

IGF-1 Therapy in Children with Liver Dysfunction

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ABSTRACT

Human growth and development occur as a result of numerous processes which gets initiated under the influence of endocrine hormones. Insulin-like growth factor 1 (IGF-1) plays a most pivotal role in the growth and organ development of a child. IGF-1 is a peptide that belongs to somatomedins group of hormones, also known as somatomedin C. It releases from the liver and other tissues under the influence of growth hormone (GH). The liver is the main protagonist source of IGF-1 hence any disease that can cause liver dysfunction will eventually lead to growth impairment. During the period of growth regulation with GH therapy in liver disease and/or post liver transplantation, the persistent deficiency of IGF-1 proves to be a big challenge to therapy. Growth hormone therapy together with IGF-1 infusion can lead to good results on growth. Therefore, it is important to focus on IGF- level in serum along with Growth hormone while treating a child with poor growth in chronic liver disease and after liver transplantation. The role of IGF-1 therapy should also be considered for better growth and development.

KEYWORDS: IGF-1 synthesis, Role in growth, Liver dysfunction.

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INTRODUCTION

Insulin-like growth factor (IGF-1) is a small peptide, molecular weight 7647 and shares structural similarities with the insulin molecule [1]. It is also known as Somatomedin C [2]. Initially, it was termed as sulfation factor [3]. It was also known to show non-suppressible insulin-like activity (NSILA) [4].

In 1970's these names were replaced by somatomedins [5]. By 1980's, it was labelled as insulin-like growth factor possibly because of its similarities to the insulin molecule [2,5]. Primarily, IGF-1 is produced by the liver. But since, it is also released from the target tissues, it is responsible for its paracrine and autocrine function [6]. In intrauterine life, IGF-1 is present at approximately 20% of its normal range [7]. IGF-1 levels fluctuates with age; the lowest levels are found in infancy and old age, while peak are seen at puberty [8].

Regulation of IGF-1

There are different factors that regulate IGF-1 level in serum such as age, nutrition, growth hormone, and some other hormones. However, growth hormone and nutrition are considered as the prime regulators of IGF-1 expression on liver. The IGF-1 level in serum varies with age, where very low concentration in infancy that reach to the maximum level at puberty and then gradually tapering off till old age. This phenomenon is called "Somatopause" [8].

Nutrition also plays an important role in regulation of IGF-1. Deprivation of energy and protein leads to significant decline in the serum levels, while on the other hand, some minerals and dairy products boost up the IGF-1 level [9].

Growth hormone (GH) is the main regulator of IGF-1. GH stimulates the liver and other target tissues to synthesize IGF-1 which then gets released in free form and binds to high-affinity carrier proteins (IGFBP) in serum. More than 99 percent of IGF-1 exists in the serum bound to IGFBP. High level of IGF-1 in serum has negative feedback on the pituitary gland which inhibits the secretion of GH [10].

Children with congenital hypothyroidism have generally low level of IGF-1. It is observed that the IGF-1 levels increases while treating them with thyroxine. In contrast estrogen has an insignificant role in the regulation of IGF-1 [11].

Mechanism of Action

IGF act as a primary mediator of growth under the influence of growth hormone [12]. Growth hormone also influences its secretion from liver and other target tissue like bone, cartilage, and some solid organs; except before birth, where its secretion is not influenced by growth hormone [13].

The secretion of GH from somatotroph cells in the anterior pituitary gland exerts its effects via two routes. By acting upon growth hormone receptors (GHR), it stimulates the liver and other target tissues to release IGF-1 which leads to an increase in linear growth of the children [13].

In serum, as already mentioned above, IGF-1 is found in two forms, free and bounded to IGFBP form. Later on, it binds to IGF-1 receptors on cells and triggers intracellular cascade series of signals that lead to cell growth, differentiation, and transformation [14]. It has been also depicted in figure 1.

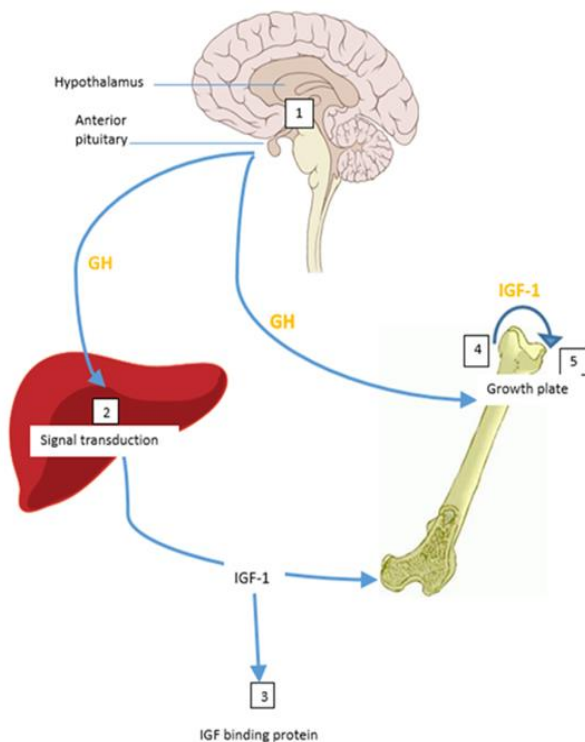


Figure 1. Secretion of IGF-1 from different routes.

The numbers in the figure 1 are as follows

1. Appetite centre,
2. Signal transduction in liver cells,
3. Release of IGF-1 from binding proteins,
4. IGF-1 expression in growth plate,
5. Proliferation of chondrocytes at growth plate.

Role of IGF-1 in Growth Regulation

IGF-1 has growth promoting effects, with dependent or independent of growth hormone. Growth hormone accelerates its action to help in regulation of somatic growth and organ development in children. It has been seen in animal studies that it also plays an important role in brain development [15-18].

IGF-1 has the significant role in the linear growth and skeletal development [10]. IGF-1 releases from both of the mechanisms, from the liver and the target tissues are important for normal postnatal growth. The major fetal factor is thought to be IGF-2 while postnatal growth is mostly by IGF-1 and genetic studies show that they contribute equally to final height [19,20].

The pygmies of Africa were reported to be born with congenital anomalies which made them unable to synthesize a significant amount of IGF-1 and subsequently, resulted in small stature, regardless of the growth hormone levels [21].

IGF-1 not only helps in somatic growth but also has an influence on the pulsatile releases of GnRH at a different stage of age that determine the onset of puberty [22]. Few studies also show that IGF-1 also plays an important role in developing the cognitive function of the brain while decrease in GH has a boosting effect on cognition [23-24].

IGF-1 in Liver Dysfunction

The liver is the source of most (75%) of plasma IGF-1 which is crucial for growth and development of children [6]. Hence, any factor that causes impairment of IGF-1 levels can notably influence the growth processes.

Chronic liver disease is a major factor that leads to decrease in linear growth, probably due to the low level of IGF-1 in serum and IGFBP, where IGFBP has comparatively less role because it is also secreted from other tissues [25,26].

In liver dysfunction, IGF-1 level gets decreased by two possible mechanisms, a decrease in GH receptors and decrease synthesis from liver.

In beta Thalassemia major, child present with a growth and maturation delay, particularly in which body is disproportionately shortened truncal wise but extremities shall be normal generally. This abnormal or poor growth is due to variety of factors including decrease levels of IGF-1 which plays the fundamental role in growth regulation [27].

Similarly, in another chronic liver disease such as chronic Cholestatic liver disease, a decrease in bone mass devalues the GH therapy. However, studies showed that alteration in IGF-1 level in chronic Cholestatic disease has a great impact on it [27].

In patients of chronic liver disease waiting for liver transplant, generally show resistance to GH, so here IGF-1 therapy should be considered [28].

Effects of IGF-1 therapy

Children with chronic liver disease present with impaired growth and short stature secondary to decrease food intake, malabsorption and abnormalities of GH-IGF system, including resistance to GH [29].

The chronic liver disease leads to low level of IGF-1 in serum while growth hormone stays normal. Such is a case of cystic fibrosis in which the patient presents with poor growth because of the low level of IGF-1, hence treating them with rGH can improve growth impairment to some extent probably due to increasing production of IGF-1 from the liver [28,30].

Nutritional deficiency also occurs in CLD that contributes to growth impairment, therefore IGF-1 infusion into a human whose on sub-optimal nutrition restores nitrogen balance to normal. Similarly, co-administration of GH and IGF-1 induces positive nitrogen balance in calorically restricted humans [31].

IGF-1 therapy is effective in children with GH insensitivity due to GH receptor mutation. FDA has approved 2 drugs that contain recombinant IGF-1, alone and together with GH which if given to the patient can boosts up growth in a child with IGF-1 deficiency [32].

A child with CLD/end-stage liver disease (ESLD) doesn't respond well to growth hormone replacement therapy possibly because of persistent deficiency of IGF-1. Therefore, co-administration of GH and IGF-1 in these patients help in good catching up on growth.

The best way to prevent this disorder, is to educate the parents and children including the adolescents, so that if there is disorder, then proper treatment can be given.

Now a days, even the children and adolescents are well educated and have great health awareness, which has helped in decreasing many disorders [33]. Hence, the role of IGF-1 therapy should also be considered for better growth and development.

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