

Optimal Therapy of Growth Hormone Deficiency in the Child and Adolescent

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Abstract

Optimal therapy of growth disorders depends on accurate diagnosis and clear goals for therapy. Understanding normal patterns of growth hormone (GH) and insulin-like growth factor (IGF) secretion are necessary to appreciate the different hormone pattern induced by therapy. Finally, monitoring efficacy and safety, identifying interfering factors and adjusting doses are all part of optimising GH therapy in childhood GH deficiency (GHD). Prevention of development of GHD would avoid the need for therapy. Options for optimising GH therapy in childhood GHD include initiating treatment as young as possible, facilitating adherence to a therapy plan and adjusting GH dose on an individual basis to achieve 'target' results. In addition, there can be consideration of regulating timing of puberty, use of higher GH doses and improving the process of transition from paediatric to adult care. Future prospects include improved depot GH preparations or alternative delivery systems. Development of depot GH-releasing hormone (GHRH)/peptide therapy could allow a more physiological pattern of GH secretion. GH therapy should be targeted to yield the best growth response, best safety profile and the best psychosocial adjustment.

Keywords

Growth hormone deficiency (GHD), pharmacokinetics, GHD diagnosis, GHD therapy, computer modelling, therapy adherence, puberty, delivery systems, transition

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Paediatric endocrinologists aspire to provide the best care for children, including improving outcomes in growth hormone deficiency (GHD). The challenging issues are sometimes simple ones, such as which children should be seen in the endocrine clinic for evaluation of their growth, or standards for diagnosis of GHD, or methods of delivering standard therapy for GHD.¹ Historically accepted solutions require review as knowledge and technology advance.^{2–4}

This article addresses ways to optimise treatment strategy for children diagnosed with GHD. Optimal therapy of growth disorders depends on accurate diagnosis of the aetiology and identification of the goals of therapy. It is important to understand normal patterns of growth hormone (GH) and insulin-like growth factor (IGF) secretion in order to appreciate differences between normal physiology and hormone patterns induced by therapy. Finally, monitoring for efficacy and safety, identification of interfering factors and making appropriate dose adjustment are all part of optimising GH therapy in childhood GHD.

Accurate Diagnosis

Many factors besides GH participate in the regulation of normal growth (nutrition, thyroid hormone, genetics, prenatal health, family growth patterns and psychosocial adjustment [see *Figure 1*]). GH has been administered to children with severe GHD since 1958. Of course, there is no difficulty in making the diagnosis of GHD when the condition is severe. However, with the increasing availability of synthetic recombinant GH, GH therapy has been used in more conditions (see *Figure 2*).⁵ There continues to be controversy about

methods for accurate diagnosis of milder degrees of GHD, as well as controversy about which children should be treated with GH. Standardisation of GH assays and cutoff values for normal GH secretion may permit more uniform diagnosis, enabling therapy decisions to be based on reliable data from assays.⁶

If persistent slow growth rate suggests hypothyroidism or GHD, then appropriate evaluation should be performed (thyroid function tests, IGF-1 or IGF binding protein 3 [IGFBP3] and GH stimulation tests).⁷ Skipping this hormonal evaluation and proceeding to pragmatic use of GH or IGF-1 therapy may lead to missing a treatable 'true' aetiology such as hypothyroidism that would require a more targeted therapy, or even missing serious pathology such as a brain tumour. With pragmatic therapy, it is also possible to miss the presence of other pituitary hormone deficiencies. In summary, appropriate use of GH therapy depends on accurate clinical and laboratory diagnosis of the aetiology of the growth disorder, in order to provide therapy effectively targeted to the aetiology.

Goals of Therapy

The purpose of GH treatment must be considered. GH therapy clearly speeds up linear growth in the GHD child and adolescent. However, GHD leads to metabolic effects in addition to slowed linear growth. In untreated GHD, body composition is altered with increased fat mass, decreased lean body mass and decreased accrual of bone mineral.^{8–10} In addition, individuals with GHD may have decreased exercise tolerance and a sense of fatigue, along with a raised risk for

Figure 1: Growth Hormone is Only One of Many Ingredients Involved in Regulating Growth in Children

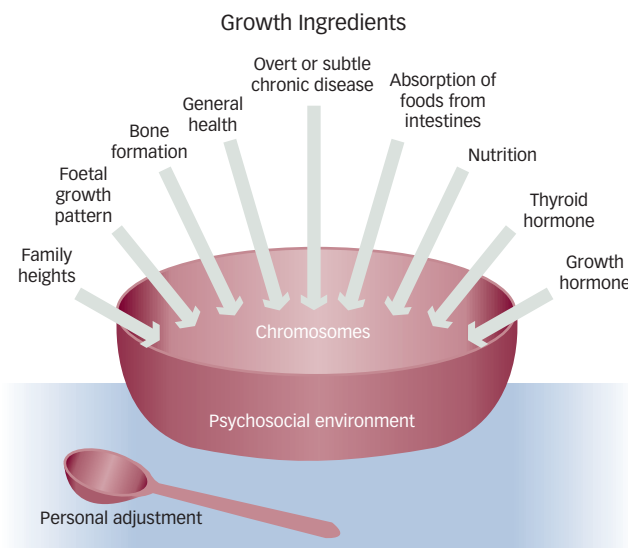
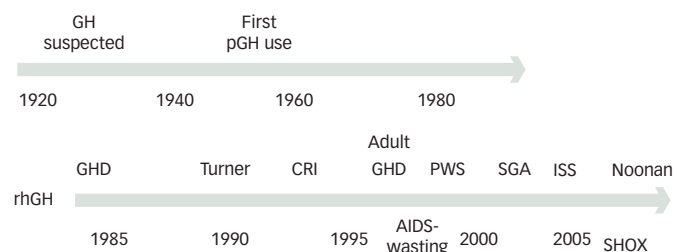


Figure 2: Timeline for Clinical Use of Growth Hormone Therapy and US Food and Drug Administration-approved Indications



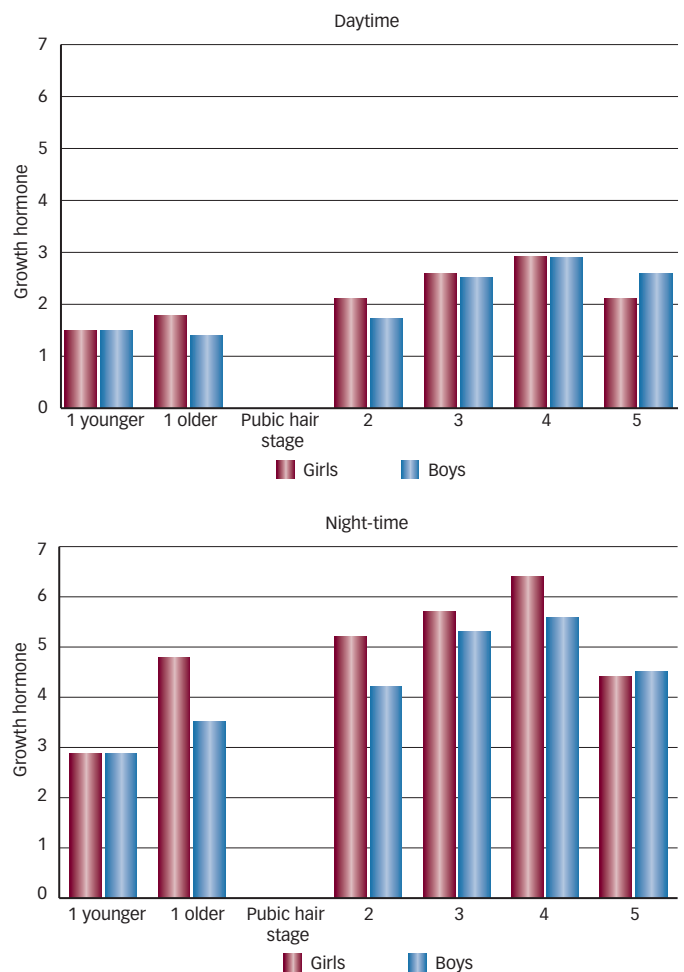
CRI = chronic renal insufficiency; GH = growth hormone; GHD = growth hormone deficiency; ISS = idiopathic short stature; pGH = pituitary derived GH; PWS = Prader-Willi syndrome; rhGH = recombinant human GH; SGA = small for gestational age; SHOX = short stature homeobox-containing gene.

cardiovascular disease. Metabolic effects of GHD are reversed by GH therapy.¹¹ Psychosocial-economic outcomes may be impaired, even with GH therapy.¹²

Normal Growth Hormone and Insulin-like Growth Factor Secretion

In order to address how to optimise GH therapy, it is important to first review the normal physiology and regulation of endogenous GH secretion and action. GH polypeptide (191 amino acids) is made in the pituitary and is released in response to multiple signals from the brain and body. While GH release is inhibited by somatostatin from the hypothalamus, somatostatin stimulates GH synthesis. Then GH release is stimulated by GH-releasing hormone (GHRH) from the hypothalamus and by gastric ghrelin during fasting.¹³⁻¹⁶ Somatostatin ‘tone’ is interrupted occasionally, resulting in GH secretion into the bloodstream in a pulsatile fashion. Pulsatile GH secretion is considered important for many of the physiological effects of GH.¹⁷ More GH pulses are released during sleep than when awake at all ages, but especially in the prepubertal child.¹⁸⁻²⁰ After the onset of puberty, daytime GH pulses increase and GH pulses are higher and more frequent in girls than in boys, leading to rising daytime mean GH and higher night mean GH in girls than in boys (see Figure 3).¹⁹

Figure 3: Gender Differences and Differences Between Mean Spontaneous Growth Hormone Levels in the Day and the Night



By pubic hair stage during 24 hours using serum sampling every 20 minutes in 132 healthy normally-growing children. Pubic hair stage 1 is shown in younger prepubertal girls (<8 years) and boys (<9 years) and older prepubertal girls (>8 years) and boys (>9 years).

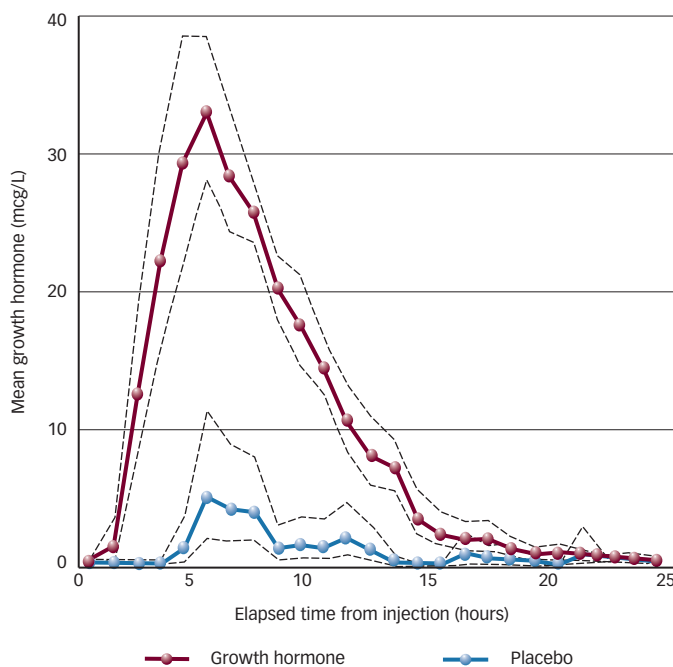
IGF-I is made in liver, bone and all tissues in response to circulating serum GH. IGF-1 is carried in the blood in a ternary complex that includes IGF-1, IGF-1 binding protein-3 (IGFBP3) and acid labile substance (ALS). Serum IGF-1 changes with age (being relatively low before four years of age), while serum IGFBP3 is more stable and changes less with age.

Understanding how the kinetics of administered GH doses compare with the kinetics of physiological pulses is important for the clinician. In contrast to endogenous GH pulses, after an injected GH dose, serum GH is above baseline for 12 hours while IGF-1 is above baseline for 48 hours (see Figure 4).²¹ On the other hand, when GHRH therapy is used as a continuous infusion, relatively normal GH pulses are observed even in childhood GHD (which is commonly a hypothalamic deficiency).^{13,22}

Interfering Factors

If the growth response to GH administration is unexpectedly low, there are many possible causes: poor compliance; incorrect technique of giving GH; morning timing of GH dose; high dose of glucocorticoid (as in adrenocorticotropic hormone (ACTH) deficiency or asthma); unrecognised hypothyroidism; inadequate nutrition

Figure 4: Mean Growth Hormone Levels in Children with Idiopathic Short Stature and Normal Baseline Growth Hormone Secretion During the First 24 Hours After a Dose of Growth Hormone or After Placebo



Dashed lines represent upper and lower 95% confidence limits of the mean values. Source: Rose SR, et al., 2000,²¹ reprinted with permission.

(protein, calories, calcium, vitamin D, or specific nutrients); intercurrent or chronic illness; antibodies to GH; or the wrong diagnosis.² If hypothyroidism develops and is not recognised, growth velocity does not improve as much as is usually expected with GH therapy, even in the presence of increased IGF-1.²³

The clinician should counsel the family about the importance of maintaining optimal nutrition. In addition, the clinician should evaluate whether the child is maintaining normal thyroid function and a good general state of health.^{2,23} A problem in any of these areas can decrease the growth response to GH therapy. In addition, the clinician should encourage consistent use of the GH therapy. The linear growth response will not be optimal if the GH therapy is not administered as prescribed. In one study, 13% of children missed more than half of their prescribed GH doses in a two-year period.²⁴

The negative impact of deficiency of GH on quality of life (QoL) may be lessened by GH therapy. However, persons with GHD should be evaluated for depression or other psychosocial factors that can affect their QoL and that as a result can impair growth response to GH therapy.^{25,26} Patients with multiple pituitary hormone deficiencies (MPHD) tend to have more difficulty in psychosocial functioning than do patients with idiopathic GHD.²⁶ Other persons with more psychosocial difficulty may include those started on GH therapy at a height shorter than -3 standard deviations (SD) or at an age older than 12 years. Intervening with counselling or other assistance is appropriate when psychosocial or socioeconomic factors affect resources, adherence, adequacy of calories and/or thyroid function.

Monitoring

Children with GHD being treated with GH require monitoring for efficacy and for adherence to the prescribed therapy. This includes

careful measurement of height and weight at three- to six-month intervals to assess rate of growth and weight gain.^{8,9} If there is scoliosis or history of spinal irradiation, the clinician can measure arm span as a surrogate for height, which is more accurate than the height measurement. Every few years, the clinician can assess rate of change in bone maturation compared with rate of change in chronological age. In addition, it is important to identify entry into and tempo of progression through puberty. At least yearly, there should be assessment of IGF-1, IGFBP3, free T4 and thyroid-stimulating hormone (TSH). At baseline and at each follow-up visit, the clinician should screen for age-appropriate developmental progress and psychosocial adjustment. If stresses are excessive or psychosocial difficulties develop or persist, referral for counselling is appropriate. It is not expected that simply growing closer to average height will resolve persistent psychosocial issues.^{12,25,26}

Monitoring should also be performed for intercurrent medical problems and for potential side effects of GH therapy. Side effects may include diabetes, pseudotumour, slipped capital femoral epiphysis, pancreatitis, or gynaecomastia. These may present with symptoms of polyuria, enuresis, headache, limp, leg pain, emesis, abdominal pain, or breast tenderness.²⁷

Current Therapy Options

Current therapy options for giving GH only include use of daily subcutaneous injections or weekly depot GH injections (in some countries). Thyroid hormone should be added if the child has hypothyroidism. Adjunctive therapy is sometimes added to modify the rate of pubertal progression (depot Lupron, aromatase inhibitor).

Dose Adjustment

Historically, when GH was first available by extraction from human pituitaries, GH treatment doses were dependent on rationing and supply, with supply only available for part of each year for each child. Subsequently, with greater availability of synthetic recombinant GH, clinicians began to adjust GH dose by body weight or by body surface area (see Figure 2).⁶

Higher GH doses are used in the US than in Europe, with mean GH dose of about 0.2mg/kg/week in Europe and 0.3mg/kg/week in the US (about 30µg/kg/day versus about 45µg/kg/day). Not surprisingly, better growth outcomes are observed with the higher dose than with the lower dose.²⁸ Physicians sometimes give a higher dose of GH per kilogram of body weight if a child's growth rate is less than expected.²⁹ Pubertal doses have been tested, using up to twice the average dose in the US, resulting in perhaps up to 20% higher growth velocity and reasonable safety profile.³⁰ Near adult height was -0.7 ± 0.9 SD with standard GH doses and 0.0 ± 1.2 SD with pubertal dosing ($p=0.024$).

Individualisation of GH dosing may result in better growth response to GH than strictly weight- or surface area-based dosing.³¹ Several factors affect individual GH responsivity, including age, parents' heights and birth weight. Modelling of growth response in the first year of GH therapy is a useful tool for estimating expected growth velocity, thus helping to identify whether interfering factors are present.²⁹ Growth velocity during GH therapy correlates positively with birth weight, current weight, size discrepancy from parents' heights, GH dose and negatively, with stimulated GH peak and age at start of GH therapy.^{32,33} Young age at GH start with longer duration of

GH therapy, correction of height deficit prior to puberty (daily GH compared with three times weekly GH injections) and higher GH doses are each associated with improved adult heights.²⁵

Among adults, women need higher GH dosing than men to achieve the same biological benefits (body composition and bone metabolism) and the same IGF-1 concentrations. Oral (but not transdermal) oestrogen replacement blunts the IGF-1 and biological response to GH in women.³⁴ Thus, with standard GH dosing, there is a risk for undertreatment in females and overtreatment in males.^{4,34} However, in children with GHD, gender has not been consistently shown to have an effect on growth response to GH therapy.^{35–38}

Finally, recent studies have evaluated the growth effects of adjusting GH dose according to IGF concentration achieved: faster growth rate is achieved with targeting the GH dose to result in a higher IGF-1.^{39,40} Individualised GH doses reduce how many children are outliers in their growth rate.⁴¹

Optimal Therapy

Prevention of Growth Hormone Deficiency

Prevention of GH deficiency might be possible through efforts to provide safe newborn delivery, including improvements in prenatal care along with appropriate medical and nursing facilities. Other interventions that may reduce the occurrence of GHD include accident prevention, both through individual efforts to learn skills needed for the activity and use of helmet or seatbelt and through industry safety standards and societal efforts. Finally, in specific populations such as children with cancer, improved cancer treatment regimens may reduce future risk for endocrine late effects.

Accurate and Early Identification of Growth Hormone Deficiency

Early detection and GH treatment of GHD is cost-effective for achieving taller adult height, as fewer milligrams of GH are required in younger children to achieve the same catch-up effect.^{2,25,42} Late diagnosis and late initiation of treatment lead to shorter adult height related to less remaining time to continue growing taller.⁴² Early intervention with GH (at a young age and before height SD drifts to -3 SD) can lead to not only better height outcome, but also better long-term psychosocial adjustment.^{26,36}

Delay of initiation of GH therapy often occurs in cancer survivors. Notably, GHD may develop in about 35% (29–39% in a meta-analysis of 33 studies) of cancer survivors after cranial irradiation.^{43–45} Delay of diagnosis also occurs in conditions where GHD has not yet been anticipated, such as after traumatic brain injury (TBI).^{42,46,47} There is a growing awareness that TBI can cause GHD.^{46,47} Patients with GHD after TBI experience QoL benefit from GH replacement.⁴² Compared with children with idiopathic GHD, children with TBI-induced GHD were older, growing slower before GH treatment and had more pituitary hormone deficiencies. Clinicians need to recognise the risk for endocrinopathies after medical events like these and to perform early endocrine evaluation.

Improvement of Adherence Through Improved Delivery System and Reducing Interfering Factors

Development of a system to help the patient take on a systematic schedule can improve adherence and subsequent outcome of GH

therapy. Necessity of daily injections potentially compromises compliance with the GH treatment plan.^{48,49} Attempts to improve adherence include use of injection pens, pens with a memory, needle-free devices and weekly GH administration. In addition, it might improve systematic adherence if future therapy for GHD were oral, transdermal, inhaled, or given as a depot injection.⁵⁰

Children on GH therapy should be monitored for efficacy and for side effects. Counselling should be obtained when appropriate. For optimal adherence to a GH treatment plan, we need to find ways to decrease pain/discomfort of injections, to use pen devices and to provide injections less often. The administration device must be simple to learn, simple to use and accepted by patients and their parents or guardians.⁵¹ In general, an injection pen is perceived by parents as reliable and easy to use and is well accepted. With the pen device, patients and parents tend to have confidence that GH will be injected properly with the correct dose.⁵¹

Individualisation of Therapy to Achieve ‘Target’ Results

IGF titration involves adjusting the GH dose to keep IGF-1 in the upper part of the normal range with a high IGFBP3. The IGF-1 target chosen affects GH dose requirements, while adjustment of the GH dose to achieve a higher IGF-1 target leads to a faster growth rate.^{39,40} However, there are not yet any long-term data regarding whether using a higher serum IGF-1 target will lead to taller adult height. Alternative IGF-1 targets can be chosen and achieved through GH dose adjustment. In an otherwise normal child with GHD, adjusting dose to achieve an IGF-1 target of $+1$ SD will result in an excellent growth rate at less than 0.3mg/kg/week. In contrast, in cancer survivors, it is probably appropriate to keep IGF-1 closer to the mean, rather than near the high end of the normal range.^{3,52} Of note, adult height and growth rate in GH-treated children after brain tumours or leukaemia are affected by whether the spine or the long bone growth centres were exposed to radiation therapy (spinal or total body irradiation) and by tempo of pubertal development.⁵² IGF titration permits adjustment for differences in GH sensitivity between individuals and by gender and by changes in GH sensitivity with age.^{20,39,40,53}

With standard GH dosing, there is a significant variation in growth rate response and in adult height achieved. More consistently, optimal response might be achieved with individualising treatment.^{41,54–59} Factors affecting variability in response include genetic polymorphisms and mutations of genes participating in the GH–IGF-1 cascade and in receptors (pharmacogenomic and pharmacoproteomic markers).^{54,60} An example is the GH receptor polymorphism exon 3, which may affect response to GH therapy. Adjusting dosing in view of these individual differences may reduce the number of poor responders.^{41,55} Comparing observed growth response to GH (especially in the first year of therapy) with the expected growth rate on GH therapy according to growth prediction models and then adjusting the GH dose, can be used to optimise therapy outcomes. Modelling of GH response can provide an accurate estimate of potential growth rate on GH therapy, to obtain improved height with lowest risk and lowest cost.^{29,33,56,61,62} First-month changes in IGF-1 and IGFBP3 correlate with first-year growth rate on GH therapy.⁶³ IGF-1 therapy or combined GH + IGF-1 should not be necessary in patients with ‘true’ GHD, as GHD patients should respond to GH as a sole therapy by inducing an endogenous rise in both IGF-1 and IGFBP3. In addition, the direct effects of GH on lipolysis are desirable.

Alteration of Timing of Skeletal Maturation by Controlling Timing of Puberty

GH treatment often falls short of helping patients achieve their full genetic height potential (within mid-parental height range). Patients with multiple pituitary hormone deficiencies (MPHD) generally have a slightly better long-term height outcome compared with patients with isolated GHD, related to lack of endogenous puberty.⁶⁴ Those patients with isolated GHD enter puberty at a typical or slightly delayed age. In contrast, patients with MPHD are often placed on therapy to induce puberty at an older age, after the clinician has observed for their spontaneous entry into puberty.^{59,65}

Treating with GH in combination with therapy to induce pubertal delay can prolong the total period of time that the adolescent can continue to keep growing taller.^{2,3,66} In brain tumour survivors with GHD treated with GH, use of gonadotrophin-releasing hormone analogue (GnRHa) therapy improved adult height compared with patients not treated with GnRHa.^{3,66-68} Overall, adult height in cancer survivors with GHD treated with GH has improved during the last 25 years.³ When height prediction is adversely affected by early puberty, the combination of GnRHa and GH improves prospects of achieving target height.^{3,66-68} Using aromatase inhibitors in adolescent boys on GH therapy may also increase adult height potential.⁶⁹⁻⁷¹ Combination of GnRHa and aromatase inhibitor may have even more benefit in preserving growth potential.⁷²

Utilisation of Pubertal Doses of Growth Hormone

Compared with standard GH doses, high-dose GH therapy in adolescents (pubertal dosing) increased near-adult height and height SD without significantly increasing skeletal maturation and without important side effects.^{57,73} However, preliminary analysis suggests that GH dose may have only a small effect on total pubertal growth.⁷⁴

Development of Depot Dosing of Growth Hormone

The need for daily injections is a potential barrier contributing to inconsistent use of GH. Maintaining IGF-1 levels in a therapeutic range should be possible without daily injections.^{75,76} One option is to use a sustained-release form of GH that might be given once each week.^{75,77,78} A prior depot GH product could be given once weekly or every two weeks, but efficacy was not as good as daily GH, so it is no longer available for use in the US.⁷⁹

There is a theoretical concern that depot GH doses are non-physiological. With administration of a depot GH product, serum GH levels will be above physiological levels for a higher percentage of time each day. The typical physiological pattern (described above) includes a GH peak, then a return to unmeasurable baseline, then another peak, etc (two to six pulses each night). In contrast, depot GH yields levels that are more like those seen in acromegalic patterns, which never decline to baseline (see *Figure 4*). It is not currently known whether there is a higher risk of cancer with sustained GH elevation.

Matching of Physiological Levels and Pattern of Growth Hormone Secretion

In most instances of GHD in children, hypothalamic deficiency of GHRH is the cause (with intact pituitary GH secretory capability). Therapeutic use of GHRH to enhance GH secretion is limited by the short duration of action of GHRH.^{17,75,80} GHRH therapy produces pulsatile release of GH, similar to normal physiology; however,

therapy using GHRH requires several injections daily or an infusion. If it were possible to develop a depot form of GHRH, then it could be given monthly, every three months, yearly and theoretically still could induce pulsatile GH release.⁷⁵ A depot GH releaser should be effective at producing a pulsatile GH pattern unless there has been a direct pituitary insult.⁸¹ Intravenous or subcutaneous GH infusion pumps to induce physiological pulses are not currently practical.

Slow-release preparations of GHRH might improve adherence if found to have long-term efficacy and safety.⁵⁰ Studies of a new long-acting GHRH analogue have shown increases in trough GH levels and enhanced GH pulsatility.⁷⁵ After a single injection of long-acting GHRH analogue, mean plasma GH increased by two- to 10-fold for six days or more with preserved pulsatility and mean plasma IGF-1 increased by 1.5- to three-fold for nine days or more. The depot GHRH was well tolerated in healthy adults, with no significant side effects.^{17,80} A depot therapy that releases pulses of GH could mimic normal physiology better than weekly or even daily GH injections.

Development of an Alternative Delivery System

Options for alternative delivery of GH are limited because of the size of the GH molecule. Inhaled GH was tested and found to have only 3.5% bioavailability, but was tolerated well. IGF-1 failed to rise in 25% of the GHD children treated.⁸² Transdermal administration is not possible with GH, because the protein is too big. In addition, GH itself is not active orally, as it is digested. A better option would be to work on further development of an oral GH-releasing peptide (GHRP) that could cause pulses similar to GHRH or ghrelin. Orally active secretagogues (ghrelin analogues) release GH, but have not yet been tested for prolonged therapy in children.⁸³

Improvement of the Process of Transition from Paediatric to Adult Care

For optimal GH therapy, it is important to perform re-evaluation of GH release at the time of achieving adult height, in order to see whether there is a continued need for GH therapy as an adult (adult GHD).⁸⁴⁻⁸⁶ In childhood-onset adult GHD, stopping GH therapy at reaching adult height can lead to decreased QoL, abnormal lipid panel, truncal adiposity, decreased muscle, fatigue, atherogenic risk, cerebrovascular and cardiac morbidity/mortality and decreased bone mineral density. Those with severe GHD will benefit from pausing GH therapy only long enough for re-evaluation.⁸⁴ In patients in whom it is clear that there will be persistence of GHD in adulthood, as in an organic aetiology or MPHD, continuing GH therapy during transition to adult care may be helpful in order to optimise bone mineral and body composition and to avoid patients being lost to follow-up.^{59,85,86}

Perspectives for the Future

Options for optimising GH therapy in childhood GHD include:

- prevention of GH deficiency when possible;
- early identification and initiation of GH treatment when a child is young;
- adherence to the prescribed therapy;
- adjustment of GH dose on an individual basis to achieve close to 'target' results;
- regulation of timing of puberty;
- consideration of higher GH doses, given daily;
- development of a depot GH preparation;
- development of GHRH/peptide therapy in order to match the

- physiological pattern of GH secretion;
- development of alternative delivery systems; and
- improvement of the transition process from paediatric to adult care.

Theoretically, future developments in treatment of the child with GHD might include therapies that are currently difficult to imagine, such as gene therapy to re-establish GH secretion, placental transplantation to supply chorionic somatomammotropin (in place of

GH), long-term oral GHRP, or a year-long depot GH-releaser that would allow continuing pulsatile GH release. Of note, these speculations are not based on literature evidence. The primary focus of this review has been to address how to optimise therapy for paediatric patients who have GHD. Once the decision has been made to treat a child with GH, therapy should be administered in a way that yields the best growth response with the best safety profile and the best psychosocial adjustment. ■

- Hardin DS, Woo J, Butsch R, Huett B. Current prescribing practices and opinions about growth hormone therapy: results of a nationwide survey of paediatric endocrinologists, *Clin Endocrinol (Oxf)*, 2007;66:85–94.
- Grumbach MM, Bin-Abbas BS, Kaplan SL. The growth hormone cascade: progress and long-term results of growth hormone treatment in growth hormone deficiency, *Horm Res*, 1998;49(Suppl. 2):41–57.
- Gleeson HK, Stoeter R, Ogilvy-Stuart AL, et al., Improvements in final height over 25 years in growth hormone (GH)-deficient childhood survivors of brain tumors receiving GH replacement, *J Clin Endocrinol Metab*, 2003;88:3682–9.
- Wilson TA, Rose SR, Cohen P, et al., Update of guidelines for the use of growth hormone in children: The Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee, *J Pediatr*, 2003;143:415–21.
- Richmond E, Rogol AD. Current indications for growth hormone therapy for children and adolescents, *Endocr Dev*, 2010;18:92–108.
- Juul A, Bernasconi S, Clayton PE, et al., Drugs and Therapeutics Committee of the European Society for Paediatric Endocrinology (ESPE). European audit of current practice in diagnosis and treatment of childhood growth hormone deficiency, *Horm Res*, 2002;58:233–41.
- Rose SR, Vogiatzi MG, Copeland KC, A general pediatric approach to evaluating a short child, *Pediatrics in Review*, 2005;26:410–20.
- Högler W, Shaw N. Childhood growth hormone deficiency, bone density, structures and fractures: scrutinizing the evidence, *Clin Endocrinol (Oxf)*, 2010;72:281–9.
- Cowell CT, Woodhead HJ, Brody J. Bone markers and bone mineral density during growth hormone treatment in children with growth hormone deficiency, *Horm Res*, 2000;54(Suppl. 1):44–51.
- Decker R, Albertsson-Wikland K, Kriström B, et al., Metabolic outcome of GH treatment in prepubertal short children with and without classical GH-deficiency, *Clin Endocrinol (Oxf)*, 2010;73(3):346–54.
- Widdowson WM, Gibney J. The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a meta-analysis, *J Clin Endocrinol Metab*, 2008;93:4413–7.
- Stochholm K, Gravholt CH. Socio-economic parameters in adults with childhood onset growth hormone deficiency, Presented at: the Endocrine Society 92nd Annual Meeting, San Diego, US, 19–22 June, 2010:P2–360.
- Root AW, Root MJ. Clinical pharmacology of human growth hormone and its secretagogues, *Curr Drug Targets Immune Endocr Metabol Disord*, 2002;2:27–52.
- Bluet-Pajot MT, Tolle V, Zizzari P, et al., Growth hormone secretagogues and hypothalamic networks, *Endocrine*, 2001;14:1–8.
- Camiña JP, Carreira MC, Micic D, et al., Regulation of ghrelin secretion and action, *Endocrine*, 2003;22:5–12.
- Wagner C, Caplan SR, Tannenbaum GS. Interactions of ghrelin signaling pathways with the GH neuroendocrine axis: a new and experimentally tested model, *J Mol Endocrinol*, 2009;43:105–19.
- Ionescu M, Frohman LA. Pulsatile secretion of growth hormone (GH) persists during continuous stimulation by CJC-1295, a long-acting GH-releasing hormone analog, *J Clin Endocrinol Metab*, 2006;91:4792–7.
- Rose SR, Municchi G, Barnes KM, et al., Spontaneous growth hormone secretion increases during puberty in normal girls and boys, *J Clin Endocrinol Metab*, 1991;73:428–35.
- Rose SR, Municchi G. Six-hour and four-hour nocturnal sampling for growth hormone, *J Pediatr Endocrinol Metab*, 1999;12:167–73.
- van den Berg G, Veldhuis JD, Frolich M, Roelfsema F. An amplitude-specific divergence in the pulsatile mode of growth hormone secretion underlies the gender difference in mean GH concentrations in men and premenopausal women, *J Clin Endocrinol Metab*, 1996;81:2460–7.
- Rose SR, Baron J, Bernstein D, et al., Suppression and recovery of GH secretion after GH injection in non-GH-deficient short children, *J Pediatr Endocrinol Metab*, 2000;13:281–8.
- Gelato MC, Malozowski S, Nicoletti MC, et al., Growth hormone responses to growth-hormone releasing hormone during pubertal development in normal boys and girls: comparison to idiopathic short stature and growth hormone deficiency, *J Clin Endocrinol Metab*, 1986;63:174–9.
- Smyczyńska J, Hilczer M, Stawerska R, Lewinski A. Thyroid function in children with growth hormone (GH) deficiency during the initial phase of GH replacement therapy – clinical implications, *Thyroid Res*, 2010;3:2.
- Desrosiers P, O'Brien F, Blethen S. Patient outcomes in the GHMonitor: the effect of delivery device on compliance and growth, *Pediatr Endocrinol Rev*, 2005;2(Suppl. 3):327–31.
- Sandberg DE, MacGillivray MH. Growth hormone therapy in childhood-onset growth hormone deficiency: adult anthropometric and psychological outcomes, *Endocrine*, 2000;12:173–82.
- Lagrou K, Xhrouet-Heinrichs D, Massa G, et al., Quality of life and retrospective perception of the effect of growth hormone treatment in adult patients with childhood growth hormone deficiency, *J Pediatr Endocrinol Metab*, 2001;14(Suppl. 5):1249–62.
- Bell J, Parker KL, Swinford RD, et al., Long-term safety of recombinant human growth hormone in children, *J Clin Endocrinol Metab*, 2010;95:167–77.
- Sas TC, de Ridder MA, Wit JM, et al., Adult height in children with growth hormone deficiency: A randomized, controlled, growth hormone dose-response trial, *Horm Res Paediatr*, 2010;74(3):172–81.
- Bakker B, Frane J, Anhalt H, et al., Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children, *J Clin Endocrinol Metab*, 2008;93:352–7.
- Mauras N, Attie KM, Reiter EO, et al., High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group, *J Clin Endocrinol Metab*, 2000;85:3653–60.
- Ranke MB. Clinical considerations in using growth hormone therapy in growth hormone deficiency, *Endocr Dev*, 2010;18:83–91.
- Ranke MB, Lindberg A, Chatelain P, et al., Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. KIGS International Board. Kabi Pharmacia International Growth Study, *J Clin Endocrinol Metab*, 1999;84:1174–83.
- de Ridder MA, Stijnen T, Hokken-Koelega AC. Prediction of adult height in growth-hormone-treated children with growth hormone deficiency, *J Clin Endocrinol Metab*, 2007;92:925–31.
- Cook DM, Ludlam WH, Cook MB. Route of estrogen administration helps to determine growth hormone (GH) replacement dose in GH-deficient adults, *J Clin Endocrinol Metab*, 1999; 84:3956–60.
- Rose SR, Shulman DI, Larsson P, et al., Gender does not influence prepubertal growth velocity during growth hormone therapy—Analysis of United States KIGS data, *J Pediatr Endocrinol Metab*, 2005;18:1045–51.
- Ross J, Lee PA, Gut R, Germak J. Factors influencing the one- and two-year growth response in children treated with growth hormone: Analysis from an observational study, *Int J Pediatr Endocrinol*, 2010; (Epub ahead of print).
- Kemp SR, Kuntze J, Attie KM, et al., Efficacy and safety results of long-term growth hormone treatment of idiopathic short stature, *J Clin Endocrinol Metab*, 2005;90:5247–53.
- Carel JC, Ecosse E, Nicolina M, et al., Adult height after long term treatment with recombinant growth hormone for idiopathic isolated growth hormone deficiency: Observational follow up study of the French population based registry, *Br Med J*, 2002;325:370.
- Cohen P, Germak J, Rogol AD, et al., Variable degree of growth hormone (GH) and insulin-like growth factor (IGF) sensitivity in children with idiopathic short stature compared with GH-deficient patients: evidence from an IGF-based dosing study of short children, *J Clin Endocrinol Metab*, 2010;95:2089–98.
- Cohen P, Rogol AD, Howard CP, et al., Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study, *J Clin Endocrinol Metab*, 2007;92:2480–6.
- Kriström B, Aronson AS, Dahlgren J, et al., Growth hormone (GH) dosing during catch-up growth guided by individual responsiveness decreases growth response variability in prepubertal children with GH deficiency or idiopathic short stature, *J Clin Endocrinol Metab*, 2009;94:483–90.
- Kreitschmann-Andermahr I, Poll EM, Reineke A, et al., Growth hormone deficient patients after traumatic brain injury—baseline characteristics and benefits after growth hormone replacement—an analysis of the German KIMS database, *Growth Horm IGF Res*, 2008;18:472–8.
- Mulder RL, Kremer LC, van Santen HM, et al., Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review, *Cancer Treat Rev*, 2009;35:616–32.
- Darzy KH. Radiation-induced hypopituitarism after cancer therapy: who, how and when to test, *Nat Clin Pract Endocrinol Metab*, 2009;5:88–99.
- Rose SR. Endocrinopathies after childhood cancer, *The Endocrinologist*, 2003;13:488–95.
- Kaulfers AMD, Backeljauf PF, Blum S, et al., Traumatic brain injury in children: Endocrine sequelae, *J Pediatr*, 2010;157(6):894–9.
- Ghigo E, Masel B, Aimaretti G, et al., Consensus guidelines on screening for hypopituitarism following traumatic brain injury, *Brain Inj*, 2005;19:711–24.
- Smith SL, Hindmarsh PC, Brook CG. Compliance with growth hormone treatment—are they getting it?, *Arch Dis Child*, 1993;68:91–3.
- Hamilton JG. Needle phobia: a neglected diagnosis, *J Fam Pract*, 1995;41:169–75.
- Aguiar-Oliveira MH, Meneguz-Moreno RA, Nascimento-Junior AC. New options and preparations in growth hormone therapy, *Arg Bras Endocrinol Metabol*, 2008;52:917–24.
- Fuchs GS, Mikkelsen S, Knudsen TK, Kappelgaard AM. Ease of use and acceptability of a new pen device for the administration of growth hormone therapy in pediatric patients: an open-label, uncontrolled usability test, *Clin Ther*, 2009;31:2906–14.
- Beckers D, Thomas M, Jamart J, et al., Adult final height after GH therapy for irradiation-induced GH deficiency in childhood survivors of brain tumors: the Belgian experience, *Eur J Endocrinol*, 2010;162:483–90.
- Mauras N, Bishop K, Welch S. Growth hormone action in puberty: Effects by gender, *Growth Horm IGF Res*, 2007;17:463–71.
- Rosenfeld RG. The future of research into growth hormone responsiveness, *Horm Res*, 2007;71(Suppl. 2):71–4.
- Jorge AA, Marchisotti FG, Montenegro LR, et al., Growth hormone (GH) pharmacogenetics: influence of GH receptor exon 3 retention or deletion on first-year growth response and final height in patients with severe GH deficiency, *J Clin Endocrinol Metab*, 2006;91:1076–80.
- Ranke MB, Lindberg A, KIGS International Board. Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables, *J Clin Endocrinol Metab*, 2010;95:1229–37.
- Albertsson Wikland K, Alm F, Aronsson S, et al., Effect of growth hormone (GH) during puberty in GH-deficient children: preliminary results from an ongoing randomized trial with different dose regimens, *Acta Paediatr Suppl*, 1999;88:80–4.
- Buzi F, Mella P, Pilotta A, et al., Growth hormone receptor polymorphisms, *Endocr Dev*, 2007;11:28–35.
- Drake WM, Howell SJ, Monson JP, Shalet SM. Optimizing gh therapy in adults and children, *Endocr Rev*, 2001;22:425–50.
- Wassenaar MJ, Dekkers OM, Pereira AM, et al., Impact of the exon 3-deleted growth hormone (GH) receptor polymorphism on baseline height and the growth response to recombinant human GH therapy in GH-deficient (GHD) and non-GHD children with short stature: a systematic review and meta-analysis, *J Clin Endocrinol Metab*, 2009;94:3721–30.
- Land C, Blum WF, Shavrikova E, et al., Predicting the growth response to growth hormone (GH) treatment in prepubertal and pubertal children with isolated GH deficiency—model validation in an observational setting (GeNeSIS), *J Pediatr Endocrinol Metab*, 2007;20:685–93.
- Kriström B, Dahlgren J, Niklasson A, et al., The first-year growth response to growth hormone treatment predicts the long-term prepubertal growth response in children, *BMC Med Inform Decis Mak*, 2009;9:1.
- Chatelain P, Tato L, Peterkova V, et al., Relationship between 1-month biomarker changes and 1-year growth response in prepubertal children with growth hormone deficiency or Turner syndrome treated for 1 year with GH: The PREDICT multicentre, observational follow-up study, Presented at: the Endocrine Society 92nd Annual Meeting, San Diego, US, 19–22 June, 2010: P1–677.
- Reiter EO, Price DA, Wilton P, et al., Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database, *J Clin Endocrinol Metab*, 2006;91:2047–54.
- Magnhie M, Ambrosini L, Cappa M, et al., Adult height in patients with permanent growth hormone deficiency with and without multiple pituitary hormone deficiencies,

- J Clin Endocrinol Metab*, 2006;91:2900–5.
66. Pasquino AM, Pucarelli I, Roggini M, Segni M, Adult height in short normal girls treated with gonadotropin-releasing hormone analogs and growth hormone, *J Clin Endocrinol Metab*, 2000;85:619–22.
 67. Kamp GA, Mul D, Waelkens JJJ, et al., A randomized controlled trial of three years growth hormone and gonadotropin-releasing hormone agonist treatment in children with idiopathic short stature and intrauterine growth retardation, *J Clin Endocrinol Metab*, 2001;86:2969–75.
 68. Cassoria F, Mericq V, Eggers M, et al., Effects of luteinizing hormone-releasing hormone analog-induced pubertal delay in growth hormone (GH)-deficient children treated with GH: preliminary results, *J Clin Endocrinol Metab*, 1997;82:3989–92.
 69. Maurus N, Gonzalez de Pijem L, Hsiang HY, et al., Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years, *J Clin Endocrinol Metab*, 2008;93:823–31.
 70. Maurus N, Strategies for maximizing growth in puberty in children with short stature, *Endocrinol Metab Clin North Am*, 2009;38:613–24.
 71. Dunkel L, Update on the role of aromatase inhibitors in growth disorders, *Horm Res*, 2009;71(Suppl. 1):57–63.
 72. Papadimitriou DT, Papadimitriou A, An open label 1–3 year clinical trial on the effects of the aromatase inhibitor Anastrozole combined to the LHRH analogue Leuprorelin in girls with compromised growth potential, Presented at: the Endocrine Society 92nd Annual Meeting, San Diego, US, 19–22 June, 2010:P3–688.
 73. Maurus N, Attie KM, Reiter EO, et al., High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group, *J Clin Endocrinol Metab*, 2000;85:3653–60.
 74. Ranke MB, Lindberg A, on behalf of the KIGS International Board, Pubertal growth (TPG) in adolescents with idiopathic growth hormone deficiency (GHD), Turner syndrome (TS), short stature born small for gestational age (SGA), and idiopathic short stature (ISS) documents a minor role for GH in puberty, Presented at: the Endocrine Society 92nd Annual Meeting, San Diego, US, 19–22 June, 2010:P1–680.
 75. Clemmons DR, Long-acting forms of growth hormone-releasing hormone and growth hormone: effects in normal volunteers and adults with growth hormone deficiency, *Horm Res*, 2007;68 (Suppl. 5):178–81.
 76. Rasmussen MH, Bysted BV, Anderson TW, et al., Pegylated long-acting human growth hormone is well-tolerated in healthy subjects and possesses a potential once-weekly pharmacokinetic and pharmacodynamic treatment profile, *J Clin Endocrinol Metab*, 2010;95:3411–7.
 77. Peter F, Savoy C, Ji HJ, et al., Pharmacokinetic and pharmacodynamic profile of a new sustained-release GH formulation, LB03002, in children with GH deficiency, *Eur J Endocrinol*, 2009;160:349–55.
 78. Bidlingmaier M, Kim J, Savoy C, et al., Comparative pharmacokinetics and pharmacodynamics of a new sustained-release growth hormone (GH), LB03002, versus daily GH in adults with GH deficiency, *J Clin Endocrinol Metab*, 2006;91:2926–30.
 79. Kemp SF, Fielder PJ, Attie KM, et al., Pharmacokinetic and pharmacodynamic characteristics of a long-acting growth hormone (GH) preparation (nutropin depot) in GH-deficient children, *J Clin Endocrinol Metab*, 2004;89:3234–40.
 80. Teichman SL, Neale A, Lawrence B, et al., Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults, *J Clin Endocrinol Metab*, 2006;91:799–805.
 81. Ogilvy-Stuart AL, Stirling HF, Kelnar CJ, et al., Treatment of radiation-induced growth hormone deficiency with growth hormone-releasing hormone, *Clin Endocrinol (Oxf)*, 1997;46:571–8.
 82. Walvoord EC, de la Peña A, Park S, et al., Inhaled growth hormone (GH) compared with subcutaneous GH in children with GH deficiency: pharmacokinetics, pharmacodynamics, and safety, *J Clin Endocrinol Metab*, 2009;94:2052–9.
 83. Garcia JM, Polvino WJ, Pharmacodynamic hormonal effects of anamorelin, a novel oral ghrelin mimetic and growth hormone secretagogue in healthy volunteers. *Growth Horm IGF Res*, 2009;19:267–73
 84. Kotowska-Häggström M, Geffner ME, Jönsson P, et al., Discontinuation of growth hormone (GH) treatment during the transition phase is an important factor determining the phenotype of young adults with nonidiopathic childhood-onset GH deficiency, *J Clin Endocrinol Metab*, 2010;95:2646–54.
 85. Saggese G, Baroncelli GI, Vanacore T, et al., Indications and strategies for continuing GH treatment during transition from late adolescence to early adulthood in patients with GH deficiency: the impact on bone mass, *J Endocrinol Invest*, 2004;27:596–602.
 86. Cuttler L, Silvers JB, Singh J, et al., Physician decisions to discontinue long-term medications using a two-stage framework: The case of growth hormone therapy, *Med Care*, 2005;43:1185–93.