Chapter 5
Undernutrition, Inflammation and Catabolic Illness, and Growth Hormone Secretion

Charumathi Baskaran and Madhusmita Misra

> Adapt or perish, now as ever, is nature's inexorable imperative.
>
> H.G. Wells.

Introduction

The adjustment that the human body undergoes in states of fasting and chronic starvation is a fascinating example of nature's indispensable phenomenon of adaptation. In an attempt to preserve basic metabolic functions and to provide essential fuels to the brain, malnourished individuals develop a state of growth hormone (GH) excess, which should facilitate increased lipolysis and availability of gluconeogenic substrates, while hepatic GH resistance results in low insulin-like growth factor-I (IGF-I) levels and conservation of energy otherwise expended for primarily IGF-I-dependent functions (such as statural growth and bone accrual). The neuroendocrine secretion of GH is profoundly sensitive to alterations in nutritional status, with this regulation being species specific. Humans are characterized by GH resistance that is associated with elevated GH and low IGF-I levels. In contrast, rodents exhibit low systemic levels of GH [1] and yet demonstrate GH resistance with decreased IGF-I response to GH injections and infusions [2].

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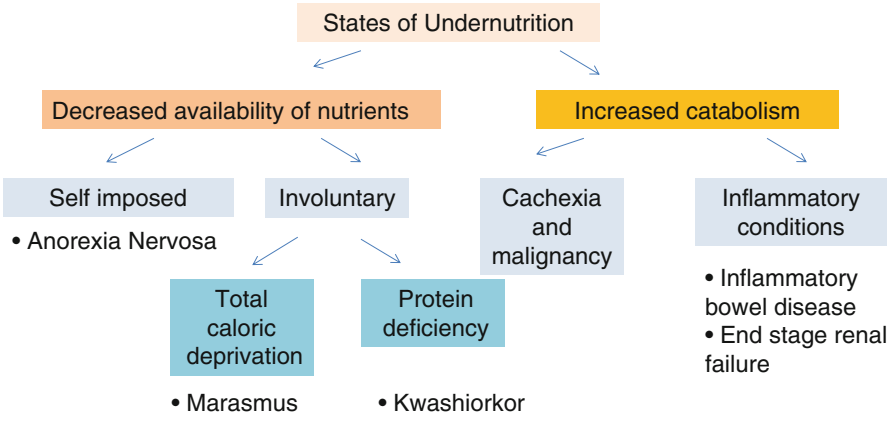
Normal Growth Hormone Secretion

Growth hormone is secreted in a pulsatile manner with pulse dynamic studies revealing ten pulses lasting for about 104 min over the course of 24 h [3]. The two major regulators of GH secretion are growth hormone-releasing hormone (GHRH), which stimulates GH secretion, and somatostatin (SRIH), which inhibits secretion of GH. Multiple other physiological factors influence the secretion of GH including age, sex, nutritional status, and the state of wakefulness and hunger. As discussed in earlier chapters, by virtue of being a peptide hormone, actions of GH are mediated through receptors and second messengers. GH acts on the liver to induce the production of IGF-I through signaling along the Janus kinase (JAK) signal transduction and activators of transcription (STAT) pathway, which mediates most of GH effects. In the following sections, we will examine alterations in GH secretion and action in conditions of undernutrition.

Growth Hormone Concentrations in States of Undernutrition

For ease of understanding, we will classify undernutrition as states resulting from (i) decreased availability of substrate (involuntary or self-imposed) and (ii) increased catabolism, as seen in conditions of cachexia and inflammatory conditions.



Decreased Availability of Nutrients

Decreased energy availability can be classified into conditions that result from acute energy limitation as in fasting or from long-term food and nutrient deprivation. Chronic malnutrition consequent to decreased food availability is relatively rare in

the modern era, although still evident in developing countries. A chronic reduction in energy availability can further be categorized as complete caloric deprivation as in marasmus or limited to specific nutrients such as proteins as in kwashiorkor.

Involuntary Reduction in Nutrient Availability

Both acute and chronic malnutrition result in increased GH levels. In one study in humans, 5 days of fasting led to an increase in GH pulse frequency and maximum pulse amplitude [4] with a decrease in IGF-I levels. Similar to the fasting studies, GH levels have been found to be elevated in patients with marasmus and kwashiorkor [5–8]. Additionally, in some of these studies, because protein supplementation in addition to caloric replenishment, but not caloric replenishment alone, led to restoration of GH levels, severe protein deficiency is believed to be a stimulus for increased GH secretion [6]. These findings lead to the general consensus that GH levels are high in conditions of undernutrition.

Despite high GH levels, children with protein-energy malnutrition have low systemic IGF-I (consistent with a state of GH resistance) that improves with protein supplementation [5]. Furthermore, multiple authors have demonstrated low IGF-I levels in humans following fasting and malnutrition [8, 9]. The concluding evidence for GH resistance came from studies such as that of Shapiro et al., which demonstrated that there was a lack of increase in IGF-I following administration of human/bovine GH in protein-malnourished animals [10].

Of note, in one of the early studies from the 1960s, malnourished infants who failed to demonstrate weight gain despite receiving an appropriate dietary regimen were treated with 2 mg human GH (hGH) extract weekly for 4 weeks. GH therapy led to significant weight gain (15 ± 8 g/day vs. 1.1 ± 0.4 g/day without treatment), possibly from its anabolic effects on the muscle [11]. Indeed, these patients had significant retention of nitrogen, phosphorus, and potassium following GH administration, as indicated by metabolic balance studies, suggesting better utilization of these sources with GH treatment.

Hypoglycemia and stress associated with undernutrition, and predominantly the low IGF-I levels found in these conditions, act as stimuli to increase GH production. The direct lipolytic effect of GH results in increased availability of free fatty acids to the brain, an important metabolic fuel. Additionally, low IGF-I level results in decreased protein synthesis in a compromised state of nutrition. Changes in the GH-IGF-I axis in states of starvation are likely an adaptive response to preserve energy for vital bodily functions at the cost of stunted growth.

Factors Influencing Secretion and Action of GH in Marasmus and Kwashiorkor (Fig. 5.1)

Hypothalamus: Role of GHRH and SRIH Animal studies investigating mRNA expression of GHRH and SRIH in chronically food restricted sheep show an increased expression of GHRH in the arcuate nucleus and decreased expression of

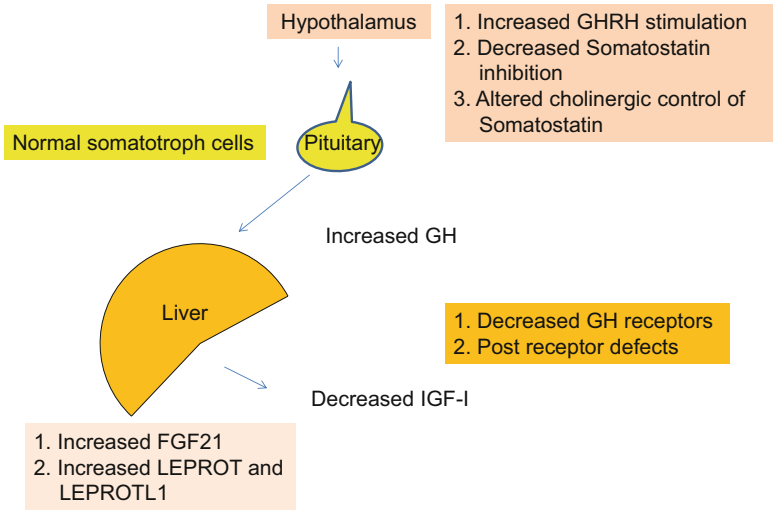


Fig. 5.1 Mechanism mediating GH resistance in under nutrition

SRIH in the rostral periventricular and ventromedial nuclei of the hypothalamus [12]. Further, some studies have speculated that increased GH secretion by the pituitary somatotrophs may be a consequence of reduced sensitivity of pituitary cells to the inhibitory effect of SRIH [13].

Pituitary Studies assessing changes in pituitary morphology and histology in conditions of chronic energy depletion have reported conflicting findings with Paullada [14] reporting no morphological changes in the pituitary, Zubiran and Gomez-Mont reporting degenerative changes in the pituitary, and Tejada and Russfield reporting hypertrophy of trophic cells in autopsies of children with protein-energy malnutrition [15, 16].

Studies evaluating GH secretion in response to provocative stimuli in children with malnutrition have also had variable results. One study suggested that children with marasmus may have impaired GH secretion following arginine stimulation, whereas children with kwashiorkor have a robust response [17]. Subsequent studies confirmed normal GH secretion in both marasmus and kwashiorkor [18, 19].

Liver: Receptor and post-receptor modifications A proposed mechanism for low IGF-I production in conditions of chronic energy deficiency despite robust GH secretion is a reduction in GH receptor expression [20]. Young rat pups aged 3, 6, and 8 weeks that were fed a low-protein diet (~5 % of total caloric intake) for a week demonstrated decreased number of hepatic GH receptors associated with low IGF-I levels. However, the lack of an association between decreased hepatic GH receptors and IGF-I levels in older rat pups led the authors to propose a post-receptor defect in the nutrient-deficient state in addition to decreased GH receptor expression. Further evidence of a post-receptor defect comes from a lack of increase in

IGF-I levels in these animals despite normalization of GH receptors with continuous GH infusion [2]. Furthermore, the same authors demonstrated the inability of recombinant IGF-I to produce adequate tail growth in protein-deficient rats suggesting an element of IGF-I resistance in these animals [21].

More recently, multiple other mechanisms have been proposed by researchers to explain this state of GH resistance in malnutrition. FGF21, which belongs to the family of fibroblast growth factors, has gained significant interest in this front with fasting studies showing increased expression of FGF21 in the liver and cartilage [22]. FGF21 has further been shown to mediate GH resistance through its inhibitory action on STAT-5 (which otherwise potentiates GH action) [23] resulting in decreased IGF-I production. In addition, it has been proposed that GH resistance by FGF21 is mediated by increased expression of leptin receptor overlapping transcript (LEPROT) and LEPROT-like 1 (LEPROTL1) [24]. LEPROT and LEPROTL1 are genes that code for small proteins that regulate intracellular protein trafficking. Importantly, overexpression of LEPROT and LEPROTL1 is associated with decreased cell surface GH receptors [25]. When compared with animals fed ad lib, the expression of LEPROT and LEPROTL1 in the liver and cartilage was increased in rats that were food restricted for 4 weeks. Further this increase was not noted in FGF21 knockout animals, indicating that FGF21 might act via the LEPROT and LEPROTL1 to cause GH resistance [24].

Another factor postulated to mediate GH resistance through STAT-5 inhibition is Sirtuin1 (SIRT1). Yamamoto et al. reported that SIRT1 was able to inhibit GH-induced IGF-I production in hepatocytes through its inhibitory effect on STAT-5 [26].

Self-Imposed Food Restriction: Anorexia Nervosa (AN)

Low body weight is a distinctive feature of this common psychiatric disorder that is characterized by an abnormal body image and an intense fear of gaining weight. This disorder is the most frequent cause of mortality in adolescent girls, and its effects on the GH-IGF-I axis are similar to those observed in marasmus or kwashiorkor. Multiple studies have demonstrated high levels of GH with low levels of IGF-I in patients with AN. Similar to the other states of malnutrition, GH resistance constitutes an important feature of this eating disorder. Advances in techniques to assess secretory hormone dynamics have helped quantify the secretory activity of hormones in this condition. Deconvolution analysis of GH levels in adult women with AN revealed a fourfold increase in the daily pulsatile secretion of GH with a 20-fold increase in basal secretion [27]. In a study conducted by our group, adolescent girls with AN, in addition to having increased pulsatile and basal secretion, also had increased disorderliness of GH secretion associated with low IGF-I levels [28] (Fig. 5.2). Indicators of nutritional status such as body mass index (BMI), leptin, and body fat were inversely correlated with GH in this study, indicating the impact of nutritional status on the neuroendocrine regulation of GH secretion.

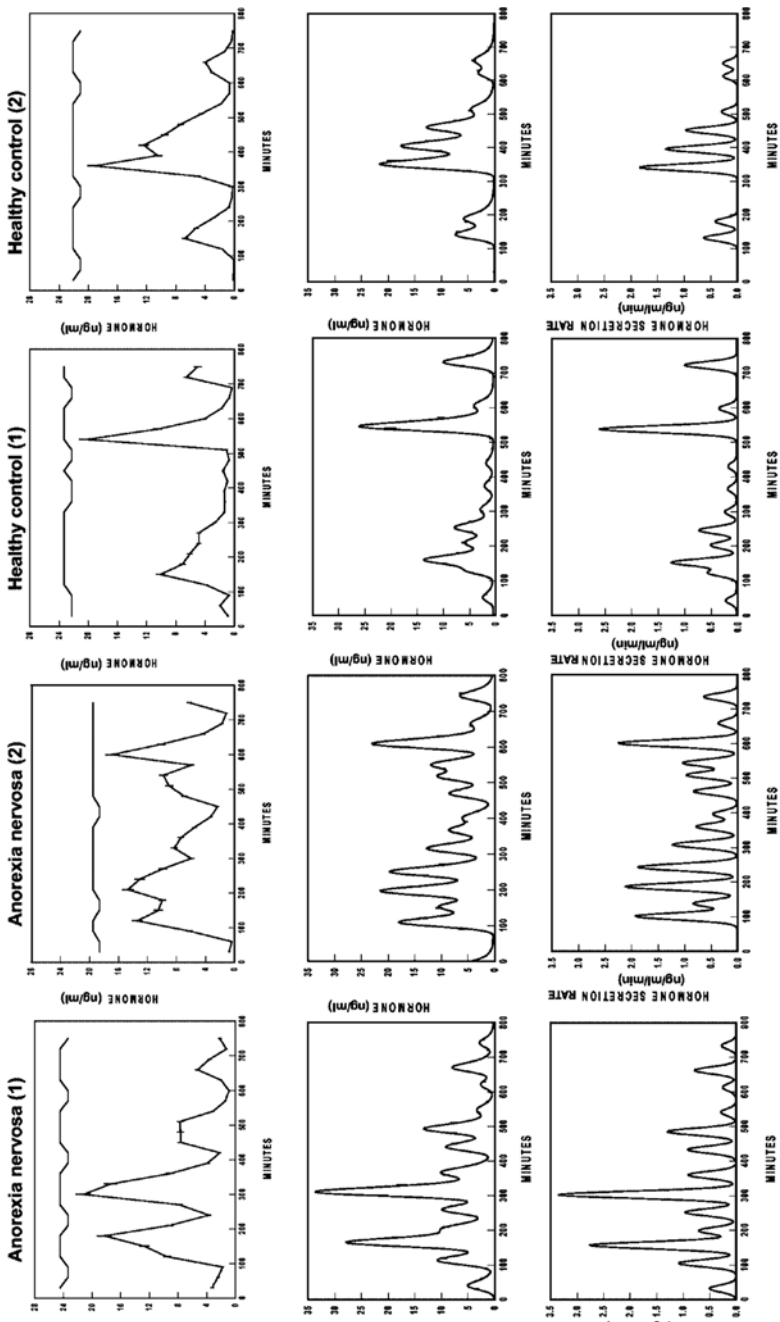


Fig. 5.2 Cluster and deconvolutional analyses in AN patients and controls. (**a**) Cluster analysis in two girls with AN (*two left panels*) and two healthy adolescent girls (*two right panels*). The mean and nadir GH concentrations and the total AUC were greater in girls with AN than in controls. (**b**) Deconvolutional analysis in the two girls with AN and the two healthy controls analyzed by cluster in A. The *upper panels* show GH concentrations over the sampling period; the *lower panels* show the individual secretory bursts. Girls with AN had higher basal GH secretion and a greater number of secretory episodes than healthy adolescents of comparable chronological and bone ages. Republished with permission of the Endocrine Society, from Misra et al., Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. J Clin Endocrinol Metab. 2003. 88(12): 5615–23. Permission conveyed through Copyright Clearance Center, Inc.

Convincing evidence in support of GH resistance in patients with AN emerged from a randomized placebo-controlled study conducted by our group administering supraphysiological doses of recombinant human growth hormone (rhGH) to women with AN. rhGH at a maximum dose of 1.4 ± 0.12 mg/day was administered to these women for 12 weeks with no resultant increase in IGF-I levels, suggesting no role for high-dose rhGH treatment to overcome GH resistance in AN [29, 30].

Factors Influencing Secretion and Action of GH in Anorexia Nervosa

Hypothalamus In addition to GH resistance, there is evidence that GH secretion is dysregulated in AN. However, it is unclear whether increased GH secretion in AN is secondary to decreased negative feedback at the hypothalamus from low IGF-I levels or whether there is a primary hypothalamic defect in GHRH/SRIH secretion. Low-dose rhIGF-I given to AN patients inhibits GHRH-mediated GH release only partially, suggesting a coexistent hypothalamic defect in the regulation of GH secretion [31]. The somatostatinergic control of GH secretion, which is mediated by cholinergic pathways, might also be altered in AN [32, 33]. In one study of eight women with AN and eight age- and sex-matched controls, participants were given one of the following infusions: (a) GHRH, (b) GHRH plus low-dose SRIH, and (c) GHRH plus high-dose SRIH, and GH area under the curve (AUC) was assessed over 120 min following the specific infusion [32]. Compared with controls, women with AN showed an exaggerated GH response to GHRH infusion alone. SRIH infusion in low doses inhibited the GHRH-mediated increase in GH secretion, indicating that the sensitivity of pituitary cells to SRIH is preserved in AN. Nevertheless, this dose was unable to inhibit GHRH-induced GH release in control women indicating alterations in somatostatinergic control of GH secretion.

Similar to these findings, Fassino et al. demonstrated an exaggerated GH response to GHRH in women with AN compared with controls. Additionally, following treatment with cholinergic drugs, GHRH no longer caused this increase in GH levels, suggesting an impaired cholinergic regulation of GH secretion in AN [34].

Another possible mediator of high GH levels in AN is the GH secretagogue, ghrelin. Ghrelin is an orexigenic hormone, and levels of ghrelin are appropriately increased in patients with AN compared with controls [35–37]. Misra et al. reported positive associations of ghrelin with GH secretory parameters, and ghrelin was an independent predictor of GH secretion in AN [36].

Pituitary Histopathological examination of pituitary biopsies obtained from patients who died from AN has not revealed specific changes to suggest a primary pituitary abnormality [38].

Liver Serum GH-binding protein (GHBP) levels, a good indicator of GH receptor expression, are low in patients in AN suggesting a decrease in GH receptors [39, 40], similar to patients with malnutrition. Further, the binding capacity of GHBP is

reduced in AN compared with controls [39]. Studies conducted by our group have demonstrated a positive association of FGF21 with GH-AUC in adolescents with AN even after controlling for body fat and insulin resistance, indicating a possible role of FGF21 in GH resistance in AN, similar to that seen in animal models of malnutrition [29, 30].

Effects of Acquired GH Resistance in AN on End Organs

1. *Body composition and glycemia*: GH has lipolytic effects, and our studies have demonstrated a strong inverse association of GH-AUC with total, and particularly trunk, fat in adolescents with AN, suggesting that reduced body fat in this condition may be consequent to high GH concentrations [35, 37]. This is consistent with the role of GH as a gluconeogenic hormone that, through lipolysis, provides gluconeogenic substrate at times of chronic energy deficiency. Effects of GH on fat are direct end-organ effects not mediated via IGF-I and thus are evident even when IGF-I levels are low. Consistent with this, administration of rhGH in supraphysiological doses to adult women with AN led to a reduction in body fat mass over a 3-month period despite no significant increase in IGF-I levels [29, 30]. In contrast, there was no effect of rhGH on lean mass.

2. *Bone*: In addition to a hepatic resistance to GH in AN as evidenced by low circulating IGF-I levels, AN is characterized by a resistance to GH at the level of the bone, which contributes to impaired bone metabolism. Both GH and IGF-I are bone anabolic hormones, and in normal-weight adolescents, we have shown strong positive associations between GH concentrations and bone turnover markers [28]. However, this association is completely lost in adolescent girls with AN, indicative of GH resistance in the bone [28]. Consistent with these findings, administration of supraphysiological doses of rhGH for 3 months to adult women with AN did not result in a significant increase in levels of bone formation markers compared with placebo [29, 30]. In contrast, administration of rhIGF-I in replacement doses does cause an increase in bone formation markers in both adults and adolescents with AN [41, 42].

Disorders Characterized by Increased Catabolism

Cachexia

Cachexia is defined as a metabolic syndrome characterized by weight loss of at least 5 % over 12 months (or a BMI < 20 kg/m^2) resulting from muscle wasting secondary to chronic disease [43]. Cachexia can be consequent to a number of chronic disease states such as congestive heart failure, chronic kidney disease, and infectious disorders such as HIV or secondary to malignancy. Cachexia is distinct

from AN in that it is irreversible with nutritional repletion and thus is not just a consequence of anorexia. Similar to other states of undernutrition, alterations in the GH-IGF-I axis are a major feature of cachexia. Although GH levels may be variable at different stages of the underlying conditions that eventually lead to cachexia, an acquired state of GH resistance is evident once cachexia develops. Cachexic states are thus characterized by elevated GH and low IGF-I levels [44, 45]. However, deconvolution analysis examining secretory dynamics of GH in patients with rheumatoid cachexia with diminished body cell mass did not show any significant differences in GH secretion compared with controls [46]. Because of the anabolic effects of GH and IGF-I, many studies have attempted to use these hormones to improve the underlying nutritional status of cachexic patients with variable results. Administration of rhGH to 21 patients with AIDS induced cachexia resulted in a less significant response in IGF-I levels compared with age-matched controls, suggestive of a partial GH-resistant state [47]. Furthermore, low IGF-I levels are a marker of nutritional status and predict mortality in these subjects. Ghrelin and ghrelin receptor agonists, which are potent GH secretagogues, can improve IGF-I levels in cachexic states [48–50]. Inflammatory cytokines thought to mediate cachexia are also believed to be responsible for GH resistance in this condition.

Factors Influencing GH Secretion and Action

Hypothalamus While there are no studies to our knowledge that address the impact of GHRH and SRIH on GH release in cachexic states, some understanding of the regulation GH secretion in cachexia comes from studies using ghrelin in this condition. Ghrelin is a potent GH secretagogue (GHS) that acts through the GHS type 1 alpha receptor. Ghrelin is believed to be beneficial in these conditions because of its orexigenic and GH-independent anti-inflammatory effects, and studies in cachexia have shown an increase in GH and IGF-I levels following ghrelin administration suggesting a GH-mediated effect as well [49].

Pituitary One study from Japan reported that the pituitary gland of patients dying from senile cachexia weighed less than in controls (0.46 g vs. 0.60 g, $p \leq 0.01$), with a significant reduction in somatotrophs [51].

Liver Evidence points toward suppressed/decreased transcription of GH receptors in the liver induced by tumor cytokines as a possible mechanism for GH resistance in cachexia. Overexpression of inflammatory cytokines in transgenic mice induces GH resistance with reduced growth. One study reported a tumor necrosis factor (TNF)-mediated reduction in DNA binding of GH receptor gene promoter Sp1/Sp3 transactivators in the mouse liver cells [52]. Further, IL-6 has been implicated in mediating post-receptor defects in GH signaling by upregulating cytokine-inducible inhibitor of signaling (CIS) and suppressor of cytokine-inducible signaling (SOCS)-3 genes, thereby leading to inhibition of STAT-5 phosphorylation [53].

Inflammatory Conditions

Stunted growth constitutes a major feature of inflammatory conditions in childhood, as seen in conditions such as inflammatory bowel disease (IBD) and juvenile idiopathic arthritis. Varying response to GH stimulation tests have been noted in IBD with Tenore et al. reporting normal GH peak response following insulin and McCaffery et al. showing a blunted GH response to insulin [54, 55]. A more recent retrospective study of children with colitis who presented with growth retardation revealed a spectrum of GH abnormalities ranging from GH deficiency to GH resistance. These children were subjected to insulin tolerance tests, and GH deficiency was diagnosed when the peak GH response was <6 mcg/L. Of the 28 children who underwent testing, 15 had low GH (four children with <3 mcg/L, 11 children with values between 3 and 6 mcg/L and low IGF-I indicating GH deficiency), 11 children had normal GH secretion with low IGF-I indicating GH resistance, and two children had normal to high GH levels and IGF-I-SDS >0 indicating some degree of IGF-I resistance in addition to GH resistance [56]. In rat models that were induced with colitis, 60 % of the subsequent growth retardation was explained by undernutrition and the remaining attributed to the underlying inflammatory process [57]. Thus inflammatory disorders represent a unique situation where GH secretion is impacted not only by the underlying undernutrition but also by the presence of pro-inflammatory cytokines such as TNFα, interleukin (IL)-1 and IL-6.

Deconvolution analysis of GH parameters in premenopausal women with active rheumatoid arthritis has shown nonsignificant elevation of integrated GH levels compared with normal controls, with no difference in secretory dynamics of GH [58] except for a shorter GH half-life in patients with active rheumatoid arthritis. However, in this study IGF-I and IGFBP-3 trended lower than in controls, which along with unaltered 24 h GH secretion suggests GH resistance.

Cytokines and the GH-IGF-I Axis Cytokines are pro-inflammatory in nature and are produced by different cell types. They mediate their effect on the GH-IGF-I axis by altering GH action at the level of GH receptors as well as by post-receptor mechanisms (Fig. 5.3).

TNFα inhibits expression of the hepatocyte GH receptor [52]. IL-6, the other major cytokine involved in inflammatory bowel disorders, acts through SOC3 proteins to inhibit the JAK-STAT pathway, thereby resulting in GH resistance [53]. Furthermore, in rat hepatocytes, IL-1 has been shown to decrease the ability of GH to induce acid-labile subunit (ALS) mRNA expression. In effect, this leads to decreased IGF-I levels since ALS is one of the three main components of the circulating 150 Dka complex [59].

Additional evidence for the role played by cytokines in mediating the GH resistance comes from a study where administration of a TNF-alpha receptor blocker to adult patients with inflammatory bowel disease resulted in significant increases in IGF-I and IGFBP-3 levels [60].

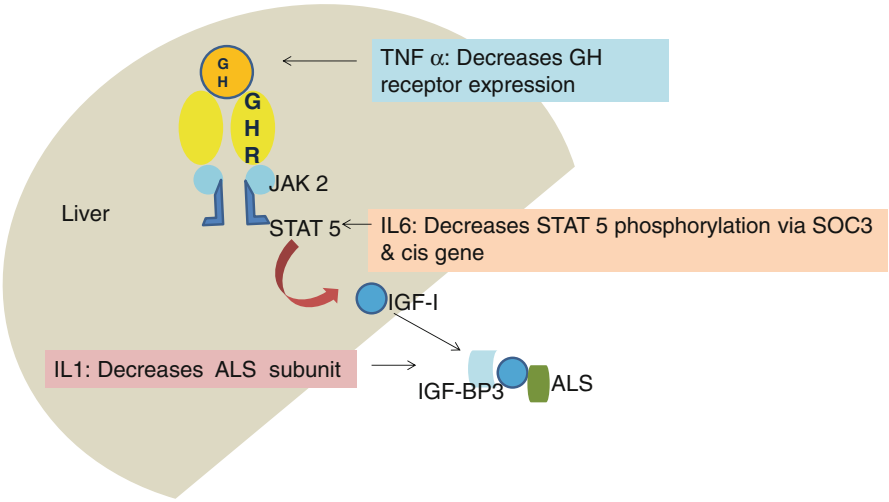


Fig. 5.3 Influence of cytokines on GH-IGF-I axis

Some rodent studies reveal intriguing details regarding the mucosal protective role played by GH in IBD. Transgenic mice overexpressing GH demonstrated increased survival associated with decreased inflammation and enhanced mucosal repair compared to wild-type controls [61]. However, trials using GH for improvement of inflammatory disease have yielded inconsistent results. In adults with chronically active Crohn's disease, administration of GH (1.5 mg/day for 1 week following a loading dose of 5 mg/day) for four months led to a decrease in Crohn's disease activity index compared to those treated with placebo [62]. In contrast, a pediatric randomized-controlled trial using 0.075 mg/kg/day of GH plus corticosteroid treatment versus corticosteroid alone in 20 patients aged 7–18 years showed no difference in endoscopic disease activity with use of GH. They concluded that despite an increase in height *z*-scores in the GH group, GH therapy did not promote mucosal repair [63].

The confluence of poor nutrition, inflammatory effect of cytokines, and side effects of medications used for these conditions appears to lead to growth failure in inflammatory disorders such as IBD [64]. Similar to the response seen with GH therapy, treatment with cytokine inhibitors has failed to elucidate a unifying response in terms of improvement in growth [64]. At the present, there is limited evidence in favor of endocrine treatments for improving growth in inflammatory conditions.

Conclusion

Regardless of the underlying mechanism that leads to undernutrition, humans exhibit a state of GH excess with low IGF-I levels in conditions of undernutrition, indicating a state of GH resistance. Alterations at the level of the

hypothalamus and the liver, including downregulation of the GH receptor and post-receptor defects, have been implicated in this phenomenon. Additionally, cytokines play a major role in mediating GH resistance in inflammatory states. Attempts at using GH for these conditions have yielded variable results reflecting the adaptive nature of this phenomenon. The elevated GH levels promote lipolysis and availability of fatty acid substrates to the brain at times of energy deficiency, while the low level of IGF-I facilitates a decrease in anabolic activities. Therefore, GH resistance in undernutrition is a key regulatory mechanism to improve survival.

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