Review Article

Iron deficiency and iron deficiency anaemia in children: physiology, epidemiology, aetiology, clinical effects, laboratory diagnosis and treatment: literature review

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Objective: This review article aims to describes iron deficiency and iron deficiency anaemia in children including its physiology, epidemiology, aetiology, clinical effects, laboratory diagnosis and treatment.

Background: Iron deficiency is a nutritional disorder, it is the most common nutritional disorder worldwide. There are three main stages of reduction of body iron which is a continuous process from iron depletion followed by iron deficiency and then iron deficiency anaemia. Iron is a cation necessary for blood formation. Apart from its role in haemoglobin, it is also needed in various enzyme reactions and cytochromes. It is distributed as an active metabolite and also in storage pools. Iron is an essential component of virtually all living cells, specifically human cells. Iron is an essential micronutrient. it occurs as haem (organic) and non-haem iron (non-organic) in the diet. Maternal supplies are the source of the developing fetus iron stores. [41]A normal term infant is born with iron stores for the first four to 6 months after birth except maternal iron deficiency is severe. Iron is also needed for growth and metabolism in the post-natal life. It has been estimated that 39% of children younger than 5 years and 48% of children between 5 to 14 years are iron deficient in non-industrialized world, as against 20% in less than 5 years and 5.9% in 5–14 years from industrialized world by the World Health Organization. Children in the developing world are especially vulnerable because of the increased requirements of growth, diets with low iron bioavailability, and high helminthic burden.

Methods: A search of publications before October 2020 was done. It was limited to publications in English. Searches were performed using PubMed, Medline, Web of Science, Psych Info and CINAHL, Google, Access to Research for Development and Innovation (ARDI), Health Inter Network Access to Research Initiative (HINARI), JSTOR ARCHIVES, EBSCO HOST, Ohio LINK, DOABOOK.

Conclusions: This review article describes the iron deficiency and iron deficiency anaemia in children: physiology, epidemiology, aetiology, clinical effects, laboratory diagnosis and treatment.

Keywords: Iron; iron deficiency; iron deficiency anaemia; children; treatment

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Introduction

Iron deficiency is a nutritional disorder, it is the most common nutritional disorder worldwide (1). Sufficient supply of iron is important for the functioning of major processes and reactions involving electron transfer (2). Hypoxia and attendant secondary erythrocytosis causes polycythemia and consumption of iron stored (3). Iron depletion can also be caused by the bleeding tendency as a result of thrombocytopenia and abnormalities of the haemostatic mechanism (4,5).

There are three stages involved when iron stores in the body is reduced, this ranges from iron depletion, to iron deficiency and then, iron deficiency anemia (6). When there is iron depletion, the amount of Iron required in the body is more than the amount ingested leading to a gradual reduction in iron stores (6). The reduction in iron stores shows up as low concentration of serum ferritin (6). In Iron deficiency, stored iron is low, associated low absorption of iron to replace normal body losses, there is low mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and serum ferritin (6). The last and most severe stage is Iron deficiency anaemia; it is characterized by red blood cells (RBCs) with a lower level of iron, low MCV, low mean MCH, low haemoglobin (Hb) level and a reduction serum ferritin. The distinction between "iron deficiency" and "anaemia" is important.

Various laboratory tests for the detection of iron deficiency such as MCV, serum ferritin and transferrin saturation (Tfsat) are limited in their value because their sensitivities and specificities may be affected by acute inflammatory conditions (7), chronic inflammations (8), genetic polymorphisms (9), and by sickle cell disease states (8). The World Health Organization (WHO) recommended combination of various laboratory tests to define iron status in a population (1).

Methods

The search included publications before October 2020. It was limited to publications in English and a subset of medical databases. Searches were performed using PubMed, Medline, Web of Science, Psych Info and CINAHL, Google, Access to Research for Development and Innovation (ARDI), Health Inter Network Access to Research Initiative (HINARI), JSTOR ARCHIVES, EBSCO HOST, Ohio LINK, DOABOOK. The keywords used were: iron deficiency in children, Iron deficiency anaemia in children, latent iron deficiency in children among others. The materials used included textbooks, journals, magazines, newspapers, policy documents, academic papers, conference papers, Internet materials which consist of abstracts, reviews, dictionaries, and encyclopedias. This review article aims to describes iron deficiency and iron deficiency anaemia in children including its physiology, epidemiology, aetiology, clinical effects, laboratory diagnosis and treatment. Hence, we present this article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jxym-21-6).

Discussion

Physiology of iron

Iron is a cation necessary for blood formation. Also, it is one of the constituents of Hb, it is also needed in reactions in various enzyme reactions and cytochromes. It is distributed as an active metabolite and also in storage pools (1). Iron is reused effectively from ageing RBCs in humans. It is absorbed by the small intestine, (only 10% of dietary iron is absorbed). A daily intake of iron is necessary to cover the iron lost from desquamation of cells of the skin and intestine and also, to maintain growth in children (1). The demand for iron is highest during periods of high growth found in infancy and adolescence. The form of iron when consumed determines how well it is absorbed (2). It is better absorbed in the haem form when compared with the non-haem state. The non-haem form requires reduction to the ferrous state and its release from food binders by gastric juices. Also, food items such as vegetable fiber phytates in cereals and pulses, calcium and tannins in tea reduces the absorption of non-haem iron (2). Some other food items such as vitamin C encourages the absorption of iron. The absorbed iron is transported by transferrin, a binding protein produced by the liver. The synthesis of transferrin by the liver is affected by the iron status. The synthesis increases when there is iron deficiency and reduces in chronic disease states. Iron is stored as either ferritin or hemosiderin. It is used during erythropoiesis. Ferritin is freely available and soluble, it is stored in the hepatocytes, macrophages (spleen), bone marrow, serum, and RBCs. The amount of ferritin in circulation is parallel to the amount of the total body store (1,2).

Reduction of body iron develops in stages and there are three main stages: in the first stage referred to as iron depletion, this is followed by iron deficiency without

anaemia (10).

Iron metabolism

Iron is an important component of virtually all living cells, specifically human cells (11). Under physiological conditions the ability of iron to convert between two oxidation states that are thermodynamically stable, the ferric (Fe^{3+}) form and the ferrous (Fe^{2+}) form, makes it well suitable for the catalysis of various biochemical reactions (10). Quite a number of enzymes depend on iron to perform their functions (12). These include, transfer of electron, storage, and activation of oxygen, detoxification of activated oxygen species, nitrogen fixation and deoxyribonucleotide synthesis from ribonucleoside diphosphates (12). It is involved in brain development, it is also an important nutrient involved in immune response, and energy metabolism (9-13). During the processes of iron absorption and distribution, it is bound to proteins (transferrin) tightly, leaving an extremely low concentration of free intracellular iron (11). The regulation of intracellular iron is very important, because even low concentrations of "free iron" can result is severe damage to a number of cellular constituents including membranes and DNA (11).

Dietary iron intake and intestinal absorption

Iron is an essential micronutrient. it occurs as haem (organic) and non-haem iron (non-organic) in the diet (14,15). Haem iron is obtained from poultry and meat. It is also obtained from fish. Haem iron has a higher bioavailability than non-heme iron. Non-haem iron is mostly obtained from vegetables and grains and nuts (14,15). Ascorbic acid, citric acid, haem iron and breast milk promote the absorption of non-haem iron (15,16). The absorption of non-haem iron is inhibited by polyphenols (from plants, phytates (from seeds and grains), cows' milk and calcium (17,18). Phytates and polyphenols reduces the absorption of non-heme iron by forming complexes which are insoluble, hence makes the non-haem iron unavailable for absorption (19). Ascorbic acid keeps iron available for absorption through several mechanisms (20,21). Firstly, it promotes an acidic environment which facilitate iron absorption, secondly, it chelates Fe^{3+} and maintains it in a stable complex, and lastly, it reduces Fe^{3+} to Fe^{2+} forming a soluble complex available for absorption (22,23). Iron in breast milk is readily absorbed because it is bound to lactoferrin which aids the absorption of iron through the lactoferrin receptor into the enterocyte (24). The concentration of iron in breast milk starts relatively low (0.6 mg/L), and reduces to about 0.2–0.3 mg/L 5–6 months of age (24,25). Although, the bioavailability of breast milk iron is high (15–42%) (26). Cows' milk is low in iron hence consumption of cow milk has an adverse effect on iron status (19). Also, cow milk has high casein and high calcium which also inhibit iron absorption (14,27). Also, cows' milk allergy can cause intestinal blood loss which predisposes to the development of iron deficiency (27).

Mechanism of iron absorption

Iron absorption takes place primarily at the small intestine, at the apical surface of the duodenum and the upper of the jejunum (28). Different pathways are responsible for the absorption of heme and non-heme iron (29). Haem iron is absorbed intact by an intestinal transporter called heme carrier protein 1 (HCP1) (29). It is hydrolyzed from the protein to which it is attached and is absorbed relatively easily, whereas non-heme iron exists in an oxidized form that is not bioavailable (29). Dietary components or by ferric reductase enzyme need to reduce non-heme iron for it to be transported by the divalent metal ion transporter 1 (DMT1) across the intestinal epithelium (29). The efflux of iron from the duodenum into the plasma is mediated by the iron oxidase, hephaestin and ferroportin 1, a transport protein (29,30).

Transport and distribution of iron in the body

In the body, iron is transported between sites of absorption, utilization by the plasma glycoprotein transferrin and storage (Tf) (31). The specific cell membrane Tf receptors (TfR), is crucial for cellular iron acquisition, it recognizes the plasma transferrin (32). The receptors bind to iron-transferrin complex at the surface of the cell and carry the complex into the cell, for iron to be released. Fe^{3+} released from the Tf-TfR complex is reduced within endosomes (32). This is an important step because it helps facilitate iron uptake by red cell precursors as excess iron enters functional compartments or is stored as ferritin (32).

Regulation of systemic iron

For systemic iron homeostasis to be maintained, there has to be an effective communication between cells duodenal enterocytes that absorb iron from the diet, and the

erythroid precursors which utilize iron and iron stored (33). Iron release from the Hb of erythrocytes that are destroyed, the degradation of iron-containing enzymes, and myoglobin are the major pathways of iron turnover (34). The average lifespan of erythrocyte is about 120 days, they are degraded by macrophages in the spleen and Kupffer cells (34). Sixty to seventy percent of functional iron in the body is contained in circulating Hb (34). Iron bound to transferrin form is the way up to 85% of how iron derived from the breakdown of Hb is re-released to the body (34). The cycle is completed when new RBCs enter the circulation in the following 7–10 days (34). Iron absorption is increased when erythropoietic activity is enhanced (35). Erythropoietin is produced by the kidneys. The process of erythropoiesis is controlled by erythropoietin concentration (35). When there is iron deficiency, iron transfer is increased by stimulating hepatic synthesis of transferrin, ferroportin expression on macrophages, and increased expression of transferrin receptor (TfR1) in the bone marrow and other tissues (34).

Hepcidin is produced in the liver, it is a hormone and a 25-amino peptide., it is the key regulator of iron homeostasis in the systemic circulation (36). Hepcidin controls the circulating iron concentration by inhibiting its uptake from duodenal enterocytes, hepatocytes and macrophages, it does so by binding to the iron transporter ferroportin on these cells (37). This leads to a decrease in the absorption of dietary iron absorption and a reduction in circulating iron in the blood, while intracellular iron stores increase (36). Iron overload, infection and inflammation stimulates the synthesis of hepcidin, while hypoxia, iron deficiency, anaemia and conditions which increase erythropoietic activity decreases its production (38).

Stages of iron deficiency

In iron deficiency state, iron is not available in sufficient amount to maintain the normal physiological function of body tissues like the brain, muscles blood and the brain (39). It results from long-term negative iron balance. Hemosiderin and ferritin which are forms of Iron stores are diminished progressively and are not able to meet the needs of the body any longer (40). As a result, an array of systemic evidence of iron deficiency becomes evident. Symptoms caused by iron deficiency are subtle and non-specific, and often become apparent only in its severe stages (39). Iron status ranges from iron deficiency with anaemia (IDA), to iron deficiency without anaemia, to normal iron status, and finally iron overload (1).

Iron deficiency without anemia has two stages: iron deficient erythropoiesis and iron depletion (1). In iron depletion, the amount of stored iron is reduced but the amount of iron needed to may not be affected, hence an individual with iron depletion has no iron stores to make available if the body needs more iron (1). In iron-deficient erythropoiesis, there is depletion of stored iron and further reduction in transport iron, the absorbed iron is not sufficient to replace the amount of iron lost or the amount required for body function and growth (1). In Iron deficiency anaemia, which is the most severe form of iron deficiency, the reduction of iron (storage and transport) causes underproduction of iron-containing compounds needed to function, such as Hb, and myoglobin (1).

Iron needs during infancy and childhood

The fetus iron stores are built from maternal supplies (41), a term infant is born having enough iron stores for at least the first four to 6 months for growth after birth except the mother has a severe iron deficiency (42), the preterm infant is born with lower iron stores because he has less time to accumulate iron in utero (41). Also, a preterm infant may deplete their iron stores within 2 to 3 months after birth. because they have a faster rate of growth than the term infant (41).

The neonate uses iron at a high rate in the first months of life for accelerated growth and expansion of blood volume (42). There is a need for adequate iron to meet the demands from rapid growth and erythropoiesis after birth (42). An infant's iron stores would have reduced by 50% by 4 months of age; when birth weight is expected to have doubled (43). Children become exclusively dependent on dietary iron intake around 6 months of age (43). in infancy up to about 66% of iron losses are from cells that are shed from the mucosa of the intestine, skin and urinary tract (44). about 0.8 mg/d of dietary iron needs to be absorbed by a normal infant (0.6 mg for growth, 0.2 mg to replace ongoing losses in the first year of life (45). There is a need for supplementation of iron intake so as to meet iron needed to replace normal iron loss and for growth. The recommended daily allowance (RDA) ranges from 7.0 to 11.0 mg per day and 5.8 to 9.0 mg per day for infant between the age of 5 months to less than 1 year and 1 to 3 years respectively (45). Towards the second year of life, routine diet supplies sufficient iron-rich foods to meet demands (45). The RDA reduces to 10mg per day for children aged between 4 to 10 years of age. The RDA at the age of 11 years increases to 18 mg per day to provide for the increased growth that

characterizes adolescence (46). In males, iron needs are highest during peak pubertal development because of increase in blood volume, myoglobin and muscle mass (47). In females, iron needs remain high due to blood loss from menstruation, which is approximately 20 to 58 mg in a month (48). Thus, the recommended iron intake for pubertal girls is 15 to 22 mg per day while it is 10 to 13 mg per day for boys (49).

Epidemiology of iron deficiency in children

Worldwide, iron deficiency is the most commonly reported nutritional deficiency (1). According to the WHO, up to 39% of children who are less than 5 years and 48% of children who are between 5 to 14 years of age are iron deficient in non-industrialized world, as against 20% in less than 5 and 5.9% in 5–14 years from industrialized world (1). Prevalence rates vary among countries; it affects 2.4 million children in the USA (50), 5.4% of children in Spain (51), 14.0% in Estonia (52), 30.8% in Brazilian children (53).

Various studies in Africa have reported prevalence rates of between 9.8%% and 20.8% (54-56). The prevalence of iron deficiency in Nigerian children vary according to age group (57-59). A nationwide survey involving 12 states in Nigeria in 2001 using the serum ferritin model as an indicator, reported that 27.5% of children under 5 years of age were iron-deficient (57). Fajolu *et al.* (12) investigated the prevalence of iron deficiency in children between 6 to 24 months of age. A total of 282 children who were delivered at term were recruited into the study over a 6-month period. The authors reported iron deficiency prevalence of 14.9%. Akodu *et al.* (58) investigated 87 children up to 5 years. In that study subjects were subcategorized into children up to 2 years and greater than 2 years. Amongst the 42 children less than or equal to 24 months, the prevalence (19%) was higher than the earlier report by Fajolu *et al.* (12). The prevalence among children up to 5 years reported by Akodu *et al.* (58) was 10.1%. Other investigators who studied children up to 5 years reported a prevalence of between 9.8% and 27.5% (60,61). For children up to 8 years, Jeremiah *et al.* (59) in South Southern Nigeria reported overall prevalence of 13.7%. In that study, the authors did not categorize the prevalence based on age subcategories. It was therefore not possible to compare their findings in under-5 children with other studies.

Aetiology of iron deficiency

The underlying cause must always be stated in the diagnosis of iron deficiency. Children in the developing world are more prone to developing iron deficiency due of their need for growth (62), diets with low iron bioavailability (63), and high helminthic burden (60).

When there is a disparity between the maximal amount of iron absorbed from the diet, and the physiological requirements which occur when there is increased physiologic demand leads to iron deficiency (62). In an infant not given iron-fortified weaning foods or formulae, rapid body growth will be the cause of iron deficiency (62). Growth is associated with high iron requirements (48). This is clearly demonstrated in preterm babies during the first few months and in infancy and adolescence during peak periods of growth (63,64). These periods of rapid growth, cause exhaustion of iron stores if additional dietary iron is not provided.

In a study conducted by Ferlin *et al.* (63) among 25 Brazilian newborns who were preterm birth weight of 1,000 to 1,800 g, and 30 to 35 weeks gestational age, it was observed that offering iron to these children at 15 days of life as an alternative was justified because at 2 months of age, infants who had not been supplemented were showing depleted iron stores already.

In populations consuming monotonous plant-based diets with little meat, dietary iron bioavailability is low (28). Up to 30–70% of iron is haem iron in meat, out of which 15–35% is absorbed (18). On the contrary, in plant-based diets most of the dietary iron is non-haem iron, and less than is absorbed is often (15). The risk of deficiency is highest when iron requirements are greater than energy needs (65). Low dietary iron intake has been associated with iron deficiency (28).

Onimawo *et al.* (66) assessed the iron intake of school children in Abia state. When the iron content of collected food samples was assessed, the iron content of foods consumed in the community was found to be poor. Cereals, legumes, roots and tubers were observed to be the predominant foods consumed during the interview on food intake, also, these types of diet are known to contain high content of iron inhibitors such as polyphenols and provide low amounts of bioavailable iron (67). These children also consumed in low quantities, meat, poultry and fish, which are excellent sources of haem iron and are enhancing factors for non-haem iron absorption. The researchers concluded that the high prevalence of iron deficiency (77.8%) in the population was attributed to low dietary iron intake below the recommended value.

Hook worm infestation and menstruation are among the common causes of iron deficiency following blood loss.

Menstruation in adolescent girls has been documented to be associated with decreased iron stores (68,69). This is more problematic in a population that consumes low iron diet (63). Menstruation results in an average loss of around 20 mg of iron in a month, the iron loss but may be up to 58 mg per month in some individuals (48).

Moschoni *et al*. (68), studied adolescent girls aged 9–13 years in Greece. A comparison of the iron status of children who were menstruating with controls, revealed that menses was significantly associated with ID among the study subjects. This position was corroborated by authors in Nigeria who demonstrated that iron status was inversely related to menstrual blood loss (63,69).

Chronic intestinal blood loss is one of the mechanisms through which hookworm infestation induces iron deficiency (70). *Ancylostoma duodenale* and *Necator americanus* are the two species of hookworms, about 0.2 and 0.15 mL of blood loss per day are caused respectively (70). Hookworms also release anti-clotting factors which contributes to continuous blood loss. The susceptibility of children to parasitic infections is due to their lower immune response (71) compared to adults, poor hygiene, and poor sanitary and environmental conditions. Hookworm infestation afflicts 740 million people in developing nations of the tropics (72). A study of children Zanzibar in his study of children showed that 62% of the subjects were anaemic, 82% of this anaemia was attributable to iron deficiency, of which the strongest predictor was hook worm infestation (73). Osazuwa *et al.* (60) in Edo State, Nigeria studied 316 children aged 1 to 15 years living in rural communities. The authors reported a significant association between hookworm infestation and iron deficiency. This finding was corroborated by authors who studied children in other regions of Nigeria (74,75).

Protein energy malnutrition will impair absorption of iron thereby worsening the iron deficiency that the malnourished children have almost invariably (76). Other causes impaired iron absorption, which are rare in children, includes chronic diarrhoea and malabsorption syndromes such as inflammatory bowel disease (77), partial or total gastrectomy (78) and rarely genetically determined absorptive defect for iron (79).

Clinical effects of iron deficiency

The clinical manifestations seen in iron deficiency are attributed to depletion of iron stores. The functions of iron in all cells includes; metabolism of energy, regulation of genes, growth and differentiation of cells, binding and transport of oxygen, use and storage of oxygen in the muscles, enzyme reactions, synthesis of proteins and neurotransmitters (13). Thus, deficiency of iron is a multi-systemic disorder, rather than a purely haematological condition associated with anaemia only. Adverse health effects of iron deficiency in children includes; growth retardation (62), impaired immune function (13), impaired behavioural, mental and psychomotor development (7,80) as well as decreased work capacity (81).

Iron is required for cell growth and differentiation (82). The iron-containing enzyme ribonucleotide reductase initiates the synthesis of DNA, which is a limiting factor in the rate of the replication of the cells. Thus, iron deficiency limits cellular proliferation (83). Soliman *et al.* (62), studied linear growth of 40 children with iron deficiency aged 17.2±12.4 months before and after iron supplementation. The authors reported that children with iron deficiency were statistically significantly shorter and had reduced growth when compared with their controls. Also, it was reported that after treatment, the growth indices of children with iron deficiency significantly improved.

Iron is also an important component of the nitrous oxide-generating enzymes and the peroxide-generating enzymes that are important for the functioning of enzymes involved in immune cells (13). Also, iron is involved in the regulation of the production of cytokine (13). The relationship between iron deficiency and immune status was investigated by Ekiz *et al.* (84). The authors compared the percentages of T-lymphocyte, phagocytic activity, the level of serum interleukin-6 (IL-6), levels of immunoglobulin of children with iron deficiency to those of controls. It was thus concluded that iron deficiency significantly impairs cellular and humoral immunity as well as synthesis of immunoglobulin. This position was supported by the findings of Macdougall *et al.* (85), when the cellular and humoral defense mechanisms were evaluated in 20 children with iron deficiency, and in seven children with latent iron deficiency. The serum immunoglobulin concentrations, complements and salivary IgA were measured. The subsequent assessment of lymphocyte and neutrophil function showed impaired delayed hypersensitivity reaction and decreased bactericidal function respectively. The finding of these abnormalities in patients with latent iron deficiency, suggests that alteration in immunologic function was an early feature of iron deficiency (85).

The effect of iron deficiency on central nervous system (CNS) is also very important. Iron is required for

brain cell proliferation, differentiation, myelination and dopamine neurotransmission (86). Iron deficiency thus leads to reduced learning capacity and impaired cognitive function (87). In a short-term treatment trial conducted in children less than 3 years of age, it was observed that children that received short-term iron preparations showed improvement in Bayley Test of Mental Development (88).

Studies have also reported that iron deficiency during early life can have lasting cognitive effects even after iron repletion (87,89). Lozoff *et al.* (7) in a longitudinal study investigated the likelihood that iron deficient infants may be "functionally isolated". He compared the behaviour of 52 Costa Rican infants with iron deficiency aged 12 to 24 months with that of control who had better level of iron status. The investigator observed the during free play and also tested them with the same motor and mental protocols. Infants with iron deficiency were made fewer attempts at test items easily tired, hesitant and warier, they were less attentive to instructions, and were less playful. This finding supports the authors' hypothesis that iron-deficient infants engage less with their environment. The authors also documented persistent cognitive impairment as well as poor socio-emotional function, in children with ID over the 10-year period.

Decreased work capacity has been associated with iron deficiency (90). Muscular work which lasts for more than a few minutes needs the oxidative production of energy in the mitochondria of the muscles, which requires the iron containing cytochromes, iron-sulphur proteins and electron transport proteins (91).

Tay *et al.* (81) studied the relationship between iron deficiency and exercise tolerance in 25 iron-deficient patients with cyanotic congenital heart disease (CHD) over a period of 5 months. Iron replacement therapy was administered to the subjects and cardiopulmonary exercise testing was carried out at onset and after 3 months of treatment. The researchers reported that 3 months of iron replacement therapy in iron-deficient subjects gave a significant improvement in the quality of life of subject their tolerance to exercise. In severe iron deficiency, symptoms of anaemia such as fatigue, shortness of breath, irritability, weakness and anorexia may occur (92).

Laboratory diagnosis of iron deficiency

In order to understand the laboratory measurement of iron status, there is a need to be familiar with the major internal iron circuit resulting from about 30–40 mg Hb iron in senescent RBCs each day which get removed and replaced (34). After macrophages in the bone marrow and spleen has ingested the aged red cells, iron is removed from Hb and returned to the plasma where it becomes bound to transferrin tightly, which is its dedicated extracellular carrier (40). After 1–2 hours, the iron-containing transferrin attaches to specific receptors located predominantly on the surface of red-cell precursors in the bone marrow (39). The newly formed erythrocytes are returned to the circulation over the next 7 to 10 days and this completes the iron cycle (34). It is important to interpret the measurements of iron status according to the specific compartments of iron they represent. A deficit in storage iron is the first to occur, then deficits in the iron transport, followed by deficit in the erythroid compartments (40).

Ferritin contains approximately 20% iron, and it is a high-molecular-weight protein (93). It occurs as iron reserves reticuloendothelial cells, hepatocytes and normally in almost all tissues of the body (94). It is also present in small amounts in the serum, where it reflects iron stores in normal individuals (90). Ferritin is important in the absorption, storage, and release of iron. It is the storage form of iron, and it remains in the body tissues until it is needed for erythropoiesis (65). When iron molecule is needed, they are released from the apo ferritin shell and bind to transferrin, the circulating plasma protein that transports iron to the erythropoietic cells (62).

Serum ferritin is the most useful laboratory measure of iron status (10). It is a readily available test which has measurement that is well-standardized (90). An important characteristic of the measurement is that the concentration is directly proportional to body iron stores in healthy individuals; 1 mg/L serum ferritin corresponds to 8–10 or 120 mg storage iron/kg body weight (42). Serum ferritin of less than 15 ng/mL for children greater than or equal to 5 years and 12 ng/mL in children less than 5 years has been defined as Iron deficiency criterion by the WHO with a sensitivity and specificity of 89% and 96% respectively (1,94). Using a cut off of less than 30 ng/mL in inflammatory states, which has a specificity and a sensitivity and of 98% and 92% respectively improves the diagnostic yield of serum ferritin (95). Various studies have documented that ferritin measurement is superior to other markers of iron deficiency (94,96).

Khan (97) studied the significance of serum ferritin in iron deficient children in comparison to other biochemical and haematological indices of serum iron. Children aged

5 months to 12 years were studied. Red cell morphology, Hb, serum iron and ferritin levels were measured. Serum ferritin had a sensitivity of 100% while total iron binding capacity (TIBC) and Tfsat had a sensitivity of 95% and 82% respectively. The researchers concluded that serum ferritin was a more sensitive indicator as compared to other parameters. Similarly, Guyatt *et al.* (95) studied the diagnostic values of laboratory test used in the diagnosis of iron deficiency. The authors reported ferritin to have a predictive value of 0.95 in diagnosis iron deficiency compared to 0.77 for MCV, 0.74 for Tfsat and 0.62 for absolute red cell distribution width (RDW). Serum ferritin is elevated in patients with acute or chronic inflammation, malignancy, or liver disease hence its use as a marker of iron status in those patients is limited (39). Hence, ferritin results should be interpreted with C-reactive protein (CRP), a biomarker of acute infection (98). CRP is an acute phase protein which performs a crucial role in the removal of damaged apoptotic cell, pathogen killing, and complement activation. (94). During infections or inflammatory disease states, the level of CRP increases rapidly in the first 6 to 8 hours and peak at levels of about 350–400 mg/L after 48 hours (99). CRP binds to phosphocholine on the surface of damaged cells, and the Pepto saccharides and polysaccharides and present on micro-organism like parasites, fungi and bacteria (100). This binding activates the classical complement cascade of the immune system, modulates the activity of phagocytic cells, hence, supporting the role of CRP in the opsonization of infectious agents and dead or dying cells (100). The CRP level falls once the inflammation is resolve. This makes CRP a useful marker for monitoring disease activity (98,101). A serum CRP level of <5 mg/L was suggested by WHO to define normal values when using a rapid test, or <3 to 10 mg/L when using immunoassays (e.g., ELISA) (101)

Latent iron deficiency depicting the phase of iron depletion before iron deficiency occurs has been described as serum ferritin levels less than 20 ng/mL (102). Further decline in body iron after iron stores are fully depleted, leads to a reduction in the concentration of plasma iron which is measured in tandem with transferrin its specific plasma transport protein (65). Tfsat is often determined from serum iron and the TIBC (40). As iron stores are depleted, serum iron reduces (101). Measurement of serum iron may not represent iron stores accurately because serum iron level is affected by the absorption of iron from meals, inflammation, inflammation and diurnal variation (40). The TIBC measures the availability of iron at the binding sites (1). The extracellular iron is transported by binding to transferrin, thus TIBC measures the transferrin level indirectly. Transferrin level increases as serum iron concentration decreases (41). The TIBC is low in patients who have malnutrition, malignancy and chronic infection (1).

Tfsat reflects iron transport, it indicates the number of iron-binding sites that are occupied (40). It is calculated by dividing the serum iron concentration divided by TIBC, expressed as a percent (40). Low Tfsat suggests low serum iron levels compared with the iron-binding sites that is available, suggesting low iron stores (31). It decreases before anaemia develops, but not early enough to identify iron depletion (31). It is influenced by the same factors that affect TIBC and serum iron concentration and is less sensitive to changes in iron stores than serum ferritin (40). A reduction in transferrin below 16% is a reliable index of an under supply of iron to the developing red cell (1).

The red cell indices [mean corpuscular Hb concentration (MCHC), MCV, Red cell count, mean corpuscular Hb (MCH), Hb concentration and haematocrit] are all low in Iron deficiency anaemia (1). Red cell abnormalities tend to occur relatively late in the progression from depletion in iron stores to absent iron store (102). Hb or haematocrit determination has been used widely as a screening tool for detection of iron deficiency anaemia (1). The major limitation is that it has low sensitivity and specificity because many other factors such as malnutrition, haemoglobinopathies, and chronic infection (103). The amount and Hb content of red cells are evaluated by the standard indices MCV and MCH. The major limitation of these haematological parameters is the time required after the onset of iron deficiency for the level to become abnormal (40). Beutler *et al.* (104) documented that MCH and MCV were not sensitive indicators for either exclusion or confirmation of iron deficiency. The researchers found that the controls had abnormal indices in 10% of cases while the subjects had normal MCH and MCV in 20% and 50% of cases respectively. It was also observed that the likelihood of abnormal indices increased with increasing severity of anaemia, which suggest that abnormal indices are a late occurrence in the progression to iron deficiency clinically (104).

RDW is a sensitive indicator for Iron deficiency anaemia, and used as a screening tool (105). High RDW equivalent to anisocytosis observed in a peripheral blood smear (102). When the level of RDW is significantly increased, it can be used to diagnose Iron deficiency anaemia (sensitivity 81.0%, specificity 53.4%) (105). There is an inverse relationship

between the serum Hb and the RDW in iron deficiency anaemia (40). The absolute values of red cell indices may vary and be confusing in diseases such as heterozygous thalassemia syndromes. The trend of RDW and MCV over time can be quite instructive (104); Iron deficiency manifests as a falling MCV accompanied by a rising RDW initially, due to the increasing preponderance of microcytes in the circulation (106). With iron treatment, marked reticulocytosis occurring in the first four weeks following therapy. This manifest as a sudden increase of RDW, sometimes to over 30% (58). Thus, a pattern of falling MCV accompanied by a rising RDW should alert the clinician to the suspicion of the presence of possible iron deficiency anaemia.

Zinc erythrocyte protoporphyrin (ZEP) is the immediate precursor of Hb (107). ZEP is formed when zinc is incorporated into protoporphyrin in place of iron during the final step of heme biosynthesis (107). The concentration of ZEP in blood increases when insufficient iron is available for Hb production (40). In iron deficiency anaemia, divalent metal transporter-1 (a protein that transports a number of divalent metals, including Fe^{2+}) is up regulated, which increases zinc transport across the intestinal membrane to replace the missing iron in the formation of the protoporphyrin ring (95).

ZEP assay is a sensitive test, but its specificity is limited because ZEP increases when there is lead poisoning, inflammation, and haemoglobinopathies (95). The sensitivity of ZEP to predict iron deficiency in children and adolescents aged 6 months to 17 years is 42%, its estimated specificity is 61% (107). Serdar (108) studied the function of zinc erythrocyte protoporphyrin in the diagnosis of iron deficiency in children. The researchers evaluated 72 subjects and assayed their serum zinc erythrocyte protoporphyrin, serum ferritin and MCV values were measured. ZEP was found to be the most sensitive test in diagnosing iron deficiency but less specific that serum ferritin while MCV was the least diagnostic test. The researchers recommended that ZEP can be used as a screening tool in the evaluation of iron deficiency. Similar findings have been documented by other authors (109,110).

TfRs are the membrane-binding sites for circulating transferrin-bound iron prior to uptake into the cell (32). It has been suggested that serum TfR provides a new and reliable method for assessing cellular iron status (40). TfR is a transmembrane protein, present in all cells, it binds transferrin and iron and transports it to the cell interior (34). Any reduction in iron supply results in an increase in TfR synthesis (40). In established cellular iron deficiency, serum TfR rises proportionally to the degree of iron deficiency (109). When combined with serum ferritin, serum TfR will give a complete information on iron status. The serum ferritin reflects iron stores in the absence of chronic inflammatory diseases and the TfR reflecting tissue iron store (111). The plasma TfR concentration is not increased with infection or inflammation, unlike plasma ferritin. Hence, measurement of the plasma TfR concentration may be especially helpful in differentiating between anaemia of iron deficiency and the anaemia associated with chronic inflammatory disorders (111). However, cytokines such as tumor necrosis factor and IL-6 have been suggested to reduce TfR expression in in-vitro experiments (112). Various authors have studied the plasma TfR concentration as a diagnostic tool for iron deficiency (95,113). Mast *et al.* (96) studied the clinical utility of plasma TfR in diagnosing iron deficiency. The researchers studied 62 anemic patients whose bone marrow examination had showed iron deficiency. The diagnostic sensitivity and specificity of plasma TfR were 92% and 84% respectively with a positive predictive value of 42%. Similarly, Nadeem *et al.* (114) studied 80 anemic subjects who had absent iron stores on bone marrow examination. The plasma TfR assay in the subjects showed a diagnostic accuracy of 91%. Other studies have compared the plasma TfR to ferritin as a diagnostic method of iron deficiency have found plasma TfR to have a specificity and sensitivity of 82% and 92% respectively while serum ferritin had a specificity of 84% and sensitivity of 92% (115). The researchers concluded that assaying plasma TfRs did not provide additional information to ferritin assay and thus not warrant it routine use in diagnosing iron deficiency (115).

The peripheral blood smears examination for the morphology of red cells is not specific in diagnosing iron deficiency anaemia, because the blood cells are often normochromic and normocytic and the blood smear may be within normal limits in mild degree of anemia. Also, when hypochromia and microcytosis are seen, it may be due to other causes including the anaemia of chronic disease, sideroblastic anemia and thalassemia (40). The peripheral blood smear may show microcytic, hypochromic RBCs with occasional target, elliptical, teardrop, fragmented red cells and anisocytosis in iron deficiency anaemia (116). Fairbanks (117) studied the reliability of peripheral blood film in diagnosing iron deficiency anaemia. Serum iron was assayed in subjects and controls and compared to their erythrocyte morphology. The researchers found out that the

experienced observers suggested features of iron deficiency in 5.8% of the 24 controls, and were unable to detect features of iron deficiency in 49% of the 38 patients with iron deficiency. The researchers concluded that erythrocyte morphology is an insensitive indicator for either exclusion or confirmation of iron deficiency anemia.

Examination of a slide of a bone marrow aspirate is generally regarded as the definitive marker of iron deficiency but involves an invasive, cumbersome procedure that is impractical for routine use (118). Bone marrow examination in iron deficiency anaemia would show normoblastic hyperplasia of erythroid elements, and decreased or absent stainable iron (119). If stainable iron in a bone marrow aspirate that contains spicules is absent with a simultaneous control specimen containing stainable iron indicates significant iron depletion, but is not conclusive evidence of this as iron may be available in the form of histochemical unstainable ferritin (118). The bone marrow examination is not helpful in the diagnosis of iron deficiency in infants and small children because little or no iron is stored as marrow hemosiderin at those ages (120).

Treatment of iron deficiency

The treatment of iron deficiency is done with oral iron salts, most of the time, over-the-counter ferrous sulfate, which is cheap and well absorbed relatively. Dosages are calculated using the elemental iron: children receive 3 to 6 mg/kg per day, while 60 mg/dose is given to adolescents (40). The response to iron therapy typically is rapid if the iron deficiency is nutritional (39). If oral iron is not tolerated, parenteral form is given; intramuscular iron injections usually are not appropriate (40). The use of erythrocyte transfusion is advised if there is any of the following: severe cardiovascular compromise or hypovolemia. Cardiac dilatation may result if correction of the anaemia is done rapidly (119).

Hb measurement should be repeated after 1 month of therapy. An increase of 1 g/dL or greater confirms the diagnosis of iron deficiency anaemia (120). Lack of improvement in Hb should prompt further evaluation of the anaemia with additional laboratory tests, including MCV, RDW, and serum ferritin, including a search for possible sources of blood loss (120). Iron therapy should be continued for an additional 2 to 3 months after Hb has returned to a normal level. Hb should be re-measured approximately 6 months after discontinuation of iron therapy (120). Current guidelines recommend avoidance of inappropriate venesection and cautious treatment of iron deficient cyanotic patients with close monitoring of Hb level (121).

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Footnote

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References

1. World Health Organization. Iron Deficiency Anemia: Assessment, Prevention, and Control- A Guide for Program Managers. Geneva, Switzerland: World Health Organization; 2001. WHO/NHD/01.3
2. Cairo G, Bernuzzi F, Recalcati S. A precious metal: Iron, an essential nutrient for all cells. Genes Nutr 2006;1:25-39.
3. Rosove MH, Perloff JK, Hocking WG, et al. Chronic hypoxaemia and decompensated erythrocytosis in cyanotic congenital heart disease. Lancet 1986;2:313-5.
4. Verel D. Blood volume changes in cyanotic congenital heart disease and polycythemia rubra vera. Circulation 1961;23:749-53.

5. Tempe DK, Virmani S, Rigler B, et al. Coagulation abnormalities in patients with cyanotic congenital heart disease. J Cardiothorac Vasc Anesth 2002;16:752-65.
6. Oechslin E. Hematological management of the cyanotic adult with congenital heart disease. Int J Cardiol 2004;97:109-15.
7. Lozoff B, Jimenez E, Wolf AW. Long-Term Developmental Outcome of Infants with Iron Deficiency. N Engl J Med 1991;325:687-94.
8. Kochanowski BA, Sherman AR. Cellular growth in iron-deficient rats: effect of pre- and postweaning iron repletion. J Nutr 1985;115:279-87.
9. Ogunkunle OO. Erythrocyte indices of iron status in children with cyanotic congenital heart disease at the University College Hospital, Ibadan. Niger J Paed 2013;40:75-8
10. Kaemmerer H, Fratz S, Braun SL, et al. Erythrocyte indexes, iron metabolism, and hyperhomocysteinemia in adults with cyanotic congenital cardiac disease. Am J Cardiol 2004;94:825-8.
11. Mangosongo B, Kalokola FM, Munubhi EK, et al. Iron deficiency in sickle cell anaemia patients in Dar es Salaam. Tanzania Med J 2004;19:5-8.
12. Fajolu IB, Grange OA, Renner JK, et al. Prevalence of iron deficiency in children 6-24 months in Lagos. Nig Q J Hosp Med 2007;17:97-100.
13. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001;131:568S-579S.
14. Hurrell RF, Reddy MB, Juillerat M, et al. Meat protein fractions enhance nonheme iron absorption in humans. J Nutr 2006;136:2808-12.
15. Reddy MB, Hurrell RF, Cook JD. Meat consumption in a varied diet marginally influences nonheme iron absorption in normal individuals. J Nutr 2006;136:576-81.
16. Cowin I, Emond A, Emmett P. ALSPAC Study Group. Association between composition of the diet and haemoglobin and ferritin levels in 18-month-old children. Eur J Clin Nutr 2001;55:278-86.
17. Thorisdottir AV, Ramel A, Palsson GI, et al. Iron status of one-year-olds and association with breast milk, cow's milk or formula in late infancy. Eur J Nutr 2013;52:1661-8.
18. Domellöf M, Thorsdottir I, Thorstensen K. Health effects of different dietary iron intakes: a systematic literature review for the 5th Nordic Nutrition Recommendations. Food Nutr Res 2013. doi:10.3402/fnr.v57i0.21667.
19. Thankachan P, Walczyk T, Muthayya S, et al. Iron absorption in young Indian women: the interaction of iron status with the influence of tea and ascorbic acid. Am J Clin Nutr 2008;87:881-6.
20. Kapsokefalou M, Miller DD. Lean beef and beef fat interact to enhance nonheme iron absorption in rats. J Nutr 1993;123:1429-34.
21. Cook JD, Reddy MB. Effect of ascorbic acid intake on nonheme-iron absorption from a complete diet. Am J Clin Nutr 2001;73:93-8.
22. Hallberg L, Brune M, Rossander L. The role of vitamin C in iron absorption. Int J Vitam Nutr Res Suppl 1989;30:103-8.
23. Dorea JG. Iron and copper in human milk. Nutrition 2000;16:209-20.
24. Feeley RM, Eitenmiller RR, Jones JB, et al. Copper, iron, and zinc contents of human milk at early stages of lactation. Am J Clin Nutr 1983;37:443-8.
25. Hicks PD, Zavaleta N, Chen Z. Iron deficiency, but not anemia, upregulates iron absorption in breast-fed Peruvian infants. J Nutr 2006;136:2435-8.
26. Onur CB, Sipahi T, Tavil B, et al. Diagnosing iron deficiency in cyanotic heart disease. Indian J Pediatr 2003;70:29-31.
27. Fernandes SMR, de Morais MB, Amancio OMS. Intestinal Blood Loss as an aggravating Factor of Iron Deficiency in Infants Aged 9 to 12 Months Fed Whole cow's Milk. J Clin Gastroenterol 2008;42:152-6.
28. Muñoz M, Villar I, García-Erce JA. An update on iron physiology. World J Gastroenterol 2009;15:4617-26
29. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet 2007;370:511-20.
30. Ganz T, Nemeth E. Regulation of iron acquisition and iron distribution in mammals. Biochim Biophys Acta 2006;1763:690-9.
31. el Hage Chahine JM, Pakdaman R. Transferrin, a mechanism for iron release. Eur J Biochem 1995;230:1102-10.
32. Ponka P, Lok CN. The transferrin receptor: role in health and disease. Int J Biochem Cell Biol 1999;31:1111-37.
33. Andrews NC. Forging a field: the golden age of iron biology. Blood 2008;112:219-30.
34. Baker E, Morgan EH. Iron transport. In: Brock JH, Halliday JW, Pippard MJ, et al. editors. Iron metabolism in health and disease. London: WB Saunders, 1994:63-95.
35. Jelkmann W. Regulation of erythropoietin production. J Physiol 2011;589:1251-8.
36. Frazer DM, Anderson GJ. Iron imports. I. Intestinal iron absorption and its regulation. Am J Physiol Gastrointest Liver Physiol 2005;289:G631-5.

37. Breda L, Gardenghi S, Guy E, et al. Exploring the Role of Hepcidin, an Antimicrobial and Iron Regulatory Peptide, in Increased Iron Absorption in Thalassemia. Ann N Y Acad Sci 2005;1054:417-22.
38. Ganz T, Nemeth E. Hepcidin and iron homeostasis. Biochim Biophys Acta 2012;1823:1434-43.
39. Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol 2005;18:319-32.
40. Thompson RB, Proctor SJ. Iron metabolism: Iron deficiency: Iron overload. In: A Short Textbook of Haematology 6th ed. Hong Kong: Longman Group, 1984:153-87
41. Rao R, Georgieff MK. Iron in fetal and neonatal nutrition. Semin Fetal Neonatal Med 2007;12:54-63.
42. Siddappa AM, Rao R, Long JD, et al. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. Neonatology 2007;92:73-82.
43. Beard J, deRegnier RA, Shaw MD, et al. Diagnosis of iron deficiency in infants. Lab Med 2007;38:103-8.
44. Oski FA. Iron deficiency in infancy and childhood. N Engl J Med 1993;329:190-3.
45. Domellöf M, Braegger C, Campoy C, et al. Iron Requirements of Infants and Toddlers. J Pediatr Gastroenterol Nutr 2014;58:119-29.
46. Sturgeon P. Studies of iron requirements in infants and children. Pediatrics 1954;13:107-25.
47. Mesías M, Seiquer I, Navarro MP. Iron nutrition in adolescence. Crit Rev Food Sci Nutr 2013;53:1226-37.
48. Alton I. Iron deficiency anemia, prevalence of iron deficiency and iron deficiency anemia in adolescent males and nonpregnant females. In: Stang J, Story MT. editors. Guidelines for adolescent nutrition services. Minneapolis: Center for Leadership, Education and Training in Maternal and Child Nutrition, 2005.
49. Scientific Opinion on Dietary Reference Values for iron. EFSA J 2015;13:4254.
50. Brotanek JM, Gosz J, Weitzman M, et al. Iron Deficiency in Early Childhood in the United States: Risk Factors and Racial/Ethnic Disparities. Pediatrics 2007;120:568-75.
51. Muñoz Pérez MA, García Vera C, Galve Royo F, et al. Is general screening for anemia and iron deficiency justified in nursing infants? Aten Primaria 1995;15:446-8.
52. Vendt N, Grünberg H, Leedo S, et al. Prevalence and causes of iron deficiency anemias in infants aged 9 to 12 months in Estonia. Medicina 2007;43:947-52.
53. Vieira AC, Diniz AS, Cabral PC, et al. Nutritional assessment of iron status and anemia in children under 5 years old at public daycare centers. J Pediatr (Rio J) 2007;83:370-6.
54. Kisiangani I, Mbakaya C, Makokha A, et al. Assessment of iron status among preschool children (6 to 59 months) with and without malaria in Western Province, Kenya. Pan Afr Med J 2015;21:62.
55. Hlatswayo BPS, Ntshangase S, de Villiers FPR. The effects of iron deficiency and anaemia on primary school learners' scholastic performance. S Afr J Child Health 2016;10:111-5
56. Sikosana PL, Bhebhe S, Katuli S. A prevalence survey of iron deficiency and iron deficiency anaemia in pregnant and lactating women, adult males and pre-school children in Zimbabwe. Cent Afr J Med 1998;44:297-305.
57. Nigeria Food Consumption and Nutrition Survey. 2001. Available online: http://pdf.usaid.gov/pdf_docs/PNADC880
58. Akodu OS, Disu EA, Njokanma OF, et al. Iron deficiency anaemia among apparently healthy pre-school children in Lagos, Nigeria. Afr Health Sci 2016;16:61-8.
59. Jeremiah ZA, Buseri FI, Uko EK. Iron deficiency anaemia and evaluation of the utility of iron deficiency indicators among healthy Nigerian children. Hematology 2007;12:249-53.
60. Osazuwa F, Ayo OM, Imade P. A significant association between intestinal helminth infection and anaemia burden in children in rural communities of Edo state, Nigeria. N Am J Med Sci 2011;3:30-4.
61. Ekwochi U, Odetunde O, Maduka I, et al. Iron deficiency among non-anemic under-five children in enugu, South-East, Nigeria. Ann Med Health Sci Res 2013;3:402-6.
62. Soliman AT, Al Dabbagh MM, Habboub AH, et al. Linear Growth in Children with Iron Deficiency Anemia Before and After Treatment. J Trop Pediatr 2009;55:324-7.
63. Ferlin MLS, Jorge SM, Ricco RG, et al. Prematurity anemia: effect of iron supplementation. Nutr Res 2001;21:149-58.
64. Drossos C, Thanapoulos B, Papadimitrou T, et al. Incidence of anaemia in congenital heart diseases (author's transl). Pediatr Med Chir 1981;3:309-12.
65. Torre M, Rodriguez AR, Saura-Calixto F. Effects of dietary fiber and phytic acid on mineral availability. Crit Rev Food Sci Nutr 1991;30:1-22.
66. Onimawo IA, Ukegbu PO, Asumugha VU, et al. Assessment of anaemia and iron status of school age children (aged 7-12 years) in rural communities of Abia state, Nigeria. Afr J Food Agric Nutr Dev 2010;10:2570-86.

67. Barr F, Brabin L, Agbaje S, et al. Reducing iron deficiency anaemia due to heavy menstrual blood loss in Nigerian rural adolescents. Public Health Nutr 1998;1:249-57.
68. Moschonis G, Papandreou D, Mavrogianni C, et al. Association of iron depletion with menstruation and dietary intake indices in pubertal girls: the healthy growth study. Biomed Res Int 2013;2013:423263.
69. Adinma ED, Adinma JI. Menstrual characteristics amongst south-eastern Nigerian adolescent school girls. West Afr J Med 2009;28:110-3.
70. Hotez PJ, Molyneux DH, Sylla K, et al. Tropical Anemia: One of Africa's Great Killers and a Rationale for Linking Malaria and Neglected Tropical Disease Control to Achieve a Common Goal. PLoS Negl Trop Dis 2008;2:e270.
71. Odebunmi JF, Adefioye OA, Adeyeba OA. Hookworm Infection among School Children in Vom, Plateau State, Nigeria. American-Eurasian Journal of Scientific Research 2007;2:39-42.
72. de Silva NR, Brooker S, Hotez PJ, et al. Soil-transmitted helminth infections: updating the global picture. Trends Parasitol 2003;19:547-51.
73. Stoltzfus RJ, Albonico M, Chwaya HM, et al. Hemoquant determination of hookworm-related blood loss and its role in iron deficiency in African children. Am J Trop Med Hyg 1996;55:399-404.
74. Agbolade OM, Agu NC, Adesanya OO, et al. Intestinal helminthiases and schistosomiasis among school children in an urban center and some rural communities in southwest Nigeria. Korean J Parasitol 2007;45:233-8.
75. Nmorsi OPG, Isaac C, Aashikpelokhai IS, et al. Geohelminthiasis among Nigerian preschool age children. International Journal of Medicine and Medical Sciences 2009;1:407-11.
76. Schuftan C, Ramalingaswami V, Levinson FJ. Micronutrient deficiencies and protein-energy malnutrition. Lancet 1998;351:1812.
77. Gasche C, Lomer MCE, Cavill I, et al. Iron, anaemia, and inflammatory bowel diseases. Gut 2004;53:1190-7.
78. Stevens AR, Pirzio-Biroli G, Harkins HN, et al. Iron Metabolism in Patients After Partial Gastrectomy. Ann Surg 1959;149:534-8
79. Andrews NC. Iron homeostasis: insights from genetics and animal models. Nat Rev Genet 2000;1:208-17.
80. Lozoff B, Klein NK, Nelson EC, et al. Behavior of infants with iron-deficiency anemia. Child Dev 1998;69:24-36.
81. Tay ELW, Peset A, Papaphylactou M, et al. Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. Int J Cardiol 2011;151:307-12.
82. Pourcelot E, Lénon M, Mobilia N, et al. Iron for proliferation of cell lines and hematopoietic progenitors: Nailing down the intracellular functional iron concentration. Biochim Biophys Acta 2015;1853:1596-605.
83. Arslan MT, Ozcetin M, Ozyurek R, et al. Rate of Abnormal Coagulation Test Results in Patients with Congenital Heart Disease. J Contemp Med 2011;1:6-10.
84. Ekiz C, Agaoglu L, Karakas Z, et al. The effect of iron deficiency anemia on the function of the immune system. Hematol J 2005;5:579-83.
85. Macdougall LG, Anderson R, McNab GM, et al. The immune response in iron-deficient children: Impaired cellular defense mechanisms with altered humoral components. J Pediatr 1975;86:833-43.
86. Carlson ES, Tkac I, Magid R, et al. Iron is essential for neuron development and memory function in mouse hippocampus. J Nutr 2009;139:672-9.
87. Jáuregui-Lobera I. Iron deficiency and cognitive functions. Neuropsychiatr Dis Treat 2014;10:2087-95.
88. Wang B, Zhan S, Gong T, et al. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. In: Lee L. editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd., 2013.
89. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001;131:649S-666S.
90. Haas JD, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:676S-688S.
91. Bogdanis GC. Effects of physical activity and inactivity on muscle fatigue. Front Physiol 2012;3:142.
92. Hurrell RF, Lynch SR, Trinidad TP, et al. Iron absorption in humans as influenced by bovine milk proteins. Am J Clin Nutr 1989;49:546-52.
93. Addison GM, Beamish MR, Hales CN, et al. An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. J Clin Pathol 1972;25:326-9.
94. Finch CA, Bellotti V, Stray S, et al. Plasma ferritin determination as a diagnostic tool. West J Med 1986;145:657-63.
95. Guyatt GH, Oxman AD, Ali M, et al. Laboratory diagnosis of iron-deficiency anemia: an overview. J Gen Intern Med 1992;7:145-53. Erratum in: J Gen Intern Med 1992 Jul-Aug;7(4):423.

96. Mast AE, Blinder MA, Gronowski AM, et al. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. Clin Chem 1998;44:45-51
97. Khan AS, Shah SA. Iron deficient children and significance of serum ferritin. J Pak Med Assoc 2005;55:420-3.
98. Marnell L, Mold C, Du Clos TW. C-reactive protein: Ligands, receptors and role in inflammation. Clin Immunol 2005;117:104-11.
99. Beard JL, Murray-Kolb LE, Rosales FJ, et al. Interpretation of serum ferritin concentrations as indicators of total-body iron stores in survey populations: the role of biomarkers for the acute phase response. Am J Clin Nutr 2006;84:1498-505.
100. Gershov D, Kim S, Brot N, et al. C-Reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. J Exp Med 2000;192:1353-64.
101. C-reactive concentrations as a marker of inflammation or infection for interpreting biomarkers of micronutrent status. Available online: http://apps.who.int/iris/bitstream/10665/133708/1/WHO_NMH_NHD_EPG_14.7_eng.pdf
102. McDonnell SM, Witte D. Hereditary hemochromatosis. Preventing chronic effects of this underdiagnosed disorder. Postgrad Med 1997;102:83-5, 88-91, 94.
103. Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. Therap Adv Gastroenterol 2011;4:177-84.
104. Beutler E. the red cell indices in the diagnosis of iron-deficiency anemia. Ann Intern Med 1959;50:313.
105. Aulakh R, Sohi I, Singh T, et al. Red cell distribution width (RDW) in the diagnosis of iron deficiency with microcytic hypochromic anemia. Indian J Pediatr 2009;76:265-8.
106. Bessman JD, Gilmer PR, Gardner FH. Improved classification of anemias by MCV and RDW. Am J Clin Pathol 1983;80:322-6.
107. Margolis HS, Hardison HH, Bender TR, et al. Iron deficiency in children: the relationship between pretreatment laboratory tests and subsequent hemoglobin response to iron therapy. Am J Clin Nutr 1981;34:2158-68.
108. Serdar MA, Sarici SU, Kurt I, et al. The role of erythrocyte protoporphyrin in the diagnosis of iron deficiency anemia of children. J Trop Pediatr 2000;46:323-6.
109. Siegel RM, LaGrone DH. The use of zinc protoporphyrin in screening young children for iron deficiency. Clin Pediatr (Phila) 1994;33:473-9.
110. Parsons PJ, Reilly AA, Hussain A. Observational study of erythrocyte protoporphyrin screening test for detecting low lead exposure in children: impact of lowering the blood lead action threshold. Clin Chem 1991;37:216-25.
111. Jayaranee S, Sthaneshwar P. Serum soluble transferrin receptor in hypochromic microcytic anaemia. Singapore Med J 2006;47:138-42.
112. Wish JB. Assessing Iron Status: Beyond Serum Ferritin and Transferrin Saturation. Clin J Am Soc Nephrol 2006;1:S4-8.
113. Yoon SH, Kim DS, Yu ST, et al. The usefulness of soluble transferrin receptor in the diagnosis and treatment of iron deficiency anemia in children. Korean J Pediatr 2015;58:15-9.
114. Nadeem S, Shah S, Iqbal T, et al. Serum transferrin receptor, serum ferritin and serum transferrin receptor-ferritin index in adults with iron deficiency anaemia. J Ayub Med Coll Abbottabad 2011;23:44-6.
115. Allen J, Backstrom KR, Cooper JA, et al. Measurement of soluble transferrin receptor in serum of healthy adults. Clin Chem 1998;44:35-9.
116. Phiri KS, Calis JCJ, Kachala D, et al. Improved method for assessing iron stores in the bone marrow. J Clin Pathol 2009;62:685-9.
117. Fairbanks VF. Is the peripheral blood film reliable for the diagnosis of iron deficiency anemia? Am J Clin Pathol 1971;55:447-51.
118. Zhu A, Kaneshiro M, Kaunitz JD. Evaluation and treatment of iron deficiency anemia: a gastroenterological perspective. Dig Dis Sci 2010;55:548-59.
119. Hay W, Levin M, Sondheimer JM. Haematologic disorders. In: Hay WW Jr, Hayward AR, Levin MJ, et al. Current Paediatrics Diagnosis and Treatment. 16th edition. McGraw-Hill Companies, 1903:843.
120. Perloff JK, Rosove MH, Child JS, et al. Adults with cyanotic congenital heart disease: hematologic management. Ann Intern Med 1988;109:406-13.
121. Baumgartner H, Bonhoeffer P, De Groot NMS, et al. ESC Guidelines for the management of grown-up congenital heart disease. Eur Heart J 2010;31:2915-57.

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