World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i31.9233

World J Gastroenterol 2015 August 21; 21(31): 9233-9238
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Iron deficiency anemia in celiac disease

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Author contributions: Freeman HJ contributed all to this paper.

Conflict-of-interest statement: Freeman HJ declares no conflict of interest related to this publication.

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Received: December 24, 2014
Peer-review started: December 25, 2014
First decision: March 10, 2015
Revised: March 30, 2015
Accepted: June 16, 2015
Article in press: June 16, 2015
Published online: August 21, 2015

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 in 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.

Freeman HJ. Iron deficiency anemia in celiac disease. *World J Gastroenterol* 2015; 21(31): 9233-9238 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i31/9233.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i31.9233

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[1] and may persist for variable periods after initiation of a gluten-free diet[2]. Iron deficiency anemia in children and adults may also be the presenting clinical feature of celiac disease, and may be the only finding present[3-5]. Unfortunately, this interesting relationship between iron deficiency anemia and celiac disease has been poorly appreciated, even among subspecialty physicians, including practicing hematologists[6].

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[7]. 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 the absence of anemia, especially in females[8-10]. Due to menses, premenopausal females are at increased risk for iron deficiency and pregnancy further increases daily iron requirements. A separate risk group for iron deficiency includes athletes. Blood loss from the gastrointestinal tract has been documented in athletes along with low grade intravascular hemolysis causing increased urinary loss of iron[11,12]. Inflammation caused by exercise may also cause iron deficiency and impaired performance[13,14]. Each of these risk factors recognized particularly in healthy women (and healthy athletes) may occur if underlying celiac disease is also present. As a result, the degree of iron deficiency may be exacerbated. Although detailed epidemiological data on iron deficiency in celiac disease are limited, some recent studies suggest that iron deficiency may be significant in both children[15,16] and adults[17] with celiac disease.

IRON ABSORPTION

Iron enters the epithelial cell of the duodenal mucosa in ferrous form through an apical or brush border membrane transport protein termed the divalent metal transporter (DMT1). DMT1 is a protein that spans the entire brush border membrane. It has the capacity to transport iron as well as several other divalent metals[18]. Normally, this carrier protein functions in a co-transport mode with univalent protons[19]. Microcytic anemia caused by DMT1 mutations have also been identified in human subjects[20]. Iron transport by DMT1 also requires conversion of ferric iron, the predominant dietary form, to ferrous iron by means of ferric reductases at the apical surface of the intestinal enterocyte prior to cellular uptake. An acidic apical surface membrane microenvironment is also required. Inside the enterocyte, ferritin within the cytoplasmic compartment appears to be able to store large amounts of iron and may be important for controlled delivery of iron to the basolateral membrane.

Iron exits the duodenal enterocyte by means of a different carrier protein, ferroportin, also termed the metal transporter 1 (MTP 1). Studies have demonstrated that this critical protein is localized to the basolateral membrane. Iron then binds a separate glycosylated protein, transferrin, to permit iron delivery through the bloodstream to developing red cells. 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 (*e.g.*, hephaestin, ceruloplasmin)[21]. 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[22]. Iron homeostasis is regulated by hepcidin discovered almost 2 decades ago[23].

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[24,25] 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[26,27]. 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[28,29].

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[16]. Interestingly, pica may be the presenting clinical symptom of celiac disease coupled with iron deficiency anemia in children[34].

Gastrointestinal blood loss

Reports have also appeared in celiac disease with occult gastrointestinal bleeding as a cause of iron deficiency anemia[35,36]. 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 histopathologic 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.

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P- Reviewer: Pellegrino S **S- Editor**: Yu J **L- Editor**: A
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ISSN 1007-9327