INTRODUCTION

Anemia in childhood is defined as a hemoglobin (Hb) concentration below cut-off levels established by the World Health Organization: <11 g/dl in children aged 6–59 months, <11.5 g/dl in children aged 5–11 years and 12 g/dl in older children (aged 12–14).[1]

The likely cause of childhood anemia varies in different regions, with iron deficiency anemia (IDA) being the most common cause. In the developing world, infectious diseases such as malaria, helminth infections, HIV and tuberculosis are other important causes of anemia.[2] Inherited forms of anemia are occasionally encountered in certain racial groups. Sickle cell disease is more common in people of Central African origin while \( \beta \)-thalassemias are more common in Mediterranean, Middle Eastern and Southeast Asian populations.[3,4]

In infants and young children, severe chronic anemia may lead to delayed growth and long term effects on neurodevelopment and behavior, mediated by changes in neurotransmitter myelination, monoamine metabolism in striatum, functioning of the hippocampus and energy metabolism. Growth and pubertal delay are common complications of thalassemia major.[5-7]

Iron is essential for all tissues in a young child’s developing body. Iron is reversibly stored within the liver as ferritin and hemosiderin and is transported between different compartments in the body by transferrin. Ferritin is the stored form of iron used by the cells, and a better measure of available iron levels than serum iron. Fe performs vital functions including carrying of oxygen from lung to tissues, transport of electrons within cells, acting as co-factor for essential enzymatic reactions, including synthesis of steroid hormones and neurotransmission. Mitochondria supply cells with adenosine triphosphate, heme, and iron-sulfur clusters (ISC), and mitochondrial energy metabolism involves both heme-and ISC-dependent enzymes. Mitochondrial iron supply and function require iron regulatory proteins that control messenger RNA translation and stability and iron is positively correlated with mitochondrial oxidative capacity.[8-10]

EFFECT OF IRON SUPPLEMENTATION ON GROWTH OF NORMAL CHILDREN

Many authors have reviewed the effect of routine iron supplementation on growth in children. A systematic review analyzed 25 randomized controlled trials (RCTs) that evaluated the effect of iron supplementation on physical growth in children (interventions included oral or parenteral iron supplementation, or iron-fortified formula milk or cereals). The pooled estimates (random effects model) did not document a statistically significant \( (P > 0.05) \) positive effect of iron supplementation on any anthropometric variable (Weight [Wt]-for-age, Wt-for-height [Ht], Ht-for-age, mid-arm circumference [MAC], skinfold thickness). However, greater Wt-for-age in supplemented children in malaria hyper-endemic regions and greater Wt-for-Ht for children above 5 years of age were noted, along with a negative effect on linear growth in developed countries and with supplementation for 6 months or longer.[11] Two other meta-analysis of 21 RCTs examining iron (supplementation) interventions in children aged <18 years found that the iron-supplementation had no significant effect on growth.[12]
The second meta-analysis included iron-fortified foods, iron-fortified formula, or iron supplements and evaluated Ht, Wt, MAC, head circumference (HC), birth weight, or length of gestation in infants, children, and adolescents, and seven studies conducted in pregnant women.[13]

The overall pooled result (random-effects model) showed no significant effects of iron intervention on any of the parameters measured. When results were stratified according to dose of iron, duration of intervention, age, and baseline iron status, only doses of 40–66 mg of supplemental iron and intervention in children ≥6 years of age showed a slight but significant association with weight and MAC.[13]

Effect of antenatal and infant anemia on growth
Early ID appears to have specific effects on the central nervous system. In the rat, a brief period of ID during the brain growth spurt (10–28 days) causes a lasting deficit in brain iron, which persists into adulthood despite correction of the anemia. Altered neurotransmitter function is present in the brains of iron-deficient rats. The activity of monoamine oxidase and aldehyde oxidase are reversibly diminished, as is the functional activity of dopamine Dd2 receptors. Many dopamine-mediated behaviors are modified.[14-16] Pregnant rats on Fe restricted diet produced litters with a significant reduction in the physical growth indexes (body weight, body length, tail length, and head length) compared with the control group. These results suggest that adequate Fe is essential during both intrauterine and neonatal life.[17]

In human, both brain and body growth, especially during the phase of rapid infantile growth, requires relatively high energy supply and metabolism. Cellular energy metabolism is dependent on oxygen. Fe deficiency decreases oxygen dependent cellular energy metabolism due to decreased heme and Hb synthesis, decreased red blood cells (RBC) synthesis, and decreased RBC survival due to increased oxidative stress in RBC, Hb autoxidation, generation of toxic oxygen radicles scrambling and increased removal by macrophage. Consequently, IDA leads to impaired cognitive abilities and defective linear growth.[18-23]

Effect of anemia and iron supplementation, on growth in anemic children
Only few controlled studies have investigated the effect of IDA, and the effect of treatment with iron, on growth in children with IDA. Aukett et al., showed that treatment of IDA with oral iron for 2 months was associated with a significantly greater increase in weight velocity compared to the placebo group.[24] Other studies have confirmed these observations, and also suggest that the correction of anemia is associated with a reduction in the increased morbidity (fever, respiratory tract infections, diarrhea) seen in children with IDA.[21,22] Bandhu et al., studied the effects of IDA, and its correction with Fe, in school going children on anthropometric parameters. Pre-supplementation values of IDA children were significantly lower for MAC and HC in girls and for Ht and MAC in boys, when compared to the control group. Iron supplementation-induced improvement in hematological parameters was associated with significant improvement of Ht, Wt and MAC. Post therapy, the anemic girls and boys grew faster than their respective control groups.[23]

Soliman et al. measured growth and parameters in 40 children (aged 17.2 ± 12.4 months) with IDA before and for 6 months after iron therapy in comparison with normal controls. Before treatment children with IDA were significantly shorter and had slower growth compared with age-matched controls. After treatment, their growth velocity (GV), length standard deviation scores (SDS) and body mass index (BMI) increased significantly (significant catch-up of growth). Their GV was correlated significantly with mean Hb concentration.[26] Similarly, Bhatia et al. assessed the growth status of 117 anemic (Hb 7–10 g/dl) and 53 normal (11 g/dl) children (3–5 years). The anemic children had significantly lower body weight, height and weight for age. Iron treatment (40 mg elemental iron/day) for both groups of children for 6 months produced a significant increase in Hb levels of both groups (1.6 g/dl in the anemic and 0.8 g/dl in the non-anemic) compared to their respective controls who received sugar placebos.[27] Growth performance of anemic children supplemented with iron was superior to that of anemic placebo-treated children as indicated by a better weight gain and a significantly higher weight for height.[28] In summary, IDA in children, especially during the first 2 years of life significantly impairs growth that can be corrected by adequate iron therapy.

Effect of iron deficiency anemia and iron treatment on growth hormone-insulin-like growth factor-I axis
Novel endocrine pathways have been proposed to explain the effect of IDA on growth. Anemia imposes a hypoxic condition on hepatocytes. Hepatic protein synthesis is inhibited by hypoxia. In vitro, low oxygen conditions inhibit insulin-like growth factor-I (IGF-I) action by increasing IGF binding protein -1 (IGFBP-1), especially phosphorylated IGFBP-1, which inhibits IGF-I action. In addition, IGF-I-induced cell proliferation is also inhibited in low oxygen conditions.[27,29,30] Transferrin (Tf) is the major circulating iron binding protein. In addition to its function as the Fe3+-carrier protein in serum has a unique ability to bind IGFs and to interact with IGFBP-3. Tf can abolish IGFBP-3-induced cell proliferation and apoptosis in different cell lines. On the other hand, the
Fe3 ± Tf complex might facilitate the transport of IGFs across the capillary wall by receptor-mediated transcytosis. Therefore, increased Tf during IDA may adversely affect the integrity of IGF-I system.[33]

Animal studies
In Wistar rats, dietary ID decreased hematocrit and Hb concentrations, IGF-1, 1,25-dihydroxycholecalciferol, IGF-I, and osteocalcin concentrations and bone mineral density of the femur and vertebrae compared with control rats. Bone histomorphometric parameters showed that the bone formation rate and osteoclast surface in the lumbar vertebra were significantly reduced in the ID group compared with the control group.[32-34] Calves with IDA were found to have low plasma IGF-I concentrations. After recombinant growth hormone (GH) administration, increments in IGF-I in IDA calves were reduced despite high plasma GH levels. This suggested decreased sensitivity (partial resistance) to GH during anemia.[35] Gestational ID in rats inhibited growth hormone (GH) secretion and increments in IGF-I and IGF-II concentrations were still observed in the ID group compared with the control group.[36] Early postnatal iron treatment attenuates postnatal hippocampal IGF signaling and results in markedly suppressed hippocampal IGF activation and protein kinase B signaling. Early postnatal iron treatment of gestational ID reactivates the IGF system and promotes neurogenesis and differentiation in the hippocampus.[37]

Human studies
In 40 infants and young children with IDA (Hb = 8.2 ± 1.2 g/dl) treated for 6 months with iron therapy, circulating IGF-I increased significantly, along with acceleration of GV and increased length SDS and BMI.[38] Isguvlen et al., studied 25 prepubertal children with IDA and 25 healthy controls. IGF-I, Ghrelin, and insulin levels were significantly lower in the ID group.[39] They suggested that low ghrelin and insulin levels might be the cause of the appetite loss in IDA. In addition, low Ghrelin (a GH secretagogue) may decrease GH and subsequently IGF-I secretion. They related growth delay both to low IGF-I secretion and appetite loss.[39]

In adolescents, Choi and Kim reported significant correlation between Hb concentration and serum iron on the one hand and IGF-I concentration on the other hand.[40]

In a large adult cohort (n = 1,093) the association of IGF-1 with Hb concentration was studied. Anemic adults exhibited significantly lower IGF-1 compared with non-anemic controls.[41]

Effect of thalassemia on growth and growth hormone-insulin-like growth factor-I axis
Thalassemia and growth are linked by different, multifactorial mechanisms. Growth retardation occurs almost invariably in homozygous β-thalassemia. Significant size retardation is observed in stature, sitting height, weight, biacromial (shoulder), and bicipital (iliac crest) breadths. After the age of 4 years, the longitudinal growth patterns display rates consistently behind those of normal controls. Growth retardation becomes markedly severe with the failure of the pubertal growth spurt.[38,42-44] With the introduction of high transfusion regimes and efficient iron chelation in thalassemia management, prepubertal linear growth has improved markedly.[44,45] However, abnormal growth is still observed in the majority of patients during late childhood and adolescence.[46] Hemosiderosis (secondary to repeated packed cell transfusion) induced damage of the endocrine glands (pituitary, thyroid, gonads, pancreas), liver, and growth plate, is a major cause of growth failure.[44]

However, other important factors also contribute to this growth delay [Table 1].[45-51]

Many studies done on children with thalassemia have shown a variable prevalence of defective GH secretion in response to different stimuli (clonidine, glucagon, Insulin hypoglycemia, GrowthGH-releasing hormone). Some of the short thalassemic children with normal GH secretion, have neurosecretory dysfunction of GH secretion.[44,47,49] In addition, IGF-I concentrations have been shown to be low in the majority of children and adults with thalassemia, with or without GH deficiency. One-day-IGF-I generation tests have shown lower IGF-I generation in thalassemic children compared with normal short children and those with GHD. Defective GH secretion and hepatic siderosis are major causes of low IGF-I secretion.[49-51] Acute correction of anemia, by packed cell transfusion, significantly increases the serum concentration of IGF-I but does not affect GH secretion or IGF-I in response to GH stimulation. Increasing caloric intake and improving nutrition has been shown to increase IGF-I and growth in these patients. Some acceleration of linear growth can be achieved by GH therapy; however this growth response appears inferior to the response of non-thalassemic children with GH deficiency.[45,46,51]

Summary
Chronic anemia has a negative effect on linear growth during all stages of growth (infancy, childhood and adolescence). In addition, infants with chronic IDA have delayed cognitive, motor, and affective development that may be long-lasting. The mechanisms of defective growth in IDA includes defective IGF-I secretion. Correction of anemia is associated with an improvement of catch-up growth and a significant increase in IGF-I secretion.
Table 1: Effect of iron deficiency anemia versus chronic hemolytic anemia on and thalassemia on growth and endocrine glands

| Effect of treatment of anemia | Chronic hemolytic anemia on repeated RBC transfusion | Iron deficiency anemia |
|-----------------------------|-----------------------------------------------|------------------------|
| Early brain growth and metabolism | No effect | In-utero and early life leads to altered neurotransmission and monoamine oxidase and other enzyme metabolism |
| Psychomotor development | No effect | Defective psychomotor development that may persist later |
| Childhood linear growth | Marked effect | Defective intrauterine and early postnatal growth |
| Pubertal growth spurt | Marked effect because of delayed and/or failure of puberty and defective GH-IGF-I axis | Marked effect |
| GH secretion | Significant decrease in variable number of patients (pituitary iron overload) | Less significant effect |
| IGF-I secretion | Decreased IGF-I secretion Hepatic siderosis | Decreases IGF-I secretion |
| Effect on appetite and weight gain | Decreases appetite and many have low BMI (correction of nutrition increases IGF-I and weight gain) | Decreases appetite and is associated with underweight in many children and adolescents |
| Effect on other endocrine glands | Hypothryoidism | No effect (in adults thyroid dysfunction may occur) |
| Effect on liver | Liver fibrosis, cirrhosis and failure may occur secondary to iron overload (siderosis) | Heart failure is rare and occurs in severe prolonged cases |
| Effect on heart | Arrhythmia and heart failure still occur secondary to iron overload and hypoxia | No effect on hepatic function |
| Effect of treatment of anemia | Adequate blood transfusion and iron chelation improves IGF-I secretion, weight gain and linear growth but short stature is still common complication | Fe therapy; 1 increases IGF-I, weight gain and linear growth (complete catch-up growth) |

GH: Growth hormone, RBC: Red blood cell, IGF-I: Insulin-like growth factor 1

In view of the significant impact of IDA on growth, endocrinologists should advocate primary prevention and screening for ID. Although the use of iron supplemented formulas offers an easy method of primary prevention of IDA, evidence now indicates that routine iron supplementation appears useful only in areas with high prevalence of IDA, including malaria-endemic areas, and may present some risks for those with normal Hb. Hence, universal iron supplementation cannot be supported.

In thalassemia, adequate packed cell transfusion (hypertransfusion) and proper iron chelation, sound nutrition, early diagnosis and management of dysfunction of growth and pubertal axes can improve the final outcome of these children.

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