



Review

Growth hormone therapy in children and adults

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Abstract:

Growth hormone (GH) is a polypeptide hormone, secreted by somatotrophic cells of the anterior part of the hypophysis. Its application in therapy, first limited to GH deficient children, has now been widened to various other clinical conditions, not necessarily related to short stature. Clinical trials conducted in recent years have proved the safety of its administration in both children and adults. The efficacy of this form of therapy varies, according to different authors, from enthusiastic data to very critical opinions. For many pediatric diseases, such as GH deficiency or Turner syndrome, GH is regarded by many experts, despite the high costs of the therapy, as the first-line treatment. Mounting evidence suggests that GH is safe and effective also in children with chronic renal failure and cystic fibrosis. Recently, it has also been administered to adults with GH deficiency and short bowel syndrome. The aim of this paper is to summarize the current data on GH administration in modern pharmacotherapy. In this paper we have included the results of the recently published studies and discussed not commonly known indications for GH therapy, as well as its experimental administration in both children and adults.

Key words:

growth hormone, indications, contraindications, adverse effects, experimental administration, adults, children

Abbreviations: AGHD – adult growth hormone deficiency, BMD – bone mineral density, CF – cystic fibrosis, GH – growth hormone, GHD – growth hormone deficiency, GHRH – growth hormone-releasing hormone, GnRH – gonadoliberein, gonadotropin-releasing hormone, IGF-1 – insulin-like growth factor 1, IGFBP – insulin-like growth factor binding protein, ISS – idiopathic short stature, PN – parenteral nutrition, PWS – Prader-Willy syndrome, REM – rapid eye movement, SBS – short bowel syndrome, SDS – standard deviation scores, SGA – small for gestation age

Introduction

Growth hormone (GH) was isolated for the first time from human pituitaries in 1956 but its biochemical

structure was established only in 1972. Despite the fact that GH has various effects on the human organism, its clinical application for many years was restricted to children with growth hormone deficiency (GHD). For decades, the only way of obtaining GH was by its extraction from human pituitaries. At the beginning, these extracts were administered orally but later, because of unsatisfactory results of the treatment, in the form of injections. However, concerns about the potential risk of Creutzfeld-Jacob disease transmission as well as insufficient efficacy of this form of therapy resulted in attempts to find safer means of its production [68, 72]. Since 1985 progress in molecular biology has allowed clinicians to administer GH obtained by genetic recombination, whose amino acid sequence and conformation is identical to

the native molecule [72]. Therefore, its application in children was widened to such diseases as Turner or Noonan Syndromes, chronic renal failure, children born small for gestation age (SGA) and Prader-Willi syndrome (PWS). Nowadays, not only children benefit from GH therapy. Recent discoveries of severe or moderate disturbances in GH/(insulin-like growth hormone-1 (IGF-1)) axis activity in many conditions of short stature combined with metabolic disorders was an incentive for various trials of GH administration in adults. Currently, FDA has approved its usage in adults with GHD, while clinical trials of GH application in such disorders as AIDS wasting, severe burns or chronic fatigue syndrome are in progress.

GH/IGF axis

GH is a pituitary hormone, produced by the somatotrophic cells of the anterior part of the hypophysis, considered, as the name suggests, to be the most important endogenous factor responsible for body growth. The secretion of this polypeptic hormone is under strict hormonal control. Growth hormone-releasing hormone (GHRH) and ghrelin are the most significant stimulators of its production while somatostatin produces the strong inhibitory action. Both GHRH and somatostatin are released into the portal system from the hypothalamus. GH has an intermittent and mainly nocturnal pattern of secretion, occurring especially during REM (rapid eye movement) sleep. The frequency and amplitude of pulses increase during the growth spurt in adolescence and decline thereafter. Both acute stress and hypoglycemia stimulate GH release, while hyperglycemia produces the opposite effect [83]. A separate GH stimulating system involves a distinct receptor, which interacts with ghrelin – a peptide released by gastric cells in the fundus of the stomach and, though to a lesser extent, by the intestines, lungs and kidneys. The presence of receptors for ghrelin in the arcuate nucleus and in the anterior lobe of the hypophysis suggests that this hormone acts both at the hypothalamic and pituitary level to modulate GH secretion [56]. Most authors even suggest that the former region is the main site of ghrelin's activity. It has been shown that circulating ghrelin levels in healthy volunteers are related to GH pulses, suggesting that ghrelin participates in the pulsative regu-

lation of GH secretion or that the two hormones are regulated in parallel [56]. Through neuroendocrine, para- and autocrine ways of signaling, ghrelin exhibits a synergistic effect with GHRH on GH release. GH pulsatility and responsiveness to ghrelin are decreased by GHRH antagonist administration. It is not known how this complex network co-operates. Ghrelin was initially identified as a ligand of the orphan GH secretagogues receptor, but now many other activities of this hormone are known, such as adipogenic properties and a stimulatory effect on body weight. However, details of these regulations remain unclear and further studies are required to determine possible clinical implications of GH/ghrelin axis disturbances in the pathogenesis of renal failure and other disorders, like Prader-Willy syndrome or obesity, resulting in short stature and metabolic abnormalities [56].

GH is also under the inhibitory control of IGF-1, its major protein effector, synthesized in the liver in response to GH. The bone and connective tissue, in which GH stimulates collagen synthesis and increases the activity of chondroblasts and chondrocytes, are the effector tissues of GH/IGF-1 [14]. GH is not only the hormone of growth, it shows various effects on almost every tissue in the human organism. It is one of the most important anabolic agents enhancing whole body protein synthesis, increasing plasma glucose level and lipolysis *via* the direct effect on adipocytes as well as lipid oxidation by increasing substrate availability [39, 44]. New research continues to reveal other potential roles of GH, including regulation of cardiac and immune function, mental agility and aging [27].

Preparations of GH available on the market

Nowadays, all the GH preparations used in clinical practice are obtained exclusively by genetic engineering. Recommended doses and forms of GH administration in many conditions are still a matter of debate.

Most of the trials indicate that GH should be supplemented by a subcutaneous route at least once a day at bedtime. There are various GH formulations available on the market, such as Genotropin, Serosim, Zorbitive, Humatrope, Nutropin, Nutropin AQ, or Pro-

tropin. Most of the GH preparations are produced by *E. coli*, apart from Zorbitive, which is made in a mammalian cell line. Although no head-to-head studies of these formulations have been conducted so far, it appears that in most indications they can be administered one instead of another. The only exception is short bowel syndrome in which only Zorbitive has gained the approval of FDA [76].

A recent study, carried out to determine whether GH given as a single dose or twice daily would produce different metabolic effects in adult GHD patients, proved the superiority of a single injection strategy. After 12 months, single dose-treated patients had a much more pronounced reduction in BMI and had a lower content of body fat than the group receiving GH in two doses [38]. There were also no differences between the two treatment groups in the indices of glucose and lipid metabolic dysfunctions. Therefore, the single-dose regimen should be advocated, as more convenient and having the same, or even more prominent efficacy than GH administration divided into two daily injection [38].

In recent years, other forms of GH therapy have been tested. Due to the fact that for many patients a daily subcutaneous administration is highly inconvenient, recently new depot forms of the hormone (Nutropin Depot, hGH Biosphere) have been introduced to the market. New formulas of GH therapy utilize recombinant GH embedded in polymeric microspheres, with continuous release, what enables the injections to be performed once or twice a month [72]. Only a few studies have been conducted to examine their safety and efficiency, but the outcomes of these studies suggest that the long-acting formula provides comparable results and therefore, can replace everyday injections. Nutropin Depot, a long-acting GH preparation, was approved for use in pediatric patients with GHD in 1999. One of the studies was designed to compare the efficacy of GH in daily injections vs. depot form and indicated that the both tested groups were almost equal in growth promotion. Moreover, the long-acting GH preparation is able to maintain IGF-1 levels within the normal age-range, which is particularly important for the safety of the therapy. Additionally, this form of the hormone was comparable to daily GH injections in the number of side effects reported during the treatment [49]. Although nowadays this preparation is unavailable on the market, this study proved that depot forms are an

alternative to daily GH administration [49]. Another study, comparing the pharmacokinetic and pharmacodynamic aspects of a new depot form also proved that weekly doses of a sustained-release GH appeared safe and well tolerated [6]. Unfortunately, there is a lack of head-to-head, long-term trials comparing clinical efficacy of short- and long-acting forms of the hormone.

Most of the current forms of somatropin replacement try to closely mimic the physiological nocturnal pattern of GH secretion by daily injections, administered at bedtime. Recent developments in drug delivery technology have enabled to use the slow-release preparations of somatropin in humans [6]. Most of the outcomes from multi-center trials in both children and adults have been presented for Nutropin Depot: catch-up growth was observed in children, although to a lesser degree than historic comparative data obtained with the use of daily somatropin injections. The effects on metabolism appeared similar to those observed with daily injections [6, 49]. The discrepancy of unexpectedly good outcomes of depot GH forms may be partially explained by the fact that GH acts mainly through IGF-1 and continuous somatropin administration may actually enhance longitudinal growth [6]. Improved sustained-release somatropin preparations will require further investigations of their long-term efficacy, but, if successful, they will be highly attractive in terms of patient compliance and convenience.

The doses of GH used in particular patients differ and depend on age, gender and the disease. For example, many authors suggest administering higher doses if the therapy is initiated shortly before puberty. In adults, GH is usually administered with titration to IGF-1 values, which should be maintained within normal limits (-2 SDS).

Diagnosis of GH deficiency

GH deficiency may be both, congenital or acquired [46, 82]. Congenital GH deficiency can be caused by anatomical malformations of the brain, such as aplasia or hypoplasia of hypophysis, dysgenesis of the stella, empty stella syndrome, septo-optical dysplasia, holoprosencephaly and encephalocoele [46, 82]. Acquired GH deficiency is usually induced by a neo-

plasm of the pituitary region [46, 73, 82]. In children and adolescents, the most commonly found is craniopharyngioma, the tumor originating from the Rathke's pouch [14, 73], whereas in adults more frequent are pituitary adenomas, or less often glioma, astrocytoma, germinoma [14].

The therapy with GH must be preceded by careful and detailed diagnosis. It should be conducted in all children with growth failure of unknown origin and in adults with clinical manifestation of GH deficiency, hypophysis or hypothalamus injury, after the skull radiation and in case of GH deficiency diagnosed in childhood [1].

Due to the pulsative pattern of GH secretion, the single sample measurement has a very limited application [63, 65]. The so-called "provocative tests" including insulin, glucagon, GHRH, clonidine, L-Dopa or arginine tests administered in order to stimulate GH secretion, play a much more important role.

Nowadays, the insulin test is regarded as the first choice test, due to its greater sensitivity in comparison with others tests [1, 3, 82]. Insulin-induced hypoglycemia stimulates GH secretion by somatostatin suppression and α -adrenergic activity [73]. The average dose of insulin is 0.05–0.1 IU/kg *iv*, with the exception of patients with a high risk of hypoglycemia, in whom the dose of insulin should be reduced by 50% [73]. The positive result of the test is when GH level increases at least 5-fold after insulin. The insulin test is contraindicated in patients with epilepsy, seizures, and mental retardation, as well as in infants and small children, in whom severe hypoglycemia is difficult to diagnose [3, 71, 82]. Another advantage of this test is the possibility to assess the cortisol level and hypothalamus/hypophysis/adrenal gland axis activity at the same time [71, 73].

Glucagon increases GH level both, directly and indirectly by stimulating secondary hypoglycemia [65]. Glucagon should be administered at a dose of 1 mg *sc* and blood samples have to be collected at 0, 60, 90, 120, 180 min. In the opinion of some authors, this test is equal to insulin provocation [71], but various adverse effects of glucagon, such as nausea, vomiting and abdominal pain, cause that it is far less popular in GH deficiency diagnosis [63, 73]. Another provocative test uses clonidine as the stimulus to GH secretion. Clonidine acts through GHRH, increasing its secretion in the hypothalamus [65]. Clonidine is usually administered orally, at a dose of 0.075 mg. The side effects of this drug, such as hypotension and hyper-

somnia are most important reasons why this test is less popular than the test with insulin [63, 73].

In recent years, some authors have suggested that the GHRH test has greater ability to produce significant GH increase. Unfortunately, this test has poor reproducibility and in children with GH deficiency of hypothalamic origin, it may produce false positive results [3, 71]. Therefore, GHRH should be co-administered with agents like arginine or pyridostigmine, in order to diminish the possibility of false result [1, 71].

One of the most important problems concerning provocative tests is that they may produce completely different results in the same patients examined at different time points or with different test [14]. Therefore, it is assumed that a single negative test result must be always confirmed by another provocative test, and only after obtaining negative results of the two provocative tests the GH deficiency can be ruled out.

Another weakness of provocative tests is that in these tests GH release is induced by nonphysiological stimuli, and, therefore, they may not reflect the true GH secretion. Some tests are free of this disadvantage, like the 24 h GH profile, spontaneous nocturnal GH output and the stress test [63, 65].

The 24 h GH profile is one of the most expensive methods and, therefore, despite its high sensitivity, is usually restricted to scientific studies [63, 71, 73]. Instead, spontaneous GH secretion during sleep is widely used as a first line screening for GH deficiency. GH levels above 10 IU/l are considered to indicate that hypothalamic-pituitary axis reacts correctly [1, 3].

The stress test is relatively easy to perform and less expensive but it also has some disadvantages because its results are highly dependent on the efficiency of the exercise and standardization [65, 71]. This test cannot be performed in small children, and in one-third of children may give false negative results [3, 71, 73].

In patients with the low GH levels, other hormones should be evaluated with special emphasis on TSH, cortisol and gonadotropines [14, 65]. Thyroid hormones should be monitored and supplemented if necessary, and GH level should be re-evaluated, prior to the decision of GH administration [65].

In order to discriminate between the children with GHD and those with constitutional delayed puberty, the short-term androgen/estrogen therapy may be implemented prior to GH provocative test [71].

The alternative GH deficiency diagnostic method is IGF-1 and IGFBP-3 evaluation [63, 65]. It is impor-

tant to emphasize that IGF-1 as well as IGFBP-3 levels decrease during adult life and in childhood are highly dependent on the stage of puberty [1, 73]. IGF-1 is regarded as the best marker of GH therapy monitoring. Unfortunately, its levels in adults may be affected by many various disorders, like liver diseases, malnutrition, diabetes, renal failure and thyroid gland dysfunction, and, therefore, its measurements are less useful in diagnosis than in therapy [63, 72].

IGF-1 evaluation is particularly important in short stature patients in whom the GH level is not reduced, the situation suggesting the presence of GH receptor defect or resistance to GH (like in Laron syndrome) [55]. In those patients, IGF-1 and IGFBP-3 levels are markedly decreased, whereas the level of another binding protein, IGFBP-1, is increased [55].

Diagnostic imaging plays a pivotal role in GH deficiency diagnosis. In both children and adults imaging of the skull should be always performed to exclude any expanding process or congenital malformations. MRI (the sagittal section) is considered the first choice for diagnostic imaging because it shows in detail the pituitary fossa and adjacent structures. It is superior to the CT scanning and readily reveals any pituitary masses [1, 46]. In children, the X-ray examination of the non-dominant hand and wrist in children allows to assess the bone age by comparison with special charts and to decide whether the patient will benefit from GH therapy or not [1, 46].

Indications for GH therapy in children

Growth hormone deficiency

Childhood-onset GHD may be a result of pituitary or hypothalamic pathologies. The origin of GH deficiency is usually concealed, therefore, the common name for this condition is idiopathic GHD. The growth retardation is arbitrarily described as stature below 3 SDS for gender and age. After excluding other diseases related to short stature and performing laboratory stimulation tests, in which, if the induced GH peak does not exceed 10 IU/l, GHD can be diagnosed [18]. This definition of GHD has been criticized by many authorities, because clinical trials revealed that provocative tests have poor reproducibility and there is a great number of falsely positive results in normal

children. What is more, in most children free of any abnormalities of the pituitary gland, GH response to stimuli normalizes spontaneously with time, especially during puberty [87]. Recommended doses vary, but most experts suggest 0.17–0.3 mg/kg/week (0.35–0.85 IU/kg/week), divided into 6 or 7 daily doses, which are injected subcutaneously at bedtime [68]. This therapy allows GHD children to achieve their adult final height within a normal, midparental-adjusted range [18].

The best results were found in subjects with severe GHD and when the predicted final height was very low. In children with such a prognosis, most of the research suggested co-administration GH with gonadoliberein (GnRH) analogues to delay puberty and prolong the period of growth [85]. Additionally, most of the authors suggest that children with severe growth retardation should be treated with higher GH doses [85].

The discontinuation of the therapy should be considered if growth velocity is below 1 cm during the first 6 months of the therapy, despite the proper technique of injections [18]. Naturally, all the possible conditions coexisting with the GHD, such as hypothyreosis, sprue, systematic diseases, malnutrition and glucocorticoid therapy, should be ruled out before initiation of the treatment, because they may affect the final outcome.

The duration of the therapy is a matter of much controversy. For many years the GH administration had been conducted until final adult height was achieved, but this strategy was associated with many concerns about potential catch-down growth after discontinuation of the therapy [53]. However, a recently published trial on pubertal population with previously diagnosed GHD has shown that the hormone withdrawal in subjects with GH normalization at re-testing did not produce any significant consequences in terms of growth velocity [87]. These findings are in accordance with other authors' opinions that provocative tests should be performed, even if their previous results clearly indicated GHD [71] and they recommend withdrawal of the therapy if GHD is not confirmed at puberty [71, 87]. If provocative tests remain negative, the GH therapy should be continued, but with the lower doses, maintaining IGF-1 within the normal limits [68].

There are discrepancies between opinions concerning the safety of GH withdrawal and some authors have suggested positive effects of life-long admini-

stration of this hormone [18, 42, 53]. Moreover, some data have disclosed that various metabolic disorders, including an increase in visceral adipose tissue, a decrease in the lean body mass and lipid profile disturbances, might appear 12–24 months after discontinuation of the therapy [47, 62]. Due to the fact that GH administration is likely to be associated with reversal of metabolic disturbances occurring in many conditions associated with GH deficiency, and with different beneficial effects on cardiac function, bone mineral density (BMD) or coagulation system, some authors do not recommend the re-evaluation and withdrawal from the therapy [18, 42]. The question whether and/or when GH should be withdrawn must be considered individually taking into account the cost-risk-benefit analysis.

Supplementation of other pituitary hormones is necessary in multi-hormone deficiency [85]. In some patients, GH administration can change the metabolism of other hormones, therefore, vasopressin, thyroxin and glucocorticoids may be required at higher doses than usual.

Turner syndrome

Turner syndrome is caused by a total or partial absence of X chromosome (karyotype 45 X0 or mosaicism 46XX/X0). One of the most common features of Turner syndrome is short stature, which, as much research has shown, is not simply associated with GH deficiency or GH/IGF-1 axis disturbances. Some investigators claim that the growth failure is a result of SHOX gene haploinsufficiency [78], whereas others consider short stature to be a result of bone tissue resistance to IGF [28]. The first attempts of GH therapy in girls with Turner syndrome were undertaken in the early 1990s' and now it is a standard therapy in these subjects [69]. The first randomized controlled trial indicated that GH-treated Turner children achieved a final adult height which was 7.2 cm taller than in children belonging to the control group [80]. Doses recommended in girls with Turner syndrome are higher than those given to GHD children (FDA approved the dose of 0.375 mg/kg/week injected daily) [83].

There are concerns about administering higher doses of the hormone. The arguments in favor of their implementation have been provided by some studies [28] which showed a dose-dependent linear growth after GH treatment. However, other studies did not support these results [74]. Therefore, presently, most

of the experts initiate GH therapy with the FDA-approved dose (0.375 mg/kg/week) [7]. The dose can be then adapted individually according to the patient's growth response and IGF-1 level [7].

The optimal age for the initiation of GH therapy has not been clearly determined so far, but the data from the Toddler Turner Study suggest that treatment with GH should begin as soon as growth failure is found, even at the age of 9 months. According to the authors, early initiation of GH treatment resulted in final growth improvement associated with the reduced costs of the therapy [15]. The outcomes of another trial also suggest that patients with Turner syndrome benefit most from GH administration when GH therapy is started at a very young age and the hormone is given in more than 6 injections per week [74]. Both the longer therapy duration (younger age at initiation of GH therapy) and growth velocity in the first year of GH administration correlate positively with final adult height [47]. Similarly, height at the beginning of the therapy and tall parents have been found to be predictors of more significant height gain [7]. An important aspect of the management is that the early introduction of GH allows for an earlier implementation of sex hormone therapy. Apart from GH supplementation, female patients with Turner syndrome should be given estrogens as a replacement therapy. Typical initial doses for systemic estrogens preparations are 2.5 µg/day for ethinyl estradiol in the first year, 5.0 µg/day in the second year and then cycling therapy with 20 µg on days 1–24 of each month. Oral estrogens should be administered at the dose of 0.5 mg/day [15, 74]. Usual delay between the initiation of estrogen and progestin treatment is about 2 years [15, 74]. The results of the study by Soriano-Guillen et al. [74] indicated that transdermal estradiol (at the dose of one quarter of a 25 µg/day patch) combined with GH therapy might actually enhance final adult height. In recent years, some concerns about the unfavorable effects of oral estrogens therapy on IGF-1 level have come to light. It has been documented that oral and transdermal estrogens may have different effects on different levels of GH/IGF-1 axis, resulting in a significant reduction in IGF-1 level despite a three-fold increase in GH concentration [7, 15].

Because GH-deficient subjects suffering from this disorder usually have low BMD, GH was initially deemed to produce a beneficial bone-strengthening effect. However, recently conducted studies on Turner syndrome patients have not supported these assump-

tions as in both studies GH therapy has not changed BMD [4, 5].

Noonan syndrome

Noonan syndrome is characterized by complex clinical features that, apart from short stature, encompasses: pulmonary trunk valvular stenosis, facial dysmorphism with hypertelorism, paddle neck, thoracic cage excavation, moderate mental retardation, deafness, hypogonadism or cryptorchidism and coagulation abnormalities [10]. This autosomal dominant condition is quite common, occurring with a frequency of 1:1000 to 1:2500 live births, with an almost equal male to female ratio.

Because of the similarity to Turner syndrome, and the occurrence of GH/IGF-1 axis abnormalities, the administration of GH seems to provide many benefits to patients with this disorder [48]. However, the lack of randomized controlled trials with a large number of subjects, and objections to the methodology of recently completed studies (short-term duration, unidentified reasons of drop-outs) does not enable the provision of reliable data on the safety of GH administration in these patients [48]. Most of the trials revealed, however, that GH increases growth velocity and, as a consequence, significantly improves final adult height in most of the subjects [48, 51].

It was also noticed that some patients with Noonan syndrome treated with GH present no or only small increases in final adult height. A recently discovered mutation in gene PTPN 11, which is responsible for GH/IGF-1 signal transduction in cells, can, at least partly, explain the lack of the predicted clinical efficacy of the therapy in these patients. Patients with this mutation have lower basal height and seem not to achieve the expected final adult height after the therapy [20].

Chronic renal failure

Short stature is a common complication that occurs during chronic renal failure, especially if the onset of the disease is in early childhood. Growth retardation in pediatric renal failure is multifactorial, with relative GH resistance in addition to conditions like water-electrolyte disturbances, metabolic acidosis, nephrogenic osteodystrophy, malnutrition and deteriorated tissue metabolism of some growth factors [41]. Most of the patients with renal disease exhibit high levels of GH, secondary to the decreased renal

clearance of this hormone. However, markedly decreased numbers of GH receptors and increased levels of IGF binding proteins 1 and 3 (IGFBP1, IGFBP3) play an important role in disturbances of GH/IGF-1 axis activity [53].

The findings of the recent trials on chronic renal failure patients indicated that short stature was positively correlated with the duration of renal failure, with the greatest growth retardation in patients with urological and congenital renal malformations [26] and an increased number of years on dialysis [41]. The positive correlation between the renal failure stage and the results of the therapy (the better renal function, the better growth response) can indicate the benefits of implementing GH therapy as soon as possible, without any unnecessary delay [30, 34]. Nowadays, chronic renal failure is regarded to be a proven indication for the commencement of GH administration. The therapy should be implemented if short stature persists for longer than 6 months or in subjects with marked deceleration of growth velocity, and continued until transplantation is performed [86].

The results of clinical studies suggest that GH resistance can be overcome only at the first stage of chronic renal failure and that the period of dialysotherapy should be as short as possible [26, 86].

Doses recommended in children with chronic renal failure are higher than in GHD patients, i.e. about 0.35 mg/kg/week [82] because growth patterns in these patients have been found to be dose-dependent [53]. Long-term therapy results in quick catch-up and most of subjects achieve their adult height within normal limits [31, 85]. It is worth remembering that in most chronic renal failure patients, the disease itself delays puberty by an average of 2 years, and GH does not accelerate the beginning and progress of puberty, as in GHD and ISS children [29]. Therefore, if properly treated, there is no risk of worsening of the final growth.

The most important predictive factor of successful therapy is the growth velocity in the first year of treatment [30]. The continuation of the GH administration after renal transplantation is still a matter of controversy because growth velocity decreases after the transplantation [44, 85]. Therefore, a long-term, post-transplant GH therapy should be a matter of further investigation.

Due to the fact that GH is deemed to increase the creatinine level, this parameter should be monitored during the therapy [53].

Children born small for gestation age

SGA children represent about 20% of all patients with short stature [17]. SGA is arbitrarily defined as the birth weight and/or length at least two standard deviation scores below the mean for gender and gestational age. Most of the children express postnatal growth acceleration or catch-up, which, according to various studies, results in up to 90% of population achieving normal height by the age of 2 [17]. The most pronounced catch-up growth occurs during the first 6 months [45], but can be delayed in preterm infants [35]. Still about 10% of SGA born infants remain small (below -2 SDS) until adult life. Recombinant GH was approved for SGA children therapy in USA in 2001 and in Europe in 2003. Despite the lack of randomized, controlled trials, most of the studies evaluating the efficacy and safety of GH in SGA children showed positive results of this treatment.

Most pediatricians accept that GH therapy should be initiated in short stature SGA children (height below 2.5 SDS) at the age of four or above (to exclude late catch-up growth) when growth velocity is below average [52]. All possible causes of short stature should be ruled out prior to the therapy. Recently, an endocrinologic study comparing SGA children with or without catch-up growth revealed that the latter tend to have higher TSH and cortisol levels, and, therefore, some authors suggest that the disturbances of the pituitary-thyroid/adrenal axes may also influence SGA postnatal growth [43].

The pathophysiology of the height deficiency in children born SGA remains unclear. Most of these children show a transiently elevated concentration of the GH and IGF-1 whereas cord IGF-1, IGF-2 and insulin levels are lower than in neonates born at term at appropriate size for gestation age. This disturbance in the GH/IGF-1 axis may be responsible for growth retardation and poor catch-up. Interestingly, a small group of SGA children has typical GH deficiency and, therefore, should be treated with the supplementation protocol [17]. The efficacy of GH therapy was the focus of many clinical studies. Most of the trials conducted in recent years presented coherent findings. Patients treated with GH had significant growth acceleration within the first and subsequent years of the therapy when compared to untreated subjects and achieved final adult height within normal limits [16].

The optimal dose of GH in SGA children is still a controversial issue. The recently published epi-

analysis of the randomized trials comparing the growth-promoting effect of GH administration at two different doses (33 $\mu\text{g}/\text{kg}/\text{day}$ vs. 67 $\mu\text{g}/\text{kg}/\text{day}$) has shown that height gain is dose-dependent only in short-term therapy (1–5 years) [16]. Due to the fact that large doses of GH accelerate bone maturation and are often associated with supraphysiological IGF-1 levels, this form of therapy cannot be accepted as a standard. However, higher doses could be used in subjects initiating GH therapy in their mid-childhood, and in subjects with severe growth retardation (below 3 SDS at the beginning of the treatment) [11]. For the other SGA children, the dosage of 30 $\mu\text{g}/\text{kg}/\text{day}$ seems to be adequate [17].

Age and bone age are the most important predictive factors of adult height achievement. The younger the child is at the GH initiation, the more marked growth response is observed. Other variables, such as parental height, growth velocity before therapy and basal growth retardation, were not deemed predictable factors of final adult growth [58].

GH in SGA patients, apart from the growth increase, contributes positively to the changes in body composition, increasing the muscle and lean body mass and decreasing adipose tissue content [17].

Children born SGA have a clearly documented increased risk of metabolic disorders in their later life, including hypertension, hyperlipidemia, insulin resistance or cardiovascular disease [34]. Although it is well established that GH has the potentially adverse effect of promoting diabetes mellitus, unexpectedly, in one study the risk of diabetes mellitus was found to be higher in the group of children with spontaneous catch-up than in GH-treated population [17]. Insulin resistance that occurred during the therapy with GH was in most cases reversible after discontinuation of the treatment [16]. The potential risk of the carbohydrate metabolism disorders indicates that GH-treated patients should have long-term surveillance for the occurrence of glucose metabolism disturbances.

A recent study has proved that GH can be successfully administered not only to SGA children, but also to children born very preterm ($< 32\text{HBD}$), but with the appropriate size to gestational age that show growth retardation in the first months. Authors of the trial suggest that children with preterm growth retardation born very preterm should be treated with GH if their height is still below 2 SDS at the age of 5 [23].

Prader-Willy syndrome

PWS is a genetic disorder, usually caused by a micro-deletion of a part of the paternal chromosome 15q11-13 or uniparental maternal disomy of the same region. It is characterized by a number of symptoms including facial dysmorphism, hypotonia, hypogonadism, short stature and mental retardation as well as hypothalamic dysfunction resulting in obesity with compulsory eating attacks [25, 36]. Most of the patients in later life experience certain disorders, having an increased risk of cardiovascular diseases, diabetes mellitus and osteoporosis [37].

In 2000 FDA approved recombinant GH for the treatment of PWS children [60]. The observation of over 200 subjects treated with GH for 6–36 months revealed a significant improvement in growth velocity and most of the children achieved their final height within the normal range [25, 37]. Moreover, PWS patients benefited from positive changes in lipid profile (increase in HDL cholesterol and decrease in LDL cholesterol levels), as well as from the enhanced vital activity, lean body mass and muscle force [25]. The standard dose of GH in PWS children is 0.24 mg/kg/week, based on ideal body weight [60].

A recently conducted study involving normal-weight children with PWS has proved that GH therapy at a dose of 1 mg/m²/day caused an increase in the serum adiponectin level when compared to the control group. Fasting insulin and glucose levels increased significantly during the first year of GH-treatment, but returned to the baseline in the second year. An important fact is that, although adiponectin level was not associated with BMI decrease in PWS subjects, higher level of adiponectin is deemed highly beneficial due to its protective effect on the cardiovascular system and insulin resistance [21].

Some years ago there were reported deaths after initiating therapy with GH in pediatric PWS patients [19]. The risk factors of the fatal outcome were severe obesity, the history of upper airway obstruction or unidentified respiratory infections. Most of the incidents were noticed in male subjects and, therefore, boys with one or more of these factors may be at increased risk compared to girls [19]. These deaths were probably attributable to the deterioration of breathing disorders (obstructive and central sleep apnea). Recent studies carried out on a group of subjects with sleep abnormalities have led to the conclusion that GH should not be used in patients with chronic

respiratory or lung infections as well as in PWS patients suffering from severe obesity [60]. Patients with PWS should be evaluated for the signs of upper airway obstruction and sleep apnea before GH treatment is begun. If, during treatment with GH, the patient shows any signs of upper airway obstruction (including appearance or enhancing in snoring) and/or new onset sleep apnea, treatment should be terminated [60, 52]. All PWS patients treated with GH should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively [60].

Idiopathic short stature

Children with ISS represent a diverse group of patients with short stature and poor growth velocity without any hormonal deficiencies or systemic illnesses. The efficacy of the GH therapy in ISS children varies between the articles published within recent years. Most of the findings have limited value, usually due to the small number of patients enrolled. In 2005, a large study, including data from the NCGS (*National Cooperative Growth Study*) was conducted and focused on the long-term efficacy and safety of GH therapy in ISS patients [50]. The results of this study proved that GH administration resulted in rapid catch-up during the first and subsequent years of the therapy [50]. However, other findings show a great inter-personal variability of the response, with failure to maintain improvements in height velocity [57].

Therefore, there still exists controversy as to whether GH therapy should be implemented or not in ISS children. It is known that untreated children with ISS usually do not achieve normal adult height compared with their peers or mid parental target height, and their final adult height SD score varies from 1.5 to 2.5 SDS below the normal limit [85]. Studies conducted so far have not provided sufficient data to prove the influence of GH on final adult height [50]. Some findings indicated that although the first year of GH therapy resulted in a substantial catch-up growth, the adult height was not significantly different from the control group [57, 85]. Those studies are in contrast with a recent meta-analysis on GH administration in ISS, which showed a significant increase in adult height, with the mean height gain up to 5 cm [22].

The ISS patients have variable degrees of response to GH therapy and sometimes require high doses of GH to promote optimal linear growth. Data from the

cohort of ISS subjects in pubertal age suggest that although the benefits of the therapy are limited in their case only to the time of puberty, they can still benefit from GH therapy, with a significant increase in growth rate and height SD score [50]. Recently reported data from a randomized controlled trial of GH and GnRH analogues in early pubertal ISS adolescents revealed, however, that this form of therapy provides positive but modest height gain with potential adverse effects on BMD in male subjects. The results of this study suggest that this drug combination should be restricted to subjects, especially girls, with an extremely low predicted adult height and early puberty [81].

For many clinicians it still remains unresolved whether ISS children should be treated despite the increased availability of GH. The response to the treatment is highly variable and unpredictable, and further studies are required to identify a group of ISS patients who really benefit from GH therapy [57].

Cystic fibrosis

Early reports on GH administration in children with cystic fibrosis (CF) demonstrated that the therapy significantly improved growth velocity and enabled children to achieve higher final adult height [34]. However, only recent trials focused on the weight gain (especially lean body mass increase) as the result of GH administration [33]. In a randomized clinical study involving 10 children treated with GH, the participants had greater weight gain velocity after one year of the therapy than the control subjects [32]. Moreover, the research revealed that the GH-treated children had better accrual of bone minerals [32].

Other benefits of GH therapy in CF include a reduction in the number of hospitalizations or the need for intravenous antibiotics courses [33]. In some studies, the therapy also improved forced vital capacity. However, the increase in the latter, which is one of the most important parameters of pulmonary function, seems to be secondary to accelerated growth rather than being directly related to the effect of GH on the lungs, because the effect of GH disappeared when it was adjusted to improved longitudinal growth [32].

There have been no adverse effects recorded in GH-treated CF patients except for two cases of glucose intolerance observed during puberty. However, their incidence may not be associated with GH administration because neither of these subjects had glu-

cose tolerance assessed before the beginning of the therapy [33].

Although most of the studies suggest that GH is safe and effective in CF, the question of who among CF sufferers benefits the most from this therapy still remains unresolved.

Experimental applications

A single randomized pilot study revealed that 18-month-long GH therapy in subjects with a spastic form of cerebral palsy was associated with a significant improvement in the spinal BMD and linear growth [2]. The clinical significance of these results remains, however, uncertain because of a small number of subjects included in this trial (12 males) and their heterogeneity. For these reasons, further studies are warranted to support these results and, in case they are encouraging, also to determine the optimal dose and duration of treatment.

The short-term GH therapy given to severely burned children revealed a marked increase in lean body mass, bone density and growth. A recently published study in which GH was administered for 12 months from the day of hospital discharge and which also involved subsequent 12-month follow-up period demonstrated that, compared with a placebo, height, weight, lean body mass and BMD significantly improved during the GH therapy. Moreover, GH administration improved left ventricular function during the treatment period. What is interesting, however, both height and BMD in the GH-treated group continued to increase in the year after therapy withdrawal. The subjects belonging to the GH group had a reduced, by about 50%, number of operative reconstructive procedures in the first two years after the burn. This is an important issue, because the costs of the operating procedure, hospitalization and further rehabilitation of children requiring an operation taken together were similar to the costs of 10 months of GH therapy [67].

Indications for GH therapy in adults

Adult growth hormone deficiency

Adult growth hormone deficiency (AGHD) results from intracranial tumors, including hormone-secreting

and non-functional pituitary adenomas, craniopharyngioma, empty sella syndrome or Sheehan's syndrome. Because these disorders usually also affect the synthesis and release of other pituitary hormones, isolated GH deficiency occurs less frequently than in children. Contrary to deeply rooted opinions that GHD in adults proceeds asymptotically, it has recently become clear that this condition is associated with a constellation of many, more or less prominent, disturbances. They include the decreased mass and strength of muscles, increase in body fat (especially visceral fat), the reduced mass and impaired contractility of the heart, abnormally low bone density, unfavorable changes in lipid profile and some psychiatric and sexual problems (emotional lability, feeling of social isolation, often abnormal sexual functions, and sometimes anxiety and depression) [13]. The results of long-term clinical trials have revealed that adult patients with GHD are subjected to an increased risk of cardiovascular disorders and cardiovascular mortality [18]. The implementation of GH in most of the patients resulted in a reversal of the unfavorable lipid profile disturbances, decreasing total cholesterol and LDL cholesterol level, as well as fibrinogen and homocysteine, independent predictors of cardiovascular events. GH is also deemed to have a beneficial effect on muscle strength or cardiac function, increasing cardiac output [18, 42, 53]. For these reasons, in 1996 GH was licensed for the treatment of GHD in adult subjects. Although it seems reasonable to administer GH to all adult patients with GHD, economic reasons stipulate that, unlike the situation with children, in adults GH treatment is limited to patients with only a severe form of this disease [13, 18].

The most frequently used doses are smaller than those administered to children as initially GH is given at doses from 0.15 to 0.30 mg/day [64, 82]. The doses of GH in AGHD are usually adjusted to patient's weight at baseline and titrated according to IGF-1 level. The results of a long-term open label trial conducted on a group of AGHD patients, showed different effects of the treatment on metabolism and body composition. While the effect on the latter was transient, metabolic effects, not only were sustained but they even became stronger as the study progressed. Women had a more marked decrease in blood glycated hemoglobin levels, whereas men had a more prominent treatment response in their IGF-1 SD score, body composition (increased lean body mass and BMI, decreased body fat) and serum HDL chole-

sterol level [27]. The authors of this study observed that after the initial deterioration, blood glycated hemoglobin levels improved over the long-term therapy with GH. The discrepancy between the increased glucose levels, measured each morning, and the decreased glycated hemoglobin levels found by these authors suggests that fasting blood glucose does not reflect glucose homeostasis in GHD adults receiving hormone replacement [27].

An important aspect of GHD in adults is the decreased quality of life, observed in many trials. Typical syndromes of that condition are memory problems and chronic fatigue. Analysis of the questionnaires of patients receiving a long-term GH substitution indicated that after 12 months of treatment, most of them experienced the significant improvement in their quality of life, and achieved mean population range after 4 years of the therapy [52].

It should be stressed that if co-administered with oral estrogens, GH should be given at doses up to 50% higher than normal [68]. If estrogens are administered transdermally, the modification of the GH dose is not required [13].

Short bowel syndrome

SBS is a disorder caused by the resection of a large part of the intestinal tract. It can occur both in infants, due to necrotizing enterocolitis or congenital intestine malformations as well as in adults, in whom it results from inflammatory bowel disease, post radiation enteritidis or critical conditions, such as trauma or mesentery thrombus [59]. In 2004 the FDA approved GH as the adjunctive therapy for the treatment of SBS-induced malabsorption and malnutrition in patients with parenteral nutrition (PN) [66]. Unfortunately, most of the studies conducted on SBS patients were open-label, with a relatively small number of patients included. Most of the studies carried out recently have revealed that GH therapy significantly increased body weight, lean body mass, but in some of these studies the observed effects were only transient [59, 76]. One of the most promising studies showed that GH therapy combined with a modified diet and glutamine provided much better, long-lasting effects, with a more marked reduction in PN volume and calorie intake than glutamine plus diet [9]. However, it is still unclear whether the beneficial effect of GH and glutamine administered together results from their synergism because the group receiving GH plus gluta-

mine and diet was not compared with the groups treated with GH and diet alone [9]. Some studies did not prove any favorable effects of GH administration [40, 70], but their value is limited by a small number of patients with often long-duration disease and shorter residual small bowels length as well as after total colectomy [40, 70].

Although GH has been approved for SBS therapy in parenterally-nourished patients, the data from clinical trials are inconsistent [40, 70]. Therefore, the decision which patient could be treated successfully with GH should be made very cautiously, with a detailed examination of the present status of the patient. GH is more likely to be beneficial in patients who are well-nourished, with remaining jejunum-ileum length of at least 50–200 cm without the colon, more than 15 cm small intestine with > 30% functioning colon or > 90 cm of small intestines with < 30% functioning colon [9, 59].

The timing of GH implementation was established at about 6–24 months after the operation [66]. The only formulation approved for SBS patients is Zorbitive administered at a dose of approximately 0.1 mg/kg/day, up to 8 mg/day [66]. Due to insufficient data, the optimal duration of the therapy, as well as the optimal dose and formula of GH are still unknown and need further investigation [76].

Experimental applications

The FDA approved GH administration in AIDS wasting syndrome. This indication is, however, rather theoretical, because no randomized control trial has been conducted so far to prove efficacy and safety of GH administration in these patients. Some authors recommend administration of GH in other disorders such as achondroplasia, hypochondroplasia or hypophosphatemic rickets [82].

The process of aging is associated with a marked decrease in GH and IGF-1 secretion, estimated at about 14% per 10 years for the former [13]. It is often referred to as 'somatopause' because many symptoms of human aging (decreased muscle and bone mass, dyslipidemia, and psychological disturbances) resemble the clinical presentation of AGHD. This similarity provided backgrounds for GH therapy in aging patients. However, studies conducted so far on subjects with somatopause have given contrasting results [54].

Contraindications to GH therapy

GH should not be administered to patients with acute critical illnesses caused by complications of open heart or abdominal surgery, multiple accidental trauma, or to patients with acute respiratory failure [79]. Two large placebo-controlled clinical trials in non-growth hormone deficient adult patients with these conditions revealed a significant increase in mortality (41.9% vs. 19.3%) in somatotropin-treated patients (5.3–8.0 mg/day) compared to those receiving the placebo. GH hormone also should not be used for growth promotion in pediatric patients with closed epiphyses [79]. It is recommended that GH therapy should not be initiated in patients in case of active infection or sepsis.

Furthermore, GH should not be initiated in patients with active neoplasm, either newly diagnosed or recurrent as well as in subjects with a history of cancer shorter than one, or even two years [14, 76]. As an early screening for the prostate cancer, PSA levels need frequent evaluation and a diagnostic periodical colonoscopy and mammography should be regularly performed [68]. The GH therapy should be discontinued even if the slightest suspicion of cancer appears.

Other contraindications for GH are end-stage diabetic microangiopathy including proliferative retinopathy or nephropathy, and benign cranial hypertension [14, 82]. Some of the diseases associated with an increased risk of neoplasm such as Bloom, Down or Fanconi syndrome are also contraindications to the therapy [14, 64, 72].

Insufficient data on the safety of GH therapy in pregnant women justifies caution in the recommendation of this form of therapy in pregnant women and suggest that GH therapy should be discontinued in the second trimester of pregnancy, and resumed after delivery [62]. Although no adverse effects for women or fetus have been observed, limited experience with GH administration, together with frequent side effects and the common optional character of the therapy give reasons for GH withdrawal in these patients [62]. Moreover, during the second trimester of the pregnancy, the placenta provides its own GH secretion [64, 72]. The GH administration in nursing mothers is another questionable issue, because safety of the infant has not been determined yet and, therefore, the application of GH during lactation requires further examination.

Side-effects of the GH

Adverse effects of GH therapy are summarized in Table 1. Most of them are local injection-site reactions which usually do not lead to therapy discontinuation. Other side effects, such as headache, nausea or fever were generally self-limiting and well-tolerated [8, 75]. They were noticed in 10–17% of patients, especially in obese subjects and in late onset GHD [8, 21]. The risk of side effects in some obese patients was increased two-fold compared with non-obese patients [13]. Probable causes of other adverse effects, such as edema or carpal tunnel syndrome, are attributed to GH-induced fluid retention [13].

Less commonly seen side effects were paresthesia and increased skin pigmentation. Fortunately, the latter, was not associated with the increased risk of melanoma [14]. It is worth remembering that most of the reported effects were associated with excessive GH doses, whereas GH, if maintained within normal therapeutic range, produced no or only minimal side effects [72, 75].

Adverse effects in children treated with GH were slightly different than in adult subjects. They included transient intracranial hypertension, gynecomasty, slipped capital femoral epiphysis [21, 68]. The former occurred more often in subjects with endocrine disorders or in patients with growth spurts. The intracranial hypertension in subjects with Turner syndrome or craniopharyngioma-induced GHD were noticed in a small number of patients. Symptoms usually occurred within the first 8 weeks of therapy and were resolved after its termination or after the reduction of GH dose [14, 85].

In recent years, there have been many concerns about the potential role of GH in the development of cancer. They were enhanced by the results of one study [24] that revealed the increased probability of certain tumors, especially colorectal cancer or Hodgkin's disease, as well as by the findings that indicated that plasma IGF-1 level was correlated with an increased risk of breast and prostate cancer, while patients with acromegaly presented a slightly increased risk of colon and rectum cancer [84]. However, a recently conducted cohort study on subjects receiving GH as children, did not evidence any risk of the development of malignancies [77], in accordance with the results of a long-term surveillance [61]. Similarly,

Tab. 1. Adverse effects of GH therapy

Frequency of side effects	Adverse effect
Most frequent	<ul style="list-style-type: none"> • Injection site reactions (nodules, erythema, pain post injection, bruising, itching, lipoatrophy, swelling)
Less frequently, considered probably related to the drug	<ul style="list-style-type: none"> • Headache • Nausea • Lower extremity pain • Fever • Vomiting
Other side effects	<ul style="list-style-type: none"> • Metabolic: mild, transient peripheral edema • Musculoskeletal: arthralgy, carpal tunnel syndrome, paresthesia • Skin (rare): increased growth of pre-existing nevi, increased skin pigmentation • Endocrinological: gynecomasty • Pancreatitis (rare)
Specific side effects in children	<ul style="list-style-type: none"> • Transient intracranial hypertension • Slipped femoral epiphysis • Gynecomasty

no relationship between GH and the risk of neoplasm was found in adult subjects [68].

The majority of trials assessing the impact of GH on glucose metabolism revealed a slight increase in fasting and post-glucose load insulin levels, resulting probably from the reduction in insulin sensitivity [39]. Most short-term clinical studies did not reveal, however, an impaired glucose tolerance or new onset diabetes as a result of GH treatment. It should be stressed that in those studies which revealed disturbances in carbohydrate metabolism, baseline (e.g. before treatment) glucose levels were not investigated or the abnormalities in glucose metabolism were present only in patients having insulin resistance prior to the therapy [39, 44]. The safety of a long-term administration of the hormone remains, at present, still unclear because in one study the therapy led to persistent glucose disturbances that occurred six-fold more often than in control subjects and persisted after discontinuation of the therapy [39, 44]. For these reasons, more randomized controlled long-term trials should be performed to determine the safety of the treatment.

It is worth remembering that efficiently treated diabetes mellitus is not regarded to be a contraindication for GH therapy. What is more, some diabetic patients can benefit from this therapy due to the decreased fat content and insulin resistance [13]. In individual cases, however, the modification of insulin doses may be required when GH therapy is instituted [13].

Monitoring of the therapy

The monitoring of the efficacy of GH therapy is relatively easy because it usually involves the measurement of height and its growth velocity. Determination of the GH level is not necessary, but pretreatment measurements of such parameters as IGF-1, IGFBP3, insulin level, glucose and lipid profile are recommended. Serum levels of IGF-1 and IGFBP-3 seem to be independently correlated with the change in height SDS: patients with higher IGF-1 levels, regardless of their GH dose, were found to grow more rapidly. Pre-pubertal gender differences in GH sensitivity were also found; only males had a linear growth response with increasing GH dose [12]. IGF-1 monitored therapy allows for the avoiding of potential metabolic and hypothetical malignant diseases. Moreover, studies in GH deficient adults indicated that IGF-1 maintained within the normal range during the therapy was associated with the reduced risk of edemas and arthralgy. In children, especially neonates, IGFBP-3 is deemed a more accurate parameter of GH therapy monitoring [17].

GH administration at a standard dose of 33 µg/kg/day is usually not associated with an increased risk of overdose, but while using high doses of GH there is a theoretical risk of acromegaly. Therefore, IGF-1 and IGFBP3 should be monitored, at least annually, and the GH dose should be reduced if IGF-1 exceed the 2 SDS for age and gender.

Conclusion

GH is one of the most widely used hormones in supplementation. Years of administration of this agent have proved its safety and efficacy in the therapy of

various conditions associated with short stature. Recent findings of the beneficial effect of GH on metabolism widened the array of its indications. Although indications for possible GH administration could be very wide, the high costs of a long-term therapy suggest that selection of potential candidates for the therapy should be very carefully made. One of important aspects of GH treatment in children is whether the supplementation should be continued when the final growth is achieved or when growth velocity is not significantly accelerated. Due to insufficient data to provide a clear resolution of these problems, risk-benefit and cost analyses should be performed, and every case of this disorder needs to be treated individually. GH therapy in adults still appears to be costly in comparison to the predicted objective benefits, however, further investigations may more clearly establish the role of this hormone in adult therapy.

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Received:

April 19, 2007; in revised form: October 4, 2007.