

Insulin-like growth factor- I and factors affecting it in thalassemia major

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ABSTRACT

Despite improvement of blood transfusion regimens and iron chelation therapy growth and maturational delay, cardiomyopathy, endocrinopathies and osteoporosis still occur in good number of thalassaemic patients. Decreased IGF-1 secretion occurs in the majority of the thalassaemic patients particularly those with growth and pubertal delay. Many factors contribute to this decreased synthesis of IGF-I including disturbed growth hormone (GH) - insulin-like growth factor - I (IGF-I) axis. The possible factors contributing to low IGF-I synthesis in thalassemia and the possible interaction between low IGF-I secretion and the occurrence of these complications is discussed in this mini-review. Improvement of IGF-I secretion in thalassaemic patients should be intended to improve linear growth and bone mineral accretion in thalassaemic patients. This can be attained through adequate correction of anemia and proper chelation, nutritional supplementation (increasing caloric intake), correction of vitamin D and zinc deficiencies, induction of puberty and correction of hypogonadism at the proper time and treating GH deficiency. This review paper provides a summary of the current state of knowledge regarding IGF-I and factors affecting it in patients with thalassaemia major (TM). Search on PubMed and reference lists of articles with the term 'IGF-I, GH, growth, thalassemia, thyroxine, anemia, vitamin D, and zinc' was carried out. A hundred and forty-eight articles were found and used in the write up and the data analyzed was included in this report.

Key words: Anemia, ferritin, growth hormone, growth, Insulin-like growth factor-I, nutrition, puberty, thalassemia, thyroxine, vitamin D, zinc

INTRODUCTION

Growth and maturational delay are striking features of beta-thalassaemia major (BTM). After the age of four years, growth faltering sets in but becomes obvious after the age of eight years that involves stature, sitting height, weight and skeletal maturation. After this age, a slowing down of growth and a reduced or absent pubertal growth spurt are observed. There is marked attenuation or loss of pubertal growth spurt and the growth plate fusion is usually delayed until the end of the second decade of life.

The pathogenesis of growth failure is multi-factorial and is

mainly due to chronic anemia and hypoxia, iron overload of different organs, chronic liver disease, nutritional deficiency, inadequate use of chelating agents and endocrinopathies (hypogonadism, delayed puberty, hypothyroidism and GH-IGF-1 axis deregulations).^[1-4]

Insulin-like growth factor-I (IGF-I) is the major mediator of (GH)-stimulated somatic growth and a mediator of GH-independent anabolic responses in many cells and tissues. It is synthesized by multiple mesenchymal cell types, and mediates most of the physiological actions of GH and is the major effector of bone growth.^[5-9]

Two major mechanisms regulates IGF-I secretion. The endocrine part of IGF-I, which is mainly synthesized in the liver and secreted into the blood, is under the control of growth hormone (GH). Locally produced IGF-I (the autocrine/paracrine part of IGF-I) is important in the activity of several organ systems. This is controlled by GH and by other factors that are secreted locally by the surrounding cell types. Growth hormone, parathyroid

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DOI:
10.4103/2230-8210.131750

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hormone (PTH), and sex steroids regulate the production of IGF-I in bone.

Sex steroids are the main regulators of local production of IGF-I in the reproductive system. However, some of the autocrine/paracrine IGF-I that is secreted enters into the systemic circulation.^[10-16]

After birth, IGF-I appears to have the predominant role in regulating growth and differentiation of functions. It binds specifically to high-affinity membrane-associated receptors that are tyrosine kinases.^[17] During childhood, IGF-I increases progressively and reaches the maximum during puberty (between 12 and 16 years) corresponding to the pubertal growth spurt, and then decreases gradually with age.^[18,19]

Liver derived circulating IGF-I and local bone-derived IGF-I overlap in their growth-promoting effects and may replace each other in the maintenance of normal longitudinal bone growth. In contrast, locally derived IGF-I cannot replace liver-derived IGF-I for the regulation of GH secretion, cortical bone mass, kidney size, liver size, prostate size and insulin sensitivity.^[20-22]

In population-based cohort studies, higher IGF-I levels predicted greater childhood height gains and higher levels of insulin secretion for the degree of insulin sensitivity.^[23] Hence it is hypothesized that alterations in IGF-I regulation can provide an attractive explanation for thalassaemia-associated growth impairment. The most potent regulator of IGF-I expression in postnatal life is GH. On the other hand IGF-I mediates growth hormone negative feedback. Additionally, other hormones e.g. insulin, sex-steroids and thyroxin as well as nutrition play important role in IGF-I regulation.^[24-26]

Growth hormone- IGF-I axis in thalassemia

Growth hormone deficiency (GHD) in BTM patients can explain in part low IGF-I synthesis. However, in numerous cross-sectional studies, patients with BTM at different ages who have normal GH secretion (GHS) still have high prevalence of low serum IGF-1 and IGFBP3.^[27-29]

In a longitudinal study, the age-related changes in serum IGF-I concentrations in thalassemic subjects ($n = 20$), compared to normal standards for age and sex, showed significantly lower IGF-I concentrations from early childhood to 18 years of age. Thalassemic children with GHD did not show any peak of IGF-I level till the age of 18 years. Thalassemic males with GHS achieved their peak IGF-I level late (at 16–18 years of age) whereas normal males (at 13 years of age) and their peak IGF-I level was

attenuated (3 times from infancy to puberty *vs* 8–9 times in normal males). In addition, no statistical differences in age, height standard deviation score (HSDS), target HSDS and bone-age between thalassemic patients with GHD and those with GHS.^[28] The basal IGF-I levels did not differ between the 2 groups at different ages until the age of 12 years. After 12 years of age, IGF-I levels were significantly higher in thalassemic children with GHS *vs* those with GHD.^[28,29] These significantly lower age-related longitudinal changes in IGF-I secretion and attenuation at its peak during pubertal years corresponds to the slow growth pattern of thalassemic patients during childhood that is exaggerated during adolescence.

In addition, children with BTM had a significant, but lower IGF-I response after GH administration, compared with the IGF-I response in the GHD.^[27] Many thalassemic children with normal GH response to provocation had low IGF-I secretion suggesting a degree of neuro-secretory dysfunction or decreased GH sensitivity in the liver. The percent increment of IGF-I level in response to exogenous GH stimulation was lower in thalassemic patients *vs* those with GHD.^[27]

Studying the spontaneous nocturnal GH secretory pulse-pattern has demonstrated neuro-secretory dysfunction in some thalassemic patients with normal GH response to stimulation and low IGF-I.^[27-34] Moreover, the low basal GH level in these children in the presence of low IGF-I concentrations suggested an additional disturbance in the (centrally mediated) negative feedback mechanism.^[27]

Although exogenous administration of GH has improved the growth rate and increased circulating IGF-1, concentration in children with BTM with normal GH secretion, and their growth rate was less than that seen in GH-deficient children treated with GH. These data suggest that thalassemic patients had some degree of GH insensitivity.^[13,14] However, serum GH-binding protein (GHBP) level was normal in short thalassemic patients without GH deficiency ruling significant GH receptor defect.^[35] One study reported decreased IGF-I binding to its cellular receptors in short thalassemic patients *vs* those with normal stature.^[36]

Puberty and GH- IGF-I axis in thalassemia

Puberty, spontaneous, precocious that are pharmacologically induced has profound effects on the physiology of the GH/IGF-I axis. Both spontaneous and stimulated GH secretion increase with puberty. The increase in spontaneous GH secretion is the result of increased GH pulse amplitude. Analogous to the increase in GH secretion at puberty, circulating IGF-I and IGF binding protein-3 also increase. The pubertal increase in IGF-I correlates with stages of

puberty as well as sex steroid levels. GH, IGF-1 and sex steroids all markedly increase during puberty and their actions are amplified mutually to mediate the pubertal growth spurt, and increase muscle mass and mineralization of the skeleton.^[37,38]

Delayed and/or failure of puberty due to hypo gonadotropic hypogonadism with or without gonadal dysfunction is common in patients with thalassaemia with consequent deficiency of sex steroids. Hypogonadism is associated with low IGF-I secretion and can influence growth through the modulation of IGF-I induced cellular response and these effects can explain the loss and/or attenuation of pubertal growth spurt in BTM patients.^[39-42] Thalassaemic patients treated with androgen and/or human chorionic gonadotropin (HCG), to stimulate puberty have increased IGF-I levels associated with significant acceleration of growth.^[42]

Moreover, deprivation of GH and IGF-I delay the timely onset of puberty; slow the pace of pubertal maturation; attenuate phallic growth (human); and reduce adult testicular size. In thalassaemic patients, low IGF-I may contribute to all of these pathologic features.^[43]

Effect of anemia on IGF-I secretion in thalassemia

Correction of anemia by packed red cell transfusion increases IGF-I secretion and improves linear growth in thalassaemic children. However, increased level of Hb is inadequate to increase the level of GH secretion or IGF-I response to exogenous GH. These studies indicate that the effect of increasing Hb concentration on IGF-I secretion explains partial improvement of growth in well-transfused thalassaemic children.^[28,44]

Nutrition and IGF I in thalassemia

Nutrition is a major factor in growth and development. Low body weight, BMI, mid-arm circumference and skin fold thickness as well as low plasma values of essential amino acids are features of children with thalassemia suggesting a form of under-nutrition. Increased energy expenditure secondary to hyper-metabolism with or without heart failure, nutritional deprivation with or without feeding difficulties arising from fatigue, breathlessness and psychological problems and gastrointestinal hypoxia have been proposed as etiologic factors. In a prospective controlled study, children with thalassaemia major who received high caloric diet had significantly increased IGF-I levels, BMI, mid-arm circumference and skin fold thickness.^[45-47]

Vitamin D Deficiency and IGF-I in thalassemia

Vitamin D deficiency was detected in 50-100% of thalassaemic adolescents. An IM injection of a mega dose of cholecalciferol is an effective therapy for treatment

for 3 months. Vitamin D has been shown to increase circulating IGF-I and IGFBP-3 with the consistent finding of a positive correlation between vitamin D and IGF-I serum values in population-based cohorts of healthy subjects. Moreover, in children and adolescents, vitamin D deficiency can decrease IGF-I synthesis and their replacement has been associated with increased IGF-I synthesis and improved growth in thalassaemic patients.^[48-52]

Zinc deficiency and IGF-I in thalassemia

Zinc deficiency is observed in many thalassaemic patients due to chronic hemolysis, desferrioxmine therapy and increased urinary excretion.^[53-54] Zinc deficiency might contribute to delayed growth and decreased IGF-I synthesis in these patients.^[55-57] In fact, zinc supplementation can increase hepatic synthesis of IGF-I and is reported to increase linear growth in thalassaemic patients.^[58]

Chelation, liver and serum ferritin level, and IGF-I secretion in thalassemia

Stature growth appears to be significantly associated with the quality of chelation therapy during the prepubertal years in thalassemia.

Studies show that the state of chelation, as reflected by serum ferritin level, significantly affects growth and final height in thalassaemic patients. Those with higher serum ferritin grow slower and become shorter adults than those with lower ferritin concentrations.^[59-65] Recent data from our group show that IGF-I concentrations are correlated significantly with serum ferritin levels, the latter are correlated with hepatic enzyme levels (ALT and AST). These indicate that liver dysfunction, secondary to iron overload and/or hepatitis, may negatively affect growth in thalassaemic patients through defective hepatic IGF-I synthesis. Alternatively, certain hepatic complications, chiefly those of nutritional and metabolic in nature (insulin resistance, malnutrition, osteopenia, hypogonadism), may be or partly related to this IGF-I deficiency.^[66]

Hepatic stellate cells are stimulated by IGF-1 and high IGF-1 levels attenuate fibro genesis and accelerate liver regeneration. This effect is mainly mediated by upregulation of hepatic growth factor and downregulation of transforming growth factor β 1. Thus, decreased IGF-1 levels in thalassaemic patients may impair regeneration potential in patients with chronic hepatitis, cirrhosis, or fibrosis.^[67]

Thyroid and IGF-I in thalassemia

The frequency of hypothyroidism in thalassemia patients ranges from 6 to 30% among different countries depending on chelation regimens. Progressive worsening of thyroid

function is observed in 35% of thalassemic patients by the age of 18 years.^[68]

Thyroid hormones are among the important direct biological regulators of growth plate and bone accretion. In addition, thyroid hormones influence and interact with the GH – IGF-I system and other hormones that control stature and bone growth. Hypothyroid patients show low plasma levels of IGF-I and reduced IGF bioactivity. Besides, a hypothyroidism is associated with decrease in hepatic IGF-I messenger RNA (mRNA) expression. Correction of hypothyroidism is associated with increased IGF-I secretion and improved linear growth.^[69,70]

Parathyroid and IGF-I in thalassemia

Hypoparathyroidism is one of the important complications of BTM due to iron deposition notably in the second decade of life. The prevalence varies greatly from very low i.e. 4% to as high as 27%.^[71,72] IGF-I and PTH have synergistic actions on bone and some effects of the anabolic actions of PTH are mediated by local production of IGF-I, as has been shown *in vitro* and *in vivo* studies both in animals and humans.^[73] Therefore, prevention and treatment of hypoparathyroidism can possibly improve bone anabolism through increasing secretion and/or action of IGF-I.

IGF-I and osteoporosis in thalassemia

Osteoporosis and decreased bone mineral density has been described extensively in children and adult thalassemics. IGF-1 has a fundamental role to stimulate osteoblastic function and bone formation. IGF-1 has modest effects on the proliferation of cells of the osteoblastic lineage and enhances the function of the mature osteoblast.^[74] Additionally, IGF-1 upregulates collagen synthesis and decreases its degradation, which is important for maintaining the appropriate levels of bone matrix and bone mass. In addition, osteoclasts express IGF-1 receptors and IGF-1 has direct effects on their function.^[75] Defective GH - IGF-I secretion contributes to osteoporosis and demineralization in TM patients.^[76,77] In thalassemic children, bone mineral density is correlated with the circulating concentrations of IGF-I and IGFBP3, as well as with the auxanologic parameters (age, weight, height, HSDS, and BMI). It is suggested that increasing the circulating IGF-I concentration through aggressive nutritional therapy and/or GH/IGF-I therapy with supplementation of vitamin D and/or calcium might improve bone growth and mineralization and prevent the development of osteoporosis and consequent fractures in these patients.^[77]

IGF-I and heart in thalassemia

Heart disease represents the main determinant of survival in BTM. Cardiac involvement in thalassemia major (TM)

is mainly characterized by left ventricular dysfunction caused by iron overload.^[78] Heart remodeling with increased interstitial fibrosis and heart failure is persistent even with optimal chelation in BTM patients.^[79]

IGF-I possesses specific myocardial receptors and is able to promote cardiac remodeling and even inotropic effects in both humans and other animals. In fact, reduced cardiac mass and performance are present in GH deficiency and these alterations are counteracted by recombinant human GH replacement, restoring IGF-I levels. Recently, the acute administration of 60 µg/kg of rhIGF-I has also been reported to improve cardiac performance evaluated by echocardiography or impedance cardiography in normal subjects.^[80] The potential use of IGF-I therapy for thalassemic patients with heart failure has not yet been demonstrated.

CONCLUSION

Decreased IGF-1 secretion occurs in the majority of thalassemic patients especially those with growth and pubertal delay. Many factors contribute to this decreased synthesis of IGF-I including: [Figure 1].

1. GH deficiency, neurosecretory dysfunction of GH and partial resistance to GH (hepatic siderosis and bone), and/or IGF-I resistance
2. Delayed and/or failure of puberty due to hypogonadism with lack of stimulatory actions of sex steroids on pituitary release of GH and hepatic release of IGF-I and attenuation of pubertal growth spurt
3. Under-nutrition due to hyper-metabolism with a degree of caloric deficiency (macronutrient deficiency) or micronutrient deficiency (vitamin D, zinc) can impair IGF-I synthesis
4. Insufficient blood transfusion with significant periods of anemia
5. Inadequate iron chelation with iron overload of the pituitary gland (GH, LH, FSH, TSH deficiencies), liver (systemic IGF-I deficiency) and growth plate (local IGF-I deficiency) and the co-occurrence of other endocrine disorders such as hypothyroidism and diabetes mellitus.

Improvement of IGF-I secretion should be aimed at to improve linear growth and bone mineral accretion in thalassemic patients through adequate correction of anemia and proper chelation, nutritional supplementation (increasing caloric intake), correction of vitamin D and zinc deficiencies, induction of puberty and correction of hypogonadism and hypothyroidism at the proper time and treating GH deficiency.

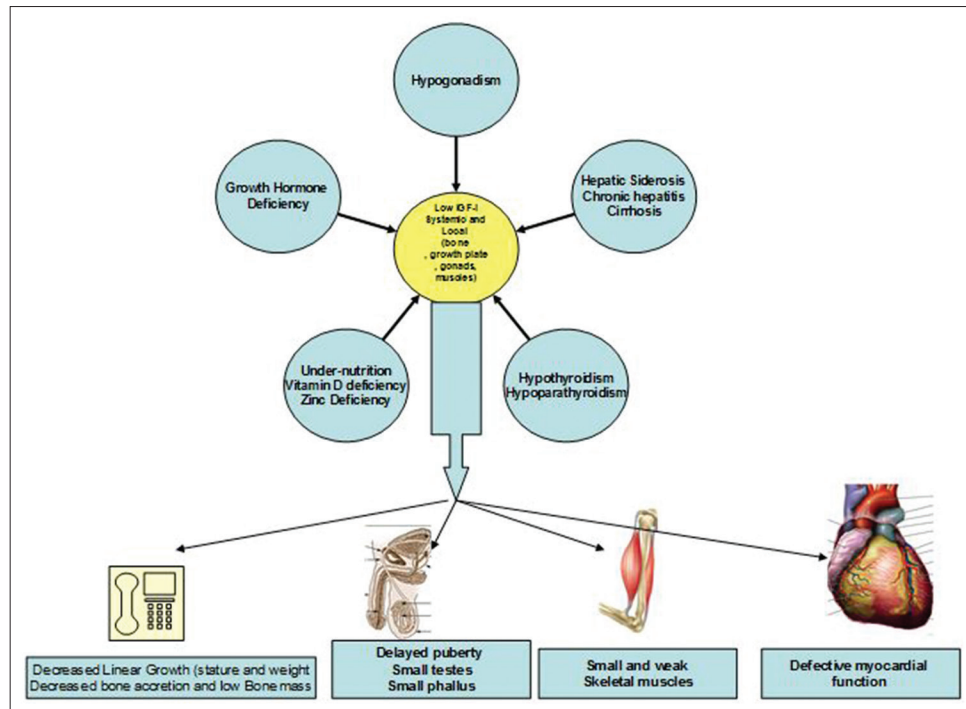


Figure 1: Etiology and pathological effects of low IGF-I secretion in thalassemic patients (From: Ashraf T Soliman, 2013)

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Cite this article as: Soliman AT, Sanctis VD, Elalaily R, Yassin M. Insulin-like growth factor- I and factors affecting it in thalassemia major. *Indian J Endocr Metab* 2015;19:245-51.

Source of Support: Nil, **Conflict of Interest:** None declared.