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

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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

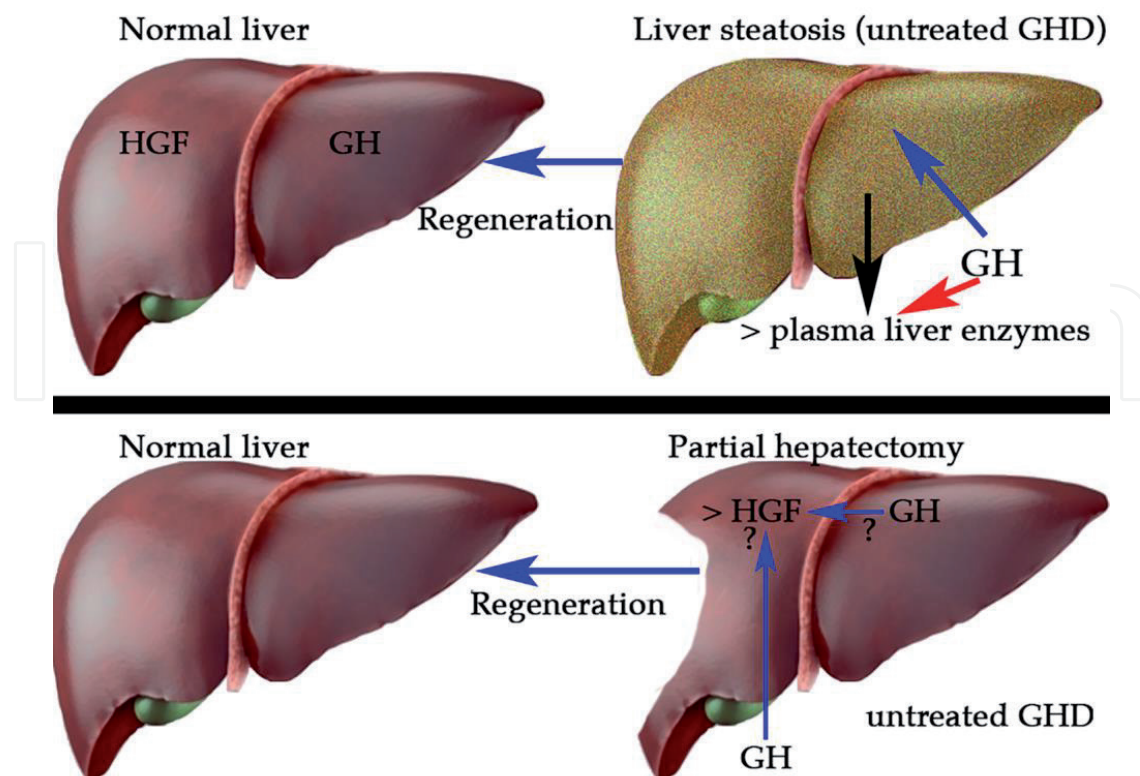


Figure 1. Effects of GH on the liver. Upper graph: There is GH expression in the normal liver (left), although this organ has its own regeneration factor (hepatocyte growth factor—HGF). Untreated GHD may suffer non-alcoholic liver steatosis (right), showing increased plasma levels of liver enzymes (transaminases); 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, translated 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].

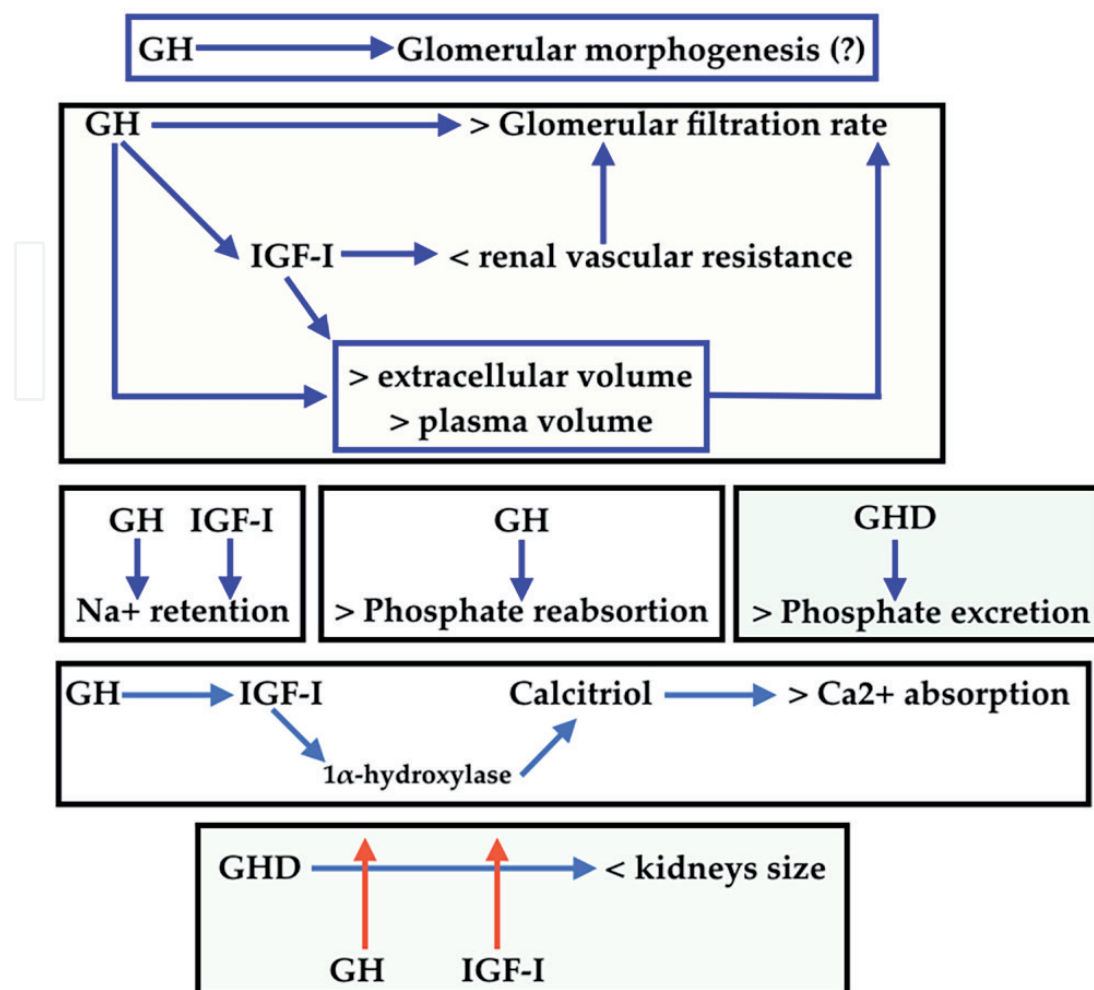


Figure 2. GH effects on the kidney. It is possible that GH participates in the early stages of the development of the kidneys by inducing glomerular morphogenesis. GH administration increases glomerular filtration rate, in this effect also participates GH-induced IGF-I, although the effects of both hormones 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 Ca²⁺, 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.

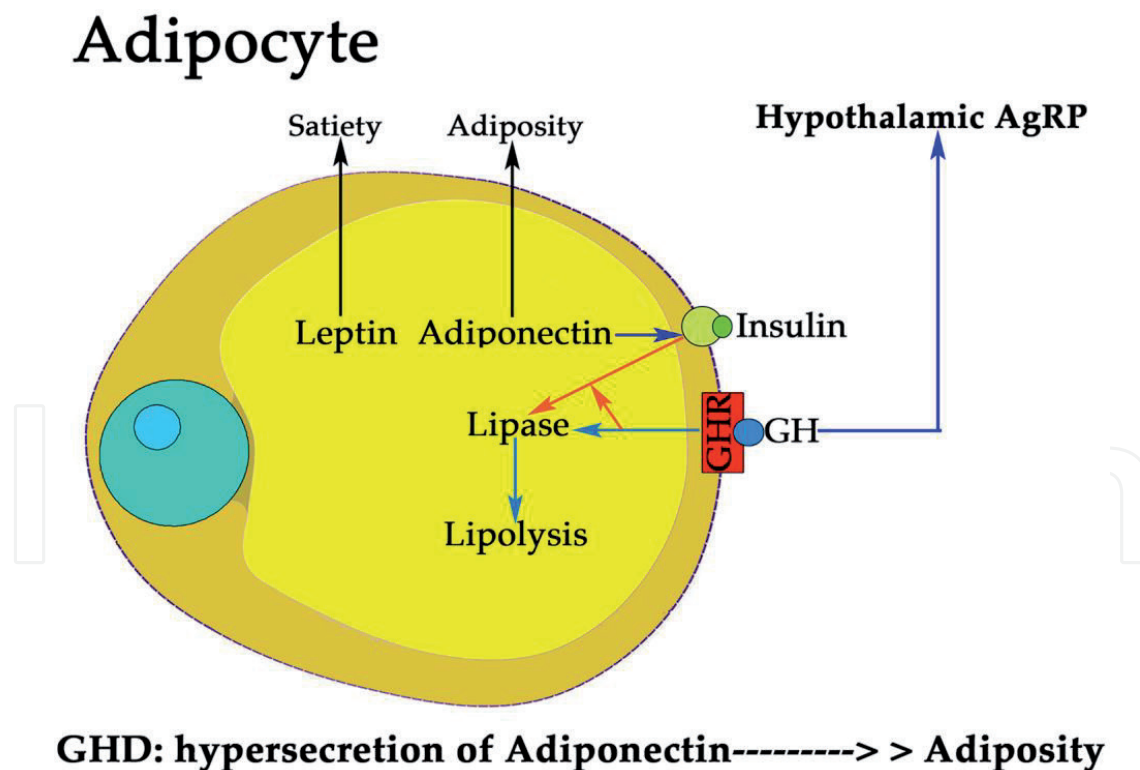


Figure 3. GH effects on fat mass. There are GHR in the membrane of adipocytes. After interacting with endocrine GH, the activity of the lipase (blue arrow) is increased leading to increased lipolysis. In addition, GH-GHR interactions lead to the inhibition of lipase activity (red arrow) induced by insulin. 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.

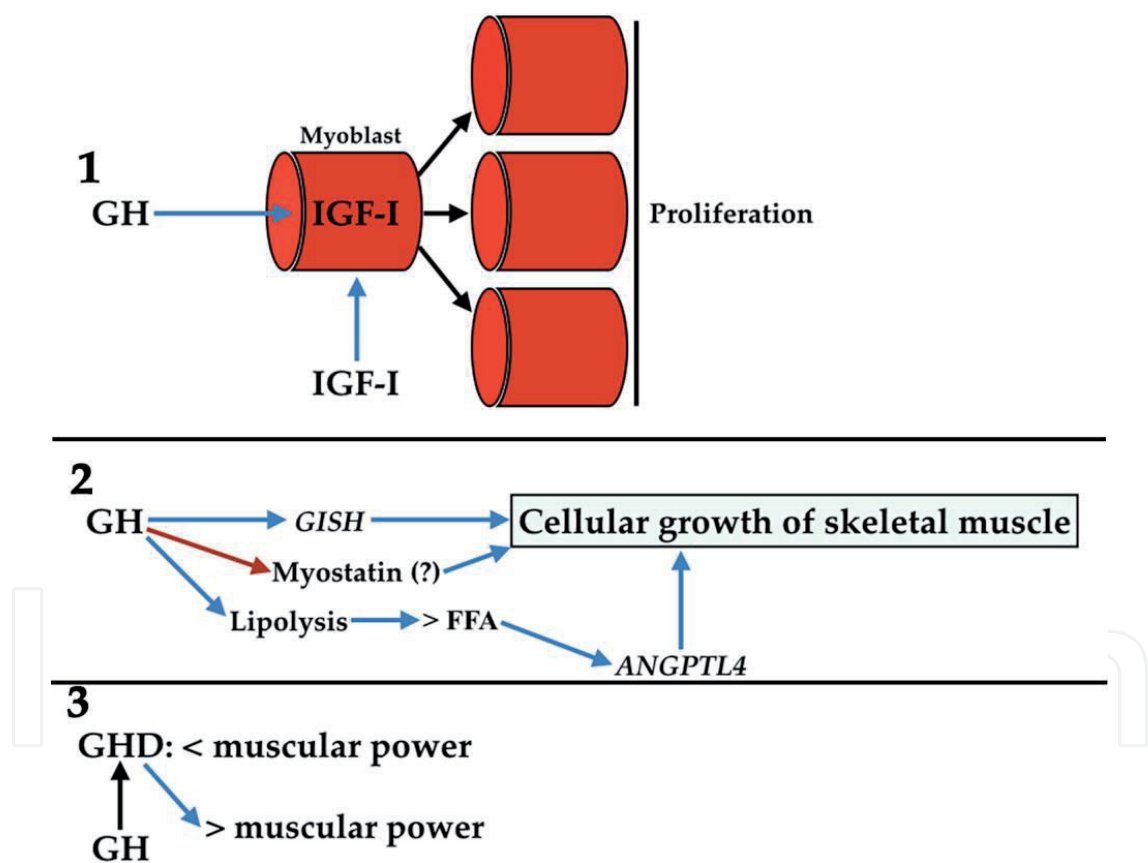


Figure 4. GH effects on skeletal muscle. 1: GH induces IGF-I expression in myoblasts. In turn, IGF-I leads to the proliferation of these myoblasts and produces muscular hypertrophy. The effects of GH and IGF-I are additive. 2: GH induces cellular growth in skeletal muscles by different mechanisms. One 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 1 α 2 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 IFN γ 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.

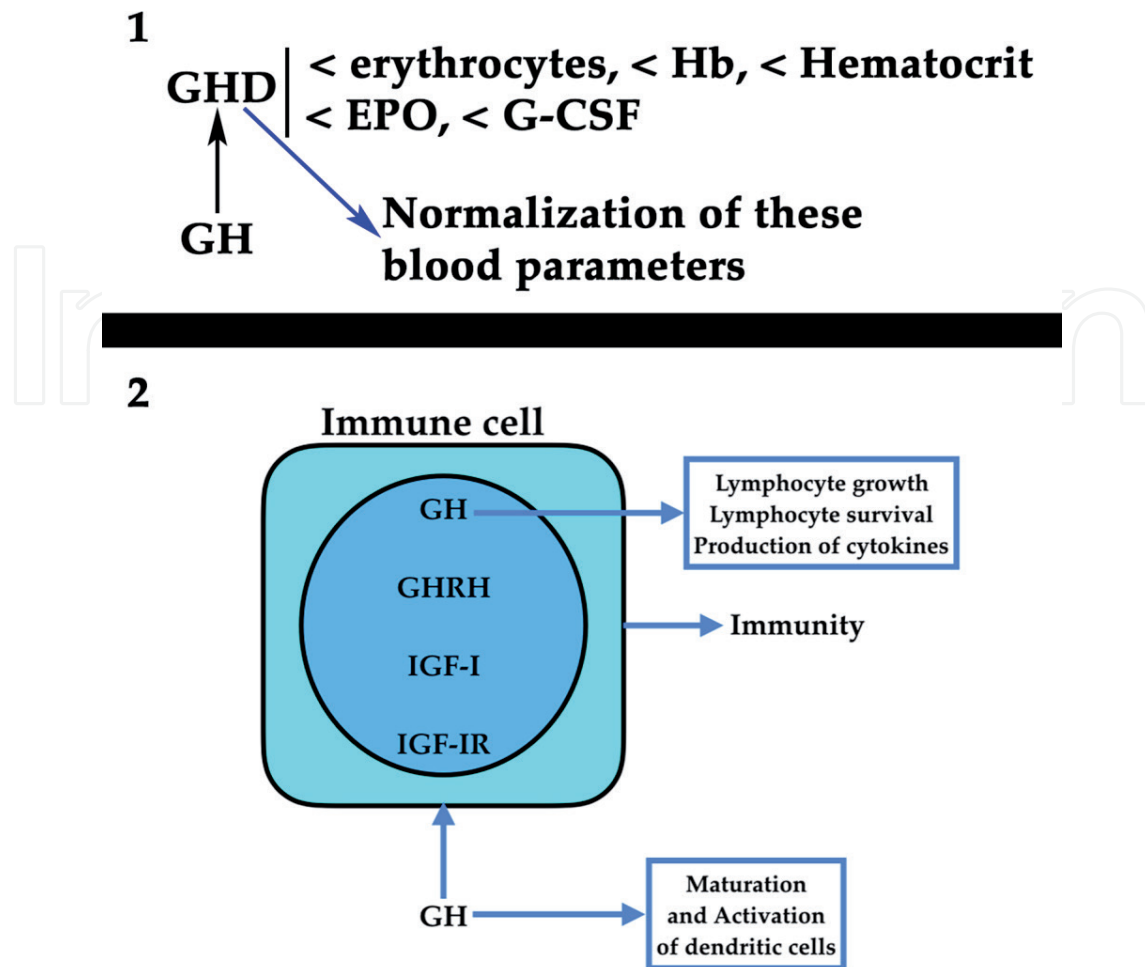


Figure 5. (1) GH plays an important role on hematopoiesis. This is the reason by which untreated GHD patients present deficits in the number of red blood cells, Hb, and hematocrit. Curiously, in these patients, there are also decreased plasma levels of EPO and G-CSF. GH administration normalizes these 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 11 β -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.

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Conflict of interest

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

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