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Iron deficiency anaemia: with the conclusion of a need for iron reader

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Abstract. In our bloodstream, there are plenty of red blood cells (RBC), which function as an important oxygen carrier in our bodies. Each RBC consists of millions of haemoglobin (Hb), which is made up from globin and iron. If any deficiency/malfunction of any globin, it will lead to anaemia as indicated in low Hb level while iron deficiency anaemia (IDA) is anaemic due to the lacking of iron as indicated in low Hb and ferritin levels. IDA affects almost two billion people globally while anaemia without iron deficiency, such as thalassaemia, affects almost 4.5% in Malaysian population. These anaemic conditions have similar clinical symptoms like fatigue, dizziness, in which disturb their cognitive development and productivity in workplace. In areas without proper medical access, many anaemic individuals were misdiagnosed and treated with iron tablets because they were thought to have iron deficiency anaemia due to low Hb content. But, excess iron is toxic to the body. Misdiagnosis can be avoided by iron status assessment. We hereby review the currently available iron status parameters in laboratory and field study with the conclusion of demonstrating the importance of a need for iron reader, in the effort to reduce the prevalence of IDA globally.

1. Introduction

Iron deficiency anaemia (IDA) is a common nutritional deficiency as well as a major cause of anaemia globally that affects approximately two billion people globally in many developing countries [1-2]. Dietary iron deficiency, iron malabsorption, chronic blood loss and certain infectious disease are the causes of IDA [3]. Among these two billion anaemic people, around 50% of them are anaemic with iron deficiency (Figure 1) [2, 4].

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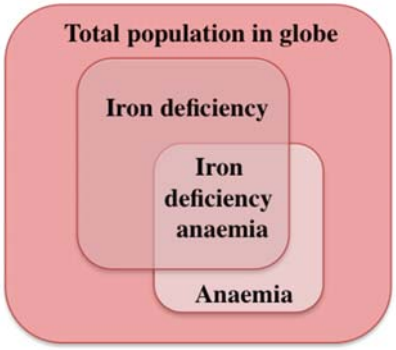

Fig. 1. Prevalence of iron deficiency anaemia in global view.

Moreover, the clinical symptoms of IDA and other haemoglobinopathies, such as thalassaemia are very similar in terms of their clinical appearance and diagnosis. Thalassaemia is characterised by either a reduced or absent production of haemoglobins but a normal or increased iron absorption that affects almost 4.5% of Malaysian population [5]. In areas without proper medical access, many haemoglobinopathic-affected individuals were misdiagnosed and treated with iron tablet due to low haemoglobin (Hb) content. Wrong diagnosis in addition with iron supplements will further worsen the disease leading to cardiac failure and kidney dysfunction. Therefore, one of the ways to differentiate IDA and thalassaeamia is by quantifying the iron level in the body.

Bone marrow iron is a gold standard to estimate body iron stores accurately [6]. Due to its invasive technique in bone marrow aspiration, several other indirect tests such as red cell and biochemical parameters are generally used to assess iron status [7]. In most cases, combining iron status parameters is necessary to make a definitive diagnosis to avoid the diagnostic error of individual biochemical test, which is attributed by other clinical factors. It is of great importance to summarize the currently available laboratory parameters followed by reviewing the potential need of an iron reader for IDA screening, especially in remote and rural areas.

2 Red cell parameters

Red cell parameters can be analysed from automated blood cell analyser for red cell and other blood cell counting as well as haemoglobin (Hb) content [7]. The red cell patterns of iron deficiency anaemia (IDA) are reviewed in the following section.

2.1 Haemoglobin, mean cell volume, mean cell haemoglobin, haematocrit and red cell distribution width

A standard automated blood cell analyser measure haemoglobin (Hb), mean cell volume (MCV), mean cell haemoglobin (MCH), haematocrit (HCT) and red cell distribution width (RDW). Hb is a direct indicator in diagnosing whether an individual suffers from anaemia when Hb level is below the reference range, regardless anaemia with or without iron deficiency. Iron deficiency anaemia (IDA) individuals have anaemic red cells with reduced cell size as evaluated by MCV and reduced Hb content as evaluated by MCH, respectively. A decrease in Hb, HCT and red cell levels as well as an increase in red blood cell distribution width (RDW) – the red cell size variation, can also be seen in IDA individuals.

In Aslan study focusing on RDW level, IDA group (18.00±1.94%) showed significant differences from normal (12.49±0.63%) as well as β-thalassaemia trait (14.88±1.77%) individuals [8]. However, RDW demonstrated only 53.4% specificity in detecting IDA among microcytic hypochromic anaemic children [9]. To diagnose iron deficiency during pregnancy, RDW demonstrated the highest sensitivity (82.3%) and specificity (97.4%) as compared to Hb level, MCV, MCH, mean cell haemoglobin concentration (MCHC) and peripheral blood film [10]. According to a recent study, MCH and MCHC

are only moderately accurate to detect empty iron stores, implying that individuals with normal MCH and MCHC might have a risk of empty iron stores [11].

2.2 Zinc protoporphyrin

In iron deficient condition, the iron's binding site is being replaced by zinc, thereby forming zinc protoporphyrin (ZPP). ZPP represents an inefficient red cell synthesis in a condition where a lack of iron in the body.

A study illustrated that both MCH and ZPP parameters could be used to discriminate between iron deficiency and beta-thalassaemia carriers [12]. Other study displayed that combined both MCV and ZPP could differentiate patients with iron deficiency and thalassaemia effectively, up to 95% [13]. A positive response of iron therapy in paediatric population showed a reduction of ZPP [14]. However, ZPP could not distinguish those with and without iron deficiency among pregnant women from Kenya [15]. This implies that the diagnostic potential of ZPP is limited to only certain groups of people.

In short, red cell parameters are mainly detecting the severe stages of iron deficiency, whereby functional iron deficiency has not been addressed unless with combined analysis with biochemical parameters.

3. Biochemical parameters

Biochemical parameters are used to assess iron status using immunoturbidimetric assay by biochemistry autoanalyser and/or enzyme-linked immunosorbent assay (ELISA). Biochemical parameters can be divided into two groups: transport iron and storage iron.

3.1 Transport iron: plasma iron, total iron binding capacity, transferrin saturation, soluble transferrin receptor

Both transferrin and transferrin receptor are transport proteins. Plasma iron (PI) is determined by iron bound to transferrin. The capacity of transferrin to bind iron is indicated as total iron binding capacity (TIBC). A derivative parameter from PI and TIBC known as transferrin saturation (%TSAT), which is calculated from the ratio of [PI/TIBC]. More transferrin receptors are being expressed in iron deficient cells, indicating by the presence of soluble transferrin receptor (sTfR) in plasma. This suggests a balance between cellular iron demand and iron supply.

sTfR is the only biochemical marker to detect mild tissue iron deficiency, also known as iron deficient erythropoiesis (IDE) [16]. A study demonstrated sTfR is the only reliable marker to diagnose advanced IDE individuals with ZPP level >70 μmol/mol heme [17]. Combined sTfR and ZPP analysis could better illustrate the status of erythropoietic activity.

3.2 Storage iron: plasma ferritin

Plasma ferritin is the important storage protein. It is the widely accepted parameter that reflects the size of the iron stores similar to bone marrow iron [18]. However, ferritin is an acute phase protein that can be confounded by inflammation and infection. This suggests that in the presence of inflammation and infection, ferritin level might not reflect the iron status accurately. Therefore, ferritin level should be evaluated together with inflammatory marker, such as C-reactive protein (CRP) [19].

To better demonstrate body iron status in both storage iron and functional iron, the ratio of transferrin receptor to ferritin (sTfR-F index) is a widely applied parameter together with at least one acute phase protein in order to provide a more reliable diagnosis than a single test [19-20].

4. Classification of iron status

Iron deficiency can be divided into three major stages, i.e. iron depletion (IDP), iron deficiency erythropoiesis (IDE) and iron deficiency anaemia (IDA). Those stages are classified with respect to the iron balance, which is regulated by our bodies. There are functional iron (haemoglobin, myoglobin, cytochromes, enzymes), transport iron (transferrin) and storage iron (macrphage, ferritin, haemosiderin).

4.1 Iron depletion, iron deficiency erythropoiesis and iron deficiency anaemia

Iron depletion (IDP) is the onset of iron deficiency with a reduced in storage iron but still with normal iron for erythropoiesis in functional compartment, as examined in low plasma ferritin (PF).

As the iron deficiency progresses, there is insufficient iron delivery for erythropoiesis, as examined in reduced plasma iron (PI), increased total iron binding capacity (TIBC), reduced percentage of transferrin saturation (%TSAT), increased plasma transferrin receptor (TfR) and increased red blood cell zinc protoporphyrin (ZPP). This iron-deficient condition termed as iron deficiency erythropoiesis (IDE).

Lastly, long-term iron deficiency can be very severe that causes IDA, an iron-deficient condition to a certain extent that causes anaemic condition. There is a reduction in functional iron leading to inadequate haemoglobin synthesis, as indicated in mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) [19, 21]. Figure 2 demonstrate the iron status classification with respect to the iron distribution compartment [22].

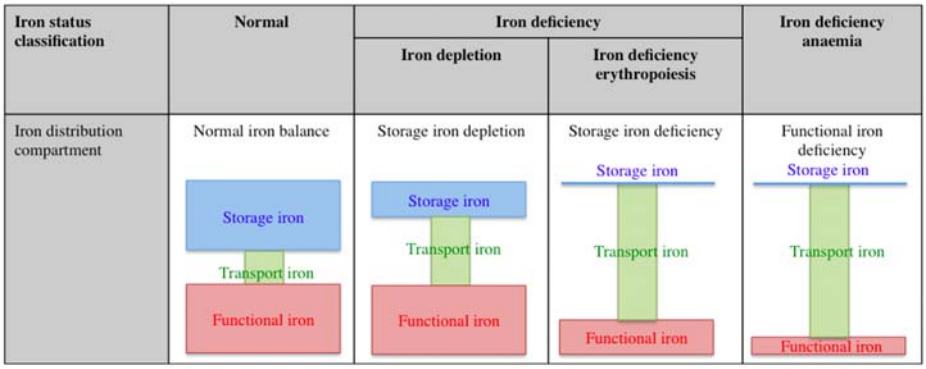

Fig. 2. Classification of iron deficiency severity with respect to the iron distribution compartment.

5. A need for iron reader

To date, global estimates of iron deficiency is only relied on the global estimates of anaemia based on haemoglobin (Hb) level. Hb level has often been applied as a proxy marker for iron deficiency [2, 23-24]. In this section, we emphasize the need for an iron reader by reviewing the current medical facilities among countries with high income inequality and the existing instruments in the market.

5.1 Current medical facilities

Although middle- and high-income countries having public and private healthcare center, it is always full of people, crowded which results in long waiting time. Furthermore, they might need to have a long walk to hospital due to limited parking spaces. In poor countries, malnutrition might lead to anaemia and there is almost 72% children in India are anaemic. Although there are mobile clinics to support them, some of them have to walk from as early as 5 a.m. to reach the place to get treatment and this mobile clinic limited to only once a week due to lack of medical personnels. Again, results take time to release as it involves the sample transportation to the laboratory (Figure 3).

Fig. 3. Issue we want to solve in low-, middle- and high-income countries: a need of an iron reader.

Issue we want to solve aligned with what World health organization stress: 'It is time to act to eliminate iron deficiency anaemia' [25]. In order to target low-, middle- and high-income countries, there is an urgent need to devise a portable, low-cost and user-friendly iron reader to not only save time, money and resources, but also save more lives eventually.

5.2 Current existing instruments

To diagnose iron deficiency anaemia (IDA), the conventional methods are based on current existing instruments, i.e. red cell analyser and biochemistry autoanalyser to ensure definitive diagnosis. Both of these analysers are big and bulky and cost up to RM75.000 (DXH500, Beckman Coulter) and RM200.000 (ILAB Aries, Instrumentation Laboratory). Although these instruments enable definitive diagnosis, they are inconvenient for field study as a trained personnel is needed to operate and analyse the results.

Single-parameter device such as haematofluorometer and hemocue are used to measure haemoglobin (Hb) and red blood cell protoporphyrin content, respectively. These portable devices are relatively low-cost as compared to the previously discussed analysers. Furthermore, these devices require only minimal sample processing and immediate result will be possible. Table 1 summarises the instruments/devices available in the laboratory and for field study.

Table 1. The instruments/devices available to diagnose iron deficiency anaemia.

Instrument	Multi-parameters laboratory instruments		Single-parameter devices	
Name	Red cell analyser	Biochemistry autoanalyser	Haematofluorometer	Hemocue
Brand	Beckman Coulter	Instrumentation Laboratory	Aviv Biomedical	Haemocue®
Cost	~RM 75,000	~RM 200,000	Not available	~RM 1,000
Pros	Multi-parameters for definitive diagnosis	Multi-parameters for definitive diagnosis	Small and portable Convenient and affordable for rural area	Small and portable Convenient and affordable for rural area
Cons	Big, bulky, high-cost and inconvenient	Big, bulky, high-cost and inconvenient	Moderate in size	Detect only end-stage of iron deficiency anaemia and other anaemia without iron deficiency
Image				

6. Conclusion

Thus far, there is no portable iron reader in the market especially for iron parameter. There is an urgent need for a portable iron reader in an affordable format to reduce/eliminate the iron deficiency anaemia (IDA), especially in developing countries and rural areas. Currently, our group are devising a novel, low-cost and portable iron reader that is able to commercialise globally. Eventually in years to come, the prevalence of anaemia/IDA could be reduced, especially in rural areas.

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