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Iron Deficiency Anemia: A Public Health Problem of Global Proportions

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1. Introduction

Iron deficiency anemia (IDA) is the most common micronutrient disorder in the world, negatively affecting the health and socio-economic wellbeing of millions of men, women, and children (Baltussen et al., 2004). According to the World Health Organization (WHO), IDA constitutes a significant public health problem requiring immediate attention from governments, researchers and healthcare practitioners (McLean et al., 2008). Iron deficiency (ID) is inherently associated with poverty, and is thus particularly prevalent in the developing world where the problem is often exacerbated by limited access to appropriate healthcare and treatment (DeMaeyer & Adiels-Tegman, 1985).

Iron deficiency and IDA result from a long term negative iron balance, culminating in decreased or exhausted iron stores (Allen, 2000; Clark 2008; Ramakrishnan & Yip, 2002). Iron, a component of every living cell, is intrinsically involved in numerous biochemical reactions in the body and is associated with oxygen transport and storage, energy production, DNA synthesis, and electron transport (Crichton et al., 2002; Theil, 2004).

Although the etiology of IDA is multifaceted, it generally results when iron demands are not met by iron absorption for any number of reasons. Individuals with IDA may have inadequate intake of iron due to poor quantity and/or quality of diet, impaired absorption or transport of iron, or chronic blood loss due to secondary disease (McLean et al., 2008).

Consequences of IDA are devastating: inhibited growth, impaired cognitive development, poor mental and motor performance, reduced work capacity, and an overall decreased quality of life (Macdougall et al., 1975; Newhouse et al., 1989; Preziosi et al., 1997; Soewondo et al., 1989; Walter et al., 1989; Zhu & Haas, 1997).

Prevention and control is typically achieved through iron fortification of food staples like flour, rice, and pasta, and/or through administration of iron supplements most often in iron pill or, more recently sprinkle form (Baltussen et al., 2004; Faqih et al., 2006; Mumtaz et al. 2000; Ramakrishnan & Yip, 2002). Although iron supplements are widely available and fortified foods constitute a major component of the diet in the developed world, access is limited in the developing world and cost if often prohibitive.

National, regional and global efforts to combat the problem of iron deficiency and IDA have garnered momentum in recent years, but the prevalence does not appear to be decreasing and the disorder remains a severe global public health problem. The current review will provide a general summary of the problem, touching upon the physiological aspects related to iron and hemoglobin, the etiology and epidemiology of IDA, and current prevention and control measures.

2. Defining iron nutritional status

Iron deficiency is defined as a condition in which there are no mobilizable iron stores, resulting from a long-term negative iron balance and leading to a compromised supply of iron to the tissues (Beutler et al., 2003). Iron status can be considered as a continuum: the ideal stage is normal iron status with varying amounts of stored iron within defined ranges; this is followed by iron deficiency, characterized by the absence of measurable iron stores; next, iron-deficient erythropoiesis shows evidence of a restricted iron supply in the absence of anemia; finally, the most significant negative consequence of ID is anemia, usually microcytic, hypochromic in nature (McLaren et al., 1983).

Anemia in general is characterized by a decrease in number of red blood cells or less than the normal quantity of hemoglobin. The condition is determined by the expected normal range of hemoglobin in a population, and is defined as existing in an individual whose hemoglobin concentration (Hb) has fallen below a threshold lying at two standard deviations below the median for a healthy population of the same demographic characteristics, including age, sex and pregnancy status (McLean et al., 2008). Anemic conditions can result from a myriad of causes that can be isolated, but more often than not co-exist. These causes include hemolysis with malaria and other infectious diseases, enzyme deficiencies, a variety of hemoglobinopathies, and other micronutrient deficiencies (McLean et al., 2008). That said, the most significant contributor to the onset of anemia worldwide is iron deficiency, and thus the terms ID, IDA, and anemia are often falsely used interchangeably. IDA represents the most severe form of iron deficiency, and has corresponding alterations in hematological laboratory values and observable signs and symptoms. Currently, the World Health Organization accepts that generally a little less than 50% of all anemias can be attributed to iron deficiency (McLean et al., 2008).

3. Biochemical and physiological importance of iron in the blood

3.1 Human iron metabolism:

Iron is important in the formation of a number of essential compounds in the body, including but not limited to hemoglobin, myoglobin, and other metalloproteins (Lynch, 1997). Most well-nourished adults in industrialized countries contain approximately 3 to 5 grams of iron, of which about 65% is in the form of hemoglobin (Bothwell, 1995). The remaining iron in the body is in the form of myoglobin, other heme compounds that promote intracellular oxidization, or is stored as ferritin in the reticuloendothelial system and cells of liver hepatocytes, bone marrow, and spleen (Frazer & Anderson 2005). Typically men have more stored iron than women, as women are often required to use

iron stores to compensate for iron loss through menstruation, pregnancy, and lactation (Bothwell, 1995).

3.2 Dietary iron sources

In food, two basic forms of iron exist: non-heme (inorganic) and heme (organic) (Bothwell, 1995; Charlton & Bothwell 1983). In an average diet, non-heme iron accounts for approximately 90% of total dietary iron content, while heme iron constitutes the remaining 10% (Bothwell et al., 1979).

Heme iron is highly bioavailable, and present in meat, fish, and poultry. In contrast, non-heme iron is not as readily bioavailable absorption is greatly influenced by diet composition (Harvey et al., 2000). Enhancers, such as ascorbic acid, and inhibitors, such as phytates and polyphenols, significantly affect inorganic iron absorption (Baynes & Bothwell, 1990, Tseng et al., 1997). Although total iron content in a meal is an important consideration, it is crucial to appreciate that the overall composition of the meal is of far greater significance for iron nutrition than the amount of total iron provided (McLean et al., 2008).

3.3 Dietary iron absorption

Dietary iron digested from food and/or supplements is absorbed by the mature villus enterocytes of the duodenum and proximal jejunum (McKie et al., 2001). Non-heme and heme iron are absorbed via different pathways, though the understanding of heme iron absorption is somewhat more limited.

Non-heme iron in ferrous form is transported across the apical membrane of enterocytes by a non-specific divalent metal transporter (DMT1) (Aisen et al., 1999, Hentze et al., 2004). Because much of the iron that enters the gastrointestinal tract is in the oxidized or ferric form, a duodenal ferric reductase (Dcytb) in the apical membrane of enterocytes reduces dietary iron prior to uptake (Latunde-Dada et al., 2002).

In contrast, heme iron molecules bind to an apical membrane protein and are absorbed intact. With the discovery of heme carrier protein 1 (HCP1), understanding has improved (Shayeghi et al., 2005). HCP1 is a polypeptide belonging to a superfamily of transporter proteins, and is predicted to have nine transmembrane domains by which heme iron is taken up. Though the mechanism is unclear, research has shown that by altering gene expression in animal models, heme absorption can be enhanced or limited by overexpressing or silencing HCP1 genes, respectively (Shayeghi et al., 2005).

Duodenal basolateral iron export into blood is mediated by the transmembrane protein ferroportin 1 (FPN1) (Zoller et al., 2001). The exact mechanism by which FPN1 functions is unclear, though it is thought to be facilitated by the ferroxidase activity of a membrane bound oxidase called hephaestin (Fleming & Bacon, 2005; Han & Kim 2007).

After moving into the plasma, iron binds to transferrin and is transported by the blood to sites of use and storage (Bailey et al., 1988). Cellular iron uptake is mediated by transferrin receptor 1 (TfR)-mediated endocytosis (Fleming & Bacon, 2005). Once inside the cell, iron has two possible fates: incorporation into iron proteins (usually as heme) or storage as ferritin for later use during times of iron deficiency (Bleackley et al., 2009).

3.4 Regulation of iron homeostasis

Since the discovery of the hormone hepcidin in 2000, the understanding of how iron homeostasis is achieved has shifted (Krause et al., 2000; Park et al. 2001). Hepcidin, a peptide hormone that is produced and predominately expressed in the liver, appears to be the master regulator of iron homeostasis in humans and other mammals (Ganz, 2003).

When iron levels are high, several regulatory molecules including hemochromatosis gene product, hemojuvelin and transferrin receptor 2, increase hepatic hepcidin expression, stimulating downstream molecular pathways. With up-regulation of hepcidin expression, iron levels are effectively regulated by binding to FPN1 which is found on the surface of iron storage cells. When iron levels are high, hepcidin causes internalization and degradation of FPN1, leading to decreased iron release from iron storage cells and a reduction in intestinal iron uptake (Dunn et al., 2007). In addition, hepcidin may also play a role in negatively regulating divalent metal transporter-1 (DMT1) and duodenal cytochrome-b (Dcytb) which are involved in intestinal iron absorption; currently, the mechanism and extent of control is unknown (Viatte et al., 2005).

In situations where iron requirements are increased, during periods of increased erythropoietic activity, anemia and hypoxia, the down-regulation of hepcidin expression is observed, though again the mechanism is not clear (Dunn et al., 2007; Pak et al., 2006; Vokurka et al., 2006)

4. Hemoglobin

4.1 Formation of hemoglobin

Hemoglobin is an allosteric protein with primary function of binding and transporting of oxygen in the blood to tissues in order to meet metabolic demands (Baldwin & Chothia, 1979). Synthesis of Hb involves a series of complex steps occurring in the erythrocytes, with production continuing through the early phases of the development and maturation of red blood cells (London et al., 1964). The coordinated production of heme, the group that mediates reversible oxygenation, and globin, which is responsible for protection of the heme group during transport, is required during synthesis (Schwartz et al., 1961).

Fully functional hemoglobin molecules consist of four globular protein subunits, each made of a protein chain that is tightly associated with a non-protein heme group (Perutz 1969, 1976; Perutz et al., 1960). The first step in the synthesis of Hb is the binding of succinyl-CoA (formed during the Krebs cycle) with glycine to form a pyrrole molecule. Next, four pyrroles combine to form protoporphyrin IX, which subsequently binds with iron to form the heme molecule. Each heme molecule then combines with a ribosomal-derived long polypeptide chain called a globin, forming a globular subunit of hemoglobin called a hemoglobin chain. Lastly, four Hb chains are loosely bound to produce a whole hemoglobin molecule. The most common form of Hb in adult humans, hemoglobin A, is a combination of two alpha and two beta chains arranged as a set of alpha-helix structural segments connected in a globin fold arrangement (Forget, 1979).

4.2 Reversible oxygenation of hemoglobin:

Aerobic metabolism is critically dependent on maintaining normal concentrations of Hb, and the protein's ability to combine with oxygen in a reversible manner is essential for normal physiological functioning (White & Beaven, 1954). Oxygen binds with Hb in the lungs during respiration and is later released in peripheral tissue capillaries in the form of molecular oxygen where the gaseous tension of the molecule is much lower than in the lungs (Campbell, 1927). This is a cooperative process as the binding affinity of hemoglobin for oxygen is increased by the oxygen saturation of the molecule (Perutz, 1980).

In addition to hemoglobin's ability to bind oxygen, the protein can also bind with carbon dioxide and carbon monoxide, though not in a cooperative manner (Christiansen et al., 1914; Hill, 1913). In the presence of carbon monoxide, hemoglobin's ability to bind with oxygen is hampered as both gases compete for the same binding site with a much greater binding affinity for carbon monoxide than oxygen (Douglas et al., 1912). As a result, small amounts of carbon monoxide can dramatically reduce the oxygen transport in the body and carbon monoxide poisoning can ensue (Hill, 1913). On the other hand, hemoglobin's ability to bind carbon dioxide is a necessary process to allow for removal of carbon dioxide and by-products from the system. Because carbon dioxide occupies a different binding site on the hemoglobin molecule, this type of ligand binding is allosteric in nature (Christiansen et al., 1914; Roughton, 1970).

4.3 Physiological control of hemoglobin levels:

The primary factor regulating the production of hemoglobin is tissue oxygenation. The peptide hormone erythropoietin (EPO), responding to a feed-back mechanism measuring blood oxygenation, is synthesized in times of decreased tissue oxygenation within 24 hours of the stimulus (Faura et al., 1969). EPO release triggers erythrocyte production in the bone marrow in an effort to achieve homeostasis of tissue oxygenation (Fandrey, 2004). As erythrocyte production increases, transferrin from plasma directly from diet and/or from iron stores enters the erythroblasts of bone marrow and is delivered to the mitochondria where heme synthesis occurs, thus inducing the formation of hemoglobin.

5. Functional consequences of iron deficiency and anemia

5.1 Cognitive development

Over the past three decades a large number of studies on the relationship between iron status and cognitive development have been conducted, often with varying results (Lozoff & Georgieff 2006). Iron and other micronutrient deficiencies often occur in the context of poverty and among individuals and families who are influenced by multiple stressors that may interfere with health and well-being, further confounding the issue. While an association between IDA and impaired cognitive development has been reported, research that takes into consideration the multi-diseased state common among individuals with IDA is needed (Lozoff & Georgieff, 2006).

Experiments employing animal models have demonstrated a key role for iron in brain development and function (Beard et al., 2006; Dallman et al., 1975; Felt & Lozoff, 1996;

Jorgenson et al., 2005; Nelson et al., 2002). Iron-containing enzymes and hemoproteins are necessary in many important development processes such as myelination, dendritogenesis, synaptogenesis, and neurotransmission. Iron deficiency disrupts these processes in a regionally specific manner depending on brain development at the time of deficiency. This disruption may lead to a variety of neurodevelopmental effects that usually do not respond to iron replenishment (Lozoff & Georgieff, 2006).

In humans, the majority of research has focused on developmental and behavioural effects of ID on infancy during 6-24 months of age. Delayed psychomotor development, cognitive performance, and social/emotional functioning have been observed in numerous studies (Grantham-McGregor & Ani, 2001; Lozoff& Georgieff, 2006).

A number of observational studies have found that children who suffered from IDA early in life continued to demonstrate lower academic performance during their school-age years. In Costa Rican children born at term and free of health problems other than moderate iron deficiency, persistence of motor differences, more grade repetition, anxiety, depression, and other social problems have been observed (Lozoff et al., 2000). When compared with children that were not anemic during infancy, these children achieved lower scores on intelligence and other cognitive performance tests upon entry into school, despite controlling for socioeconomic factors that may have acted as confounders (Lozoff et al., 1991). A recent meta-analysis estimated the long term effects on IQ to be 1.73 points lower for each 10 g/L decrease in hemoglobin during infancy (Stoltzfus et al., 2005).

The detrimental effects of iron deficiency have been ameliorated with iron supplementation. Randomized controlled trials of iron supplementation consistently show improvement in motor (Moffatt et al., 1994), social-emotional (Williams et al., 1999), and language outcomes (Stoltzfus et al. 2001).

5.2 Resistance to infection

The role that iron deficiency plays in decreased immune response has been reported in both animal and human studies (Dallman, 1987). Leukocytes (neutrophils, in particular) appear to have a reduced capacity to ingest and neutralize microorganisms (Chandra, 1973; Macdougall et al. 1975; Srikantia et al. 1976), while mitogen-stimulated lymphocytes exhibit a decreased ability to replicate (Neckers & Cossman, 1983). Additionally, depressed T-cell responses have been widely documented, with the depression proportional to the severity of iron deficiency (Chandra, 1973; Srikantia et al., 1976, Bagchi et al., 1980; Prema et al., 1982). Treatment regimens such as iron supplementation and food fortification programs have been reported to reduce morbidity from infectious disease, further implicating a role for iron in immune response (Walter et al., 1997).

5.3 Working capacity

Anemia has long been known to impair work performance, endurance, and productivity (Walker 1998). Studies in developing countries in South America (Walker, 1998; Desai et al., 1984), East Africa (Davies, 1973; Davies &Haaren, 1973), and Sri Lanka (Gardner et al., 1977) report a linear relationship between ID and work capacity. Iron supplementation studies carried out on Indonesian rubber tappers (Basta et al., 1979), and Sri Lankan (Gardner et al.,

1977) and Indonesian tea pickers (Basta et al., 1979) note significant gains in productivity following treatment of those individuals with significant IDA. One investigation conducted in China revealed that a rise of 10 g/L in Hb level was associated with an improvement in production efficiency of 14% in response to iron supplementation to treat IDA (Li et al., 1994).

A meta-analysis of 29 studies demonstrated a strong causal effect of severe and moderate IDA on aerobic work capacity in animals and humans (Haas & Brownlie, 2001). The presumed mechanism for this effect is reduced oxygen transport and reduced cellular oxidative capacity due to tissue iron deficiency (Haas & Brownlie, 2001; Davies et al., 1984). In laboratory and field trials, iron deficiency and IDA at all levels of severity also appears to affect energetic efficiency (Zhu & Haas 1997; Li et al., 1994) and endurance capacity (Edgerton et al., 1972; Rowland et al., 1988). Conversely, iron supplementation has been shown to improve endurance and aerobic work capacity in iron-depleted humans (Hinton et al., 2000; Brownlie et al., 2004; Brownlie et al., 2002).

5.4 Maternal mortality

Two meta-analyses drawing upon the same published studies reported on an association between ID and maternal mortality. In a 2001 paper, Brabin et al. suggested that there is an association between a higher risk of maternal mortality with severe anemia (Brabin et al., 2001). Stoltzfus and colleagues, using a methodologically-different analysis, corroborated these findings, suggesting that the risk of maternal mortality increased with decreasing hemoglobin levels, though not in a linear manner. Causal evidence for the role that mild or moderate anemia may play in maternal mortality is lacking (Stoltzfus et al., 2005).

In spite of these findings, a causal link between iron deficiency and mortality related to pregnancy and childbirth (ie. maternal mortality) remains unclear due to methodological concerns. To date there have been no large scale, placebo-controlled, prospective interventions to test the effect of iron supplementation on maternal mortality as large sample sizes would be required and it is considered unethical to withhold treatment from pregnant, anemic women. In addition, research in this field often does not take into consideration other possible causes of anemia and maternal mortality, such as concurrent micronutrient deficiencies, infectious disease, and other related conditions (Allen, 2000; Rush, 2000). For this reason, better observational data that controls for confounders are required (Stoltzfus et al., 2005).

5.5 Preterm delivery and growth

A negative correlation between maternal IDA with length of gestation is well established (Allen, 2001). There are currently two widely accepted biological mechanisms that explain this phenomenon (Allen, 2001). One theory suggests that anemia (leading to hypoxia) and iron deficiency (which increases serum nor-epinephrine concentrations) induces maternal and fetal stress, ultimately leading to stimulation of the production of corticotropin-releasing hormone (CRH) (Allen, 2001; Dallman, 1987; Emanuel et al., 1994). Elevated CRH is a major risk factor for preterm labour, pregnancy-induced hypertension, eclampsia, premature rupture of the membranes, maternal infection (leading to yet more

CRH synthesis), and increased fetal cortisol production (inhibiting longitudinal growth of the fetus) (Allen, 2001; Falkenberg et al., 1999; Lin et al., 1998; Linton et al., 1990, McLean et al., 1995). A second theory suggests that iron deficiency may increase oxidative damage to erythrocytes and the fetal-placental unit (Cester et al., 1994; Poranen et al., 1996).

Maternal iron deficiency with and without anemia is also strongly associated with low birth weight and impeded growth (Stoltzfus et al., 2005). While full-term infants are normally born with sufficient iron stores, infants have high iron requirements and the diets offered to infants in the developing world are frequently inadequate in terms of satisfying the iron requirements for growth. Although iron in breast milk is highly bioavailable, maternal iron reserves are depleted after 4-6 months of feeding, thus infants commonly develop iron deficiency and IDA if the diet is not altered to include a readily absorbable source of iron (Friel et al., 1990).

Iron supplementation of infants appears to ameliorate the problem of impaired growth. A number of studies conducted in Indonesia (Soewondo et al., 1989), Kenya (Latham et al. 1990), Bangladesh (Briend et al., 1990), and the United Kingdom (Aukett et al., 1986) provide evidence that iron supplementation of iron deficient children leads to improved growth.

5.6 Heavy-metal absorption

An important consequence of iron deficiency is an enhanced ability for heavy-metal uptake, leading to heavy-metal poisoning. Iron deficiency is strongly associated with an increased absorption capacity that is not specific to iron, resulting in the uptake of divalent heavy-metals like lead, cadmium, mercury and arsenic from the environment (Peraza et al., 1998). Heavy metal poisoning is a particular concern in children, as impaired cognitive development and irreversible physical and mental disability can result (Byers, 1959; Cebrian et al., 1983). For this reason, prevention of iron deficiency is important, predominantly in areas where exposure to heavy metals is common.

6. Prevalence and epidemiology

6.1 Prevalence of iron deficiency and iron deficiency anemia

Globally, nearly two billion people are affected by anemia (McLean et al., 2008). The majority of those affected live in developing countries where the problem is exacerbated by limited access to inadequate resources and appropriate treatment (Baltussen et al., 2004). IDA is unique in that it is the only nutrient deficiency which is significantly prevalent in virtually all industrialized nations as well. Currently there are no figures specifically for IDA, but it is widely accepted that approximately 50% of all cases of anemia are caused by iron deficiency (McLean et al., 2008; DeMaeyer & Adiels-Tegman, 1985). While the extent to which anemia is a problem in women and children has been widely documented, data on the prevalence of anemia in adolescents, men, and the elderly are scarce.

The level of hemoglobin concentration in the blood is used as an indicator to estimate the prevalence of anemia. Hemoglobin values that indicate the threshold for anemia have been published by the WHO and are widely accepted (Table 1) (McLean et al., 2008).

Age or gender group	Hemoglobin (g/L)
6 – 59 months	110
5 – 11 years	115
12 – 14 years	120
Non-pregnant women (>15 years)	120
Pregnant women	110
Males (>15 years)	130

Table 1. Hemoglobin levels below which anemia is present in a population.
Source: McLean et al., 2008.

Worldwide, the prevalence of anemia is highest in non-industrialized nations where prevalence is three to four times higher than developed countries (Table 2). Africa, Eastern Europe and the Western Pacific have a large burden of disease, with over 1 billion people in these three regions estimated to be anemic (McLean et al., 2008). That said, anemia in South-East Asia is more prevalent than any other region in the world, with nearly 800 million affected. While the prevalence of IDA among women and children in the developed world is lower when compared to the developing world, a high prevalence is still reported in high-risk groups, including preschool-aged children and pregnant women.

	Preschool-aged Children		Pregnant Women		Non-pregnant Women	
WHO Region	Prevalence (95% CI)	Number affected (millions)	Prevalence (95% CI)	Number affected (millions)	Prevalence (95% CI)	Number affected (millions)
Africa	67.6 (64.3-71.0)	83.5 (79.4-87.6)	57.1 (52.8-61.3)	17.2 (15.9-18.5)	47.5 (43.4-51.6)	69.9 (63.9-75.9)
Americas	29.3 (26.8-31.9)	23.1 (21.1-25.1)	24.1 (17.3-30.8)	3.9 (2.8-5.0)	17.8 (12.9-22.7)	39.0 (28.3-49.7)
South-East Asia	65.5 (61.0-70.0)	115.3 (107.3-123.2)	48.2 (43.9-52.5)	18.1 (16.4-19.7)	45.7 (41.9-49.4)	182.0 (166.9-197.1)
Europe	21.7 (15.4-28.0)	11.1 (7.9-14.4)	25.1 (18.6-31.6)	2.6 (2.0-3.3)	19.0 (14.7-23.3)	40.8 (31.5-50.1)
Eastern Mediterra-nean	46.7 (42.2-51.2)	0.8 (0.4-1.1)	44.2 (38.2-50.3)	7.1 (6.1-8.0)	32.4 (29.2-35.6)	39.8 (35.8-43.8)
Western Pacific	23.1 (21.9-24.4)	27.4 (25.9-28.9)	30.7 (28.8-32.7)	7.6 (7.1-8.1)	21.5 (20.8-22.2)	97.0 (94.0-100.0)
Global	47.4 (45.7-49.1)	293.1 (282.8-303.5)	41.8 (39.9-43.8)	56.4 (53.8-59.1)	30.2 (28.7-31.6)	468.4 (446.2-490.6)

Table 2. Anemia prevalence and number of individuals affected in pre-school aged children, pregnant women, and non-pregnant women by WHO region.
Source: (McLean et al., 2008).

Women and children are hardest hit by this nutritional disorder due to increased iron requirements during periods of growth as well as during menstruation and pregnancy. Nearly 40% of preschool children and women (aged 15-59 years) and more than 50% of all pregnant women in developing countries estimated to be anemic (McLean et al., 2008).

6.2 Etiology of iron deficiency and iron deficiency anemia

The prevalence of ID and IDA varies greatly from population to population according to a variety of host and environmental factors. The etiology of anemia is multifaceted and often several factors are at play in an anemic individual. Nutritional anemia as a result of iron deficiency is the most common cause of anemia worldwide, with approximately 50% of all cases attributed to a lack of iron in the diet. A number of host and environmental factors are associated with iron deficiency, and in more severe forms contribute to IDA as well. These include:

1. *Inadequate dietary iron intake*: Diets low in iron or diets low in adequate amounts of bioavailable iron are a major cause of IDA, particularly in non-industrialized countries. Typically, high levels of IDA are also observed in old age when dietary quality and quantity deteriorates (Clark, 2008; Fiatarone-Singh et al., 2000).
2. *Menstruation and pregnancy*: Blood losses associated with menstruation and pregnancy are common causes of ID and IDA. Typically non-menstruating women lose about 1 mg of iron per day, while menstruating women lose an additional 10 mg of iron per day during menses. Pregnancy is associated with an iron loss of approximately 1000 mg in a 55kg woman (Bothwell, 1995).
3. *Infectious disease:* In the developing world common infections which may be both chronic and recurrent are associated with blood loss leading to iron deficiency, and ultimately to IDA. Hemolytic malaria and parasitic infections such as hookworm, trichuriasis, amoebiasis, and schistosomiasis are particularly common diseases that contribute to the depletion of iron stores and often result in IDA (Oppenheimer, 2001).
4. *Interactions with medication*: Several pharmacological agents can interfere with iron uptake and/or transport leading to iron loss or defective absorption. These include H2 blockers, proton pump inhibitors, aspirin or non-steroidal anti-inflammatory drug use (Rockey & Cello, 1993).
5. *Gastrointestinal conditions*: Both acute and chronic gastrointestinal illness is associated with IDA and is an important consideration in clinical diagnosis of the condition. Duodenal or gastric ulcers, carcinoma, polyps, irritable bowel disease, erosive gastritis, celiac disease, altered hepatic function for any number of reasons, and/or compromised protein status may lead to IDA (Clark, 2008).
6. *Periods of growth*: Iron deficiency and IDA are particularly prevalent during peak periods of growth. Though full-term infants are normally born with adequate iron stores, if complementary foods containing iron are not introduced to the diet after six months of age then an infant is at risk of developing ID, and ultimately IDA. Iron requirements on a body weight basis are proportional to growth velocity, thus iron deficiency and IDA are common in preschool years and during puberty (McLean et al., 2008; Tolentino & Friedman 2007; Turner et al., 2003).
7. *Socioeconomic status*: Iron deficiency and IDA are most common among groups of low socioeconomic status for a number of reasons, including but not limited to:

malnutrition, poor education regarding health and hygiene, and greater presence of concomitant disease when compared to populations of higher socioeconomic status (Bhargava et al., 2001; Thankachan et al., 2007).

7. Prevention and control

Interventions to control iron deficiency and associated anemia are available, affordable, and sustainable (McLean et al., 2008, ACC/SCN, 2000). Food-based approaches are the most desirable and sustainable method of preventing IDA, with dietary improvement representing the most cost-effective and sustainable option. Advancements in the fortification of food staples and compliment have also shown promise. In addition, supplementation using multivitamins and vitamin complexes containing high levels of iron are accessible, though often at a higher cost than other preventive and treatment methods.

7.1 Dietary improvement

Efforts towards promoting the availability of, and access to iron-rich foods are a key prevention technique. Foods containing high levels of iron include: meat and organs from cattle, fish, and poultry, as well as non-animal foods such as legumes and green leafy vegetables (WHO, 2001).

As overall meal composition is as important as total iron content of a meal, it is important to promote the consumption of foods that enhances iron absorption and while limiting the consumption of foods that act as inhibitors (Layrisse et al. 1969; Layrisse & Martinez-Torres, 1968; Hallberg et al., 1986; Hallberg et al. 1991; Hallberg et al., 1989). Foods that enhance absorption of iron typically contain high levels of vitamins A, vitamin C, and folic acid; this includes various fruits, vegetables, and tubers. Conversely, phytates, found in cereal grains, tannins and other polyphenols found primarily in tea and coffee, and calcium from milk and milk products should be avoided where possible to limit the inhibition of iron absorption.

Typically, diets of individuals in the developing world do not provide adequate iron. In a typical South-East Asian diet consisting of rice, vegetables and spices, iron absorption was reported to be inadequate (Hallberg et al. 1974; Hallberg et al. 1977). Even with the addition of fruit, meat and fish to these simple meals, iron absorption remained lower than the estimated requirement. These findings would suggest that individuals consuming such a diet could only maintain their iron balance in a state of iron deficiency, and would therefore greatly benefit from ID and IDA treatment and prevention programs (Hallberg et al., 1974).

7.2 Iron fortification

Iron fortification involves the addition of iron to an appropriate food vehicle that is distributed widely to the general population. Fortified flour and other cereals have historically been the most commonly used (Baltussen et al., 2004; Ramakrishnan & Yip 2002). Research into self-fortification through plant breeding is also gaining momentum and in the future may have a great impact on improving nutritional status (Lucca et al., 2001).

7.2.1 Fortification in the developed world

Fortification has played an important role in the reduction of ID in the developed world since the latter half of the 20th century (Ramakrishnan & Yip 2002; Rees et al., 1985). The addition of elemental iron powder to flour and other cereals has since been commonplace, with levels of enrichment ranging from approximately 30 to 60 μg/g (Baltussen et al., 2004). In Canada, for example, it has been mandatory to enrich all white flours, enriched pastas, enriched precooked rice and certain substitute foods since 1976 (Guggenheim, 1995).

As the demand for processed foods has increased over the past 50 years, vitamins and minerals have slowly been added to an increasing array of foods. Ready-to-eat cereals in particular play an important role in daily iron intake in the Western world. Research in the last decade suggests that approximately 40% of total iron intake in women of reproductive age from the U.S. (Ramakrishnan& Yip, 2002), and approximately 78% of total iron intake in German children aged 2 to 13 years (Guggenheim, 1995) can be attributed to ready-to-eat cereals.

The fortification of infant formulas and foods provides particularly convincing evidence for the benefits of food fortification (Walter et al., 1993). Following the introduction of fortification guidelines in the U.S. in the late 1960's a clear reduction in IDA among infants and young children was noted (Yip et al., 1987).

7.2.2 Fortification in the developing world

In developing countries a much lower consumption of food from animal sources is observed and typically the overall nutritional value of the diet is lower when compared to developed nations (Yip & Ramakrishnan, 2002). In addition, both a high relative cost and a decreased availability of fortified products like cereal flours, ready-to-eat cereals, and infant formula leads to an overall decreased use of industry-prepared food that would otherwise benefit the population (Yip & Ramakrishnan, 2002). Thus, the relative absence of fortified food products from diets in developing nations could at least partly explain the high prevalence of iron deficiency and IDA and why current fortification practices have not ameliorated the situation. Research into fortifiable products that are culturally acceptable and desirable in developing nations should be conducted.

7.3 Iron supplementation

Iron supplementation is the most common and cost-effective strategy used to control ID and IDA in the developing world and is used as both a preventive measure and a treatment option (Baltussen et al., 2004). World Health Organization guidelines suggest that iron supplementation should include administration of 60 mg of iron daily with a dose of 400 μg of folic acid for women of reproductive age, 30 mg of iron and 250 μg of folic acid for school-aged children, and approximately 2 mg/kg body weight per day for preschool-aged children (McLean et al., 2008). Weekly iron supplementation also exists, though is considered to be a less effective treatment option and requires additional research and evaluation (ACC/SCN, 2001).

The majority of supplementation studies to date have examined a variety of treatments in women of reproductive age, as infants, preschool and school-aged children (Preziosi et al.,

1997; Faqih et al., 2006, Mumtaz et al. 2000; Menendez et al. 1997; Suharno et al. 1993; Schultink et al. 1995; Berger et al. 1997; Viteri, 1997). It is becoming increasingly clear that a main target group for iron supplementation in the developing world should be all women of reproductive age, regardless of pregnancy status at the time, thereby ensuring adequate iron reserves for both the mother and fetus during pregnancy and lactation (Yip & Ramakrishnan, 2002). Of concern is the relative cost of iron supplements in developing nations, coupled with issues surrounding delivery to infants and children. Other problems with iron supplementation include: undesirable side effects (including gastrointestinal irritation, black stools, and constipation); poor adherence to treatment guidelines; awareness and motivation of the target group to take supplements, often due to inadequate health and nutrition education; quality and packaging of iron supplements; and risk of iron overload if supplementation guidelines are not followed correctly (WHO, 2001).

7.4 The use of adventitious iron sources

Research conducted in the latter half of the 20th century has reported on the use of iron pots for cooking as an innovative way to reduce IDA, with the first study conducted in 1986 (Martinez & Vannucchi, 1986). Wistar rats fed a basal diet low in iron though cooked in an iron pot demonstrated comparable hemoglobin, hematocrit, protoporphyrin, serum iron, and transferrin saturation levels to those rats fed a complete diet, thus implicating the iron pot as an adventitious source of iron.

Since this time several studies have examined this supplementation technique in humans with similar findings. Experiments conducted on Ethiopian children aged 2-5 years and pre-term infants (between months 4 and 12) from Brazil reported that cooking food in iron pots led to lower rates of anemia than children whose food was cooked in non-iron pots (Adish et al. 1999; Borigato, Martinez 1998). Significantly improved hematologic values between iron pot and non-iron pot groups were noted, including increased hemoglobin, hematocrit, mean corpuscular volume, free erythrocyte protoporphyrin, and serum ferritin. In addition, the Ethiopian study indicated moderate height and weight gains in children assigned to treatment groups (Adish et al. 1999). A more recent study conducted in Malawi verifies this research, noting a reduction in iron deficiency among children and increased hemoglobin levels in adults living under malarial endemic conditions (Geerligs et al. 2003a, 2003b).

Research into the beneficial aspects of contaminant iron and adventitious iron sources, should be conducted. This supplementation technique has the possibility of providing a low-cost and sustainable way of improving dietary iron content, and may be particularly effective in the developing world where resources are limited.

8. Conclusion

Anemia is a global public health problem with serious consequences for human and socioeconomic health and development. Despite a concerted effort to improve treatment and prevention of iron deficiency and anemia in recent years, the problem does not appear to be going away.

In 2004, the Copenhagen Consensus brought together a panel of world-renowned development economists to consider and confront the ten most pressing challenges to "global welfare" that we face today (Copenhagen Consensus, 2004). Micronutrient interventions, including iron fortification, ranked at the top of the list and offered the highest benefit: cost ratio of any development intervention. These findings were confirmed in 2008, at the most recent Consensus meeting, where iron and zinc fortification were placed within the top three global challenges (Copenhagan Consensus, 2008). This prioritization of iron and other micronutrient interventions emphasizes the need for well-designed, sustainable and effective programming efforts to combat iron deficiency anemia.

The adverse effects of anemia on mortality, morbidity and development are abundantly clear. Anemia affects how individuals participate in all areas of life, including work, school and social activities, and this limits the ability to generate income and afford iron-rich sources of food, medical treatment, and school fees. In turn, this leads to constrained social and economic development, ultimately contributing to a viscous cycle of poverty that is difficult to overcome.

The widespread prevalence of anemia, both in the developed and developing worlds, is great cause for concern. The current review highlights some of the most promising research on the etiology, prevention and control of the disorder. From this, it should be clear that although we have made strides, there is still much that we do not understand about iron deficiency and anemia, especially in relation to treatment and prevention. A renewed effort to find effective ways to combat this problem is needed, as anemia is unique and complex public health crisis that is of global proportions.

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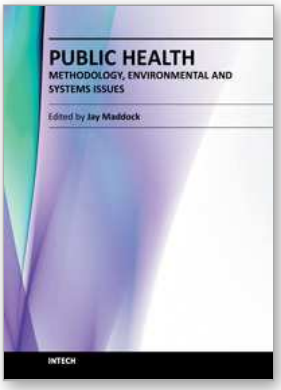

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Public health can be thought of as a series of complex systems. Many things that individual living in high income countries take for granted like the control of infectious disease, clean, potable water, low infant mortality rates require a high functioning systems comprised of numerous actors, locations and interactions to work. Many people only notice public health when that system fails. This book explores several systems in public health including aspects of the food system, health care system and emerging issues including waste minimization in nanosilver. Several chapters address global health concerns including non-communicable disease prevention, poverty and health-longevity medicine. The book also presents several novel methodologies for better modeling and assessment of essential public health issues.

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