Iron deficiency anemia in celiac disease

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Abstract

Iron is an important micronutrient that may be depleted in celiac disease. Iron deficiency and anemia may complicate well-established celiac disease, but may also be the presenting clinical feature in the absence of diarrhea or weight loss. If iron deficiency anemia occurs, it should be thoroughly evaluated, even if celiac disease has been defined since other superimposed causes of iron deficiency anemia may be present. Most often, impaired duodenal mucosal uptake of iron is evident since surface absorptive area in the duodenum is reduced, in large part, because celiac disease is an immune-mediated disorder largely focused in the proximal small intestinal mucosa. Some studies have also suggested that blood loss may occur in celiac disease, sometimes from superimposed small intestinal disorders, including ulceration or neoplastic diseases, particularly lymphoma. In addition, other associated gastric or colonic disorders may be responsible for blood loss. Rarely, an immune-mediated hemolytic disorder with increased urine iron loss may occur that may respond to a gluten-free diet. Reduced expression of different regulatory proteins critical in iron uptake has also been defined in the presence and absence of anemia. Finally, other rare causes of microcytic anemia may occur in celiac disease, including a sideroblastic form of anemia reported to have responded to a gluten-free diet.

Key words: Anemia; Iron deficiency; Autoimmune hemolysis; Celiac disease; Iron absorption; Ferroportin; Hepcidin; Divalent metal transporter; Enterocyte

Core tip: Iron is a critical micronutrient that may be deficient in well-established celiac disease or be the presenting clinical feature even in the absence of diarrhea or weight loss. Most often, impaired duodenal mucosal uptake of iron is evident since surface absorptive area in the duodenum is reduced, in large part, because celiac disease is an immune-mediated disorder largely focused in the proximal small intestine. Other superimposed small intestinal complications of celiac disease may be responsible causing blood loss, including ulceration or neoplasia. Finally, associated gastric or colonic causes of blood loss, immune-mediated hemolysis and reduced expression of different regulatory proteins critical in iron uptake may be present.
INTRODUCTION

Anemia, associated with iron deficiency, is most often due to increased blood loss, or impaired iron absorption. Iron-deficiency anemia is often recorded in newly diagnosed celiac disease and may persist for variable periods after initiation of a gluten-free diet. Iron deficiency anemia in children and adults may also be the presenting clinical feature of celiac disease, and may be the only finding present. Unfortunately, this interesting relationship between iron deficiency anemia and celiac disease has been poorly appreciated, even among subspecialty physicians, including practicing hematologists.

IRON DEFICIENCY AND ANEMIA

From a global perspective, iron-deficiency anemia is probably the most common cause of microcytic anemia while other causes include thalassemia, anemia associated with chronic inflammation and sideroblastic anemia. Iron plays a crucial role in the heme group of hemoglobin in order to transport oxygen. Iron is also detected in other proteins including cytochromes and myoglobin and may play a role in fatigue associated with iron deficiency alone in athletes. Blood loss from the gastrointestinal tract has been documented in athletes. Transferrin has the capacity to transport two ferric ions to distant target tissues. Prior to transferrin binding, any ferrous ions must be initially converted to ferric ions by ferroxidases. A deficiency of these latter oxygen-dependent enzymes impedes iron uptake into cells. Excessive iron can also be stored within the liver, and made available later for transport to maturing red blood cells.

REGULATION OF IRON ABSORPTION

Body iron storage levels are well maintained in a consistent range. With iron deficiency, iron absorption may be increased, but with iron overload, decreased. Iron homeostasis is regulated by hepcidin discovered almost 2 decades ago. Hepcidin is actively synthesized by hepatocytes and then hepatocyte secrete this protein into circulating plasma. The concentration of hepcidin is affected by both iron stores. Hepcidin is found mostly in free form in the bloodstream, and is eventually filtered by the kidneys. Hepcidin regulates iron flow into the blood plasma by controlling the membrane protein, ferroportin. Hepcidin first appears to bind to ferroportin. Then, endocytosis of ferroportin occurs followed by destruction of the hepcidin within the cell in lysosomes. This process impairs iron absorption. As a result, release of iron into the circulation is prevented from both the enterocyte and hepatocyte stores. Mutations in this ferroportin protein have been described that prevent hepcidin binding and lead to iron overload. Hepcidin may also be controlled by a bone marrow suppressor of hepcidin that responds to increased erythropoietin caused by hypoxia or significant bleeding. Other possible homeostatic...
mechanisms that may not be reliant on hepcidin include hypoxia and cellular iron deficiency. Both may result in an increase in ferroportin that may be independent of hepcidin control. Further information on role of hepcidin and details on systemic iron homeostasis can be found elsewhere\(^ {20, 29}\).

**IRON DEFICIENCY IN CELIAC DISEASE**

*Reduced duodenal iron absorption*

Clinical and other features of celiac disease have been extensively reviewed in earlier reports in this journal\(^ {30, 31}\). Iron deficiency anemia is itself an independent clinical manifestation of either well established celiac disease, or may lead to its initial recognition, especially if other causes, such as a colonic cancer, have been excluded and iron deficiency appears refractory to oral iron treatment\(^ {32}\). In part, this reflects the prominent duodenal mucosal geographic distribution of celiac disease and concurrence with the principal site of enterocyte uptake of iron by proximal small intestinal enterocytes. As a result of disease localized in the proximal small intestinal mucosa, impaired duodenal iron absorption can be expected, even if there is provision of added oral iron. Recently, more and more emphasis has been placed on micronutrient deficiency as a diagnostic clue to occult celiac disease, particularly for iron, and iron deficiency anemia\(^ {33}\). In children, iron deficiency anemia in celiac disease is common and further screening with tissue transglutaminase antibodies has been strongly recommended\(^ {34}\). Interestingly, pica may be the presenting clinical symptom of celiac disease coupled with iron deficiency anemia in children\(^ {35}\).

**Gastrointestinal blood loss**

Reports have also appeared in celiac disease with occult gastrointestinal bleeding as a cause of iron deficiency anemia\(^ {36, 37}\). In a study of young males presenting with iron deficiency anemia, peptic ulcer disease was the most common finding in 30%\(^ {37-39}\). However, in this report, malignant causes were not detected but celiac disease was subsequently diagnosed in 4%. In celiac disease, added common causes of blood loss should be considered. Most experts would recommend a thorough evaluation, including endoscopic and radiologic imaging studies\(^ {40}\). Routine duodenal biopsies obtained during upper endoscopic evaluation for iron deficiency\(^ {41}\) or other upper gastrointestinal symptoms\(^ {42}\) could lead to recognition of histopathological changes of untreated celiac disease in the proximal small intestinal mucosa. In a recent report, celiac disease with iron deficiency anemia was more likely to be observed in Caucasians, than non-Caucasians\(^ {43}\). Moreover, celiacs initially manifesting with anemia appeared to have more severe disease than celiacs presenting with diarrhea\(^ {44}\). It should also be noted, however, that celiac disease may be complicated by a superimposed ulcerative small bowel disorder. Either benign mucosal ulcers, so-called non-granulomatous ulcerative jejunitis, or malignant ulcers due to a malignant lymphoma in celiac disease may cause occult or overt blood loss, positive fecal occult blood tests, and if chronically present over time, iron deficiency and anemia.

**Iron deficiency and hemolysis**

Intravascular hemolysis, usually related to an associated autoimmune disorder, with increased urinary iron losses should be considered. Although rare\(^ {45, 46}\), improvement with a gluten-free diet has been recorded, even when prior steroid treatment failed\(^ {46}\). To screen for hemosiderin, colorimetric methods on a collected urine sample may be considered along with hematopathological review of the peripheral blood smear. These initial studies may lead to a more detailed hematologic evaluation.

**Unusual causes or associations of microcytic anemia**

Occasionally, microcytic anemia may be due to other rare conditions in celiac disease. These include occasional anemias associated with co-existent chronic inflammatory diseases along with a rare sideroblastic anemia associated with pyridoxine deficiency\(^ {47}\). Interestingly, the hematologic disorder in this initial case report of sideroblastic anemia responded completely to a gluten-free diet. Further screening studies for celiac disease in patients with sideroblastic anemia should be considered. A rare disorder of iron deficiency anemia in children with celiac disease and pulmonary hemosiderosis has been detailed, the so-called Lane-Hamilton syndrome\(^ {48}\). In this series, the authors reported on improvement with a gluten-free diet. This contrasted with a larger series from France of 25 pediatric cases with idiopathic pulmonary hemosiderosis and hemoptysis. In these, 28% had celiac disease antibodies. Most children in this study required corticosteroids and immunosuppressants\(^ {49}\). Finally, gastric changes have been reported in studies of children\(^ {50}\) and adults\(^ {51, 52}\) with celiac disease, and some believe that these are complicated by superimposed *Helicobacter pylori* infection and be responsible for iron deficiency anemia.

**REGULATION OF IRON ABSORPTION IN CELIAC DISEASE**

*Related to reduced mucosal surface absorptive area*

Modern studies on the absorption of inorganic iron have been limited in celiac disease. Initial, essentially historically reported studies\(^ {53}\) evaluated the absorption of iron from a 5 mg dose of ferrous iron using a total body counter and confirmed that ferrous iron absorption was limited in untreated celiac disease, particularly if already iron deficient. However, improved
absorption resulted from a gluten free diet. In celiac disease, iron deficiency has generally been attributed to reduced surface area, particularly in the proximal small intestine.

**Studies of iron regulatory proteins in celiac disease**

Interestingly, iron regulatory proteins have been evaluated in celiacs compared to controls and iron deficient patients using duodenal biopsies\(^{54,55}\). Results showed that DMT1, ferroportin, hephaestin and transferrin receptor protein mRNA were increased while body iron stores were reduced in celiac disease. These different iron regulatory proteins were also increased with iron deficiency (unrelated to celiac disease) suggesting that the upregulation in iron absorption capacity that appears to occur in celiac disease is primarily due to iron deficiency per se, while increased enterocyte proliferation in celiac disease does not have a specific effect on iron uptake regulation\(^{54}\). In contrast, a recent study showed that expression of DMT1 and ferroportin are increased in celiac disease with or without iron deficiency\(^{55}\). In this study, ferritin expression was also found to be increased in celiac disease, but only in those with iron deficiency.

**CONCLUSION**

Iron is a key micronutrient that may be depleted in children and adults with celiac disease. Iron deficiency anemia may also complicate well-defined celiac disease, or actually represent the initial extra-intestinal clinical feature. Iron deficiency anemia should lead to careful exclusion of other common causes, such as colon cancer. Even with well-established celiac disease, other superimposed causes should be excluded, including occult lymphoma. In celiac disease, impaired iron uptake from the duodenal lumen is the most likely cause, even if other common features of classical celiac disease, such as diarrhea or weight loss, are absent. Although reduced duodenal mucosal surface area in unrecognized and untreated celiac disease may be present, recent studies have also evaluated duodenal biopsies from celiac disease patients in the presence and absence of anemia and documented reduced expression of important iron regulatory proteins.

**REFERENCES**

1. Halfdanarson TR, Litwak MR, Murray JA. Hematologic manifestations of celiac disease. *Blood* 2007; 109: 412-421 [PMID: 16973955 DOI: 10.1182/blood-2006-07-031104]

2. Annibale B, Severi C, Chistolini A, Antonelli G, Lahner E, Marcheggiiano A, Iannoni C, Monarca B, Delle Fave G. Efficacy of gluten-free diet alone on recovery from iron deficiency anemia in adult celiac patients. *Am J Gastroenterol* 2001; 96: 132-137 [PMID: 11197242 DOI: 10.1111/j.1572-0241.2001.003463.x]

3. Hoffman AD. Anaemia in adult coeliac disease. *Clin Gastroenterol* 1974; 3: 71-89 [PMID: 459261]

4. Unsworth DJ, Lox FJ, Harvey RF. Iron-deficiency anemia in premenopausal women. *Lancet* 1999; 353: 1100 [PMID: 10199377 DOI: 10.1016/S0140-6736(05)67654-9]

5. Bottaro G, Cataldo F, Rotolo N, Spin A, Corazza GR. The clinical pattern of subclinical/silent celiac disease: an analysis on 1026 consecutive cases. *Am J Gastroenterol* 1999; 94: 691-696 [PMID: 10806653 DOI: 10.1111/j.1572-0241.1999.tb03819-3]

6. Smukalla S, Lebwohl B, Mears JG, Leslie LA, Green PH. How often do hematologists consider celiac disease in iron-deficiency anemia? Results of a national survey. *Clin Adv Hematol Oncol* 2014; 12: 100-105 [PMID: 24892255]

7. DeLoughery TG. Microcytic anemia. *N Engl J Med* 2014; 371: 1324-1331 [PMID: 25271605 DOI: 10.1056/NEJMra1215361]

8. Vaucher P, Druais P, Waldvogel S, Favrat B. Effect of iron supplementation on fatigued in nonanaemic menstruating women with low ferritin: a randomized controlled trial. *CMAJ* 2012; 184: 1247-1254 [PMID: 22777991 DOI: 10.1503/cmaj.110950]

9. Verdon F, Bumand B, Stubli CL, Bonard C, Graff M, Michaud A, Bischoff T, de Veyve M, Studer JP, Herzlig C, Chapuis C, Tissot J, Pécout A, Favrat B. Iron supplementation for unexplained fatigue in non-anemic women: a double blind randomized placebo controlled trial. *BMJ* 2003; 326: 1124 [PMID: 12763985 DOI: 10.1136/bmj.326.7399.1124]

10. Kraynbeel PA, Battegay E, Breymann C, Furrer J, Schultes G. Intravenous iron for the treatment of fatigue in nonanaemic, premenopausal women with low serum ferritin concentration. *Blood* 2011; 118: 3222-3227 [PMID: 21705493 DOI: 10.1182/blood-2011-04-346304]

11. Peeling P, Dawson B, Goodman C, Landers G, Trinder D. Athletic induced iron deficiency: new insights into the role of inflammation, cytokines and hormones. *Eur J Appl Physiol* 2008; 103: 381-391 [PMID: 18365240 DOI: 10.1007/s00421-008-0726-6]

12. Robertson JD, Maughan RJ, Davidson RJ. Faecal blood loss in response to exercise. *Br Med J (Clin Res Ed) 1987; 295: 303-305 [PMID: 3115419 DOI: 10.1136/bmj.295.6953.303]

13. Pasricha SR, Low M, Thompson J, Farrell A, De-Regil LM. Iron supplementation benefits physical performance in women of reproductive age: a systematic review and meta-analysis. *J Nutr* 2014; 144: 906-914 [PMID: 24717371 DOI: 10.3945/jn.113.189589]

14. Mei Z, Cogswell ME, Parvanta I, Lynch S, Beard JL, Stoltzfus RJ, Grummer-Strawn LM. Hemoglobin and ferritin are currently the most efficient indicators of population response to iron interventions: an analysis of nine randomized controlled trials. *J Nutr* 2005; 135: 1974-1980 [PMID: 16046725]

15. Gokse S, Arslantas E. Changing face and clinical features of celiac disease in children. *Pediatr Int* 2015; 57: 107-112 [PMID: 25040342 DOI: 10.1111/ped.12448]

16. Ertekin V, Tozum MS, Küçük N. The prevalence of celiac disease in children with iron-deficiency anemia. *Turk J Gastroenterol* 2013; 24: 334-338 [PMID: 24254265]

17. Cannizzaro R, Da Ponte A, Tabuso M, Mazzucato M, De Re V, Caggiari L, Fornasarig M, Maior O, Orzes E, Canzonieri V. Improving detection of celiac disease patients: a prospective study in iron-deficient blood donors without anemia in north Italy. *Eur J Gastroenterol Hepatol* 2014; 26: 721-724 [PMID: 24841904 DOI: 10.1097/MEG.0000000000000100]

18. Illing AC, Shawki A, Cunningham CL, Mackenzie B. Substrate profile and metal-ion selectivity of human diveralt metal-ion transporter-1. *J Biol Chem* 2012; 287: 30483-30496 [PMID: 22736759 DOI: 10.1074/jbc.M112.364208]

19. Gunshin H, Mackenzie B, Berger UV, Gunshin Y, Romero ME, Boron WF, Nussberger S, Gollan JL, Hediger MA. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature* 1997; 388: 482-488 [PMID: 9242408 DOI: 10.1038/41343]

20. Iolascon A, De Falco L. Mutations in the gene encoding DMT1: clinical presentation and treatment. *Semin Hematol* 2009; 46: 358-370 [PMID: 19786204]

21. Cherukuri S, Potra R, Sarkar J, Nurko S, Harris ZL, Fox PL. Unexpected role of ceruloplasmin in intestinal iron absorption.
Pica as a presenting symptom in childhood celiac disease. Detection of adult celiac disease with duodenal biopsy: necessary for the detection of celiac disease in patients presenting with iron deficiency anemia? Int J Prev Med 2012; 3: 273-277 [PMID: 22624084 DOI: 10.1186/1751-9458-3-273]

Freeman HJ. Detection of adult celiac disease with duodenal screening biopsies over a 30-year period. Can J Gastroenterol 2013; 27: 405-408 [PMID: 23862172 DOI: 10.1186/1751-9458-27-405]

Freeman HJ, McLachlan S, Adams PC, Eckfeldt JH, Garner CP, Valpe CD, Gordeuk VR, Brantner T, Leindeecker-Foster C, Killeen AA, Acton RT, Barcellos LF, Nickerson DA, Beckman KB, McLaren GD, McLaren CE. Association between celiac disease and iron deficiency in Caucasians, but not non-Caucasians. Clin Gastroenterol Hepatol 2013; 11: 808-814 [PMID: 23416278 DOI: 10.1016/j.cgh.2013.02.009]

Abu Daya H, Lebowohl B, Lewis SK, Green PH. Celiac disease patients presenting with anemia have more severe disease than those presenting with diarrhea. Clin Gastroenterol Hepatol 2013; 11: 1472-1477 [PMID: 23756221 DOI: 10.1016/j.cgh.2013.05.030]

Miller DG. Celiac disease with autoimmune haemolytic anemia. Postgrad Med J 1984; 60: 629-630 [PMID: 6483707 DOI: 10.1136/pgmj.60.707.629]

Ivanovski P, Nikolić D, Dimitrijević N, Ivanovski I, Perišić V. Autosomal dominant hereditary hemochromatosis associated with a novel ferroportin mutation and unique clinical features. Am J Med Genet A 2014; 164A: 1964-1969 [PMID: 24994858 DOI: 10.1002/ajmg.a.36255]

Mastrogiannaki M, Tzotzopoulou P, Vaulont S, Peyssonnaux C. Hepatic hypoxia-inducible factor-2 down-regulates hepcidin expression in mice through an erythropoietin-mediated increase in erythropoiesis. Haematologica 2009; 94: 827-834 [PMID: 22207682 DOI: 10.3324/haematol.2009.04.002]

Chopra A, Clandinin MT, Thomson AB. Recent developments in adult coeliac disease. Gut 1964; 5: 304-308 [PMID: 14209912 DOI: 10.1136/gut.5.4.304]

Hendricks GF, Somers K, VandenPlas Y. Lane-Hamilton syndrome: case report and review of the literature. Eur J Pediatr 2011; 170: 1597-1602 [PMID: 21947219 DOI: 10.1007/s00431-011-1568-5]

Tayyab J, Nathan N, de Blic J, Fayon M, Epaud R, Deschidre A, Troussier F, Lubrano M, Chiron R, Reix P, Croz P, Mahloul M, Michon D, Clement A, Corvol H. New insights into pediatric idiopathic pulmonary hemosiderosis: the French RespiRare® cohort. Orphanet J Rare Dis 2013; 8: 161 [PMID: 24125570 DOI: 10.1186/1750-1172-8-161]

Nenna R, Magliocca FM, Tiberti C, Mastrogiovanni G, Petrarca L, Mennini M, Lucantoni F, Luparia RP, Bonamico M. Endoscopic and histological gastric lesions in children with celiac disease: mesocolic involvement is not only confined to the duodenum. J Pediatr Gastroenterol Nutr 2012; 55: 728-732 [PMID: 22773062 DOI: 10.1097/MPG.0b013e31826e2f7b]

Wolber O, Owen D, DeBuono L, Appelman H, Freeman H. Lymphocytic gastritis in patients with celiac sprue or sprue-like intestinal disease. Gastroenterology 1990; 98: 310-315 [PMID: 229586]

Arnason T, Brown IS, Goldsmith JD, Anderson W, O'Brien BH, Wilson C, Winter H, Lauwers GY. Collagenous gastritis: a morphologic and immunohistochemical study of 40 patients. Mod Pathol 2015; 28: 533-544 [PMID: 25234289 DOI: 10.1038/modpathol.2014.119]

Anand BS, Callender ST, Warner GT. Absorption of inorganic and haemoglobin iron in celiac disease. Br J Haematol 1977; 37: 409-414 [PMID: 603771 DOI: 10.1111/j.1365-2457.1977.tb01012.x]

Barisani D, Parafioriti A, Bardella MT, Zoller H, Conte D, Arimarglio E, Trovato C, Koch RO, Weiss G. Adaptive changes of duodenal iron transport proteins in celiac disease. Physiol Genomics 2004; 17: 316-325 [PMID: 15054143 DOI: 10.1152/
Sharma N, Begum J, Eksteen B, Elagib A, Brookes M, Cooper BT, Tselepis C, Iqbal TH. Differential ferritin expression is associated with iron deficiency in coeliac disease. *Eur J Gastroenterol Hepatol* 2009; 21: 794-804 [PMID: 19404207 DOI: 10.1097/MEG.0b013e328308676b]
