Chapter 1

Iron Deficiency Anaemia

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Additional information is available at the end of the chapter

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Abstract

Iron deficiency anaemia as the most common nutrition disorder has only marginal reduction globally during recent decades, with the highest burden in pregnant women and young children. Insufficient iron storage and/or excessive loss of iron are common causes of iron deficiency anaemia. Therefore, understanding the complexity of the regulatory network required to maintain iron homeostasis and identifying the functional variants associated with iron metabolism should be fundamental and crucial to control and treat the iron deficiency anaemia. Sensitive and inexpensive measures to distinguish iron deficiency anaemia from the other kinds of anaemia should be developed for precise treatment. Original disease treatments combined with oral or intravenous iron therapy are key approaches in clinical practices. The integrated, multifactorial and multi-sectoral approach with food-based strategy and iron supplementation as the leading public health inventions is required to achieve iron deficiency anaemia control target. This chapter will focus on the advanced knowledge associated with iron metabolism, disease burden and health consequences of iron deficiency anaemia in different life course, newly parameters development in the diagnosis of iron deficiency anaemia, therapy choice in clinical practice and public health strategies to reduce iron deficiencies in high-burden areas.

Keywords: iron deficiency, iron deficiency anaemia, iron metabolism, hepcidin, iron supplementation, food fortification, ferritin, transferrin saturation

1. Introduction

As the most common nutrition disorder in both the developed and developing world, affecting more than two billion people, iron deficiency anaemia is recognized not only a clinical condition but also a serious public health issue, with pregnancy women and pre-school-age children at the highest risk [1–5]. The annual economic loss because of iron deficiency anaemia

in 10 developing countries was estimated about 4% of gross domestic product [2]. Despite considerable economic and scientific advancement during recent decades, there has been only marginal reduction in the global prevalence of anaemia with more than 50% of cases caused by iron deficiency [2, 4].

This chapter will summarize the advanced knowledge associated with iron metabolism, health burden, newly parameters development in the diagnosis of iron deficiency anaemia, therapy choice and public health strategies to reduce iron deficiencies in high burden areas.

2. Iron metabolism and hepcidin, potential regulators associated with iron metabolism

2.1. Iron metabolism pathway

The absorption of dietary iron is a variable and dynamic process, depending on the two primary forms of haem and non-haem iron. Haem is a component of haemoglobin and myoglobin and haem iron is complexed as ferrous iron (Fe^{2+}) in the haem form, which is present in animal tissues such as meat, poultry, fish and shellfish [6]. Most of non-haem iron (Fe^{3+} or ferric iron) is provided by the vegetarian diet (black tea, cacao, cereals, dried fruit etc.). Although haem iron could represent ~40% of animal tissue iron and be better absorbed, it only accounts for less than 15% of total iron intake [7, 8]. In spite of the low absorption rate, the majority of the dietary iron is obtained from non-haem iron. Studies have confirmed that animal tissues (meat, poultry and fish) and vitamin C and organic acids could enhance iron absorption, while high intake of phytates, tannins, calcium and zinc may tend to inhibit the absorption of iron [9, 10].

It is currently well known that most of dietary iron is absorbed by enterocytes of the duodenal lining. The first step to absorb iron is that the insoluble ferric iron (Fe^{3+}) has to be converted into the ferrous form (Fe^{2+}) by a brush border ferric reductase (duodenal cytochrome B, DCYTB) in the duodenum and upper jejunum. The ferrous iron is then transferred across the enterocyte membrane into the cell by divalent metal transporter 1 (DMT1). Afterwards, the iron is stored in these intestinal lining cells as ferritin which is accomplished by Fe^{3+} binding to apoferritin, or could be released into the body via the only known iron exporter ferroportin. Cooperated with either of the ferroxidases hephaestin (enterocytes) or ceruloplasmin (other cell types) that facilitate iron extraction from the ferroportin channel, ferroportin at the basolateral membrane transports Fe^{2+} that is subsequently loaded onto plasma transferrin (Tf) [11].

In blood, plasma iron-loaded transferrin (Tf-Fe^{2+}) transports iron to all cells in a transferrin receptor-mediated endocytotic process [6]. Iron-loaded Tf binds to transferrin receptor 1 (TfR1), and their complex internalizes and enters into cells, wherein iron releases by pH-dependent mechanism. As it provides most of the iron required for various functions of an organism, plasma transferrin plays a crucial role in iron metabolism. TfR1 is highly expressed on haemoglobin-synthesizing erythroblasts. Most of plasma iron is used by bone marrow to synthesize haemoglobin in red blood precursors. Several other cell types, such as enterocytes, hepato-

cytes and reticuloendothelial macrophages, are considered to be major iron storage sites. Iron release from or store in enterocytes, hepatocytes and macrophages depends on plasma iron levels, to meet the physiological demand. In a review published in Cell, Hentze et al. carefully discussed these mechanisms and summarized them in a single figure (**Figure 1**) [11].

2.2. Hepcidin and potential regulators associated with iron metabolism

In the human body, the iron homeostasis is tightly regulated to avoid both deficiency and excess. Hepcidin is a core regulator of the entry of iron into the circulation, which is a peptide hormone synthesized mainly in the liver, which was discovered in 2000. Previous studies have confirmed that hepcidin is not liver specific but also expressed in other tissues, such as the kidney, heart and lungs [12]. Hepcidin is first synthetized as an 84-amino acid (aa) prepropeptide, and then further processed into 60–64-aa prohepcidin. Finally, mature and biologically active 25-aa hepcidin is produced by truncating the proregion from prohormon convertase furin [13]. When the hepcidin level is abnormally high, serum iron falls due to iron trapping in macrophages and liver cells, and decreased gut iron absorption by reducing iron transport across the gut mucosa (enterocytes). In the instances, it is clear that anaemia will develop due

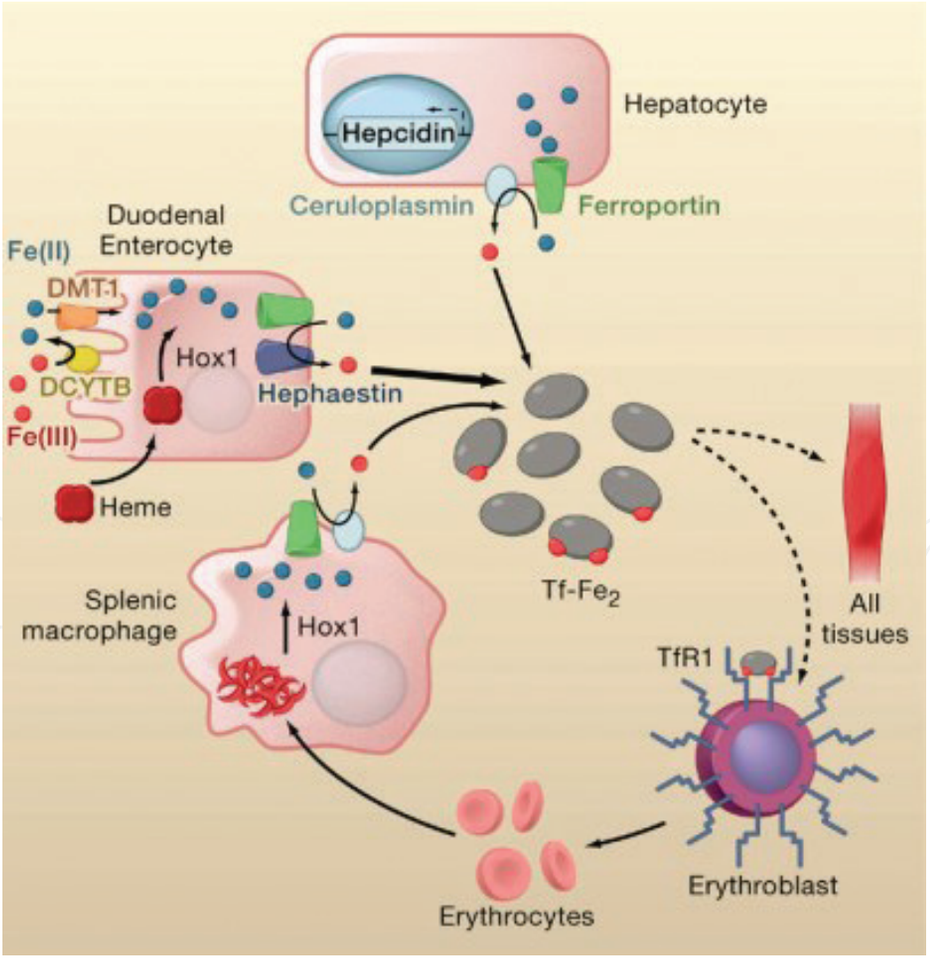

Figure 1. Mechanism of systemic iron metabolism. Derived from: Hentze et al. [11].

to lack of inadequate amount of serum iron being available for developing red cells. In the state in which the hepcidin level is abnormally low, on the contrary, iron overload occurs due to increased iron efflux from storage and gut iron absorption. Tandara et al. have discussed the mechanisms of hepcidin regulating iron homeostasis and summarized them in a single figure (**Figure 2**) [14].

So far, at least four major separate pathways in hepcidin regulation have been confirmed, such as regulation by iron status; dietary iron and iron stores; regulation by inflammation; regulation by hypoxia/anaemia and regulation by erythroid factors [15, 16]. These different regulatory inputs are integrated transcriptionally.

At the molecular level, it is not still completely clear that iron stores regulate hepcidin synthesis, but haemojuvelin (HJV), haemochromatosis protein (HFE) and transferrin receptor 2 (TfR2) have been proven to be upstream regulators of hepcidin. HFE acts as a bimodal switch between two sensors of the concentration of Tf-Fe^{2+}, TfR1 and TfR2, on the plasma membrane of hepatocytes [17]. HFE binds the ubiquitously expressed TfR1 at a site that overlaps the transferrin binding domain, and Tf-Fe^{2+} thus competes with HFE binding to TfR1. By contrast, TfR2 can bind both HFE and Tf-Fe^{2+} simultaneously [18]. Although HFE and TfR2 clearly contribute to hepcidin activation, the bone morphogenetic protein (BMP) signalling pathway is quantitatively the most critical. It has been proposed that HJV acts as co-receptor that binds to bone morphogenetic protein (BMP) ligands and BMP type I and type II receptors on the cell surface. This complex (HJV-BMP ligand-BMP receptors) consequently induces an intracellular BMP signalling pathway which in turn activates the SMAD4 signalling pathway.

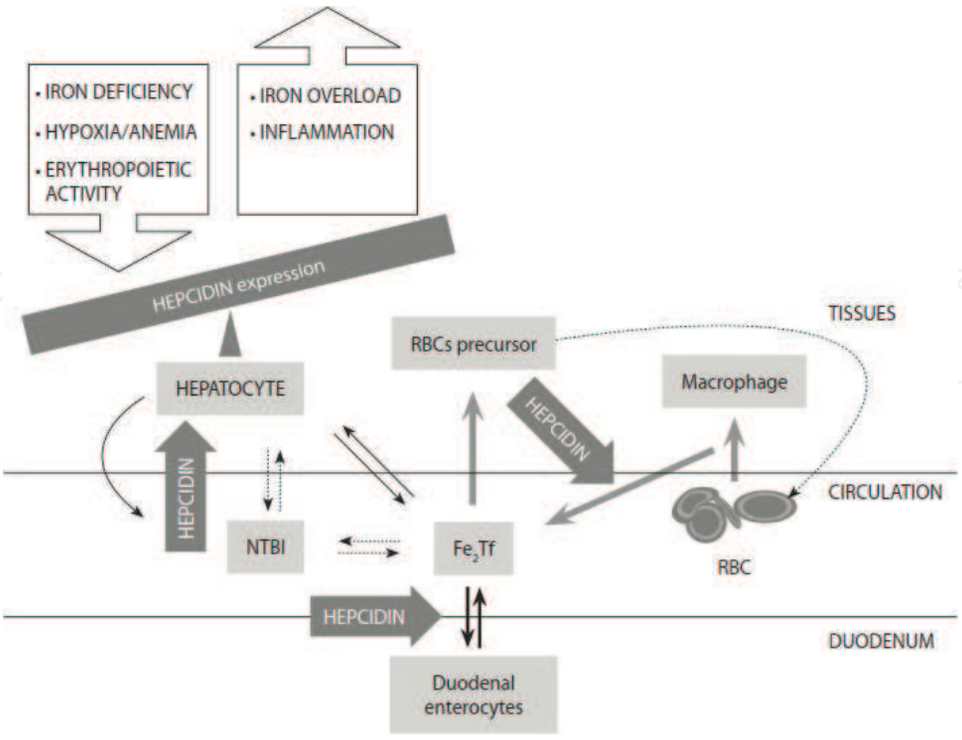

Figure 2. Maintenance of systemic iron homeostasis regulated by hepcidin. Derived from: Tandara and Salamunic [14].

The drosophila mothers against decapentaplegic (SMAD) complex translocate to nucleus and directly increases hepcidin gene transcription [19–21]. BMP/SMAD signalling cascade of HJV is important for basal regulation of hepcidin transcription [22]. Thus, HJV is central for hepcidin expression, and the point of convergence of multiple regulatory inputs. Transmembrane protease, serine 6 (encoded by the TMPRSS6 gene) has been identified as an inhibitor of hepcidin activation by cleaving membrane HJV under normal conditions [11, 23, 24]. If TMPRSS6 gene mutations occur, hepcidin levels increase and result in insufficient iron absorption [25].

Hepcidin synthesis is also dramatically induced by infection and inflammation. In particular, interleukin 6 (IL-6) is the central inducer of hepcidin synthesis during inflammation [14, 26, 27], which acts on hepatocytes and stimulates hepcidin production through signal transducer and activators of transcription (STAT3) signalling pathway [28]. Hepcidin mediated by IL-6 often results in cellular iron retention and hypoferremia, thus anaemia develops due to restricted iron availability in haemoglobin synthesis [14]. In the condition in which anaemia/hypoxia develops, hepcidin gene expression decreases along with the increase of erythropoietin expression. Tissue hypoxia increased erythropoiesis and further suppress hepcidin expression. Several bone marrow-derivated signal molecules that regulate the process of erythropoiesis mediating hepcidin have been found, including growth differentiation factor 15 (GDF15), twisted gastrulation protein homologue 1 (TWSG1), hypoxia inducible factors (HIF) and hormone erytropoetin [29–31]. Furthermore, iron responsive element (IRE)/iron responsive proteins (IRP) system also tightly regulates cellular iron uptake and storage and coordinatively keeps cell iron homeostasis.

Iron responsive proteins 1 (IRP1) and 2 (IRP2) in cytoplasmic can sense the level of iron in transit pool and bind specifically to RNA stem-loops (iron responsive element, IRE), and post-transcriptionally modify the expression of proteins involved in iron metabolism [14].

2.3. Genetic variants associated with iron deficiency anaemia from genome-wide association studies

The iron metabolism is tightly and precisely regulated by several interacting iron-binding factors. The development of genome-wide association studies (GWAS) has confirmed that the mutation of genes in iron metabolism, like transferrin, transferring receptors, matriptase-2, hepcidin, may determine the phenotypic variation in iron homeostasis between individuals [32]. Mutations in the gene (HAMP) encoding hepcidin can increase iron absorption and lead to juvenile haemochromatosis [33]. Due to the same regulatory pathway, mutations in these genes, including those encoding HJV, HFE and TfR2, clearly result in iron loading syndromes [32].

However, limited information is available about gene variants associated with iron deficiency anaemia. The inherited disorders of iron metabolism played an important role in iron deficiency anaemia. For example, in two association studies of iron metabolism disorders, the SNP rs235756 in BMP2 brings about the decrease of serum ferritin level [34, 35]. Mutations in the DMT1 gene occur in patients with microcytic anaemia, low serum ferritin and liver iron overload [36]. Studies also showed that mutations in the matriptase gene (TMPRSS6) cause iron-refractory iron deficiency anaemia [11]. It has been suggested that the mutation G277S of the TF gene alone does not affect iron absorption in iron deficient women and a

combination of polymorphisms may be involved in iron metabolism [32, 37]. The recently determined mutation in the glutaredoxin 5 (GLRX5) gene leads to microcytic, hypochromic anaemia with iron overload and the presence of ringed sideroblasts in the bone marrow upon Perl's staining [38]. According to the European Network of Rare Congenital Anaemia, 62 rare anaemia subtypes are shown recently, including haemolytic anaemia and anaemia arising from mutations in genes that control duodenal iron absorption (e.g. SLC11A2), systemic iron homoeostasis (e.g. TMPRSS6) or erythroid iron absorption and utilization [8]. The genetic forms of sideroblastic anaemia such as mutations in glutaredoxin 5, aminolevulinic acid synthetase 2 and ABCB7 genes provide the updated information.

3. Disease burden and adverse health consequences of iron deficiency anaemia in different life courses

3.1. Disease burden

WHO estimated that the highest prevalence of anaemia was in the population of pre-school-aged children, pregnant and non-pregnant women, but lower for school-aged children, men and the elderly [8]. Data in 2010 showed more than 2.2 billion people were affected by anaemia and global prevalence of anaemia was 32.9%, and iron deficiency was reported as the most common cause of anaemia [4]. WHO estimates that 50% of cases are due to iron deficiency, and regional disparities exist [4, 39]. In detail, results from studies conducted in the United States reported the prevalence of iron deficiency ranges from 4.5 to 18.0%. But the proportion of anaemia caused by iron deficiency in central Asia, south Asia and Andean Latin America were 64.7, 54.8 and 62.3%, respectively [8, 40].

In 2010, global anaemia causing 68.36 million years lived with disability (8.8% of total for all conditions) [4]. The distribution of anaemia prevalence was unbalanced across regions, central and West Africa and south Asia were the highest anaemia prevalence regions in middle- and low-income areas, and high-income areas had lowest anaemia prevalence (**Table 1**). In addition, this trend was similar among the higher risk population of anaemia (children under 5 years, pregnant women from 15 to 49 years, non-pregnant women from 15 to 49 years) [5].

3.2. Consequences of iron deficiency anaemia

The population of pre-school-aged children, pregnant and non-pregnant women was the highest prevalence of anaemia [8], the consequences of iron deficiency anaemia among pre-school-aged children, pregnant and non-pregnant women should be emphasized.

The consequences of iron deficiency of pregnant women are multiple. First, iron deficiency during pregnancy was significantly associated with increasing perinatal mortality. Evidence from six observational studies showed a combined odds ratio of 0.75 (association between anaemia and maternal mortality) associated with a 10 g/L increase in haemoglobin [41, 42]. In addition, the combined OR was 0.72 for perinatal mortality associated with a 10 g/L increase in haemoglobin [41, 42]. Another study (RCT) conducted in China found prenatal supplementation with iron-folic acid was associated with a reduction in early neonatal mortality compared with

	Prevalence of anaemia (%)		
	Children (<5 years)	**Non-pregnant women (15–49 years)**	**Pregnant women (15–49 years)**
Middle- and low-income areas			
Central and west Africa	71	48	56
East Africa	55	28	36
South Africa	46	28	31
South Asia	58	47	52
East and southeast Asia	25	21	25
Central Asia, Middle East and north Africa	38	33	31
Oceania	43	28	36
Andean and central Latin America and Caribbean	33	19	27
Southern and tropical Latin America	23	18	31
Central and eastern Europe	26	22	24
High-income areas	11	16	22

Table 1. Distribution of anaemia prevalence in middle- and low-income areas by different population.

prenatal folic acid supplementation only [43]. Second, many studies have determinate the association between iron deficiency anaemia and pre-term and low birth weight [44–46]. Evidence from a retrospective population-based study showed maternal anaemia during pregnancy was risk factor for pre-term delivery (OR = 1.2) and low birth weight (OR = 1.1) [44]. Results from a meta-analysis reported that analysis of cohort studies showed a higher risk of pre-term birth (OR = 1.21) and low birth weight (OR = 1.29) with anaemia in the first or second trimester of pregnancy [45]. Significant association between prenatal iron deficiency anaemia and low birth weight was also found in low and middle-income counties [42]. Third, previous study reported that the fetal brain could be at risk when iron supply does not meet iron demand [47]. In addition, several observational studies reported the reverse effect of iron deficiency during pregnancy on intellectual development and motor development of children [48, 49]. One longitudinal study conducted in China found that prenatal iron deficiency anaemia in the third trimester is significantly associated with mental development of children [48]. Another prospective study conducted in Vietnam reported that prenatal iron deficiency anaemia hasadverse effects on child cognitive development [49].

Iron deficiency is more likely in women of reproductive age because of menstrual blood loss [50]. Results from some RCTs showed that iron improves cognitive ability, physical performance and mood in iron-depleted non-anaemia women [51–53]. In detail, a study found iron supplementation improved physical performance and mood of female soldiers [51]. One study conducted in the United States reported iron status was significantly associated with cognitive

ability in women of reproductive age. The iron-sufficient women completed the cognitive tasks faster than women with iron deficiency anaemia, and got higher accuracy of cognitive function over a broad range of tasks [52]. Another study also reported the negative effect of maternal anaemia diagnosed postpartum on language comprehension of children [54].

Children under 5 years with iron deficiency anaemia test lower in social-emotional, cognitive and motor development than control group children [47, 55–59]. For motor development, an observational study conducted in African-America found poorer motor function in iron deficiency infants [56]. Another longitudinal study found lower motor scores in infants with chronic iron deficiency anaemia. In addition, long-term effect of chronic iron deficiency anaemia in infancy on motor development in early adolescence was exist, and even iron treatment at the age of 12–23 months did not prevent long-term effect of iron deficiency in infancy on motor development [57]. A study conducted in the United States showed positive effect of iron status of infants at 9 months on gross motor development and motor coordination/sequencing [58]. For cognitive development, a meta-analysis estimated that a 10 g/L haemoglobin increase was significantly associated with a 1.73 increase in IQ tests [41]. Another study found children with iron deficiency anaemia at 54–60 months age had lower score for verbal reasoning test compared to non-anaemia children [59].

Iron deficiency anaemia is prevalent in the elderly, particularly after the age of 80 [60]. Chronic blood loss, micronutrient-related anaemia and renal disease are important mechanisms for low haemoglobin level [61]. A cohort study conducted in Taiwan reported iron deficiency was significantly associated with cardiovascular disease and all-cause mortality in elderly [62]. A prospective study conducted in Korea found anaemia was associated with physical functioning impairment and instrumental activities of daily living in elderly [63]. A Norwegian prospective study reported the significant association between low iron status and increasing risk of death from ischaemic heart disease [64]. Result from a cross-sectional study conducted in England reported the significant relationship between iron status and symptoms of depression [65]. Many studies have extensively investigated the association between iron deficiency and productivity [42, 66], because the role of iron in oxygen transport to muscles and other tissues, and in other metabolic pathways by which iron deficiency can cause aerobic work capacity reduction [42]. Previous studies reported the positive effect of iron supplementation on work productivity of female cotton-mill workers in China, female tea-plantation workers in Sri Lanka and rubber plantation workers in Indonesia [66, 67]. Iron deficiency would cause work performance reduction and has substantial economic consequences accordingly in countries in which physical labour is prevalent [42, 67].

In summary, the consequences of iron deficiency anaemia in different populations were multiple. For pregnant women with iron deficiency anaemia, the effects were mainly on perinatal mortality, pre-term birth, low birth weight, offspring intellectual development and motor development. For non-pregnant women, the effects were mainly on cognitive ability, physical performance and mood. For infant, the effects were mainly focus on further social-emotional, cognitive and motor development. For elderly, the effects were mostly on cardiovascular disease, all-cause mortality, physical functioning impairment, instrumental activities of daily living, increasing risk of death from ischaemic heart disease and symptoms of depression. The effect of iron deficiency in adults on work productivity was also reported.

4. Standard diagnosis criteria of iron deficiency anaemia

At the population level, haemoglobin concentration is the most reliable indicator of anaemia. Meanwhile, measurement of haemoglobin concentration is frequently used as a proxy indicator of iron deficiency, because measurement of haemoglobin concentration is relatively inexpensive and easy. According to the criterion of World Health Organization, an adult man is considered as anaemic when the haemoglobin concentration is less than 130 g/L, whereas an adult woman is deemed anaemic when her haemoglobin concentration is less than 120 g/L, and this cut-off should be lowered to 110 g/L if the woman is in pregnancy. This cut-off threshold is 115 g/L between 5 and 11 years, and 110 g/L under 5 years (**Table 2**) [8, 68].

Patients with severe anaemia can be usually detected by clinical examination such as pallor of eyelids, tongue, palms and nail beds [8, 39, 69]. In poor areas where laboratory testing is not feasible, clinical examination should be regularly used to monitor women and children. As the frequency of conjunctivitis caused redness even in anaemia patients, palm pallor is preferred to eyelid pallor as a clinical sign for diagnosis of young children. But, clinical measures are more subjective and have more room for error accordingly compare to haemoglobin concentration [39].

Because of the complex diagnosis of iron deficiency, use of several indicators in combination could be better for us to assess iron deficiency [8]. First, red cell indices on full blood counts show a reduced mean cell volume, which corresponds to microcytosis, and a reduced mean cell haemoglobin, corresponding to hypochromia. But the thresholds are not commonly agreed [70]. Second, mean cell haemoglobin and volume are widely available, sensitive and inexpensive measures, but these indictors become abnormal only in longstanding iron deficiency. Moreover, mean cell volume could be normal if combined with nutrient deficiency [71].

Serum ferritin measurement is the most sensitive and specific test and widely used to identify iron deficiency [8, 39, 72], but it is spuriously elevate in malignancy, inflammatory conditions or liver disease. Serum ferritin below the cut-off of 15 μg/L in patients older than 5 years could be diagnosed as iron deficiency [72]. However, results from previous study indicated that if the cut-off of ferritin level increase to 30 μg/L, the diagnostic accuracy would be improved. The sensitivity would increase from 25 to 92% according, compared with the 12 μg/L (cut-off value), and specificity was unchanged (98%) [73]. For the patients with malignant disease, acute and chronic inflammatory disorders and liver disease, cut-off value equal or larger than 50 μg/L could still be iron deficient [4, 72]. Results from previous studies suggested cut-off of

Children (0–14 years)	Hb threshold (g/L)	Adult (≥15 years)	Hb threshold (g/L)
0.5–4 years	110	Non-pregnant women	120
5–11 years	115	Pregnant women	110
12–14 years	120	Men	130

Table 2. Haemoglobin threshold in different population.

100 μg/L for patients with chronic kidney disease [74], and suggested increasing cut-off to 200 μg/L in case of haemodialysis [75].

A low transferrin saturation level (less than 16%) also strongly indicates iron deficiency (iron supply insufficient to support normal erythropoiesis), but the threshold will increase to 20% in patients with inflammation. Because the serum iron will reduce with the increasing of total iron-binding capacity if the patients with iron deficiency, and finally result in reduction in transferrin saturation [8, 39].

Serum soluble transferrin receptor (sTfR) is another useful biomarker in diagnosis of iron deficiency, and is not influenced by inflammation. The synthesis of transferrin receptors will increase if patients with iron deficiency and lead to an increase in sTfR accordingly [73]. But there are some limitations when using sTfR to determine iron deficiency. One of the limitations is that if the patients with disorders associated with increased erythropoiesis (haemolytic anaemia, chronic lymphocytic leukaemia), concentrations of sTfR can be raised accordingly. Another limitation is that the guidelines are only published in the UK, but standardized cut-offs worldwide are still absent [75].

Recently, bone marrow aspiration is another option to assess iron stores, and thought of as the highly specific and not affected by inflammation for diagnosis of iron deficiency. But it is not used frequently only when other tests are conflicting or negative. As it is expensive and affected by recombinant human erythropoietin, it is uncomfortable for the patients [8, 39].

For diagnosis of iron deficiency anaemia, it is important to consider the whole picture rather than relying on single test results when determining the iron deficiency. The diagnosis of iron deficiency for the patients with inflammation is challenging and also cannot be determined on the basis of a single test result.

5. Therapy choice in clinical practices

The goals of treating iron deficiency anaemia are to treat its underlying cause and supply enough iron to normalize haemoglobin concentrations and replenish iron stores. Considering its cause and severity of iron deficiency anaemia, treatments may include dietary changes and supplements, medicines and surgery. Severe iron deficiency anaemia may require a blood transfusion, iron injections or intravenous (IV) iron therapy, which may need to be addressed in a hospital.

5.1. Oral iron therapy

Medical care starts with establishing the diagnosis and reason for the iron deficiency. Iron supplementation is used to prevent iron deficiency anaemia in at-risk populations, or to treat patients with proven disease. Treatment with oral iron supplements is simple, inexpensive and a relatively effective way of treating iron deficient conditions. WHO has recommended daily iron supplementation with 60 mg of elemental iron to prevent iron deficiency in menstruating adolescent girls and women, and 2 mg/kg daily in children aged 0–5 years and 30 mg daily in children aged 5–12 years [76–78]. In general, four common iron preparations

are often adopted, i.e. ferrous sulphate, ferrous sulphate exsiccated, ferrous gluconate and ferrous fumarate. When side effects occur (dark stools, constipation, stomach irritation and heartburn), iron can be taken with meals, but doing so decreases absorption to 40% [8]. The best source of iron is red meat, especially beef and liver. The body tends to absorb iron from meat better than iron from non-meat foods. However, some non-meat foods can also help you raise your iron levels. Furthermore, Vitamin C helps the body absorb iron, whose good sources are vegetables and fruits, especially citrus fruits.

In most patients, the iron deficiency should be treated with oral iron therapy, and the underlying etiology should be corrected so the deficiency does not recur. However, there are cases that iron supplements are inappropriate to patients, for example, those who have a microcytic iron-overloading disorder (e.g. thalassemia and sideroblastic anaemia).Therefore, it may be necessary to identify the etiology of the anaemia, such as gene mutation related to iron metabolism, occult blood loss undetected with chemical testing of stool specimens; for identification of a source of bleeding that requires endoscopic examinations or angiography; or for treatment of an underlying major illness (e.g. neoplasia and ulcerative colitis).

5.2. Intravenous (IV) iron therapy

The British Society of Gastroenterology guidelines suggest that all patients require iron supplementation and that parenteral iron can be used if oral preparations are not well tolerated. For therapeutic iron supplementation, treatment with IV iron in some clinical situations could present some advantages over oral iron, such as faster and higher increases of haemoglobin (Hb) levels and body iron stores. Friedrisch et al. suggest the main clinical indications for IV iron treatment, which contains post-gastrectomy/bariatric surgery, anaemia of chronic kidney disease, intestinal malabsorption syndromes, anaemia associated to inflammatory diseases, inflammatory bowel diseases, anaemia of cancer, intolerance to oral iron or non-compliance to an oral regimen, iron-refractory iron deficiency anaemias and so on [79].

Recently, three new IV iron compounds (ferric carboxymaltose [FCM], iron isomaltoside 1000 [Monofer®] and Ferumoxytol [FeraHeme®]) have been released for clinical use in patients with Iron Deficiency Anaemia (IDA) [80–82]. Do not administer IV iron therapy to patients who should be treated with oral iron, as anaphylaxis may result. Uncommonly, post-menopausal women are unresponsive to iron supplementation, including parenteral iron, because they have primary defective iron reutilization due to androgen deficiency. This condition responds only to androgen replacement. Danazol is a reasonable choice for these patients, as it is less masculinizing.

6. Public health strategies to reduce iron deficiencies in high-burden areas

Although the global anaemia burden has been actually improved and age-standardized prevalence of anaemia was down from 33.3% in 1990 to 27% in 2013, according to the analysis based on 188 countries, 20 age groups, the total population with anaemia increased from 1.83 billion in

1990 to 1.93 billion in 2013 [2]. Developing countries account for more than 89% of the burden, with the greatest prevalence in central and western sub-Saharan African and greatest number of case in South Asia. Children with the highest burden of anaemia consistently have improved less than adults [2]. Iron deficiency anaemia is the dominant cause of anaemia globally and in most populations, accounting for 62.6% of the total of anaemia cases, and IDA was also the greatest causes of anaemia-related disability with 60% of total years lived with disability (YLD) [2, 83]. Monitoring and controlling IDA has been the crucial driver of reduced global anaemia burden since 1990 [2, 3]. Individual-level and population-level interventions targeted iron deficiency anaemia were implemented and the efficacy and effectiveness of these intervention strategies were also evaluated with a priority in high-risk, high-burden population such as preschool-children and pregnant women. Especially, further actions on iron deficiency anaemia prevention and treatment are highly required in order to reach the global nutrition targets of a 50% reduction of anaemia in women of reproductive age by 2025 [84].

The World Health Organization (WHO) has published a series of guidelines that support policies for the prevention and control of iron deficiency anaemia targeted on population in highest burden of IDA [78, 85–88]. The most common cause of iron deficiency anaemia in high-burden areas is prolonged negative iron balance, caused by inadequate dietary iron intake or absorption, increased needs for iron during pregnancy or growth periods, and increased iron losses as a result of menstruation and parasitic infections [84].

Public health strategies to prevent and control iron deficiency anaemia include improvements in dietary diversity; food fortification with iron, folic acid and other micronutrients; distribution of iron-containing supplements. The efficacy and effectiveness of different strategies were evaluated, based on the evidence from the community-based large-scale intervention studies.

6.1. Improvements in dietary diversity

Health education about food and nutrition such as dietary counselling is one of three recommended intervention strategies to decrease the IDA burden. Although dietary counselling commonly resulted in a better dietary intake profile in targeted subpopulation, such as breastfed for longer and had non-human milk introduced later among infant, consumed more meat and had diets with better iron bioavailability in relation to the children or pregnant women; however, this kind of interventions was not sufficient to prevent occurrence of anaemia, ID or IDA in population with high IDA burden [89–91].

6.2. Food fortification with iron

Food fortification as one of the leading public health interventions was recommended to prevent and control micronutrient deficiencies including iron deficiency and iron deficiency anaemia by adding the micronutrients containing iron to processed food vehicles, or home fortification. The choice of processed food vehicles varies widely by region and context, depending on the subpopulation targeted, food consumption and acceptability, food availability and sustainability, as well as the financial and technical concerns. The staple food is the

most commonly used as vehicle of fortification, in addition, milk powder, beverages, biscuits, the most commonly used sauce, such as soy sauce, drink and water, can also be used as fortified foods [92–104].

More than 80 countries have mandated fortification of wheat and maize flour with at least iron and folic acid in 2015 [93]. A review of efficacy and effectiveness of flour fortification programmes on iron status and anaemia found that flour fortification is associated with consistent reductions in low ferritin prevalence in women, but not in children. Further, a reduction in anaemia prevalence was observed in only one-third of the subgroups of women and children studied [93].

A recently published review on the effect of multiple micro-nutrients (MMN) containing iron-fortified non-dairy beverages among school-aged children in low-middle-income counties showed a clear benefit of MMN fortified non-dairy beverages intervention from 8 weeks to 6 months on anaemia (42% reduction in prevalence), iron deficiency (66% reduction in prevalence) and iron deficiency anaemia (83% reduction in prevalence) compared to iso-caloric controls [99].

Biscuits have been identified to be an ideal vehicle for fortification for school-aged children due to its convenience with regard to storage, distribution and long shelf life. A nutrition intervention trial conducted in India showed that iron-fortified biscuits led to a significant enhancement in haemoglobin status of anaemic school children in rural areas [98]. Another study showed that maize porridge fortified with multi-micronutrient powder contained low dose, highly bioavailable iron can reduce the prevalence of IDA in pre-school children [102]. Home fortification with multi-micronutrient powder with low dosages of bioavailable iron may therefore be a promising strategy to improve iron status among children.

A study involved 3029 students of the boarding schools in the 27 provinces in China showed that iron-fortified soy sauce could be effective for the improvement of the haemoglobin level and reduce anaemia prevalence of boarding school students [97].

The beneficial of fortified complementary feeding supplement on the growth of young children aged 6–23 months have been confirmed by a large number of nutrition intervention programme conducted in population with low socio-economic status. Furthermore, the risk of anaemia among young children was significantly reduced after the daily fortified complementary feeding supplement introduced to infant diet in rural area, which implied that fortified complementary feeding supplement could be a best intervention strategy target on young children anaemia [105–112].

The successful implementation of food fortification programme commonly requires government-driven and multi-stakeholder participation, which has also become an obstacle to its sustainability.

6.3. Iron supplementation

Iron supplementation, provided in capsule, tablet or syrup form, is most suitable in contexts where certain subpopulation may not be reached, or when iron requirements may not be met by other intervention strategies.

A series of systematic reviews based on randomized control trial have been carried out to assess the effect of daily iron supplementation on haematologic and non-haematologic outcomes in high-burden subpopulations [113–119]. In children aged 4–23 months, daily iron supplementation effectively reduces anaemia by 39%, iron deficiency by 70% and iron deficiency anaemia by 86% [117]. In 2–5-year-old children, daily iron supplementation increases haemoglobin and ferritin; however, the evidence on the effect of iron supplementation on anaemia, iron deficiency and iron deficiency anaemia is limited [114]. In primary-school-aged children (5–12-year old), iron supplementation reduced the risk of anaemia by 50% and the risk of iron deficiency by 79% [116, 118].

The World Health Organization has published a series of iron supplementation guidelines, which provides global, evidence-based recommendations on the daily or intermittent use of iron supplements for high-burden subpopulation as a public health intervention to improve iron status and reduce the risk of iron deficiency anaemia in childhood, adolescence, pregnancy and lactation [85–88]. WHO suggested iron supplementation scheme targeted on variety of subpopulation was summarized in **Table 3**. In summary, the establishment of effective strategies, an integrated, multifactorial and multi-sectoral approach, is required to achieve IDA control target [84].

Target group	Supplementation composition	Supplement form	Frequency	Duration	Settings
Anaemic pregnant women	120 mg of elemental iron and 400 μg folic acid		Daily	Until women's Hb concentration rises to normal, then followed by the standard daily antenatal iron dose	Where prevalence of anaemia in pregnant women is 40% or higher
Non-anaemic pregnant women	30–60 mg of elemental iron and 400 μg folic acid		Daily	During pregnancy	Where prevalence of anaemia in pregnant women is 40% or higher
Non-anaemic pregnant women	120 mg of elemental iron and 2800 μg of folic acid		weekly	During pregnancy	Where anaemia prevalence among pregnant women is less than 20%
Postpartum women	iron supplementation, alone or combination with folic acid			6–12 weeks following delivery	Where gestational anaemia is of public health concern
Infants and young children aged 6–23 months	10–12.5 mg elemental iron	Drops/syrups	Daily	Three consecutive months in a year	Where the prevalence of anaemia in infants and young children is 40% or higher

Target group	Supplementation composition	Supplement form	Frequency	Duration	Settings
Pre-school-age children (24–59 months of age)	30 mg elemental iron	Drops/syrups/ tablets	Daily	Three consecutive months in a year	Where the prevalence of anaemia in infants and young children is 40% or higher
Pre-school-age children (24–59 months of age)	25 mg of elemental iron	Drops/syrups	Weekly	3 months of supplementation followed by 3 months of no supplementation after which the provision of supplements should restart	Where the prevalence of anaemia in pre-school or school-age children is 20% or higher
School-age children (5–12 years of age)	30–60 mg elemental iron	Tablets or capsules	Daily	Three consecutive months in a year	Where the prevalence of anaemia in infants and young children is 40% or higher
School-age children (5–12 years of age)	45 mg of elemental iron	Drops/syrups	Weekly	3 months of supplementation followed by 3 months of no supplementation after which the provision of supplements should restart	Where the prevalence of anaemia in pre-school or school-age children is 20% or higher
Menstruating adult women and adolescent girls (non-pregnant females in the reproductive age group)	30–60 mg elemental iron	Tablets	Daily	Three consecutive months in a year	Where the prevalence of anaemia in menstruating adult women and adolescent girls is 40% or higher

Table 3. WHO suggested scheme daily iron supplementation in different subpopulation.

7. Conclusion—key results

Considering the complexity of the regulatory network required to maintain iron homeostasis, future fine-mapping studies, including rare and uncommon variants, and functional studies should be undertaken to better characterize loci and to identify the functional variants directly influencing iron levels in iron deficiency anaemia.

New parameters which can give useful information about the iron availability for erythropoiesis and the erythropoietic activity of the bone marrow, and with stable to inflammatory conditions, should be developed for the early detection of iron deficiency, monitoring effect of iron supplementation and treatment, and discrimination the types of anaemia.

Intravenous iron formulation for rapid and high-dose replenishment of depleted iron stores with very low immunogenic potential is ideal alternative choice for the treatment of iron deficiency anaemia. Iron supplementation and fortification, as two key public health strategies in reducing the iron deficiency anaemia burden, should be selected in terms of the certain population subgroups targeted. The establishment of effective strategies, an integrated, multifactorial and multi-sectoral approach, is required to achieve IDA control target.

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