Chapter 3

Growth Hormone Deficiency: Is It Just a Problem of Growth Impairment? Part II

Jesús Devesa

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.89159

Abstract

As stated in the first part of this review, growth hormone (GH) acts on all organs and tissues, and untreated GH-deficient (GHD) patients suffer from several affectations occurring as a consequence of the lack of this key hormone. In the second part of this review, we will analyze the effects of GH on the liver, the kidney, the adrenal glands, the skeletal muscles, the bones, the hematopoietic system, the gastrointestinal system, and the adverse effects that may occur in these organs and systems in the GH deficiency not treated in children and adults. Apart from these, we conclude that GH is a co-hormone that seems to be necessary for the physiological actions of other important hormones in humans.

Keywords: GH deficiency, IGF-I, GH and liver, GH and kidney, GH and adipose tissue, GH and the hematopoietic system, GH and skeletal muscles

1. Introduction

GH, many times directly, and in other cases by cooperating with other hormones, or acting through its own mediators, plays a role in the regeneration of the liver, in the development and normal functioning of the kidney, in the amount of fat mass, in the development and maintenance of skeletal muscles, in the skeletal development and mineral acquisition in bones, and in systems as complex as the hematopoietic system and the immune system; in addition, the hormone is able to act at the gastrointestinal level and also on the adrenal glands. In this second part of this review, we will analyze the physiological effects of the hormone on these organs and systems, as well as the consequences of its loss when it is untreated with replacement therapy.

1.1. GHD and liver

The liver is an important organ, where the actions of GH take place. For instance, the loss of critical GH signaling pathways in mice with liver-specific knockouts leads these animals to share a common phenotype of hepatic steatosis [1–3], indicating that GH plays an important physiological role in hepatic triglyceride metabolism. Steatosis leads to hepatic degeneration, which may be corrected by GH administration. A high prevalence of liver dysfunction has been reported in adult GHD patients [4], while GH-replacement therapy significantly reduced serum liver enzyme concentrations in these patients and improved the histological changes in their fatty liver [4–7]. Clinical reports in children have shown the same association between untreated GHD and liver steatosis [8–12], which is recovered after GH-replacement therapy. These effects of GH on liver repair are curious because the liver produces its own factor of regeneration: hepatocyte growth factor (HGF), first identified in the sera of 70% hepatectomized rats, as a mitogen of adult rat hepatocytes [13, 14]. Animal studies, using either anti-HGF antibody or *c-Met* gene destruction techniques, revealed that both the endocrine and paracrine effects of HGF are involved in liver growth after 70% hepatectomy and for recovery from hepatitis, respectively [15–18]. In spite of its liver production and its strong liver regenerative properties, it was found that in hypophysectomized rats, the responses of hepatic HGF gene expression and DNA synthesis to partial hepatectomy were accelerated by treatment with GH [19]. Whether GH stimulates the transcription of HGF or facilitates, it is not known, but our group found that GH is expressed in the liver of hypophysectomized rats subjected to partial hepatectomy and that this GH promotes the hepatic regeneration, directly or via HGF induction [20]. In this study, the analysis of the products obtained with the enzyme of restriction RsaI demonstrated that the hepatic GH gives origin to two bands in the expected molecular weight position (238 and 90 bp), identical to the bands obtained from pituitary rat GH [20]; see Figure 7 for this reference. From these data, it is clear that there is a hepatic expression of GH that contributes to, or determines, the high degree of regenerating ability of the liver, apart from playing important metabolic functions in this organ. As suggested above in the case of testis in GHD patients, it would be interesting to investigate whether the hepatic expression of GH exists or not in untreated GHD humans. In any case, GH-replacement therapy plays an important reparative function in non-alcoholic liver steatosis, and perhaps in other liver diseases (**Figure 1**).

1.2. GHD and kidney

GH exerts important effects on the kidney, affecting renal function and kidney growth. GHR mRNA expression has been found in rat kidney during fetal development and adulthood [21]. This GHR expression was found in all nephron segments, with the strongest signals in the distal convoluted tubule and the collecting duct and a very weak signal in the glomeruli [22]. GHR expression has also been found in human fetal kidneys as early as 8.5–9 weeks of gestation [23]. GHR expression was stronger in the outer medulla than in the cortex and remained similar at midgestation and after birth. The fact that weak staining was also found in immature glomeruli in early gestation but disappeared at later developmental stages [23] suggests that GH is involved in glomerular morphogenesis. The kidney expression of GHR

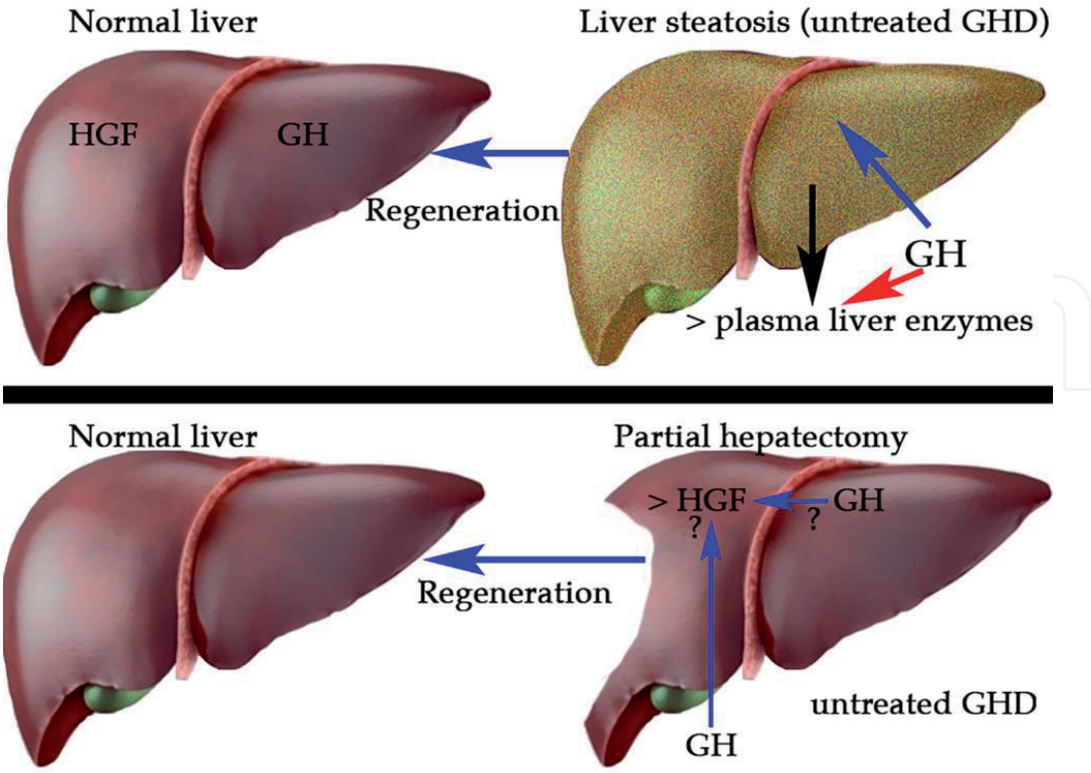

Figure 1. Effects of GH on the liver. Upper graph: There is GH expression in the normal liver (left), although this organ has its own regeneration factor (hepatocyte growth factor—HGF). Untreated GHD may suffer non-alcoholic liver steatosis (right), showing increased plasma levels of liver enzymes (transaminases); GH treatment recovers the damaged liver (blue arrows); and plasma liver enzymes come back to normal levels (red arrow). Lower graph: Untreated GHD patients cannot recover a normal liver in spite of the liver expression of GH and HGF, but GH treatment leads to regeneration of the damaged liver (blue arrows)—it is not known if this regeneration occurs because GH administration increases the hepatic expression of HGF or if it is due to a direct effect of GH on the liver.

seems to be induced by GH because hypophysectomy reduces GHR mRNA levels in rat kidneys, whereas GH therapy restores them [21]. There is also renal IGF-I biosynthesis, as it has been demonstrated in dogs [24] and confirmed by the fact that GH treatment increased IGF-I mRNA levels in the kidney of hypophysectomized rats [25, 26]. This is the reason by which GHR knockout leads to small kidneys in mice [27], and compensatory renal hypertrophy is directly dependent on GH-induced IGF-I expression [28]. It has been suggested that for GH-mediated kidney mass stimulation hepatic IGF-I production was crucial, while renal production of IGF-I has little or no effects on kidney growth [29]. In any case, studies in rodents demonstrated the importance of the GH/IGF-I system in the growth of kidneys during ontogenesis and development; however, no data indicate that a defective GH-/IGF-I signaling plays a significant role on kidney growth in humans.

In humans, short-term treatment with GH increases the glomerular filtration rate (GFR) [30]. This GH action is due to an IGF-1-mediated decrease in renal vascular resistance, leading to increased glomerular perfusion [31–33]. In addition to increasing glomerular perfusion, GH and IGF-1 augment extracellular volume and plasma volume [34], thereby also contributing to increased glomerular filtration.

The GH-IGF-1 system is a modulator of renal tubular sodium and water reabsorption [34]. Many years ago, the sodium-retaining properties of GH have been demonstrated in rats [35] and normal men [36]. This effect, traduced in an increase in extracellular volume, is stronger in men than in women [37] and seems to be dependent on the activation of the renin-angiotensin-aldosterone system because it has been seen that GH induces a rapid increase in plasma renin activity and plasma aldosterone levels in normal men [38]. However, further studies demonstrated that plasma angiotensin II and aldosterone did not increase during a treatment with GH, but plasma levels of atrial natriuretic peptide fell significantly [39]. Later studies in healthy volunteers [40] and GHD patients [41, 42] demonstrated that GH exerts a sodium-retaining effect that is independent of the renin-angiotensin-aldosterone system.

IGF-I has also antinatriuretic effects, as it has been seen in GHD children in whom the GHR is inactive because of Laron syndrome [43], and in healthy men [44]. Therefore, GH and IGF-I seem to act by different independent mechanisms in the retention of sodium by the kidney.

GH and IGF-1 are very important in the periods of increased bone formation, such as the growth stage, in which the phosphate metabolism must be well adjusted. As shown in almost 60 years ago, GH treatment led to decreased urinary phosphate excretion and increased plasma phosphate concentrations in men [45]. This effect of GH on the retention of phosphate is due to an increase in the maximum tubular phosphate reabsorption rate, as demonstrated in normal men [30] and dogs [46], and it is independent of PTH [46].

Conversely, hypophysectomy and inhibition of pulsatile GH release in rats produce increased urinary phosphorus losses [47, 48]. This has also been observed in normal humans [49–51] and in GHD patients [52–54].

As it happens with phosphate, GH and IGF-1 play an important role in adapting calcium homeostasis to the increased demands during the period of juvenile growth with accelerated bone formation. GH and IGF-1 affect calcium homeostasis mainly through their effect on vitamin D metabolism. GH stimulates calcitriol production in experimental animals [55] and men [56]; further investigations in mice and isolated cells showed that this GH action was mediated by IGF-1 stimulation of 1α-hydroxylase in the proximal tubule [57]. Chronic GH and IGF-1 deficiencies are accompanied by significant changes in renal morphology and functions, as well as by altered body composition, osteoporosis with fractures, and an increased cardiovascular risk [58–60]. Several studies have analyzed kidney size in GHD human patients. After hypophysectomy, kidney size fell by 20% after 5 months [61]. GH-untreated patients with Laron syndrome present larger ultrasonographic measured kidneys than control subjects when corrected for body surface area [62], but the kidney size is increased after long-term treatment with IGF-I [62]. GH treatment of adults with childhood-onset GH deficiency increases kidney length [63]. These effects of GH/IGF-I on the kidney are shown schematically in **Figure 2**.

The size of the kidneys in untreated GHD patients is lower than in normal people, but the administration of GH or IGF-I corrects this defect.

GH and IGF-1 deficiencies are associated with decreased glomerular filtration and renal plasma flow [64–66]. GH replacement therapy increased the GFR and renal plasma flow in some patients [64, 65] but it depends on the dose and duration of treatment. Treatment with IGF-I in patients with GH insensitivity also increases glomerular filtration [65].

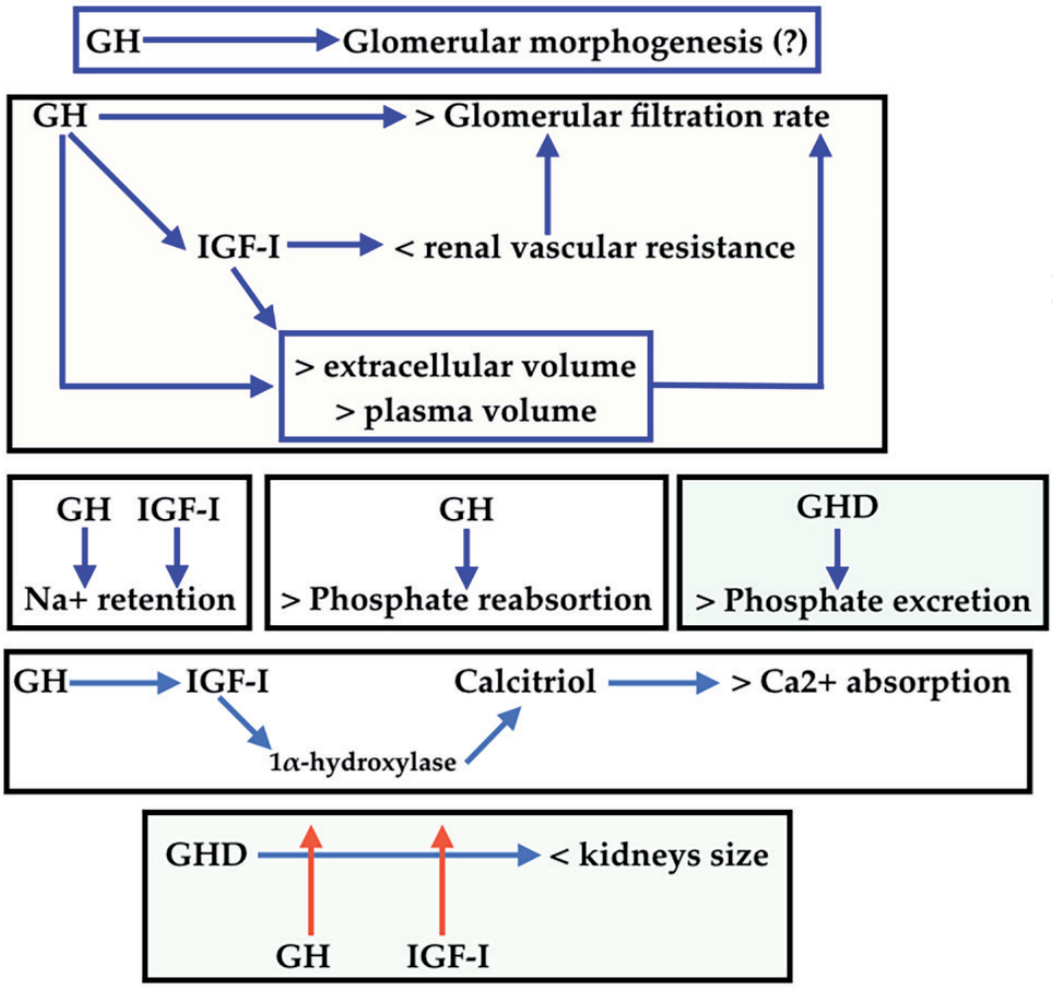

Figure 2. GH effects on the kidney. It is possible that GH participates in the early stages of the development of the kidneys by inducing glomerular morphogenesis. GH administration increases glomerular filtration rate, in this effect also participates GH-induced IGF-I, although the effects of both hormones on the glomerular filtration rate are independent. GH and IGF-I increase the retention of Na+, by decreasing its renal excretion. GH also increases the reabsorption of phosphate, while untreated GHD patients present an increase in the excretion of phosphate. GH also induces an increase in the intestinal absorption of Ca^{2+}, but this effect is mediated by IGF-I, which leads to the formation of Calcitriol.

An ancient study in hypopituitary children and young adults showed an increase in total body volume, extracellular volume, and intracellular volume after 1 year of GH therapy [67]. Two clinical trials in GHD adults posteriorly showed beneficial effects of GH treatment on body composition, with an increase in lean body mass [68, 69].

It is well known that adult GHD patients present osteoporosis with a high risk of vertebral and femoral fractures. Low bone mass can be partially improved by GH replacement [70–73] because GH therapy in GHD adults causes a transient increase in plasma calcium concentrations and urinary calcium excretion, which usually lasts between 3 and 6 months.

GH treatment increases plasma phosphate concentrations in GHD children [73, 74] and adults [52, 53, 75]. In contrast to plasma calcium concentrations, this increase in plasma phosphate persisted during 12–24 months of GH therapy [53, 73–75], while urinary phosphate excretion was decreased.

These data show the importance of GH on a normal renal function, although most of its effects at this level are mediated by IGF-I. Disordered regulation of the IGF system has been implicated in a number of kidney diseases. IGF-I activity is enhanced in early diabetic nephropathy and polycystic kidneys, whereas IGF-I resistance is found in chronic kidney failure. Moreover, IGFs have a potential role in enhancing stem cell repair after a kidney injury [76].

Importantly, children with chronic kidney disease have growth failure that can be treated with GH improving growth velocity without adverse side effects [77, 78].

For more detailed information about the effects of GH on the kidney, see [79].

1.3. GHD and adipose tissue

GH is defined as a lipolytic hormone. Untreated GHD children and adults usually present an increase in fat mass [80, 81], preferentially visceral fat; this has been attributed to the fact that GH inhibits lipid storage in adipose tissue by increasing the activity of hormone-sensitive lipase, an enzyme that plays a key role on lipolysis [82, 83], and by decreasing the inhibiting effect of insulin on hormone-sensitive lipase activity [83], although positive changes in the secretion of certain adipokines, such as adiponectin, have also been suggested as mediators of the increased adiposity in GHD states [84]. The adipose tissue is an endocrine organ that produces several hormones and cytokines that exert autocrine, paracrine, and endocrine effects. Two of these hormones, leptin and adiponectin, play very important roles in the organism. For instance, leptin is the hormone of satiety, released from adipocytes in response to food intake, and it is correlated with total fat mass. Its function, acting on its receptors in the arcuate nucleus of the hypothalamus, is related to decreasing food intake and increasing energy expenditure; conversely, adiponectin is negatively correlated with fat mass and acts as an insulin-sensitizing hormone [85]. Although it would be expected that GH effects on adipose tissue would be different in terms of leptin and adiponectin secretion, it has been seen that, in fact, these effects are negatively correlated with the release of both hormones from adipocytes. For example, in Laron syndrome, there is a marked obesity and adiponectin hypersecretion that does not change during long-term IGF-I treatment [86]. In any case, usually GH therapy reverts the increased adiposity existing in pituitary GHD children and adults [80, 81], therefore confirming the relationship between GHD and increased fat mass. Recent publications describe that in addition to its effects on the adipose tissue, GH also acts as a starvation signal that alerts the brain about energy deficiency, triggering adaptive responses to keep a minimum of energy deposits. This mechanism takes place at the central level by activating hypothalamic agouti-related protein neurons (AgRP) [87]. **Figure 3** shows how GH acts in the adipocyte.

Among other factors, since GH secretion decreases progressively from puberty, it is likely that the increase in body fat that is generally observed as we get older is related to deficient or insufficient secretion of GH. For a more detailed review of GH and the adipose tissue, see [85].

1.4. GHD and skeletal muscles

The GH-IGF-1 axis represents an important physiological mechanism to coordinate hypertrophy and postnatal skeletal muscle expansion. Both in normal rats and adult-onset GHD human

patients, the administration of GH improves muscle strength and reduces body fat [88–90]. GHR-deficient mice have reduced muscle mass with defective myofiber specification and growth [91]; in skeletal muscles lacking GHR, there is a decrease in the size of myofibers, while the number of myofibers is normal. The administration of GH increases myonuclear number, facilitating the fusion of myoblasts with nascent myotubes, a mechanism mediated by the transcription factor NFATc2; however, during a time, it has been discussed if the positive actions of GH on muscle mass would be restricted to inducing enhanced uptake of amino acids by muscle, while the effects on muscle protein synthesis, and consequently the increase in muscle mass, would be dependent on GH-induced IGF-I expression, mediated by STAT5b. In fact, recent *in vitro* studies indicate that treatment of primary myoblasts with GH quickly increases IGF-I mRNA, while administration of IGF-I leads to a significant increase in primary myoblast proliferation [92]. Therefore, the role of GH on muscle would be dependent on its induction of production of IGF-I by myoblasts, and IGF-I would then be responsible for stimulating myoblasts proliferation in an autocrine manner. The real thing is that GH and IGF-I induce a hypertrophic effect on skeletal muscles by different signaling pathways, and their effects are additive (**Figure 4**). The disruption of GHR in skeletal muscle and the consequent histomorphometric changes in myofiber type and size and myonuclei number result in functionally impaired skeletal muscle. In agreement with these effects, the histology of muscles of untreated GHD patients is strongly altered, and glucose and triglyceride uptake and metabolism in skeletal muscle of GHR mutant mice are affected.

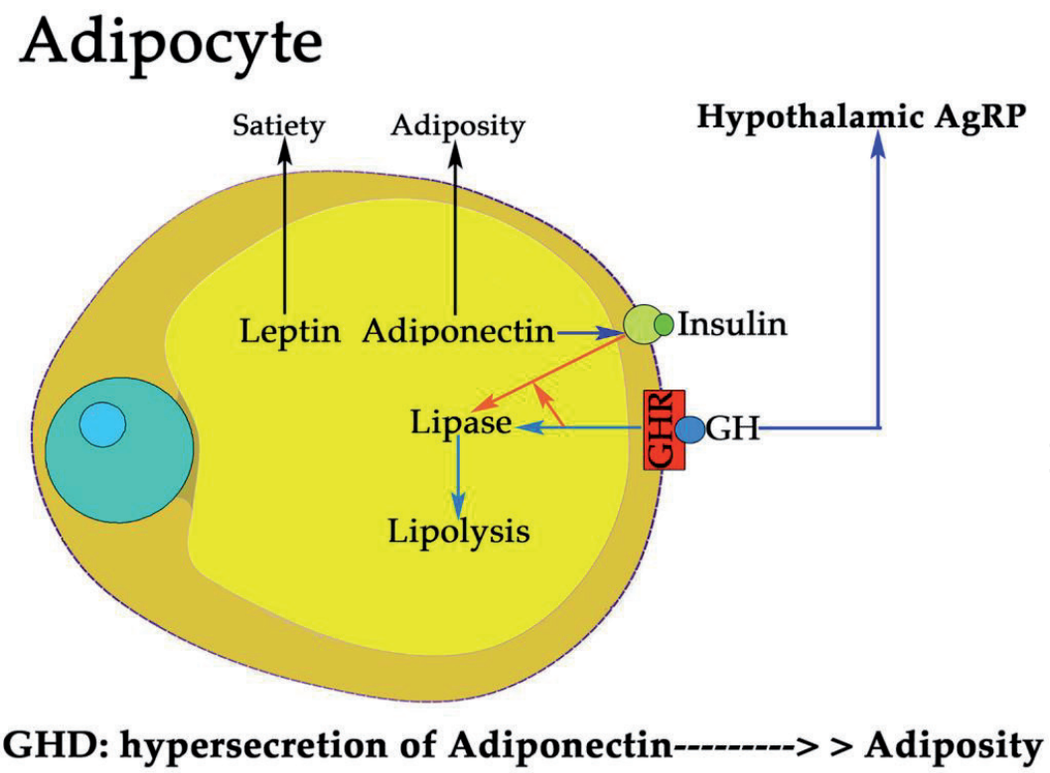

Figure 3. GH effects on fat mass. There are GHR in the membrane of adipocytes. After interacting with endocrine GH, the activity of the lipase (blue arrow) is increased leading to increased lipolysis. In addition, GH-GHR interactions lead to the inhibition of lipase activity (red arrow) induced by insulin. This insulin-inhibiting lipase activity is enhanced by adiponectin (blue arrow), a hormone secreted by adipocytes and responsible for increasing fat mass. In untreated GHD patients, there is hypersecretion of adiponectin. This is the reason by which these patients show excessive fat mass. In addition, GH acts on hypothalamic neurons that express AgRP, stimulating its production to alert the brain about energy deficiency.

In humans, a single bolus of GH induces gene expression of regulators of substrate metabolism and cellular growth of skeletal muscle *in vivo*. Some of these genes, such as *GISH* gene, seem to be directly induced by GH; however, other genes, such as *ANGPTL4* gene [93], seem to be expressed in relation to the subsequent increase in free fatty acid levels induced by GH-dependent lipolysis (**Figure 4**).

These results agree with the role that GH plays on lipid metabolism. With regard to the putative effects of GH on muscle strength, GH use has been speculated to improve physical capacity in subjects without GHD through stimulation of collagen synthesis in the tendon and skeletal muscle, which leads to better exercise training and increased muscle strength. In this context, the use of GH in healthy elderly should be an option for increasing muscle strength. However, a clinical trial showed that after 6 months of therapy, muscle strength in the bench press responsive muscles did not increase in groups treated with GH (no GHD) or placebo and showed a statistically significant increase in the leg press responsive muscles in the GH group.

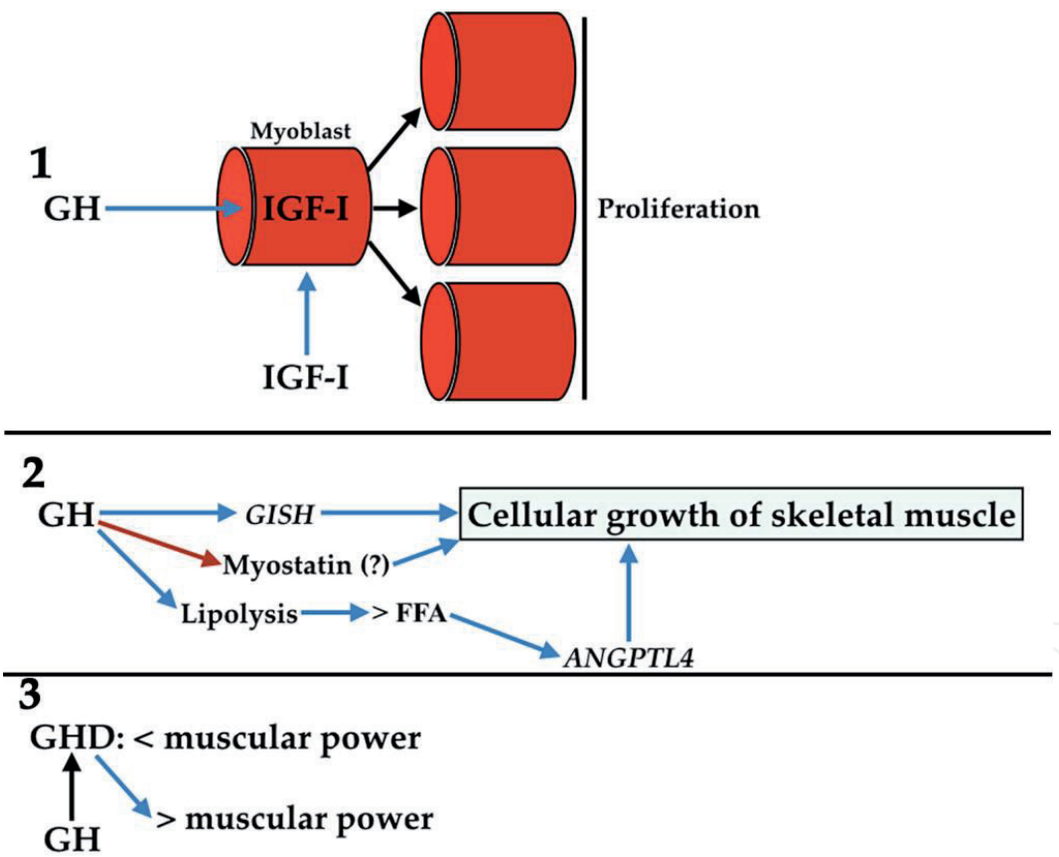

Figure 4. GH effects on skeletal muscle. 1: GH induces IGF-I expression in myoblasts. In turn, IGF-I leads to the proliferation of these myoblasts and produces muscular hypertrophy. The effects of GH and IGF-I are additive. 2: GH induces cellular growth in skeletal muscles by different mechanisms. One of them is due to the effects of GH on gene expression of regulators of substrate metabolism and cellular growth of skeletal muscle, such as *GISH*; other depends on the GH-induced lipolysis, which leads to increased levels of free fatty acids in plasma (FFA), and these stimulate the expression of *ANGPTL4* gene that acts directly on the cellular growth. In addition, GH inhibits the expression of muscular myostatin, a negative regulator of muscular growth; however, this last effect has been questioned recently. 3: According to the GH/IGF-I effects on skeletal muscles, untreated GHD patients have decreased muscular power, but this is corrected with GH treatment. Blue arrows, stimulation; red arrows, inhibition; >, increase; <, decrease.

The study demonstrated an increase in muscle strength only in the lower body part (quadriceps, for instance) after GH therapy in healthy men [94]. Therefore, GH administration does not provide significant improvements in increasing muscle power, except when GHD exists.

Of interest, sarcopenia appears while aging or after a prolonged immobilization. Although most likely this is a multifactorial process, a predominant role is played by myostatin, a muscular hormone that inhibits cell cycle progression and reduces levels of myogenic regulatory factors, thereby controlling myoblastic proliferation and differentiation during developmental myogenesis, as we and others demonstrated [95–97]. GH-induced muscular expression of the IGF-I-Akt–mTOR pathway, which mediates both differentiation in myoblasts and hypertrophy in myotubes, has been shown to inhibit myostatin-dependent signaling. Blockade of the Akt–mTOR pathway, using siRNA to RAPTOR, a component of TORC1 (TOR signaling complex 1), facilitates the inhibition by myostatin of muscle differentiation because of an increase in Smad2 phosphorylation [98]. Therefore, GH administration in these conditions of muscle wasting may be useful for recovering muscle mass at expenses of inhibiting myostatin signaling. However, a more recent study challenged these concepts, demonstrating that GH treatment in GHD did not reduce the previously elevated levels of myostatin in plasma and skeletal muscle [99]. These authors conclude that GH treatment is less effective than higher weight-based diets in increasing skeletal muscle mass. Independently of it, the role of GH/IGF-I in skeletal muscle is key and clear.

1.5. GHD and bone

The actions of the GH–IGF-I axis in the growth plate to promote longitudinal growth are already well known [100], but these are not the unique effects that the GH/IGF-I system plays at the bone level. This axis also regulates skeletal development and mineral acquisition [101]. Mouse models with disruptions of GH–IGF-I axis present a clear deterioration in parameters of bone health, dependent on GH-induced IGF-I expression, which increases bone mineral density [102]. Apart from GH, other GH-independent mechanisms regulate bone IGF-I expression, for instance, parathormone (PTH) [103]. Experimental mouse models reveal that osteoblast-derived IGF-I is a key determinant of bone mineralization. Targeted osteoblast-specific overexpression of *Igf1* via the osteocalcin promoter produced a phenotype of increased bone mineral density and trabecular bone volume [104], whereas knockout of the gene in bone (and muscle) but not liver via Cre recombinase expressed by the collagen type 1α2 promoter included a phenotype of reduced bone accretion [105].

In summary, although the effects of GH at the bone level are mainly related to the longitudinal growth of the organism before the end of puberty, and its effects are mediated by the local production of IGF-I, it cannot be discarded that GHD, both pathological and physiological (as it happens in aging), may play a role in the development of osteopenia/osteoporosis.

1.6. GHD and hematopoietic and immune systems

GH seems to play a role in the regulation of the hematopoietic system, being involved in the normal differentiation and function of blood cells [106]. GH increases plasma erythropoietin (Epo) levels and Hb in adult GHD patients [107] and increases plasma granulocyte-colony stimulating factor (G-CSF) levels and neutrophil counts in adult GHD patients [108] (**Figure 5(1)**).

Another study carried out in GHD patients treated with GH showed that the treatment significantly increased erythrocytes, Hb, and hematocrit and led to the recovery from anemia (typical of GHD patients during childhood), without affecting the number of leukocytes or platelets [109]. In all, these data indicate that GH exerts a positive role on the hematopoietic system, similar to that played by G-CSF [110]. Circulating levels of G-CSF are significantly lower in GHD than in non-GHD children, although in non-GHD children, the number of red blood cells, Hb, and hematocrit values significantly increased after 1 year of GH treatment [106]. Interestingly, unpublished data from our group indicate that short-term GH administration exerts the same effect on the hematopoietic system than G-CSF in 12-year-old Beagle dogs.

In the last years, it has been postulated that GH has a strong influence on the immune system. The production and action of immune cell-derived GH are now well known, although its important role in immunity is still being unveiled. Cells of the immune system express GH, GHRH, IGF-I, and its receptor, who through autocrine/paracrine and intracrine, but also endocrine, pathways, play a role in the immune function [111] (**Figure 5(2)**). The intracellular mechanisms of action of immune cell-derived GH are not well known, but, for instance, GH promotes the maturation and activation of dendritic cells that, as antigen-presenting cells, participate in the immune response of the organism [112].

There is GH production in lymphocytes; this GH is important for lymphocyte growth, survival, and production of cytokines [113–121]; therefore, lymphocyte GH may be an important mediator of cellular immune function mediated by the TH-1 pathway [122]. Lymphocyte GH appears to stimulate IFNγ production with a small positive effect on IL-10 production [122]. Treatment of rat lymphocytes with a specific GH antisense oligodeoxynucleotide decreased the amount of lymphocyte GH synthesized and, at the same time, reduced lymphocyte proliferation [113], what confirms the production by lymphocytes of the hormone and its effects on these cells, which is inhibited by noradrenaline and cortisol. However, it is likely that some of the effects of lymphocyte GH are due to GH-induced IGF-I production. In fact, IGF-I has also been found in lymphocytes, and studies using neutralizing antibodies to GH found that the number of cells positive for IGF-I decreased two-fold. This indicated that endogenously produced GH induces the production of IGF-I by lymphocytes [114]. Consequently, it seems that lymphocyte GH acts as an intracrine hormone [123]. It has been shown that overexpression of GH in a lymphoid cell line, devoid of the GHR, decreases the production of superoxide and increases the production of nitric oxide and the expression of IGF-I and IGF-IR, resulting in protection from apoptosis by a mechanism most likely involving an increase in the production of BcL-2 [115–118].

In all, it seems that there is a complex intracrine/autocrine regulatory circuit for the production and function of leukocyte-derived GH and IGF-I within the immune system. Therefore, this circuit could fulfill local tissue needs for these hormones independent of the pituitary or liver without disrupting homeostasis of other organ systems. For example, cells of the immune system would recognize the association of bacteria, virus, and tumors as an oxidative stress event and signal the release and transport GH, or different GH isoforms generated into the cytoplasm, and GHR into the nucleus. Once in the nucleus, GH-GHR would be free to influence transcriptional responses to the stress event and to defend the cell against oxidative damage. The results from a study by Weigent [124] support the concept that changes in the cellular redox status influence the intracellular levels of lymphocyte GH, which may exert effects on elements mediating the oxidative stress response.

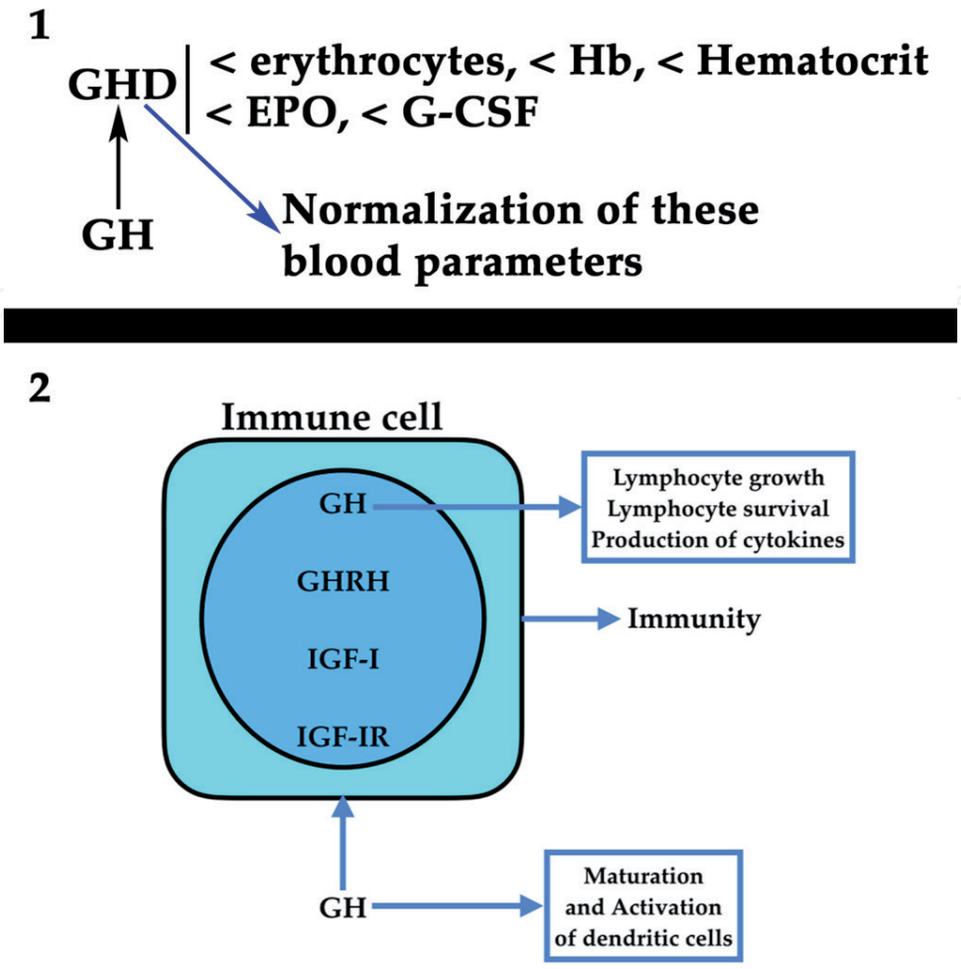

Figure 5. (1) GH plays an important role on hematopoiesis. This is the reason by which untreated GHD patients present deficits in the number of red blood cells, Hb, and hematocrit. Curiously, in these patients, there are also decreased plasma levels of EPO and G-CSF. GH administration normalizes these deficits (blue arrow) and increases plasma levels of EPO and G-CSF. (2) GH is expressed in cells of the immune system, as it happens with IGF-I and its receptor IGF-IR. There is also expression of GHRH, but its role in these immune cells is unknown. In all, these expressions contribute to increase immunity, and GH, particularly, increases the growth and survival of lymphocytes and the production of cytokines. Endocrine GH induces the activation and maturation of dendritic cells, the antigen-presenting cells. Therefore, GH and its mediators play an important role in immunity.

A very recent study indicates that GH treatment in GHD children led to some positive changes in the cellular and humoral immune profiles [125]. These data are similar to former results obtained after GH treatment in adults with childhood-onset GHD [126] and to more ancient studies in children with idiopathic short stature being treated with GH [127], although other study did not show changes in the immune function or immune parameters in GHD children after being treated with the hormone [128].

1.7. GHD and gastrointestinal functioning

Untreated GHD is associated with metabolic inflammation that usually is decreased when GH treatment is given [129]. However, situations of systemic inflammation, such as inflammatory bowel diseases (IBD), may induce GH resistance because inflammation negatively affects GH signaling. The GHR is expressed in the intestine [130, 131] for responding to GH signaling and enhancing the intestinal barrier function and mucosal healing [132, 133]. STAT5b, a key

mediator of GH effects in the cells, maintains colonic barrier integrity by modulating the survival of colon epithelial cells; this is the reason by which STAT5b-deficient mice present increased susceptibility to develop colitis. In addition, GH enhances epithelial proliferation. However, the expression of GHR in the colon is reduced in patients with ulcerative colitis [134], which favors the development of resistance to the beneficial effects of GH on the function of the intestinal barrier. According to these data, it is likely that GHD patients may suffer intestinal dysfunctions. An example of it might be the relatively elevated prevalence of GHD in children suffering coeliac disease, although this disease is a genetically determined gluten-sensitive enteropathy.

1.8. GHD and adrenal glands

The system GH/IGF-I also plays a role in adrenal glands. In rats, we demonstrated that the compensatory adrenal hypertrophy that follows a unilateral adrenalectomy seems to be mediated by adrenal GH expression [135]. GH and IGF-I enhance steroidogenesis responsiveness to ACTH in cultured adrenal cells and adrenal steroid responsiveness to ACTH increases in Turner syndrome after long-term treatment with high GH doses [136]. GH is an important modulator of the activity of 11β-hydroxysteroid dehydrogenase type 1 enzyme in the adrenal gland [137], as indicated by the fact that plasma DHEAS levels are significantly lower in GHD patients (even in the patients with normal ACTH secretion) than in age-matched controls. GH replacement therapy in these GHD patients significantly increases DHEAS plasma levels. This suggests that if there is a normal secretion of ACTH, GH stimulates adrenal androgen secretion in GHD patients. Conversely, GHD patients present an increased cortisol/cortisone ratio, and GH replacement therapy reduces the increased cortisol production [138]. However, in normal subjects or laboratory animals, the stimulation of adrenal steroidogenesis by GH seems to be restricted to the fetal period [139]. Years ago, it was demonstrated that GHR is strongly expressed in the ovine fetal adrenal gland [140], but GH infusion did not affect plasma steroid levels. This suggested that the steroidogenic effects of GH may depend on the gestational age, at least in the ovine fetus.

In all, besides from the putative effects of GH on adrenal steroidogenesis, the hormone may also play a trophic regenerative role on the adrenal glands.

1.9. GHD and other effects of GH

In addition to the well-known metabolic effects of GH, and the effects of the hormone on virtually all organs and tissues of the body, reviewed previously, untreated GHD patients present some other alterations. For instance, blood pressure is higher in GHD children and adults than in normal controls [141]. This specially affects the systolic blood pressure; moreover, since GHD is associated with increased obesity, both factors contribute to increase the risk of future cardiovascular affectations. Quality of life and psychosocial behavior are affected in GHD children and adults [142], usually they are more susceptible to suffer from depression, fatigue, and less physical activity, and all these are improved after GH treatment [143]. GH is also a key modulator of neonatal hypersensitivity and pain-related behaviors during developmental inflammation. It has been found in rats in which the GHR had been deleted that there was behavioral and afferent hypersensitivity to different stimuli, mainly during early developmental stages [144].

This led the authors to postulate that GH treatment might be a therapeutic weapon for pediatric pain. Regarding the effects of GH at the brain level, it has been recently shown that GHD mainly affects the brain network involving the somatosensory, somatic motor, and cerebellum networks, which may contribute to the behavioral problems existing in GHD children [145].

2. Conclusions

As it has been analyzed throughout this review, GH and its mediators play a very important role in practically the entire human organism, already from the early stages of development. This role goes far beyond than the classical concepts attributing to the hormone a merely metabolic role and an effect on longitudinal growth. Besides the pituitary production of GH that acts as an endocrine hormone, there is a peripheral production of GH that acts in autocrine/paracrine and even intracrine in the cells, which produce it. As a consequence of its physiological actions, the deficit of GH or its receptor leads to very important affectations. Consequently, GH replacement therapy improves the affectations occurring in GHD patients and their quality of life. Since GH secretion declines progressively from 20 years of age until being practically undetectable from 50 years old, it is likely that most of the age-related diseases and the decreased quality of life occur as a consequence of the absence of this hormone. In some cases, GH acts coordinately with other hormones; therefore, for carrying out some of its effects, it has to be considered as a co-hormone.

Acknowledgements

We thank the therapists of Foltra Medical Center (Teo, Spain) and researchers from the Department of Physiology of the Faculty of Medicine of the University of Santiago de Compostela who contributed their work to a large part of the information provided in this review. We also acknowledge the Foltra Foundation (Teo, Spain) for the help provided to write this review. This review has been funded by Foundation Foltra (Teo, Spain), grant F2019-7.

Conflict of interest

The author declares that there is not any conflict of interest.

Author details

Jesús Devesa

Address all correspondence to: devesa.jesus@gmail.com

Scientific Direction, Medical Center Foltra, Teo, Spain

References

[1] Cui Y, Hosui A, Sun R, Shen K, Gavrilova O, Chen W, et al. Loss of signal transducer and activator of transcription 5 leads to hepatosteatosis and impaired liver regeneration. Hepatology. 2007;**46**:504-513. DOI: 10.1002/hep.21713

[2] Fan Y, Menon RK, Cohen P, Hwang D, Clemens T, DiGirolamo DJ, et al. Liver-specific deletion of the growth hormone receptor reveals essential role of growth hormone signaling in hepatic lipid metabolism. The Journal of Biological Chemistry. 2009;**284**:19937-19944. DOI: 10.1074/jbc.MC109.014308

[3] Sos BC, Harris C, Nordstrom SM, Tran JL, Balázs M, Caplazi P, et al. Abrogation of growth hormone secretion rescues fatty liver in mice with hepatocyte-specific deletion of JAK2. The Journal of Clinical Investigation. 2011;**121**:1412-1423. DOI: 10.1172/JCI42894

[4] Nishizawa H, Iguchi G, Murawaki A, Fukuoka H, Hayashi Y, Kaji H, et al. Nonalcoholic fatty liver disease in adult hypopituitary patients with GH deficiency and the impact of GH replacement therapy. European Journal of Endocrinology. 2012;**167**:67-74. DOI: 10.1530/EJE-12-0252

[5] Takahashi Y, Iida K, Takahashi K, Yoshioka S, Fukuoka H, Takeno R, et al. Growth hormone reverses nonalcoholic steatohepatitis in a patient with adult growth hormone deficiency. Gastroenterology. 2007;**132**:938-943. DOI: 10.1053/j.gastro.2006.12.024

[6] Xu L, Xu C, Yu C, Miao M, Zhang X, Zhu Z, et al. Association between serum growth hormone levels and nonalcoholic fatty liver disease: A cross-sectional study. PLoS One. 2012;**7**:e44136. DOI: 10.1371/journal.pone.0044136

[7] Matsumoto R, Fukuoka H, Iguchi G, Nishizawa H, Bando H, Suda K, et al. Long-term effects of growth hormone replacement therapy on liver function in adult patients with growth hormone deficiency. Growth Hormone & IGF Research. 2014;**24**:174-179. DOI: 10.1016/j.ghir.2014.07.002

[8] Takano S, Kanzaki S, Sato M, Kubo T, Seino Y. Effect of growth hormone on fatty liver in panhypopituitarism. Archives of Disease in Childhood. 1997;**76**:537-538. DOI: 10.1136/adc.76.6.537

[9] Gilliland T, Dufour S, Shulman GI, Petersen KF, Emre SH. Resolution of non-alcoholic steatohepatitis after growth hormone replacement in a pediatric liver transplant patient with panhypopituitarism. Pediatric Transplantation. 2016;**20**:1157-1163. DOI: 10.1111/petr.12819

[10] Wada K, Kobayashi H, Moriyama A, Haneda Y, Mushimoto Y, Hasegawa Y, et al. A case of an infant with congenital combined pituitary hormone deficiency and normalized liver histology of infantile chole- stasis after hormone replacement therapy. Clinical Pediatric Endocrinology. 2017;**26**:251-257. DOI: 10.1297/cpe.26.251

[11] Rufinatscha K, Ress C, Folie S, Haas S, Salzmann K, Moser P, et al. Metabolic effects of reduced growth hormone action in fatty liver disease. Hepatology International. 2018;**12**:474-481. DOI: 10.1007/s12072-018-9893-7

[12] Miranda-Lora AL, Zamora-Nava LE, Marín-Rosas DL, Klünder-Klünder M, Sánchez-Curiel M, Dies-Suárez P. Resolution of fatty liver disease after growth hormone replacement in a pediatric survivor of thyroid cancer. Boletín Médico del Hospital Infantil de México. 2019;**76**:38-145. DOI: 10.24875/BMHIM.18000114

[13] Nakamura T, Nawa K, Ichihara A. Partial purification and characterization of hepatocyte growth factor from serum of hepatectomized rats. Biochemical and Biophysical Research Communications. 1984;**122**:1450-1459. DOI: 10.1016/0006-291x(84)91253-1

[14] Nakamura T. Structure and function of hepatocyte growth factor. Progress in Growth Factor Research. 1991;**3**:67-85. DOI: 10.1016/0955-2235(91)90014-U

[15] Kinoshita T, Hirao S, Matsumoto K, Nakamura T. Possible endocrine control by hepatocyte growth factor of liver regeneration after partial hepatectomy. Biochemical and Biophysical Research Communications. 1991;**17**:330-335. DOI: 10.1016/0006-291x(91)91987-n

[16] Matsumoto K, Nakamura T. Hepatocyte growth factor: Molecular structure, roles in liver regeneration, and other biological functions. Critical Reviews in Oncogenesis. 1992;**3**:27-54. DOI: 10.1111/j.1440-1746.1991.tb00897.x

[17] Birchmeier C, Gherardi E. Developmental roles of HGF/SF and its receptor, the c-met tyrosine kinase. Trends in Cell Biology. 1998;**8**:404-410. DOI: 10.1016/S0962-8924(98)01359-2

[18] Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology. 2006;**43**(Suppl 1):S45-S53. DOI: 10.1002/hep.20969

[19] Ekberg S, Luther M, Nakamura T, Jansson JO. Growth hormone promotes early initiation of hepatocyte growth factor gene expression in the liver of hypophysectomized rats after partial hepatectomy. The Journal of Endocrinology. 1992;**135**:59-67. DOI: 10.1677/joe.0.1350059

[20] Devesa J, Almengló C, Devesa P. Multiple effects of growth hormone in the body: Is it really the hormone for growth? Clinical Medicine Insights: Endocrinology and Diabetes. 2016;**9**:47-71. DOI: 10.4137(CMED.S38201

[21] Chin E, Zhou J, Bondy CA. Renal growth hormone receptor gene expression: Relationship to renal insulin-like growth factor system. Endocrinology. 1992;**131**:3061-3066. DOI: 10.1210/endo.131.6.1446640

[22] Lobie PE, García-Aragón J, Wang BS, Baumbach WR, Waters MJ. Cellular localization of the growth hormone binding protein in the rat. Endocrinology. 1992;**130**:3057-3065. DOI: 10.1210/endo.130.5.1374020

[23] Simard M, Manthos H, Giaid A, Lefèbvre Y, Goodyer CG. Ontogeny of growth hormone receptors in human tissues: An immunohistochemical study. The Journal of Clinical Endocrinology and Metabolism. 1996;**81**:3097-3102. DOI: 10.1210/jcem.81.8.8768881

[24] Schimpff RM, Donnadieu M, Duval M. Serum somatomedin activity measured as sulphation factor in peripheral, hepatic and renal veins in normal mongrel dogs: Early effects of intravenous injection of growth hormone. Acta Endocrinologica. 1980;**93**:155-161. DOI: 10.1530/acta.0.0930155

[25] Murphy LJ, Bell GI, Friesen HG. Growth hormone stimulates sequential induction of c-myc and insulin-like growth factor I expression in vivo. Endocrinology. 1987;**120**:1806-1812. DOI: 10.1210/endo-120-5-1806

[26] Roberts CT Jr, Lasky SR, Lowe WL Jr, Seaman WT, LeRoith D. Molecular cloning of rat insulin-like growth factor I complementary deoxyribonucleic acids: Differential messenger ribonucleic acid processing and regulation by growth hormone in extrahepatic tissues. Molecular Endocrinology. 1987;**1**:243-248. DOI: 10.1210/mend-1-3-243

[27] List EO, Sackmann-Sala L, Berryman DE, Funk K, Kelder B, Gosney ES, et al. Endocrine parameters and phenotypes of the growth hormone receptor gene disrupted (GHR−/−) mouse. Endocrine Reviews. 2011;**32**:356-386. DOI: 10.1210/er.2010-0009

[28] Flyvbjerg A, Bennett WF, Rasch R, van Neck JW, Groffen CA, Kopchick JJ, et al. Compensatory renal growth in uninephrectomized adult mice is growth hormone dependent. Kidney International. 1999;**56**:2048-2054. DOI: 10.1046/j.1523-1755.1999.00776.x

[29] Nordstrom SM, Tran JL, Sos BC, Wagner KU, Weiss EJ. Liver-derived IGF-I contributes to GH-dependent increases in lean mass and bone mineral density in mice with comparable levels of circulating GH. Molecular Endocrinology. 2011;**25**:1223-1230. DOI: 10.1210/me.2011-0047

[30] Corvilain J, Abramow M, Bergans A. Some effects of human growth hormone on renal hemodynamics and on tubular posphate transport in man. The Journal of Clinical Investigation. 1962;**41**:1230-1235. DOI: 10.1172/JCI104584

[31] Guler HP, Schmid C, Zapf J, Froesch ER. Effects of recombinant insulin-like growth factor I on insulin secretion and renal function in normal human subjects. Proceedings of the National Academy of Sciences of the United States of America. 1989;**86**:2868-2872. DOI: 10.1073/pnas.86.8.2868

[32] Hirschberg R, Rabb H, Bergamo R, Kopple JD. The delayed effect of growth hormone on renal function in humans. Kidney International. 1989;**35**:865-870. DOI: 10.1038/ki.1989.65

[33] Guler HP, Eckardt KU, Zapf J, Bauer C, Froesch ER. Insulin-like growth factor I increase glomerular filtration rate and renal plasma flow in man. European Journal of Endocrinology. 1989;**121**:101-106. DOI: 10.1530/acta.0.1210101

[34] Møller J. Effects of growth hormone on fluid homeostasis. Clinical and experimental aspects. Growth Hormone & IGF Research. 2003;**13**:55-74. DOI: 10.1016/S1096-6374(03)00011-X

[35] Whitney JE, Bennett LL, Li CH. Reduction of urinary sodium and potassium produced by growth hormone in normal female rats. Proceedings of the Society for Experimental Biology and Medicine. 1952;**79**:584-587. DOI: 10.3181/00379727-79-19454

[36] Beck JC, McGarry EE, Dyrenfurth I, Venning EH. Metabolic effects of human and monkey growth hormone in man. Science. 1957;**125**:884-105. DOI: 10.1126/science.125.3253.884

[37] Ehrnborg C, Ellegård L, Bosaeus I, Bengtsson BA, Rosén T. Supraphysiological growth hormone: Less fat, more extracellular fluid but uncertain effects on muscles in healthy, active young adults. Clinical Endocrinology. 2005;**62**:449-457. DOI: 10.1111/j.1365-2265.2005.02240.x

[38] Ho KY, Weissberger AJ. The antinatriuretic action of biosynthetic human growth hormone in man involves activation of the renin-angiotensin system. Metabolism. 1990;**39**:133-137. DOI: 10.1016/0026-0495(90)90065-K

[39] Møller J, Jørgensen JO, Møller N, Hansen KW, Pedersen EB, Christiansen JS. Expansion of extracellular volume and suppression of atrial natriuretic peptide after growth hormone administration in normal man. The Journal of Clinical Endocrinology and Metabolism. 1991;**72**:768-772. DOI: 10.1210/jcem-72-4-768

[40] Hansen TK, Møller J, Thomsen K, Frandsen E, Dall R, Jørgensen JO, et al. Effects of growth hormone on renal tubular handling of sodium in healthy humans. American Journal of Physiology. Endocrinology and Metabolism. 2001;**281**:E1326-E1332. DOI: 10.1152/ajpendo.2001.281.6.E1326

[41] Johannsson G, Sverrisdóttir YB, Ellegård L, Lundberg PA, Herlitz H. GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis. The Journal of Clinical Endocrinology and Metabolism. 2002;**87**:1743-1749. DOI: 10.1210/jcem.87.4.8394

[42] Johannsson G, Gibney J, Wolthers T, Leung KC, Ho KK. Independent and combined effects of testosterone and growth hormone on extracellular water in hypopituitary men. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**:3989-3994. DOI: 10.1210/jc.2005-0553

[43] Walker JL, Ginalska-Malinowska M, Romer TE, Pucilowska JB, Underwood LE. Effects of the infusion of insulin-like growth factor I in a child with growth hormone insensitivity syndrome (Laron dwarfism). The New England Journal of Medicine. 1991;**324**:1483-1488. DOI: 10.1056/NEJM199105233242107

[44] Møller J, Jørgensen JO, Marqversen J, Frandsen E, Christiansen JS. Insulin-like growth factor I administration induces fluid and sodium retention in healthy adults: Possible involvement of renin and atrial natriuretic factor. Clinical Endocrinology. 2000;**52**:181-186. DOI: 10.1046/j.1365-2265.2000.00931.x

[45] Henneman PH, Forbes AP, Moldawer M, Dempsey EF, Carroll EL. Effects of human growth hormone in man. The Journal of Clinical Investigation. 1960;**39**:1223-1238. DOI: 10.1172/JCI104138

[46] Corvilain J, Abramow M. Effect of growth hormone on tubular transport of phosphate in normal and parathyroidectomized dogs. The Journal of Clinical Investigation. 1964;**43**:1608-1612. DOI: 10.1172/JCI105036

[47] Caverzasio J, Faundez R, Fleisch H, Bonjour JP. Tubular adaptation to pi restriction in hypophysectomized rats. Pflügers Archiv. 1981;**392**:17-21. DOI: 10.1007/BF00584576

[48] Mulroney SE, Lumpkin MD, Haramati A. Suppression of growth hormone release restores phosphaturic response to PTH in immature rats. The American Journal of Physiology. 1991;**261**(6 Pt 2):F1110-F1113. DOI: 10.1152/ajprenal.1991.261.6.F1110

[49] Marcus R, Butterfield G, Holloway L, Gilliland L, Baylink DJ, Hintz RL, et al. Effects of short-term administration of recombinant human growth hormone to elderly people. The Journal of Clinical Endocrinology and Metabolism. 1990;**70**:519-527. DOI: 10.1210/jcem-70-2-519

[50] Holloway L, Butterfield G, Hintz RL, Gesundheit N, Marcus R. Effects of recombinant human growth hormone on metabolic indices, body composition, and bone turnover

in healthy elderly women. The Journal of Clinical Endocrinology and Metabolism. 1994;**79**:470-479. DOI: 10.1210/jcem.79.2.7519191

[51] Joseph F, Ahmad AM, Ul-Haq M, Durham BH, Whittingham P, Fraser WD, et al. Effects of growth hormone administration on bone mineral metabolism, PTH sensitivity and PTH secretory rhythm in postmenopausal women with established osteoporosis. Journal of Bone and Mineral Research. 2008;**23**:721-729. DOI: 10.1359/jbmr.071117

[52] Bengtsson BA, Edén S, Lönn L, Kvist H, Stokland A, Lindstedt G, et al. Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. The Journal of Clinical Endocrinology and Metabolism. 1993;**76**:309-317. DOI: 10.1210/jcem.76.2.8432773

[53] Ahmad AM, Thomas J, Clewes A, Hopkins MT, Guzder R, Ibrahim H, et al. Effects of growth hormone replacement on parathyroid hormone sensitivity and bone mineral metabolism. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**:2860-2868. DOI: 10.1210/jc.2002-021787

[54] White HD, Ahmad AM, Durham BH, Patwala A, Whittingham P, Fraser WD, et al. Growth hormone replacement is important for the restoration of parathyroid hormone sensitivity and improvement in bone metabolism in older adult growth hormone-deficient patients. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**:3371-3380. DOI: 10.1210/jc.2004-1650

[55] Spanos E, Barrett D, MacIntyre I, Pike JW, Safilian EF, Haussler MR. Effect of growth hormone on vitamin D metabolism. Nature. 1978;**273**:246-247. DOI: 10.1038/273246a0

[56] Brown DJ, Spanos E, MacIntyre I. Role of pituitary hormones in regulating renal vitamin D metabolism in man. British Medical Journal. 1980;**280**:277-278. DOI: 10.1136/bmj.280.6210.277

[57] Menaa C, Vrtovsnik F, Friedlander G, Corvol M, Garabédian M. Insulin-like growth factor I, a unique calcium-dependent stimulator of 1,25-dihydroxyvitamin D3 production. Studies in cultured mouse kidney cells. The Journal of Biological Chemistry. 1995;**270**:25461-25467. DOI: 10.1074/jbc.270.43.25461

[58] Gola M, Bonadonna S, Doga M, Giustina A. Clinical review: Growth hormone and cardiovascular risk factors. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**:1864-1870. DOI: 10.1210/jc.2004-0545

[59] Mazziotti G, Bianchi A, Bonadonna S, Nuzzo M, Cimino V, Fusco A, et al. Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: Influence of GH replacement therapy. Journal of Bone and Mineral Research. 2006;**21**. DOI: 520:8. DOI: 10.1359/JBMR.050603

[60] Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: A Metaanalysis of blinded, randomized, placebo-controlled trials. The Journal of Clinical Endocrinology and Metabolism. 2004;**89**:2192-2199. DOI: 10.1210/jc.2003-030840

[61] Falkhedent T, Sjoegren B. Extracellular fluid volume and renal function in pituitary insufficiency and acromegaly. Acta Endocrinologica. 1964;**46**:80-8l. DOI: 10.1530/acta.0.0460080

[62] Oliveira CR, Salvatori R, Nóbrega LM, Carvalho EO, Menezes M, Farias CT, et al. Sizes of abdominal organs in adults with severe short stature due to severe, untreated, congenital GH deficiency caused by a homozygous mutation in the GHRH receptor gene. Clinical Endocrinology. 2008;**69**:153-158. DOI: 10.1111/j.1365-2265.2007.03148.x

[63] Link K, Bülow B, Westman K, Salmonsson EC, Eskilsson J, Erfurth EM. Low individualized growth hormone (GH) dose increased renal and cardiac growth in young adults with childhood onset GH deficiency. Clinical Endocrinology. 2001;**55**:741-748. DOI: 10.1046/j.1365-2265.2001.01413.x

[64] Jørgensen JO, Pedersen SA, Thuesen L, Jørgensen J, Ingemann-Hansen T, Skakkebaek NE, et al. Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet. 1989;**1**:1221-1225. DOI: 10.1016/s0140-6736(89)92328-3

[65] Caidahl K, Edén S, Bengtsson BA. Cardiovascular and renal effects of growth hormone. Clinical Endocrinology. 1994;**40**:393-400. DOI: 10.1111/j.1365-2265.1994.tb03937.x

[66] Klinger B, Laron Z. Renal function in Laron syndrome patients treated by insulin-like growth factor-I. Pediatric Nephrology. 1994 Dec;**8**(6):684-688. DOI: 10.1007/BF00869089

[67] Parra A, Argote RM, García G, Cervantes C, Alatorre S, Pérez-Pasten E. Body composition in hypopituitary dwarfs before and during human growth hormone therapy. Metabolism. 1979;**28**:851-857. DOI: 10.1016/0026-0495(79)90212-9

[68] Whitehead HM, Boreham C, McIlrath EM, Sheridan B, Kennedy L, Atkinson AB, et al. Growth hormone treatment of adults with growth hormone deficiency: Results of a 13-month placebo controlled cross-over study. Clinical Endocrinology. 1992;**36**:45-52. DOI: 10.1111/j.1365-2265.1992.tb02901.x

[69] Binnerts A, Deurenberg P, Swart GR, Wilson JH, Lamberts SW. Body composition in growth hormone-deficient adults. The American Journal of Clinical Nutrition. 1992;**55**:918-923. DOI: 10.1093/ajcn/55.5.918

[70] Kaufman JM, Taelman P, Vermeulen A, Vandeweghe M. Bone mineral status in growth hormone-deficient males with isolated and multiple pituitary deficiencies of childhood onset. The Journal of Clinical Endocrinology and Metabolism. 1992;**74**:118-123. DOI: 10.1210/jcem.74.1.1727808

[71] O'Halloran DJ, Tsatsoulis A, Whitehouse RW, Holmes SJ, Adams JE, Shalet SM. Increased bone density after recombinant human growth hormone (GH) therapy in adults with isolated GH deficiency. The Journal of Clinical Endocrinology and Metabolism. 1993;**76**:1344-1348

[72] Holmes SJ, Economou G, Whitehouse RW, Adams JE, Shalet SM. Reduced bone mineral density in patients with adult onset growth hormone deficiency. The Journal of Clinical Endocrinology and Metabolism. 1994;**78**:669-674. DOI: 10.1210/jcem.78.3.8126140

[73] Boot AM, Engels MA, Boerma GJ, Krenning EP, De Muinck Keizer-Schrama SM. Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. The Journal of Clinical Endocrinology and Metabolism. 1997;**82**:2423-2428. DOI: 10.1210/jcem.82.8.4149

[74] Saggese G, Baroncelli GI, Bertelloni S, Cinquanta L, Di Nero G. Effects of long-term treatment with growth hormone on bone and mineral metabolism in children with growth hormone deficiency. The Journal of Pediatrics. 1993;**122**:37-45. DOI: 10.1016//S0022-3476(05)83484-5

[75] Hansen TB, Brixen K, Vahl N, Jørgensen JO, Christiansen JS, Mosekilde L, et al. Effects of 12 months of growth hormone (GH) treatment on calciotropic hormones, calcium homeostasis, and bone metabolism in adults with acquired GH deficiency: A double blind, randomized, placebo-controlled study. The Journal of Clinical Endocrinology and Metabolism. 1996;**81**:3352-3359. DOI: 10.1210/jcem.81.9.8784096

[76] Bach LA, Hale LJ. Insulin-like growth factors and kidney disease. American Journal of Kidney Diseases. 2015;**65**:327-336. DOI: 10.1053/j.ajkd/2014.05.024

[77] Müller-Wiefel D, Frisch H, Tulassay T, Bell L, Zadik Z. Treatment of growth failure with growth hormone in children with chronic kidney disease: An open-label long-term study. Clinical Nephrology. 2010;**74**:97-105. DOI: 10.5414/cnp74097

[78] Mehls O, Lindberg A, Haffner D, Schaefer F, Wühl E. Long-term treatment growth hormone treatment in short children with CKD does not accelerate decline of renal function: Results from the KIGS registry and ESCAPE trial. Pediatric Nephrology. 2015;**30**:2145-2151. DOI: 10.1007/s00467-015-3157-8

[79] Kamenicky P, Mazziotti G, Lombès M, Giustina A, Chanson P. Growth hormone, insulin-like growth factor-1, and the kidney: Pathophysiological and clinical implications. Endocrine Reviews. 2014;**35**:234-281. DOI: 10.1210/er.2013-1071

[80] Beshyah SA, Freemantle C, Thomas E, et al. Abnormal body composition and reduced bone mass in growth hormone deficient hypopituitary adults. Clinical Endocrinology. 1995;**42**:179-189. DOI: 10.1111/j.1365-2265.1995.tb01860.x

[81] Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocrine Reviews. 2009;**30**:152-177. DOI: 10.1210/er.2008-0027

[82] Dietz J, Schwartz J. Growth hormone alters lipolysis and hormone-sensitive lipase activity in 3T3-F442A adipocytes. Metabolism. 1991;**40**:800-806. DOI: 10.1016/0026-0495(91)90006-I

[83] Johansen T, Richelsen B, Hansen HS, Din N, Malmlöf K. Growth hormone- mediated breakdown of body fat: Effects of GH on lipases in adipose tissue and skeletal muscle of old rats fed different diets. Hormone and Metabolic Research. 2003;**35**:243-250. DOI: 10.1055/s-2003-39481

[84] List EO, Berryman DE, Funk K, Gosney ES, Jara A, Kelder B, et al. The role of GH in adipose tissue: Lessons from adipose-specific GH receptor gene-disrupted mice. Molecular Endocrinology. 2013;**27**:524-535. DOI: 10.1210/me.2012-1330

[85] Berryman DE, List EO. Growth hormone's effect on adipose tissue: Quality versus quantity. International Journal of Molecular Sciences. 2017;**18**:1621. DOI: 10.3390/ijms18081621

[86] Kanety H, Hemi R, Ginsberg S, Pariente C, Yissachar E, Barhod E, et al. Total and high molecular weight adiponectin are elevated in patients with Laron syndrome despite marked obesity. European Journal of Endocrinology. 2009;**161**:837-844. DOI: 10.1530/EJE-09-0419

[87] Furigo IC, Teixeira PDS, de Souza GO, Couto GCL, Romero GG, Perelló M, et al. Growth hormone regulates neuroendocrine responses to weight loss via AgRP neurons. Nature Communications. 2019;**10**:662. DOI: 10.1038/s41467-019-08607-1

[88] Ullman M, Oldfors A. Effects of growth hormone on skeletal muscle I. Studies on normal adult rats. Acta Physiologica Scandinavica. 1989;**135**:531-536. DOI: 10.1111/j.1748-1716.1989.tb08612.x

[89] Baum HB, Biller BM, Finkelstein JS, Cannistraro KB, Oppenheim DS, Schoenfeld DA, et al. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. A randomized, placebo-controlled trial. Annals of Internal Medicine. 1996;**125**:883-890. DOI: 10.7326/0003-4819-125-11-199612010-00003

[90] Weber MM. Effects of growth hormone on skeletal muscle. Hormone Research. 2002;**58**(Suppl 3):43-48. DOI: 10.1159/000066482

[91] Sotiropoulos A, Ohanna M, Kedzia C, Menon RK, Kopchik JJ, Kelly PA, et al. Growth hormone promotes skeletal muscle cell fusion independent of insulin-like growth factor 1 up-regulation. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**:7315-7320. DOI: 10.1073/pnas.0510033103

[92] Mavalli MD, DiGirolamo DJ, Fan Y, Riddle RC, Campbell KS, van Groen T, et al. Distinct growth hormone receptor signaling modes regulate skeletal muscle development and insulin sensitivity in mice. The Journal of Clinical Investigation. 2010;**120**:4007-4020. DOI: 10.1172/JCI42447

[93] Clasen BF, Krusenstjerna-Hafstrøm T, Holm Vendelbo MH, Thorsen K, Escande C, Møller N, et al. Gene expression in skeletal muscle after an acute intravenous GH bolus in human subjects: Identification of a mechanism regulating ANGPTL4. Journal of Lipid Research. 2013;**54**:1988-1997. DOI: 10.1194/jlr.P034520

[94] Tavares AB, Micmacher E, Biesek S, et al. Effects of growth hormone administration on muscle strength in men over 50 years old. International Journal of Endocrinology. 2013;**2013**:942030-942036. DOI: 10.1155/2013/942030

[95] Thomas M, Langley B, Berry C, Sharma M, Kirk S, Bass J, et al. Myostatin, a negative regulator of muscle growth, functions by inhibiting myoblast proliferation. The Journal of Biological Chemistry. 2000;**275**:40235-40243. DOI: 10.1074/jbc.M004356200

[96] Ríos R, Carneiro I, Arce VM, Devesa J. Myostatin is an inhibitor of myogenic differentiation. American Journal of Physiology. Cell Physiology. 2002;**282**:C993-C999. DOI: 10.1152/ajpcell.00372.2001

[97] Langley B, Thomas M, Bishop A, Sharma M, Gilmour S, Kambadur R. Myostatin inhibits myoblast differentiation by down-regulating MyoD expression. The Journal of Biological Chemistry. 2002;**277**:49831-49840. DOI: 10.1074/jbc.M204291200

[98] Trendelenburg AU, Meyer A, Rohner D, Boyle J, Hatakeyama S, Glass DJ. Myostatin reduces Akt/TORC1/p70S6K signaling, inhibiting myoblast differentiation and myotube size. American Journal of Physiology. Cell Physiology. 2009;**296**:C1258-C1270. DOI: 10.1152/ajpcell.00105.2009

[99] Paul RG, McMahon CD, Elston MS, Conaglen JV. GH replacement titrated to serum IGF-1 does not reduce concentrations of myostatin in blood or skeletal muscle. Growth Hormone & IGF Research. 2019;**44**:11-16. DOI: 10.1016/j.ghir.2018.12.001

[100] Nilsson O, Marino R, De Luca F, Philip M, Baron J. Endocrine regulation of the growth plate. Hormone Research. 2005;**64**:157-165. DOI: 10.1159/000088791

[101] Yakar S, Courtland HW, Clemmons D. IGF-1 and bone: New discoveries from mouse models. Journal of Bone and Mineral Research. 2010;**25**:2543-2552. DOI: 10.1002/jbmr.234

[102] Yakar S, Rosen CJ, Beamer WG, Ackert-Bicknell CL, Wu Y, Liu JL, et al. Circulating levels of IGF-1 directly regulate bone growth and density. The Journal of Clinical Investigation. 2002;**110**:771-781. DOI: 10.1172/JCI15463

[103] Bikle DD, Sakata T, Leary C, Elalieh H, Ginziger D, Rosen CJ, et al. Insulin-like growth factor I is required for the anabolic actions of parathyroid hormone on mouse bone. Journal of Bone and Mineral Research. 2002;**17**:1570-1578. DOI: 10.1359/jbmr.2002.17.9.1570

[104] Zhao G, Monier-Faugere MC, Langub MC, Geng Z, Nakayama T, Pike JW, et al. Targeted overexpression of insulin-like growth factor I to osteoblasts of transgenic mice: Increased trabecular bone volume without increased osteoblast proliferation. Endocrinology. 2000;**141**:2674-2682. DOI: 10.1210/endo.141.7.7585

[105] Govoni KE, Wergedal JE, Florin L, Angel P, Baylink DJ, Mohan S. Conditional deletion of insulin-like growth factor-I in collagen type 1α2-expressing cells results in postnatal lethality and a dramatic reduction in bone accretion. Endocrinology. 2007;**148**:5706-5715. DOI: 10.1210/en.2007-0608

[106] Meazza C, Bonomelli I, Pagani S, Travaglino P, Laarej K, Cantoni F, et al. Effect of human recombinant growth hormone therapy on circulating levels of erythropoietin and granulocyte-colony stimulating factor in short children. Journal of Pediatric Endocrinology & Metabolism. 2009;**22**:837-843. DOI: 10.1515/JPEM.2009.22.9.837

[107] Sohmiya M, Kato Y. Effect of long-term administration of recombinant human growth hormone (rhGH) on plasma erythropoietin (EPO) and haemoglobin levels in anaemic patients with adult GH deficiency. Clinical Endocrinology. 2001;**55**:749-754. DOI: 10.1046/j.1365-2265.2001.01417.x

[108] Sohmiya M, Kanazawa I, Kato Y. Effect of recombinant human GH on circulating granulocyte colony-stimulating factor and neutrophils in patients with adult GH deficiency. European Journal of Endocrinology. 2005;**152**:211-215. DOI: 10.1530/eje.1.01831

[109] Esposito A, Capalbo D, De Martino L, et al. Long-term effects of growth hormone (GH) replacement therapy on hematopoiesis in a large cohort of children with GH deficiency. Endocrine. 2016;**53**:192-198. DOI: 10.1007/s12020-015-0781-9

[110] Carlo-Stella C, Di Nicola M, Milani R, Longoni P, Milanesi M, Bifulco C, et al. Age- and irradiation-associated loss of bone marrow hematopoietic function in mice is reversed by recombinant human growth hormone. Experimental Hematology. 2004;**32**:171-178. DOI: 10.1016/j.exphem.2003.11.007

[111] Weigent DA. Lymphocyte GH-axis hormones in immunity. Cellular Immunology. 2013;**285**:118-132. DOI: 10.1016/j.cellimm.2013.10.003

[112] Liu QL, Zhang J, Liu X, Gao JY. Role of growth hormone in maturation and activation of dendritic cells via miR-200a and the Keap1/Nrf2 pathway. Cell Proliferation. 2015;**48**:573-581. DOI: 10.1111/cpr.12206

[113] Weigent DA, Blalock JE, LeBoeuf RD. An antisense oligodeoxynucleotide to growth hormone messenger ribonucleic acid inhibits lymphocyte proliferation. Endocrinology. 1991;**128**:2053-2057. DOI: 10.1210/endo-128-4-2053

[114] Baxter JB, Blalock JE, Weigent DA. Characterization of immunoreactive insulin-like growth factor-I from leukocytes and its regulation by growth hormone. Endocrinology. 1991;**129**:1727-1734. DOI: 10.1210/endo-129-4-1727

[115] Arnold RE, Weigent DA. The inhibition of superoxide production in EL4 lymphoma cells overexpressing growth hormone. Immunopharmacology and Immunotoxicology. 2003;**25**:159-177. DOI: 10.1081/IPH-120020467

[116] Arnold RE, Weigent DA. The production of nitric oxide in EL4 lymphoma cells overexpressing growth hormone. Journal of Neuroimmunology. 2003;**134**:82-94. DOI: 10.1016/S0165-5728(02)00420-4

[117] Arnold RE, Weigent DA. The inhibition of apoptosis in EL4 lymphoma cells overexpressing growth hormone. Neuroimmunomodulation. 2004;**11**:149-159. DOI: 10.1159/000076764

[118] Weigent DA, Arnold RE. Expression of insulin-like growth factor-1 and insulin-like growth factor-1 receptors in EL4 lymphoma cells overexpressing growth hormone. Cellular Immunology. 2005;**234**:54-66. DOI: 10.1016/j.cellimm.2005.04.016

[119] Farmer JT, Weigent DA. Expression of insulin-like growth factor-2 receptors on EL4 cells overexpressing growth hormone. Brain, Behavior, and Immunity. 2007;**21**:79-85. DOI: 10.1016/j.bbi.2006.02.006

[120] Farmer JT, Weigent DA. TGF-beta1 expression in EL4 lymphoma cells overexpressing growth hormone. Cellular Immunology. 2006;**240**:22-30. DOI: 10.1016/j.cellimm.2006.06.003

[121] Weigent DA. Regulation of Id2 expression in EL4 T lymphoma cells overexpressing growth hormone. Cellular Immunology. 2009;**255**:46-54. DOI: 10.1016/j.cellimm.2008.10.003

[122] Malarkey WB, Wang J, Cheney C, Glaser R, Nagaraja H. Human lymphocyte growth hormone stimulates interferon gamma production and is inhibited by cortisol and norepinephrine. Journal of Neuroimmunology. 2002;**123**:180-187. DOI: 10.1016/S0165-5728(01)00489-1

[123] Re RN, Cook JL. Senescence, apoptosis, and stem cell biology: The rationale for an expanded view of intracrine action. American Journal of Physiology. Heart and Circulatory Physiology. 2009;**297**:H893-H901. DOI: 10.1152/ajpheart.00414.2009

[124] Weigent DA. High molecular weight isoforms of growth hormone In cells of the immune system. Cellular Immunology. 2011;**271**:44-52. DOI: 10.1016/j.cellimm.2011.06.001

[125] Caballero-Villarraso J, Aguado R, Cañete MD, Roldán L, Cañete R, Santamaría M. Hormone replacement therapy in children with growth hormone deficiency: Iimpact on immune profile. Archives of Physiology and Biochemistry. 2019;**19**:1-5. DOI: 10.1080//13813455.2019.1628070

[126] Lebi J, Sediva A, Snajderova M, Pruhova S, Rakoskinova V. Immune system in adults with childhood-onset growth hormone deficiency: Effect of growth hormone therapy. Endocrine Regulations. 2000;**34**:169-173

[127] Rekers-Mombarg LT, Rijkers GT, Massa GG, Wit JM. Immunologic studies in children with idiopathic short-stature before and during growth hormone therapy. Dutch growth hormone working group. Hormone Research. 1995;**44**:203-207. DOI: 10.1159/000184626

[128] Spadoni GL, Rossi P, Ragno W, Galli E, Cianfarani S, Galasso C, et al. Immune function in growth hormone-deficient children treated with biosynthetic growth hormone. Acta Paediatrica Scandinavica. 1991;**80**:75-79. DOI: 10.1111/j.1651-2227.1991.tb11733.x

[129] Höybye C, Faseh L, Himonakos C, Pielak T, Eugen-Olsen P. Serum soluble urokinase plasminogen activator receptor (suPAR) in adults with growth hormone deficiency. Endocrine Connections. 2019;**8**:772-779. DOI: 10.1530/EC-19-0159

[130] Lobie PE, Breipohl W, Waters MJ. Growth hormone receptor expression in the rat gastrointestinal tract. Endocrinology. 1990;**126**:299-306. DOI: 10.1210/endo-126-1-299

[131] Lincoln DT, Kaiser HE, Raju GP, Waters MJ. Growth hormone expression and colorectal carcinoma: Localization of receptors. In Vivo. 2000;**14**:41-49

[132] Gilbert S, Zhang R, Denson L, Moriggi R, Steinbrecher K, Shroyer N, et al. Enterocyte STAT5 promotes mucosal wound healing via suppression of myosin light chain kinase-mediated loss of barrier function and inflammation. EMBO Molecular Medicine. 2012;**4**:109-124. DOI: 10.1002/emmm.201100192

[133] Han X, Ren X, Jurickova I, Groschwitz K, Pasternak BA, Xu H, et al. Regulation of intestinal barrier function by signal transducer and activator of transcription 5b. Gut. 2009;**58**:49-58. DOI: 10.1136/gut.2007.145094

[134] Soendergaard C, Kvist PH, Thygesen P, Reslow M, Nielsen OH, Kopchil JJ, et al. Characterization of growth hormone resistance in experimental and ulcerative colitis. International Journal of Molecular Sciences. 2017;**18**:2046. DOI: 10.3390/ijms18102046

[135] Devesa J, Devesa P, Reimunde P. Growth hormone revisited. Medicina Clínica (Barcelona). 2010;**135**:665-670. DOI: 10.1016/j.medcli.2009.10.017

[136] Balducci R, Toscano V, Larizza D, Mangiantini A, Gaiasso C, Municchi G, et al. Effects of long-term growth hormone therapy on adrenal steroidogenesis in turner syndrome. Hormone Research. 1998;**49**:210-215. DOI: 10.1159/000023173

[137] Isidori AM, Kaltsas GA, Perry L, Burrin JM, Besser GM, Monson JP. The effect of growth hormone replacement therapy on adrenal androgen secretion in adult onset hypopituitarism. Clinical Endocrinology. 2003;**58**:601-611. DOI: 10.1046/j.1365-2265.2003.01759.x

[138] Ciresi A, Radellini S, Vigneri E, Guarnotta V, Bianco J, Mineo MG, et al. Correlation between adrenal function, growth hormone secretion, and insulin sensitivity in children with idiopathic growth hormone deficiency. Journal of Endocrinological Investigation. 2018;**41**:333-342. DOI: 10.1007/s40618-017-0747-2

[139] Devaskar UP, Devaskar SU, Voina S, Velayo N, Sperling MA. Growth hormone stimulates adrenal steroidogenesis in the fetus. Nature. 1981;**290**:404-405. DOI: 10.1038/290404a0

[140] McFarlane AC, Edmondson SR, Wintour EM, Werther GA. GH-receptor distribution in the ovine foetal adrenal gland: Ontogenic and functional studies. The Journal of Endocrinology. 1999;**162**:197-205. DOI: 10.1677/joe.0.1620197

[141] Li Y, Zhang Y, Zhang M, Yang W, Ji B, Pan H, et al. Growth hormone peak modifies the effect of BMI on increased systolic blood pressure in children with short stature. Scientific Reports. 2019;**9**:7879. DOI: 10.1038/s41598-019-44299-9

[142] Butler G, Turlejski T, Wales G, Bailey L, Wright N. Growth hormone treatment and health-related quality of life in children and adolescents: A national, prospective, one-year controlled study. Clinical Endocrinology. 2019;**91**:304-313. DOI: 10.1111/cen.14011

[143] Butler T, Harvey P, Cardozo L, Zhu YS, Mosa A, Tanzi E, et al. Epilepsy, depression, and growth hormone. Epilepsy & Behavior. 2019;**94**:297-300. DOI: 10.1016/j.yebeh.2019.01.022

[144] Ford ZK, Dourson AJ, Liu X, Lu P, Green KJ, Hudgins RC, et al. Systemic growth hormone deficiency causes mechanical and thermal hypersensitivity during early postnatal development. IBRO Report. 2019;**6**:111-121. DOI: 10.1016/j.ibror.2019.02.001

[145] Hu Y, Liu X, Chen X, Chen T, Ye P, Jiang L, et al. Differences in the functional connectivity density of the brain between individuals with growth hormone deficiency and idiopathic short stature. Psychoneuroendocrinology. 2019;**103**:67-75. DOI: 10.1016/j.psyneuen.2018.12.229

IntechOpen