Growth Hormone Deficiency During the Transition Phase

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Abstract

The growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis has several roles. While achievement of a satisfactory height is probably the most important and well-known, it is now clear that it also affects body composition, metabolism, muscle mass and bone density during the transition period. Recombinant-growth hormone (Rec-GH) therapy is normally administered to GH-deficient children to achieve a reasonable final height. Retesting with a provocative test (insulin tolerance test or growth-hormone-releasing hormone + arginine test) is necessary during the transition period, after measuring IGF-1 levels. If the patient is still GH-deficient, rec-GH therapy should be restarted at 0.2–0.5 mg/day up to a final dosage of 0.8–1.0 mg/day (albeit there is no general consensus on the dosage). In fact, there is widespread literature evidence of the negative impact of GH-deficiency during the transition period, which provokes increased visceral fat and waist/hip ratio, decreased muscle mass and bone density and increased cardiovascular morbidity and mortality.

Keywords

Growth hormone, growth hormone deficiency, transition period, bone mineral density, peak bone mass, body composition, dysmetabolism, fertility, quality of life, retesting

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The transition period is the span of time in which people complete their somatic and psychological development after reaching their full stature (also known as late teenage years, post-adolescence or young adulthood). It starts in late puberty and comes to an end at around 25 years of age, thus lasting from three to 10 years. It includes hormonal and many lifestyle changes that lead to a different perception of the self and one's capacity to relate to others. There is also a change in the mental and physical needs of patients with growth hormone deficiency (GHD) who are leaving childhood to become adolescents and then young adults.[1,2]

Peak bone mass and complete reproductive maturation (demonstrated, in males, by the refinement of semen parameters) are achieved in the transition period. As confirmed by the literature over the last decade, the growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis is essential to achieve optimal body composition and bone density and maintain a safe metabolic profile (thereby decreasing cardiovascular risk). It also has a generally positive influence onquality of life.[3–6] Normally, recombinant GH (rec-GH) therapy is administered to GH-deficient children to enable them to achieve a satisfactory height, the main target for this period of life. However its use is now accepted and recognised for patients entering the transition period who were GH-deficient during childhood and adolescence, given these other important effects.[7,8] It should also be considered if there is a possibility of youth-onset GHD (e.g. following a road accident), which is presumably more difficult to diagnose and would generate less concern, especially if final height had already been reached. Given this, a retest during the transition period is essential, in order to evaluate if there is still a GH-deficiency and if a replacement therapy is still required.

It is useful to comment briefly that GH is a polypeptide hormone produced by somatotrope cells of the adenohypophysis: its release is stimulated by growth hormone-releasing hormone (GHRH) produced by the hypothalamus, and inhibited by somatostatin. GH does not work alone, but has a peripheral effector known as IGF-1 due to its structural similarity with insulin. IGF-1 is produced by the liver under GH stimulation and is the substance that actually interacts with peripheral tissues.

Role of Growth Hormone During the Transition Period

As briefly mentioned above, GH plays an important role during the transition phase. First, its contribution to lipid profile regulation is essential.[9–12] Many of the studies concerning this topic demonstrated that rec-GH therapy has an overall positive effect, with a significant decrease in low-density lipoprotein cholesterol (LDL-c) and no important increase in high-density lipoprotein cholesterol (HDL-c) widely reported. There is a very slight increase in triglyceride levels, but this does not have a great effect on metabolic profile.[13] However, another study described a significant decrease in triglyceride levels after three months of rec-GH, which had a positive correlation with changes in IGF-1 levels.[14]

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There is no literature evidence of significant changes to glucose-insulin metabolism. After one year of rec-GH therapy, an insignificant increase in fasting insulin and a slight decrease in insulin sensitivity was reported, but both remained within the normal range.[13]

Naturally, as confirmed by the literature and our own experience,[15] better results are obtained when GH treatment is restarted during early adolescence. This aspect is very important and should motivate the endocrinologist to retest patients promptly to avoid the establishment of a more adverse lipid profile and high cardiovascular risk.[16,17]

Body composition is described by the relative proportions of fat and lean mass (LBM). The first comprises subcutaneous and visceral fat, while the second consists of water (73 % of the entire LBM) plus bone mineral mass and muscle mass. The GH-IGF-1 axis, together with sex steroids, has a significant effect on body composition, but this effect is mainly seen in cases of GHD. In fact, an important article quoted extensively in the medical literature[9–15] demonstrated that a long period of rec-GH therapy discontinuation induces a consistent increase in per cent fat mass and trunk fat, with a decrease in LBM. This aspect is also stressed by several studies that compared groups of GHD patients treated with rec-GH therapy against patients treated with placebo.[18]

The effect of rec-GH on leptin and ghrelin levels is also interesting. The first is produced primarily in the adipocytes of white adipose tissue (and therefore fat mass positively correlates with leptin levels), and its circulating levels depend on the total amount of fat in the body. The role of leptin is to inhibit appetite by its counteractive effects on neuropeptide Y, a potent feeding stimulant secreted by gut and hypothalamus cells. A lack of leptin or a genetic failure of leptin receptors leads to marked obesity. Ghrelin is mainly produced by P/D1 cells lining the fundus of the stomach and epsilon cells in the pancreas. It is considered the counterpart of leptin; as its levels increase before meals and decrease after meals, it evidently induces hunger. It is also a potent stimulator of GH production by the pituitary gland.[19] An important study by Roemmler et al.[20] demonstrated that GHD patients under long-term rec-GH replacement therapy have significantly lower leptin levels (due to lower amounts of fat mass) and slightly but not significantly higher ghrelin levels than untreated age- and BMI-matched GHD patients.

The transition period is probably best known for the accrual of peak bone mass. Here too, GH and its peripheral effector have an essential role, as confirmed by the mitogenic effect of GH and IGF-1 on osteoblasts, the cells involved in the deposition of bone matrix. Peak bone mass is defined as the quantity of bone mineral tissue (bone mineral content - BMC) reached at the end of somatic development. From that moment and throughout adulthood, bone mineral density (BMD) will remain in a 'steady state', before decreasing progressively and inexorably during aging. The peak bone mass reached during the transition period is therefore fundamental. In fact the higher the peak bone mass reached during puberty and transition, the lower the risk of bone fractures during ageing, again demonstrating the essential role of the GH-IGF-1 axis.

It is well known that young adults with GHD have a diminished BMC and BMD. This double reduction is more marked in childhood-onset GHD (CO-GHD) than adult-onset GHD, providing further evidence of the role of the GH-IGF1 axis on the accrual of peak bone mass.[21] Stopping rec-GH therapy after final height has been achieved could lead to a significant reduction in cortical thickness, cross-sectional area and overall content. Furthermore, markers of bone remodelling (such as bone-specific alkaline phosphatase) are raised during GH therapy in young adults with GHD.[22]

However, bones may have different responses to GH, which could depend on the type of bone stimulated (cortical or trabecular). Some studies have shown a significant increase in both lumbar spine and total hip mineral density, without any evidence of improvement in other bone areas.[23] In any case the effects of rec-GH therapy on other bone areas may only become evident a considerable time later. The first outcomes of a study of the effects of 10 years of rec-GH therapy on patients with adulthood-onset GHD were observed after nine months in the lumbar spine and total body, but only after prolonged replacement therapy in the femur, probably reflecting the different actions of GH on cortical and trabecular bone.[24]

During the transition period, it is very important that treatment is scheduled to last at least 9–10 months. This is due to a paradox effect induced at the start of GH-therapy, when bone mineral resorption predominates over deposition as more bone remodelling units are activated, resulting in a net loss in BMD. With the passing of time this ends and there is a progressive increment in BMD.[25]

There is no clear literature consensus about the relationship between GHD, decreased BMD and higher risk of fractures. Hogler et al. concede the negative consequences of GHD on bone structure, but do not report an unquestioning association with a higher risk of fractures. In contrast, a Swedish national database demonstrated that GHD adults have a 2–3 times risk of bone fractures than gender- and age-matched normal subjects.[26,27]

The effect of rec-GH therapy (and thus of the GH-IGF-1 axis) on the reproductive system has largely been neglected. An important exception was a study by our own group,[28] as also cited in our 2011 review.[15] The study population consisted of ten infertile men with severe idiopathic oligozoospermia, normal or moderately raised blood gonadotropin and IGF-1 at low levels or within the lower limit of normal. They underwent short-term rec-GH therapy, which appeared to enhance sperm concentration and motility in five of the 10 patients. However, there is no unambiguous perspective in the literature. Some studies confirm the positive influence of the GH-IGF-1 axis, its role in the differentiation of progenitor Leydig cells into mature cells and its direct effect on steroidogenesis through the stimulation of steroidogenic enzymes (thus increasing testosterone production). GH's effects on the testis are carried out through IGF-1, which enhances the number of testicular LH receptors on Leydig cells, as underlined by studies on mice.[29] A broad distribution of IGF-1 receptors has also been described in the brain, pituitary, gonads and reproductive tract. This could demonstrate that any tract of the hypothalamus-pituitary-gonadal axis can be influenced by IGF-1, which has a paracrine-like action when stimulated by GH (e.g. in the testis, IGF-1 is synthesised by Sertoli and Leydig cells).[30,31]

It is useful at this point to comment briefly on the safety of rec-GH therapy with respect to testicular function. A study by Bertelloni[32] is alone in reporting gonad dysfunction in short patients treated with recombinant therapy, while other studies demonstrate its total safety. Our group[33] found that GH treatment did not affect testicular

development and function in non-GHD short stature (with normal levels of IGF-1), as there is no negative influence on inhibin B values (and therefore rec-GH therapy does not affect tubular or Sertoli cell function).

In females, the GH-IGF-1 axis seems to be essential in both proliferation and differentiation of granulose cells and, as in the testis, stimulates steroidogenesis in large follicles and thecal cells. GH receptor mRNA and protein have been found in ovarian cells, suggesting that GH also has a direct, IGF-1-independent action as an important modulator of gonadotropin-dependent and -independent functions.[34,35]

Quality of Life

The irreplaceable role of GH, both during the transition period and after the achievement of final height, is clear. We have seen how this important hormone, with the help of its peripheral effector IGF-1, modulates several aspects of the body, such as metabolism and cardiovascular safety, bone and body composition and fertility. Considering that the transition period, as mentioned in the introduction, is a phase of life involving many lifestyle changes and in which the psychological component has an essential role in individual wellbeing, it is almost a given that the GH-IGF-1 axis is an important determiner of quality of life (QoL).

An important study by Attanasio et al. evaluated quality of life during the transition period in GHD patients at the baseline and after one and two years of GH treatment. They specifically analysed various dimensions of QoL, such as body shape, concentration, initiative and drive, physical stamina, self-confidence and the ability to become sexually aroused and to tolerate stress. QoL was significantly lower after rec-GH suspension, particularly with respect to body shape and sexual arousal.[36] However, another recent study disputed Attanasio's conclusions, as no evident difference in QoL was found between treated and untreated patients in a younger cohort (mean age 15 years) of CO-GHD patients.[37] To conclude this section, we note a final study which demonstrated that the psychological difficulties of a GHD group were improved by GH treatment, but reverted after the end of the treatment.[38]

Retesting and Proper Therapy Dosage

rec-GH therapy is usually stopped when the bone growth plates shut down, in the hope that satisfactory linear growth will be achieved through the effect of the increased gonad steroids. The endocrinologist and/or paediatrician should thus request a wrist X-ray for a conclusive evaluation of bone age. A knee X-ray may also give more accurate information on growth plate status. As noted in the literature, GH-treatment is generally stopped when growth velocity decreases to <1 cm/year or after a bone age of 15 years in girls or 17 in boys is attained, indicating a remaining growth potential of <1 %.

The guidelines of the European Society for Paediatric Endocrinology Consensus statement drawn up in collaboration with the Growth Hormone Research Society provide a clearer description of suitable clinical conduct after rec-GH withdrawal.[2] Among the main concepts is the need for revaluation of the axis (retesting) during the transition period, from one to three months after rec-GH discontinuation. Two possibilities are described: adolescents with CO-GHD presenting well-known mutations, congenital abnormalities, lesions or irreversible structural damage to the central nervous system (CNS), in which GH and IGF-1 must be measured and a provocative test carried out only if the baseline IGF-1 level is <-2 SD; and idiopathic isolated GHD patients, who must be reassessed both by measuring IGF-1 and with a provocative test.

The gold-standard provocative test is GHRH + Arginine test (not recommended with childhood-onset idiopathic isolated GHD, as it may give a false normal response in some cases). This is better than the insulin tolerance test (ITT), which is not easily repeatable due to the possibility of side effects. GHD diagnosis must be reconsidered whenever the GH response to the test is above the established cut-off, which is 6.1 mcg/L for ITT and 20 mcg/L for GHRH + Arginine.[39–41]

As suggested by the Endocrine Society's Clinical Practice Guidelines,[42] rec-GH therapy should be reintroduced after a short period, usually known as a 'GH-holiday', in which retesting can be carried out. Circulating IGF-1 levels are a critical guide for the choice of the right dosage. Patients should restart midway between puberty and adulthood, if necessary, at a dose of 0.2–0.5 mg/day,[2,42] up to a final dosage of 0.8–1.0 mg/day.[2] A useful review article by Saggese et al. shows a hypothetical pattern for the dosage to be given to GHD patients during transition, depending on the length of the GH-holiday. If GH has been stopped for a long time (years) after attainment of final height, rec-GH therapy should be restarted with a low dose and titrated up in line with circulating IGF-1 levels. In contrast, if GH was discontinued only a short time ago (one to three months), a dosage closer to the paediatric dose should be administered, titrating down in line with IGF-1 levels.[43]

Conclusions

This review shows both the biological importance of the transition period in gaining complete physical maturity and the critical role of the GH-IGF-1 axis during this period. It is unquestionable that during this phase of life, GHD has a negative impact on many important physical functions, even if they are less measurable and perceptible than short stature, the main problem during childhood. It can in fact be affirmed that the negative consequences of GHD during the transition period become clearer in the future: osteoporosis, with a higher risk of bone fractures, dysmetabolism, involving an increased risk of stroke and changed body composition, with increased visceral fat and waist/hip ratio and reduced muscle mass. Its effects on male and female fertility need further study, to gain conclusive evidence of all the negative consequences of GHD.

Retesting after the achievement of final height is fundamental and the endocrinologist/paediatrician must inform patients and relatives of the importance of retesting and any resulting therapy. Three aspects still requiring definitive answers are the best time for retesting after stopping the childhood therapy, the duration of the GH-holiday and the introduction of a definitive dosage, about which there is still no consensus (in contrast with childhood, in which the agreed dosage is between 0.025 and 0.035 mg/kg/day). ■

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