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Nutritional Regulation of Growth Hormone/ Insulin-like Growth Factor-1 Axis

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Abstract

The growth hormone (GH)/insulin-like growth factor-1 (IGF-1), a central growth-regulatory system in human, can be affected by multiple factors, of which nutrition is an important regulatory factor. Low GH/IGF-1 status is usually regarded as a functional condition of nutritional disorder, and it could be largely reversible after a nutritional supplement. The GH/IGF-1 axis consists of a series of finely regulated molecular mechanisms that are susceptible to protein calorie deficiency. In addition, malnutrition could induce the nutritionally responsive proteins that block hepatic GH signal transduction by inhibiting the JAK/STAT pathway, thereby limiting the generation of IGF-1. Taken together, nutrition is an important regulator of for human growth and development. However, to date, the association between nutrition and GH/IGF-1 axis remains incompletely understood. The present paper aims at reviewing existing literatures on the probable effects of nutrition on the GH/IGF-1 axis.

Keyword: Nutrition; Growth hormone/insulin-like growth factor-1 axis; Growth; Intervention

Introduction

The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis is critical for the regulation of linear growth in children. GH stimulates transcription of IGF-1 in the liver, resulting an increased IGF-1 concentration, which mediates many of the growth-promoting effects of GH. Insufficient or lack of IGF-1 can present clinically as short stature. IGF-1 concentration is usually affected by multiple factors, apart from genetics and hormones, especially nutrition has been considered to be the key factor for IGF-1. Moreover, IGF-1 level is sensitive to short and long-term changes in the nutritional state. Based on the information above, the accurate assessment of IGF-I level is essential to understand the nutritional status of children. This review aimed at pointing to some of the key aspects of the association between nutrition and GH/IGF-1 in light of recently published studies.

Role of GH/IGF-1 axis in Regulation of Linear Growth

.Linear growth is a physiological process that occurs during human fetal life, infancy, childhood, and puberty. The GH/IGF-1 axis is central to the regulation of linear growth. The GH releasing hormone (GHRH), GH receptor (GHR), GH, IGF-1 receptor (IGF-1R) and IGF-1 were the main members of that axis. IGF-binding proteins (IGFBPs), the acid labile subunit (ALS) that carry IGF-1 in circulation, and the GHR downstream mediator, such as the Signal Transducer and Activator of Transcription 5 (STAT5) and Janus kinase 2 (JAK2) involved in the functional regulation of axis [1]. Its main mechanism for regulating growth is as follows: Firstly, hypothalamus secretes GHRH and somatostatin, the secretion of GH from the pituitary is promoted by GHRH, whereas is inhibited by somatostatin [2]. Then, the combination of GH and GHR causes the conformation change of the receptor's intracellular domain and intracellular domain binds JAK2 [3]. This activates related signaling pathways, especially the STAT5 which stimulates transcription of IGF-1 [4]. Serum levels of the IGFBP-3 and ALS, which prolong IGF-1 half-life in serum and regulates IGF-1 bioavailability, are important for maintaining the level of IGF-1. Finally, IGF-1 binds to the tyrosine kinase receptor IGF-1R, which allows IGF-1 to stimulate chondrocyte proliferation in growth plates by activating osteoblast differentiation programs, providing a major stimulus for bone growth regulation [5].

Effects of Nutrition on the GH/IGF-1 axis

IGF-1 concentration is usually affected by multiple factors, apart from genetics and hormones, especially nutrition has been considered to be the key factor for IGF-1 [6]. Nutrition has been described as having a profound effect on the GH/IGF axis

[7]. Either malnutrition or overnutrition both have adverse effect on IGF-1 concentration and low GH/IGF-1 status could be largely reversible after a nutritional intervention [8].

Effects of malnutrition on the GH/IGF-1 axis

Children with malnutrition can present with poor growth and development. Although the exact mechanism remains unclear, a lot of evidence have shown that a reduction of IGF-1 concentration has a major role in growth restriction mediated by malnutrition. It was reported that malnutrition significantly reduced circulating concentrations of IGF-1 in mice [9-10]. Additionally, a number of observational studies have found that malnourished children showed higher serum levels of GH and lower hepatic production of IGF-1, suggesting a state of GH resistance [11-13]. Considering GH is an anti-regulation hormone that mobilize energy reserves during malnutrition, increased GH can be measured in a state of malnutrition [14]. Malnutrition can alter the GH/IGF-1 axis at multiple levels including decreasing expression of GHR and IGF-1 mRNA in liver [15-16], accelerating IGF-1 decomposition, and reducing the biological activity of serum IGF-1 [17].

Effects of Overnutrition on the GH/IGF-1 axis

Obesity is considered as a reliable indicator of evaluating overnutrition [18]. Obese population usually present a low GH status as evidenced by a study that per unit of body mass index (BMI) increased could decrease the secretion of GH by 6% [19]. Another study conducted in short children reported that BMI SDS negatively associated with the peak GH level [20]. Therefore, the application of GH provocative testing in obesity may also lead to an incorrect diagnosis of GH deficiency (GHD). The underlying mechanism may be that obesity enhances the regulation of somatostatin and attenuates GHRH regulation [21]. In addition, insulin resistance is also contributing to a decreased GH secretion in obesity [22]. Nevertheless, IGF-1 concentration measured in obese population is inconclusive, it can present with low IGF-1 [19], normal IGF-1 [23] or high IGF-1 levels [24]. Moreover, Cornford AS et al found that increased IGF-1 bioactivity was caused by decreased IGFBP-1 expression in obese population [24].

Nutritional Intervention Improves GH/IGF-1 status

It was well established that nutritional intervention could improve IGF-1 concentration. IGF-1 concentration is considered to be related to nutritional intake from infancy [25]. Hoppe et al. demonstrated that milk intake was positively correlated with IGF-1 concentration. They found that increased milk intake from 200 to 600ml/day contributes to a 30% increase in IGF-1 concentration [26]. Further investigation of the components in milk showed that casein has a major role in stimulating the growth of children [27]. In addition, Zn is important for the metabolic activity of more than two hundred enzymes. It was reported that Zn supplementation has positive effects on growth and IGF-1 levels both in Zn-deficient and non-Zn-deficient children [28-29]. However, the exact mechanism of action has not been well delineated.

Conclusion

This paper provides an overview of the effect of nutrition on the GH/IGF-1 axis. Normal nutritional status is essential for linear growth in childhood. IGF-1 concentration is sensitive to short and long-term changes in nutritional status. Either malnutrition or overnutrition may have an adverse effect on GH/IGF-1, whereas normal nutritional status has a beneficial effect. In addition to GH and IGF-1 treatment, nutritional supplementation is also a therapy option for increasing growth of children and adolescents. Further studies is needed to conduct on the ecologically relevant changes in food intake to determine the importance of nutrition as an environmental regulator of the GH / IGF-1 axis.

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