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Persistence of anemia in patients with Celiac disease despite a gluten free diet: a retrospective study

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Abstract

Background The main treatment for Celiac Disease (CD) is the gluten-free diet (GFD). However, in some CD patients, iron deficiency anemia can be persistent despite a GFD.

Aim In this study, we aim to evaluate the prevalence of anemia in both adults and children with CD at the diagnosis and during the GFD.

Methods In this cross-sectional study including both adults and children with CD, the demographic characteristics and hemoglobin, iron, folate and vitamin B12 levels were retrospectively retrieved from patients' medical records at the time of diagnosis (T0); after 3–5 years (T1) and after 8–10 years (T2) of GFD.

Results 311 CD patients (184 adults and 127 pediatric patients) were included in the study. No difference was observed in the prevalence of anemia in the overall population after 3–5 years of GFD in both adult and pediatric patients compared to the diagnosis. At 8–10 years, in the adult patient's group, a significant reduction in the prevalence of anemia was observed (24% vs. 17.8% $p = 0.043$).

Conclusions Despite the GFD and a very long observational period the diagnosis of anemia persists in 17.8% and 4.4% of adult and pediatric patients, respectively. The diagnostic delay (longer in adult patients) and a more pronounced ultrastructural mucosal injury could play a role in the persistence of anemia despite the GFD.

Keywords Celiac disease, Gluten-free diet, Anemia, Iron deficiency

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Introduction

Celiac disease (CD) is an autoimmune disease affecting the small bowel mucosa linked to gluten ingestion in genetically predisposed subjects [1, 2]. The diagnosis of CD in adults is based on clinical manifestations, serology, genetics, and histopathological changes of intestinal mucosa which usually shows, intraepithelial lymphocytosis (IEL), crypt hyperplasia, and villous atrophy [2, 3].

In children with positive serology, such as anti-tissue-transglutaminase antibodies (tTG) IgA > 10 times the upper limit of normal values and positive anti-endomysial antibodies (EMA), diagnosis of CD can be made without histological evaluation. However, in the case of the no-biopsy approach HLA DQ should have also been performed. On the other hand, children with positive tTG IgA class antibodies but lower titers (< 10 times the upper limit of normal) should undergo biopsies to decrease the risk of false positive diagnosis [2, 4].

CD is a global healthcare problem. The estimated prevalence of CD in Western countries based on serological evaluation is 1%, whereas the biopsy-confirmed cases of CD range between 1.6 and 2.4% according to different studies and different Countries, and its incidence is continuously increasing [2, 4–6]. It is highest in females and children [7], although CD incidence is increasing in adults as well [5, 8–10]. In a recent multicenter study involving school-age children, the overall prevalence of celiac disease was 1.65% (95% CI, 1.34-2.01%) and only 40% of celiac children had been diagnosed prior to the school screening [11].

Since CD affects the duodenum, which is the tract that adsorbs iron from the diet, iron-deficiency anemia (IDA) represents a frequent clinical sign of CD both in children and in adults. Often the IDA is the only sign in subclinical/atypical forms of CD [12–14].

Other factors contributing to IDA include blood loss from intestinal lesions and chronic inflammation, during which pro-inflammatory cytokines sequester iron from the serum and reduce erythropoietin production [15, 16].

Kochhar et al. reported that 39% out of 434 CD patients had anemia as the only presenting feature [12].

In an Italian multicenter study, including 1026 patients with subclinical/silent CD, the most frequent extra-intestinal manifestation was IDA, in about 39% of cases [17].

Folate and vitamin B12 malabsorption can also be included in CD clinical manifestations. More extensive CD lesions could cause anemia (indeed folate is adsorbed in the jejunum and vitamin B12 in the terminal ileum). However, the real causes of this condition are still debated and far from being clarified [18, 19].

Interestingly, an observational study showed that the ratio of small-bowel villous height to crypt depth and results from serology tests correlate with reported symptoms and quality of life of patients with celiac disease [20]. Moreover, the presence of advanced villous atrophy at diagnosis is associated with more severe clinical characteristic in pediatric patients.

The only efficient treatment for CD is the gluten-free diet (GFD), no adjunctive therapy is supported by the current evidence [21]. In the majority of cases, strict adherence to GFD leads to the disappearance of clinical symptoms, serological alterations, histology modification in the duodenum, and the prevention of complications of CD [22].

In some patients with CD on a GFD, IDA can be persistent. These cases can be due to various conditions: nonadherence to the GFD, involuntary intake of food contaminated with gluten, a low-iron GFD, the persistence of atrophy of the intestinal mucosa or to some physiological causes of IDA, such as copious menses in fertile women, and gastrointestinal occult blood loss [23–25].

Furthermore, some patients are refractory to oral iron supplementation for possible side effects (such as abdominal discomfort, constipation, diarrhea) and require periodic intravenous iron administration [26].

In patients with persistent IDA, despite normal histology of duodenal mucosa and the administration of oral iron supplementation, ultrastructural alterations of the enterocytes that can impair iron absorption should also be considered, meanwhile, intravenous iron administration is necessary in these cases [27–29].

This study aims to evaluate the prevalence of anemia in both adults and children with CD at the diagnosis and during a long period of GFD.

Methods

Study design and population

This is a cross-sectional study including all adult CD patients followed at the Gastroenterology, Hepatology and Nutrition division, and all the pediatric CD patients followed at the Pediatric division of the University Hospital of L'Aquila (L'Aquila, Italy).

Considering the retrospective study design, CD diagnosis was based according to the criteria reported in the guidelines available at the time.

For adult patients, the diagnosis was based on standard clinical, serologic, and histological criteria as mentioned in the 2014 British guidelines [30]. All the adult patients included in the study were diagnosed at the Gastroenterology Unit during adulthood (> 18 years of age).

All patients between 0 and 18 years of age were diagnosed with CD according to the 2012 ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition) criteria [31].

All clinical investigations were conducted according to the principles laid down in the Declaration of Helsinki and reported according to the Strengthening the

Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines [32].

Internal Review Board of the University of L'Aquila issued ethics approval [protocol number: IRB 25/2018]. All subjects gave their consent to participate in the current study and in data processing.

Patient information was retrospectively retrieved from medical records at the time of diagnosis (T0), and at follow-up time: after 3–5 years (T1) and after 8–10 years (T2) of GFD.

The following data were collected from the patient's medical records if available:

- Age;
- Gender;
- Date of diagnosis;
- Histolopathology reports.
- HLA genotyping (HLA DQ2 and HLA DQ8);
- Presence of intestinal (diarrhea, steatorrhea, abdominal pain) and extra-intestinal symptoms/manifestations (dermatologic, musculoskeletal, ocular, oral and gynecological symptoms, anemia);
- Comorbidities (diabetes and thyroiditis).
- Laboratory analysis including CD antibodies, blood count, Iron levels.
- Iron deficiency (threshold was set as follows: Adult 50–170 µg/dL (U); Children 40–100 µg/dL (age < 1 year); 53–119 µg/dL (age > 1 year) [33, 34].

The CD antibodies measured consisted of IgA anti-tissue transglutaminase (IgA anti-TTG), IgA anti-endomysium (EMA) levels. Total IgA levels were also evaluated.In the case of IgA deficiency, IgG anti-tissue transglutaminase (IgG anti-TTG) was also measured [35].

The biopsy assessment was carried out as recommended in the reported guidelines [30, 31]. At least six biopsies were taken in case of suspected CD for the adult patients (4 in the duodenum second portion and at least 2 in the duodenal bulb) [36]. For pediatric patients, the biopsy assessment was carried out only in case of a not definitive diagnosis based on the serological tests (positive tTG IgA class antibodies with titers > 10 times the upper limit of normal). In the case of the no-biopsy approach HLA DQ evaluation was performed [31].

In the case of biopsy assessment, the diagnosis of biopsy-proven CD was made if Marsh 2 or 3 findings were mentioned in the pathology report from a duodenal biopsy.

All patients were evaluated by a celiac expert nutritionist and/or a gastroenterologist to assess the GFD adherence. In the case of a GFD non-adherence, the patients were excluded.

All patients received appropriate supplementation (Iron, folic acid or Vitamin B12) when needed as usual in our division.

Inclusion and exclusion criteria

Inclusion criteria

- Definite diagnosis of CD according to the available guidelines.
- Clinical and laboratory data (a complete blood count and CD serology) at diagnosis and at least one of the two follow-up times after the start of the GFD.

Exclusion criteria

- Incomplete clinical charts.
- No clinical or laboratory follow-up.
- Comorbidities which might influence anemic status (e.g. Inflammatory Bowel Disease, chronic kidney disease, thalassemia, microcytic anemia, need for blood transfusion, other blood disorders, etc.)
- GFD non-adherence after the CD diagnosis.

Outcomes

Our primary outcome was the assessment of the prevalence and severity of anemia in patients with celiac disease at diagnosis and after the introduction of the GFD (at T1 and T2).

The frequency and severity of anemia were assessed by evaluating hemoglobin concentration (HGB).

In the adult population, the anemia was defined as values below 12 g/dL for women and 13 g/dL for men. For the other reference values of the parameters used in children and the definition of the severity of anemia see Supplementary Table 1 [37].

Statistical analysis

Statistical analysis was performed with Stata v. 17.0. (StataCorp. College Station, TX, USA; https://www.stata.com; 2021). Data were summarized using absolute and relative frequencies for categorical variables and mean and standard deviation (SD) for numerical variables. Data were compared using Student's t-tests for continuous variables and Chi-Squared test for dichotomous variables. The variables that were thought to be candidate predictors for Hb value modification, and for the insurgence of anemia, were investigated in univariate regression analysis. Multilevel regression (patient < time) was then used to investigate the relationship between primary outcomes and candidate predictors. The risk of anemia was investigated using a logistic model. The statistical significance level was set at $p = 0.05$ for all inferential analyses.

Table 1 Baseline demographic and clinical characteristics of patients

	Adults			Paediatrics		
	Anemic ***N*** **= 44**	**Non anemic** ***N*** **= 139**	***p***	**Anemic** ***N*** **= 7**	**Non-anemic** ***N*** **= 119**	***p***
Sex gender (Male %) N. (%)	1/44 (2%)	34/136 (25%)	**< 0.01** [a]	1/7 (14%)	42/119 (35%)	0.17 [a]
Age at diagnosis years mean (± SD)	36.7 (± 12.5)	37 (± 12.1)	0.54 [b]	3.9 (± 1.9)	5.5 (± 3.4)	**0.03** [b]
Genotype (HLA) N. (%)			0.49 [a]			0.17 [a]
DQ2	8/12 (66.6%)	28/43 (65.1%)		3/4 (75%)	72/89 (80.9%)	-
DQ8	2/12 (16.6%)	3/43 (6.9%)		0/4 (0%)	13/89 (14.6%)	-
Both	2/12 (16.6%)	12/43 (27.9%)		1/4 (25%)	4/89 (4.5%)	-
Clinical presentation N. (%)			0.17 [a]			0.38 [a]
None	0/42 (0%)	8/130 (6.2%)		0/5 (0%)	0/107 (0%)	
Gastrointestinal manifestation	9/42 (21.4%)	40/130 (30.8%)		2/5 (40%)	62/107 (57.9%)	
Extraintestinal manifestation	2/42 (4.7%)	3/130 (2.3%)		0/5 (0%)	11/107 (10.3%)	
Both	31/42 (73.8%)	79/130 (60.8%)		3/5 (60%)	34/107 (31.7%)	
Autoimmune thyroiditis N. (%)	6/35 (17.1%)	30/124 (24.2%)	0.38 [a]	0/7 (100%)	105/114 (7.9%)	0.44 [a]
Diabetes N. (%)	2/35 (5.7%)	2/123 (1.7%)	0.17 [a]	0/7 (0%)	0/116 (0%)	-
Iron deficiency N. (%)						
Iron	4/15 (35.7%)	15/42 (26.6%)	0.52 [a]	5/5 (100%)	23/65 (35.4%)	**< 0.01** [a]
Ferritin	5/11 (45.5%)	24/47 (51.1%)	0.73 [a]	4/6 (66.6%)	5/56 (8.9%)	**< 0.01** [a]
Vitamin B12	0/11 (0%)	1/42 (2%)	0.82 [a]	0/5 (0%)	0/15 (0%)	-
Folic Acid	3/11 (27.2%)	10/47 (21.2%)	0.52 [a]	0/6 (0%)	0/15 (0%)	-

a: Pearson's χ^2 test; b: unpaired t test;

Table 2 Prevalence and mean of hb levels in Celiac disease patients

	T0 mean ± SD (*N*)	**T1 mean ± SD (*N*)**	**T2 mean ± SD (*N*)**	**T0 vs. T1 (*p* value)**	**T0 vs. T2 (*p* value)**	**T1 vs. T2 (*p* value)**
Paediatrics						
Prevalence N (%)	7 (5.6%)	2 (1.6%)	3 (4.4%)	-3.97% (0.173)	**-1.21% (0.405)**	-2.76% (0.709)
Tot	13.01 ± 1.1 (126)	13.67 ± 0.97 (126)	13.92 ± 1.1 (69)	**+0.6 (< 0.001)**	**+0.9 (< 0.001)**	+0.3 (0.054)
Male	13.21; ±1.0 (43)	13.71; ±1.1 (43)	14.42; ±1.00 (22)	**+0.5 (0.017)**	**+1.2 (< 0.001)**	**+0.7 (0.006)**
Female	12.93; ±1.2 (83)	13.65; ±0.87 (83)	13.70; ±1.1 (47)	**+0.7 (< 0.001)**	**+0.8 (< 0.001)**	+0.1 (0.405)
Adults						
Prevalence N (%)	44 (24.0%)	26 (19.4%)	26 (17.8%)	-4.64% (0.111)	**-6.36% (0.043)**	-1.72% (0.333)
Tot	13.00; ±1.8 (182)	13.38; ±1.8 (134)	13.49; ±1.7 (147)	**+0.4 (0.036)**	**+0.5 (0.006)**	+0.1 (0.309)
Male	14.99; ±1.2 (35)	12.96; ±1.5 (22)	13.11; ±1.7 (32)	**-2 (< 0.001)**	**-1.1 (< 0.001)**	+0.15 (0.367)
Female	12.53; ±1.6 (147)	13.46; ±1.9 (112)	13.59; ±1.6 (115)	**+0.9 (< 0.001)**	**+1.9 (< 0.001)**	+0.13 (0.296)

T0: diagnosis; T1: 3–5 years of disease duration; T2: 8–10 year of disease duration; SD: Standard Deviation

Results

Overall population and prevalence of anemia

311 CD patients (184 adults and 127 pediatric patients) were included in the study. The baseline characteristics and the mean value of HGB levels are reported in Tables 1 and 2.

The overall mean HGB levels increased over time in all the sub-groups analyzed, except in male adult patients (only 22 and 32 subjects included at T1 and T2 respectively).

Among the anemic patients, a moderate mean HGB levels were observed in both adult and pediatric patients (10.56 ± 1.23, $n = 44$ and 10.24 ± 0.85, $n = 7$, respectively).

However, no difference was observed in the prevalence of anemia in the overall population after 3–5 years of GFD in both adult and pediatric patients (Table 2). At 8–10 years, in the adult patients' group, a significant

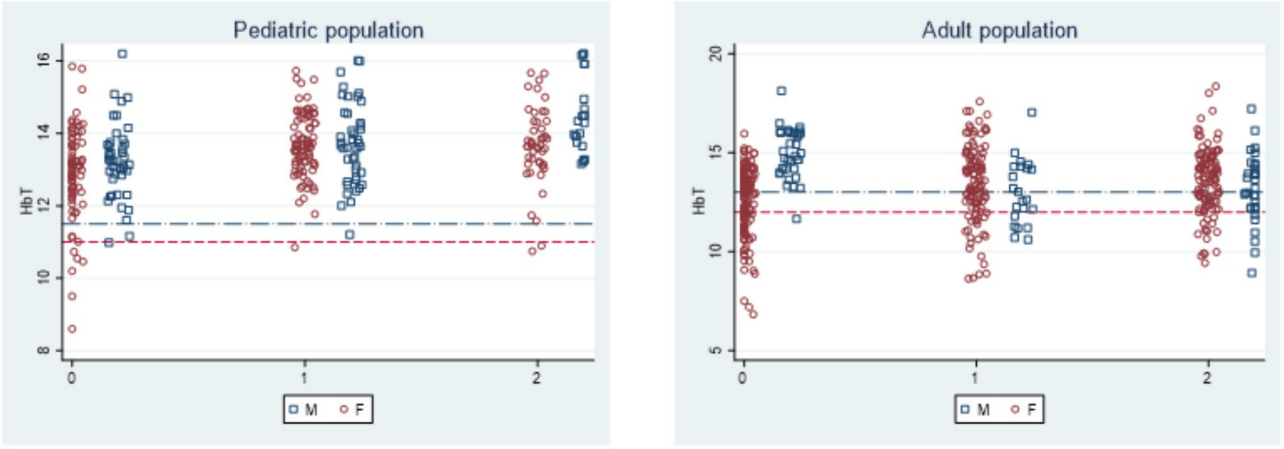

Fig. 1 Hb levels in the included populations (both pediatric and adult patients at T0, T1, and T2)

Table 3 Marsh degrees in anemic adult Celiac disease patients

Histological data available (*N*)		T0 (44/44)	T1 (23/26)	T2 (9/26)
Anemia prevalence (N anemic/total included patients)		44/183 (24.0%)	26/134 (19.4%)	26/147 (17.8%)
Marsh degrees	**0**	0/44	4/23 (17%)	6/9 (67%)
	I	0/44	13/23 (57%)	2/9 (22%)
	II	9/44 (20%)	2/23 (9%)	0/9 (1%)
	III	35/44 (80%)	4/23 (17%)	1/9 (1%)

reduction in the prevalence of anemia was observed (24% vs. 17.8% $p = 0.043$) (Table 2; Fig. 1; Supplementary Figs. 1–4).

Baseline characteristics of patients with CD

Among the adult and pediatric groups, the prevalence of anemia was higher in the female populations (adults: $p = 0.001$; pediatrics: 0.010), while in the pediatric group, the mean age of anemic patients was lower compared to the non-anemic group, and they more commonly had Iron deficiency (Table 1). The data concerning the severity of anemia at the diagnosis are reported in Supplementary Table 2.

In the majority of adults patients with anemia at T1 (3–5 years after diagnosis), mucosal changes defined as Marsh 0 (4/23) or Marsh 1 (13/23) were described (17/23; 88%). Two patients had Marsh 2 and four Marsh 3. Among the adults with anemia at T2 (8–9 years after diagnosis), histological data was available only in 9/26 patients. Marsh degree of 1 or 2 was observed in 8/9 of the included patients. One patient presented a Marsh 3 (Table 3).

Multivariate analysis

The multivariate model analysis showed that only the group at diagnosis (adult or pediatric) represents an independent risk factor to present persistent anemia during the disease history (Table 4). Gender and genotype did not influence the persistence of anemia during the observation period.

As shown in Fig. 2, adult patients had a higher marginal predicted incidence rate of anemia compared to pediatric patients (0.037 vs. 0.193, $p < 0.002$).

Table 4 Generalized linear model of anemia outcome vs. several candidate predictors

	Odds Ratio	Standard Error	Z	*P*>z	Confidence Interval [95%]	
Group						
Pediatrics	reference					
Adult	6.1797	2.6283	4.28	**0.000**	**2.6849**	**14.2234**
Gender						
Female	Reference					
Male	1.2067	0.5198	0.44	0.663	0.5187	2.8072
Genotype (HLA)						
DQ2	reference					
DQ8	1.4123	0.7688	0.63	0.526	0.4859	4.1048
Both	0.6624	0.3586	-0.76	0.447	0.2292	1.9144

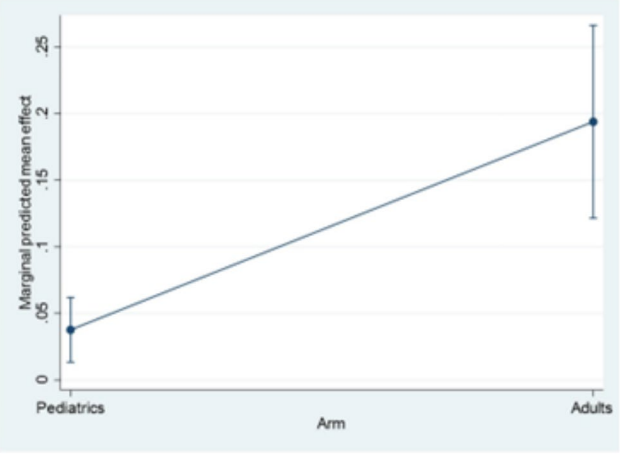

Fig. 2 Marginal effect of age (x-axis) on risk of anemia incidence in adults and children with celiac disease

Discussion

In this study we reported the data concerning the prevalence of anemia and the HGB levels in the CD population followed at the University Hospital of L'Aquila (L'Aquila, Italy). At the diagnosis, the prevalence of anemia was 5.6% and 24% in pediatric and adult patients, respectively.

At the baseline, the prevalence of anemia was higher in the female CD patients, among the adult group only. Probably it is linked to the menstrual cycle considering the mean age at the diagnosis in this group (mean age 36.7 ± 12.5). While, the anemic pediatric patients presented more often young age and iron deficiency at the diagnosis, probably due to a more severe clinical presentation at the diagnosis (Table 1). Moreover, younger children more often present with malabsorptive CD which with their already reduced iron storage and high iron demand makes them more susceptible for IDA [38].

At the end of the observation period, the prevalence of anemia was 4,4% and 17.8% with a significant reduction observed in the adult group only.

CD symptoms or signs can include typical gastrointestinal or extra-intestinal manifestations [35]. Among the latter, anemia is the most common, and its prevalence is reported from 12 to 69% in patients with a new CD diagnosis [33, 39]. Moreover, a recent retrospective study showed a prevalence of 18.9% in children with a new diagnosis of CD [7]. Another prospective study, after two years of follow up 81% and 89% of CD patients normalized their Hb levels within 1 year and 2 years of beginning a GFD, respectively [40]. Patients with persistent anemia had at diagnosis a higher prevalence of female gender ($p = 0.02$), lower body mass index (BMI, $p = 0.01$), higher prevalence of poly/hypermenorrhea ($p = 0.02$) and skin atopy ($p = 0.04$) compared to the non-anemic CD patients [33].

Anemia of CD is due mainly to impaired absorption of iron: in fact, the duodenum is the main site of iron absorption, and CD primarily affects this bowel tract. Less frequently, anemia can be due to other vitamins deficiency (e.g. folate, vitamin B12) [39]. Some studies reported improved anemia in about 90% of patients with CD after starting GFD [41]. Interestingly, an observational prospective study showed no fully restored ferritin levels during the follow-up of patients with CD on a GFD [42]. In our study, despite the mean HGB level increased after starting GFD, anemia prevalence didn't significative differ after 3–5 years of GFD. Instead, after 8–10 years of GFD and only in the adult group, a significant reduction in the prevalence of anemia was observed. Thus, after 3–5 and 8–10 years of GFD, about 1/5 of adult celiac patients continue to be anemic despite the healing of duodenal mucosa. The most of anemic patients at T1 (3–5 years after CD diagnosis) had Marsh 0 or 1 (88%; 4/23 and 13/23, respectively). These data partially disprove the idea that the improvement of duodenal villous atrophy alone is enough to resolve anemia thanks to the restoration of iron absorption. A hypothesis that could explain the anemia persistence is that iron absorption could be impaired by enterocyte ultrastructural alterations that persist beyond the evidence of duodenal histological healing [24]. Some anemic patients are refractory to oral iron supplementation despite the recovery of duodenal mucosa, and it supports the possible role of enterocyte ultrastructural alterations [43]. Medium or high-power scanning electron microscopy of enterocytes after GFD in patients with CD showed ultrastructural alterations such as disrupted and decreased glycocalyx, and irregular or absent microvilli [27–29]. Another role could be played by the variable expression of proteins involved in iron regulation, such as DMT1, DCYTB, ferroportin 1, hephaestin, and transferrin receptor 1.

In our study, the prevalence of anemia was higher in adults compared with pediatric patients. The reasons are unknown, but some aspects must be taken into account to try to explain this difference. First, duodenal mucosa recovery is faster and more complete in children than in adults [44]. Probably, the latter is partially due both to the diagnostic delay in adults and a greater GFD adherence of children compared to adults [41, 45]. However, to clarify this hypothesis further studies are needed.

Our study had a few important limitations. First, the inherent limits are due to the retrospective design of the study. In particular, we had limited or no information concerning the comorbidities and the patient's home therapies. Moreover, some data at T1 and T2 were available in only a small percentage of the included patients.

However, we have the opportunity to show real-world, unselected, data in a very long follow-up. Moreover, during the considered observational period, all the patients

followed in our unit were forced to have an outpatient visit, to obtain the meal voucher for the gluten-free products. This makes the results more reliable and provides the advantage of enrolling a sample representative of the general population followed in our Unit.

In conclusion, this study shows that anemia prevalence at the diagnosis is more common in adult patients compared to children. Moreover, despite the GFD and a very long observational period the diagnosis of anemia persists in 17.8% and 4.4% of adult and pediatric patients, respectively.

The diagnostic delay (longer in adult patients) and the presence of enterocyte ultrastructural alterations could play a role in the persistence of anemia despite the GFD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03712-6.

Supplementary Material 1

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Author contributions
M.V: conception of the work, methodological assessment, write original draft; C.G: write original draft, data collections; A.V (Antonio Vinci): write original draft, statistical analysis; S.F, G.S and N.C: write original draft; C.C: and M.M: interpretation of data; A.V (Angelo Viscido) and G.L: conception of the work, interpretation of data and critical revision of the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Internal Review Board of the University of L'Aquila issued ethics approval [protocol number: IRB 25/2018]. All subjects gave their consent to participate in the current study and in data processing. Informed consent was obtained from all the participants. For patients under the age of eighteen informed consent was obtained from the parents/legal guardians of these participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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