Original Article

Iron deficiency anemia, diagnosis, and treatment in primary health care centre

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Abstract

Background: Anemia affects around two-thirds of the world's population, and the majority of them are caused by iron deficiency anemia. Iron deficiency is more prevalent in women with childbearing age. Different factors contribute to iron deficiency, of which some of them are physiological and others caused by critical underlying conditions. **Objective:** Our objectives in this study to summarize and review the prevalence, possible risk factors, diagnostic tests, and management of iron deficiency anemia. **Methodology:** We searched the PubMed database looking for relevant articles to the topic using two Mesh terms, "Iron deficiency anemia" and "Management." **Conclusion:** Iron deficiency anemia can be attributed to various factors, and identifying the underlying etiology is essential to rule out serious hidden conditions. Diagnosis is mainly achieved by blood investigations, and treatment is only by oral or intravenous replacement. Ideally, the cause behind iron deficiency must be addressed and treated.

Keywords: Iron Deficiency anaemia, Diagnosis, Management

Introduction

Around 5% of the earth's crust is composed of iron in redox states [1]. In the human body, the most abundant protein containing iron is Hemoglobin (Hb) [1]. The majority of body iron is comprised of hemoglobin [1]. Although the earth is plentiful in iron and is considered the 2nd most abundant metal in the earth, iron deficiency is commonly found in humans [1]. It is the most common cause of anemia worldwide [1-3]. It is estimated that one-third of the world's population (around two billion people) is anemic, and the majority of them are caused by IDA [3, 4]. Additionally, IDA is commonly found in the elderly population, >10% at the age of 65, and >20% at the age of 20% [5]. Iron deficiency anemia (IDA) can significantly impact motor, mental, and behavioral development in childhood and adolescence [2, 4]. Additionally, IDA may impair auditory and visual functioning and is mildly correlated with decreased cognitive development in children [2].

In adults, IDA's clinical symptoms can be ambiguous and cannot directly attract physicians to the diagnosis [4]. IDA symptoms might occur before the development of true anemia (Low Hb), including; easy fatigability, restless leg syndrome, and pica (ingestion of materials that unusually used in the human diet) [1, 4]. IDA is insidiously developed, and it is correlated with symptoms that appear gradually [3]. The classic signs and symptoms are pallor, fatigue, exertional dyspnea, tachycardia, palpitations, poor physical activities, irritability, anorexia, paraesthesia, headache, growth retardation, papillary atrophy of the tongue (glossitis), Koilonychia, angular cheilitis, swollen limbs, decrease appetite, mood changes, attention disorders, and weak school performance [3].

Iron homeostasis's primary mechanism by absorption and iron is not normally excreted from the body, aside from blood loss and mucosa shedding (menses), which is not part of homeostasis [2, 6]. Generally, men and non-menstruating

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women lose around 1mg of iron each day [2]. Menstruating women lose from 0.6 to 2.5% more per day [2]. Pregnancy takes about 700mg of iron, and the whole blood donation of 500cc carries 250mg of iron [2]. Iron absorption occurs primarily through the enterocyte in the terminal duodenum by the divalent metal transporter (DMT1) [6]. Iron is exported from the enterocyte through the basolateral membrane by the regulatory protein ferroportin-1 [6]. Consequently, iron is transported by transferrin protein through transferrin receptor-1 (TfR1) into the storage sites [6]. Serum iron levels solely indicate the amount of iron bound to transferrin [7]. Ferritin is the primary storage protein in the body, as free iron is cytotoxic, it immediately binds to ferritin if it is not utilized after internalization [3, 6]. The main iron storage sites are the reticuloendothelial system within the macrophages, particularly in the liver, spleen, and bone marrow [3, 6].

Iron homeostasis is mainly regulated via iron regulatory protein (IRP)/iron responsive elements (IRE) and hepcidin [6]. The IRP/IRE control uptake and storage, while hepcidin regulates iron export from the enterocyte [6]. Hepcidin plays a major role in iron homeostasis through binding to ferroportin-1; this results in internalization and degradation of this molecule by lysosome [6-8].

Subsequently, the result is decreased ferroportin-1 expression and block iron export [6]. Hepcidin is synthesized in the liver in response to iron overload or inflammatory process via cytokines such as IL-6 [7, 8]. This condition leads to iron trapping inside the cells, which gives false low serum iron and transferrin saturation [7, 8]. The raised hepcidin level is the basis behind anemia of chronic diseases (ACD) [7, 8]. Mice studies have found that hepcidin gene deletion results in iron overload, and conversely, overexpression of this gene resulted in anemia [8].

Discussion

Etiology

Iron deficiency results when the demand for iron in the body is not sufficient by iron absorption from dietary intake [2]. Therefore, most patients with IDA seeking medical advice have inadequate dietary, impaired absorption, or physiological blood losses in menstruating women [2, 9]. Nutritional demands are markedly increased in adolescence for growth and muscle development during this period, resulting in an increased blood volume [3]. In this adolescence, lifestyle and eating disorders must be taken into account [3]. Fast food lacks important nutritional values since it is quickly prepared and includes high fat and sodium with low fibers, vitamins, calcium, and iron [3]. Dietary intake should be rich in iron content, whether heme iron, such as red meat (rich in hemoglobin and myoglobin) or non-heme iron such as cereals, egg yolk, and green leafy vegetables [9]. Non-heme iron is not completely absorbed and needs vitamin C to enhance the absorption by adding citrus fruits [9]. Oppositely, tea should be avoided by 1-2 hours after the meal due to an inhibitory effect for the iron absorption [9]. Dietary evaluation is essential in counseling and treating IDA's patients, but it is insufficient alone to replace iron, and the patient will need iron supplements [9].

The most common cause of IDA in women with reproductive age is menstrual blood loss, while men and non-menstruating women are gastrointestinal (GI) blood loss [8]. **Table 1** summarises the most important risk factors contributing to IDA in adolescents [3].

Assessment and Diagnosis

When a suspicion of IDA is raised, careful points must be taken into account when taking patient history, including a history of IDA, history of recent blood donation, detailed dietary intake, family history of IDA or colon cancer, and hemoglobinopathies [8, 10]. Moreover, a careful drug history should be taken (refer to Table 1) [8, 11]. Ordinarily, Investigating IDA starts with the serum ferritin level (formerly known as apoferritin), the best indicator for iron status [3, 7, 8] Ferritin reflects the intracellular body storage of iron in normal circumstances except in the presence of infection, malignancy and inflammatory process [7, 8, 12]. Approximately one-third of total body iron in the ferritin form or hemosiderin, while two-thirds are incorporated in erythrocyte hemoglobin [9]. Although the diagnosis of IDA can be achieved by low mean corpuscular volume (MCV) and ferritin level below 15ng/mL, a cutoff 30ng/mL can be used and improves sensitivity from 25 to 92 percent, while specificity remains the same at 98 percent [12]. In chronic inflammatory condition, the diagnosis of IDA is likely accepted when the ferritin level is less than 50ng/mL, and the level of greater than 100ng/mL generally excludes IDA [12].

Table 1. The most contributory factors for IDA development. Abbreviations: NSAIDs: Non-Steroidal Anti-inflammatory Drugs. H.pylori: Helicobacter pylori.

Risk factor	Comment
Inadequate dietary intake	Insufficient intake of certain nutrients such as; iron, folic acid, vitamin A, vitamin B12, and vitamin D.
Medications & Certain food	Certain medications and food inhibit iron absorption such as; NSAIDs, antacids, aspirin, excessive phytate, phosphate, oxalate, and tannin (tea) intake.
Overweight/Obesity	Low macronutrients, calorie-rich diet to a greater need for an iron that is associated with body weight.
Malnutrition	Malabsorption syndrome or excessive iron loss
Adolescent athletes	Known as “sports anemia” and occurs by various factors including dilutional pseudoanemia, mechanical intravascular hemolysis, and iron loss
Traumatic/Iatrogenic	Accidents, injuries, or blood donation
GI infection	GI parasitosis (Entamoeba histolytica, Necator americanus, Ascaris lumbricoides, Schistosoma mansoni) or H.pylori
Genitourinary blood loss	PNH and glomerulonephritis.
Pregnancy-	Pregnancy, childbirth and intrauterine device use

related	
Menarche/Menstruation	Heavy menstruation is the commonest cause of IDA in women with childbearing age.
Miscellaneous	Atrophic gastritis, esophagitis, angiodysplasia, Coeliac disease, IBD, hemorrhoids, bariatric surgery, and atrophic gastritis.

Serum iron is generally bound to transferrin protein for transport, and total iron-binding capacity (TIBC) measures the maximum amount of iron bound with transferrin [8]. In conditions of low iron level, transferrin synthesis increased to maximize iron absorption and transportation [7]. In contrast, when iron overload in the body, transferrin synthesis undergoes downregulation, and ferritin synthesis will increase [7]. The transferrin saturation is the measure of iron bounded to transferrin, displayed as a percentage of TIBC [8]. Soluble transferrin receptor (sTfR) is responsible for transferrin-bound iron for entering the cells, and in conditions with low iron in serum and storage, sTfR is markedly raised [7]. Soluble TfR is a valuable test to differentiate between IDA and ACD, but with limited availability and usage [7, 8]. Serum iron is the amount of iron that is bound to transferrin in the plasma, and it rapidly turnover in circulation [6]. Thus, serum iron can be affected by diet, and evaluation of serum iron alone is insufficient to establish the diagnosis of IDA [6].

Complete blood count (CBC) gives an initial impression when low Hb is found with low MCV and mean cell hemoglobin (MCH), resulting in microcytosis and hypochromia [6-8]. In the absence of vitamin B12 and folic acid deficiency, MCV can be considered sensitive, but MCH is more reliable as it is not affected by storage [8]. Besides, Low MCV is found in non-iron deficient conditions, such as thalassemia trait or the anemia of chronic disease, and also can be low, normal, or high if vitamin B12 or folic acid deficiency coexist [4, 8]. Laboratory findings suggestive for IDA are shown in **Table 2** [12].

Table 2. Laboratory findings for isolated IDA.

Ferritin	Serum iron	Transferrin saturation	TIBC	sTfR
↓	↓	↓	↑	↑

Iron deficiency anemia in Celiac disease and Malignancies

In men (mainly adult), postmenopausal women, or pre-menopausal women without menorrhagia, GI cancer must be ruled out by bidirectional endoscopies [8, 12]. There are no clear recommendations on which endoscopy should be performed first [12]. However, patients above 60 years old need to perform endoscopy within two weeks, as GI tract cancer will be discovered in 8-15% of them [8]. The use of a fecal occult blood test (FOBt) is recommended by the National Institution for Health and Care Excellence (NICA) in patients under 60 years of age as an alternative diagnostic test [8, 13-16]. Nevertheless, the low sensitivity of FOBt makes it with low value, as pathology can be easily missed [8].

A cohort study concluded that 6% and 9% of patients above 50 and 65 years, respectively, will be diagnosed with GI malignancy within two years of IDA diagnosis [12]. Another cohort for patients presenting to the general practitioner with IDA diagnosis for the first time [17]. According to the case individual, 43% had further investigations within three months, and critical pathology was found in 30% [17]. Additionally, a retrospective study for 126 gastric cancer patients has shown that 40% of them have IDA at the time of diagnosis, and 18% have a self- reported the previous history of IDA [18]. All patients with IDA should have urine analysis to discover hematuria, as 1% of IDA patients found to have a renal tract malignancy [8]. The prevalence of celiac disease-causing IDA is 0.5-1%; therefore, celiac serology tests must be checked in adult patients and unexplained IDA [8, 10, 12]. Celiac diagnosis is confirmed by upper endoscopy with duodenal biopsies after positive serologic testing [12].

Treatment of iron deficiency anemia

Oral iron therapy:

Oral iron therapy is considered the first-line replacement for IDA, and almost always favored to intravenous (IV) replacement [10, 19, 20]. Adults with IDA are ideally replaced with iron salt-containing 100-200mg of elemental iron, and children are replaced with a liquid formula (3-6mg/Kg) [19]. Many forms of iron are now available in the market, including ferrous iron compounds such as ferrous sulfate (The gold standard), and other alternative compounds, such as iron fumarate, gluconate, carbonyl iron, and polysaccharide-iron complex [19, 20].

Slowly released preparations must be avoided due to the release of iron beyond the duodenum, which is the highest site of iron absorption [19]. Various medications and supplements can decrease iron absorption, such as multivitamins, calcium, or antacids, and patients must be counseled to keep at least 2 hours of space between iron and other tablets [10]. Vitamin C 600-1200mg with an iron tablet can improve the absorption significantly [10]. Common side effects occur in up to 70% of patients, including dyspepsia, nausea, vomiting, abdominal pain, constipation, diarrhea, or dark stools [10, 19, 20]. Upper GI upset mainly occurs when the pill is ingested on an empty stomach, and GI adverse effects are less in IV iron in comparison to oral [19, 20]. Moreover, oral iron is associated with mucosal iron deposition in 16% of patients [20]. Due to this annoying effects of oral pills, premature discontinue is common before completing the total treatment duration (3-6 months); thus, always check for adherence [19, 20]. **Table 3**. summarize strategies to minimize adverse effects [10].

In conditions with active inflammatory bowel disease, the use of oral iron is debatable, and an increase in the pathogenic

microbiome has also been noticed [19, 20]. In patients with pre-existing GI pathology, oral iron may worsening symptoms due to the toxic effects on the mucosa [20]. The response of oral iron is usually monitored CBC testing after 2-4 weeks [10]. Hb is expected to be increased by 1-2g/dL by the 4th week, and it may take up to 6 months to replenish the iron store [10]. Hence, oral iron therapy is advised to be continued for 4-6 months after anemia correction [10]. Ferritin should be tested every 3-6 months, and the target level must be >100ug/L [10].

Table 3. Certain strategies to minimize oral iron adverse effects

- Start with a low dose and increase gradually after 5 days until reaching the target dose in a few weeks
- Divide the dose per day
- Prescribe the lowest effective dose.
- Take the pill with meals. Keep in mind that the absorption of iron pills increased on an empty stomach.
- Try an alternative iron preparation.
- Try alternative dosing courses, such as every other day (may take a longer time for symptoms improvement and store replenishment).

Intravenous iron therapy:

IV iron replacement is the only alternative option for oral [19]. The intramuscular iron injection has been withdrawn because of unsustainable pain, a dark discoloration of the skin, and sarcoma development in the site of injection [19]. Indications and contraindications of IV iron are listed in Table 4 [10, 19]. Maximum Hb response to IV iron is usually observed within two to three weeks of the last dose [10]. Similar to oral iron, IV iron has different forms and courses of treatment [19, 20]. Some preparations need multiple infusions, while others may replace the total need with one single infusion (reaching 1000mg) [19]. Risks of IV iron among physicians is exaggerated [20]. High-molecular-weight iron dextran is an older iron preparation that carries a high risk of reactions [20]. However, this preparation has been eliminated from the market and replaced by new preparations, such as low-molecular-weight iron dextran, ferumoxytol, ferric carboxymaltose, and iron isomaltoside [20]. All iron forms have a good safety profile with a lower rate of reactions than penicillin or rituximab [21].

Conclusion:

Iron deficiency anemia is the most prevalent type of anemia worldwide. Adults must be counseled and encouraged to take a healthy iron-rich diet, and dietary education and awareness must expand in those populations. Iron plays a significant role in hemoglobin composition and function. Signs and symptoms of iron deficiency can range from asymptomatic, mild to moderate, and severe manifestations of anemia. Physical examinations might reveal unremarkable results in early disease, and physicians must have a high level of suspicion. Diagnosis of iron deficiency anemia should be made with blood testing, and further investigations might be needed as iron deficiency can conceal serious underlying causes. Generally, the cause behind iron deficiency must be discovered and treated. The patient should be replaced by iron, either orally or intravenously. Oral iron therapy is used as a first-line treatment, but certain adverse effects can alter the compliance of the patient and result in the failure of treatment. Parenteral iron is another alternative option in conditions where adverse effects are unfavorable, and when prompt hemoglobin elevation is needed.

Table 4. Parenteral iron indications and contraindications

Indications:
• Failure of oral iron treatment when the patient is fully adherent
• Intolerance to oral iron therapy
• Impaired intestinal absorption
• Rapid Hb increase is needed (Continued bleeding)
• Emergent surgery in a patient with IDA (second-third trimester pregnancy)
• Chronic kidney disease, including dialysis patients
Contraindications:
• Active infection
• First-trimester pregnancy
• History of an allergic reaction to iron

References

1. Miller JL. Iron deficiency anemia: a common and curable disease. Cold Spring Harb Perspect Med. 2013;3(7):a011866. Published 2013 Jul 1. doi:10.1101/cshperspect.a011866
2. Killip S, Bennett JM, Chambers MD. Iron deficiency anemia [published correction appears in Am Fam Physician. 2008 Oct 15;78(8):914]. Am Fam Physician. 2007;75(5):671-678.
3. De Andrade Cairo RC, Rodrigues Silva L, Carneiro Bustani N, Ferreira Marques CD. Iron deficiency anemia in adolescents; a literature review. Nutr Hosp. 2014;29(6):1240-1249. Published 2014 Jun 1. doi:10.3305/nh.2014.29.6.7245.
4. Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol. 2016;91(1):31-38. doi:10.1002/ajh.24201.
5. Lindblad, A. J., Cotton, C., & Allan, G. M. (2015). Iron deficiency anemia in the elderly. Canadian family physician Medecin de famille canadien, 61(2), 159.
6. Peng YY, Uprichard J. Ferritin and iron studies in anaemia and chronic disease. Ann Clin Biochem. 2017;54(1):43-48. doi:10.1177/0004563216675185
7. Diagnosing and managing iron deficiency anaemia in adults; A practical, clinical approach to iron deficiency anaemia. KAREN GUNTHER, MB ChB, MMed (Haem). Private Practice, Floro Clinic / Mayo Centre, Johannesburg. May 2008 Vol.26 No.5. pg. 232-236.indd 233.
8. Bouri, Sonia, and John Martin. "Investigation of iron deficiency anaemia ." Clinical medicine (London, England) vol. 18,3 (2018): 242-244. doi:10.7861/clinmedicine.18-3-242.
9. Alleyne, Michael et al. "Individualized treatment for iron-deficiency anemia in adults." The American journal of medicine vol. 121,11 (2008): 943-8. doi:10.1016/j.amjmed.2008.07.012.
10. BCGuidelines.ca: Iron Deficiency – Diagnosis and Management (2019). https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/iron-deficiency.
11. Atia A. Physician trends of drug prescription in Libya: A pharmacoepidemiological study. Pharmacophores an International Research Journal. 2019;10(3):33-38.
12. Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. Am Fam Physician. 2013;87(2):98-104.
13. Fauziah F, Surachman E, Muhtadi A. Integration of service quality and quality function deployment as an effort of pharmaceutical

service improvement on outpatient in a referral Hospital Karawang Indonesia. J. Adv. Pharm. Educ. Res. 2019 Apr;9(2):13-23
14. Sundus A, Ismail NE, Gnanasan S. Exploration of healthcare practitioner's perception regarding pharmacist's role in cancer palliative care, Malaysia. Pharmacophores. 2018 Jul 1;9(4):1-7.
15. Darkhor S, Estebsari F, Hosseini M, Charati JY, Vasli P. Effect of health promotion intervention on Nurses' healthy lifestyle and health-promoting behaviors: RCT study. J. Adv. Pharm. Educ. Res | Jan-Mar. 2018;8(1):108-114.
16. Hanawi, S A, Saat, N Z M, Zulkafly, M, Hazlenah, H, Taibukahn, N H, Yoganathan, D et al. Impact of a Healthy Lifestyle on the Psychological Well-being of University Students. Int. J. Pharm. Res. Allied Sci. 2020;9(2):1-7.
17. Yates JM, Logan EC, Stewart RM. Iron deficiency anaemia in general practice: clinical outcomes over three years and factors influencing diagnostic investigations. Postgrad Med J. 2004;80(945):405-410. doi:10.1136/pgmj.2003.015677
18. Tang GH, Hart R, Sholzberg M, Brezden-Masley C. Iron deficiency anemia in gastric cancer: a Canadian retrospective review. Eur J Gastroenterol Hepatol. 2018;30(12):1497-1501. doi:10.1097/MEG.0000000000001251
19. Camaschella C. Iron deficiency: new insights into diagnosis and treatment. Hematology Am Soc Hematol Educ Program. 2015;2015:8-13. doi:10.1182/asheducation-2015.1.8
20. DeLoughery TG. Safety of Oral and Intravenous Iron. Acta Haematol. 2019;142(1):8-12. doi:10.1159/000496966
21. Szebeni J, Fishbane S, Hedenus M, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. Br J Pharmacol. 2015;172(21):5025-5036. doi:10.1111/bph.13268.