Iron metabolism

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Resumen

El hierro es un metal de transición que juega un papel esencial en el cuerpo humano en el intercambio de electrones. Algunas de las funciones más importantes del hierro son la oxigenación tisular producción de energía inactivación de drogas y toxinas síntesis del ADN, así como el metabolismo de la mayor parte de las células. La solubilidad del hierro en su forma natural es extremadamente baja y, aunque es uno de los elementos más abundantes en la naturaleza paradójicamente su deficiencia en el cuerpo humano es uno de los problemas nutricionales mas comunes en la humanidad. consecuentemente la evolución ha proveído mecanismos eficientes para la obtención y almacenamiento pero no la eliminación del exceso de hierro.

Palabras clave:
Hierro metabolismo de hierro, anemia, gastritis

Summary

Iron is a transition metal and plays an essential role in the body as an electron donor and acceptor. Some of the most important functions of iron proteins are oxygen transport, mitochondrial oxidative energy production, inactivation of drugs and toxins, and DNA synthesis. Iron solubility in its stable, oxidized form is extremely low and, although iron is one of the most abundant elements in nature, paradoxically, iron deficiency is one of the most common human nutritional problems. Consequently, evolution has provided efficient mechanisms of iron acquisition and storage but none excreting excess iron.

Key words:
Iron, iron metabolism, anemia, gastritis

Mechanisms of iron regulation

In order to gain access to the duodenal enterocyte ferric iron in the intestinal lumen is first reduced to ferrous iron by duodenal cytochrome b and subsequently transported through the duodenal brush border membrane by divalent metal transporter 1 (DMT1), a proton transporter requiring low pH for efficient functioning.[1,2] Heme iron is transported by a different mechanism by heme carrier protein 1 (HCP1) and is subsequently split by heme oxygenase to mix with the pool of intracellular iron. Iron export through the basolateral membrane is performed by the basolateral iron transport protein ferroportin (FPN, IREG1).[3] Ferroportin is essential for the basolateral transport of iron from enterocytes, for placental iron transfer and, for exporting the catabolic iron derived from senescent erythrocytes from tissue macrophages. The discovery of hepcidin and its role in iron homeostasis represents a major advance in understanding iron regulation.[4,5]

Mutations of five unrelated genes are known to result in genetic hemochromatosis in man:[6] the classic hereditary hemochromatosis HFE, transferrin receptor 2 TFR-2, the iron transporter ferroportin FPN, hemojuvelin HJV and hepcidin HAMP. All forms of genetic hemochromatosis are characterized by decreased hepcidin production or activity. Since HFE, TFR-2 and HJV are all expressed on the surface of hepatocytes, it was reasonable to expect that they all may participate in the control of hepcidin expression. More recently, the mechanism of hepcidin suppression in iron deficiency by the serine protease TMPRSS6[7] and the mechanism of hepcidin suppression by increased rates of erythropoiesis caused by growth and differentiation factor GDF15[8] have been described.

Mechanisms of iron deficiency

Despite the carefully orchestrated mechanism of normal iron homeostasis, iron deficiency is still a major health problem. Its development is the result of an interplay between three distinct risk factors: increased host requirements, limited external supply, and increased blood loss.

Increased requirements are the outcome of increased physiologic needs associated with normal development. This category of iron deficiency is often designated physiologic, or nutritional. By contrast, pathologic iron deficiency is most often the result of gastrointestinal disease associated with abnormal blood loss or malabsorption. Consequently, in grown males and post-menopausal females, complete gastroenterologic investigation is recommended to identify pathological lesions responsible for abnormal blood loss. However, conventional endoscopic and radiographic methods

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fail to identify a probable source of gastrointestinal blood loss in about one third of males and post-menopausal females and in most young women with iron deficiency anemia. These patients are referred for hematologic consultation for unexplained or refractory iron deciciency anemia.

Obscure or refractory iron deficiency

In recent years, there is an increasing awareness of subtle, non-bleeding gastrointestinal conditions that may result in abnormal iron absorption leading to IDA in the absence of gastrointestinal symptoms. Thus, the importance of celiac disease as a possible cause of IDA refractory to oral iron treatment, without other apparent manifestations of malabsorption syndrome is increasingly recognized. In addition, Helicobacter pylori has been implicated in several recent studies as a cause of IDA refractory to oral iron treatment, with a favorable response to H pylori eradication.[9,10] Likewise, autoimmune atrophic gastritis, a condition associated with chronic idiopathic iron deficiency, has been shown to be responsible for refractory IDA in over 20% of patients with no evidence of gastrointestinal blood loss.[11,12]

In a prospective study, we have screened 300 consecutive IDA patients referred to a hematology outpatient clinic, employing the above methods for identifying non-bleeding GI conditions including celiac disease, autoimmune atrophic gastritis and H pylori gastritis The mean age of all subjects was 3918 y, and 251 of the 300 (84%) were women of reproductive age. We identified 18 new cases of adult celiac disease (6%). Seventy-seven IDA patients (26%) had autoimmune atrophic gastritis of whom 39 (51%) had coexistent H pylori infection. H pylori infection was the only finding in 57 patients (19%), but was a common coexisting finding in 165 (55%) of the entire group. Refractoriness to oral iron treatment was found in 100% of patients with celiac disease, 69% with autoimmune atrophic gastritis, 68% with H pylori infection, but only 10% of subjects with no underlying abnormality. In the following we wish to discuss the implications of the above findings to the pathogenesis and management of "unexplained" iron deficiency anemia.

Autoimmune atrophic gastritis

The concept of gastric atrophy as a cause of iron deficiency anemia is not new. Achylia gastrica associated with iron deficiency anemia has been described as a clinical entity by Faber as early as 1909[13] and achlorhydric gastric atrophy, a synonym for the same entity, has long been recognized as a major cause of iron deficiency anemia[14] but largely forgotten, and completely ignored in subsequent major surveys of gastrointestinal causes of iron deficiency anemia. More recently, achlorhydric gastric atrophy has been rediscovered by Dickey et al,[12] and implicated in 20% of iron deficiency anemia patients with no evidence of gastrointestinal blood loss. This observation was confirmed and greatly extended in a series of important studies by Annibale et al.[11] Although atrophic gastritis may impair both B_{12} and iron absorption simultaneously, in young women in whom menstruation represents an added strain on iron requirements, iron deficiency will develop many years before the depletion of vitamin B_{12} stores. It is, however, the crucial development of anti-intrinsic factor antibodies with subsequent loss of the remaining gastric intrinsic factor that determines the prevalence of pernicious anemia.

Helicobacter pylori gastritis

The role of H pylori in the causation of IDA is at present unsettled as H pylori infection is very common in the normal population. Because menstrual blood loss is a serious compounding factor in evaluating alternative causes of IDA, we have focussed on our 29 male IDA patients with negative gastorintestinal workup distinguished by their poor initial response to oral iron treatment, and high prevalence of H pylori infection (25 of 29) with (10) or without (15) coexistent autoimmune gastritis.[9] Following H pylori eradication, all patients achieved normal hemoglobin levels with follow-up periods ranging from 4 to 69 months (38±15 months mean± 1SD). This was accompanied by a significant decrease in H pylori IgG antibodies and serum gastrin. Sixteen patients discontinued iron treatment, maintaining normal hemoglobin and ferritin and may be considered cured. Remarkably, 4 of the 16 achieved normal hemoglobin without ever having received oral iron after H pylori eradication. A number of possible mechanisms have been invoked to explain the relation between H pylori gastritis and IDA including occult gastrointestinal bleeding and competition for dietary iron by the bacteria . However, the most likely explanation is the effect of H pylori on the composition of gastric juice. Studies by Annibale and others[10] have shown that gastric acidity and ascorbate content, both of which are critical for normal iron absorption, are adversely effected by H pylori infection and, that H pylori eradication results in normalization of intragastric pH and ascorbate content.

Possible role of Helicobacter pylori in the pathogenesis of autoimmune gastritis

In order to define the relation between IDA associated with autoimmune gastritis and pernicious anemia, we have studied 160 patients with autoimmune gastritis of whom 83 presented with IDA, 48 with autoimmune gastritis and normocytic indices, and 29 with macrocytic anemia.[15] Stratification by age cohorts of autoimmune gastritis from <20 to >60 y showed a high prevalence of H pylori positivity in young patients with autoimmune gastritis and its almost total absence in elderly patients with pernicious anemia. These correlations imply that H pylori infection in autoimmune gastritis may represent an early phase of disease in which an infectious process is gradually replaced by an autoimmune disease terminating in burned-out infection and the irreversible destruction of gastric body mucosa. H pylori-infected subjects have circulating IgG antibodies directed against epitopes on gastric mucosal cells. Of these, the H+K+-ATPase protein, the most common autoantigen in pernicious anemia is the most likely target of an autoimmune mechanism triggered by H pylori and directed against gastric parietal cells by means of antigenic mimicry.[16,17] Conversely, H pylori eradication in patients with autoimmune

atrophic gastritis is followed by improved gastric acid and ascorbate secretion in many, and complete remission of atrophic gastritis in a variable proportion of patients. Failure to achieve complete remission by H pylori eradication in the majority of patients does not necessarily argue against the role of H pylori in the pathogenesis of autoimmune gastritis but, more likely indicates that a point of no-return may be reached beyond which the autoimmune process may no longer require the continued presence of the inducing pathogen.

Recommendations for the diagnostic workup of refractory or obscure IDA

In view of the above considerations, a rapid screening for celiac disease (anti-endomysial antibodies) autoimmune type A atrophic gastritis (gastrin, antiparietal antibodies) and H pylori (IgG antibodies confirmed by urease breath test) may provide a high-sensitivity screening and an effective starting point for further investigations. This is particularly recommended in all patients with obscure IDA and in those refractory to oral iron treatment. The implications of diagnosing celiac disease or autoimmune atrophic gastritis for abnormal iron absorption are obvious. Interpretation of positive serology for H pylori confirmed by positive urease breath test requires clinical judgment as 20 to 50% of the general and largely healthy population in industrialized countries will have such findings. In such patients, refractoriness to oral iron treatment may justify a «test-and-treat» approach of H pylori eradication as currently advocated for the management of dyspeptic patients. Cure of previously refractory IDA by H pylori eradication could then be regarded as evidence supporting a. cause-and-effect relation.

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