Insulin-Like Growth Factors, Nutrition and Growth

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Abstract

Nutritional status is a key factor in the regulation of human linear growth. The growth hormone (GH)-IGF axis consists of a cascade of finely tuned molecular mechanisms which are vulnerable to protein-calorie deficiency. The most notable evidence for this is the presence of IGF-1 deficiency, that can be caused by failure of a number of processes including abnormal pituitary GH secretion, decreased GH binding to its receptor (GHR), post-GHR signal transduction, IGF-1 gene transcription, IGF binding protein (IGFBP) deficiency and decreased IGF-1 binding to its own receptor (IGF1R). Nutritional deficiency is seldom present as an isolated pathogenesis. In diarrhoeal states, intercurrent infection is frequently present which impairs the function of the growth plate. In chronic inflammatory disorders, where nutritional deficiency may be present due to increased energy expenditure, co-existing excess cytokine production also disrupts the GH-IGF-1 axis causing a complex mixed pathogenesis.

Linear growth is a physiologic process which takes place during human fetal life, infancy, childhood and puberty. As a quantifiable index of general health, growth is vulnerable to pathological insults of which insufficient nutritional support ranks highly, particularly on a global level. Protein-energy malnutrition remains a major public health problem, notably in developing countries. According to the World Health Organisation, one third of children around the world and 43% in developing countries suffer from protein-energy malnutrition and as a result have compromised linear growth [1].

This chapter discusses the mechanisms by which malnutrition can disturb growth physiology. Dysfunction of the growth hormone (GH)-IGF axis will be reviewed, with evidence of disturbance of its key mechanisms ranging from pituitary GH secretion, GH binding to its cell-surface receptor (GHR), post-receptor signal transduction, IGF-1 gene transcription and IGF-1 secretion, transport and binding to the type
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1 IGF-1 receptor (IGF1R) [2]. Pure malnutrition however is rare in childhood clinical pathology, usually being combined with infection, particularly in diarrhoeal conditions, or with excess secretion of pro-inflammatory cytokines [3] in chronic disorders such as coeliac disease, cystic fibrosis and Crohn’s disease. The interface between nutritional deficiency and the effects of increased cytokine concentrations on growth physiology will also be discussed.

**Role of IGF-1 in Human Linear Growth**

The human insulin-like growth factors (IGFs) are small single chain peptides of 7.5 kDa composed of 70 amino acids for IGF-1 and 67 amino acids for IGF-2. This chapter will concentrate on IGF-1 which is the key effector peptide for childhood linear growth in response to stimulation by growth hormone (GH). The actions of GH are mediated by a combination of components of the IGF system, including IGF-1, IGF-binding proteins (IGFBPs), the IGF1R and IGF-independent effects through direct GH action. The original ‘somatomedin hypothesis’ proposed that GH binding to its receptor stimulated IGF-1 production, which independently affected growth [4]. However, the discovery that IGFs are expressed in most tissues questioned this original hypothesis. The ‘dual effector hypothesis’ was proposed in 1985, based on studies with adipocytes, suggesting that GH regulates the expression of locally produced IGF-1, which then acts in an autocrine/paracrine manner [5]. Expression of the *IGF1* gene was found in multiple tissues throughout embryonic and post-natal development [6]. In addition, injection of GH into hypophysectomized rats increased *IGF1* mRNA in numerous non-hepatic tissues [7].

These and other studies suggested that GH stimulated differentiation of chondrocytes in the growth plate, while IGF-1 stimulated their clonal expansion. Le Roith and colleagues presented a revised somatomedin hypothesis in 2001 [8], taking into account gene deletion experiments in mice that questioned the role of liver IGF-1 and its circulating endocrine form in controlling post-natal growth. Liver-specific *Igf1* knockout mice grow normally despite significant reduction in circulating IGF-1, indicating that locally produced IGF-1 is an important growth mediator [9]. The so-called augmentative/counteractive hypothesis was then proposed suggesting that the IGFs are augmentative hormones that amplify the anabolic actions of GH while countering the potentially undesirable GH effects of gluconeogenesis and lipolysis [10].

In addition, serum levels of the acid-labile subunit (ALS) and IGF-binding protein (IGFBP)-3 which are regulated through the GHR are important for maintaining circulating IGF-1 [2]. Human pre-natal growth is regulated principally by nutritional supplies, which influence fetal IGF-1 and, perhaps, IGF-2 [11]. The importance of normal IGF-1 production in humans was confirmed by the pre-natal growth failure reported in patients with *IGF1* and *IGF1R* gene mutations [2].
Growth Hormone-GH Receptor Regulation of IGF-1

Pituitary-derived GH exerts its growth effects primarily by regulating the expression of IGF-1 (fig. 1). The binding of GH to cell surface GH receptors (GHR) on hepatic and nonhepatic (peripheral) tissues leads to the recruitment of JAK2, which phosphorylates tyrosine residues within GHR, resulting in activation of the STAT, MAPK and other signalling pathways [2]. In the liver, STAT5b signalling is most critical for the regulation of IGF-1. Cytosolic STAT5b, recruited to the activated GH–GHR complex, is itself phosphorylated by JAK2, and translocates to the nucleus as a dimer, where it binds to GH responsive elements on genomic DNA and transcriptionally regulates IGF1, as well as IGFBP3 and IGFALS gene expression [12]. The resultant peptides, IGF-1, IGFBP-3, and ALS, circulate in serum as a ternary complex. Circulating IGF-1 is delivered and binds to IGF-1 receptors (IGFIR) on IGF-1-responsive cells and tissues, ultimately leading to cell proliferation and other metabolic effects. In nonhepatic tissues, GH, as well as other growth factors and cytokines, can exert local growth effects by regulating IGF-1 production (fig. 1).

Effects of Malnutrition on the GH-IGF-1 Axis

Role of Protein Intake
Serum IGF-1 levels are decreased in patients with protein-calorie malnutrition [13, 14]. Serum GH levels are also often abnormal, being increased in acutely malnourished patients [14], but decreased after long-term nutritional deficit. In nutritionally restricted rats chronic malnutrition significantly impairs pulsatile secretion of GH. However administration of GH to fasted or protein restricted rats does not produce a normal increase of IGF-1 in the blood demonstrating that GH resistance is present. Evidence suggests that malnutrition causes reduction in hepatic binding of GH to the GHR contributing to low IGF-1 levels [14]. However in rats there was only a negligible decline in the number of somatogenic-binding sites which suggests that a post-receptor defect may participate in the GH resistance observed in protein restriction [14]. It is likely that limited amino acid availability also impairs IGF-1 gene expression. A summary of the effects of malnutrition on the GH-IGF-1 axis is shown in figure 2.

Effects on Insulin and IGF Binding Proteins
Dietary restriction also causes insulin concentrations to decrease [15]. Insulin may regulate serum IGF-1, probably through changes in liver GH binding and also potentiates the stimulatory effect of GH and amino acids on IGF-1 production, acting at a transcriptional level [14]. The IGFBPs prolong the plasma half-life of IGF-1 and thus influence the rate of IGF transport from the vascular compartment to its receptor on the cell surface [2]. Nutrient intake is a major regulator of the IGFBPs, dietary manipulations changing the abundance of serum IGFBPs in humans and animals. In general, dietary restriction
decreases IGFBP-3 and increases IGFBP-1 and IGFBP-2. The affinity of IGFBP-3 for IGF-1 is also decreased which in theory might increase the bioavailability of IGF-1 for the tissues. However, in humans with malnutrition, as in other situations of IGF-1 deficiency, protease activity is increased which destabilises the circulating 150 kDa ternary complex, hence increasing IGF-1 clearance [16] and diminishing IGF-1 bioactivity.

**Effect on Peripheral IGF-1 Production**
Growth hormone stimulates hepatic IGF-1 production controlling circulating levels of IGF-1 and also has a direct effect on ‘peripheral’ IGF-1 production resulting in its autocrine or paracrine actions [8, 9]. As discussed above, protein-energy restriction...
modulates the responsiveness of the liver to GH and thus decreases circulating IGF-1. Elegant studies from Le Roith’s group have also demonstrated that in a liver-specific IGF-1-deficient mouse model, in which circulating IGF-1 is decreased by 75%, protein calorie malnutrition also affects peripheral IGF-1 production [17]. Liver-specific IGF-1 deficient mice were fed protein restricted diets for a period of 10 days. The animals with a low protein intake showed decreased nonhepatic IGF-1 secretion and increased circulating GH. Consequently, both hepatic and peripheral IGF-1 production is vulnerable to impaired protein and calorie intake.

Clinical States of Malnutrition Affecting the IGF System

Nutritional Deficiency in Developing Countries
In children with protein-energy malnutrition serum IGF-1 levels are significantly decreased. This was demonstrated in patients from Egypt under 3 years of age with marasmus or kwashiorkor whose IGF-1 levels correlated with the degree of percentage weight deficiency being markedly decreased compared to normally nourished subjects [13]. During nutritional rehabilitation, IGF-1 increased into the normal range. It appears however that IGF-1 levels do not have a linear relationship with nutrient status and it is likely that nutrient intake must be reduced to a critical threshold before IGF-1 in serum declines [14]. In terms of restoration of normal IGF-1 levels, sufficient energy intake is also essential. Protein intake, particularly including essential amino acids, will only result in induction of an anabolic state when energy intake is adequate [18].
Similar experience was demonstrated in malnourished children in Burkina Faso [19]. Fifty nine children aged less than 3 years were hospitalised for nutritional rehabilitation, of whom 55 had marasmus, 2 kwashiorkor and 2 marasmus and kwashiorkor. Out the 57/59 children with a weight for height SDS of <-2, 51 (89.5%) had an IGF-1 SDS value of <-2. After 14 days of nutritional rehabilitation, 37.9% had a weight for height SDS of >-2 and 91% of these children also attained an IGF-1 SDS of >-2. The recovery of IGF-1 and linear growth during treatment of malnutrition is also dependent on normal zinc status as was reported in growth-retarded Vietnamese children [20]. It is likely that zinc deficiency limits growth in nutritionally deprived children because zinc supplementation was associated with increase in both growth velocity and serum IGF-1.

Interface of Nutritional Deficiency and Inflammatory Cytokine Secretion on Chronic Inflammatory Disorders

As described above, the function of the GH-IGF-1 axis depends on finely tuned mechanisms, which can be influenced by non-endocrine factors seen in states of nutritional deficiency. Pure nutritional deficiency, however, is rare and in chronic disorders such as coeliac disease, Crohn’s disease and cystic fibrosis an added pathogenetic mechanism is present in the form of chronic inflammatory activity resulting in excessive pro-inflammatory cytokine secretion. In these three disorders catabolism is present combined with increased energy expenditure and deficient nutritional support [3]. Pro-inflammatory cytokine secretion combines with nutritional deficiency to cause reduction in serum IGF-1 (fig. 3). Inflammatory cytokines, notably tumour necrosis factor (TNF)-α, interleukin-6 (IL-6) and interleukin-1β (IL-1β) have been shown to decrease liver GH receptor numbers and disturb STAT 5b phosphorylation and IGF-1 gene transcription [4]. Nutritional deficit can also impair GH secretion and increase protease activity to reduce the stability of the ternary complex and decrease the affinity of IGF-1 for its carrier proteins, IGFBP-3 and ALS. Changes in the GH-IGF-1 axis combine to create a state of relative GH resistance, which is manifested both in Crohn’s and cystic fibrosis disease by decreased or subnormal serum IGF-1 concentrations [21] and by impaired linear growth.

Conclusions

Normal nutritional status is required for physiological linear growth to proceed in childhood. Nutritional deficiency may disturb the function of a number of mechanisms within the GH-IGF-1 axis leading to a characteristic biochemical triad of low IGF-1, low insulin and increased GH levels. The combination of low IGF-1 and high GH indicates the presence of GH resistance. Both protein and calorie replacement,
together with adequate zinc and micronutrient status, are required for catch-up growth and normalisation of IGF-1. In childhood, nutritional deficiency is frequently associated with infections in developing countries and with increased cytokine secretion in chronic paediatric disorders. Such disorders also impair linear growth and the strategy for their effective management consists of dietary supplementation combined with anti-inflammatory medication aimed at restoring the functional integrity of the endocrine control of growth.

References


