

Diagnostic and therapeutic aspects of GH deficiency (GHD) in the transition period

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INTRODUCTION

Until the recognition of the impact of GH Deficiency (GHD) in adulthood, GH replacement therapy in children with GHD was discontinued at final height¹. Now it is widely accepted that adults with GH deficiency (GHD) have impaired health, which improves with GH replacement²⁻⁶.

Adult GHD syndrome is associated with changes in body composition, including increased fat mass, a possible reduction in bone mass, adverse changes in the blood lipid profile and cardiac function, reduced energy levels and reduced psychosocial well-being²⁻¹⁰. The diagnosis of GHD in adulthood is generally done in patients who have acquired GHD from pituitary or hypothalamic disease, or its treatment, in adult life⁴⁻⁶. GH therapy in adults has therefore been started with the long-term aim of reducing cardiovascular and osteoporotic risk, and the short-term aim of improving quality of life^{2,3,8-10}. In fact it has been shown that these therapeutic end-points should be reached with an optimal rhGH replacement and now in many European countries and in US, GH therapy is allowed by the Ministries of Health.

The considerable number of children who undergone GH therapy for classical and non classical GH deficiency implies the problem of considering who, when and how should continue the treatment in adulthood¹¹⁻¹⁵. It is well known that, GH secretion physiologically declines after puberty^{16,17}. Some children with less severe form of GHD may have adequate GH secretion in adulthood and will not suffer adverse consequences from the discontinuation of GH replacement therapy¹³. A percentage of children will, however, remains severely GH deficient in adulthood if treatment is discontinued^{12,14,18}. Children with GHD are therefore at risk of being withdrawn from potentially beneficial GH replacement therapy on reaching final height.

Aim of the present paper is to answer the following questions regarding the transition adolescent:

1. Are there consequences of withdrawing GH replacement in childhood-onset GHD at final height?

2. Does restarting GH replacement modify these consequences?

3. Should the diagnosis of GHD be reconfirmed in adulthood? If yes, how?

4. When retesting should be performed?

5. How persistent severe GHD should be treated in the transition adolescence?

ARE THERE CONSEQUENCES OF WITHDRAWING GH REPLACEMENT IN CHILDHOOD-ONSET GHD (CO-GHD) AT FINAL HEIGHT?

GH secretion increases markedly during puberty and thereafter continues to decline throughout the adult life¹⁶. Thus, when considering to achieve physiological replacement, the GH doses used in children should be typically much higher than those used in adults. This whenever children diagnosed as having GHD fulfil the criteria for the diagnosis of GHD on reaching adulthood. GHD in children is typically defined by the lack of GH response to two classical provocative tests (usually GH peak below 7-10 $\mu\text{g/L}$ after IIT, arginine, glucagon, clonidine, levodopa)¹⁹, while definition of severe GHD in adulthood has generally been based on a peak GH response to single IIT of less than 3 $\mu\text{g/L}$ ⁴.

As expected there is already evidence that stopping GH replacement has consequences in the transition adolescent and the young adult with persistent severe GHD. The withdrawal of GH replacement in patients with CO-GHD after adolescence can result significant decreases in muscle mass and strength, and increases in bodyweight and fat mass^{11,13,20}. Other studies show that young adults who have discontinued GH replacement therapy are disadvantaged in terms of body composition, cardiovascular and psychometric parameters when compared with their healthy peers²¹. In fact, 1 year after rhGH discontinuation, besides decrease in lean mass and increase in body fat increased, there was a decrease in left ventricular mass index, cardiac index and exercise capacity (more marked among the hypophysectomised patients) as well as in total peripheral resistance was increased.

Moreover, studies of adults with GHD (of either childhood or adult onset) have demonstrated relatively reduced bone mass and bone mineral density (BMD), as assessed by dual-energy X-ray absorptiometry (DXA), in comparison with matched healthy control populations²². Thus, premature discontinuation of GH in adolescents likely favours a failure to attain the genetic potential for peak bone mass (PBM)²³. In fact, the most rapid increase in bone mineral content (BMC) occurs during puberty in most trabecular sites, but BMC continues to increase into the middle of the third decade of life, as does skeletal muscle mass²⁴. After discontinuation of GH replacement upon final height, the risk of osteoporotic fractures later in life would be therefore increased though following GH discontinuation, BMD has been reported to increase any way despite adverse changes in body composition and cardiovascular function²⁴.

There is little doubt that GH increases bone size and hence BMC and this too may influence the likelihood of fracture²⁴. Moreover, adults with GHD do have an increased fracture risk²⁵. Bone mineralization and volume is a function of various factors, including genetics, diet, physical activity, gender and complex interactions between endocrine factors, including sex steroids, cortisol and peptide growth factors²⁴. The role of GH in determining peak bone mass, vBMD and the long-term consequences of a relative deficit of GH in early adult life will be clarified by further studies.

DOES RESTARTING GH REPLACEMENT MODIFY THESE CONSEQUENCES?

Based on the foregoing, there is evidence that discontinuation of GH replacement therapy after adolescence can have adverse consequences but some of these consequences could be counteracted by re-starting GH replacement in adulthood.

Marked differences in term of quality of life, lower body mass index, lower waist/hip (W/H) ratios, a lower lean body mass and lower serum levels of insulin-like growth factor I (IGF-I) have been shown between patients with CO- and adulthood- onset (AO) GHD²⁶. Under GH replacement there were significant improvements in body composition (increased lean body mass and decreased fat mass) in both groups in response to GH replacement therapy, accompanied by normalisation of levels of IGF-I and IGF-binding protein-3 (IGFBP-3)²⁶. Thus, re-introduction of GH replacement therapy in adulthood is beneficial for patients with CO severe GHD who discontinued therapy at final height²⁷.

SHOULD THE DIAGNOSIS OF GHD BE RECONFIRMED IN ADULTHOOD? IF YES, HOW?

Several studies have shown that when patients with CO-GHD are retested at final height, some are found to test positively for GHD, while others produce a normal

GH-response^{11-15,18,28,29}. To a large extent this may reflect the criteria that were applied in the original diagnosis. GH replacement therapy is offered only to children with classical GHD by some clinicians, while others prefer extending treatment to children with non classical GHD¹⁹. Classical GHD had been defined as total or partial failure to respond to two classical provocative tests¹⁹. However, later on it has been demonstrated that short children with normal response to provocative tests may show insufficient 24 h GH secretion (so called GH neurosecretory dysfunction-GHNSD) and this cohort of patients benefit from GH therapy^{19,30,31}. More recently, it has been recognised that even short children with normal GH secretion but low-normal IGF-I levels would benefit from GH treatment¹⁹. This extensive concept of GH insufficiency in childhood coupled with the assumption that only severe GHD needs GH replacement in adulthood. Thus, all patients with CO-GHD are at risk for persistent GHD in adulthood but it is clear that the diagnosis must be confirmed by retesting upon reaching final height, though there are some potential exceptions to this rule^{4,11,13,19}.

Patients with childhood-onset multiple hypopituitarism very likely remain GH deficient in adulthood; theoretically they too should undergo provocative tests to confirm the severe GHD to be replaced also in adulthood¹⁸. However, when GHD is part of multiple hypopituitarism persistence of low IGF-I after appropriate discontinuation of GH replacement therapy may be considered sufficient evidence to confirm the presence of severe GHD, which needs GH replacement therapy throughout life. We have found that 85% of patients with childhood-onset multiple hypopituitarism including severe GHD (confirmed by provocative retesting in adolescence) have IGF-I levels persistently below the age-related normal limits (personal data unpublished). These adolescents could be treated as severe GHD in adulthood based on low IGF-I levels only. On the other hand, it is clear that normal IGF-I levels do not rule out the presence of severe GHD and therefore patients with multiple hypopituitarism but normal IGF-I levels must be studied by provocative tests (personal data unpublished).

Whenever provocative tests have to be used, the question is how to test the adolescent? Following the consensus guidelines of the GH Research Society, within the appropriate clinical context severe GHD in adulthood has to be shown biochemically by provocative testing^{4,19}. In fact, the measurement of IGF-I and/or IGFBP-3 levels as well as the evaluation of spontaneous 24 h GH secretion does not clearly distinguish between normal and GHD adults^{4,5,7}. IGF-I measurement, however, remains the first step in the diagnostic screening.

Among provocative stimuli, ITT has been proposed as golden standard and GHRH + arginine as the most promising alternative^{4-6,33-34}. The reproducibility of the GH response to ITT in normal subjects has been questioned by some authors³⁵ and ITT is at risk for inducing seizures and

severe cardiovascular disease⁴ which imply contraindication to ITT in patients who underwent neurosurgery as well as in elderly subjects.

GHRH + ARG test is one of the most potent stimuli of GH secretion in childhood as well as in adulthood showing impressive specificity, a good reproducibility and is not dependent on age persisting marked in elderly^{4,33,36-37}. GHRH + ARG is as sensitive as ITT for the diagnosis of adult GHD; in fact, there is clear concordance between the two tests, provided that appropriate cut-off limits are assumed: 16.5 and 5 µg/L as 3rd and 9.0 and 3 µg/L as 1st centile limit^{34,36}.

We recently performed a study that shows the reliability of GHRH + ARG for retesting adolescents who had been treated with rhGH in childhood¹⁸. We studied the GH response to GHRH + ARG in patients who had been defined as having organic GHD, isolated GHD and the so called GHNSD in childhood. In the GHNSD group no subjects showed impaired GH response. On the other hand, GHD was confirmed in all hypopituitary patients with organic GHD (severe GHD in 94%) and in approximately 60% of patients who had been classified as isolated idiopathic GHD (severe GHD in 52.1%). All patients with organic and idiopathic GHD in whom GHD was confirmed by retesting with GHRH + ARG also showed impaired response to ITT, indicating that these tests have similar sensitivity. Our study pointed toward a big percentage of persistent GHD (approximately 50% of subjects). This picture, probably does not reflect the real persistence of GHD in adulthood at retesting; in fact, the majority of short children treated for GHD belongs to the so category of non classical GHD and GHNSD. Only multicenter trials of retesting who had been treated with rhGH in childhood will definitely clarify the persistence of GHD in adulthood.

Are there other alternative tests as reliable as ITT and GHRH + ARG? Synthetic GH Secretagogues (GHS) and ghrelin, a natural ligand of the GHS receptor are the most potent stimuli of GH secretion and even synergies with GHRH^{38,39}. The GH response to GHS is reproducible though it varies throughout life showing decrease in ageing⁴⁰. Recently it has been provided definitive evidence that testing with GHRH + GHRP is very specific and sensitive test for the diagnosis of adult GHD⁴¹. This test is as sensitive as ITT, is devoid of side effects and therefore represents another alternative for retesting the transition adolescent too.

WHEN RETESTING SHOULD BE PERFORMED?

Looking at the papers in literature, it is apparent the mean age for retesting was generally above 20 yr., reflecting the fact that the importance of this issue is a recent clinical problem. If an adolescent is retested positively for GHD at final height, GH replacement should be continued without interruption into adulthood. Our opinion is that it's unclear why the clinician should wait for consequences of

GHD to treat the patient with severe GHD, which has been confirmed.

Taking into account evidence that withdrawing GH replacement probably implies consequences^{20,21,27}, it is now suggested to perform retesting when the patient reach final height, so that patients in whom GHD is confirmed continue appropriate treatment during adolescence toward adulthood.

It has been suggested that retesting is done after appropriate withdraw of GH therapy in order to avoid interference of exogenous GH on the somatotroph responsiveness to provocative stimuli^{13,19}. This action is probably limited to short time but it has been suggested that retesting be performed at least three months after stopping rhGH treatment^{4,19}. Notice that, however, there is evidence that the GH response to GHRH + ARG is refractory to the negative GH autofeedback action⁴². In patients with multiple pituitary deficits it is recommended that testing with provocative stimuli of GH secretion is performed under optimised replacement of the other endocrine deficits^{4,13,19}.

HOW PERSISTENT SEVERE GHD SHOULD BE TREATED IN THE TRANSITION ADOLESCENCE?

Guidelines for downward dose titration from a "childhood" to an "adult" dose are lacking.

Several methods have been employed for calculating GH doses, based on body weight, body surface area or by monitoring IGF-I during replacement. In adult GHD, recent studies have tended to titrate the GH dose against IGF-I levels and the clinical response^{3,4,7}. Predictably, overweight patients have been shown to receive excessive doses of GH, in terms of the IGF-I response, when their initial dose was based only on body weight. This is of some concern due to the possibility of increased risks of left ventricular hypertrophy and neoplasia with over-treatment, based on observations in acromegalic patients. Side effects, particularly those related to fluid retention, are also more likely to occur in adults with AO-GHD treated on the basis of body weight²⁶. When adjusting the GH replacement in adulthood, the clinician will have to take into account also evidence that the appropriate dose for women is higher than that for men, reflecting the lower sensitivity of women to GH^{7,43}.

In the transition age, following the GHRS consensus guidelines^{7,19}, we suggest that GH replacement is firstly continued with the last pubertal dose (around 40-50 µg/kg/day). It is recommended that the dosage be soon titrated toward reduction by monitoring IGF-I levels, which should be maintained well within the age- and sex-related normal limits (in between the 50th-75th centile limit). Though in the absence of any clear demonstration, based on the age-related reduction in the 24 h GH production rate from puberty to young adulthood¹⁶ one could foresee that the progressive titration toward reduction would lead to reduce the

rhGH dose by 50% in 2-4 years. Then it could be that progressive reduction reaches the appropriate dose for replacement in a young adult in other 4 years i.e. approximately when the peak in bone mass is physiologically obtained²⁴. As anticipated, this is a hypothesis and a comprehensive series of studies during the transition age are required before any definite guidelines. In fact, it is important to identify safe regimens that can maximise linear growth potential and final adult height, but it is important to investigate the impact of age-adjusted regimens on carbohydrate and lipid metabolism, bone accretion and on attainment of peak bone mass, body composition, structure functions as well as on behaviour, psychosexual function and quality of life. Once again, it has to be recommended that side effects have to be carefully monitored though they are unlikely to occur if the replacement rhGH dose is really appropriate.

CONCLUSIONS

Aim of this paper was to answer questions about the GHD transition adolescent.

The first major question was: should treatment be continued in adulthood? The answer is yes, provided that severe GHD is confirmed by retesting. When the persistence of severe GHD is confirmed it is suggested that the patients restart GH replacement.

The second major question was: who has to be treated? The answer is: all patients in whom severe GHD is confirmed by retesting with provocative tests; ITT or GHRH + ARG are indicated as tests of choice, provided that appropriate cut-off limits are assumed. However, though normal IGF-I levels do not rule out severe GHD, low IGF-I levels can be definitive confirmation of GHD in genetic forms and panhypopituitarism.

The last major question was: how severe GHD in transition adolescence should be treated with rhGH? The answer is: individual titration of the rhGH dose is recommended and after puberty the rhGH dose is likely to be progressively reduced from paediatric to adult doses. Definite guidelines for downward dose titration from a "childhood" to an "adult" dose are still lacking and will come from future studies.

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