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Chronic inflammation and the growth hormone/insulin-like growth factor-1 axis

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Abstract

Interactions between growth hormone (GH), insulin-like growth factor-1 (IGF-1), and the immune system are complex, bidirectional, but not fully explained. Current reviews based on numerous studies have indicated that chronic inflammation could suppress the GH/IGF-1 axis via several mechanisms such as relative GH and/or IGF-1 insufficiency, peripheral resistance to GH and/or IGF-1 resulting from down-regulation of GH and IGF-1 receptors, disruption in the GH/IGF-1 signalling pathways, dysregulation of IGF binding proteins (IGFBPs), reduced IGF bioavailability, and modified gene regulation due to changes in the microRNA system. It is well-known that relationships between the immune system and the GH/IGF-1 axis are mutual and GH as well as IGF-1 could modulate inflammatory response and the activity of systemic inflammation. Available data indicate that the GH/IGF-1 axis exerts both pro-inflammatory and anti-inflammatory effects. Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and interleukin-1β (IL-β) are some of the most significant factors, besides malnutrition, chronic stress, and prolonged use of glucocorticoids, which impair the activity of the GH/IGF-1 axis, and consequently lead to growth retardation in children suffering from childhood-onset chronic inflammatory diseases. In this review, we discuss the mechanisms underlying the impact of chronic inflammation on the GH/IGF-1 axis and growth processes during childhood and adolescence, based on a number of experimental and human studies.

Key words: *pro-inflammatory cytokines, growth hormone, insulin-like growth factor-1, growth impairment, children and adolescents.*

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Introduction

Complex interactions between the growth hormone (GH), insulin-like growth factor-1 (IGF-1), and the immune system have been confirmed, but not fully explained [1-7]. Current reviews based on numerous studies have indicated that chronic inflammation could suppress the GH/IGF-1 axis via several mechanisms such as relative GH and/or IGF-1 insufficiency, peripheral resistance to GH and/or IGF-1 resulting from down-regulation of GH and IGF-1 receptors, disruption in the GH/IGF-1 signalling pathways, dysregulation of IGF binding proteins (IGFBPs), reduced IGF bioavailability, and modified gene regulation due to changes in the microRNAs (miRNAs) system [1, 8-10]. On the other hand, it is well-known that relationships between the immune system and the GH/IGF-1 axis are mutual, and GH as well as IGF-1, which is the main mediator of its action, could modulate inflammatory response and the activity of systemic inflammation [4, 11-13]. Available data indicate that the GH/IGF-1 axis exerts both pro-inflammatory and anti-inflammatory effects [4, 11, 14-17].

The main role of the GH/IGF-1 axis is to promote postnatal linear growth in children and adolescents. In fact, the GH/IGF-1 axis exerts a number of additional effects including modulation of carbohydrate, lipid, protein and mineral metabolism, and controlling of aging, cancer development, and a number of physiological processes related mainly to the cardiovascular and renal systems [18-22]. GH is produced in, and released from, the anterior pituitary somatotrophs. Its secretion is regulated mainly by two hypothalamic hormones, the growth hormone-releasing hormone and somatostatin (growth hormone-inhibiting hormone), and by the GH secretagogue ghrelin, released primarily by the stomach, but also by the hypothalamus, pituitary, lung, adrenal cortex, kidney, bone, testis, placenta, pancreatic islet cells, and intestinal tract [19, 23-25]. GH acts directly on the GH receptor (GHR) located mainly in epiphyseal plates in long bones and spine, liver, muscles, and adipose tissue or indirectly via initiating IGF-1 production by the hepatocytes [19, 24, 26]. GH binding to its receptor leads to activation of tyrosine kinase, Janus kinase 2 (JAK2), and tyrosyl phosphorylation of both

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JAK2 and GHR. These changes result in recruitment to GHR of a number of molecules, including a signal transducer and activator of transcription (STAT) 1, 3, 5a, and 5b, mitogen-activated protein kinases (MAPKs), insulin receptor substrates, and intracellular calcium, which are crucial for GH signalling [19, 27]. IGF-1, produced mainly in the liver but also locally in several tissues, is involved in regulation of proliferation, differentiation, and apoptosis in many cell types. It circulates bound to IGFBPs, which act as transport proteins, modulate IGF-1 bioavailability, prolong its half-life, and regulate its activity in target tissues and clearance [8, 28-30].

A number of studies, both experimental and clinical, were conducted to better explain the impact of chronic inflammation on postnatal growth and pubertal development during childhood. It has been confirmed that the effects of pro-inflammatory cytokines, such as interleukin 6 (IL-6), tumour necrosis factor-α (TNF-α), and interleukin 1β (IL-1β), are some of the most significant factors, besides malnutrition, chronic stress, and prolonged use of glucocorticoids, which impair the activity of the GH/IGF-1 axis, and consequently lead to growth retardation in children suffering from childhood-onset chronic inflammatory diseases [8, 10, 23, 31-38]. In everyday clinical practice, the most common chronic inflammatory diseases associated with growth impairment are inflammatory bowel disease (IBD) – especially Crohn's disease, cystic fibrosis (CF), and juvenile idiopathic arthritis (JIA) [8, 9, 28, 39, 40].

In this review, we discuss the mechanisms underlying the impact of chronic inflammation on the GH/IGF-1 axis action and growth processes during childhood and adolescence, based on a number of experimental and human studies.

A summary of the animal model and human studies

Numerous studies have confirmed close relationships between chronic inflammation, especially colitis and arthritis, and somatic growth and development. Most of them focused on the impact on those processes of IL-6, TNF-α, and IL-1β, which seem to be the main pro-inflammatory cytokines involved in such interactions [9, 28, 41, 42]. Current data indicate that IL-6, TNF-α, and IL-1β could affect the GH/IGF-1 axis through both systemic and local mechanisms, acting individually or in combination. Systemic action of pro-inflammatory cytokines leads mainly to hepatic GH resistance and suppression of IGF-1 action in target tissues, while their local action directly affects the growth plate [2, 28, 31, 41-45]. It has been confirmed that IL-6 could suppress GH action leading to reduction in JAK/STAT signalling by induction of suppressor of cytokine signalling (SOCS)-3 protein [1, 46]. IL-1β could impair GH signalling acting on the expression of STAT3 and STAT5 [1, 47]. Moreover, IL-6, IL-1β, and TNF-α could inhibit IGF-1 action by dysregulation of its intracellular mediators, such as MAPK/extracellular signal-regulated kinases and phosphoinositide 3-kinase (PI3K) in chondrocytes [1, 32, 48]. It has also been confirmed that IL-1β and TNF-α suppress gonadal sex steroid production in Leydig cells and ovarian cells and decrease hypothalamic secretion of gonadotropin-releasing hormone (GnRH), which results in delayed puberty and consequently aggravates growth retardation [49-51].

Systemic effects of pro-inflammatory cytokines on the GH/IGF-1 axis

Numerous studies indicate that inflammation-induced hepatic GH resistance results from two main mechanisms. The first mechanism is downregulation of GHR and the second is the upregulation of the members of the SOCS family, especially SOCS1 and SOCS3, which contribute to the negative regulation of the growth-promoting actions of GH [2, 23, 28, 52-55]. TNF-α and IL-1β primarily inhibit hepatic GHR expression, while IL-6 inhibits hepatic GH signalling by inducing SOCS3 expression and has no effect on GHR expression [2, 28, 53, 56-58]. Experimental data by Zhao *et al.* [2] show that neutralisation of TNF-α and IL-1β in mouse inflammation models does not significantly alter SOCS3 expression stimulated by the inflammation process but restore GHR and IGF-1 expression suppressed by inflammation. On the other hand, neutralisation of IL-6 does not alter inflammation-suppressed GHR expression, but significantly reduces inflammation-stimulated SOCS3 expression and restores IGF-1 expression. Moreover, IL-6 action seems to be superseded by TNF-α and IL-1β [2].

Despite inducing hepatic GH resistance, pro-inflammatory cytokines could systemically suppress IGF-1 action by influencing the metabolism of IGFBPs and consequently IGF-1 clearance. De Benedetti *et al.* [31] confirmed, using the transgenic mouse model with growth defective phenotype (NSE-hIL-6 mice), that overexpression of IL-6 early after birth leads to a 50-70% size reduction compared to normal non-transgenic mice due to a decrease in circulating IGF-1 levels. Simultaneously, that effect was partially reverted by the administration of a monoclonal antibody to the murine IL-6 receptor. The authors also emphasise that those changes were accompanied by normal distribution of GH pituitary cells and normal GH production and secretion [31]. More recent studies by De Benedetti *et al.* [59, 60] showed that NSE/hIL-6 mice had normal liver IGF-1 production, while IGF-binding protein 3 (IGFBP-3) levels were decreased and serum proteolysis of IGFBP-3 was increased. A reduction in IGFBP-3 levels resulted in a significant decrease in the circulating 150-kDa ternary complex (IGF-1/IGFBP-3/acid labile subunit complex), which led to a reduction in IGF-1 half-life and to acceleration of IGF-1 clearance. Secondary to those changes, IGF-1 serum levels were decreased [59, 60].

Local effects of pro-inflammatory cytokines on the growth plate

The epiphyseal growth plates, located in the proximal and distal parts of the long bones, are the final target organs for growth factors [8]. Negative direct local effects of pro-inflammatory cytokines on the growth plate have been reported by many authors [32, 44, 61-63]. It has also been confirmed that a combination of IL-1β, IL-6, and TNF-α enhances their growth inhibitory effects [44, 45, 63]. Martensson *et al.* [44] showed, in a model of cultured foetal rat metatarsal bones, that TNF-α and IL-1β could act in synergy at the growth plate chondrocytes to inhibit longitudinal growth due to a decrease in chondrocyte proliferation and an increase in its apoptosis. Simultaneously, the authors noticed that this effect could be partially reversed by IGF-1 [44]. MacRae *et al.* [45] confirmed a dose- and duration-dependent inhibitory effect of IL-1β and TNF-α on metatarsal growth and concluded that the extent of recovery following cytokine exposure may be incomplete following longer periods of exposure [45]. On the other hand, it is worth noting that both TNF-α and IL-1β, produced endogenously in the growth plate chondrocytes, seem to play a role in normal growth, while the above-mentioned negative effects of those cytokines on chondrocytes have been seen at their supraphysiological levels [42, 61, 64]. Experimental studies have also confirmed that IL-6 could act locally at the growth plate chondrocytes [62, 63, 65]. Nakajima *et al.* [62] reported that IL-6 leads to inhibition of early differentiation of ATDC5 chondrogenic progenitor cells and could be considered as a cellular-level factor in growth retardation in systemic JIA. Moreover, IL-1β, IL-6, and TNF-α could affect the function of the growth plate by suppressing IGF-1 intracellular signalling and by inhibiting the effect of IGF-1 on chondrocytes proliferation and differentiation at the growth plate [9, 32].

The effects of childhood-onset chronic inflammatory diseases on longitudinal growth

Chronic inflammation could lead to significant growth retardation in children and adolescents [59, 65-68]. Experimental data indicate that this effect is independent of undernutrition and occurs even in well-nourished patients [28, 69-71]. It is also emphasised that the degree of growth retardation correlates with the activity of the inflammatory disease [9]. Abnormalities reported in the GH/IGF-1 axis in patients with chronic inflammatory diseases are manifold. Increased levels of pro-inflammatory cytokines are related positively to the activity of the disease and adversely to IGF-1 and IGFBP-3 levels in patients with IBD [66, 67], JIA [31, 65, 72, 73], and CF [68, 74]. Those changes usually coexist with normal physiological or stimulated serum GH levels, which confirms a state of GH resistance, but other mechanisms of growth impairment are also considered [9, 28, 42, 38, 75, 76]. On the other hand, it should be taken into account that IGF-1 as a valuable laboratory indicator of nutritional status could be decreased in states of poor nutrition due to limited nutrient intake and malabsorption, which often accompany chronic inflammation [23, 28, 69]. Serum levels of IGFBP-3 do not seem to be as dependent on nutritional deprivation as IGF-1, and they better reflect GH signalling [77].

The study by Bozzola *et al.* [78] indicates that GH resistance observed in JIA children results from a significant reduction in GHR gene expression, which is related to the activity of the disease. The authors noticed that the restoration of both GHR mRNA gene expression and IGF-1 secretion observed after 2 years of JIA therapy correlated with a reduction in the activity of the disease expressed as a decrease in IL-6 levels [78]. Other postulated mechanisms that could result in growth retardation in JIA children are decreased pituitary GH secretion, which was observed both in children treated with systemic glucocorticoids [79] and also independently of such therapy [80], decreased IGFBP-3 levels due to increased IGFBP-3 proteolysis [59], and relative resistance to IGF-1, reported mainly in patients treated with glucocorticoids [81, 82]. MacRae *et al.* [83] reported significant impairment in chondrogenesis at the growth plate and consequently in the growth of cultured murine metatarsal exposed to serum and synovial fluid obtained from JIA children. It is noteworthy that effects observed after using synovial fluid were resistant to treatment with IL-1β, IL-6, and TNF-α specific antibodies and IGF-1, which suggest that other factors presented in those fluid also have an effect on longitudinal growth through IGF-1-independent mechanisms [83].

In children with IBD growth retardation seems to be related mainly to GH resistance, but low IGF-1 levels reported in that group of patients may result not only from the inflammation process itself, but also from malnutrition and prolonged use of glucocorticoids [9, 23, 35, 84]. The number of studies evaluating IGFBP metabolism in those patients is not satisfactory [9, 28]. Despite the wide range of abnormalities in both GH and IGF-1 secretion (functional deficiency) and sensitivity (systemic and/or hepatic resistance), which has been reported in IBD children, the exact mechanisms of the associations between activity of the disease and the GH/IGF-1 axis are not clear [9, 28, 85-90].

Results of studies evaluating the GH/IGF-1 axis in patients with CF confirm relative resistance to GH, but data concerning the pattern of GH secretion are scarce [9, 68, 91-93]. Ciro *et al.* [91] reported both GH insufficiency and reduced IGF-1 levels in CF children. They concluded that impaired GH secretion is more frequent among CF patients compared to the prevalence of GH deficiency in the general population [91]. An overall reduction in IGF bioactivity has also been reported in that group of patients

due to abnormalities in IGFBPs levels, mainly reduced IGFBP-3 levels and increased IGFBP-1 and IGFBP-2 [68, 94, 95]. Moreover, it has been confirmed that IGF-1 and IGFBP-3 levels are associated with lung function parameters, such as forced expiratory volume in 1 second (FEV1) and forced vital capacity [95-97].

In light of the studies conducted in the last few years, it should also be emphasised that changes in the miRNAs seem to be additional factors linking chronic inflammation and growth retardation observed in childhood-onset chronic inflammatory diseases [1, 8]. Numerous studies indicate that miRNAs, as post-transcriptional regulators of gene expression, could impact a number of proteins and cytokines, which are involved in the control of the GH/IGF-1 axis [98-102]. The mechanisms of those associations, their biological role, and clinical utility requires further investigation.

Conclusions

In summary, the immune system and especially chronic inflammation exert significant effects on the GH/IGF-1 axis and longitudinal growth. Those relationships seem to be multi-faceted, often coexisting with other factors such as malnutrition and prolonged use of glucocorticoids, which significantly hampers efforts to precisely explain these mechanisms. Available data indicate that supraphysiological levels of pro-inflammatory cytokines lead mainly to GH resistance but could also impair IGF-1 signalling and metabolism of IGFBPs.

The authors declare no conflict of interest.

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