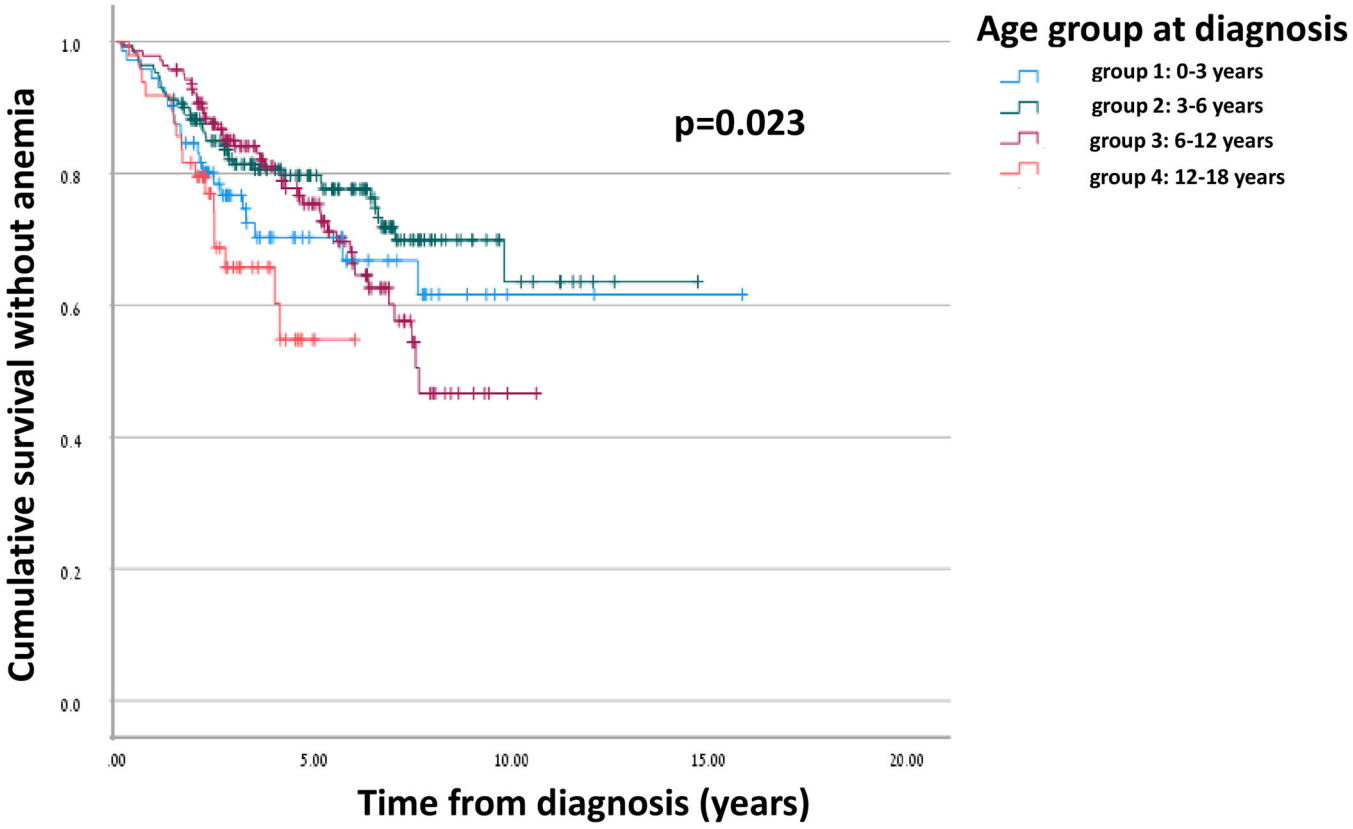

FIGURE 1 Kaplan-Meier (KM) curve of time to first anemia reoccurrence, by age groups at diagnosis.

Vitamin D deficiency affected 39/116(33.6%) patients at diagnosis and resolved in 33/39(84.6%), Table 2. No significant associations were found between gender, age group or TTG levels at diagnosis and time to vitamin D normalization. During follow-up, vitamin D deficiency occurred in 30/116(25.9%) patients (Table 3). Patients with vitamin D deficiency at diagnosis showed a nonsignificant trend toward faster reoccurrence compared to those with normal levels. No significant associations were found between gender or age group at diagnosis and time to vitamin D deficiency reoccurrence.

Zinc deficiency at diagnosis was observed in 26/87(29.9%) patients and resolved in 22/26(84.6%), Table 2. Males normalized zinc faster than females, mean(±SD) 0.6(±0.2) vs 1.4(±0.5) years, $p = 0.05$. No significant associations were found between age group or TTG levels at diagnosis and time to zinc normalization. During follow-up, zinc deficiency occurred in 10/87(11.5%) patients (Table 3). No significant associations were found between gender, age group at diagnosis or adherence to GFD and time to zinc deficiency reoccurrence.

AST and ALT elevations at diagnosis were observed in 51/401(12.7%) and 22/414(5.3%) patients, respectively, resolving in all them, Table 2. No significant associations were found between gender, age group or TTG levels at diagnosis and time to both AST and ALT normalization. During follow-up, ALT elevation occurred in 21/414(5.1%) patients (Table 3). No significant associations were found between gender or age group at diagnosis and time to elevated AST and ALT reoccurrence. Patients with elevated AST and ALT at diagnosis had shorter mean (±SD) time to reoccurrence of AST and ALT elevation (9.2(±0.5) and 9.2(±0.8) years, respectively), compared to those with normal AST and ALT at diagnosis, (13.9(±0.3) and 14.1(±0.3) years, respectively) $p = 0.02$ for each. Patients with poor adherence to GFD had faster time to ALT elevation, mean(±SD) 6.2(±1) years, $p = 0.05$.

Folic acid deficiency at diagnosis was observed in 24/163(14.7%) patients, normalizing in 21/24(87.5%), Table 2. No significant associations were found between gender, age group or TTG levels at diagnosis and time to folic acid normalization. During follow-up, folic acid deficiency occurred in 48/163(29.4%) patients (Table 3). Patients from the oldest age group (group 4) had shortest time to reoccurrence of folic acid deficiency, compared to other age groups, mean(±SD) 3.8(±0.4) years, $p < 0.0001$. No significant associations were found between gender, TTG levels at diagnosis or adherence to GFD and time to folic acid deficiency reoccurrence.

Vitamin B12 deficiency at diagnosis was rare, affecting 2/189(1.1%) patients and appeared in 4/187(2.1%) during follow-up (Tables 2 and 3).

Elevated TSH at diagnosis was observed in 2/282(0.7%) of patients and was observed during follow-up in 14/280(5%) patients (Table 3). No significant associations were found between gender or adherence to GFD and time to elevated TSH reoccurrence.

Tables 2 and 3 provide additional details on laboratory abnormalities at diagnosis and during follow-up, respectively.

4 | DISCUSSION

In this large-scale retrospective study of 500 pediatric patients with CeD, we found that nutritional deficiencies and laboratory abnormalities are common at the time of diagnosis and may persist throughout long-term follow-up even on a GFD. Moreover, some abnormalities that not present initially, may emerge later during follow-up. Despite overall good reported adherence to GFD, some nutritional deficiencies were common, including iron deficiency in about a third of the cohort and vitamin D deficiency in a quarter of the cohort.

The most prevalent laboratory abnormalities observed were anemia and hypoferritinemia, both at diagnosis and during follow-up (including new-onset abnormalities). The rates of anemia at diagnosis in our cohort align with previous studies,[7,22] however the rates of new onset of anemia post-diagnosis were higher in our cohort compared to those reported by Wessels et al. in children and Burger et al in adults.[11,23] While hypoferritinemia rates were similar to prior pediatric studies,[24,25] the rate of new-onset hypoferritinemia during follow-up was higher than previously reported in children[11] and adults.[23] This discrepancy may be explained by different cutoff values, which were lower in other studies compared to ours (defined by WHO[16]). Patients diagnosed in the oldest age group showed the shortest time to reoccurrence of hypoferritinemia, that may suggest increased iron requirements during periods of accelerated growth, hormonal changes, or menstrual blood loss in adolescents. Alternatively, it could indicate lower adherence to a GFD, which is more common in adolescents and adults[26,27] and might be under-reported.

The shorter period to occurrence of anemia or hypoferritinemia in patients with low ferritin at diagnosis, suggests increased vulnerability to iron deficiency in certain patients.[28] In addition, the long average time (3 years) to occurrence of anemia or hypoferritinemia during follow-up suggests that iron status monitoring should be a long-term consideration.

The rates of vitamin D, folic acid and zinc deficiencies at diagnosis were comparable to those reported in other studies.[12,23,29] The variability in vitamin D deficiency rates during follow-up described in the literature,[23,29] may be influenced by factors such as sun exposure and the use of UV protection across different populations.[30]

The appearance of folic acid deficiency during follow-up was more common in our cohort, compared to lower rates in other studies.[11,22,29] This could be attributed to a longer follow up period in our study and the high rates of reported adherence to GFD, which in previous studies was shown to be associated with risk of low-folate intake.[31] Zinc levels were not frequently measured in this real-life data set, and hence the relatively high rates of deficiency could possibly be attributed to selective testing in high-risk patients.

Vitamin B12 deficiency was rare (1–2%) at both diagnosis and follow-up, consistent with previous reports,[11,23,32] suggesting a low yield in routinely monitoring of this vitamin level in CeD patients. As previously reported by our group, hypoalbuminemia is more common in patient with CeD diagnosed at a young age.[7] Given that the occurrence of low albumin levels during follow-up was extremely rare, routine monitoring of this parameter may be also unnecessary.

In our cohort, good adherence to GFD was high (>80%), based both on patients' reports and normalization of celiac serology. However, assessment of micronutrient intake was not routinely performed, thus limiting the ability to determine whether the observed deficiencies were due to low intake or due to ongoing intestinal damage and malabsorption. A low intake is consistent with previously described deficiencies of iron, folic acid, and zinc in GFD.[11,31] The average time to the emergence of micronutrient deficiencies during long-term follow-up is poorly described in the literature and ranged between 2 and 4 years in our cohort, indicating that continuous monitoring may be beneficial. At diagnosis, the rates of elevated TSH levels were very low (0.7%), in contrast to higher rates (12–13%) reported by others.[23,33] Although patients with pre-existing endocrinological diseases were excluded from our study, we did monitor thyroid function during follow-up. Rates of TSH elevation during follow-up were similar to previously reported ranges of 5–19%.[11,33,34]

Elevations of liver enzymes are known to be associated with CeD and were reported in 5% of our patients at diagnosis. These abnormalities, as in other studies, resolved within 1 year of GFD.[35–37] However, data regarding liver enzymes elevation during long-term follow-up is scarce.[10,35,36] Current guidelines do not advocate for routine TSH assessment during follow-up and ALT should be monitored only if abnormal at diagnosis.[13] Some studies described high risk of autoimmune thyroid diseases in CeD, while other showed no added benefit of TSH testing in asymptomatic patients due to similar rates of autoimmune thyroiditis between those on a GFD and controls.[11,22,34,38] The incidence of autoimmune hepatitis(AIH) in patients with CeD is relatively high and ranges between 2.3% and 6.4%.[38,39] In our cohort, both TSH and ALT elevation were observed during follow-up in patients with normal values at diagnosis (5% for both), although

there were no reported cases with confirmed autoimmune hepatitis, and patients with TSH elevation mainly continued follow-up by the endocrine unit. Given the high known prevalence of autoimmune conditions in patients with CeD, and the observed prevalence of these laboratory abnormalities in our study, we suggest routine monitoring of TSH and ALT levels, even in asymptomatic individuals, during long-term follow-up.

This study has several limitations. The retrospective study design hindered uniform data collection and scheduled follow-up, leading to missing data for some laboratory variables, and some patients being lost to follow-up. Dietary assessment including micronutrient intakes, were not routinely performed. Adherence to GFD was assessed in clinical practice through patient/proxy's reports, with no standardized questionaries or structured interviews, which might overestimate compliance. Although we did analyzed correlations between reported adherence to GFD and laboratory abnormalities, the retrospective nature of the study hindered our ability to determine correlations between TTG normalization and laboratory abnormalities, as these measurements were not always taken simultaneously. In addition, we couldn't include clinical outcomes including patients' persistent symptoms, or association with growth trajectories, in this retrospective study. Despite these limitations, the major strength of our study lies in its large scale and long-term follow-up, providing a comprehensive overview of laboratory parameters over an extended period. With the limitation acknowledged, the results contribute valuable insights into long-term laboratory abnormalities and nutritional deficiencies in pediatric patients with CeD. They also provide data on the emergence of certain abnormalities during follow-up, that are not mentioned in the recommended monitoring routine in recent guidelines.[13]

In conclusion, this study highlights elevated rates of laboratory abnormalities and nutritional deficiencies in pediatric patients with CeD, many of which do not present initially but emerge during follow-up. While variables like albumin and vitamin B12 are rarely abnormal in the long-term, routine laboratory follow-up of hemoglobin, ferritin, vitamin D, zinc, folic acid, liver enzymes, and TSH is essential, even in patients reporting good adherence to a GFD.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Almallouhi E, King KS, Patel B, et al. Increasing incidence and altered presentation in a population-based study of pediatric celiac disease in North America. *J Pediatr Gastroenterol Nutr*. 2017;65:432-437.
2. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;16:823-836.e2.
3. Guandalini S, Assiri A. Celiac disease: a review. *JAMA Pediatrics*. 2014;168:272-278. doi:10.1001/jamapediatrics.2013.3858
4. Van Kalleveen MW, de Meij T, Plötz FB. Clinical spectrum of paediatric coeliac disease: a 10-year single-centre experience. *Eur J Pediatr*. 2018;177:593-602.
5. Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med*. 2002;346:180-188.
6. Catassi C, Fabiani E. The spectrum of coeliac disease in children. *Baillière's Clin Gastroenterol*. 1997;11:485-507.
7. Krauthammer A, Guz-Mark A, Zevit N, et al. Age-dependent trends in the celiac disease: a tertiary center experience. *J Pediatr Gastroenterol Nutr*. 2021;72:894-899.
8. Stefanelli G, Viscido A, Longo S, Magistroni M, Latella G. Persistent iron deficiency anemia in patients with celiac disease despite a gluten-free diet. *Nutrients*. 2020;12:2176.
9. Ahlawat R, Weinstein T, Markowitz J, Kohn N, Pettei MJ. Should we assess vitamin D status in pediatric patients with celiac disease? *J Pediatr Gastroenterol Nutr*. 2019;69:449-454.
10. Regev A, Ben-Tov A, Yerushalmy-Feler A, et al. Elevated liver enzymes of newly diagnosed pediatric celiac patients-a prospective-observational study. *Eur J Pediatr*. 2022;181:753-762.
11. Burger JP, van der Laan JJ, Jansen TA, et al. Low yield for routine laboratory checks in follow-up of coeliac disease. *J Gastrointest Liver Dis*. 2018;27:233-239.
12. Wessels M, Dolinsek J, Castillejo G, et al. Follow-up practices for children and adolescents with celiac disease: results of an international survey. *Eur J Pediatr*. 2022;181:1213-1220.
13. Mearin ML, Agardh D, Antunes H, et al. ESPGHAN position paper on management and follow-up of children and adolescents with celiac disease. *J Pediatr Gastroenterol Nutr*. 2022;75:369-386.
14. Husby S, Koletzko S, Korponay-Szabó I, et al. European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr*. 2020;70:141-156.
15. World Health Organization [homepage on the Internet]. Guideline on haemoglobin cutoffs to define anaemia in individuals and populations. WHO. [updated Mar 2024]. Available from: https://www.who.int/publications/i/item/9789240088542.
16. World Health Organization. PDF file available from: https://iris.who.int/bitstream/handle/10665/75368/9789241596107_eng.pdf?sequence=1&isAllowed=y.
17. Jatla M, Bokhari A, Bierly P, Russo P, Verma R. Anthropometric, serologic, and laboratory correlation with villous blunting in pediatric celiac disease: diabetics are different. *J Clin Gastroenterol*. 2009;43:622-626.
18. Selhub J, Jacques PF, Dallal G, Choumenkovitch S, Rogers G. The use of blood concentrations of vitamins and their respective functional indicators to define folate and vitamin B12 status. *Food Nutr Bull*. 2008;29:S67-S73.
19. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266-281.
20. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics*. 2008;122:398-417.
21. Alkhouri RH, Hashmi H, Baker RD, Gelfond D, Baker SS. Vitamin and mineral status in patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2013;56:89-92.
22. Sahin Y. Celiac disease in children: a review of the literature. *World J Clin Pediatr*. 2021;10:53-71.

23. Wessels MMS, van Veen II, Vriezinga SL, Putter H, Rings EHHM, Mearin ML. Complementary serologic investigations in children with celiac disease is unnecessary during follow-up. *J Pediatr*. 2016;169:55-60.
24. Kreutz JM, Heynen L, Vreugdenhil ACE. Nutrient deficiencies in children with celiac disease during long-term follow-up. *Clin Nutr*. 2023;42:1175-1180.
25. Botero-López JE, Araya M, Parada A, et al. Micronutrient deficiencies in patients with typical and atypical celiac disease. *J Pediatr Gastroenterol Nutr*. 2011;53:265-270.
26. Mouslih A, El Rhazi K, Bahra N, Lakhdar Idrissi M, Hida M. Gluten-free diet compliance in children with celiac disease and its effect on clinical symptoms: a retrospective cohort study. *Cureus*. 2023;15:e50217.
27. Kori M, Goldstein S, Hofi L, Topf-Olivestone C. Adherence to gluten-free diet and follow-up of pediatric celiac disease patients, during childhood and after transition to adult care. *Eur J Pediatr*. 2021;180:1817-1823.
28. Gallagher PG. Anemia in the pediatric patient. *Blood*. 2022;140: 571-593.
29. Deora V, Aylward N, Sokoro A, El-Matary W. Serum vitamins and minerals at diagnosis and follow-up in children with celiac disease. *J Pediatr Gastroenterol Nutr*. 2017;65:185-189.
30. Oren Y, Shapira Y, Agmon-Levin N, et al. Vitamin D insufficiency in a sunny environment: a demographic and seasonal analysis. *Israel Med Assoc J*. 2010;12:751-756.
31. Di Nardo G, Villa MP, Conti L, et al. Nutritional deficiencies in children with celiac disease resulting from a gluten-free diet: a systematic review. *Nutrients*. 2019;11:1588.
32. Jivraj A, Hutchinson JM, Ching E, et al. Micronutrient deficiencies are frequent in adult patients with and without celiac disease on a gluten-free diet, regardless of duration and adherence to the diet. *Nutrition*. 2022;103-104:111809.
33. Cassio A, Ricci G, Baronio F, et al. Long-term clinical significance of thyroid autoimmunity in children with celiac disease. *J Pediatr*. 2010;156(2):292-295.
34. Ansaldi N, Palmas T, Corrias A, et al. Autoimmune thyroid disease and celiac disease in children. *J Pediatr Gastroenterol Nutr*. 2003;37:63-66.
35. Benelli E, Naviglio S, De Leo L, et al. Changing epidemiology of liver involvement in children with celiac disease. *J Pediatr Gastroenterol Nutr*. 2019;68:547-551.
36. Lee GJ, Boyle B, Ediger T, Hill I. Hypertransaminasemia in newly diagnosed pediatric patients with celiac disease. *J Pediatr Gastroenterol Nutr*. 2016;63:340-343.
37. Villavicencio Kim J, Wu GY. Celiac disease and elevated liver enzymes: a review. *J Clin Transl Hepatol*. 2021;9:116-124.
38. Barton SH, Murray JA. Celiac disease and autoimmunity in the gut and elsewhere. *Gastroenterol Clin North Am*. 2008;37: 411-428.
39. Tunio NA, Mansoor E, Sheriff MZ, Cooper GS, Sclair SN, Cohen SM. Epidemiology of autoimmune hepatitis (AIH) in the United States between 2014 and 2019: a population-based national study. *J Clin Gastroenterol*. 2021;55: 903-910.

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