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

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Additional information is available at the end of the chapter

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## Abstract

The concept that the growth hormone (GH) is a merely metabolic pituitary hormone with effects on the longitudinal growth of the organism until the end of puberty has been questioned in recent years. We know today that the expression of GH also occurs in virtually all organs and tissues where it performs very important autocrine/paracrine and even intracrine functions. GH acts on all organs and tissues, being particularly important in the development of the brain during the fetal period. In addition, the hormone, after interacting with its membrane receptor, is internalized together with its receptor, allowing it to reach the cell nucleus where it acts as a transcription factor. In the first part of this review, we will analyze the effects of GH on the brain, the cardiovascular system, and the gonadal system, as well as the adverse effects that occur in the GH deficiency not treated in children and adults. GH is absolutely necessary for a normal brain development and also for repairing the nervous system after an injury. Moreover, GH plays a very important role in the cardiovascular system, as well as in normal gonadal functioning.

**Keywords:** GH deficiency, IGF-I, GH and nervous system, GH and cardiovascular system, GH and gonadal functioning

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## 1. Introduction

Almost a century ago it was reported that the treatment of rats with bovine anterior pituitary gland extracts led to an increase in the growth of the animals treated with these extracts [1]; however, it was not until 35 years later, when from these pituitary extracts, from humans, in this case, the factor responsible for this effect on growth could be isolated and administered to human dwarfs that then began to grow normally [2], but this growth factor had to be obtained

from human cadavers, and it was not pure and safe for its therapeutic use, until in 1971 its primary sequence was characterized and became known as growth hormone (GH). After that, and due to the development of genetic engineering, it was possible to start producing, since 1981, using recombinant DNA technology, unlimited amounts of the pure and safe hormone, obtained both from prokaryotes and eukaryotes, to be used in the treatment of children with GH deficiency (GHD).

Soon, the clinical use of GH and preclinical investigations allowed to know that the hormone was not only responsible for the longitudinal growth of the organism, but also it is a metabolic hormone with a counterregulatory function (it produces hyperglycemia since it antagonizes the actions of insulin on tissue uptake of glucose and induces lipolysis and protein anabolism). Moreover, GH induces the expression of many different growth factors (such as insulin-like growth factor I [IGF-I]) and exerts direct effects on cellular proliferation, differentiation, and survival [3].

In the last years, several investigations modified this classical description of GH as the hormone responsible for growth. While there are no doubts about the fact that GHD children grow defectively until they are treated with GH, many data indicate that the GH-growing effect mainly depends on the GH-induced liver production of IGF-I. In turn, the liver production of IGF-I is conditioned by the nutritional status of the organism, particularly the hepatic metabolism of glucose, and IGF-I is the hormone responsible for the longitudinal growth of the organism, a fact clearly seen in children of short stature in whom a defect in the hepatic receptor for GH (GHR) impedes that GH induces hepatic IGF-I expression [4, 5]. In this situation there are high levels of plasma GH but extremely low levels of plasma IGF-I, a condition that also can be seen GHR null mice [6, 7]. The administration of recombinant IGF-I reverts this growth problem, as it happens in children with Laron syndrome. Moreover, growth velocity in obese children is normal, despite that obesity leads to decreased or practically absent GH secretion, but in them, plasma IGF-I level is high [8, 9]. On the contrary, undernourished children or anorexia nervosa patients present high GH secretion but extremely reduced plasma IGF-I levels leading to decreased growth velocity [10, 11]. Curiously, there have been reported cases in which growth is normal and the final height is even above the target height in patients with persistent untreated GHD and undetectable IGF-I levels [12]; these patients suffered combined pituitary hormone deficiencies after resection of craniopharyngiomas and hypothalamic tumors. This led the authors to suggest that growth factors different to GH, IGF-I, insulin, or prolactin could play a growth-promoting role [12].

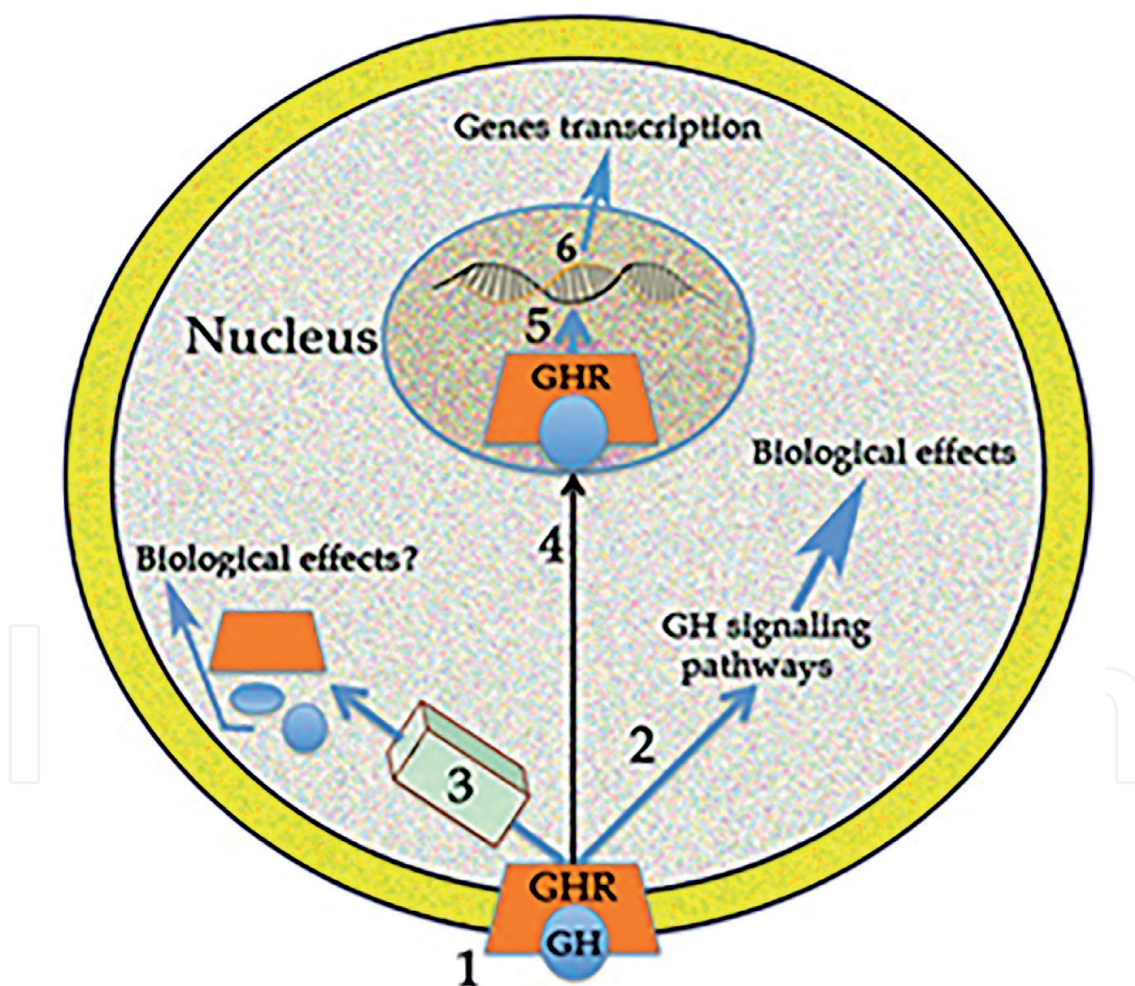
Currently, there are some other important concepts that go further to the classical description of GH. For instance, we know that there is a peripheral expression of the hormone, in practically all the tissues and organs where it plays an autocrine/paracrine role in the cells [3]. Therefore, besides the pituitary GH, there is a peripheral GH system owning specific properties. On the other side, the hormone, after interacting with its GHR in the cell membrane, is internalized together with its receptor via the endosomal pathway [13–15]. Once inside the cell, the hormone, which has arrived from the plasma, and its GHR are translocated to the nucleus where they act as transcription factors [13]. Therefore, the detection of the GHR in a

cell nucleus indicates that there has been a previous interaction between GH and its receptor at the level of the membrane of this cell. This concept is schematized in **Figure 1**.

Data from our group indicate, at least in rats, that once internalized, GH can undergo a tissue-specific proteolytic processing, which originates different molecular forms. The actions of these GH-derived forms are unknown, but the type of them depends on the sex and age of the animal [16].

A review of the multiple actions that GH performs in the organism, far beyond its classically defined effects, can be seen in [3, 17].

Of course, any child with GH deficiency should receive hormone replacement therapy, but this does not always happen, and in the case of adults whether or not they are GHD, GH secretion decreases gradually with age, after age 20 [18], which may have a causal relationship with cardiovascular events and neurodegenerative diseases typical of aging.



**Figure 1.** GH induces the translocation of its receptor to the nucleus of the cell. (1) After the binding of extracellular GH to its membrane receptor, a number of signaling pathways are activated (2) producing different biological effects. (3) GH and its receptor also are internalized via endosomes. There they suffer proteolytic degradations giving origin to shorter molecular forms which perhaps have a biological significance. (4) The internalization of GH and its receptor allows that they are translocated to the nucleus of the cell, where they act as transcription factors.



In this review we will analyze the possible harmful effects that the lack of GH can produce on a series of tissues and organs in the human body, without considering the known affection of the longitudinal growth that occurs before puberty ends in untreated GHD children.

## 2. Untreated GH deficiency

Since many years ago, to establish that there is GHD implies the analysis of the amplitude of the GH response to at least two provocative stimuli, such as insulin-induced hypoglycemia, oral clonidine administration, propranolol plus exercise, etc. However, in many cases these tests produce a number of false-positive or false-negative responses [19]. This is due to the existence of an intrinsic hypothalamic-somatotroph rhythm, as we demonstrated in 1989 [20], that can condition the GH response to a provocative stimulus. As far as we know, the unique test in which no errors occur is the clonidine-GHRH test [21], but GHRH is no longer available in Spain and many other countries. The consequence of the lack of provocative tests that do not give uncertain results is that many children do not receive GH replacement therapy when in fact they need it.

### 2.1. GHD and nervous system functioning

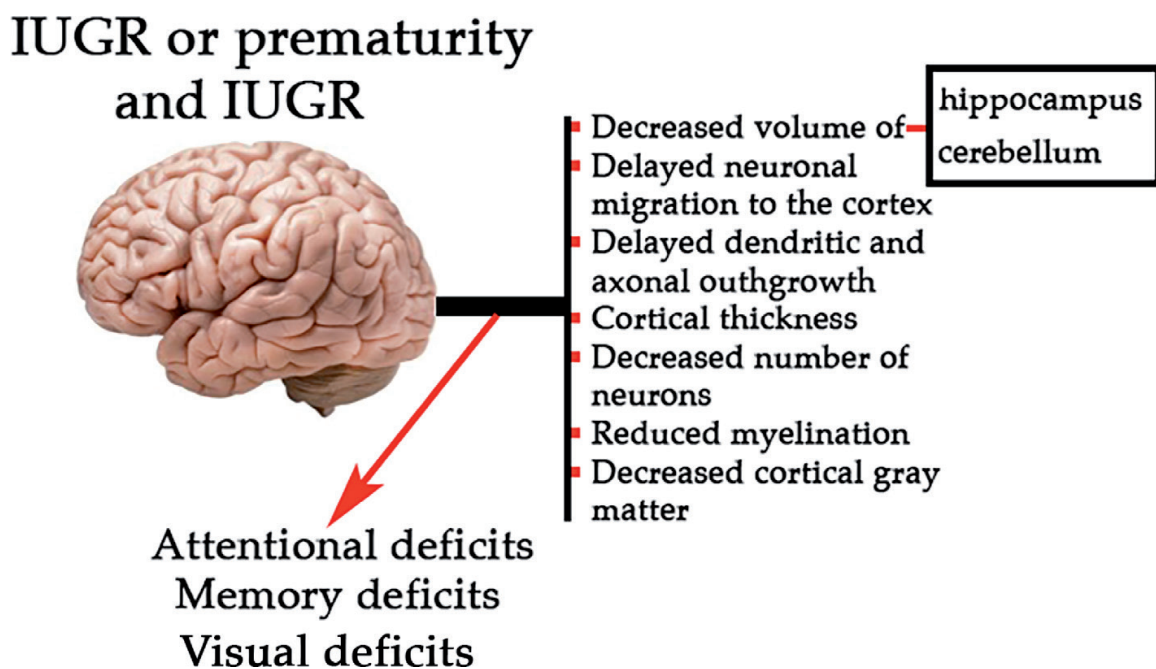
Both GH and IGF-I play key roles in the development, maturation, and function of the brain [22, 23]. In fact, the presence of GHR in the brain is detected very early during neural development [24]. This implies that GH has to be present in the brain for interacting with its receptor [24]. This cerebral GH can come from the fetal anterior pituitary gland since the presence of this hormone in this gland has been identified toward week 7 postconception, and in plasma it is already detectable by 10 weeks of pregnancy [25, 26]. However, although it is well known that plasma GH can easily reach the central nervous system (CNS) [24], since GH-binding sites exist in the choroid plexus where they may act as carriers for plasma GH, a number of data indicate that the own GH is also synthesized in the CNS [27, 28], where, curiously, its regulation seems to be different to that of the pituitary GH. IGF-I is also synthesized in the CNS [29], and its expression, induced by GH, has been detected in neural stem cells from fetal human forebrains [30]. Both GH and IGF-I play a very important reparative role after a brain injury, a hypothesis postulated a long time ago [31] and later proved by many preclinical and clinical studies, regardless of whether the experimental animals or human patients were GHD or not [32–49].

Of interest here and before analyzing the effects of the lack of GH on the functioning of the brain is the case of children born small for gestational age (SGA) because of intrauterine growth retardation (IUGR) [50]. Together with several affectations that may occur later in their life (increased cardiovascular risk, diabetes mellitus type 2, and renal diseases), these children usually show decreased intelligence and cognition [51], especially manifested by the decrease of short-term memory. Animal studies in which IUGR had been induced showed that there was a decreased volume of both hippocampus and cerebellum [52, 53], a delayed neuronal

migration to the cortex [54], and delayed dendritic and axonal outgrowth [53, 55, 56]; in addition, there was cortical thickness, decreased number of neurons [52, 53, 57, 58], and clearly reduced myelination [53, 55, 59, 60]. Similar results have been found in premature children with IUGR in whom there is a reduction of total brain volume, mainly in cerebral cortical gray matter [61–63], later traduced in attentional deficit, among other cerebral deficits, such as visual affectations. These concepts are schematized in **Figure 2**.

While it is now clear that the system GH/IGF-I plays a key role in the development of the fetal brain, although the pituitary GH does not exert any effect on the longitudinal growth of the fetus [3], there are no data indicating that IUGR children suffer from a deficient or absent GH production by the neural stem cells during the fetal development. It is also not known how the regulation of the cerebral production of this hormone takes place, but in any case and based on the data presented, it is reasonable to think that in these children with IUGR, a treatment with GH should be administered shortly after birth, to avoid and/or reduce the described deficits, something that generally does not occur. If a child with short stature is treated with GH, to increase his height, treatment usually does not begin before 4–5 years of age, but at these ages, the brain has already developed.

Similar brain deficiencies, although perhaps more marked, occur in untreated GHD children. Lack of attention and perception, deficient executive functions, and poor short-term memory are usual cognitive impairments observed in these children, who also show behavioral disorders. The same happens in GHD adults, in whom, in addition, there is a deteriorated psychological well-being. These impairments in cognitive functioning, especially subnormal memory speed, have been visualized by functional magnetic resonance imaging [64]. GH



**Figure 2.** Schematic description of the affectations that may happen in children with IUGR or prematurity plus IUGR. Red arrow indicates the main alterations that may appear in these children.

replacement therapy recovers these deficits, both in children and adults, leading to marked improvements in the quality of life [65–71].

The question that should be asked now would be: how does GH exert these important actions in cognitive functions?

GH seems to be a very important regulator of hippocampus-dependent spatial learning and memory, therefore being able to revert memory deficiencies produced by alterations in cholinergic neurons and an imbalance in hippocampal glutamatergic and GABAergic synapses [72]; in addition, GH increases the blood flow to the brain and induces, via activation of PI3K/Akt pathways, the translocation of Glut4 vesicles to the plasma membrane for allowing the entry of glucose in neurons [73], and enhancement of excitatory synaptic transmission through NMDA receptors [74–77]. Although these studies have been carried out in rats, our recent data in an older woman support these effects of GH, not only in the hippocampus but also in practically all cortical areas, as measured by PET scans performed before GH administration and 1 month later [49]. It is likely that these effects of GH on cognition and the metabolic activity of the brain are also due to the effects of the hormone on the adult neurogenesis, both in physiological conditions and after a brain injury. It is also possible that, apart from the direct effects of GH in the brain, some of its actions are mediated by the induction of the expression of several neurotrophic factors, such as IGF-I, brain-derived neurotrophic factor (BDNF), erythropoietin (EPO), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and some cytokines [3]. GH also modifies the levels of the main neurotransmitters (serotonin, noradrenaline, dopamine, the glutamatergic system, the opioid system, and the cholinergic system) in several brain areas, although the type of modification differs according to the brain area (for review, see [3]).

As stated above, the pituitary secretion of GH decreases progressively throughout aging; consequently, human adults suffer affectations in their cognitive functions, mainly short-term memory and their quality of life. Therefore, older people suffer a kind of GHD which can be reversed with GH replacement therapy.

There are other pathological situations in which a non-classic GHD appears, susceptible of being corrected, total or partially, with GH administration. This is the case, for instance, of children with cerebral palsy, traumatic brain injuries, stroke, spinal cord injuries above T5–T6, or neurosensorial hearing loss, and even injuries in central or peripheral nerves.

Data from our group indicate that in a large number of children with cerebral palsy, 70% of them lacked normal GH secretion [78]. We do not know if this GHD is a consequence of the neonatal injury or if it occurs as a result of the high spasticity that leads to a deficient production of IGF-I, but in any case GH administration in these children is very useful and helps to the kinesiotherapy and the recovery of lost brain functions [40, 79]. Similar recoveries, after GH administration and rehabilitation, have been seen in traumatic brain injuries [35–37, 39, 41–44, 47] and after a stroke, both in rats [48] and humans [80, 81]. **Figure 3** shows the recovery of a 52-year-old man who, 1 year previously, had suffered an ischemic infarction of the left middle cerebral artery, which led to aphasia and right hemiplegia. We treated him with GH and rehabilitation, and 18 months later he had fully recovered, without any sequel.



**Figure 3.** Recovery from an ischemic stroke. The patient suffered aphasia and right hemiplegia. He was treated with rehabilitation and GH (0.6 mg/day during 3 months, followed by 1 month without GH administration, and again another 3 months under GH treatment. This pattern was conducted over 18 months). At discharge he had recovered all lost functions. In the picture, it can be seen how the patient moves perfectly the right arm and leg, previously paralyzed.

In the case of the spinal cord, injuries above T5–T6, there is a loss of the afferent inputs from the spinal cord to the sympathetic ganglionic chain resulting in a decreased or absent supply of catecholamines to the hypothalamus. The result of this situation would be an increased hypothalamic somatostatin release and, consequently, deficient or insufficient GH secretion [82]. This GHD in patients with spinal cord injuries had been reported years ago [83, 84], but never were they treated with GH, until 2007, when we began to treat these patients with the hormone and rehabilitation, based on the fact that there are neural stem cells in the spinal cord ependyma whose proliferation and differentiation is stimulated by GH, with good or very good results in many cases (**Figure 4**), although we still have not published our results.

Recently, the administration of GH to this type of patients has been reported to be safe and effective [85]. The effects of GH on the spinal cord have been clearly demonstrated by our group in a young child affected by caudal regression syndrome at the L2 level [86]. The treatment started when the patient was 3 months old. Five years later and, even though the patient





**Figure 4.** Recovery from a complete spinal cord injury (level C5–C6, ASIA A). The injury occurred 6 years before, at 16 years old. (1) The patient at admission. He could only move his arms but did not reach the mouth. He had a great spasticity. He was treated with rehabilitation and GH (1 mg/day, following the same pattern described in **Figure 3**). (2) Two years later he was able to walk with the help of a walker. Currently, 10 years after discharge, he walks 5 km/day, although he still needs the walker.

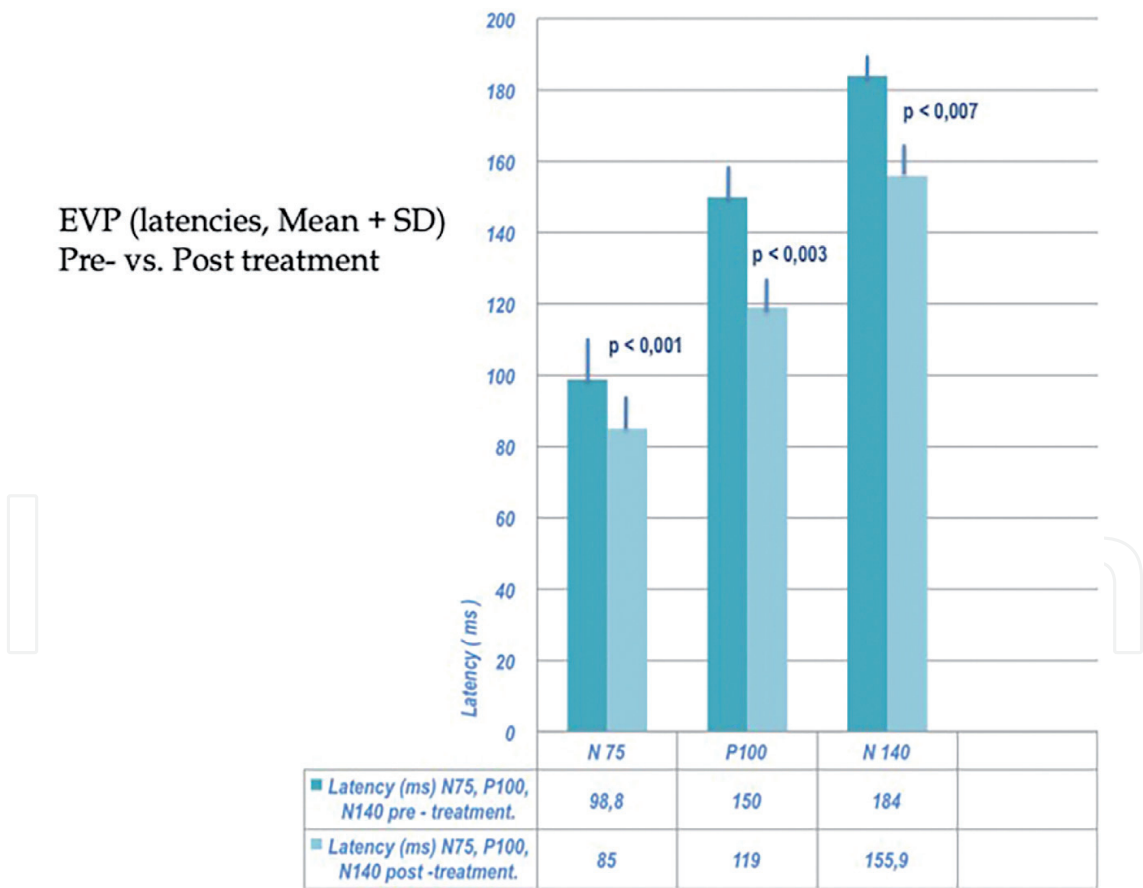
also suffered from a lack of sacral bone, he was able to walk with the help of a cane and to get up from the ground without help, has full sensitivity in the legs and feet, and has sphincter control. This indicates that, although the spinal column did not grow, new spinal roots were formed that fully innervated the legs, feet, and sphincters. These effects, the first case in the world, only can be attributed to GH.

Neurosensory hearing loss is a quite common finding in children with perinatal problems and also in children with alterations in GH secretion or its signaling pathways [87, 88]. We treated with GH and specific auditory stimulation a child with cerebral palsy,

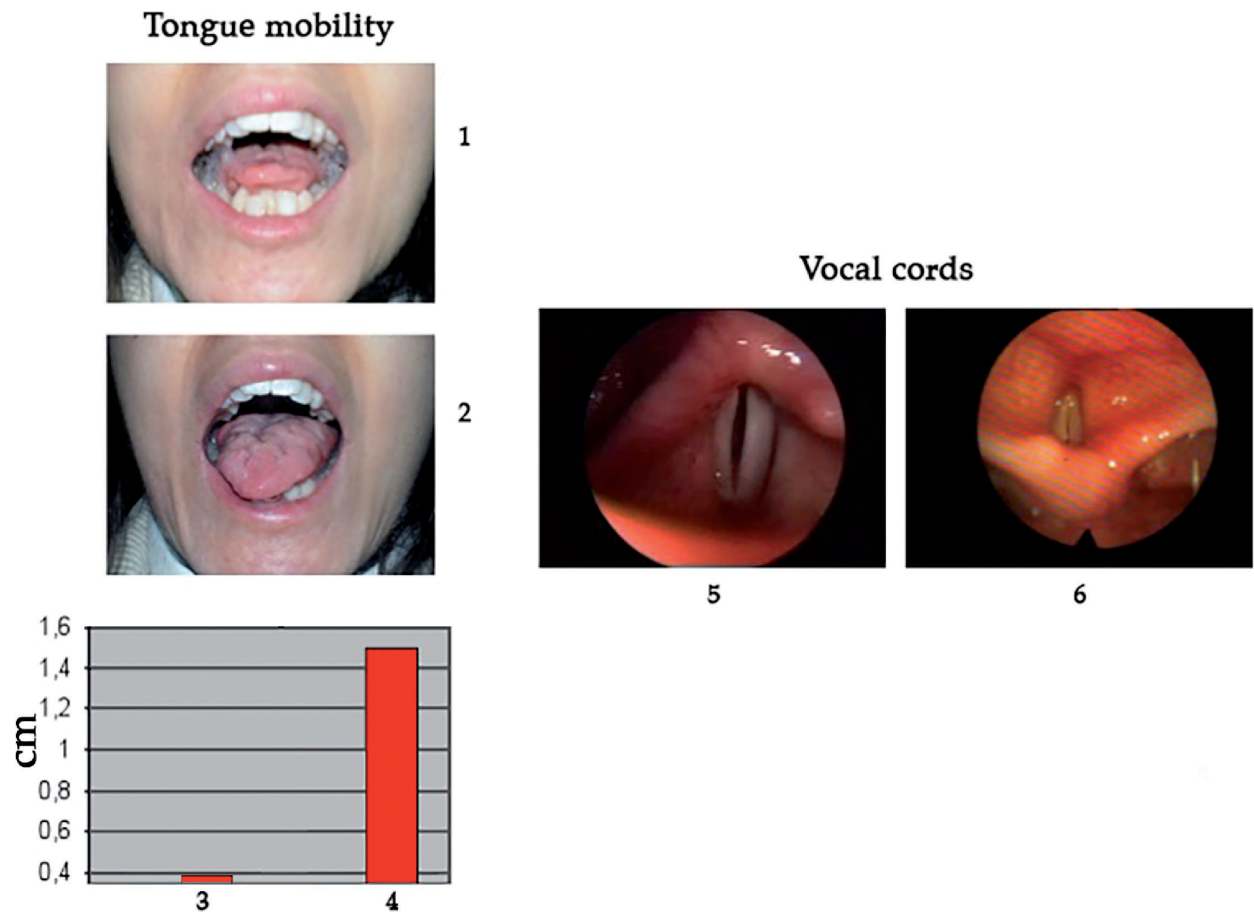
beginning when he was 3.5 months old, and 14-months later he was fully normal [89]. Most likely hearing loss was recovered due to the effect of GH on the production of hair cells from stem cells existing in the cochlear sensory epithelium. These stem cells are present only in very young children and respond to GH proliferating and differentiating. This was the first known case in which hearing loss was recovered by the administration of this hormone.

GH is also a promising therapy for central and peripheral nerve injuries. For instance, a common finding in children with cerebral palsy is a delayed conduction from the retina to the occipital cortex, but we corrected it with the administration of GH and visual stimulation with a tachistoscope [90] (Figure 5).

In this case, it is likely that the hormone increased the number of fibers in the optical nerve and promoted myelination of them. A similar regeneration was obtained in an untreated GHD patient, 15 years after she suffered a brain surgery because of a bulbar astrocytoma (what was the cause of the GHD). The surgery produced paralysis of oropharyngeal structures, paralysis of vocal cords, and lack of primary esophageal peristalsis, because of iatrogenic



**Figure 5.** Evoked visual potentials (EVP) in 36 young children with cerebral palsy. Note the significant decrease in the conduction velocity from the retina to the occipital cortex, after being treated with GH (0.04 mg/kg/day) and visual stimulation with a tachistoscope. This indicates an increase in the number of fibers and myelination of the optical nerve.



**Figure 6.** Recovery from cranial nerve pair damage 15 years after bulbar surgery. (1) The patient at admission was unable to move the tongue, it was atrophic, and the mouth continuously accumulated highly dense mucous saliva (sympathetic saliva). (2) Four months after being treated with GH (1 mg/day, 5 days/week) and speech therapy, the tongue had increased its size and showed important mobility; the patient began to speak and ceased to accumulate sympathetic saliva. (3) Indicates the inability to move the tongue forward (red rectangle). (4) Four months later these forward movements clearly improved (red rectangle). (5) At admission there was paralysis of the vocal cords. (6) Eight months later the vocal cords move normally. The patient was discharged practically recovered from her dysfunctions.

palsy of cranial nerve pairs IX, X, and XII. Therefore, the patient was unable to speak or swallow, her tongue was atrophic, and vocal cords were paralyzed. Moreover, her mouth was continuously full of sympathetic highly dense mucous saliva, and there was the need of nocturnal volumetric ventilation because of the severity and frequency of her sleep apneas. Eight months after beginning a treatment with GH and speech therapy, the patient was discharged practically recovered [91] (**Figure 6**).

Since the patient had undergone an intense oral rehabilitation for almost 15 years, without any success, it seems clear that the administration of GH was the factor responsible for the recovery of damaged cranial nerves.

We also demonstrated, in rats, that the administration of GH administration led to complete functional recovery of the sciatic nerves after their transection [92], promoting the appearance of a high number of axons and Schwann cells, while in the group of rats treated with placebo, a persistent paralysis of the affected limb was present.



In summary, from these and many other data, it is clear that GH is a hormone that plays many important roles in the development and functional maintenance of the nervous system, central and peripheral, and/or its repair when an injury exists. These effects have nothing to do with the longitudinal growth of the organism, but do not appear in untreated GHD children or adults when really they do need the replacement therapy with the hormone.

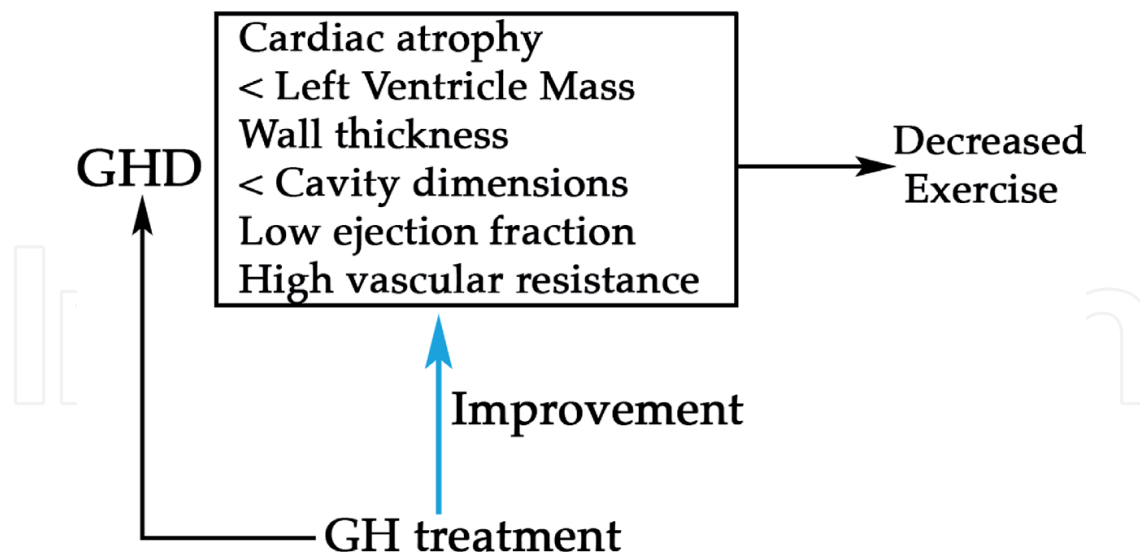
## 2.2. GHD and cardiovascular system

As it happens in the brain during fetal development, GH has direct effects in the heart of the fetus; the hormone induces myocardial growth and improves the cardiac function [93]. Fetal GH induces mRNA expression of specific contractile proteins, increases the force of cardiac contraction, and induces the phenocconversion of myosin toward the low ATPase activity V3 isoform [93]. This allows to increase the number of actin-myosin cross-bridges and their attachment time, enhances protein calcium sensitivity and calcium availability, and allows the myocardium to function at lower energy cost. Therefore, the fetal heart is able to beat at high frequency without spending too much energy. After birth, this changes, and myocardial remodeling occurs; the V1 myosin is then expressed, which implies a higher ATPase activity. Some of these effects of GH on the fetal heart may be produced by GH-induced IGF-I expression in the heart. The GH-IGF-I axis may also regulate cardiac metabolism, by increasing amino acid uptake, protein synthesis, cardiomyocyte size, and myocardial-specific gene expression. In addition, GH-induced IGF-I reduces apoptosis of cardiomyocytes, thus preventing myocyte loss, and increases the collagen deposition rate in the heart [94–99].

Although many of the aforementioned studies come from preclinical research, the important role that GH plays at the myocardial level can be easily observed by analyzing what happens in untreated GHD children and adults. In them, there is cardiac atrophy with a significant reduction in the left ventricle mass, relative wall thickness, and cavity dimensions, in comparison with age-, sex-, and height-matched controls [100–104]. These patients also have a low ejection fraction, low cardiac output, and high peripheral vascular resistance [100, 102–105]. As is logical, physical exercise increases these alterations; consequently, the intensity of exercise and its duration are reduced in both GHD children and adults [106, 107]. However, adult-onset GHD does not produce a reduction in cardiac mass. GH replacement therapy in GHD adults exerts significant positive effects on cardiac abnormalities, as it has been shown in several trials. The left ventricular mass increases, cardiac performance improves, and diastolic filling and systolic function also improve, both in GHD children and adults when they receive a GH treatment [100–102, 104, 105, 108] (**Figure 7**).

Therefore, and given the positive effects of GH on the heart, it is likely that GH treatment may be useful in patients with heart failure, even if they are not GHD. Many recent studies support such a possibility, and the treatment with GH has been proposed and carried out with very good results in untreated GHD children and adults with heart failure and also in patients suffering this affection even though they are not GHD [109–117], although there are studies suggesting that this GH therapy only provides positive results in GHD patients [118].





**Figure 7.** The effect of GH treatment on cardiovascular functioning in GHD patients. Untreated GHD patients suffer several important affectations in the heart. This leads to an increased cardiovascular risk and decreased exercise. GH administration reverts (blue arrow) these cardiac affectations and improves the quality of life in these GHD patients.

In any case, the interactions between the heart and GH are very complex. An example of it is the fact that the heart may condition body growth in children with heart diseases. This is due to the fact that, in these situations, cardiomyocytes produce and release a peptide known as GDF15, which inhibits liver signaling by GH; therefore, liver IGF-I is not released, and body growth is affected [119].

The GH/IGF-I system also exerts important actions at the vascular level. For instance, this system activates the production of nitric oxide (NO) that induces the relaxation of arterial smooth muscle cells; as a consequence, the vascular tone is reduced. In addition, NO inhibits the proliferation and migration of smooth muscle cells, decreases platelet adhesion, and decreases lipoxigenase activity and oxidized LDL cholesterol [120–124]. These are some of the reasons by which GHD patients show an abnormal vascular reactivity [125], although the lack of effect of GH on the expression of the vascular smooth muscle KATP channel may also be involved in this affected vascular tone observed in untreated GHD patients [126]. GHD have an increased risk of atherosclerosis and vascular mortality [127]. GH treatment restores the vascular resistance and vasodilation and even may reverse early atherosclerosis.

GHD patients present markedly increased muscle sympathetic nerve activity [128], which seems to be of central origin and perhaps is an important mechanism leading to secondary hypertension and increased cardiovascular morbidity in these patients. In fact, 1 year of treatment with GH induces, in adults GHD, an effect on decreasing sympathetic nerve activity in the muscular vascular bed [129].

GH also plays a significant role on angiogenesis, contributing to regulate vascular growth and function (for review, see [17]). Most likely this is the reason by which the skin of adult GHD patients shows reduced capillary density and permeability, and these are improved

after treatment with GH [130]. Retinal vascularization is reduced in children and adults GHD [131, 132], although this may be a consequence of decreased IGF-I [132], since the vascular effects of GH may be exerted by other angiogenic agents induced by the hormone [17].

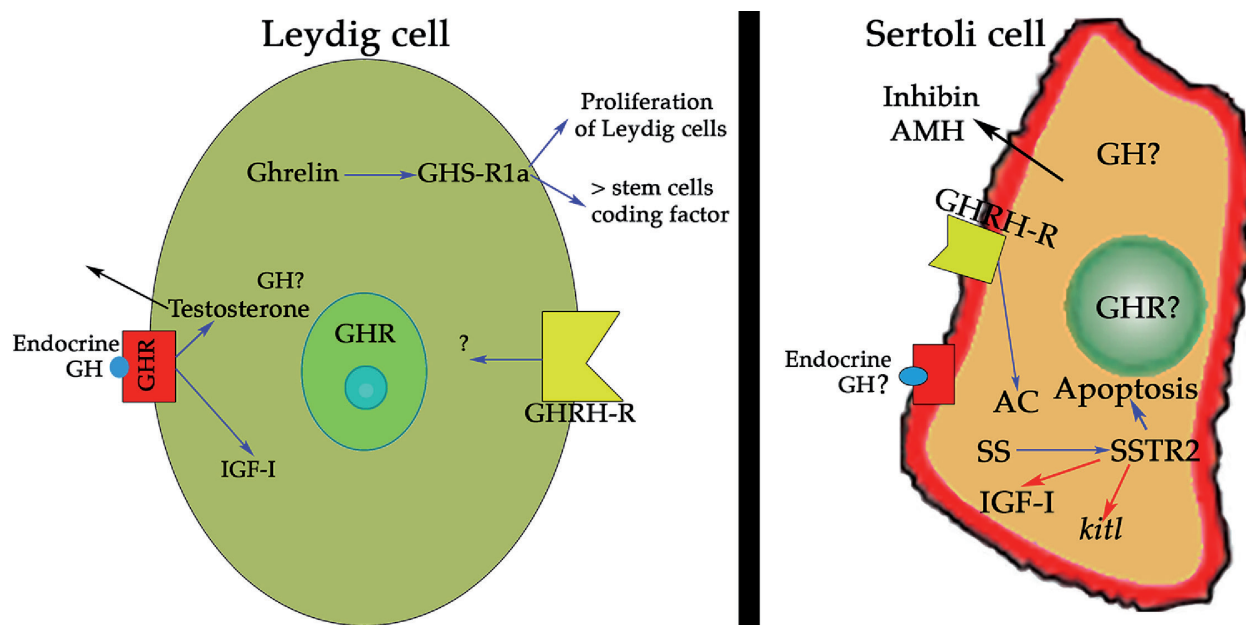
In summary, GH plays a very important role in the cardiovascular system, and untreated GHD patients suffer the consequences of the lack of the hormone and its mediators [109, 133, 134] and the risk of developing atherosclerosis, and suffering from cardiac affectations increases in them.

## 2.3. GHD and gonadal functioning

### 2.3.1. GHD and testicular functioning

In males, the effects of GH on testis seem to be different according to the species and the age of the individual. This is the case of rats and mice. Dwarf rats have small testis and normal spermatogenic function, suggesting that GH does not play a role in spermatogenesis during puberty and adult life, although the small testicular size may indicate that these animals have a small number of Sertoli cells, which in turn would indicate that GH may be important for the development of prepubertal testis [135]. However, homozygous GH-deficient mouse mutants (Snell dwarf mice) present infantile seminal vesicles, and spermatogenesis appears later in life [135]. From this study, the authors concluded that GHD only partially affects the reproductive axis, and this affectation occurs at an early age.

Unlike what happens in the CNS, plasma GH cannot easily access testicular cells within the blood-testis barrier. GH gene expression has been detected within the rat, human, and chicken testes [136, 137]. GHR has been detected in the human testis, mainly in Leydig cells [138]. Factors which regulate GH secretion are similarly expressed in the testis. This is the case of growth hormone releasing hormone (GHRH) found in the testis of rats, chicken, and humans [136, 137]. This testicular GHRH is capable of stimulating the pituitary release of GH, which indicates that it is similar or the same than the hypothalamic GHRH, but it is also able to induce the activity of adenylate cyclase (AC) in Sertoli cells [136]. At the testicular level, receptors for GHRH have been found in Leydig cells, Sertoli cells, germ cells, and even in the prostate, suggesting that this GHRH can exert specific actions on the testicle, different from those of GH itself [139]. Another inducer of pituitary secretion of GH, such as ghrelin, has also been found in mature Leydig cells of rat and human testis, where it has been shown that acting on its GHS-R type 1a receptor modulates the proliferation of Leydig cells and the expression of important testicular genes, such as the stem cell coding factor [140]. Interestingly, negative regulators of GH secretion and the actions of this hormone, such as somatostatin (SS) and its receptors (SSTR1–SSTR5), have been detected in Sertoli cells of mice [141]; treatment with somatostatin significantly promotes the apoptosis of these cells and decreases the expression of IGF-I together with a dose-dependent suppression of the mRNA level of the *kitl* gene, which is important in the regulation of spermatogenesis. These findings suggest that somatostatin and its receptors (mainly SSTR2 and SSTR5) play an important role in the regulation and development of Sertoli cells [141]. All these data indicate that practically all the components of the hypothalamus-somatotroph axis exist in the testicle, although it is



**Figure 8.** Hormonal factors involved in the functioning of testicular Leydig and Sertoli cells. Left: In Leydig cells there is expression of a number of hormones related to GH. There is GHR in the nucleus of these cells, indicating that there is GH expression in Leydig cells (GH?), although the nuclear GHR could proceed from the interaction of endocrine GH with its membrane receptor. This interaction leads to the expression of IGF-I inside the Leydig cell, and it is also responsible for the production of testosterone (induced by LH), which is secreted to the plasma. Interestingly, there are receptors for GHRH in the membrane of Leydig cells, although its role is unknown. In addition, another important inducer of GH secretion, such as ghrelin, has been found to be expressed in Leydig cells. Ghrelin acts (blue arrow) on its receptor GHS-R1a inducing the proliferation of Leydig cells and increasing the activation of stem cell coding factor. Right: As in Leydig cells there are GHR in the membrane of Sertoli cells; this may explain the presence of the GHR in the nucleus of these cells, although it is not well known, as it is not known if GH is expressed in Sertoli cells (GH?). In Sertoli cells there are receptors for GHRH (GHRH-R) which activate adenylylate cyclase, although the effects produced are not known. Curiously, somatostatin (SS) and its receptors (mainly SSTR2 and SSTR5) are expressed in Sertoli cells. The interaction of SS with its receptors (blue arrow) leads to the inhibition of IGF-I and *kitl* gene expression (red arrows) and induces apoptosis of these Sertoli cells.

unknown exactly how they act and if there is any relationship with the similar endocrine axis. These concepts are shown in **Figure 8**.

Despite the fact that, in this regard, the testis seem to behave like a small hypothalamic-pituitary gland, endocrine GH promotes testicular growth and development and stimulates gametogenesis and steroidogenesis in the adult testis. These actions seem to be mediated by IGF-I, since it can recover testicular differentiation in fetal mice treated with GH antibodies and testicular growth in children with Laron syndrome [142, 143].

In vitro, GH is a potent steroidogenic factor that stimulates androgen and estradiol production by Leydig cells in a number of species including humans. In vivo, GH treatment has been seen to increase the production of testosterone, induced by chorionic gonadotropin, and seminal plasma volume, in fertile GHD human patients [144, 145]. Similar effects have been described in boys with GHD after being treated with GH [146]. However, and contrarily to what should be expected, GH treatment in hypopituitary or moderately obese

men decreases the concentrations of total serum testosterone [147, 148]; most likely this effect is due to an increased aromatase activity and the resulting increased conversion of testosterone to estradiol [149]. In this study it was also found that high GH plasma levels were associated with reduced activity of the anti-Müllerian hormone (AMH), a marker of the Sertoli cells.

At this point it would be of interest to analyze if there is GH expression in the testis of GHD patients (children or adults) or experimental animals, both in cases of GHD due to a traumatic brain injury and a GH gene mutation or deletion, since it has been shown that in males born small for gestational age GH treatment does not affect the testicular production of inhibin and AMH [150]. That is, it seems that the pituitary GH does not play a key role in the testicular functioning, but acts as a co-gonadotropin that improves the secretion of gonadotropins (Gns), particularly LH, by acting directly or through IGF-I in the activation of GnRH pulse generator by means of the stimulation of hypothalamic kisspeptin [151].

It is also important to reflect that the GH variant GHV, seems to be the most abundant GH mRNA isoform in the human testis [152], while in chicken the GH 17 kDa variant is predominant [153].

In summary, from these data, it is likely that, in a normal man, endocrine GH synergizes with gonadotropins, potentiating the effects of these hormones on testicular cells, while the role of the testicular GH axis and its relationships with endocrine GH remain unknown.

### *2.3.2. GHD and ovarian functioning*

The relationship between GH and ovarian functioning has been widely analyzed since many years ago. In humans, and in many other species, GH seems to play a direct role in the nuclear maturation of oocytes [154, 155]. In 1990, the existence of a strong immunoreactivity for the GH receptor at the nuclear level was described not only in rat oocytes but also in practically all the reproductive systems of the rats studied [156]. These data led to suggest that GH could play important and direct actions on reproduction. In human oocytes, the GHR has been detected in the membrane, in cumulus cells and in the nucleus in mature ovaries [157], confirming that GH has to act at this level improving nuclear maturation and the expansion of cumulus cells, as has been demonstrated in primates [158], and also improving the cytoplasmic maturation of mature oocytes [159]. There is a genetic expression of GHR in cumulus cells, mature oocytes, and preimplantation human embryos, in which the expression of GHR increases from the 4-day morula onwards [154]. This study led to the conclusion that, in humans, GH plays a role in the maturation of the oocyte and embryogenesis, from its early stages.

Most of the GH effects on the ovarian functioning are exerted by the hormone locally produced in the ovaries; however, plasma GH released by the pituitary gland or exogenously administered also plays an important role in the normal function of the female gonad and reproduction [160]. In fact, GH participates in the regulation of puberty and fertility,



although these effects may depend on GH-induced changes in Gns secretion, directly or via IGF-I [161, 162].

Preclinical and clinical data indicate that an appropriate secretion of GH is needed for sexual maturation and maintenance of reproductive functions, while GH deficiency may affect the beginning of the puberty and can produce infertility. In humans, the interaction of GH-GHR in the ovary promotes the synthesis of sex steroids and induces gametogenesis, inhibits follicular apoptosis, and upregulates ovarian receptors for LH [160, 162, 163]. GHD women, in which puberty is delayed and the reproductive function is affected, recover a normal ovarian function when they are treated with GH [163]; the same happens in infertile eugonadal women with GH deficiency in whom GH treatment restores fertility and leads to successful pregnancies [164].

Although the onset of puberty in girls is a very complex process in which many factors participate (genetic, nutritional status, ethnicity, among others), there seems to be a relationship between increased GH secretion and puberty, since this hormone seems to act as a co-gonadotropin that enhances the effects of Gns on the ovarian production of sex steroids [165]. In fact, GH deficiency has been identified as the only cause of primary amenorrhea in three adolescent women in whom the secretion of gonadotropins was normal, suggesting that GH would play a complementary role to gonadotropins for the onset of menarche [166]. Therefore, and as stated above, GH deficiency negatively affects ovarian function in humans delaying sexual maturation and fertility, a situation that is reversed with GH replacement therapy. In addition, GH plays a very important role in ovarian angiogenesis, inducing the increased vascularization of one of the primary follicles that begin to mature during a menstrual cycle allowing it to be the dominant follicle which will release the ovule (for review, see [167]).

GH also plays a role in the uterus, where the hormone acts very early in gestation. Both GH and GHR are expressed in the uterus, independently of the existence or not of pregnancy [3]. GH induces uterine hypertrophy facilitating the implantation of the embryo. In women with thin endometrium, the administration of GH leads to greater endometrium thickness; very early, the hormone leads to higher implantation rates and greater clinical pregnancy rates than with untreated patients [168]. These effects are due to the proliferation of endometrial cells and increased vascularization via induction of the expression of VEGF-A. The increased rates of implantation seem to be a consequence of GH-induced increased production of metalloproteinases and stimulation of trophoblast cells proliferation, thus allowing the formation of the blastocyst cavity and invasion of the endometrium, as it has been seen in mice [169].

In summary, GH plays very important roles in all stages of the ovarian development and functioning, and recent studies indicate that this hormone can be an important factor as adjuvant therapy for in vitro fertilization and embryo transfer in infertile women or poor ovarian responders. Untreated GHD females present delayed (or absent) onset of the puberty, and impaired fertility is more marked in female patients with childhood-onset hypopituitarism; they have lower fertility rates and less positive pregnancy outcomes [170]. GH replacement therapy reverts these alterations.

### 3. Conclusions

GH is a key hormone for the normal development of the brain and for repairing the nervous system when it suffers any injury. This hormone also contributes to the repair of the cardiovascular system, particularly increasing the blood flow by inducing the formation of collateral vessels that allow overcoming a circulatory obstruction and repairing the arterial intimate layer damaged by an arteriosclerotic process. In addition, the hormone plays an important role at the gonadal level in both sexes, perhaps more important in women, facilitating fertility. Untreated GHD patients suffer the consequences of the lack of the hormone when any of the organs here described is damaged, as it has been analyzed in this review.

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### Conflict of interest

The author declares that there is no conflict of interest.

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