Blood Reviews 31 (2017) 225–233

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

New insights into iron deficiency and iron deficiency anemia

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ARTICLE INFO

Keywords:
Iron deficiency
Anemia
Inflammation
Hepcidin

ABSTRACT

Recent advances in iron metabolism have stimulated new interest in iron deficiency (ID) and its anemia (IDA), common conditions worldwide. Absolute ID/IDA, i.e. the decrease of total body iron, is easily diagnosed based on decreased levels of serum ferritin and transferrin saturation. Relative lack of iron in specific organs/tissues, and IDA in the context of inflammatory disorders, are diagnosed based on arbitrary cut offs of ferritin and transferrin saturation and/or marker combination (as the soluble transferrin receptor/ferritin index) in an appropriate clinical context. Most ID patients are candidate to traditional treatment with oral iron salts, while high hepcidin levels block their absorption in inflammatory disorders. New iron preparations and new treatment modalities are available: high-dose intravenous iron compounds are becoming popular and indications to their use are increasing, although long-term side effects remain to be evaluated.

1. Introduction

Iron deficiency (ID) and iron deficiency anemia (IDA) are common medical conditions worldwide; still uncertainties exist on their correct diagnosis and treatment. This insecurity is related at least in part to a recent broader interpretation of ID, but especially to the explosive knowledge of iron metabolism in the last 20 years, that makes physicians uncertain of which approach to iron disorders is correct. A further level of complexity derives from the increasing number of conditions (with high prevalence) recognized as associated with altered iron metabolism. While it is easy to diagnose ID and IDA due to decreased iron intake, increased iron demands, chronic blood loss or decreased intestinal absorption, it is definitely more complex to recognize ID when it is masked by chronic inflammatory disorders. Inflammatory cytokines influence iron metabolism: they stimulate hepcidin production, cause iron sequestration in macrophage stores and decrease saturation of circulating transferrin and thus tissue iron availability. Variable degrees of inflammation characterize several common human disorders, such as atherosclerosis, obesity, diabetes and metabolic syndrome. ID together with inflammation is common in many types of cancer and in chronic kidney disease (CKD), both in patients undergoing dialysis and in predialysis state. ID and iron restriction may occur in the elderly, often affected by multiple comorbidities, as well as in middle age overweight subjects and in obese individuals at any age.

A further problem is related to the diagnostic approach. Classic tests for diagnosis are blood cell count, serum ferritin, serum iron and transferrin (or total iron binding capacity) and transferrin saturation (or saturated iron binding capacity). The rapid advances of the field lead physicians uncertain of the tests to be prescribed and of their interpretation: which ferritin cut off levels are indisputable indexes of ID? Is there room for testing soluble transferrin receptor (sTFRC) or red cell zinc protoporphyrins in ID? Are serum hepcidin level measurements useful in ID and by which method should they be evaluated? Which is the role of the novel reticulocyte or red cell indexes, as reticulocyte hemoglobin content (RHC) or percent hypochromic red cells (HRC), now provided by automated counters? When have I to suspect a genetic form of IDA? Moreover, once the diagnosis of IDA is established, how have I to treat patients? Is oral iron therapy still up to date? What about patients who are intolerant or non-compliant to oral iron therapy? Concerning intravenous iron, which is the best protocol: is it the use of multiple low doses or a single high-dose injection? Finally, in the era of disease prevention, uncertainties exist as to whether only IDA should be treated or whether treatment should be started earlier in ID before anemia develops. ID goes across all medical specialties of internal medicine from hematology to gastroenterology, nephrology, oncology, infectious diseases, cardiology, pneumology not to mention obstetrics and gynecology, surgery etc.… Guidelines may vary according to specialties and often, because of the above raised questions guidelines do not provide clear-cut answers [1].

This review aims at clarifying the general problem of ID and IDA and at providing at least some clues to tackle the above questions. Etiology, signs and symptoms, traditional diagnosis and treatment of IDA are extensively discussed in recent reviews [2,3]. Here the ambition is to explore and discuss the novelties in the field. However, the issue is in rapid evolution; this explains the heterogeneity of guidelines and even their lack of agreement.

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http://dx.doi.org/10.1016/j.blre.2017.02.004
0268-960X/

2. Iron metabolism

Iron is a trace element indispensable for all cell life. As a heme constituent it participates to hemoglobin, myoglobin, cytochromes and enzymes synthesis and is essential for respiration, mitochondrial function and energy production. As a component of iron-sulfur clusters iron is essential for the prosthetic group of enzymes involved in cell proliferation, DNA repair, heme synthesis and many other functions, including the activity of Iron Regulatory Protein 1 (IRP1) which, when acquires the iron-sulfur cluster, ceases to control iron acquisition and acquires the role of aconitase, the enzyme that converts citrate to isocitrate in the tricarboxylic acid [4]. This inter-conversion strengthens the iron role in both metabolism and energy production.

Iron is conserved in mammals. Iron derived from erythrocyte breakdown is quickly recycled to the circulating iron carrier transferrin by macrophages. Iron from damaged muscles is locally recycled to regenerating fibers [5] and iron released from damaged red cells in the circulation, e.g. in acute intravascular hemolysis, is recycled by a "on demand" transient population of liver macrophages [6]. Virtually all body iron is reutilized prevalently in erythropoiesis, as only 1 mg iron is lost daily and is replaced by an equal amount absorbed from duodenal enterocytes. The capacity to absorb iron may increase, but remains lower than the capacity of erythropoiesis expansion; this is one reason why IDA may easily develop after blood loss (or even blood donation), if iron stores are limited.

2.1. Iron trafficking

The iron carrier transferrin is produced and secreted in the circulation by all cells, mainly by the hepatocytes. In normal condition one third of transferrin is bound to iron representing the "saturated" transferrin. However, only diferric transferrin (one transferrin molecule bound to two molecules of iron) is the natural high-affinity ligand of transferrin receptor 1 (TFRC) that imports iron in most cells including the hemoglobin synthesizing erythroblasts in bone marrow. Transferrin is itself a regulator of iron homeostasis, as assessed in animal models, through its ability to bind, although with lower affinity than TFR1, the second transferrin receptor, TFR2, which is an iron sensor in the liver [7] and in erythroid cells [8]. *Tfr1* KO mice die during embryonic life because of severe anemia and brain abnormalities [9], while *Tfr1* selective inactivation in different organs showed that this receptor is indispensable for heart [10], skeletal muscle [11] and intestine [12] function. *Tfr1* haplo-insufficient mice have ID in the absence of anemia, with reduced total body iron and also low MCV and MCH [9]. Additional players in TFR1 endosomal cycle are Solute Carrier Family 11 Member 2 (SLC11A2) commonly called Divalent Metal-Transporter-1 (DMT1) and the metalloreductase Six-Transmembrane Epithelial Antigen of Prostate 3 (STEAP3). DMT1 on the apical membrane of the duodenal enterocytes uptakes iron and other metals from the lumen and works in tight association with the membrane ferrireductase DCYT-B. The expression of DMT1, DCYT-B as well as of ferroportin, are highly increased by HIF-2alpha in hypoxia; thus the iron flux from the lumen and its transfer to the circulation is enhanced [13]. Mutations of DMT1 lead to a recessive disorder that causes an atypical form of microcytic anemia, with increased transferrin saturation and increased total body iron [14], also defined "anemia, hypochromic microcytic, with iron overload 1 (AHMIO1)" (OMIM #206100). Other iron transporters as SLC39A14 (Zip14), a member of metal-ion transporters family, known to transport zinc [15] and low voltage calcium channels play a role in iron uptake in specific tissues. Zip14 has been shown to uptake non-transferrin-bound iron (NTBI), which increases in plasma when transferrin saturation is high, and to import it in acinar cells of the pancreas and in hepatocytes [16]. Low voltage calcium channels have been proposed to import iron in the heart [17] in condition of iron overload.

Several other proteins are involved in intracellular iron trafficking. *SLC25A37* encodes mitoferrin 1, a mitochondrial iron transporter that mediates iron flux from cytosol to mitochondria in erythroblasts, in response to the high requirements of iron for heme and hemoglobin synthesis [18]. *SLC25A28* encodes mitoferrin 2, which transfers iron to mitochondria for heme and iron sulfur cluster biogenesis in non-erythroid cells. Poly (rC) binding protein 1 (PCBP1), a ubiquitous cytosolic chaperone, delivers iron to the storage protein ferritin [19]. The Nuclear Receptor Coactivator 4 (NCOA4) is emerging as the cargo protein that addresses ferritin to autophagosomes for degradation [20] in a process called "ferritinophagy" and has been reported to be important for the recovery of stored iron in case of need [21].

2.2. Iron regulation

A tight regulation of the available iron is operated at both cellular and systemic level: the two systems cooperate to ensure perfect homeostasis of the metal, providing adequate organs supply and avoiding both ID and iron overload.

2.2.1. Cellular iron regulation

In all cells iron homeostasis is maintained through the function of Iron regulatory proteins (IRP1 and IRP2). IRP1 is ubiquitous and works at the normal oxygen concentration, while IRP2 is active in hypoxia through a hypoxia responsive element (HRE) located in its promoter [4]. Well-known effects of IRP2 are the induction of erythropoietin synthesis in the kidney [22,23] and the increased expression of intestinal DMT1, DCYTB and ferroportin in hypoxia [13]. High iron levels abolish the IRP function: on one side iron favors the interconversion of IRP1 to aconitase through the acquisition of the iron/sulfur cluster, on the other side iron induces the degradation of IRP2 [24]. The high number of genes regulated by IRPs indicates that a wide network of mRNAs and proteins are iron-dependent [25]. IRPs are also essential for mitochondrial function. Combined inactivation of both IRP1 and IRP2 genes in hepatocytes, the cells central to body iron homeostasis, cause hepatic steatosis, due to a mitochondriopathy because of deficiency of the electron chain transport and of the tricarboxylic acid, liver failure and death, strengthening that IRPs play a critical role for mitochondrial and liver function [26].

2.2.2. Systemic iron regulation

Systemic iron homeostasis is ensured by the hepatic hormone hepcidin. Hepcidin is an antimicrobial peptide mainly produced by the liver, which controls both iron entering to plasma from absorptive sites and iron released from stores. Hepcidin performs its function by binding and degrading the sole cell iron exporter ferroportin [27], an ubiquitous protein, which is highly expressed on macrophage surface and enterocyte basolateral membrane. Hepcidin is mainly controlled at transcriptional level and its expression increases in response to increased circulating and tissue iron, inflammatory cytokines (especially IL-6) and metabolic needs. Hepcidin transcription is suppressed by erythropoiesis expansion, ID and hypoxia [4], testosterone [28] and likely other stimuli. Among the proposed hepcidin inhibitors *TMPRSS6*, encoding matriptase 2 [29], is the liver inhibitor, which, cleaving the BMP co-receptor hemojuvelin [30], attenuates the BMP signaling pathway and hepcidin transcription. Erythroferrone is considered the erythroid regulator produced by maturing erythroblasts, which suppresses hepcidin when erythropoiesis is expanded, through a still unknown mechanism [31].

In absolute ID hepcidin suppression is a compensatory mechanism that allows increased iron acquisition from the intestinal lumen. Low hepcidin also accounts for the positive response to orally administered pharmacologic iron, provided that the intestinal mucosa is intact [32].

3. Classification of iron deficiency

Traditionally and based on etiology and pathophysiology we distinguish absolute and relative ID, based on laboratory and clinical results ID