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Research article

Anemia in celiac disease is multifactorial in etiology

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Anemia in celiac disease (CD) has been attributed to nutritional deficiencies; however, the clinical manifestations of CD have changed with nongastrointestinal presentations predominating. We collected hematologic parameters from a cohort of patients seen at a tertiary care center for CD to assess the characteristics of anemia in this population. Hematological parameters measured ≤3 months of diagnosis and degree of villous atrophy from 405 patients diagnosed >1995 was analyzed. Ferritin levels were compared with population controls (NHANES III). Iron deficiency was common, occurring in 33% of men and 19% of women ($P < 0.001$). Folate deficiency was seen in ~12% of the total sample and B12 deficiency in ~5%. Anemia was present in ~20% of the cohort. Among the anemic patients, ferritin was less than the 10th percentile in 45%, between the 10th and 50th percentile in 39% and greater than the 50th percentile in 13%. Ferritin > 50th percentile was more common in anemic men (24%) than in anemic women (9%; $P > 0.20$). Macrocytic anemia with concurrent B12 or folate deficiency was rare (3%). Elevated ESR was observed in patients with ferritin < 10th percentile and >50th. A gluten-free diet resulted in increased serum ferritin in iron-deficient patients, and decreased ferritin levels in those with high ferritin ($r^2 = 0.46$, $P < 0.001$). Although anemia is still a common presentation of celiac disease, nutritional deficiencies alone do not explain this phenomenon in all cases; inflammation appears to contribute as evidenced by the presence of anemia of chronic disease in some individuals. Am. J. Hematol. 00:000–000, 2007. © 2007 Wiley-Liss, Inc.

Introduction

Celiac disease is an autoimmune disorder characterized by intolerance to dietary gluten, the major storage protein found in wheat [1]. In response to gluten exposure, characteristic histologic abnormalities of the small bowel mucosa are observed, including intraepithelial lymphocytosis, lymphoplasmacytic infiltration of the lamina propria, and varying degrees of villous atrophy [2]. Current estimates suggest that ~1% of the general population in the United States has celiac disease [3,4].

Patients with celiac disease have a predisposition to develop iron deficiency, thought to be due to the predominant site of mucosal damage—the duodenum—in celiac disease, which is also the site of maximal iron absorption [5]. Iron-deficiency anemia is often the presenting complaint in adults diagnosed with celiac disease [6,7]. Individuals with celiac disease are also predisposed to a number of other hematologic abnormalities, including vitamin B12 or folate deficiency and hyposplenism [8]. The clinical picture of celiac disease has changed considerably since the advent of serologic screening, with an increase in the frequency of individuals presenting with atypical (i.e. nongastrointestinal) manifestations [9].

In view of these changes in the clinical presentation of celiac disease, we assessed a variety of hematologic and associated nutritional parameters in a large cohort of celiac disease patients.

Results

Patient demographics

The demographic characteristics of the study group are shown in Table II (compare with database demographics as listed in Methods). Anemia was the reason for evaluation for celiac disease in ~11% of the patients.

Hematologic parameters of the overall study group are listed in Table III. While a similar percentage of men and women were anemic at presentation (~20%), men with celiac disease had a higher frequency of iron deficiency at baseline as compared to women (33% vs. 19%, $P < 0.01$). Macrocytic anemia with concurrent vitamin B12 and/or folate deficiency was rare (<3% of all cases of anemia); however, folate deficiency was present in about 12% of the study population, and vitamin B12 deficiency in about 5%.

The mean ferritin values in men and women (<55 years old and ≥55 years old) are listed in Table IV. Ferritin is listed both in terms of the mean log value and mean *z*-score by age and gender: a *z*-score of zero would signify equivalence to the population ferritin mean. Also included are the reference ferritin means from the NHANES III dataset listed in log units and in standard units (ng/ml).

Across all age and gender groups, celiac disease patients had lower mean serum ferritin levels compared with their age- and gender-matched cohort in the general population ($P < 0.001$ for all groups). The difference in mean ferritin between the age and gender groups was also significant ($P < 0.001$).

The mean ferritin *z*-score for all celiac disease patients was −0.58 (SD 1.10). Therefore, ~70% of celiac disease patients had a serum ferritin below the mean for their age- and gender-matched cohort.

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TABLE I. Excluded Comorbid Conditions[a]

Autoimmune hepatitis ($n = 2$)
Crohn's disease ($n = 2$)
Hemochromatosis ($n = 2$)
Idiopathic mast cell disease ($n = 1$)
Polymyalgia rheumatica ($n = 2$)
Polymyositis ($n = 1$)
Psoriatic arthritis ($n = 1$)
Rheumatoid arthritis ($n = 5$)
Sarcoidosis ($n = 2$)
Systemic lupus erythematosus ($n = 4$)
Ulcerative colitis ($n = 6$)

[a]Some patients had multiple comorbid disorders, so the total number given in Table I is greater than the total number excluded.

TABLE II. Demographic Characteristics of Cohort ($n = 400$)[a]

Age at diagnosis (mean ± SD)		46.5 ± 16.2 years
Sex (%)		
Male		33
Female		67
Degree of villous atrophy (%)		
PVA		51
S/TVA		49
	PVA ($n = 167$)	S/TVA ($n = 158$)
% Female	64	68
Age (female) (±SD)	46.0 (15.5)	44.7 (15.6)
Age (male) (±SD)	53.9 (15.8)	47.0 (18.5)

[a]All ages in years.

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%)

[a]Anemia 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.

Characterization of ferritin levels in anemic patients with celiac disease

Approximately 20% of all patients with celiac disease had anemia at presentation. These patients were categorized according to their ferritin percentile referenced to their population standard in Table V.

The mean ferritin *z*-score for anemic celiac disease patients was -1.18 (SD 1.26). Therefore, ~88% of all anemic celiac disease patients had a serum ferritin level less than the mean serum ferritin for their age/gender cohort; conversely, 12% of anemic celiac disease patients had serum ferritin levels equal to or greater than their population mean.

Effect of degree of villous atrophy on hematologic parameters

When we examined the effect of the severity of villous damage at diagnosis on hematologic parameters, we found that the proportion of anemic individuals did not differ by degree of villous atrophy [20% of partial villous atrophy (PVA) and 24% of subtotal villous atrophy (S/TVA)]. There was, however, a significant difference in the proportion of iron deficiency at diagnosis (34% for S/TVA vs. 13% for PVA, $P < 0.001$) with no significant difference in the proportion of B12 and folate deficient individuals. Table V shows the proportions of anemic individuals with low, intermediate, and high serum ferritin according to their degree of villous atrophy.

TABLE IV. Mean Ferritin Values in Celiac Disease Patients[a]

	Female, <55 years	Female, ≥55 years	Male
Ferritin (log units)	3.20 ± 0.95	3.70 ± 0.92	4.20 ± 1.08
Ferritin (ng/ml)	37.8 ± 43	58.4 ± 49	110 ± 115
Population ferritin (log units)	3.56 ± 1.01	4.46 ± 0.91	4.86 ± 0.84
Ferritin (*z*-score)	−0.36 ± 0.94	−0.84 ± 1.01	−0.79 ± 1.08

[a]$P < 0.001$ for difference in ferritin between groups. All values are listed ± SD (standard deviation).

TABLE V. Anemia in Celiac Disease Characterized by Ferritin Percentiles[a]

	Male ($n = 23$)	Female ($n = 54$)	PVA ($n = 33$)	S/TVA ($n = 38$)
Low	54	43	20	63
Intermediate	22	48	47	31
High	24	9	33	6

[a]$P < 0.05$ for difference in proportions between PVA and S/TVA. Low ferritin refers to a *z*-score ≤ -1.28 (10th percentile), intermediate refers to a *z*-score between -1.28 and 0 (10th–50th percentile) and high ferritin refers to a *z*-score > 1.28 (greater than the 50th percentile).

Analysis of ferritin *z*-score and ESR

Those patients for whom an ESR was available ($n = 81$) were classified into three groups: low ferritin (less than tenth percentile), intermediate ferritin (between 10 and 50th percentile), and high ferritin (greater than 50th percentile). As shown in Table VI, those individuals with both low and high ferritin values had higher ESR than those with intermediate ferritin ($P < 0.05$). As also shown in Table VI, there was no significant difference between mean ESR when grouped by degree of villous atrophy.

Effect of a gluten-free diet on serum ferritin

The correlation between initial serum ferritin and a repeat serum ferritin after institution of a gluten-free diet (GFD) was analyzed to determine the effect of treatment of celiac disease on hematologic parameters. This is depicted graphically in Fig. 1.

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) ($r^2 = 0.46$, $P < 0.001$).

Discussion

The link between celiac disease and anemia is well documented. The majority of prior studies have focused on

TABLE VI. ESR by Ferritin Percentile and Degree of Villous Atrophy[a]

	Low	Intermediate	High	PVA	SVA
ESR	16.8 ± 16.8	7.9 ± 7.6	19.0 ± 25.9	11.1 ± 16.3	16.4 ± 21.3

[a]All values are mean ± SD. Low/intermediate/high refer to a ferritin percentile less than the 10th, between the 10th and 50th and greater than 50th, respectively. $P < 0.05$ for the difference in ESR between ferritin percentiles.

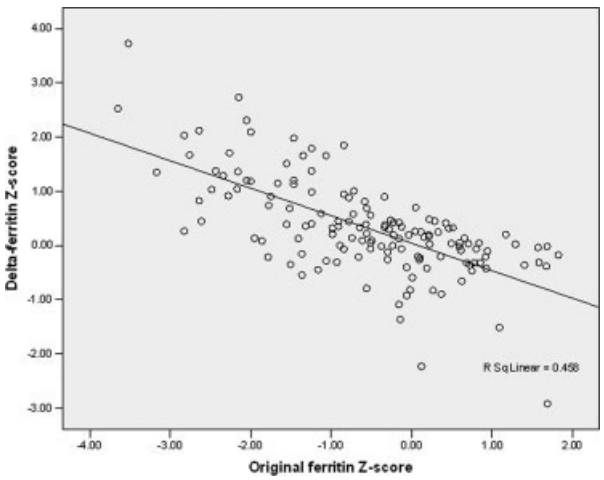

Figure 1. Effect of GFD on ferritin *z*-score. *x*-Axis is original ferritin *z*-score and *y*-axis is the change in ferritin *z*-score after institution of GFD.

micronutrient deficiencies as the cause of anemia in individuals with celiac disease [9]. Our findings suggest that this hypothesis is inadequate, and that the etiology of anemia in celiac disease is multifactorial.

In prior studies, the overall prevalence of anemia at the time of diagnosis of celiac disease has been estimated between 12 and 69% [7,9,10–12]. Our finding that ~20% of patients had anemia at the time of diagnosis is consistent with those prior estimates. In our analysis, however, only slightly more women (22%) than men (17%) presented with anemia. This is in contrast to an Italian study that found anemia as a presenting complaint leading to the diagnosis of celiac disease much more frequently among women than men [13]. Our analysis also found lower overall rates of iron deficiency at diagnosis, and significantly more men were iron deficient than women. One previous study suggested that iron deficiency was present in 46% of celiac disease patients with atypical presentations in a cohort diagnosed between 1990 and 1994, with no significant gender discrepancy [7]. Regarding the gender difference, a probable explanation is that we normalized all ferritin levels to national population standards. In many cases, absolute numerical cutoffs are used to define iron deficiency (e.g. ferritin < 30 ng/ml) [14]. This does not take into account the fact that there is a significant gender difference in average ferritin level, which, if not controlled for, can underestimate the severity and frequency of iron deficiency in men. Our findings corroborate another study recently published that suggested that malabsorption is actually worse in male celiac disease patients than females [15]. Future studies are necessary to explore this possibility.

The novel finding of our study is the frequency of cases of anemia not solely attributable to iron deficiency in individuals with celiac disease. Overall, 12–13% of anemic individuals (22% of men and 9% of women) presented with ferritin levels greater than the average for their age/gender cohort. In both men and women, the majority of anemic individuals had ferritin levels greater than the 10th percentile for their age/gender cohort. Ferritin is an acute phase reactant whose serum concentration can increase in response to systemic inflammation [16]. Also, when we correlated the ESR and ferritin values, we noted that those with both very low and very high ferritin values tended to have an elevated ESR. In individuals with low ferritin, this may be a manifestation of the relative severity of the disease, extended over such time as to allow depletion of body iron stores. The elevated ESR observed in those with high ferritin values suggests systemic inflammation without significant malabsorption. The combination of anemia associated with high serum ferritin and evidence of systemic inflammation suggests anemia of chronic disease.

In prior reviews of the literature, there has been no comment about anemia of chronic disease occurring in celiac disease [9]. In response to inflammation, cytokines such as IFN-gamma, TNF-alpha, IL-1, IL-6, and IL-10 are released into circulation. These cytokines act on the liver, causing increased production of hepcidin, an acute phase reactant whose role is to inhibit the duodenal absorption of dietary iron. These cytokines also induce the expression of DMT-1, an iron transporter on macrophages, whose role is to increase iron uptake, and they simultaneously down-regulate the expression of the iron exporting protein ferroportin-1 on macrophages. The net effect is a trapping of circulating iron in the reticuloendothelial system [17]. Recent evidence also suggests that IL-15 may play a role in this pathway [18]. IL-15 is implicated in the pathophysiology of celiac disease, and is responsible in part for sustained inflammation in active disease [19]. This suggests the idea that celiac disease could lead to the development of *de novo* anemia of chronic disease.

In addition to lower rates of iron deficiency, we found a lower prevalence of folate deficiency (about 10%) and B12 deficiency (about 5%) compared with previous studies. In one prior study of 50 individuals with celiac disease diagnosed in the early 1990's, low plasma folate was observed in 49%; this same study also found that 11% of newly diagnosed celiac disease patients were vitamin B12 deficient [20]. Another study found that 81% of a cohort of 16 children diagnosed with celiac disease had low serum folate [21]. The incidence of vitamin B12 deficiency at the time of diagnosis of celiac disease has been estimated between 8 and 41% in other studies [22,23].

Our analysis links the degree of villous atrophy and the etiology of anemia in celiac disease. Individuals with subtotal/total villous atrophy have lower serum ferritin values than do individuals with partial villous atrophy, reflecting malabsorption of iron. Furthermore, anemic individuals with subtotal/total villous atrophy have a higher frequency of anemia associated with ferritin levels less than the 10th percentile (63%) as compared with anemic individuals with partial villous atrophy (33%). Despite greater malabsorption of iron in the group with more severe villous atrophy, the frequency of anemia was similar in individuals with PVA (20%) and S/TVA (24%). Another etiologic factor besides

malabsorption, such as inflammation, would be necessary to explain this observation.

A limitation of our analysis concerns the use of serum levels of ferritin, vitamin B12, and folate as indicators of deficiency states. Although useful for retrospective and epidemiologic purposes, serum levels of vitamin B12 and folate are nonspecific for the presence of actual deficiency states. Low ferritin in the presence of anemia, while suggestive of iron-deficiency anemia, is not sufficient for the diagnosis. For epidemiologic purposes, the definition of iron deficiency consists of an abnormal value in two out of the following three measurements: ferritin, transferrin saturation and free erythrocyte protoporphyrin [24]. Although our analysis focused on ferritin, it should be noted that determining clinical iron deficiency requires multiple laboratory measurements.

Our findings raise two areas of future inquiry: the first regards the changing prevalence of hematologic abnormalities in celiac disease and the second regards the changing etiology of these abnormalities. Regarding the former, we found a lower prevalence of most hematologic abnormalities (e.g., anemia, iron/folate/B12 deficiency, etc.) than older studies. It is possible that this is a manifestation of the changes in the clinical presentation of celiac disease over the past decade or earlier diagnosis. Before the advent of sensitive serologic testing, which became widely used in the early 1990's, almost all adult patients diagnosed with celiac disease presented with total villous atrophy and a malabsorption syndrome [25]. The vast majority of the population in this study was diagnosed after 1998. As we have found, total villous atrophy predicts a higher likelihood of micronutrient deficiencies. As more cases are being diagnosed with less severe degrees of villous atrophy, the frequency of micronutrient deficiencies has decreased overall; however, this has not led to a decrease in the frequency with which celiac disease patients present with anemia.

The second issue—the unexpectedly high prevalence of anemia not due solely to iron deficiency—has not been addressed in the celiac literature to date. We do know that celiac disease is associated with inflammation that is not only intestinal but also systemic [26]. Thus, the hematologic manifestations of the disease likely reflect the interplay between local and systemic factors. Future studies addressing the role of malabsorption versus degree of inflammation in contributing to the anemia associated with celiac disease are necessary.

The finding that a GFD has a modulating effect on serum ferritin values corroborates prior studies [27]. If we assume that inflammation caused by celiac disease is the cause of the high ferritin values observed in a subset of our cohort, we would expect that resolution of their celiac disease would lead to a decrease in serum ferritin. As we did observe this, it strengthens the argument that celiac disease can induce hematologic changes similar to other chronic inflammatory disorders.

Our study demonstrates that the pathophysiologic mechanisms of hematologic abnormalities occurring in celiac disease patients are complex. The mechanisms by which patients with celiac disease develop anemia need to be further explored. Celiac disease—already an under-recognized disorder in the United States—should be considered not only in the differential diagnosis of iron-deficiency anemia, but also in anemia of chronic disease.

Materials and Methods

Subjects

From an anonymized database of 992 patients with celiac disease, originally evaluated at Columbia University's Celiac Disease center (a tertiary referral center), patients were selected for analysis if all of the following conditions were met: (1) biopsy-proven celiac disease, (2) age $\geq$ 18 years at the time of diagnosis, (3) serum ferritin measured within 3 months of initial diagnosis, and (4) absence of refractory sprue, small bowel adenocarcinoma and/or intestinal lymphoma. We identified 430 individuals who met these criteria. All patients in this analysis were diagnosed with celiac disease after 1995. The demographic composition of the entire database was as follows: 64.6% women, 99% Caucasian, and mean age at diagnosis 41.3 years (SD 16.7). Our database demographics compare similarly to a community-drawn sample of 1,602 adult celiac disease patients whose mean age at diagnosis was 45.2 years and whose male-to-female ratio was 1:2.8 [28].

From this group, individuals were excluded from analysis if they had an associated inflammatory disease that could influence hematologic findings (see Table I) or were diagnosed with celiac disease in the setting of inpatient hospitalization ($n = 5$). All patients diagnosed with iron-deficiency anemia or referred for the evaluation of iron-deficiency anemia received both upper and lower endoscopy as well as studies of the small intestine to rule out gastrointestinal causes of blood loss, which if present would exclude them from analysis. Ultimately, 400 patients were selected for analysis. Our Institutional Review Board had approved collection of patient information in the celiac disease database.

Data, including age, gender, and degree of villous atrophy, were collected. A pathologist and one of the investigators reviewed all biopsies. The severity of intestinal damage was graded according to the scale proposed by Oberhuber et al.: PVA (partial villous atrophy; Marsh IIIa), STVA (subtotal villous atrophy; Marsh IIIb), and TVA (total villous atrophy; Marsh IIIc) [2]. While all patients were diagnosed by biopsy, patients were not included in our villous atrophy analysis if the original biopsy specimen was not available for review by our pathologist. For the purposes of this study, the more severe grades of villous atrophy (STVA and TVA) were considered together as a combined S/TVA category.

Because one of the hematologic variables (ferritin) varies by age and gender, patients were grouped into one of three cohorts: women $<$ 55 years old, women $\geq$ 55 years old, and men of any age. The following hematologic variables were collected and compared between groups according to mode of disease presentation and degree of villous atrophy: ferritin ($n = 400$), serum iron ($n = 220$), TIBC ($n = 198$), vitamin B12 ($n = 223$), serum folate ($n = 200$), and hemoglobin ($n = 367$). If available, ESR at the time of diagnosis was collected ($n = 81$). Serum ferritin data by age and gender-cohort were also collected from the NHANES III national database to serve as a population comparison with celiac disease patients. If available, repeat serum ferritin values were collected after patients had been adherent to a GFD for up to 1 year after the initial diagnosis of celiac disease; adherence to a GFD was determined by consultation and follow-up with one of the clinical investigators and a clinical dietician.

Data analysis

Serum ferritin values were log-transformed to normalize the data. *z*-Scores were calculated from the mean serum ferritin of women $<$ 55 years old, women $\geq$ 55 years old and men of any age according to the NHANES III data; *z*-scores were derived by subtracting the patients' ferritin values from the relevant mean population value and dividing by the population standard deviation. The use of *z*-scores, which are unitless and dimensionless, allows comparison of ferritin values between groups, as they are equivalent across age and gender groups. For instance, a man with a ferritin of 129 ng/ml and a woman less than 55 years old with a ferritin of 35 ng/ml each has a ferritin *z*-score of zero. This allowed us to increase the power of our statistical analysis by being able to group individuals of differing age and sex into the same analysis. The NHANES data were restricted to Caucasian individuals, as the celiac disease database was overwhelmingly ($\sim$99%) composed of Caucasian patients. All numerical data was compared by unpaired, two-tailed Student's *t*-tests or for comparisons between more than two groups, one-way ANOVA. Fisher's exact test was used to compare proportions of various nutrient deficiencies and types of anemia between groups. Linear regression analysis was used to examine the effect of GFD on serum ferritin. For all analyses, significance was determined at the $P < 0.05$ level.

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