ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 8(B), pp. 28346-28350, August, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

PLEASE, LET US PUT A LID ON ANEMIA

Raghavendra Rao .M.V and Meka Balaramiah

Avalon University School of Medicine, Curacao, Central America

DOI: http://dx.doi.org/10.24327/ijrsr.2018.0908.2443

ARTICLE INFO

Article History:

Received 19th May, 2018
Received in revised form 5th June, 2018
Accepted 10th July, 2018
Published online 28th August, 2018

Key Words:

Ferric gluconate.,Helicobacter pylori, Hepcidin, hemosiderin, telangiectasia

ABSTRACT

"Research and Biosciences are the key engines for control of anemia". Enthralling antidote to Brexit angst anemias. Please, let us put a lid on anemias. Well documented causes of Iron deficiency anemia is, Increased Physiologic demand as in Infancy, adolescence, excess menstrual blood loss, repeated pregnancies, also seen in frequent blood donors. Environmental causes like-famine, poverty, malnutrition, diet(vegetarian, vegans and iron-poor diet) Due to chronic blood loss due to peptic ulcer disease, Hemorrhoids, erosive gastritis, diverticulitis, colorectal malignancies, hookworm infestation, angiodysplasia, Intravascular hemolysis (e.g. paroxysmal hemoglobinuria, march hemoglobinuria, microangiopathic hemolytic anemia secondary to damaged heart valves) Blood loss due to systemic bleeding, including chronic schistosomiasis, hemorrhagic telangiectasia, Munchausen's' syndrome (self-induced bleeding). Drug-induced causes, secondary to corticosteroids, Nonsteroidal anti-inflammatory drugs, anticoagulants and proton inhibitors (cause impaired iron absorption. Due to a combination of iron deficiency and chronic inflammation as in Ancylostoma duodenale and chronic schistosomiasis. Here, increased hepcidin, inflammatory cytokines especially interleukin-6, sequesters iron in macrophages causing it's non-availability. Also in End-stage renal disease iron deficiency anemia results from blood loss during dialysis, reduce hepcidin clearance, inflammation and certain drugs (anticoagulants and proto-pump inhibitors).

INTRODUCTION

Helicobacter pylori infection decreases iron absorption because this microorganism competes with its human host for available iron and may also lead to micro erosions that cause bleeding. (1). Since it is estimated that half the world's population is infected with H.Pylori, clinicians should be aware of the possibility of infection and provide treatment in order to eradicate this source. Partial or total gastrectomy, Bariatric surgery or any surgical procedures that bypass the duodenum can cause iron deficiency anemia because the procedure effectively removes an active iron absorption site(2).Some studies report an incidence of iron deficiency(30to50%) in patients with congestive heart failure, probably because of impaired iron absorption.

About 10% of people living in developed countries and 25% to 50% of those in developing countries are anemic. In both the settings, the most frequent cause of anemia is iron deficiency.W.H.O. estimates about 1/3 population of the world is suffering from iron deficiency anemia. Iron deficiency affects more than 2 billion people globally and it remains the leading cause of anemia and confirmed by the analysis of disease in 187 countries between 1990 to 2010.A moderate degree of Iron-deficiency anemia affects approximately 610 million people or 8.8% of the population globally.(3) Within the United States, iron deficiency anemia affects about 2% of adult males, 10.5% of Caucasian women and 20% of African-American women Prevention programs have decreased the rates of iron deficiency anemia worldwide; the prevalence is now peak in Central and West Africa and South Asia.(4,5). Iron is essential for biologic functions including respiration, energy production, DNA synthesis, cell proliferation and most importantly for the production of hemoglobin that carries and delivers oxygen, to the tissues and essential for the maintenance of healthy cells, skin, hair, and nails. The normal total body iron mass is about 2.5g for women and 3.5g for men. About 80% of functional body iron is present in hemoglobin and the remainder being found in myoglobin and iron-containing enzymes such as Catalase and Cytochromes. The normal daily Western diet contains 10 to 20 mg of iron. Most of this found in heme within the meat and poultry, and the remainder present as inorganic iron in vegetable non- heme. About 20% of heme iron and 1to 2% of non-heme is absorbable; hence the average Western Diet contains sufficient iron to balance fixed losses. There is no Regulated pathway for iron excretion. Our body has evolved to retain iron in several

Corresponding author:* **Raghavendra Rao .M.V
Avalon University School of Medicine, Curacao, Central America

ways, in the absence of an excretion mechanism. Since excess levels of iron is toxic. It's absorption is limited to 1mg to 2 mg/day that is lost through the shedding of mucosal and skin epithelial cells, and most of the iron needed daily (about 25mgs/day) is provided through recycling by macrophages that phagocytize the senescent erythrocytes. Hepcidin is one of the acute phase reactants released from the liver during chronic inflammatory conditions and cancer. It sequesters iron within storage sites (macrophages) of bone marrow and liver. The macrophages locked up iron not available for the erythroid precursors to produce heme. Hepcidin also suppresses erythropoietin production which decreases the drive on the bone marrow to produce erythrocytes.

Iron balance is tightly regulated and maintained largely by regulating the absorption of dietary iron. Iron is absorbed in the duodenum. Iron is present in Heme(meat-derived) and Non-heme(Vegetable derived) forms. Heme form is readily absorbed and is carried across the apical and basolateral membrane of enterocytes by distinct transporters(Ferroportin). After reduction of iron by ferric reductase, Ferrous iron(Fe2+) is transported across by Divalent Metal Transporter-1(DMT1) A second transporter ferritin then moves iron from the cytoplasm to the plasma across the basolateral membrane. Only a fraction of iron that enters enterocytes is delivered to transferrin by ferroportin. The remainder is incorporated into cytoplasmic ferritin and lost through the exfoliation of mucosal cells. The iron storage pool, an average of 15% to 20% of total body iron present as hemosiderin and Ferritin-bound iron in macrophages of the spleen, liver, bone marrow and skeletal muscle.

Well documented causes of Iron deficiency anemia is, a. Increased Physiologic demand as in Infancy, adolescence, excess menstrual blood loss, Repeated pregnancies, also seen in frequent blood donors. Environmental causes like-famine, poverty, malnutrition, diet(vegetarian, vegans and iron-poor diet)c. Pathologic causes: Due to chronic blood loss due to peptic ulcer disease, Hemorrhoids, erosive gastritis, diverticulitis, colorectal malignancies, Hookworm infestation, angiodysplasia, Intravascular hemolysis(e.g. paroxysmal hemoglobinuria, march hemoglobinuria, microangiopathic hemolytic anemia's secondary to damaged heart valves) Blood loss due to systemic bleeding, including chronic schistosomiasis, hemorrhagic telangiectasia, Munchausen's' syndrome(self-induced bleeding). Drug-induced causes, secondary to corticosteroids, Nonsteroidal anti-inflammatory drugs, anticoagulants and proton inhibitors(cause impaired iron absorption. Due to a combination of iron deficiency and chronic inflammation as in Ancylostoma duodenale and chronic schistosomiasis. Here, increased hepcidin, inflammatory cytokines especially interleukin-6, sequesters iron in macrophages causing it's non-availability. Also in End-stage renal disease iron deficiency anemia results from blood loss during dialysis, reduce hepcidin clearance, inflammation and certain drugs (anticoagulants and proto-pump inhibitors). Helicobacter pylori infection decreases iron absorption because this microorganism competes with its human host for available iron and may also lead to micro erosions that cause bleeding.(6). Since it is estimated that half the world's population is infected with H.Pylori, clinicians should be aware of the possibility of infection and provide treatment in order to eradicate this source. Partial or total gastrectomy, Bariatric surgery or any surgical procedures that bypass the duodenum can cause iron deficiency anemia because the procedure effectively removes an active iron absorption site(7). Some studies report an incidence of iron deficiency (30to50%) in patients with congestive heart failure, probably because of impaired iron absorption.

It is a chronic, frequently asymptomatic and may often go unnoticed. Signs and symptoms are related to the overall decrease in the number of red blood cells and the level of hemoglobin. If iron deficiency anemia is mild to moderate, there may be no symptoms or signs. Most common signs and symptoms that are unique to iron deficiency may appear as iron stores are depleted chronically which may include. Sore tongue (atrophic glossitis) Spoon-shaped or brittle nails. Ulcers at the corners of the mouth, Difficulty in swallowing due to esophageal web formation, PICA-craving to eat non-food substances such as ice and dirt. Data suggest that non-absorbed iron could be harmful to patients because of gut microbial modification, increases the concentration of intestinal pathogens (8). Plasmodium falciparum is less effective in infecting iron-deficient erythrocytes than in infecting iron-replete erythrocytes, a protection that is reversed with iron supplementation(9). Some studies show that the administration of intravenous iron improves fatigue in women without anemia whose ferritin levels are in the iron-deficient range(10). It is also observed that patients with severe iron-deficiency anemia that causes cardiovascular symptoms such as angina or heart failure should receive red-cell transfusions as this approach rapidly corrects not only hypoxia but also iron deficiency since one unit of packed red cells provides approximately 200 mg of iron. Modes of treatment. Oral iron therapy is a convenient, inexpensive and effective means of treating stable patients. Among the preparation on the market, Iron sulfate is the most frequently used; gluconate and fumarate are also effective iron salts. Recommended daily dose for adults is 100 to 200mg of elementary iron and that for children is 3 to 6 mg per kilogram body weight of a liquid preparation: for both groups, the supplement should be administered in divided doses on an empty stomach, an addition of vitamin C may improve absorption. In associated infections like H.pylori or Celiac disease, eradication with triple therapy or the introduction of the gluten-free diet, may restore the capacity for iron absorption and eliminate the need for supplementation(11). Assessment of an early response to oral iron might also be useful in the treatment of iron-deficiency anemia in patients with anemia of chronic disease. A change in the hemoglobin content of reticulocytes and in serum levels of iron and transferrin saturation may predict the response to the administration of oral iron after one week of therapy(12). Parenteral Iron Therapy: Possible hypersensitivity reactions including anaphylaxis to high-molecular-weight iron dextran have traditionally limited this approach. But newly approved following safer iron formulation are available. Ferric gluconate. Iron sucrose, Low-molecular-weight dextran, Ferumoxytol, and Ferric carboxymaltose. Because the use of intravenous iron circumvents the problem of iron absorption, it is more effective and increases hemoglobin levels more quickly than oral iron (13,14). Another advantage is that in some patients the total dose required (up to 1000mg) can be provided as a single infusion. The cost of parenteral iron therapy is high, but the

number of the hospital or clinic visits that are required is significantly decreased(15) Patients with malabsorption and genetic IRIDIA(16,17) may require intravenous iron, also it is preferred when a rapid increase in hemoglobin level is required or when iron-deficiency anemia caused by chronic blood loss cannot be controlled with the use of oral iron, as is these in patients with hereditary hemorrhagic telangiectasia. Active inflammatory bowel disease is another emerging indication as oral iron is not only ineffective but also may also increase local inflammation(18).Intravenous iron therapy is essential in the management of anemia in patients with chronic kidney disease who are receiving dialysis and treatment with erythropoiesis-stimulating agents(19,20)

Where the researches go next?

"Research and Biosciences are the key engines for the control of anemia". A multicenter European trial of patients with iron-deficiency and chronic heart failure showed that the use of intravenous iron supplements led to improvements in physical performance. New York Heart Association functional class(21) and quality of life from the correction of anemia. Transients side effects of intravenous iron supplementation include nausea, vomiting, pruritus, headache, myalgia, arthralgia, flushing back and chest pain usually resolve within 48 hours, even after the total administration. Hypersensitivity reactions are rare (22,23)as are severe or life-threatening reactions(24), These reactions are uncertain and might be exacerbated by released free iron, a phenomenon that does not occur with currently used formulations.

Predisposing conditions are rapid infusions, a history of atopy, and drug allergy. Practical recommendations for minimizing risk include a slow infusion rate, careful patient observation, and administration by trained healthcare personnel in an environment with access to resuscitation facilities(25). The test dose may provide false reassurance; premedication with antihistamine is no longer advised because hypotension and tachycardia. Clinical trials are reassuring with regard to the efficacy and side effect profile of intravenous iron.

History

The diagnosis of iron-deficiency anemia will be suggested by history that includes common causes of the condition, such as a menstruating woman or the presence of occult blood (i.e., hidden blood) in the stool. (26) A travel history to areas in which hookworms and whipworms are endemic may be helpful in guiding certain stool tests for parasites or their eggs. (27) Although symptoms can play a role in identifying iron-deficiency anemia, these are often nonspecific symptoms, especially in mild cases, which may limit their contribution to determining the diagnosis. Evidence of anemia goes back more than 4000 years. (28)

However, this was not investigated in more depth until 1849, by British physician Thomas Addison, from which it acquired the common name of Addison's anemia. In 1871, German physician Michael Anton Biermer (1827–1892) noticed the particular characteristic of the anemia in one of his patients; he later coined the term "progressive pernicious. (29)anemia".(30) William Bosworth Castle performed an experiment whereby he ingested raw hamburger meat and regurgitated it after an hour, and subsequently fed it to a group of 10 patients. (31) Pernicious anemia was a fatal disease before about the year 1920, when George Whipple suggested raw liver as a treatment Frieda Robscheit-Robbins worked closely with Whipple, co-authoring 21 papers from 1925-30.For the discovery of the cure of a previously fatal disease of unknown cause, Whipple, Minot, and Murphy shared the 1934 Nobel Prize in Medicine. (32)

Significant Gap In Research

Anemia can result from significant iron deficiency. (33) When the body has sufficient iron to meet its needs (functional iron), the remainder is stored for later use in cells, mostly in the bone marrow and liver. These stores are called ferritin complexes and are part of the human iron metabolism.

Iron is a mineral that is important in the formation of red blood cells in the body, particularly as a critical component of hemoglobin. After being absorbed in the small intestine, iron travels through the blood, bound to transferrin, and eventually ends up in the bone marrow, where it is involved in red blood cell formation. When red blood cells are degraded, the iron is recycled by the body and stored. (34)

Major Advances and Discoveries

When the amount of iron needed by the body exceeds the amount of iron that is readily available, the body can use iron stores (ferritin) for a period of time, and red blood cell formation continues normally. (35) However, as these stores continue to be used, iron is eventually depleted to the point that red blood cell formation is abnormal. Ultimately, anemia ensues, which by definition is a hemoglobin lab value below normal limits. (35,36)

Crrent Debate

Laboratory tests include Complete Blood Count, which may show. Hemoglobin-may be normal early in the disease but will decrease as anemia worsen. Red Blood Cells Indices: Early on, may be normal in size and color (Normocytic and Normochromic) but as the anemia progresses RBCs become smaller and paler (Microcytic and Hypo chromic).Mean Corpuscular Volume –decreases, Mean Corpuscular Hemoglobin Concentration- Decreases, Red Cell Distribution Width (RDW)-Increases(Increased variations in the size of RBCs).Serum Iron –Low Ferritin –Low. It is the most sensitive and specific test for used for the identification of iron deficiency (indicated by a level of <30mug per liter), A transferrin saturation level of less than 16% indicates an iron supply that is insufficient to support normal erythropoiesis. Treatment for Iron deficiency anemia patients should receive Iron supplementation. Data suggest that nonabsorbed iron could be harmful to patients because of gut microbial modification, increases the concentration of intestinal pathogens(8).In vitro studies have shown that the malaria parasite It is also observed that patients with severe iron-deficiency anemia that causes cardiovascular symptoms such as angina or heart failure should receive red-cell transfusions as this approach rapidly corrects not only hypoxia but also iron deficiency since one unit of packed red cells provides approximately 200 mg of iron. Modes of treatment Oral iron therapy is a convenient, inexpensive and effective means of treating stable patients. Among the preparation on the market, Iron sulfate is the most frequently used; gluconate and fumarate

are also effective iron salts. Recommended daily dose for adults is 100 to 200mg of elementary iron and that for children is 3 to 6 mg per kilogram body weight of a liquid preparation: for both groups, the supplement should be administered in divided doses on an empty stomach, an addition of vitamin C may improve absorption Although the history and physical examination can lead to the recognition of the condition and help establish the etiology, iron deficiency anemia is primarily a laboratory diagnosis.

Useful tests include a complete blood count (CBC); a peripheral smear; serum iron, total iron-binding capacity (TIBC), and serum ferritin; evaluation for hemosiderinuria, hemoglobinuria, and pulmonary hemosiderosis; hemoglobin electrophoresis and measurement of hemoglobin A2 and fetal hemoglobin; and reticulocyte hemoglobin content.(37)

References

1. Franceschi F,Zuccala G, RocarinaD, Gasbarrini A Clinical effects of Helicobacter pylori outside the stomach, *Nat rev Gateroenteral Hepatol* 2014;11:234-42.
2. Warsh S, Byrenes J. Emerging causes of iron deficiency anemia refractory to oral iron supplementation. *World J Garteointest Pharmacol* Ther2013;4:49-53
3. Bach V , Schruckmayer , sam 1, Kemmler G, Stauder R. Prevalence and possible causes of anemia in the elderly: a cross sectional analysis of a large European university hospital cohort. *Clin Interv Ageing* 2014;9:1187-96.
4. Kassebaum NJ, Jasrasria R, Nagavi M, *et al*. a systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014;123:615-24.
5. Stevens GA, Finucane MM, De-Regil LM,*et al*.Global, regional, and national trends in hemoglobin concentration and prevalence of total and severe anemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. *Lancet Glob Health* 2013;1(1):e16-e25.
6. Macdougall IC. Iron supplementation in nephrology and oncology: what do we have in common? *Oncologist* 2011;16:Suppl 3:25-34,
7. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral defeciency: evidence and clinical implications. *Ther Adv Drug Saf* 2013;4:125-33.
8. Kortman GA, Raffatellu M, Swinkels DW, Tjaslma H. Nutritional iron turned inside out:Intestinal stress from a gut microbial perspective. *FEMS Microbial Rev* 2014;38:1202-34.
9. Clark MA, Goheen MM, Fulford A, *et al*. Host iron status and iron supplementation mediate susceptibility to erythrocytic stage Plasmodium Falciparum. *Nat Commun* 2014;5:4446.
10. Krayenbuehl PA, Battegay E, Breymann c, Furrer J, Schutless G. Intravenous iron for the treatment of fatigue in non-anemic, premenopausal women with low serum ferritin concentration. *Blood* 2011;118:322-7.
11. Hershko C, Camaschella C. How I treat unexplained refractory iron deficiency anemia, *Blood* 2014;123:326-33.
12. Van Santen S, de Mast Q, Oosting JD, van Ede A, Swinkles DW, van der Ven AJ. Hematologic parameters predicting a response to oral iron therapy in chronic inflammation. *Hematologic* 2014;99(9): e171-e173.
13. Onken JE, Bregman D, Harrington RA, *et al*. A multicenter, randomized, active-controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Transfusion* 2014 2014:54:306-15
14. Vadhan-Raj s. Strauss W, Ford D, *et al* .Am J Hematol;89:7-12.
15. Bager P, Dahlerup JF. J Crohns Colitis 2014:427-30.
16. De Falco, Sanchez M, Silvestri L. *et al*. Iron refractory iron defeciency anemia. *Hematologica* 2013;98:845-53.
17. Heeney MM, Finberg KE.Iron deficiency anemia(IRDA). *Hematol Oncol Clin North Am* 2014;28:637-52.
18. Reinisch W, Chowers Y, Danese S, *et al*.Aliment Pharmacol Ther 2013;38:1109-18.
19. Macdougall IC, BockAH, Carreraf, *et al* FIND-CKDA randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron defeciency anemia. *Nephrol Dial Transplant* 2014;29:2075-84.
20. Baillie GR, Larkina M, Goodkin DA, *et al* Nephrol Dial Transplant 2013;28:2570-9.
21. Anker SD, Comin ColetJ, Filippatos G, *et al*. Ferric catboxymaltose in patients with heart failure and iron defeciency. *N Engl Med* 2009;361:2436-48.
22. Auerbach M, Ballard H. Hematology Am Soc HematolEdu Program 2010; 2010:338-47.
23. Rampton DFJ. Folkersens, *etal*. ematologica2014; 99:1671-6.
24. New recommendations to manage allergic reactions with intravenous iron-containing medicines.London European Medicines Agency , release/ 2013/06/WC500144874.pdf.
25. Bircher AJAM, AuerbachM. Hypersensitivity from intravenous iron products. *Immunol Allergy Clin North Am* 2014;34:707-23.
26. Brady PG (October 2007). "Iron deficiency anemia: a call for aggressive diagnostic evaluation". Southern Medical Journal. 100*(10):* *966–*967. doi:10.1097/SMJ.0b013e3181520699. PMID 17943034. Retrieved July 23, 2012.
27. Bennett, John; Dolin, Raphael; Blaser, Martin (2015). Mandell, Douglas, andBennett's Principles and Practice of Infectious Diseases, Updated Edition. pp. 3196–3198. ISBN 978-0-323-40161-6.
28. Tayles N (September 1996). "Anemia, genetic diseases, and malaria in prehistoric mainland Southeast Asia". American *Journal of Physical Anthropology.* 101 (1): 11–doi:10.1002/(SICI)1096-8644(199609)101:1<11::AID-AJPA2>3.0.CO;2-G. PMID 8876811.
29. History of Leith, Edinburgh. leithhistory.co.uk. Retrieved 11 March 2016.
30. Enersen, Ole Daniel (2016). "Whonamedit Dictionary of Medical Eponyms. whonamedit.com. Archived from the original on 3 March 2016. Retrieved 11 March 2016.
31. William B. Castle 1897–1990 A Biographical Memoir by James H. Jandl Copyright 1995 National Academies Press Washington D.C.

32. Nobel Prize archive. The Nobel Prize in Physiology or Medicine 1934" (Nobelprize.org). Archived from the original on 2012-08-02. Retrieved 2012-08-05.
33. Howard, Martin; Hamilton, Peter (2013). Haematology: An Illustrated Colour Text. 24,25– ISBN 978-0-7020-5139-5.
34. Porwit, Anna; McCullough, Jeffrey; Erber, Wendy (2011). Blood and Bone Marrow Pathology. pp. 173–195. ISBN 9780702031472.
"What Is Iron-Deficiency Anemia?-NHLBI, NIH". www.nhlbi.nih.gov.26 March 2014. Archived from the original on 16 July 2017. Retrieved 17 July 2017.
35. James L Harper, MD is a member of the following medical societies: American Society of Pediatric Hematology/Oncology, American Federation for Clinical Research, Council on Medical Student Education in Pediatrics, Hemophilia and Thrombosis Research Society, American Academy of Pediatrics, American Association for Cancer Research, American Society of Hematology

How to cite this article:

Raghavendra Rao .M.V and Meka Balaramiah. 2018, Please, Let Us Put A Lid on Anemia. *Int J Recent Sci Res.* 9(8), pp. 28346-28350. DOI: http://dx.doi.org/10.24327/ijrsr.2018.0908.2443

****