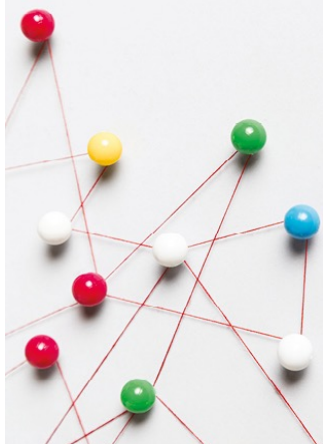


Anemia e Malattia Celiaca

Solo un 'problema di malassorbimento'?



**Università
degli Studi
di Palermo**

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Dipartimento di Promozione della Salute, Materno-Infantile, Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"

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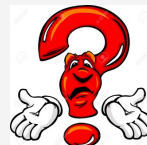
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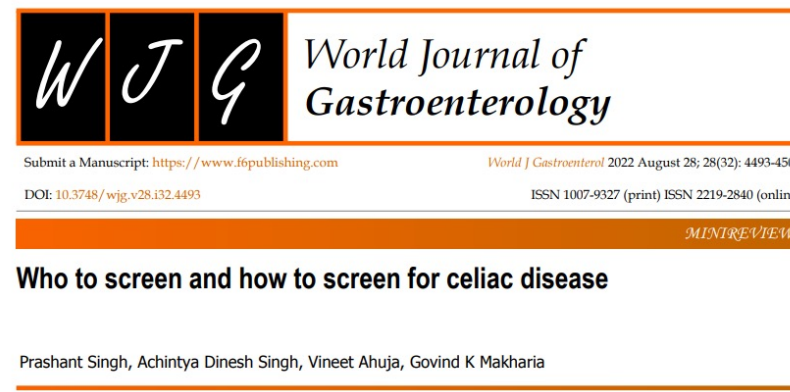
« < Page 1 of 81 > »



Una possibile scaletta...

- Chi può essere interessato al/dal problema?
- Quali sono i numeri di cui stiamo parlando?
- Quale origine ha l'anemia nei pazienti celiaci?
- Qual è l'approccio terapeutico ottimale?
-

Chi può essere interessato al/dal problema?



The clinical manifestations of CeD may be related to the gastrointestinal tract, called “classical CeD” seen in 50%-60% of all cases or non-gastrointestinal symptoms called “non-classical CeD” accounting for 40%-50% of cases [6,7].

The non-classic symptoms like short stature **anemia**, dyspepsia, infertility or hypertransaminasemia could be the sole manifestations of CeD making the clinical diagnosis more elusive.

Additionally, CeD can co-exist with type 1 diabetes or other autoimmune diseases and its **clinical manifestations may remain submerged** with the manifestations of primary disease or it may remain **clinically silent** [8,9].

Because of its diverse manifestations, patients with **CeD may present to healthcare professionals** other than gastroenterologists or pediatricians such as **hematologists with anemia**, endocrinologists for short stature or type 1 diabetes, or gynecologists with infertility.

The **lack of typical manifestations combined with unfamiliarity with the disease** lowers the index of suspicion for CeD in such clinical settings. This results in the **missed diagnosis of CeD and about 85%-90%** of the patients with CeD remain undiagnosed [10-12]. A delay in the diagnosis and institution of appropriate treatment adds to significant morbidity and even mortality in these patients [13].

Cosa dicono le linee guida negli USA...

Table 2

Conditions in which CD occurs more frequently than in the general population and/or for whom a GFD may be beneficial.

CD Common (>2 times prevalence of general population)	CD less Common but treatable
Symptomatic malabsorption	Pulmonary hemosiderosis
Diarrhea with weight loss	Unexplained male or female infertility
Chronic diarrhea with or without abdominal pain	Dyspepsia
Chronic iron deficiency and anemia	Amenorrhea
Metabolic bone disease and premature osteoporosis	Chronic fatigue
Postprandial bloating and gaseousness	Apparent malabsorption of thyroid replacement medication
Unexplained weight loss	Epilepsy or Ataxia
Abnormal elevated liver enzymes	Constipation
Incidental discovery of villous atrophy endoscopically or histologically	Recurrent abdominal pain
Dermatitis herpetiformis	
Peripheral neuropathy	
Oral aphthous ulcers	
Growth failure	
Discolored teeth or developmentally synchronous enamel loss	
Thyroid disease	
Irritable bowel syndrome	
Down's and Turner's syndromes	

AMERICAN COLLEGE OF GASTROENTEROLOGY CLINICAL GUIDELINE: DIAGNOSIS AND MANAGEMENT OF CELIAC DISEASE

Alberto Rubio-Tapia, MD¹, Ivor D Hill, MD², Ciarán P Kelly, MD³, Audrey H Calderwood, MD⁴, and Joseph A Murray, MD¹

There is no consensus regarding which symptoms, laboratory abnormalities, and/or associated diseases require evaluation for CD. The frequency of CD in common clinical scenarios varies from modestly elevated, such as irritable bowel syndrome, to substantially elevated, such as **unexplained iron deficiency anemia** (Table 2) (9,10,11)

.....

Thus, mucosal biopsies of the duodenum should be considered in patients with dyspepsia who undergo investigation with upper endoscopy because of persistent symptoms despite initial therapy, are aged >55 years old, and/or present **alarm symptoms** (e.g., weight loss or **clinical evidence of anemia**) (15)

New Guidelines for the Diagnosis of Paediatric Coeliac Disease



Coeliac Disease (CD) is underdiagnosed due to the varied presentation of clinical signs and symptoms. This advice guide provides new and updated summary guidance from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) on diagnosing children and adolescents with CD.



What's new in the 2020 guidelines?

- For initial testing, the combination of total IgA and IgA class antibodies against transglutaminase 2 (TGA-IgA) is recommended as this is most accurate and cost-effective. EMA-IgA or DGP-IgG need not be tested initially
- The no-biopsy approach for CD diagnosis is confirmed to be safe in children with high TGA-IgA values ≥ 10 times the upper limit of normal with accurate, appropriate tests and positive endomysial antibodies (EMA-IgA) in a second serum sample
- Children with positive TGA-IgA but lower titers (<10 times upper limit of normal) should undergo biopsies to decrease the risk of false positive diagnosis.
- HLA testing and presence of symptoms are not obligatory criteria for a serology based diagnosis without biopsies.

Consider testing for CD with the following symptoms, signs and conditions:



- chronic or intermittent diarrhoea/constipation/abdominal pain
- distended abdomen
- recurrent nausea and/or vomiting

Extraintestinal symptoms



- weight loss/failure-to-thrive
- delayed puberty, amenorrhea
- irritability, chronic fatigue
- neuropathy
- arthritis/arthralgia
- chronic iron-deficiency anaemia
- decreased bone mineralization (osteopenia/osteoporosis), repetitive fractures
- recurrent aphthous stomatitis
- dermatitis herpetiformis-type rash
- dental enamel defects
- abnormal liver biochemistry

Specific conditions



- first-degree relatives with CD
- autoimmune conditions: T1DM, thyroid disease, liver disease
- Down syndrome
- Turner syndrome
- Williams-Beuren syndrome
- IgA deficiency

Abbreviations
IgA: Immunoglobulin type A
TGA-IgA: IgA against type-2 transglutaminase
EMA-IgA: IgA against endomysium

IgG: Immunoglobulin type G
DGP-IgG: IgG against Deamidated Gliadin Peptide
HLA: Human leukocyte antigen
ULN: Upper limit of normal

... in Europa ...

Review Article

UNITED EUROPEAN
GASTROENTEROLOGY
ueg journal

United European Gastroenterology Journal
2019, Vol. 7(5) 583-613
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SAGE

European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders

Abdulbaqi Al-Toma¹, Umberto Volta², Renata Auricchio^{3,*}, Gemma Castillejo^{4,*}, David S Sanders⁵, Christophe Cellier⁶, Chris J Mulder⁷ and Knut E A Lundin^{8,9}

Table 1. Who should be tested for CD?

Endoscopy and duodenal biopsy even if CD serology is negative

- (1) Chronic (non-bloody) diarrhoea
- (2) Diarrhoea with features of malabsorption, especially weight loss
- (3) Iron deficiency anaemia in absence of other causes
- (4) GI symptoms with a family history of CD
- (5) GI symptoms in patient with autoimmune disease or IgA deficiency
- (6) Failure to thrive in children
- (7) Skin biopsy-proven DH
- (8) Patient with video capsule findings suggestive for villous atrophy
- (9) Unexplained high output ileo-(colo-)stomy

CD serology is indicated: biopsy is needed only when serology is positive

- (1) IBS
- (2) Elevated otherwise unexplained liver transaminases
- (3) Chronic GI symptoms without a family history of CD or a personal history of autoimmune disease
- (4) Microscopic colitis
- (5) Hashimoto's thyroiditis and Graves' disease
- (6) Osteopenia/osteoporosis
- (7) Unexplained ataxia or peripheral neuropathy
- (8) Recurrent aphthous ulcerations/dental enamel defects
- (9) Infertility, recurrent miscarriage, late menarche, early menopause
- (10) Chronic fatigue syndrome
- (11) Acute or chronic pancreatitis after excluding other known causes
- (12) Epilepsy; headaches including migraines; mood disorders; or attention-deficit disorder/cognitive impairment
- (13) Hyposplenism or functional asplenia
- (14) Psoriasis or other skin lesions than DH
- (15) Down's or Turner's syndrome
- (16) Pulmonary haemosiderosis
- (17) IgA nephropathy

... ed in Italia



L'aumentata prevalenza della malattia celiaca in condizioni cliniche specifiche supporta la ricerca della malattia in diversi setting: sintomi classici di malassorbimento ma anche quadri gastrointestinali ed extraintestinali e in patologie associate. Gli autori raccomandano la ricerca della malattia celiaca mediante lo studio sierologico in tutte le condizioni cliniche elencate di seguito:

- Familiari di I grado di pazienti celiaci
- Diarrea cronica
- Perdita di peso non spiegabile da altra causa
- **Anemia da carenza di ferro**
- Deficit di ferro, acido folico e vitamina B12

**Linee guida per la diagnosi, la terapia e il follow-up della malattia
celiaca e della dermatite erpetiforme**

**Linea guida pubblicata nel Sistema Nazionale Linee Guida
Roma, 12 giugno 2023**

popolazione generale. **Pazienti con anemia**, diabete di tipo 1, osteoporosi, patologie alla tiroide, deficit di immunoglobulina A, sindrome di Down, sindrome di Turner o familiarità per patologia celiaca hanno maggiori probabilità di avere diagnosi di malattia celiaca e a questi si dovrebbe offrire un test.

Una possibile scaletta...

- Chi può essere interessato al/dal problema?
- Quali sono i numeri di cui stiamo parlando?
- Quale origine ha l'anemia nei pazienti celiaci?
- Qual è l'approccio terapeutico ottimale?
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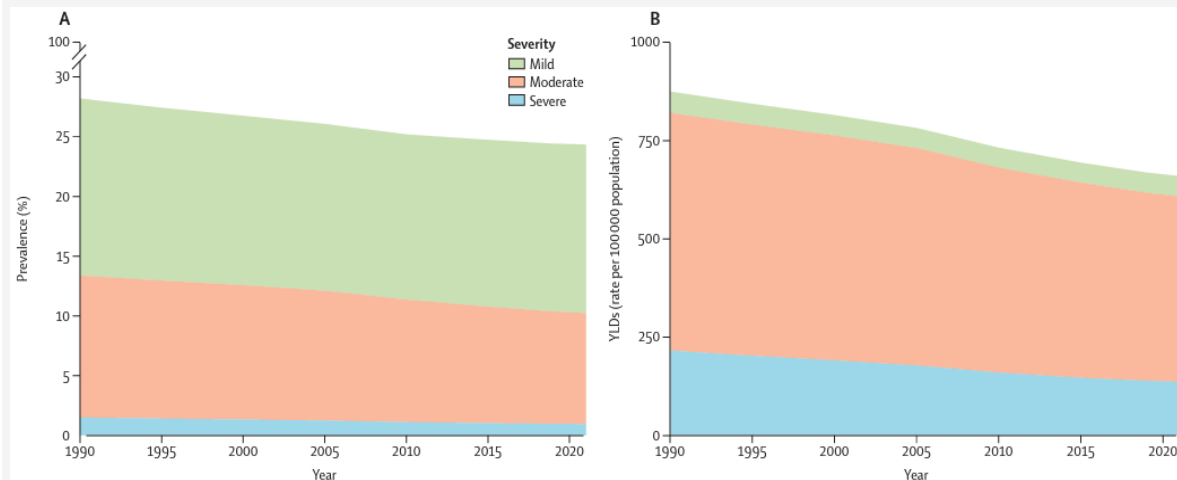
L'anemia nel mondo oggi ...

Prevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990–2021: findings from the Global Burden of Disease Study 2021

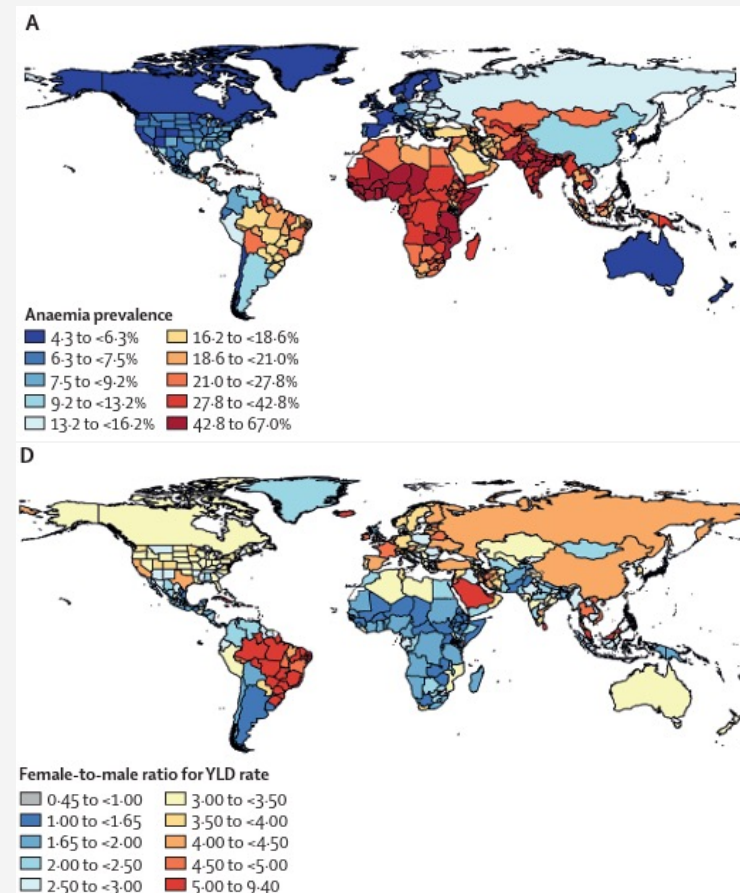


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Haematology

Lancet Haematol 2023;
10: e713–34
Published Online
July 31, 2023
[https://doi.org/10.1016/S2352-3026\(23\)00160-6](https://doi.org/10.1016/S2352-3026(23)00160-6)



YLDs=years lived with disability



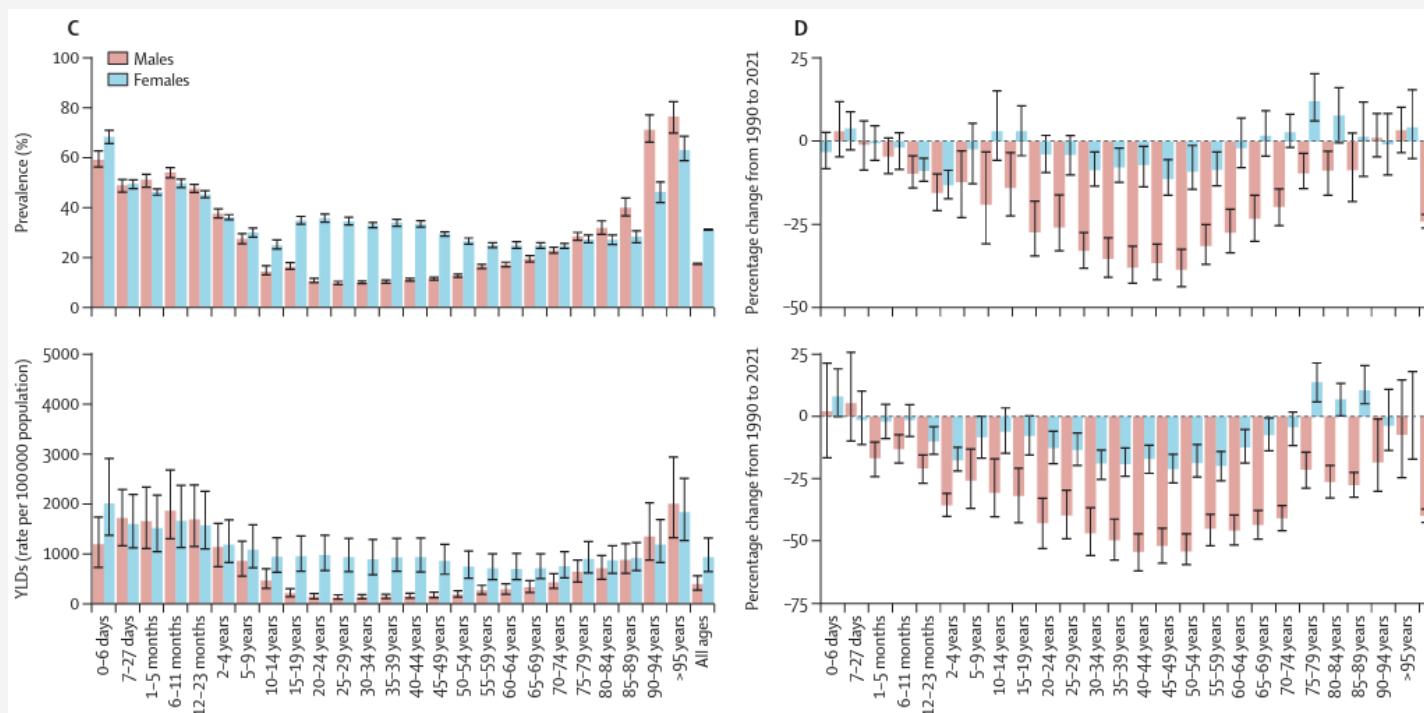
... e la sua evoluzione nel corso del tempo

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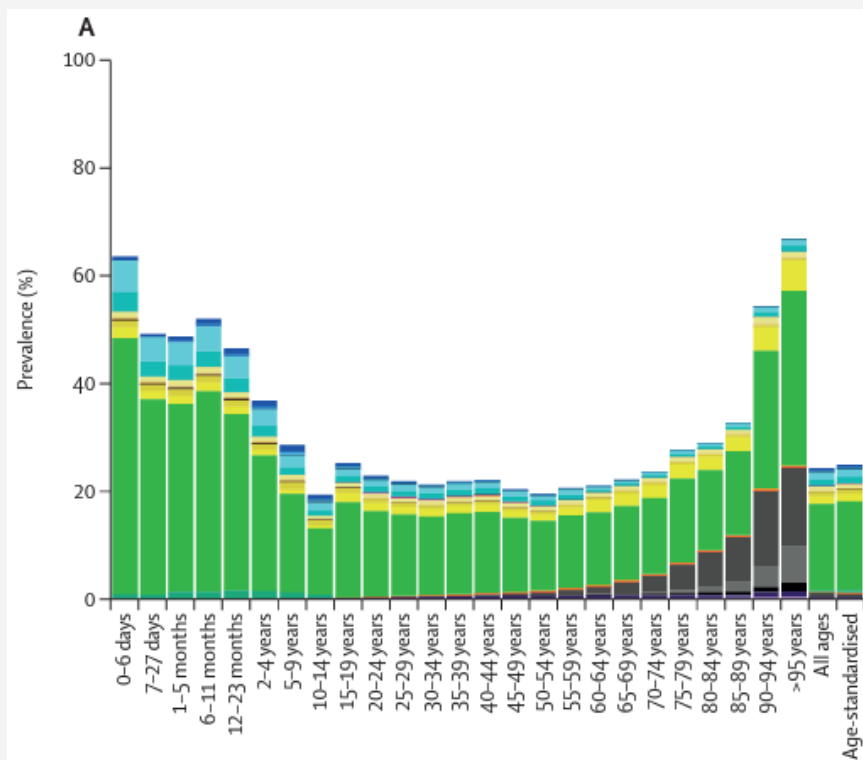


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Cause-specific anaemia prevalence by age, for male and female sexes



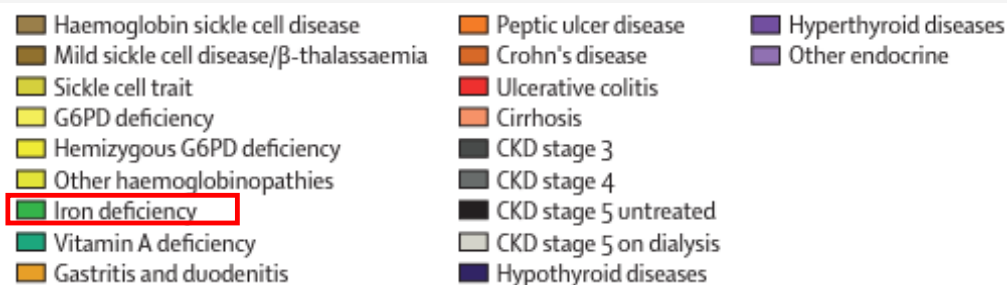
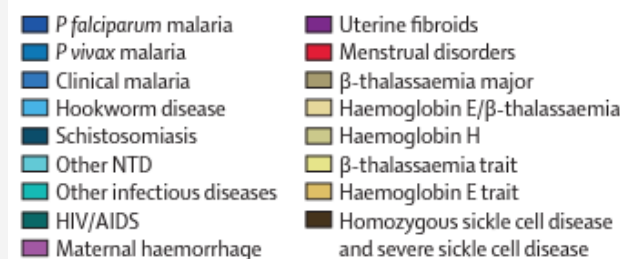
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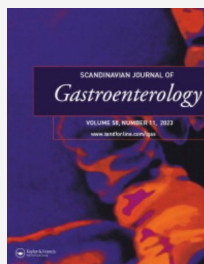
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Quanti pazienti anemici sono affetti da celiachia?





Original Article

Subclinical Coeliac Disease is a Frequent Cause of Iron-Deficiency Anaemia

G. R. Corazza, R. A. Valentini, M. L. Andreani, M. D'anchino, M. T. Leva, L. Ginaldi, L. De Feudis, D. Quaglino & G. Gasbarrini ...show less

Pages 153-156 | Received 17 Feb 1994, Accepted 24 May 1994, Published online: 08 Jul 2009

Background: Although it is known that anaemia may be the only presenting symptom in coeliac disease, prevalence figures of unsuspected coeliac disease in anaemic patients are not available. The aim of this study was to assess the clinical usefulness of anti gliadin and antiendomysial antibody tests in the diagnostic algorithm of anaemic patients. **Methods:** Two hundred consecutive anaemic patients were tested for anti gliadin antibodies, and those positive were also tested for antiendomysial antibodies. All patients positive for anti gliadin and antiendomysial antibodies underwent intestinal biopsy. **Results:** Sixteen patients were anti gliadin antibody-positive, and 10 were also antiendomysial antibody-positive. In all 10 a jejunal biopsy was consistent with coeliac disease (prevalence, 5%). This prevalence rose to 8.5% when patients with macrocytic anaemia or with microcytic anaemia due to previous bleeding or responsive to oral iron therapy were excluded from the calculation. **Conclusions:** Coeliac disease is a frequent cause of iron-deficiency anaemia, and anti gliadin and antiendomysial antibody tests should be always performed in the diagnostic algorithm of anaemic patients.

DISCUSSION

The prevalence of anaemia has already been studied in several large series of CD patients (6–8), but this is the first time that the prevalence of occult CD has been systematically studied in anaemic patients. Using highly sensitive screening tests such as AGA and EMA, we confirmed that anaemia is often the only presenting symptom of CD.

Table I. Clinical, laboratory, and histologic features of 16 anti gliadin antibody (AGA)-positive patients with anaemia

Patient no.	Sex	Age (years)	Diarrhoea	Percentage of ideal body weight	AGA (EU*)		IgA EMA†	Histology
					IgA	IgG		
1	F	15	—	98	—	6.5	1:500	Villous atrophy
2	F	26	—	95	2.6	7.5	1:50	Villous atrophy
3	F	21	—	102	8.0	8.0	1:200	Villous atrophy
4	F	4	+	93	—	4.2	1:400	Villous atrophy
5	F	33	+	79	4.7	3.7	1:500	Villous atrophy
6	F	18	—	90	4.0	22.7	1:500	Villous atrophy
7	F	43	+	102	5.0	—	1:500	Villous atrophy
8	M	26	—	74	2.3	—	1:400	Villous atrophy
9	M	14	—	80	3.2	2.2	1:500	Villous atrophy
10	M	4	—	115	7.2	9.5	1:500	Villous atrophy
11	F	18	—	Not done	—	2.6	—	Not done
12	F	37	—	Not done	—	3.6	—	Normal mucosa
13	F	27	—	Not done	—	5.3	—	Not done
14	F	49	—	Not done	—	3.8	—	Not done
15	F	12	—	Not done	—	6.8	—	Not done
16	F	21	—	Not done	—	17.5	—	Normal mucosa

* EU = ELISA units.

† EMA = antiendomysium antibodies.

JAMA Internal Medicine

Prevalence of Celiac Disease in At-Risk and
Not-At-Risk Groups in the United States
A Large Multicenter StudyAlessio Fasano, MD; Irene Berti, MD; Tania Gerarduzzi, MD; [et al](#)**Table 5. Prevalence of Celiac Disease (CD) in Specific Clinical Conditions and Prevalence of Specific Symptoms or Disorders in Newly Diagnosed Cases of CD**

Clinical Conditions	Subjects Screened, No.	Prevalence of CD, Ratio (%)	Prevalence of Symptoms or Diseases Among New CD Cases,* %
Gastrointestinal			
Chronic diarrhea	1848	1:26 (3.85)	35.3
Abdominal pain	1695	1:31 (3.23)	27.8
Constipation	1530	1:38 (2.63)	20.2
Extraintestinal			
Down syndrome	66	1:11 (9.09)	3.0
Infertility (idiopathic)	48	1:16 (6.25)	1.5
Type 1 diabetes mellitus	295	1:23 (4.35)	6.5
Anemia	73	1:24 (4.17)	1.5
Short stature	140	1:25 (4.00)	1.0
Joint pain	1779	1:31 (3.23)	29.3
Arthritis	99	1:33 (3.00)	1.5
Fatigue	1787	1:34 (2.94)	26.3
Asthma	487	1:35 (2.63)	7.1
Osteoporosis	435	1:39 (2.56)	5.5
Sjögren syndrome	98	1:49 (2.00)	1.0

*Note that patients had more than 1 symptom or disease.


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2007 109: 412-421
doi:10.1182/blood-2006-07-031104 originally published
online September 14, 2006

Hematologic manifestations of celiac disease

Thorvardur R. Halfdanarson, Mark R. Litzow and Joseph A. Murray

Table 2. Prevalence of celiac disease in patients with anemia

Study and year published	No. of patients	Positive by serology, %	Positive on biopsy, %	Comments
McIntyre and Long, ³⁸ 1993	114	n/a	2.6	IDA. Not all patients were biopsied.
Corazza et al, ³⁷ 1995	200	8	5	IDA. All patients with positive serology were biopsied.
Unsworth et al, ⁴² 2000	483	6.6	4.6	Four hundred eighty-three of 1380 blood donors with anemia were offered serologic screening; the majority of anemic CD patients had IDA. Not all seropositive patients were biopsied.
Haslam et al, ⁴³ 2001	216	2.3	n/a	Pregnant women with anemia. Four of 5 anemic women with positive serology had IDA.
Howard et al, ⁴⁴ 2002	258	10.9	4.7	The majority of patients had IDA. Four percent had folate deficiency. Not all seropositive patients were biopsied.
Ransford et al, ³⁹ 2002	484	3.5	2.3	All patients with hypochromic and microcytic anemia. Not all seropositive patients were biopsied.
Studies using endoscopy and small-bowel biopsies in patients with IDA				
Bini et al, ⁴¹ 1998	186	n/a	0	No patient was diagnosed with CD.
Kepczyk and Kadakia, ⁴⁰ 1995	70	n/a	5.7	Not all patients were biopsied.
Grisolano et al, ⁴⁵ 2004	103	n/a	8.7	All patients were biopsied.
Mandal et al, ⁴⁶ 2004	504	n/a	1.8	Not all patients were biopsied.

n/a indicates not available.

Evaluation of the gastrointestinal tract in premenopausal women with iron deficiency anemia

Edmund J Bini, MD  Philip L Micale, MD • Elizabeth H Weinshel, MD

Published: August 16, 2004 • DOI: [https://doi.org/10.1016/S0002-9343\(98\)00260-5](https://doi.org/10.1016/S0002-9343(98)00260-5)

THE AMERICAN JOURNAL
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Official Journal of the Alliance for Academic Internal Medicine

Table 1. Clinical Characteristics of 186 Premenopausal Women with Iron Deficiency Anemia Who Were Referred for Endoscopy*

Age (years)	43.8 ± 5.6 years
Severity of anemia	
Mild (10.5–11.5 g/dL)	59 (32%)
Moderate (9.5–10.4 g/dL)	78 (42%)
Severe (<9.5 g/dL)	49 (26%)
Hemoglobin (g/dL)	10.0 ± 0.9
Outpatients	158 (85%)
Race	
Caucasian	57 (31%)
Hispanic	44 (24%)
Black	36 (19%)
Asian	35 (19%)
Other	14 (8%)
Fecal occult blood test positive	23 (12%)
Abdominal symptoms	62 (33%)
Weight loss of at least 5 kg	12 (7%)
Current alcohol use	13 (7%)
Aspirin or NSAID use	66 (35%)
Current smoker	39 (21%)
History of peptic ulcer disease	14 (8%)
Family history of colon cancer	6 (3%)

* Plus-minus values are mean ± SD.
NSAID = nonsteroidal anti-inflammatory drug.

Table 2. Endoscopic Findings in 186 Premenopausal Women with Iron Deficiency Anemia

Lesion Detected	Number of Patients (%)
Upper Endoscopy	
Gastric cancer	5 (3%)
Gastric ulcer	3 (2%)
Duodenal ulcer	2 (1%)
Erosive gastritis	2 (1%)
Total	12 (7%)
Colonoscopy	
Colon cancer	6 (3%)
Colon polyps	3 (2%)
Ulcerative colitis	2 (1%)
Total	11 (6%)

0 celiac disease...
methodology errors?

Iron deficiency anemia resolved in 142 (92%) of the 155 patients in whom no cause was found by endoscopy. Eleven of the 13 patients in whom the iron deficiency anemia did not resolve were noncompliant with therapy (7 patients) or had an underlying medical illness (2 patients with chronic renal insufficiency and 2 with chronic liver disease).

Prevalence of Celiac Disease in Patients With Iron Deficiency Anemia—A Systematic Review With Meta-analysis

Srihari Mahadev,^{1,*} Monika Laszkowska,^{1,*} Johan Sundström,² Magnus Björkholm,³ Benjamin Lebwohl,¹ Peter H. R. Green,¹ and Jonas F. Ludvigsson^{1,4,5,6}

We identified 18 studies comprising 2998 patients with IDA for inclusion in our analysis. Studies originated from the United Kingdom, United States, Italy, Turkey, Iran, and Israel. The **crude unweighted prevalence of celiac disease was 4.8%** (n=143). Using a **weighted pooled analysis, we demonstrated a prevalence of biopsy-confirmed celiac disease of 3.2%** (95% CI, 2.6%-3.9%) in patients with IDA. However, heterogeneity was high ($I^2=67.7\%$). The prevalence of celiac disease was not significantly higher in studies with a mean participant age older or younger than 18 years, nor in studies with a mixed-sex vs female-predominant ($\geq 60\%$) population. On meta-regression, year of publication, proportion of females, age at celiac disease testing, and prevalence of in the general population were not associated with the prevalence of celiac disease in patients with IDA. **In the 8 studies fulfilling all our quality criteria, the pooled prevalence of celiac disease was 5.5% (95% CI, 4.1%-6.9%).**

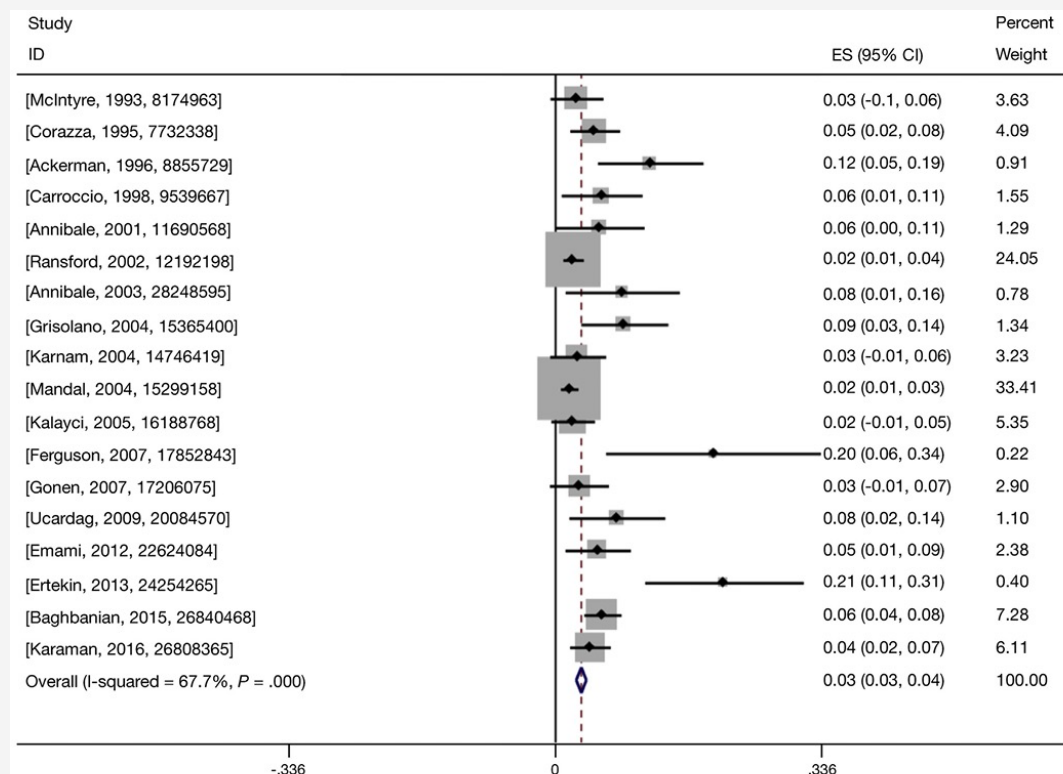


Figure 1. Prevalence of biopsy-verified celiac disease in iron-deficiency anemia. CI, confidence interval.

Quanti pazienti celiaci sono affetti da anemia?



Original Article |  Free Access**Anemia in celiac disease is multifactorial in etiology**Jason W. Harper, Stephen F. Holleran, Rajasehkar Ramakrishnan, Govind Bhagat, Peter H.R. Green First published: 18 July 2007 | <https://doi.org/10.1002/ajh.20996> | Citations: 133**TABLE III. Hematologic Characteristics of Cohort by Sex^a**

	Male	Female
Anemic	23/135 (17%)	54/238 (22%)
Iron deficient ^b	44/134 (33%)	51/266 (19%)
Folate deficient	7/67 (10%)	18/135 (13%)
B12 deficient	6/76 (8%)	6/149 (4%)

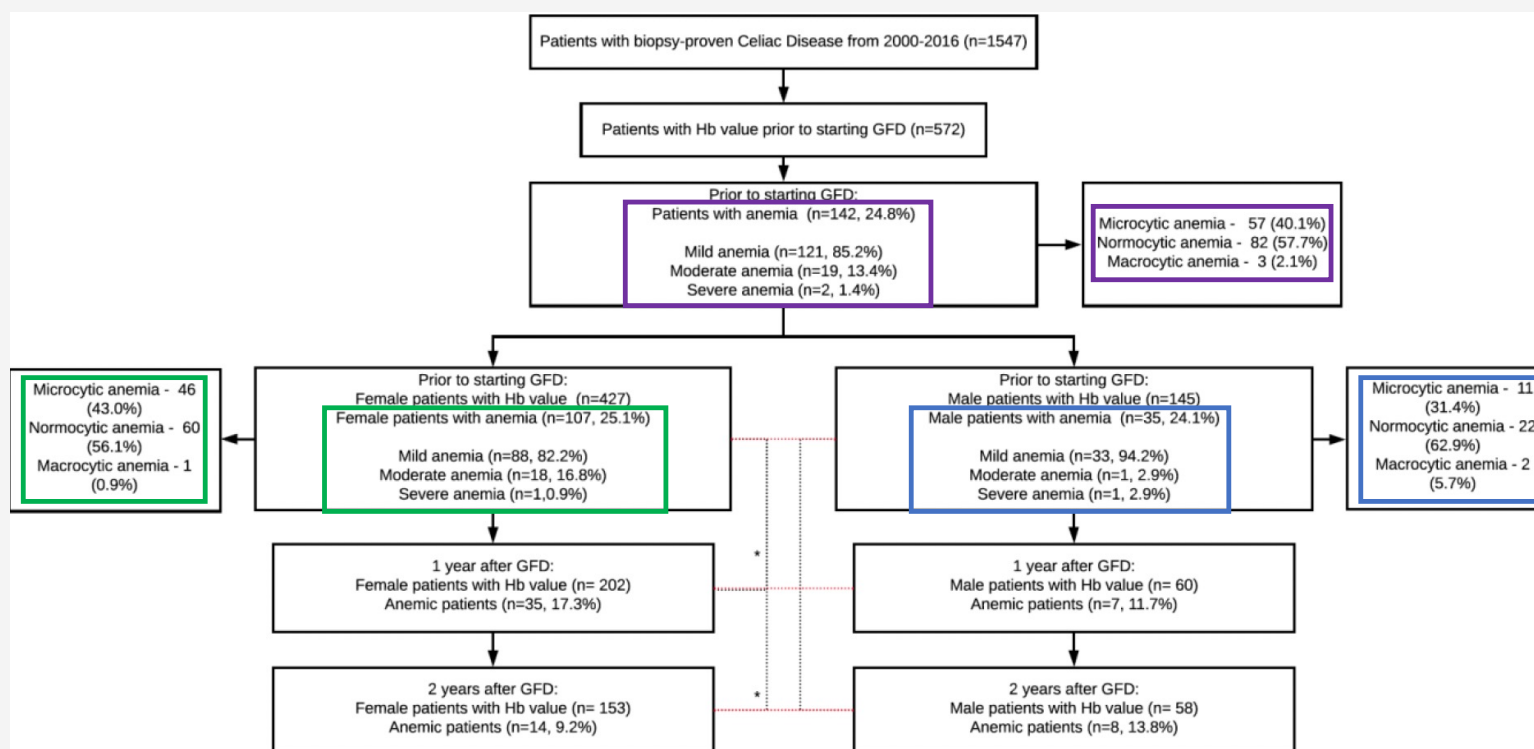
^aAnemia defined as hemoglobin < 12 mg/dl in women and < 13 mg/dl in men. Iron deficiency defined as serum ferritin < 10th percentile by age/gender. Folate deficiency defined as serum level < 5.4 ng/ml and B12 deficiency as serum level < 200 pg/dl.

^b $P < 0.01$ for difference between proportion of iron deficiency in men versus women.

Total CD patients with anemia:
77/373 (20.6%)

Anemia Etiology and the Response to a Gluten-Free Diet in Untreated Patients With Celiac Disease: A 2-Year Follow-Up

Roldan, Giovanni A. MD^{1,2}; Goyes, Daniela MD³; Villafuerte-Gálvez, Javier A. MD⁴; Urquiaga, Mariana MD⁵; Dennis, Melinda MS, RDN^{4,6}; Murray, Joseph A. MD⁷; Leffler, Daniel A. MD^{4,6}; Kelly, Ciarán P. MD^{4,6}



Celiac Disease Patients Presenting With Anemia Have More Severe Disease Than Those Presenting With Diarrhea

HUSSEIN ABU DAYA, BENJAMIN LEBWOHL, SUZANNE K. LEWIS, and PETER H. GREEN

Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York

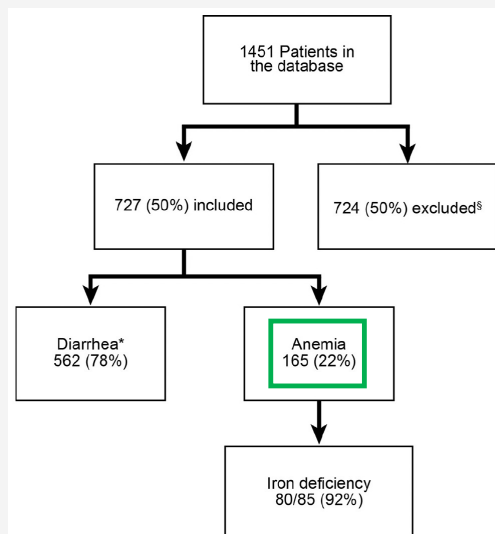


Figure 1. Flowchart showing inclusion and exclusion of CD patients in our study. [§]52 patients with reduced BMD, 64 patients diagnosed because of recognition of findings at endoscopy performed for reasons other than assessment of malabsorption/diarrhea or anemia, 126 patients diagnosed as a result of screening family members of affected individuals, and 482 patients with other presentations or with missing information on initial presentation at time of diagnosis. *Eight patients presented with both, and these were included in the diarrhea group.

RESULTS:

Of 727 patients, 77% presented with diarrhea and 23% with anemia (92% iron deficient). On multiple regression analysis, presentation with anemia was associated with lower levels of total cholesterol ($P = .02$) and high-density lipoprotein ($P = .002$) and a higher erythrocyte sedimentation rate ($P = .001$) and level of anti-tissue transglutaminase ($P = .01$). Presentation with anemia was associated with lower level of cholesterol only in women. Anemic patients were more than 2-fold more likely to have severe villous atrophy and a low bone mass density at the time they were diagnosed with celiac disease than patients who presented with diarrhea.

Table 2. Serologic and Pathologic Differences According to Mode of Presentation

Presentation on diagnosis	Anemia (n = 165) ^a	Diarrhea (n = 562) ^a	P value
Hct (%)	34 ± 5	39 ± 4	<.0001
MCV (fL/cell)	79 ± 9	87 ± 8	<.0001
Iron (μg/dL)	40 ± 30	77 ± 36	<.0001
Ferritin (ng/mL)	14 ± 30	67 ± 63	<.0001
Vitamin B ₁₂ (pg/mL)	537 ± 348	579 ± 318	.4
Folate (ng/mL)	12 ± 7	13 ± 7	.67
ESR (mm/h)	24 ± 20	10 ± 11	.02
Anti-tTG ratio ^b	7 ± 5	5 ± 5	.01
TC (mg/dL)	160 ± 33	175 ± 41	.01
LDL (mg/dL)	97 ± 25	106 ± 33	.065
HDL (mg/dL)	42 ± 15	51 ± 17	.001
TG (mg/dL)	106 ± 65	103 ± 49	.8
PVA ^c	27 (16%)	155 (28%)	.003
S/TVA ^c	88 (53%)	194 (34%)	<.0001
BMD			
Normal	13 (18%)	46 (44%)	
Osteopenia	40 (56%)	36 (35%)	
Osteoporosis	18 (26%)	22 (21%)	.001

MCV, mean corpuscular volume.

^aAmount of data available for each parameter: serum iron (n = 168), serum ferritin (n = 194), vitamin B₁₂ (n = 154), folate (n = 128), ESR (n = 86), anti-tTG ratio (n = 145), and TC (n = 197), LDL (n = 161), HDL (n = 164), and TG (n = 173) levels.

^bAnti-tTG ratio is defined as the ratio between the value obtained for each patient and the upper limit of normal used for each kit. This was done to compare anti-tTG levels obtained with different kits. Normal BMD = T-score > -1; osteopenia = -2.5 < T-score ≤ -1; osteoporosis = T-score ≤ -2.5.

^cAlthough all patients were diagnosed by duodenal biopsy, not all pathology reports were available for review (~35%).

... e nel resto del mondo?





Review

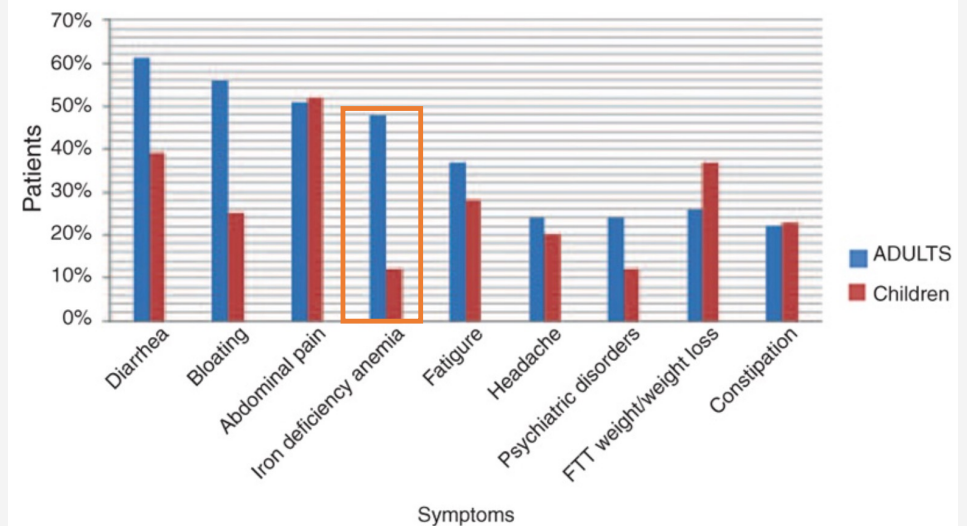
Iron Deficiency Anemia in Celiac Disease

 Valentina Talarico ^{1,*} , Laura Giancotti ², Giuseppe Antonio Mazza ³, Roberto Miniero ¹ and Marco Bertini ⁴ 
Table 1. Studies on prevalence of IDA in celiac patients.

Authors	Country	No. Of Patients	% IDA	Year of the Study
ADULTS				
Koho, et al. [13]	Finland	8	25	1998
Bergamaschi et al. [14]	Italy	132	34	2008
Berry et al. [15]	India	103	81	2018
Binicier et al. [16]	Turkey	195	53	2020
Bottaro et al. [17]	Italy	315	46	1999
Abu Daya et al. [18]	USA	727	21	2013
Sansotta et al. [19]	USA	327	48	2018
De Falco et al. [20]	Italy	505	45	2018
Akbari et al. [21]	Iran	27	52	2006
Kockar et al. [22]	India	434	84	2012
CHILDREN				
Bottaro et al. [17]	Italy	485	35	1999
Sansotta et al. [19]	USA	227	12	2018
Tolone et al. [23]	Italy	385	35	2017
Carroccio et al. [24]	Italy	130	70	1998
Kullogu et al. [25]	Turkey	109	82	2009
Sansevierio et al. [26]	Italy	518	22	2016

ORIGINAL ARTICLES: GASTROENTEROLOGY: CELIAC DISEASE

Celiac Disease Symptom Resolution: Effectiveness of the Gluten-free Diet

 Sansotta, Naire^{*,†}; Amirikian, Karine[‡]; Guandalini, Stefano[†]; Jericho, Hilary[†]
[Author Information](#) 
Journal of Pediatric Gastroenterology and Nutrition 66(1):p 48-52, January 2018. | DOI: 10.1097/MPG.0000000000001634


Most common gastrointestinal and extra-intestinal manifestations of celiac disease at presentation in adults compared with children.

American Journal of
Hematology **AJH**

RESEARCH ARTICLE |  Free Access

The role of *TMPRSS6* and *HFE* variants in iron deficiency anemia in celiac disease

Luigia De Falco , Raffaella Tortora, Nicola Imperatore, Mariasole Bruno, Mario Capasso, Domenico Girelli, Annalisa Castagna, Nicola Caporaso, Achille Iolascon, Antonio Rispo

TABLE 1 Baseline features and genetic frequencies of study population and controls

	Celiac patients (505)	Healthy controls (539)	P
Males n, (%)	106 (21)	321 (59)	<.001
Females n, (%)	399 (79)	218 (41)	<.001
Age (years ± SD)	30.2 ± 9.6	31.0 ± 8.5	NS
Clinical presentation ^a			
Classical CD n, (%)	227 (45)	NA	
Nonclassical CD n, (%)	263 (52)	NA	
Asymptomatic CD n, (%)	15 (3)	NA	
Marsh grade			
Marsh 1 n, (%)	34 (6.7)	NA	
Marsh 2 n, (%)	44 (8.7)	NA	
Marsh 3 n, (%)	427 (84.5)	NA	
Hb (g/dl)	12.2 ± 2.2	14.3 ± 1.2	<.001
MCV (fl)	81.2 ± 10.2	87.0 ± 4.7	<.001
Ferritin (ng/ml)	26.5 ± 38.1	82.7 ± 43.2	<.001
Iron (µg/dl)	55.6 ± 35.5	92.1 ± 29.0	<.001
Antitissue transglutaminase antibodies IgA (U/mL)	106.7 ± 45.5	1.8 ± 0.4	<.001
Antidendromysial antibodies positivity (%)	100%	0%	<.001

Between March 2013 and May 2017, we carried out a prospective study including all **consecutive adult CD patients** (age >18 years and <45) diagnosed and followed up at our Gastrointestinal Unit (Tertiary Centre for Food Intolerance and CD, School of Medicine “Federico II”, Naples, Italy).

Total CD patients with anemia:
229/505 (45.3%, 90.4% females)

TABLE 2 Characteristics of celiac patients at diagnosis and following a gluten-free regimen with or without IDA

	With IDA (n = 229)		Without IDA (n = 276)		P value
	At diagnosis	At follow-up	At diagnosis	At follow-up	
Sex (male/female)	22/207		84/192		<.001
Age (years)	30.9 ± 9.4		29.6 ± 9.7		.1
a-tTG IgA (U/mL)	107.7 ± 44.3	1.3 ± 0.7	106.2 ± 47.3	1.2 ± 0.9	.7
Villous atrophy n, (%)	196 (85.6)		235 (85.2)		.8
Iron supplementation, Y/N n, (%)	174 (76)/55 (24)		NA		
Hb (g/dl)	10.6 ± 1.1	12.0 ± 1.3	13.6 ± 2.0	14.0 ± 1.0	<.001
MCV (fl)	75.2 ± 9.4	84.0 ± 6.8	86.2 ± 8.2	87.7 ± 4.1	<.001
Ferritin (ng/ml)	6.9 ± 6.2	28.3 ± 27.4	42.7 ± 45.2	126.5 ± 75.4	<.001
Iron (mcg/dl)	30.4 ± 16.6	62.0 ± 32.8	76.5 ± 33.4	95.0 ± 35.3	<.001
Hepcidin (nM)	2.6 ± 4.6 (n = 22)	1.2 ± 1.1 (n = 91)	3.3 ± 4.6 (n = 31)	2.1 ± 2.1 (n = 99)	.6/<.001
HLA genotype	DQ2 or DQ8		219 (1) ^a	267 (1) ^b	NS



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PMCID: PMC9604793

PMID: [36294721](https://pubmed.ncbi.nlm.nih.gov/36294721/)

Anemia in Celiac Disease: Prevalence, Associated Clinical and Laboratory Features, and Persistence after Gluten-Free Diet

Aurelio Seidita,^{1,†} Pasquale Mansueto,^{1,†} Stella Compagnoni,² Daniele Castellucci,² Maurizio Soresi,¹ Giorgio Chiarello,¹ Giorgia Cavallo,² Gabriele De Carlo,² Alessia Nigro,² Marta Chiavetta,² Francesca Mandreucci,² Alessandra Giuliano,² Rosaria Disclafani,³ and Antonio Carroccio^{2,*}

Table 1. Demographic, clinical and histological characteristics of anemic and non-anemic CD patients.

	CD * Patients without Anemia (n = 72) (%)	CD * Patients with Anemia (n = 87) (%)	p-Value
Sex			
Female	49 (68.1)	80 (92.0)	0.0001
Male	23 (31.9)	7 (8.0)	
Age (years) at the onset (mean ± SD *)	32.6 ± 14.6	31.3 ± 14.3	NS *
Diagnostic delay (months) [median (range)]	24 (1–336)	48 (2–732)	0.05
BMI * (mean ± SD *)	22.9 ± 4.9	23.1 ± 2.9	NS *
IBS *-like symptoms			
None	13 (18.0)	19 (21.8)	NS *
Diarrhea	41 (57.0)	42 (48.3)	NS *
Constipation	11 (15.3)	13 (15.0)	NS *
Alternating bowel movements	7 (9.7)	13 (15.0)	NS *
Dyspepsia	35 (48.6)	32 (36.8)	NS *
Extra-intestinal symptoms	38 (52.8)	70 (80.5)	0.0001
Weight loss	26 (36.1)	29 (33.3)	NS *
Poly/hypermennorrhea	13 (18.0)	26 (29.9)	NS *
Associated autoimmune diseases	21 (29.2)	34 (39.1)	NS *
MFH *	8 (11.1)	4 (4.6)	NS *
Nickel hypersensitivity	8 (11.1)	7 (8.0)	NS *
SRMI *	21 (29.2)	27 (31.0)	NS *
Atopy *	15 (20.8)	11 (12.6)	NS *
Marsh-Oberhuber classification			
2	5 (6.9)	2 (2.3)	NS *
3	67 (93.1)	85 (97.7)	NS *

* BMI = Body Mass Index; CD = Celiac Disease; IBS = Irritable Bowel Syndrome; MFH = Multiple Food Hypersensitivity; NS = Not significant; SD = Standard Deviation; SRMI = Self-Reported Milk Intolerance. Atopy includes: Allergic rhino-conjunctivitis/asthma and atopic dermatitis.

2. Materials and Methods

2.1. Study Design and Population

We retrospectively reviewed the clinical charts of a group of CD patients diagnosed between January 2016 and July 2020, in three “Hub” Centers of the Sicilian Regional Network of Celiac Disease [i.e., the Department of Internal Medicine, University Hospital of Palermo, Italy; the Department of Internal Medicine, “V. Cervello” Hospital, Palermo, Italy; and the Department of Internal Medicine, Hospital of Sciacca (Agrigento), Italy], two of which are located in the Province of Palermo and one in the southern Province of Agrigento.

3. Results

During the study period a total of 373 subjects were diagnosed with CD; of these, 214 were excluded on the basis of the exclusion criteria and 159 entered the present study (see Figure S1) (129 females, mean age 35.4 ± 14.7 years). Table S2.1 shows the demographic, clinical, histological, and serological features of the patients.

3.1. Prevalence and Main Features of Anemia in CD Patients

More than half ($n = 87$, 54.7%) of the total CD patients showed mild-moderate anemia [HGB (mean ± SD) 10.3 ± 1.6 g/dL], characterized by hypochromic, microcytic and anisopoikilocytosis features (data not shown).

Table 1 shows the main demographic, clinical and histological differences between the forementioned subgroups. Anemia was more commonly associated with female sex ($p = 0.0001$), a longer diagnostic delay ($p = 0.05$), and extra-intestinal symptoms ($p = 0.0001$).

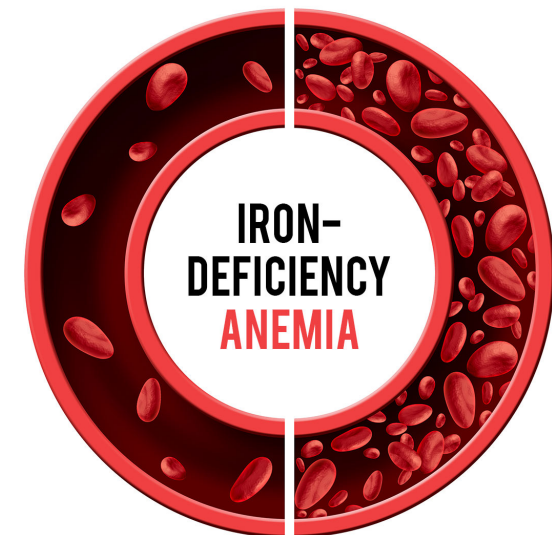
Anemia in Celiac Disease: Prevalence, Associated Clinical and Laboratory Features, and Persistence after Gluten-Free Diet

Aurelio Seidita,^{1,†} Pasquale Mansueto,^{1,†} Stella Compagnoni,² Daniele Castellucci,² Maurizio Soresi,¹ Giorgio Chiarello,¹ Giorgia Cavallo,² Gabriele De Carlo,² Alessia Nigro,² Marta Chiavetta,² Francesca Mandreucci,² Alessandra Giuliano,² Rosaria Disclafani,³ and Antonio Carroccio^{2,*}

Table 2. HGB, iron metabolism, ESR, CRP, vitamin B12, folic acid and TSH of anemic and non-anemic CD patients.

	CD * Patients without Anemia (n = 72) (%)	CD * Patients with Anemia (n = 87) (%)	p-Value
HGB * (g/dL) (mean ± SD *)	13.6 ± 1.1	10.3 ± 1.6	0.05
Total serum iron (below normal value-number and %)	7 (9.7)	72 (82.8)	0.0001
Total serum iron (μg/dL) [median (range)]	75.5 (36–157)	37 (18–79)	0.0001
Ferritin (below normal value-number and %)	19 (26.4)	82 (94.2)	0.0001
Ferritin (ng/mL) [median (range)]	36 (2–284)	5 (2–44)	0.0001
ESR * (above normal value-number and %)	7 (9.7)	61 (70.1)	0.001
ESR * (mm/h) [median (range)]	16 (2–42)	31.5 (3–75)	0.003
CRP * (above normal value-number and %)	6 (8.3)	11 (12.6)	NS *
CRP* (mg/dL) [median (range)]	0.81 (0.1–7.1)	0.5 (0.06–32)	NS *
Vitamin B12 (below normal value-number and %)	0 (0.0)	49 (56.3)	0.001
Vitamin B12 (pg/mL) [median (range)]	666 (201–727)	398 (113–903)	NS *
Folic acid (below normal value-number and %)	27 (37.5)	49 (56.3)	NS *
Folic acid (ng/mL) [median (range)]	2.3 (1–3)	4.8 (0.6–11.5)	NS *
TSH * (above normal value-number and %)	21 (29.1)	16 (18.4)	NS *
TSH * (μU/mL) [median (range)]	2 (0.8–7.6)	1.6 (0.7–8.03)	NS *

* CD = Celiac Disease; CRP = C-Reactive Protein; ESR = Erythrocyte Sedimentation Rate; HGB = Hemoglobin; NS = Not significant; SD = Standard Deviation; TSH = Thyroid-Stimulating Hormone. Reference values: C-reactive protein (CRP) <5 mg/L; Erythrocyte Sedimentation Rate (ESR) 2–20 mm/h; Ferritin 15–150 ng/mL; Folic acid 3.89–26.8 mcg/L; Hemoglobin (HGB) Male 13–18 g/dL, Female 12–16 g/dL; Thyroid-Stimulating Hormone (TSH) 0.35–4.94 μU/mL; Total Serum Iron Male 65–180 μg/dL, Female 30–170 μg/dL; Vitamin B₁₂ 197–890 ng/L.



Una possibile scaletta...

- Chi può essere interessato al/dal problema?
- Quali sono i numeri di cui stiamo parlando?
- Quale origine ha l'anemia nei pazienti celiaci?
- Qual è l'approccio terapeutico ottimale?
-

Anemia sideropenica ...

Table 2. Parameters for IDA diagnosis.

(a) Red cell parameters values for diagnosis of IDA

- Reduction of Hb, RBCs and hematocrit < 2 SD of normal values according to age and gender. For WHO in adult, anemia is defined as hemoglobin < 13 g/dL in men and < 12 g/dL in non-pregnant women. In children, reference values are lower and differ according to age.
- Reduction of MCV, MCH and MCHC
- Hypochromic cells with a tendency to microcytosis
- Increase of RDW > 15%
- Reduction of CHr < 27.5 pg

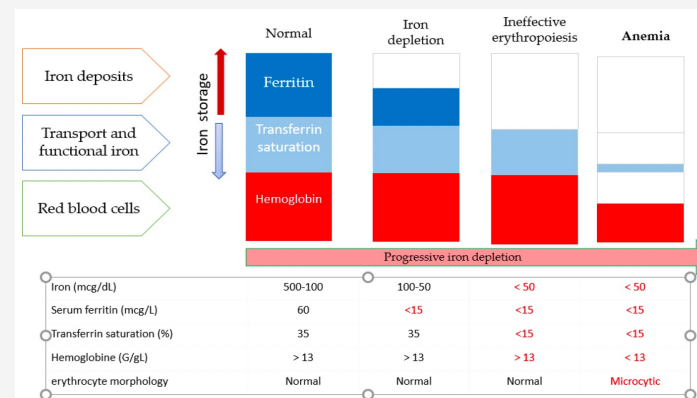
Table 2. Cont.
(b) Biochemical parameters values for diagnosis of IDA

- Reduction of serum iron < 30mg/dL; increase of total serum transferrin or of TIBC > 350 mg/dL; reduction of IS < 16%;
- Reduction of serum ferritin < 10–20 ng/mL if PRC is normal. A ferritin threshold value of < 45 ng/mL has a sensitivity for iron deficiency of 85% with a specificity of 92%. In contrast, a ferritin value of < 15 ng/mL has a sensitivity of only 59% and specificity of 99%. A ferritin threshold value of < 45 ng/mL is believed to maximize sensitivity for the diagnosis of IDA with an acceptable number of false-positive diagnoses.

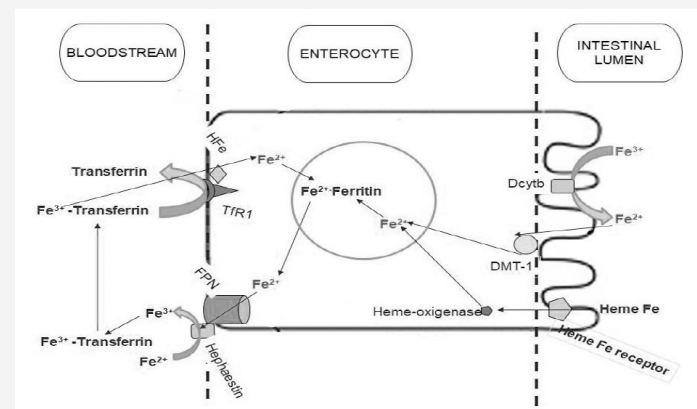
(c) Other parameters evaluable for diagnosis of IDA

- Increase of sTfR to a 10–14 mg/L
- Reduction of reticulocyte (incostant)
- Increase of zincprotoporfina > 60–80 μmol/mol-heme
- Increase of Free Erythrocyte Protoporphyrin (FEP) > 10 mg/dL
- Increase of platelets count (incostant) between 600.000–1000.000 mmc.
- Rarely modest hemolysis

Talarico V et al. Nutrients. 2021.



Montoro-Huguet MA et al. Nutrients. 2021.



Martín-Masot R et al. Nutrients. 2019.

... ma non solo

Table 1. Etiology of anemia in celiac disease.

Cause	Incidence
Iron deficiency	12–69% (adults) 10–20% (children)
Folic acid deficiency	20–30%
Vitamin B ₁₂ deficiency	8–41%
Copper deficiency	Very low
Zinc deficiency	Very low *
Bad response to the gluten-free diet	23%
Medullary aplasia	Very low (12 cases)
Chronic disease	4–17%

Scarsa aderenza
alla dieta?
Altro?

Malassorbimento

Altre cause

* It has been reported that 50% of celiac patients have low serum levels at diagnosis, but it has not been related to celiac disease (CD).

Martín-Masot R et al. *Nutrients* 2019

Anemia Etiology and the Response to a Gluten-Free Diet in Untreated Patients With Celiac Disease: A 2-Year Follow-Up

 Roldan, Giovanni A. MD^{1,2}; Goyes, Daniela MD³; Villafuerte-Gálvez, Javier A. MD⁴; Urquiaga, Mariana MD⁵; Dennis, Melinda MS, RDN^{4,6}; Murray, Joseph A. MD⁷; Leffler, Daniel A. MD^{4,6}; Kelly, Ciarán P. MD^{4,6}

Table 2. Nutritional deficiencies in patients with untreated CeD (n=572)

	Overall	Female (n=427)	Male (n=145)	*p-value
Iron deficiency, n (%)	185/364 (50.8)	157/275 (57.1)	28/89 (31.5)	0.0001
B12 deficiency, n (%)	24/370 (6.5)	16/286 (5.6)	8/84 (9.5)	0.3
Folate deficiency, n (%)	48/249 (19.3)	30/190 (15.8)	18/59 (30.5)	0.02

CeD, celiac disease; n, number

*p-value for female vs. male frequency comparison using chi-square.

Table 4. Anemia etiology and micronutrient deficiencies in untreated CeD who presented with anemia (n=142)

	Both genders	Female (n=107)	Male (n=35)	p-value*
Iron deficiency, n (%)	79/101 (78.2)	65/77 (84.4)	14/24 (58.3)	0.02
Iron-deficiency anemia, n (%)	42/77 (54.5)	38/58 (65.5)	4/19 (21.1)	0.002
B12 deficiency, n (%)	10/90 (11.0)	7/73 (9.6)	3/17 (17.6)	0.60
Folate deficiency, n (%)	19/62 (23.2)	14/49 (28.6)	5/33 (15.2)	0.25
Anemia of chronic diseases, n (%)	6/77 (7.8)	1/58 (1.7)	5/19 (26.3)	0.003

CeD, celiac disease; n, number

*p-value for female vs. male frequency comparison using chi-square.

Table 3. Characteristics of the anemic and non-anemic population (n=572)

	Female			Male		
	Non-anemic (n=320)	Anemic (n=107)	*p-value	Non-anemic (n=110)	Anemic (n=35)	*p-value
Age at diagnosis of CeD (years), mean $\pm$ SD	39.3 $\pm$ 14.7	43.1 $\pm$ 15.0	0.02	41.7 $\pm$ 14.4	51.9 $\pm$ 16.2	0.002
Age category (years), n (%)						
18-34	145 (45.3%)	29 (27.1%)	0.001	42 (38.2%)	7 (20.0%)	0.08
35-50	96 (30.0%)	52 (48.6%)	<0.001	38 (34.5%)	5 (14.3%)	0.04
50-64	57 (17.8%)	12 (11.2%)	0.14	20 (18.2%)	10 (28.6%)	0.28
Older than 65	22 (6.9%)	14 (13.1%)	0.07	10 (9.1%)	13 (37.1%)	<0.001
Race, n (%)						
Asian	3 (0.9%)	3 (2.8%)	0.34	3 (2.7%)	1 (2.9%)	1
Black African American	0 (0%)	2 (1.9%)	0.10	1 (0.9%)	1 (2.9%)	0.98
Hispanic	4 (1.2%)	3 (2.8%)	0.51	2 (1.8%)	4 (11.4%)	0.05
White	289 (90.3%)	94 (87.9%)	0.59	99 (90.0%)	27 (77.1%)	0.09
Other	14 (4.4%)	2 (1.9%)	0.37	3 (2.7%)	1 (2.9%)	1
Patient declined to answer	4 (1.2%)	2 (1.9%)	1	0 (0%)	1 (2.9%)	0.54
Unknown/Not specified	6 (1.9%)	1 (0.9%)	0.82	2 (1.8%)	0 (0%)	1
IgA anti-tTG at diagnosis of CeD (U/mL), median (IQR)	100 (42.3-120.0)	113 (95.5-120.0)	0.04	100 (42.25-120.0)	116 (95.5-120.0)	0.77
Referred from another center, n (%)	33 (10.3%)	9 (8.4%)	0.7	17 (15.5%)	5 (14.3%)	1
Hemoglobin (g/dL), mean $\pm$ SD	13.3 $\pm$ 0.80	10.7 $\pm$ 1.09	<0.001	14.9 $\pm$ 1.05	11.1 $\pm$ 1.18	<0.001

CeD, celiac disease; n, number; U, units; SD, standard deviation

*p-value for Non-anemic vs. Anemic comparison.

Meglio parlare di multifattorialità

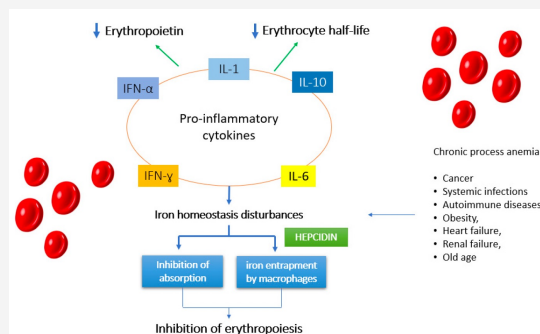


Figure 3. In CD there is a component of systemic inflammation which in some cases may also contribute to the pathogenesis of anaemia. This contribution is less than that due to malabsorption. The figure illustrates some mechanisms involved in the pathogenesis of anemia of chronic disease.

Mechanism of Copper Deficiency Anemia

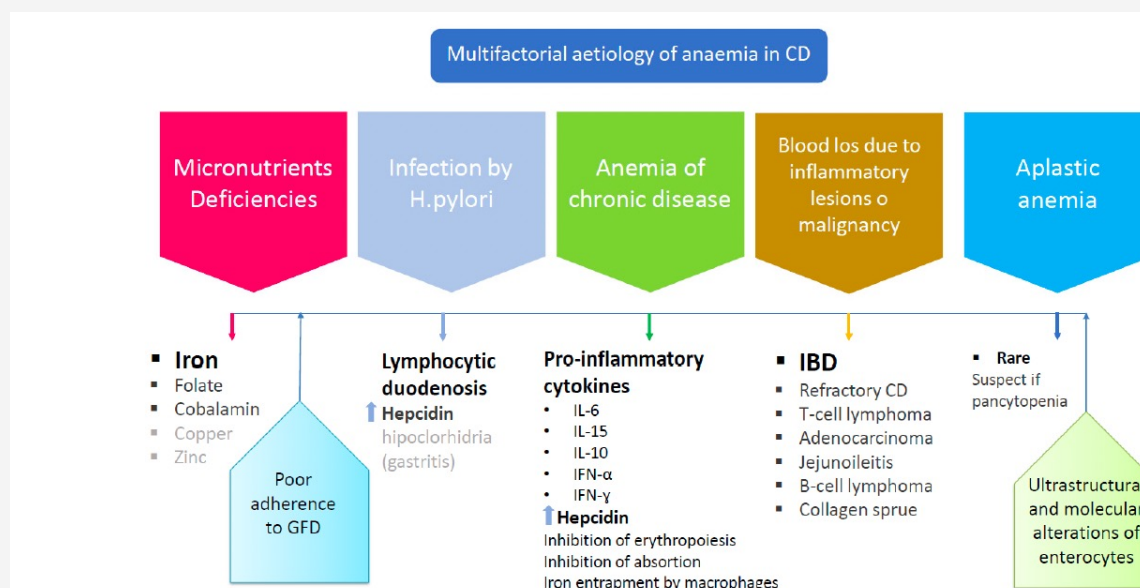
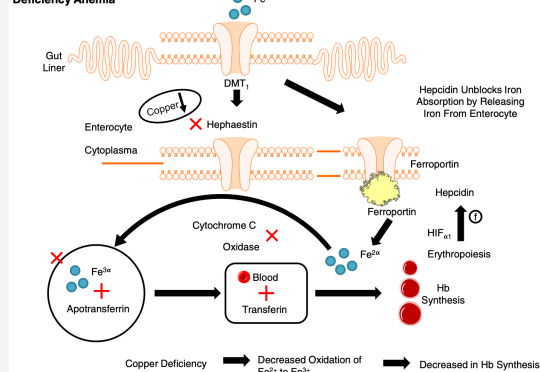


Figure 4. Factors influencing the development of anemia in CD. The main and most frequent cause of anemia in CD is malabsorption. The figure illustrates other components that may contribute to its pathogenesis to a lesser extent. CD “celiac disease”; GFD: “gluten free diet”; IBD: “inflammatory bowel disease”.

Myint ZW et al. *Ann Hematol* 2018

Montoro-Huguet MA et al. *Nutrients* 2021

Una possibile scaletta...

- Chi può essere interessato al/dal problema?
- Quali sono i numeri di cui stiamo parlando?
- Quale origine ha l'anemia nei pazienti celiaci?
- Qual è l'approccio terapeutico ottimale?
-

Un possibile protocollo decisionale

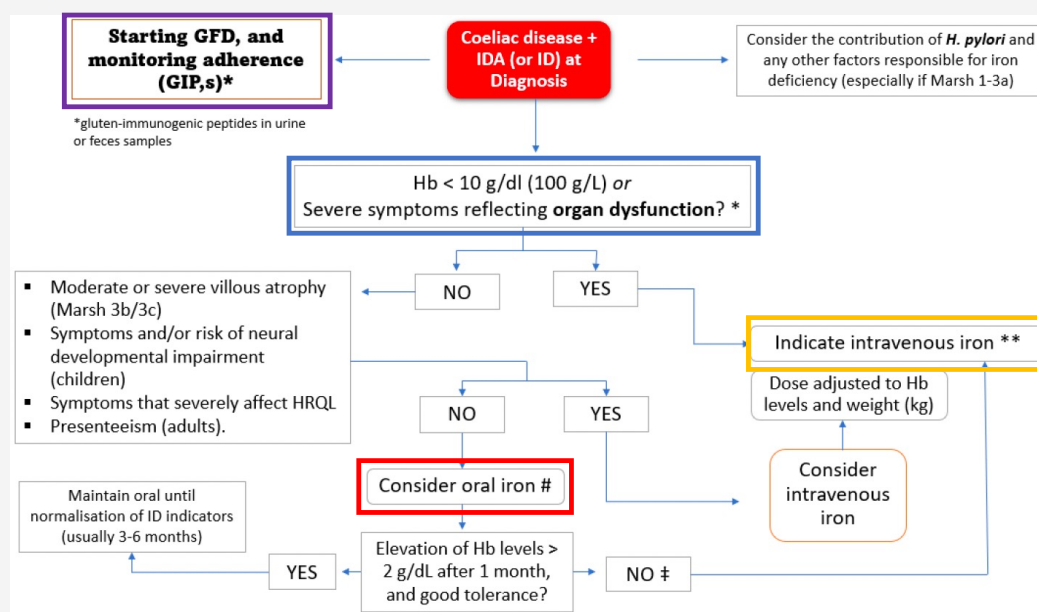
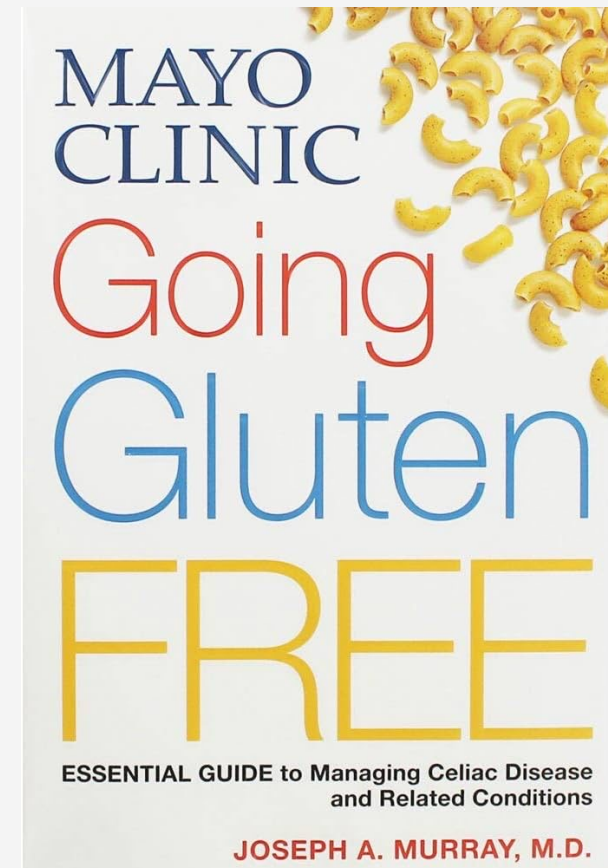


Figure 5. A proposed algorithm for iron replacement in patients with CD and IDA or ID. GFD: gluten-free diet; GIPs: gluten-immunogenic peptides in urine or feces samples; HRQL: health-related quality of life. # In the presence of mild symptoms, consider not giving oral iron and wait for resolution of lesions after GFD. ‡ Some causes of non-response to oral iron replacement include poor adherence to the GFD (consider the presence of GIPs in urine or stool samples as an indicator of poor adherence), slow histological response to the GFD (“slow responders”), refractory celiac, and blood loss due to mucosal lesions (Crohn’s disease, jejunoileitis, and malignancy). (*: Consider transfusion of red blood cells.; ** See Tables 5 and 6).

Montoro-Huguet MA et al. *Nutrients*. 2021.

Going gluten-free to resolve anemia?



Effetti della GFD sul metabolismo del ferro

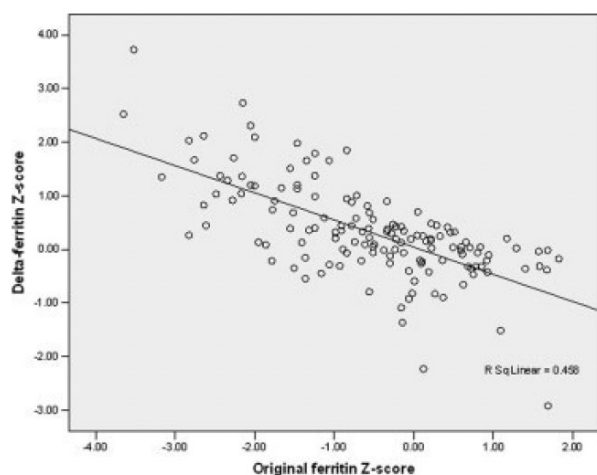
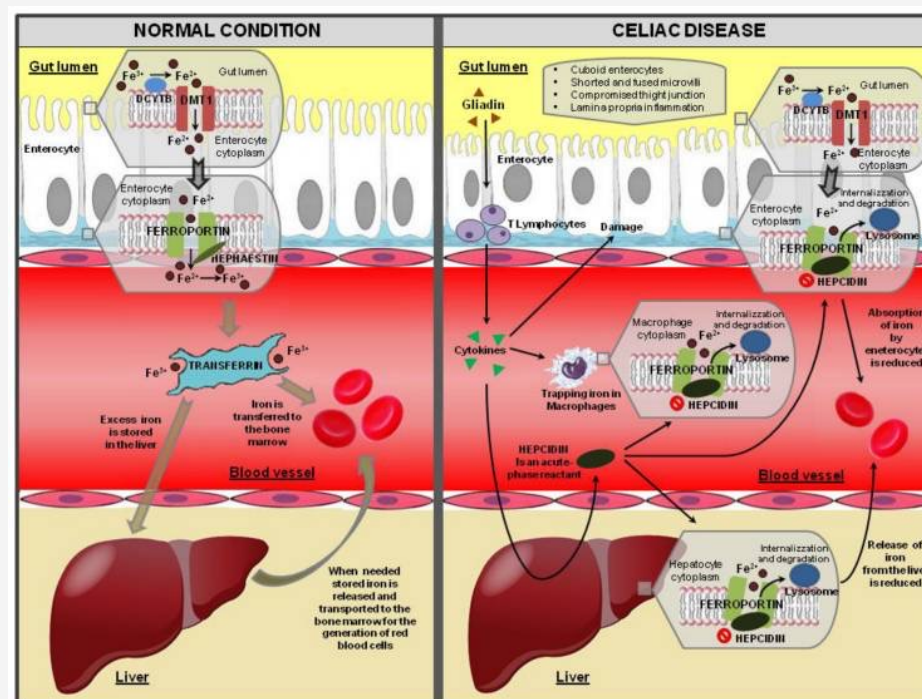


Figure 1. Effect of GFD on ferritin z-score. x-Axis is original ferritin z-score and y-axis is the change in ferritin z-score after institution of GFD.

The trend suggested by this regression is that for individuals with low ferritin before GFD, the change in ferritin would be positive (i.e. ferritin levels increase on GFD). Conversely, for individuals with high ferritin before GFD, the change in ferritin would be negative (i.e. ferritin levels decrease on GFD) ($r^2 = 0.46$, $P < 0.001$).

Harper JW et al. Am J Hematol. 2007.



Stefanelli G et al. Nutrients. 2020.

Efficacy of Gluten-Free Diet Alone on Recovery From Iron Deficiency Anemia in Adult Celiac Patients

Bruno Annibale, M.D., Carola Severi, M.D., Antonio Chistolini, M.D., Giorgio Antonelli, M.D., Edith Lahner, M.D., Adriana Marcheggiano, M.D., Carlo Iannoni, M.D., Bruno Monarca, M.D., and Gianfranco Delle Fave, M.D.

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OBJECTIVE: Iron deficiency anemia has been reported as the most frequent extraintestinal symptom in adult celiac disease. Prospective studies on the effect of gluten-free diet on recovery from iron deficiency anemia are lacking. The aim of this study was to verify in adult patients with celiac disease the efficacy of and the time course of recovery from iron deficiency anemia by a gluten-free diet alone.

METHODS: We studied 190 consecutive adult patients with iron deficiency anemia, screened for celiac disease by duodenal biopsies. New diagnosed celiac patients were invited to follow a gluten-free diet alone without iron supplementation. After 6 months of diet, duodenal biopsies were performed and hematological tests were repeated at 6, 12, and 24 months.

Table 3. Hematological Features of 18 CD Women With Iron Deficiency Anemia Before and After 6, 12, and 24 Months of a Gluten-Free Diet

	Hb (g/dl) (nv 12–16)	MCV (fl) (nv 80–100)	RDW (%) (nv 11.5–15.5)	Serum Iron (μ g/dl) (nv 50–150)	Ferritin (ng/ml) (nv 20–180)
Before diet	10.7 (6.1–11.9)	73 (54.2–95.1)	18 (12.9–22.8)	17 (3–41)	4 (1–10)
6 months	12.5* (8.3–14.4)	83.3 [†] (65–90)	13.1 (10.5–28.3)	56.5* (20–113)	11.5* (3–82)
12 months	13.3 [‡] (9.7–15.3)	85.1 [‡] (67–95)	14.2 (11.7–17.2)	68.5 [§] (30–135)	19 (5.1–63)
24 months	13.8 (10.4–14.7)	85.5 (76–99)	13.7 (11.9–17.1)	67.5 (20–132)	21 (4–58)

Data are expressed as median (range). nv = normal values

* $p < 0.0001$ 6 months vs before diet; [†] $p < 0.0005$ 6 months vs before diet; [‡] $p < 0.005$ 12 months vs 6 months; [§] $p < 0.01$ 12 months vs 6 months.

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RESULTS: Celiac disease was diagnosed in 26 (24 women, 2 men; 13.7%) adult patients. After 6 months of gluten-free diet 14 of 18 (77.8%) female patients recovered from anemia, but only 5 of 18 (27.8%) reversed from iron deficiency. At 12-month control all but one patient (94.4%) recovered from anemia and 9 patients (50%) from iron deficiency. After 24 months of diet, only the patient who did not recover from anemia at 12-month control was still anemic, whereas 10 patients (55.5%) reversed from iron deficiency. A significant inverse correlation ($r = -0.7141$, $p = 0.0003$) between increase of Hb concentrations and decrease of individual histological scores of duodenitis was observed.

CONCLUSIONS: A screening for celiac disease should be carried out in adult patients with iron deficiency anemia. Recovery from anemia occurs between 6 and 12 months on a gluten-free diet alone as a consequence of normalization of histological alterations of the intestinal mucosa. (Am J Gastroenterol 2001;96:132–137. © 2001 by Am. Coll. of Gastroenterology)

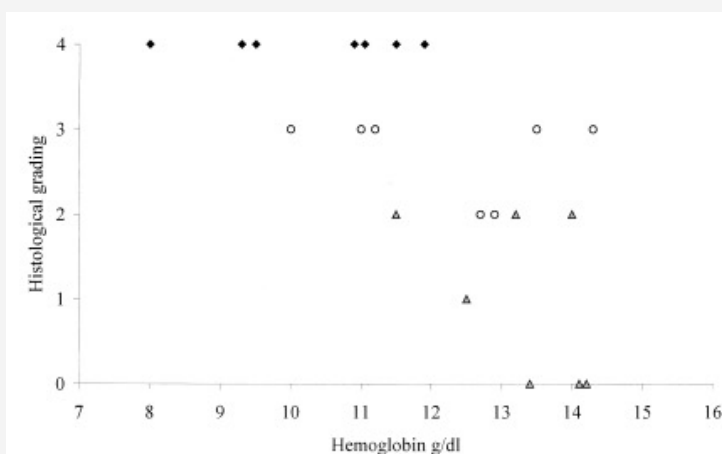


Figure 1. Correlation between histological scores (0 = resolution of duodenitis, 1 = A0, 2 = A1, 3 = A2, 4 = A3, see Materials and Methods) and Hb concentrations of seven adult CD patients before gluten-free diet (◆) and at 6 (○) and at 12 (△) months after starting of a gluten-free diet.



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Review

Persistent Iron Deficiency Anemia in Patients with Celiac Disease Despite a Gluten-Free Diet

Gianpiero Stefanelli [†], Angelo Viscido [†], Salvatore Longo , Marco Magistrini  and Giovanni Latella ^{*}

Table 1. Prevalence of IDA at CD diagnosis and after a gluten-free diet (GFD), both in adult and pediatric patients.

Adults Patients							
Study (Year)	Study Location	Study Design	Number of CD Patients	Men N. (%)	Follow-up	CD patients with IDA before the start of a GFD N. (%)	CD patients with IDA after the start of a GFD (%)
Kolho et al. (1998) [7]	Finland	Cross-sectional	8	1 (13)	n.a.	2 (25)	n.a.
Akbari et al. (2006) [8]	Iran	Cross-sectional	27	14 (52)	n.a.	14 (52)	n.a.
Bergamaschi et al. (2008) [22]	Italy	Prospective Cohort	132	47 (36)	12 months	45 (34)	n.a.
Berry et al. (2018) ^{**} [24]	India	Prospective cohort	103	48 (47)	n.a.	84 (82)	n.a.
Binicier et al. (2020) [37]	Turkey	Retrospective Cohort	195	44 (23)	58 months [*]	104 (53)	n.a.
Bottaro et al. (1999) [38]	Italy	Cross-sectional	313	n.a.	n.a.	145 (46)	n.a.
Abu Daya et al. (2013) [39]	USA	Cross-sectional	727	203 (28)	n.a.	152 (21)	n.a.
Sansotta et al. (2018) [40]	USA	Retrospective Cohort	327	n.a.	24 months [*]	157 (48)	(15)
De Falco et al. (2018) [42]	Italy	Prospective Cohort	505	106(21)	12 months	229 (45)	(21)
Pediatric Patients							
Study (Year)	Study Location	Study Design	Number of CD Patients	Men N. (%)	Follow-up	CD patients with IDA before the start of a GFD N. (%)	CD patients with IDA after the start of a GFD (%)
Bottaro et al. (1999) [38]	Italy	Cross-sectional	485	n.a.	n.a.	169 (35)	n.a.
Sansotta et al. (2018) [40]	USA	Retrospective Cohort	227	n.a.	31 months [*]	27 (12)	(16)
Tolone et al. (2017) [41]	Italy	Cross-sectional	387	152 (39)	84 months	134 (35)	n.a.

Note: N., number; CD, celiac disease; GFD, gluten-free diet; IDA, iron deficiency anemia; n.a., data not available; ^{*} mean; and ^{**} age > 12years.

Anemia Etiology and the Response to a Gluten-Free Diet in Untreated Patients With Celiac Disease: A 2-Year Follow-Up

 Roldan, Giovanni A. MD^{1,2}; Goyes, Daniela MD³; Villafuerte-Gálvez, Javier A. MD⁴; Urquiaga, Mariana MD⁵; Dennis, Melinda MS, RDN^{4,6}; Murray, Joseph A. MD⁷; Leffler, Daniel A. MD^{4,6}; Kelly, Ciarán P. MD^{4,6}

The proportion of patients with anemia after one year (16%, $p<0.01$) and two years (10.4%, $p<0.001$) on a GFD was significantly lower than at baseline (24.8%). Among the 142 patients who presented with anemia, just 19% (27/142) were still anemic after one year on a GFD. Two years after starting a GFD, anemia persisted in 11.3% (16/142) of the initially anemic patients. However, there was no statistically significant difference in the proportion of patients who remained anemic after following a GFD for one or two years ($p=0.10$) (Figure 2). Neither was a significant difference noted between the proportion of anemic patients in each period when analyzed by gender ($p>0.05$).

The mean Hb in non-anemic patients at presentation was 13.7 (CI 13.6-13.9), at one year after starting a GFD, the mean Hb remained the same 13.7 (CI 13.6-13.9), and rose slightly to 13.9 (CI 13.7-14.1) two years after a GFD whereas, the mean Hb for anemic patients were 10.8 (CI 10.6-11.0), 12.7 (CI 12.2-13.1), and 13.0 (CI 12.5-13.4) for the same periods, respectively. The increase in Hb values from one to two years on a GFD is not statistically significant in either group. Among the 430 patients with normal hemoglobin before starting a GFD, 3.5% (15) and 1.4% (6) developed anemia after one and two years on a GFD, respectively.

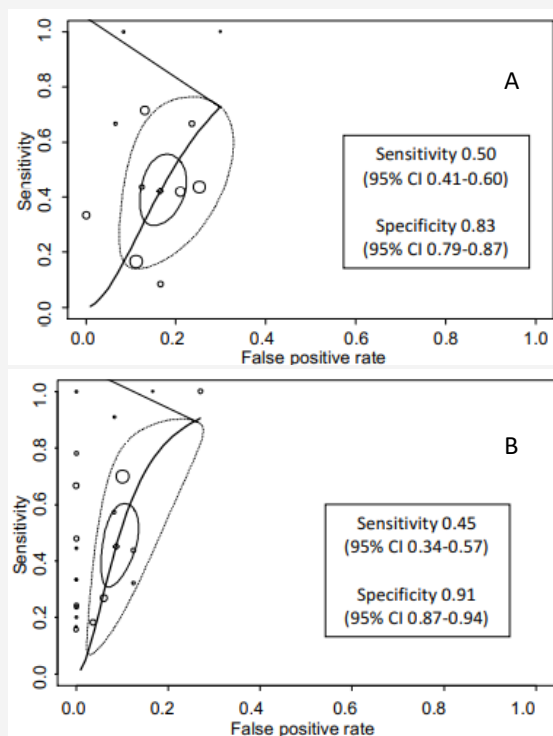
Una possibile scaletta...

- Chi può essere interessato al/dal problema?
- Quali sono i numeri di cui stiamo parlando?
- Quale origine ha l'anemia nei pazienti celiaci?
- Qual è l'approccio terapeutico ottimale?
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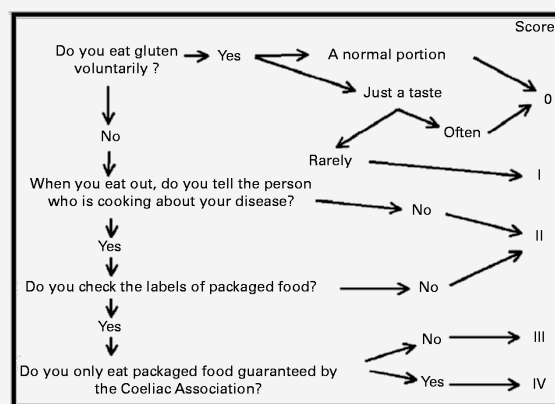
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- Anemia resistente alla GFD, perché?

Valutazione dell'aderenza alla GFD



Performance of tTG IgA (A) and EMA IgA (B) for detection of persistent villous atrophy in patients with biopsy confirmed celiac disease on a gluten-free diet.

Silvester JA, et al. *Gastroenterology*. 2017.



Biagi F et al. *Br J Nutr*. 2009.

What is the Optimal Method Assessing for Persistent Villous Atrophy in Adult Coeliac Disease?

Sarah Helen Coleman, Anupam Rej, Elisabeth Megan Rose Baggus, Michelle S Lau, Lauren J Marks, Marios Hadjivassiliou, Simon S Cross, Daniel A Leffler, Luca Elli, David Surendran Sanders

Results: 368 patients (mean age 51.0 years, 70.1% female) had D1 and D2 biopsies taken at follow-up gastroscopy. Compared to D2 biopsies alone, additional D1 biopsies increased detection of VA by 10.4% ($p < 0.0001$). 201 patients (mean age 50.3 years, 67.7% female) completed adherence questionnaires and serology. When detecting VA, sensitivities and specificities of these markers were 39.7% and 94.2% for IgA-tTG, 38.1% and 96.4% for IgA-EMA, 55.6% and 52.2% for CDAT and 20.6% and 96.4% for the Biagi score.

Conclusions: Bulbar biopsies increase detection of persisting VA by 10.4%. Serology, CDAT and Biagi performed poorly when predicting VA. The gold standard for predicting persisting VA remains repeat biopsy.



Conclusions: Weekly stool GIP identifies gluten exposure that is not always detected by commonly used GFD adherence assessment methods. The higher the concentration of stool GIP, the better the predictive value of serology and dietitian interviews. Stool GIP is a useful and practical test for GFD monitoring, particularly for risky gluten exposure in real-life scenarios.

Altre possibili cause di persistenza dell'anemia



FIG. 1. Representative example of changes occurring in the microvilli of absorptive cell in a child with celiac disease in remission after 2 years of a gluten-free diet. The microvilli are short and thick. GL, glycocalyx; M, microvilli. $\times 55,000$; reduced 40% for reproduction.

The structure of the glycocalyx was found to be intact, but in some children with treated celiac disease the layer of glycocalyx was either thin or absent on the surface of individual cell microvilli.

Dyduch A et al. J Pediatr Gastroenterol Nutr. 1993.

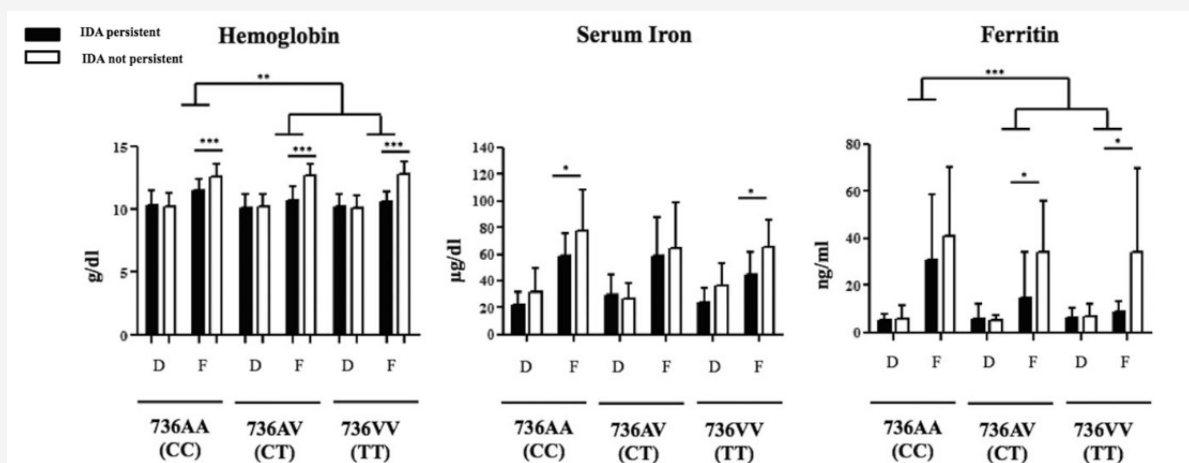


FIGURE 1 Hematological and iron parameters according to *TMPRSS6* genotype and to iron supplementation in IDA persistent and IDA not persistent CD patients. Hemoglobin (Hb), serum iron, and ferritin levels in IDA persistent and in IDA not persistent patients both at diagnosis (D) and at follow-up (F) according to different *TMPRSS6* genotypes (CC, CT, or TT). IDA persistent (filled bars, $N = 83$) and IDA not persistent (empty bars, $N = 91$) were both on gluten-free diet and iron supplementation at follow-up. The data are presented as means $\pm$ SD; statistically significant differences were determined by Student's *t*-test, * $P < .05$, ** $P < .001$, *** $P < .0001$. The graphs were created using the Software GraphPad Prism 6

De Falco L et al. Am J Hematol. 2018.

Non solo un problema di malassorbimento...



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PMCID: PMC9604793

PMID: [36294721](https://pubmed.ncbi.nlm.nih.gov/36294721/)

Anemia in Celiac Disease: Prevalence, Associated Clinical and Laboratory Features, and Persistence after Gluten-Free Diet

Aurelio Seidita,^{1,†} Pasquale Mansueto,^{1,†} Stella Compagnoni,² Daniele Castellucci,² Maurizio Soresi,¹ Giorgio Chiarello,¹ Giorgia Cavallo,² Gabriele De Carlo,² Alessia Nigro,² Marta Chiavetta,² Francesca Mandreucci,² Alessandra Giuliano,² Rosaria Disclafani,³ and Antonio Carroccio^{2,*}

The persistence of anemia [HGB (mean $\pm$ SD) 11.0 $\pm$ 0.9 g/dL] with hypochromic and microcytic features was proved in 40 patients (46% of the subjects anemic at diagnosis), with a higher prevalence in females ($p = 0.02$). Table 3 shows the pre-GFD demographic,

not normalize, indicating that other factors could be (co)responsible. We proved that a large percentage (40%) of the women with persistent IDA on a strict GFD had a low BMI and presented poly/hypermenorrhea at diagnosis, suggesting that IDA might be due to iron loss rather than malabsorption, or to their coexistence/overlap. Finally, a certain role could also be attributed to a coexisting history of atopy, but further studies with a prospective design are required to clarify the relevance of all these conditions.

Table 3. Pre-GFD demographic, clinical, and hematochemical features of patients with persistent anemia after one year of “strict” GFD compared to the whole non-anemic ones (non-anemic before GFD plus non-anemic after GFD).

	Whole Non-Anemic CD Patients (n = 94) (%)	Persisting Anemic CD Patients (n = 40) (%)	p-Value
Sex			
Female	74 (78.7)	38 (95.0)	0.02
Male	20 (21.3)	2 (5.0)	
Age (years) at diagnosis (mean $\pm$ SD *)	33.2 $\pm$ 14.2	35.8 $\pm$ 14.3	NS *
Diagnostic delay (months) [median (range)]	24 (1–456)	48 (2–660)	NS *
BMI * (mean $\pm$ SD *)	24.3 $\pm$ 4.5	22.2 $\pm$ 3.44	0.01
Dyspepsia	27 (28.7)	14 (35.0)	NS *
Extraintestinal symptoms	63 (67.0)	32 (80.0)	NS *
Weight loss	37 (39.4)	18 (45.0)	NS *
Poly/hypermenorrhea	19 (20.2)	16 (40.0)	0.02
Associated autoimmune diseases	38 (40.4)	16 (40.0)	NS *
Hashimoto thyroiditis	19 (20.2)	8 (20.0)	NS *
MFH *	9 (9.6)	3 (7.5)	NS *
Atopy *	20 (21.3)	16 (40.0)	0.04
MCV * (below normal value-number and %)	52 (55.3)	25 (62.5)	NS *
RDW * (above normal value-number and %)	13 (13.8)	10 (25.0)	NS *
Ferritin (below normal value-number and %)	59 (62.8)	35 (87.5)	0.05
ESR * (above normal value-number and %)	29 (30.8)	33 (82.5)	0.012
Vitamin B12 (below normal value-number and %)	31 (33.0)	16 (40.0)	NS *
Folic acid (below normal value-number and %)	48 (51.1)	22 (55.0)	NS *
TSH * (above normal value-number and %)	29 (30.9)	6 (15.0)	NS *
ANA * positivity (above normal value-number and %)	41 (43.6)	11 (27.5)	NS *

* ANA = Anti-Nuclear Antibodies; BMI = Body Mass Index; CD = Celiac Disease; ESR = Erythrocyte Sedimentation Rate; GFD = Gluten-Free Diet; MCV = Mean Corpuscular Volume; MFH = Multiple Food Hypersensitivity; NS = Not Significant; RDW = Red Cell Distribution Width; SD = Standard Deviation; TSH = Thyroid-Stimulating Hormone. References values: Anti-Nuclear Antibodies (ANA) negative; Erythrocyte Sedimentation Rate (ESR) 2–20 mm/h; Ferritin 15–150 ng/mL; Folic acid 3.89–26.8 mcg/L; Mean Corpuscular Volume (MCV) 80–99 fL; Red Cell Distribution Width (RDW) 11–15%; Thyroid-Stimulating Hormone (TSH) 0.35–4.94 μ U/mL; Vitamin B12 197–890 ng/L. Atopy includes: allergic rhino-conjunctivitis/asthma and atopic dermatitis.

Take-home messages

- Chi può essere interessato al/dal problema?

La malattia celiaca è una condizione proteiforme, le cui manifestazioni cliniche, estremamente mutevoli, possono portarla all'attenzione di **qualsiasi Specialista o Medico di Medicina Generale**.

- Quali sono i numeri di cui stiamo parlando?

L'anemia, specie se con i tipici aspetti del deficit marziale, rappresenta una delle più comuni (talvolta l'unica) manifestazioni extraintestinali della celiachia, interessando il **20-50% dei pazienti**.

- Quale origine ha l'anemia nei pazienti celiaci?

Il **disturbo da malassorbimento** (ferro, vitamina B12, acido folico, rame, etc.) rappresenta certamente la principale causa di anemia nel paziente celiaco, **sebbene non debbano essere sottovalutate altre condizioni**, come l'anemia da malattia cronica, la coesistenza di altre patologie, finanche l'anemia aplastica.

Una possibile scaletta...

- Qual è l'approccio terapeutico ottimale?

L'adozione di una **dieta rigorosamente priva di glutine**, da sola o associata alla **supplementazione di ferro per via enterale o parenterale**, rappresenta l'unica terapia realmente efficace per risolvere l'anemia nel paziente celiaco. Purtroppo, una quota variabile (1-45%) di pazienti anemici risponde poco a questo approccio.

- Anemia resistente alla GFD, perché?

Plurime condizioni sono state chiamate in causa per spiegare la persistenza dell'anemia nei pazienti celiaci a dieta senza glutine, **in primis la scarsa aderenza alla dieta**. Ciononostante, pazienti con elevato grado di aderenza rimangono anemici, dovendo far ipotizzare la persistenza di alterazioni microstrutturali degli enterociti, possibili varianti geniche degli enzimi legati al metabolismo del ferro o, anche, una **'iron loss' coesistente/sovrapposta al malassorbimento (origine ginecologica?)**.

11° CONVEGNO NAZIONALE AIC

Roma • 10 novembre 2023



Grazie per
l'attenzione