

THE USE OF GROWTH HORMONE IN CHILDREN AND ADULTS



Ministry of Health
Malaysia



Malaysian Endocrine and
Metabolic Society



Academy of Medicine of
Malaysia

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2010 and will be reviewed in 2014 or sooner if new evidence becomes available.

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<http://www.moh.gov.my>

<http://www.acadmed.org.my>

<http://www.endocrine.my/index.php>

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LEVELS OF EVIDENCE SCALE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

GUIDELINE DEVELOPMENT AND OBJECTIVES

GUIDELINE DEVELOPMENT

The Development Group for this Clinical Practice Guidelines (CPG) was from the Ministry of Health (MOH), Ministry of Higher Education and private sector. They consisted of paediatric endocrinologists, paediatricians, adult endocrinologists, a geriatrician, a family medicine specialist, public health physicians and a pharmacist. There was active involvement of the Review Committee during the process of development of these guidelines.

Literature search was carried out at the following electronic databases: PUBMED/MEDLINE, Cochrane Database of Systemic Reviews (CDSR), International Health Technology Assessment websites, Journal full text via OVID search engine, Database of Abstracts of Reviews of Effectiveness and Cochrane Controlled Trials Register (Refer to **Appendix 1** for Search Terms). In addition, the reference lists of all retrieved articles were searched to identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted between 20 January 2009 and 11 August 2010. This date period should be considered the starting point for searching of new evidence for future updates to these guidelines.

Reference was also made to other guidelines on Growth Hormone e.g. American Association of Clinical Endocrinologists Medical guidelines For Clinical Practice for Growth Hormone Use in Adults and Children-2003 update; American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone Deficient Adults and Transition Patients Children-2009 update; Guidelines for the Availability of Human Growth Hormone (hGH) as a Pharmaceutical Benefit, Department of Health and Ageing, Australia, July 2008; Consensus Statement on the Management of the GH-Treated Adolescent in the Transition to Adult Care, Society of European Journal of Endocrinology, 2005; Update of Guidelines for The Use of Growth Hormone in Children: The Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee, The Journal of Pediatrics, October 2003; Consensus guidelines for the Diagnosis and Treatment of Growth Hormone Deficiency in Childhood and Adolescence: Summary Statement of the GH Research Society, European Journal of Endocrinology 2005; and Consensus Guidelines for the Diagnosis and Treatment of Adults with Growth Hormone Deficiency: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency 1998. These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) prior to them being used as references.

Twenty four clinical questions were developed under three subgroups and members of the development group were assigned individual questions within these subtopics. (Refer to Appendix 2 for Clinical Questions). The group members met a total of 26 times throughout the development of these guidelines. All literature retrieved was appraised by at least two members and presented in the form of evidence tables and discussed during development group meetings. Later, all statements and recommendations formulated were agreed upon by both the development group and review committee. Where evidence was insufficient, the recommendations were made by consensus of the development group and review committee. These CPG are based mainly on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The articles were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation in these guidelines was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guideline was posted on the MOH Malaysia official website for comment and feedback. These guidelines had also been presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council, MOH, Malaysia for review and approval.

OBJECTIVES

GENERAL OBJECTIVE

To provide an evidence-based guidance on the use of growth hormone (GH) in children, transition period and adults

SPECIFIC OBJECTIVES

- To improve early recognition of GH deficiency
- To recognise suitable candidates for GH therapy
- To understand the pitfalls in diagnosis of GH deficiency
- To identify the risks and benefits of GH therapy
- To provide guidance for treatment and monitoring treatment effect and side effects of GH therapy
- To re-evaluate GH treated children during transition period and identify candidates who should continue GH therapy into adulthood

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

a. Inclusion criteria

- Short and slowly growing children
- Childhood onset growth hormone deficiency (COGHD)
- Adults in whom growth hormone usage is being considered

b. Exclusion criteria

- Children with chronic systemic diseases such as chronic lung disease and congenital heart disease

TARGET GROUP/USER

These guidelines are applicable to all healthcare professionals who are involved in the management of patients who may benefit from growth hormone therapy:-

- General practitioners and primary care doctors
- Medical officers
- Paediatricians
- Physicians
- Endocrinologists
- Pharmacists
- Other specialists (Sports Medicine Specialists, Geriatricians, Obstetrician and Gynaecologists, Rheumatologist, Intensivist, Surgeons in the Burns Unit, Clinical Psychiatrists and Psychologists)

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

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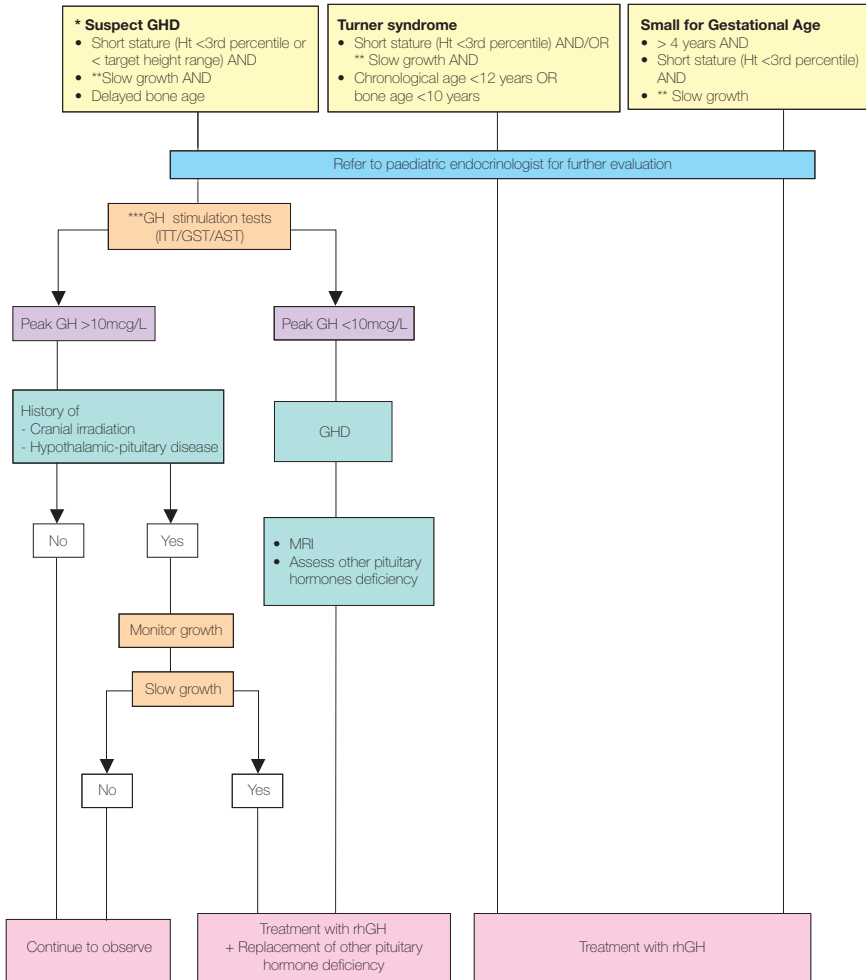
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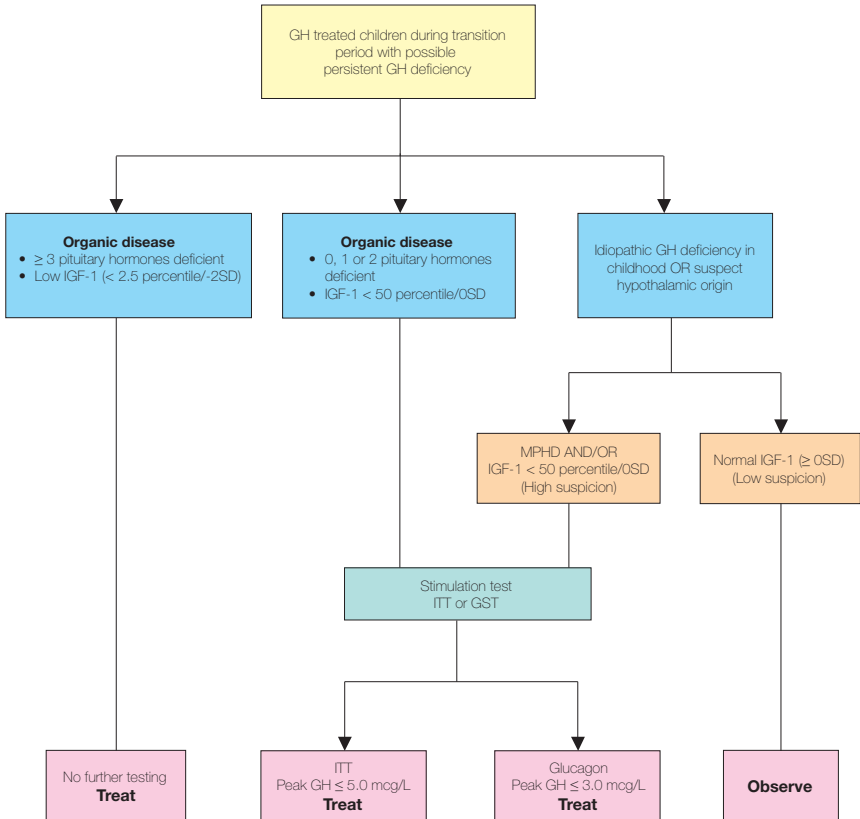
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ALGORITHM FOR GROWTH HORMONE THERAPY IN CHILDREN



- * After exclusion of systemic diseases, skeletal disorders, hypothyroidism and Turner syndrome
- ** Slow growth is defined by downward deviation of height > 1 percentile band over not less than 12 months
- *** A minimum of two GH stimulation tests using either ITT, GST, AST are needed for diagnosis

ALGORITHM FOR MANAGEMENT OF GROWTH HORMONE-TREATED CHILDREN DURING TRANSITION PERIOD



Legend

GHD : Growth Hormone Deficiency

ITT : Insulin Tolerance test

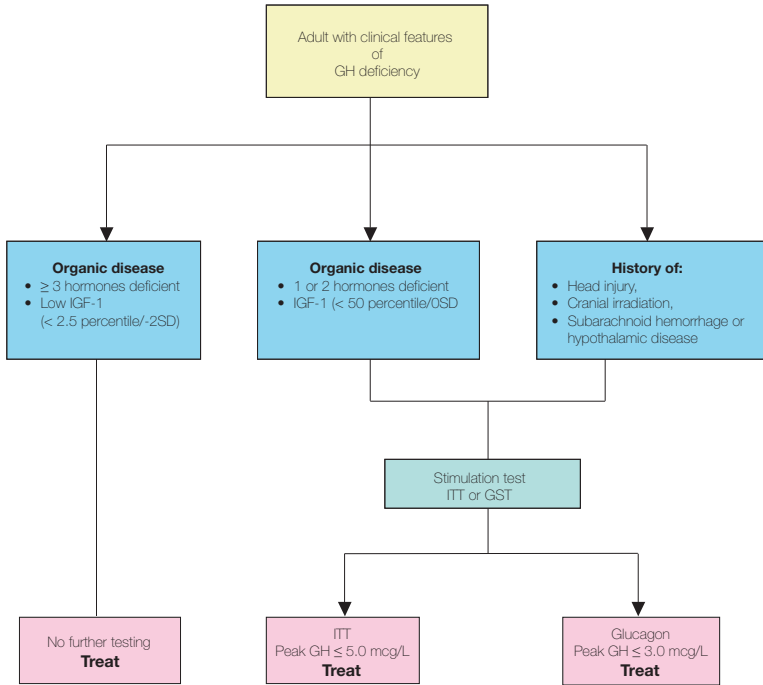
IGF-1 : Insulin-like Growth Factor 1

GST : Glucagon Stimulation test

MPHD : Multiple Pituitary Hormone Deficiency

Modified from AACE Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone Deficient Adults and Transition Patients- 2009 Update. Endocrine Practice Vol 15

ALGORITHM FOR SCREENING AND DIAGNOSIS FOR ADULT WITH POSSIBLE GROWTH HORMONE DEFICIENCY



Legend

GHD : Growth Hormone Deficiency

ITT : Insulin Tolerance test

IGF-1 : Insulin-like Growth Factor 1

GST : Glucagon Stimulation test

MPHD : Multiple Pituitary Hormone Deficiency

Modified from AACE Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone Deficient Adults and Transition Patients- 2009 Update. Endocrine Practice Vol 15

1. INTRODUCTION

Growth hormone (GH) has been used in clinical practice since 1950s. The initial source of GH was human cadaver pituitary extract. The supply was scarce and the scope of GH usage then was limited only to children with proven GH deficiency. In 1985, pituitary-derived GH was banned because of its association with Creutzfeldt Jacob disease. This triggered an acceleration in the biosynthesis of GH via recombinant DNA technology. Today there is an abundant supply of biosynthetic GH commercially. The use of GH has also expanded markedly beyond GH deficiency to conditions without GH deficiency where data regarding its efficacy and safety in these conditions are still lacking.

In Malaysia, recombinant human growth hormone (rhGH) has been commercially available since 1985. However, despite its increased availability, many GH deficient (GHD) children are still deprived of rhGH therapy due to its high cost and concerns regarding its long-term safety. On the contrary, the broadening of scope of GH therapy also has its drawbacks including its increasing use and abuse of GH in a broad variety of growth disorders without evidence of GH deficiency.

rhGH therapy should not be taken lightly in view of its high cost, the need of prolonged therapy with close follow up by practicing clinicians familiar with rhGH therapy, potential adverse effects and the negative psychological impact from unsuccessful therapy.

In a 25 kg child, at low dose of 0.025 mg/kg/day, the cost of rhGH approximates RM950 per month (RM11,400 per year). The cost escalates as rhGH dose requirement increases and the child grows in stature reaching a hefty sum of more than RM2,000 per month. The duration of rhGH therapy could range from four to ten years for optimisation of linear growth to lifelong for severe childhood-onset or adult-onset GH deficiency.

In adults, the indications for GH therapy are well defined but the enthusiasm for rhGH use has also far exceeded medical evidence. Unlike that in children, the lack of linear growth in adults renders response to rhGH therapy more difficult to measure. These CPG specifically aim to evaluate the scientific and clinical evidence of appropriate rhGH use and abuse in order to put these “indications” into their respective scientific contexts.

1.1 GROWTH HORMONE DEFICIENCY IN CHILDREN

GH deficiency in children results from developmental abnormalities or diseases affecting the hypothalamus and pituitary gland. Causes of developmental abnormalities include genetic defects affecting the GH gene, Pit-1 gene or POU1F1 gene that regulate development of pituitary cells secreting GH, prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyrotropin. Diseases of the hypothalamus and pituitary may result from acquired causes such as pituitary tumours, craniopharyngioma, Langerhans cell histiocytosis, infection of the central nervous system, traumatic head injury and whole body or cranial irradiation.

The most common presentation of GH deficiency in children is stunted growth. In view of a wide spectrum of causes of stunted growth in children, evaluation for GH deficiency in a short child should not be initiated until other causes of growth failure such as hypothyroidism, chronic systemic diseases, syndromic disorders including Turner syndrome (TS) and skeletal disorders have been considered and appropriately excluded. In neonates and infants, signs and symptoms of GH deficiency differ from older children. While deviation from linear growth is the primary presentation in older children, metabolic effects of GHD are the primary presentation in neonates and infants.

1.2 WHO SHOULD BE INVESTIGATED FOR GH DEFICIENCY?

The consensus guidelines (GH Research Group, 2000) recognised the key facts in history and physical examination that may indicate GH deficiency in the neonates. These include neonatal history of persistent hypoglycaemia, prolonged neonatal hyperbilirubinaemia, microphallus, traumatic delivery or presence of craniofacial midline abnormalities.^{1, Level III; 2, Level II, 3, level II; Positive history of intracranial tumour,^{4, level II-3} cranial surgery, head injury either from complications at birth or from trauma,^{5, Level I; 6, level II-3} central nervous system infection, cranial irradiation^{7, Level III} should also alert the clinician of the diagnosis of GH deficiency in a short and slowly growing child.}

Recommendation

In neonates/infants, evaluation for GH deficiency should be conducted if they manifest persistent, intractable hypoglycaemia \pm convulsions associated with any of the following:

- Micropenis in a male infant
- Prolonged neonatal jaundice
- Midline craniofacial defects (such as cleft palate, cleft lip, nasal or frontal encephalocele, single central incisor, visual impairment, optic nerve hypoplasia)*
- Traumatic delivery (breech) or perinatal asphyxia*
- Post-natal failure to thrive (affecting both length and weight)

(Grade C)

In older children, evaluation for GH deficiency should be conducted if history is positive for any of the following:

- Surgery to the hypothalamic pituitary region*
- Cranial irradiation*
- Intracranial tumour such as craniopharyngioma*
- Traumatic brain injury (accidental or non-accidental)*
- Central nervous system infection*
- Signs and symptoms of multiple pituitary hormones deficiency (MPHD)
- Signs indicative of intracranial lesion*
- Parental consanguinity \pm an affected family member (genetic cause)
- Failure to show normal growth spurt by breast stage 3 in girls and genital stage 3 in boys. **(Grade C)**

Note: * organic causes of GH deficiency

2. USE OF GROWTH HORMONE IN GROWTH HORMONE DEFICIENT (GHD) CHILDREN

Diagnosis of GH deficiency in childhood is a multifaceted process requiring a combination of clinical and auxological criteria, biochemical tests and radiological evaluation. growth ⁸; Level III

2.1 DIAGNOSIS OF GROWTH HORMONE DEFICIENCY IN CHILDREN

2.1.1 Clinical and Auxological Criteria

The GH Research Society Consensus Guidelines (2000) and American Association of Clinical Endocrinologists (AACE, 2003) recommend the following clinical and auxological criteria to identify GH deficiency:^{9, Level III; 8, Level II;}

- i. Severe short stature, defined as height >3 standard deviation (SD) below the mean
- ii. Height >1.5 SD below mid-parental-height (MPH)
- iii. Height >2 SD below mean and height velocity (HV) over one year >1 SD below the mean for chronological age (CA) or a decrease in height by >0.5 SD over one year in children over 2 years of age
- iv. In the absence of short stature, HV >2 SD below the mean over one year or >1.5 SD below the mean sustained over two years
- v. Signs of intracranial lesion
- vi. Signs of MPHD
- vii. Neonatal symptoms and signs of GH deficiency

In Malaysia, growth charts in SD are not available. However, National Child Health Statistics (NCHS) growth charts in centiles are available in most clinics. For this reason the following equivalents are used.^{10, level III}

- 3rd percentile is used to represent 2 SD below the mean
- 10 cm below the MPH represent 1.5SD below MPH
- One centile band on the growth chart represents 2/3 of an SD

NCHS growth charts for boys and girls are available in **Appendix 3**.

Mid-parental height for:

$$\text{Boys} = \frac{[\text{father's height (cm)}] + [\text{mother's height (cm)} + 13]}{2}$$

$$\text{Girls} = \frac{[\text{father's height (cm)} - 13] + [\text{mother's height (cm)}]}{2}$$

Pitfalls in auxology: Although auxology is a simple, non-invasive tool for defining population at risk for GH deficiency, it has its limitations in clinical use. Height measurements may be imprecise due to errors related to operator and/or measuring tool. Errors can also occur in the calculation of HV due to seasonal variation in growth and short time interval between measurements. To minimise errors in HV, serial height measurements should be performed by a trained personnel, using an appropriate tool and a longer time interval between measurements (which should not be less than three months).

However, Voss LD et al. showed no correlation between HV in two consecutive years in short normal children and GHD children which indicated severe imprecision of HV.^{11, Level II-2} Hintz also showed no significant difference in height standard deviation score (SDS) and HV between GHD and idiopathic short stature (ISS).^{12, Level II-2} Using a HV less than 25th percentile to diagnose GH deficiency has a high sensitivity (82%) but poor specificity (43%).^{13, Level II-3} Hence using auxology alone is inadequate for the diagnosis of GHD. Auxology must be interpreted in combination with other parameters.

2.1.2 Biochemical Tests

GH stimulation tests play a critical role in diagnosis of GH deficiency. The most frequently used tests include the insulin tolerance test (ITT) and glucagon stimulation test (GST). Other stimulation tests using pharmacologic agents such as arginine, growth hormone-releasing hormone (GHRH) with or without arginine, levodopa and clonidine have been used.^{14, Level II-2} In local setting, only ITT, GST and arginine stimulation test (AST) are used due to unavailability of other agents.

Peak plasma GH level of <10 mcg/L during GH stimulation tests using pharmacologic agents has been used as the biochemical criteria for the diagnosis of GH deficiency.^{9, Level III; 8, Level II;} Cut-off value of <10 mcg/L is arbitrarily used to define GH deficiency. A minimum of two stimulation tests indicating GH deficiency are required for biochemical confirmation of the diagnosis because of the high frequency of negative results for a single test.^{15, Level II-3}

Insulin growth factor-1 (IGF-1) and Insulin growth factor binding protein-3 (IGFBP-3) are helpful parameters for diagnosis of GH deficiency. IGF-1 concentration level must be carefully interpreted as the values are specific but not sensitive. Many factors such as nutritional status, sex steroid, thyroid hormone and chronic diseases affect IGF-1 concentrations. IGFBP-3 is dependent on age and pubertal

status. Hence reference ranges standardised for age and sex are imperative.^{16, Level III; 13, Level II-3}

The difficulty in diagnosing GH deficiency during the peripubertal period is acknowledged, as low GH levels in stimulation tests frequently occur. Sex-steroid priming prior to GH stimulation tests reduces the percentage of false positive for GH deficiency.^{17, Level 1; 18, Level II-3} Hence sex-steroid priming may play a role in reducing the number of false positive results in the peripubertal children. Children with MPHD should receive adequate adrenal and thyroid hormone replacement before biochemical evaluation of GH deficiency.

GH Testing in the neonate: GH level should be measured in the event of neonatal hypoglycemia in the absence of a metabolic disorder. A random GH measurement in a polyclonal radioimmunoassay of <20 mcg/L would suggest GH deficiency in the newborn. An IGFBP-3 measurement is of value for the diagnosis of GHD infant.^{9, Level III}

ITT is regarded as the gold standard for the evaluation of pituitary growth hormone reserve. In ITT, insulin is administered intravenously to produce a nadir in the plasma glucose level of ≤ 2.2 mmol/L. This is a potentially hazardous procedure and must be done only by an experienced endocrinologist in a tertiary centre.

Pitfalls in biochemical tests: GH in circulation consists of a wide variety of molecular isoforms. As a consequence, assays involving polyclonal antisera give higher results than those based on monoclonal assays. Discrepancy between results obtained from two different assays depends on factors related to the assay (antibody specificity and assay design) and also factors related to individual sample (relative abundance of isoforms present). Therefore it is impossible to compare results from different immunoassays from different laboratories.^{19, Level III}

GH stimulation tests lack precision, accuracy and have poor reliability.^{20, Level III; 15, Level II-3} The lack of reliability of these tests might be improved by performing the same test more than once.^{15, Level II-3} Factors like puberty, genetic target height SDS, height SDS, weight SDS, bone age and the pharmacologic agents used can affect peak plasma GH level.^{15, Level II-3} Spontaneous GH secretion is more specific than pharmacologic testing. However, serial testing is resource intensive and time-consuming.^{21, Level II-2}

2.1.3 Radiological Evaluation

A plain radiograph of the left hand and wrist to assess osseous maturation (bone age) is helpful in making the diagnosis of GH deficiency. A delayed bone age of at least two years compared to chronological age is a feature of GH deficiency. However it is not diagnostic of the condition.

A magnetic resonance imaging (MRI) or computed tomography (CT scan) of the brain with particular attention to the hypothalamic-pituitary region should be carried out in any child diagnosed with GH deficiency. In a cross-sectional study by Nagel et al., presence of ectopic posterior pituitary, missing stalk and hypoplastic anterior pituitary (EMH) on MRI is a significant predictor of permanent severe GH deficiency with or without other pituitary hormone deficiency.^{22, Level III} However, a normal MRI does not exclude GH deficiency. A study by Geralda et al. demonstrated that approximately 20% of the subjects with GH deficiency had mutations of GH-1, GHRH-R, PIT-1 and PROP-1 genes causing permanent disease. All patients with these genetic causes had normal pituitary stalk and normal position of posterior pituitary gland while 50% had pituitary hypoplasia.^{23, Level III}

Recommendation

All of the following criteria must be fulfilled to confirm the diagnosis of GH deficiency:

i. Clinical and auxological criteria:

- Short stature as defined by:
 - Height <3rd centile on the NCHS chart AND/OR
 - Height below target height (TH) range i.e. MPH minus 10 cm AND
- Slow growth as defined by:
 - Downward deviation of height ≥1 centile band over at least 12 months

Children with acquired hypothalamic-pituitary disease are considered to have fulfilled the above criteria if they have slow growth even in the absence of short stature.

ii. Biochemical criteria

A minimum of **TWO** growth hormone stimulation tests using either ITT, GST or AST are needed.

- Peak GH level of <10 mcg/L is diagnostic

Sex steroid priming is useful for peripubertal children. Children with MPH should have received adequate adrenal and thyroid hormone replacement before biochemical evaluation.

iii. Radiological criteria

- Delayed bone age **(Grade C)**

After confirmation of GH deficiency, subsequent investigations should include:

- i. MRI of hypothalamic-pituitary region
- ii. Genetic study (if facilities are available) **(Grade C)**

2.1.4 Criteria for Referral

Patients with the following criteria should be referred to paediatric endocrinologists for further evaluation, confirmation and appropriate therapy for GH deficiency:

- Neonates/infants with features of GH deficiency (refer to section 1.2)
- Children at risk of GH deficiency showing slow growth and/or short stature (refer to section 1.2)
- Children who fulfill the above clinical and auxological criteria for GH deficiency

2.2 TREATMENT OF GROWTH HORMONE DEFICIENCY IN CHILDREN

A healthy child should experience a normal growth and ultimately reach an adult height within his/her TH range.^{24, Level II-2} A child with GH deficiency is expected to be short, growing slowly and have extremely short adult height. Studies had shown that in these children, normalisation of height in childhood and attainment of a normal adult height could be achieved by using the lowest possible cumulative dose of GH.^{25, Level I; 24, Level II-2} Cohort studies had also demonstrated that it is possible to achieve a final height (FH) within TH range in idiopathic GHD patients when treated with GH from an early age.^{26, Level II-2; 27, Level II-2; 28, Level II-3}

The primary objectives for GH deficiency therapy are normalisation of height during childhood and attainment of normal adult height.^{8, Level III}

Target height range is ± 10 cm of the MPH.

Final adult height is achieved when the height gain in a year is < 0.5 cm AND/OR a bone age of ≥ 15.5 years for girls and ≥ 16.5 years for boys.^{29, Level I}

Near-adult height is defined as a bone age of 16 year or more for males and 14 year or more for females and a growth rate less than 2 cm/year for one year

2.2.1 Initiation

GH therapy should begin as soon as possible to optimise long-term growth.^{30, Level II-2} The GH Research Society Consensus Guidelines 2000 recommends that patients with proven GH deficiency should be treated with recombinant human growth hormone (rhGH) as soon as possible after the diagnosis is made. Every effort should be made to diagnose and treat children at the youngest possible age.^{8, Level III}

Prospective cohort and controlled studies had shown good catch-up growth in children when given early rhGH replacement.^{31, 30, Level II-2; 32, Level II-3; 33, Level II-2; 34, Level II-2}

In the National Cooperative Growth Study (NCGS) where rhGH therapy was started at peripubertal age, there was insufficient increase in the child's height SDS before the onset of puberty resulting in failure to achieve target height SDS. Hence early initiation of rhGH treatment and attainment of higher prepubertal height SDS before onset of puberty are important factors to improve FH of GHD children.^{28, Level II-3}

Recommendation

GHD children should be treated with rhGH as soon as possible after the diagnosis is made. **(Grade C)**

2.2.2 Dosage

It has been shown that 84% of GHD patients who received 0.025 mg/kg/day of rhGH for at least 5.4 years reached a FH within the normal population height range.^{35, Level II-3} Findings from the KIGS database (n=1258) showed that those treated from an early age with a median rhGH dose of 0.025 - 0.028 mg/kg/day for at least four years achieved a FH within their TH range.^{27, Level II-3}

Short-term and long-term studies among non-GH naive patients showed that higher dose of rhGH resulted in a significantly greater HV, height for CA and FH without any difference in bone age advancement, onset of puberty, fasting glucose, HbA1c or lipid metabolism.^{36, Level I; 25, Level II-2} A randomised controlled study (RCT) demonstrated that the difference in height SDS at the end of

treatment was significantly increased in those who received 0.05 or 0.1 mg/ kg/d of rhGH compared to those who received 0.025 mg/kg/d. However, another RCT found no significant difference noted in height SDS between those who received 0.05 and 0.1 mg/kg/day.^{37, Level I}

Studies had also demonstrated that catch-up growth and total height gain were greater among the daily-treated patients compared to those who received two, three or four times weekly rhGH injections at the same total weekly dose, with no significant difference in skeletal maturation and onset of puberty.^{38, Level I ; 39, Level II-1}

Studies involving pre-pubertal GH naive patients showed growth responses improved by titrating the GH dose to achieve higher IGF-1 targets or guided by individual GH responsiveness obtained from a prediction model.^{40, Level I; 41, Level I}

Factors that correlated with enhanced adult height were baseline height, younger age at onset of treatment, longer treatment duration especially during pre-pubertal years and a greater growth velocity during the first year of treatment.^{27, Level II-3}

<p>Recommendation</p> <p>GH dose should be started at 0.025 mg/kg/day and adjusted within the range of 0.025 to 0.05 mg/kg/day based on the growth response and IGF-1 level. (Grade A)</p>
<p>rhGH should be given as a daily subcutaneous injection seven days a week. (Grade A)</p>
<p>rhGH therapy should be given uninterrupted for at least four years prior to closure of the epiphyses. (Grade C)</p>

2.2.3 Monitoring

Updates of the GH Guidelines by the LWPES recommend that routine follow-up for paediatric GHD patients should be performed by a paediatric endocrinologist in partnership with the paediatrician or primary care physician and should be conducted on a 3- to 6-monthly basis, to document auxological data, monitor treatment response, compliance and safety. Adequate growth response to GH therapy is evidenced by an increase in HV within the first six month of therapy and an increase of at least 0.25 height SDS over one year period.^{42, Level III}

To ensure adequate dosing, compliance and safety (in the light of association between elevated serum IGF-1 and certain cancers),^{43, Level III} serum IGF-1 and IGFBP-3 should be monitored at least yearly.^{42, Level III} A cohort study with serial measurements at five-time points (baseline, 6 weeks, 3, 6 and 12 months during the first year of GH treatment) showed that IGF-1 levels were highest at 6 weeks and remained relatively constant thereafter. IGF-1 SDS was also found to correlate well with the dose of GH (expressed in IU/m²/week).^{44, Level II-2} A larger increase in serum IGF-1 was associated with more impressive initial growth, and greater first year growth response.^{45, Level II-2}

For patients who display a suboptimal growth response or in whom the IGF levels remain persistently low with assurance of good compliance to injection schedule, it is reasonable to increase the GH dose within the FDA approved dose guidelines (0.025 - 0.050 mg/kg/day in children, or 0.025 - 0.10 mg/kg/day in adolescents). Dose reductions should be considered in patients with serum IGF-1 levels substantially above the normal range after the first two years of therapy. Further treatment is generally futile if no increase in growth rate or serum IGF-1 concentration over baseline is detected within the first 6 to 12 months in a compliant patient receiving an appropriate dose of GH.^{42, Level III}

Growth hormone therapy guided by regular monitoring of bone age (BA) has been shown to be useful in children treated with rhGH. It has been demonstrated that subjects who had BA assessment at entry, during the first year of rhGH therapy and serially for the first three years had higher cumulative height SDS and height age change compared with those subjects without BA values at entry, without BA in the first year and those without serial BA x-rays. It was concluded that subjects with BA monitoring do better than those whose skeletal maturation were not measured.^{46, Level II-3}

One of the most important risks in GH therapy is the incidence of leukaemia and malignancy. In view of this, patients who have a history of childhood cancer or a diagnosis that predisposes them to malignancy should be monitored closely for malignancy.^{47, Level III} Monitoring of free T4 and TSH is of value for detecting hypothyroidism which may be observed during rhGH therapy.^{42, Level III}

rhGH therapy has been shown to reduce insulin sensitivity with a compensatory hyperinsulinaemia and hence increases the risk of type 2 diabetes mellitus (T2DM) in predisposed individuals.^{48, Level II-1; 49, Level II-1} As the dose of rhGH used in children is generally higher than that used in adults, it is not surprising to note that incidence of T2DM was reported as six-fold higher in children

treated with rhGH compared with age-matched untreated children. rhGH might have hastened the onset of T2DM. The study also showed that diabetes mellitus did not resolve after rhGH was stopped, hence excluding a transient drug-induced effect. The author recommended that each child's glucose status should be determined before starting rhGH therapy by measuring HbA1c, fasting plasma glucose and insulin concentration. Follow up of children at risk of T2DM such as obesity, Turner syndrome, intrauterine growth retardation, Prader-Willi syndrome and GH deficiency secondary to other causes is important.^{50, Level II-3}

At the recommended GH dose, a typical growth hormone deficient child accelerates growth from a pre-treatment rate of 3 - 4 cm/year to:

- 10 - 12 cm/year in the first year of therapy
- 7 - 9 cm/year in the second and third year

Progressive waning of GH efficacy then occurs.^{37, Level 1}

Patients who have a history of childhood cancer or a diagnosis that predisposes them to malignancy should be monitored closely for recurrence or second malignancy.

Recommendation

GHD children on rhGH therapy should be routinely monitored for:

- height: 3 to 6 monthly (**Grade C**)
- serum IGF-1: 3 monthly in the first year, then yearly (**Grade C**)
- free T4, TSH: yearly (**Grade C**)
- fasting plasma glucose, HbA1C and insulin: before starting rhGH therapy (**Grade C**)
- HbA1c: yearly or more frequently in patients at risk for type 2 diabetes mellitus (**Grade C**)
- bone age: prior to starting rhGH therapy and yearly thereafter (**Grade C**)

In patient with poor GH response over 6 to 12 months (HV <2 cm/year above pre-treatment HV):

- check patient compliance (**Grade C**)

In compliant patients with poor GH response:

- if IGF-1 is low or normal, increase rhGH dose (**Grade C**)
- if IGF-1 has exceeded the normal range, stop rhGH (**Grade C**)
- if patient is already on the maximum recommended dose, stop hGH (**Grade C**)

2.2.4 Benefits

a. Final Height

Data from the Pfizer International Growth Database (KIGS) showed differences between near-adult height and MPH ranged between -0.6 and -0.2 SDS. Results from Caucasian males with IGHD showed a median SDS of -2.4 at start of treatment and -0.8 at near adult height after rhGH treatment.^{27, Level II-3} Similar results were shown in a subset of Swedish subjects derived from the KIGS database.^{26, Level II-3}

It is possible to attain target height in GHD children with optimal rhGH therapy.

b. Metabolic effects

Several studies have shown that GH therapy improved body composition by increasing lean tissue mass and reducing percentage body fat.^{51, Level II-2; 52, Level II-2; 53, Level II-2; 54, Level II-2}

Other studies have reported improvement in lipid profiles with rhGH therapy: reduction in total cholesterol, low density lipoprotein (LDL) and triglycerides, and increase in high density lipoprotein (HDL).^{48, Level II-1; 52, Level II-2} However, not all baseline lipid profiles are abnormal in children with GH deficiency. Nevertheless, during rhGH therapy the atherogenic index (total cholesterol/HDL) decreased.^{49, Level II-1; 53, Level II-2; 54, Level II-2}

Growth hormone plays an important role in glucose and insulin metabolism. The effect of rhGH therapy on serum insulin concentration has been reported, showing a trend towards reduced insulin sensitivity with a compensatory hyperinsulinaemic response without any untoward effects on glucose metabolism.^{49, Level II-1; 48, Level II-1}

Body composition improves with rhGH therapy in children with GHD.

Abnormal lipid profiles and atherogenic index improves with rhGH therapy.

c. Bone health

Studies had reported decreased levels of bone remodelling markers in children with GH deficiency prior to their treatment with rhGH.^{55, Level II-2; 53, Level II-2} Bone formation and bone resorption markers

are reported to increase significantly during rhGH therapy.^{53, Level II-2}

Areal BMD (aBMD), which is dependent on age, height and weight, is found to be low in GHD children.^{55, Level II-2; 53, Level II-2} Replacement rhGH therapy in these children has shown significant increase in aBMD and volumetric BMD (vBMD).^{55, Level II-2; 53, Level II-2} The mean values of lumbar aBMD and vBMD in treated patients with GHD at final height did not differ from normative data.^{56, Level II-1}

Bone remodelling markers and bone mineral density increase with rhGH therapy in GH deficient children.

d. Cardiovascular effects

GHD children have impaired left ventricular (LV) mass.^{57, Level II-1; 49, Level II-1} In a few prospective case-control studies, the LV mass index was significantly lower in GHD children than in controls and it increased significantly after one year of GH replacement.^{49, Level II-1; 58, Level II-3} In another prospective case control study, GHD children at baseline had normal global systolic function with subtle LV dysfunction. One year of GH treatment was associated with a significant improvement of cardiac size and myocardial contractility.^{57, Level II-1}

GHD children have impaired LV mass and subtle LV dysfunction. rhGH therapy normalises cardiac mass and function. However the clinical significance of these findings remains unclear.

e. Quality of life (QoL)

The most obvious effect of GH is in regards to height and it has been suggested that the impact of GH on QoL relates solely to the influence of height. However, analysis of social parameters does not reveal any impairment in self-esteem, mood and well-being in short children.^{59, Level III} Similarly, there was no direct relationship between QoL and short stature resulting from Turner syndrome, chronic renal failure, GH deficiency or idiopathic short stature when QoL was measured by the time trade off method and the Nottingham Health Profile (NHP).^{60, Level II-1}

In a small cohort study, patients with acquired GH deficiency had QoL significantly below population norms which improved with treatment, whereas the subgroup with idiopathic GH deficiency did not show significant changes.^{61, Level II-2}

In a larger cohort study it was demonstrated that after rhGH therapy, behavioural scores significantly improved in patients with GH deficiency and ISS. Improvement was noted in the internalising subscales (withdrawn, somatic complications and anxiety/depression) and inattention, social problems and thought problems.^{62, Level II-2}

Behavioural scores partially improved in GHD children with rhGH therapy.

2.2.5 Safety

a. Malignancy

rhGH is both anabolic and mitogenic whilst IGF-1 is antiapoptotic. There is much experimental data to suggest that GH treatment acting via local tissue might enhance tumour cell growth. There are concerns that GH treatment may cause new malignancy (de-novo), tumour recurrence or second malignancy in those already treated for one tumour.

- **New malignancy**

Based on the data from the National Cooperative Growth Study (NCGS) in the United States and Canada, it was shown that the incidence of leukaemia in rhGH-treated patients without risk factors for leukaemia was comparable to that in the general population of age-matched children.^{63, Level II-3} Similarly in Japan, the incidence of leukaemia in rhGH-treated patients without risk factor is no greater than in the general population aged 0-15 years.^{64, Level II-3}

- **Recurrent malignancy**

Data from the Childhood Cancer Survivor Study (CCSS) showed that the relative risk (RR) of disease recurrence (first recurrence) was 0.83 for rhGH-treated survivors compared with those not treated with rhGH.^{47, Level II-3} The NCGS data (n=1262 children with brain tumour) demonstrated an overall recurrence rate of 6.6% over 6,115 patient-years follow up.^{65, Level II-3} GH outcomes from KIGS (Pfizer International Growth Database with more than 50,000 patients treated with rhGH) noted that the frequency of recurrence was 11.7% for craniopharyngiomas, 4.7% for medulloblastomas, 8.8% for ependymomas, 4.0% for germinomas and 9.8% for astrocytomas/gliomas.^{66, Level II-3}

In a case-control study of patients with craniopharyngioma, there was no evidence that rhGH replacement was associated with an increased risk of tumour recurrence; 12.5% treated with rhGH developed tumour

recurrence compared to 41.5% of those with no treatment.^{67, Level II-2} In a study that analysed cases of medullablastoma, there was no association between the use of rhGH and progression-free survival in infants or older children.^{68, Level II-3}

- **Second malignancy**

The CCSS also showed the RR of a secondary neoplasm for rhGH-treated survivors compared with those not treated with rhGH was 3.21. The overall increase was driven by a small excess number of second neoplasms in the subgroup of acute leukaemia survivors (RR= 4.98). This increase is of concern but the data needs to be interpreted with caution given the small number of events.^{47, Level II-3} The elevation of risk due to rhGH use appears to diminish with increasing length of follow up.^{69, Level II-3}

All above reported studies have significant limitations. However, a RCT cannot be performed due to ethical concerns. With some data suggesting a possible increase in new cancers in patients treated with rhGH, there is a need for continued surveillance.

There is no evidence that leukemia (de novo or relapse) or CNS tumour recurrence is increased with rhGH therapy.

There is insufficient evidence with regards to risk of secondary neoplasms with rhGH therapy.

- b. Benign intracranial hypertension (BIH)**

BIH has been recognised as an early complication of rhGH.^{70, Level II-3} It has been reported in GH deficiency but also in other conditions treated with rhGH including chronic renal insufficiency (CRI), Turner syndrome (TS), Prader-Willi syndrome (PWS), glucocorticoids usage and delayed puberty. Children receiving rhGH for CRI are more likely to develop BIH.^{71, Level II-3}

Based on a national database of rhGH-treated children in Australia and New Zealand, the incidence of BIH was low i.e. 1.2 per 1,000 cases.^{72, Level II-3}

The KIGS database showed that BIH occurred in 41 children resulting in a total incidence of 27.7 per 100,000 treatment-years. The incidence was significantly lower in patients with idiopathic GH deficiency than

in those with TS ($p=0.0004$), congenital GH deficiency ($p=0.0064$), PWS ($p=0.0263$) and CRI ($p<0.001$). No cases of BIH were reported in the idiopathic short stature (ISS) group of patients. The median duration from onset of GH therapy to BIH ranged from 0.01 to 1.3 years.^{73, Level II-3}

BIH is known to occur in patients on rhGH therapy.

c. Bone health

Different studies reported different prevalence of scoliosis. The NCGS database ($n=24,000$) reported fewer than 1% of the patients had scoliosis (prevalence of scoliosis in the general population was between 1.5 to 3.0%).^{63, Level II-3} In a retrospective study ($n= 250$) of children treated with rhGH, 4% developed scoliosis.^{74, Level II-3} A cohort study (OZGROW) showed that TS girls receiving rhGH therapy have a high prevalence of scoliosis (28%).^{75, Level II-2}

The International Cooperative Growth Study (ICGS) demonstrated that Perthes' disease developed in 12 boys (69.9 per 100,000 patient-years). Neither recurrence nor aggravation of Perthes' disease was observed during the rhGH therapy.^{76, Level II-3}

In the ICGS database, slipped capital femoral epiphyses (SCFE) developed in four cases with GHD and other pituitary hormones deficiency during GH therapy (21.5 per 100,000 patient years). Two of the patients had radiation therapy and 2 were obese. No aggravation of SCFE was observed during the rhGH therapy.^{76, Level II-3}

Data from NCGS showed that SCFE was significantly less common in children with ISS compared with GH deficiency on rhGH therapy.^{71, Level II-3} The KIGS database reported an incidence of 73.4 per 100,000 treatment-years of SCFE. The incidence was significantly lower in patients with IGHD (18.3 per 100,000 treatment-years) and ISS (14.5 per 100,000 treatment-years) than TS (84.5 per 100,000 treatment-years), cranial tumours (86.1 per 100,000 treatment-years) and craniopharyngioma groups (120.5 per 100,000 treatment-years). No cases of SCFE were reported in the SGA and PWS groups. The median duration from onset of GH therapy to SCFE ranged from 0.4 to 2.5 years.^{73, Level II-2}

There is insufficient evidence to suggest a causal relationship between rhGH therapy and scoliosis. However the prevalence of scoliosis is high in TS girls.

Children with organic causes of GH deficiency on rhGH therapy have an increase frequency of slipped capital femoral epiphyses.

d. Glucose metabolism

A study evaluated the impact of rhGH therapy on glucose metabolism in children and young adults with idiopathic GH deficiency and showed no significant change after one year of rhGH therapy (0.024 mg/kg/day).^{77, Level III} In another study, rhGH therapy in GHD children did not lead to an impaired glucose tolerance (IGT) or T2DM, although it significantly decreased insulin sensitivity.^{78, Level II-1}

The NCGS reported that the majority of patients who developed diabetes mellitus during rhGH therapy had an identifiable risk factor. The incidence of permanent diabetes in others is similar to that reported in American adolescents.^{71, Level II-3} In contrast, the KIGS database demonstrated an increased frequency of T2DM in children and adolescents receiving rhGH. Of the 43 who were confirmed to have glucose disorders, 11 had type 1 diabetes (T1DM), 18 had T2DM and 14 had impaired glucose tolerance (IGT). There was no increase in the incidence for T1DM but the incidence for T2DM (34 cases per 100,000 patient-years) was approximately six-fold higher than in children not treated with rhGH.^{50, Level II-3}

rhGH therapy decreases insulin sensitivity without impairing glucose tolerance.

The risk of T2DM may be increased in individuals on rhGH therapy.

e. Skin

There are concerns that rhGH may cause skin cancer in pre-existing pigmented naevi. The NCGS database reported 13 cases of increase in pigmented naevi during rhGH therapy.^{71, Level II-3} However, biopsies have not detected neoplasia or pre-malignant naevi transformations.^{63, Level II-3} Studies have shown that there were no difference in the naevi count between the children with GH deficiency and control group despite many years of rhGH therapy. However, children with TS had more naevi, but there was no relation to the duration of rhGH therapy and frequency of skin cancer.^{79, Level II-2; 80, Level II-2; 81, Level II-2}

There was no increase in melanocytic naevi or risk of skin cancer in GHD patient on rhGH therapy.

Melanocytic naevi were more common in TS but there were no increased frequency of skin cancer with rhGH therapy.

Other side effects are relatively rare. These include acute pancreatitis, gynaecomastia, oedema, lymphoedema and carpal tunnel syndrome.^{71, Level II-3}

3. USE OF GROWTH HORMONE IN NON-GHD CHILDREN

3.1 TURNER SYNDROME

Turner Syndrome (TS) is a genetic disorder due to abnormalities of the X chromosome resulting in an array of genetic, developmental, endocrine, cardiovascular, psychosocial and reproductive issues.^{82, Level II-2} It affects approximately one in every 2,500 liveborn females. Majority of these patients have extreme short stature, gonadal dysgenesis and hypogonadism with a normal intellectual performance and language abilities. However, visual-spatial and/or visual-perceptual abilities are impaired. The average height of untreated women with TS is 143 cm and is approximately 20 cm below the TH.^{83, Level II-1} However, they are able to reach normal adult height with high doses of rhGH.^{84, Level II-3}

3.1.1 Outcome of rhGH Therapy

a. Final height

In a recent Cochrane Systematic Review, it was shown that rhGH was effective in improving growth and FH in girls with TS.^{85, Level I; 86, Level II-1} The FH was 148 cm (1.4 ± 1.0 SD Turner chart) and 141 cm (0.2 ± 0.9 SD Turner chart) in the treated and untreated women respectively.^{86, Level II-1}

Factors affecting height gain [from start of rhGH therapy to attainment of near-adult-height (NAH)] include:^{87, Level III}

- Mid-parental-height
- Height at start of rhGH
- Index of responsiveness during first year on rhGH
- Mean dose of rhGH per week
- Age at start of puberty
- Age at start of rhGH
- Duration of rhGH therapy
- Birth weight

b. Cognitive function and psychological adjustment

The same Cochrane Review showed the possibility that girls treated with rhGH have a better psychological adjustment than untreated girls.^{85, Level I} However, there were no demonstrable effects on cognitive function, visual-spatial and/or visual-perceptual abilities.^{88, Level III}

c. Bone/body composition

rhGH therapy had little effect on cortical or trabecular BMD in girls with TS. However, rhGH therapy was associated with an increase in lean body mass and reduced adiposity.^{89, Level II-2}

3.1.2 Time to start rhGH

rhGH therapy should be considered as soon as falling height percentile is demonstrated in the linear growth of the child with TS and the decision to start rhGH is best directed by a paediatric endocrinologist.

^{90, Level III; 9, Level III}

3.1.3 Dose

rhGH doses range from 0.045 to 0.055 mg/kg/day. The current practice is to administer subcutaneous injection of rhGH 6 or 7 days per week.

^{85, Level I}

3.1.4 Oestrogen Therapy

Timing of introduction of oestrogen replacement is an important determinant of FH in rhGH-treated TS patients. Oestrogen replacement should not be started before the age of 12 years.^{85, Level I} TS patients in whom oestrogen was delayed until 15 years of age gained an average of 8.4 ± 4.3 cm over the projected FH whereas those who started oestrogen at 12 years old gained only 5.1 ± 3.6 cm. This study concluded that the duration of rhGH therapy before oestrogen replacement was a strong factor in predicting height gain.^{91, Level II-2}

However, the timing of oestrogen replacement should also take into consideration the importance of age appropriate pubertal maturation, bone health and psychosocial stress of delayed sexual maturation.

^{90, Level III; 92, II-3; 93, Level III; 84, Level II-3} The dose of oestrogen should be

increased gradually over a duration of two to three years to achieve pubertal maturation at a normal pace. The starting dose of conjugated oestrogen (premarin) should be at 0.3 mg every other day or 5 mcg ethinyl oestradiol daily. The dose should be increased gradually every 12 months to premarin 0.625 mg daily or ethinyl oestradiol 20 mcg daily when medroxyprogesterone acetate (provera) 5 mg daily for 12 days will be introduced to initiate cyclical uterine bleeding.^{93, Level III}

3.1.5 Duration of Treatment

rhGH therapy may be continued until a satisfactory height has been attained or until the bone age is 14 years or near FH is attained.^{90, Level}

^{III; 9, Level III}

3.1.6 Monitoring

Patients should be monitored as any other patients on GH therapy. IGF-1 should be monitored to ensure value within ± 2 SD.^{90, Level III}

3.1.7 Adverse Reactions of rhGH Therapy

Long-term surveillance showed that adverse effects are rare, but can be serious. Girls with TS on rhGH therapy were at increased risk for diabetes mellitus, SCFE, idiopathic intracranial hypertension, oedema, lymphoedema or scoliosis.^{85, Level I} The Genentech Drug Safety Department received 117 serious adverse events out of 5,220 patients on rhGH therapy where seven deaths were reported (five from aortic dissection/rupture) and 10 new-onset malignancies including six in patients without known risk factors.^{94, Level II-2} However, rhGH therapy does not seem to affect the diameter of ascending or descending aorta.^{90, Level III}

Recommendation

Turner syndrome with short stature should be considered for rhGH therapy and be referred early to a paediatric endocrinologist. **(Grade A)**

Oestrogen replacement therapy in TS children should not be initiated before the age of 12 years. **(Grade A)**

3.2 SMALL FOR GESTATIONAL AGE

Small for gestational age (SGA) is defined as birth weight and/or birth length of ≥ 2 SD below the mean for gestational age. Approximately between 2.3 and 10% of all infants are born SGA. Most SGA infants achieve appropriate catch-up growth by two years of age. However, approximately 15% do not catch-up and continue to experience poor growth throughout childhood.^{95, Level III} Catch-up growth is considered to have been achieved when the child's height is at or above -2 SD for age.^{96, Level III}

3.2.1 Outcome of rhGH Therapy

a. Final height

After adjustment for gender and TH, SGA subjects were significantly shorter (men 4.5 cm shorter and women 3.9 cm shorter) than those with a normal birth weight at age 20 years.^{97, Level II-1} It was shown that when rhGH therapy (0.033 or 0.067 mg/kg/day) was commenced at 8

years of age and continued for 7 - 8 years, adult height increased by ≥ 1 SD.^{98, Level III} rhGH therapy resulted in an adult height above -2 SDS in 85% of the children after a mean treatment period of 7.8 years. There is no significant difference in height gain between the low dose rhGH group (0.033 mg/kg/day) and the high dose rhGH group (0.067 mg/kg/day).^{99, Level II-1}

b. Cognitive function and psychological adjustment

There is inconclusive evidence that rhGH improves IQ in short SGA children. Long-term outcome data for children born SGA show no difference in frequency of employment, marital status or satisfaction with life. However, these individuals hold fewer professional or managerial jobs and have significantly lower income than individuals of normal size at birth.^{98, Level III}

c. Body composition

rhGH therapy in short children born SGA was shown to improve body composition, blood pressure and lipid metabolism.^{95, Level III; 97, Level II-1} In a 6-year multicentre RCT, normalisation of BMI was not accompanied by overall changes in percentage body fat but was accompanied by an increase in muscle mass. The long-term clinical significance of these changes is uncertain.^{100, Level II-1}

d. Bone Mineral Density

Bone maturation increases proportionately to height gain with rhGH therapy. Mean values of bone mineral apparent density (BMAD) (-0.6 SDS) were significantly reduced at start but normalised (0.3 SDS) during rhGH therapy.^{101, Level II-1}

e. Cardiovascular risk

Children born SGA have an inherent risk of cardiovascular disease and dyslipidaemia in later life. A 4-year study of children born SGA treated with rhGH showed that those who had elevated systolic blood pressure before treatment had a reduction in blood pressure over time.^{100, Level II-1} A six-year RCT demonstrated that total cholesterol and low-density lipoprotein cholesterol (LDL) decreased significantly by the end of the study.^{99, Level II-1}

3.2.2 Time To Start

Early intervention with rhGH can be considered for short (height below -2.5 SD) SGA children without a catch-up growth. With reference to normal population standards, 44% of infants had caught-up at three months of age, 51% at three years, 66% at four years and 73% at six years.^{102, Level II-3} In most published studies, rhGH therapy was initiated after five years of age.^{103, Level III}

The European Agency for the Evaluation for Medicinal Products (EMA) approved rhGH use to treat growth retardation in short SGA children (birth weight and/or birth length below -2 SD) with:^{104, Level III}

- Height SDS <-2.5 and parental-adjusted height SD <-1.0
- Absence of catch-up growth (HV <0 SD during the last one year)
- Age of start of treatment >4 years
- Recommended GH dose is 0.035 mg/kg/day

3.2.3 Safety and Adverse Reactions

Adverse events are not more common in this population than in other conditions treated with rhGH, nor have additional safety concerns arisen.^{105, Level III; 95, Level III; 106, Level III; 100, Level II-1}

a. Insulin resistance

There is no evidence that T2DM, IGT or dyslipidaemia occurs more commonly among children born SGA than in the normal childhood population. Although children born SGA tend to develop higher fasting insulin level and relative insulin resistance during rhGH therapy, these changes appear to be largely reversible when treatment is terminated.^{105, Level III; 95, Level III; 106, Level III; 100, Level II-1}

b. Bone age acceleration

Hokken-Koelega and colleagues showed that rhGH therapy is associated with an acceleration of bone maturation especially in the first two years regardless of the rhGH dose given.^{101, Level II-1}

c. Risk of malignancy

There is no evidence that the risk of malignancy is increased with rhGH therapy.^{105, Level III; 95, Level III; 106, Level III; 100, Level II-1}

d. Benign intracranial hypertension

As in other children treated with rhGH, BIH is a rare complication of rhGH therapy in children born SGA, occurring in approximately 1 in 1000 individuals.^{105, Level III; 95, Level III; Lee 106, Level III; 100, Level II-1}

e. Other concerns

It is currently unknown whether rhGH therapy for SGA subjects through childhood and adolescence is associated with future benefits or amplification of metabolic risks in adult life. There is no long-term surveillance data on adults who have been treated with rhGH for short stature due to SGA. It is therefore prudent to follow up this group systematically.^{105, Level III; 95, Level III; 106, Level III; 100, Level II-1}

Recommendation

SGA children who remained short (<3rd percentile) after 4 years of age should be referred to a paediatric endocrinologist for evaluation and consideration of rhGH therapy. **(Grade C)**

3.3 IDIOPATHIC SHORT STATURE

Idiopathic short stature (ISS) is used to describe children who are very short for their age for unknown reason. Precise estimates for incidence and prevalence of ISS are difficult to obtain. A systematic review showed that 5 - 9% of the shortest 3% of the population did not reach an adult height above -2 SD. This accounts for 0.2% of the normal children population.^{107, Level 1}

3.3.1 Outcome Of rhGH Therapy

a. Final height

In a systematic review by Bryant J et al, a study reported that ISS patients treated with rhGH for 6 months to 6.2 years showed that near-final-height in girls were 7.5 cm taller than untreated controls (mean height of 155.3 ± 6.4 cm and 147.8 ± 2.6 cm for GH-treated and control group respectively). Another study reported an adult height of 3.7 cm taller in the GH-treated group compared with the control. Other studies suggested that short-term height gain can range from none to approximately 0.7 SD over one year.^{107, Level 1} FH measurements were within the normal adult height range for 94% of patients who received rhGH at a dose of 0.37 mg/kg/week (0.053 mg/kg/day).^{108, Level I} Lee et

al. estimated that the potential cost of rhGH therapy is around USD 52,000 per 2.54 cm gain in height.^{107, Level 1}

b. Quality of life (QoL)

There was a significant improvement in QoL in rhGH-treated ISS children compared with the control, while no significant impact on psychological adaptation or self-perception was found.^{107, Level 1}

c. Psychosocial Functioning

Children with ISS were perceived to have psychosocial distress due to their short stature. Visser-van BH et al. showed that rhGH therapy did not improve psychosocial functioning.^{109, Level II-3} There was no difference in the psychosocial variables between the rhGH-treated and untreated subjects. Compared with the Dutch population norms, psychological and social functioning in ISS children was normal.^{110, Level II-2}

3.3.2 Dose

rhGH doses range from 0.30 to 0.37 mg/kg/week (0.043 - 0.053 mg/kg/day). The mean overall height gain (final height minus baseline predicted height) was 7.2 cm and 5.4 cm for 0.053 mg/kg/day and 0.034 mg/kg/day rhGH dose groups respectively. No dose effects on safety parameters were noted. The dose of 0.053 mg/kg/day rhGH was found to be effective to achieve normal adult height in 94% of patients.^{108, Level I} In patients with ISS, rhGH dose at 0.053 mg/kg/day did not appear to accelerate pubertal onset, pace, or bone maturation compared with rhGH dose at 0.034 mg/kg/day.^{111, Level III; 112 006, Level II-2;}

3.3.3 Adverse Reactions

No serious adverse effects of treatment were reported in a Cochrane Systematic Review 2007. A GH registry on ISS patients reported a safety profile similar to GHD patients.^{113, Level II-3}

Recommendation

rhGH should not be routinely prescribed in ISS patients for the following reasons:

- inconsistent height gain with rhGH therapy
- high dose requirement (cost issues)
- absence of psychological and social malfunctioning in ISS without therapy **(Grade C)**

3.4 FAMILIAL/ GENETIC SHORT STATURE

Familial short stature (FSS) is a condition characterised by height below the 3rd percentile for age, normal growth velocity, family history of short stature in one or both parents and normal physical examination (including body proportion). These children have normal bone age (appropriate for chronological age), normal puberty and their expected adult height is below the 3rd percentile but within the TH range (MPH \pm 10 cm).

3.4.1 Outcome of rhGH Therapy

rhGH therapy has not been proven to improve remarkably FH of children with FSS. A small RCT using two different doses (20 or 40 IU/m²/week equivalent to 0.031 or 0.063 mg/kg/day) of rhGH in FSS showed no difference in their adult height outcome. The incremental effect of both doses on stature was minimal.^{114, Level II-3}

Recommendation

rhGH should not be used in familial/genetic short stature. **(Grade C)**

3.5 CHRONIC RENAL INSUFFICIENCY

Growth retardation in chronic renal insufficiency (CRI) is influenced by factors such as nutritional insufficiency, endocrine and metabolic alteration, glucocorticoid and other immunosuppressive therapy. Despite adequate renal replacement therapy, growth retardation may persist. Studies have shown that rhGH therapy in supraphysiological doses may improve the growth velocity of these children significantly. However the cost of therapy is very high.

3.5.1 Outcome of rhGH Therapy

Renal failure is a state of growth hormone resistance and not growth hormone deficiency. The FH of CRI patients treated with rhGH improved by 0.5 - 1.7 SDS in 15 RCTs, whereas the control group lost by 0.5 SDS in comparable time interval. When a higher dose (0.05mg/kg/day) was used, the resulting height velocity in the first year was 3.8 cm/year above the untreated patient. The growth response to rhGH therapy is negatively correlated with age, height at start of rhGH therapy and duration of dialysis.^{115, Level I} The highest treatment success is obtained if treatment is started at an early age and with relatively well-preserved residual renal function.^{116, Level III} Although rhGH therapy has been used in all stages of CRI, the AACE Guideline 2003 has not recommended rhGH therapy for post-transplantation patients unless it is given as part of a research study.^{9., Level III}

3.5.2 Adverse Reactions of rhGH Therapy

The frequency of reported side effects of rhGH in CRI patients was similar to that of the control group. They were wheezing, acute rejection in transplanted patients, deterioration in kidney function, raised fasting glucose, papilloedema, glucose intolerance, granuloma formation, lymph node swelling, claudication, hypertension and worsening of pre-existing idiopathic scoliosis. Three trials reported no significant difference in glucose intolerance in patients on rhGH therapy. Nine trials reported that kidney function did not differ between the treated and untreated groups. Only one trial demonstrated a significant increase in wheezing in the rhGH group compared to the control group.^{115, Level I}

Recommendation

In local setting, rhGH therapy should not be given to short children with CRI. **(Grade C)**

3.6 PRADER-WILLI SYNDROME

Prader-Willi Syndrome (PWS) occurs in 1 in 10,000 to 1 in 16,000 live-born infants.^{117, Level III} It is caused by paternal deletion or maternal disomy of genes on the long arm of chromosome 15. Apart from short stature and mental retardation, these children have excessive body fat, decreased muscle mass, sleep disturbances and central apnoea.^{118, Level II-1; 117, Level III}

3.6.1 Outcome of rhGH Therapy

The body composition improved but did not normalise. Lean body mass (LBM) improved at near-adult-height but remained low. Body fat percentage and fat/lean ratio improved during the first year of rhGH therapy but returned to pretreatment state at near-adult-height. rhGH intervention is likely to provide benefits other than improvement of adult height.^{118, Level II-1} In 2003, the European Union has approved rhGH for improvement of linear growth and body composition in children with PWS. United States Food and Drug Administration (FDA) approved indication for rhGH use limited to documented growth failure in PWS.

In a study by Lindgren et al, all patients reached near-adult height within mid-parental height median -0.5 SDS (range -1.4 to 0.7) and 0.9 SDS (range 0.1 to 1.9) for girls and boys, respectively.^{118, Level II-1}

3.6.2 Adverse Reactions

a. Death during rhGH therapy

In a mini review of 13 mortality reports, 10 out of 13 PWS children died of respiratory insufficiency. The highest risk of mortality occurred during the first 7 months of rhGH therapy.^{119, Level III}

b. Respiratory

PWS children had an increased risk of central apnoea. However, six months of rhGH therapy did not aggravate the sleep-related breathing disorders in young PWS children.^{120, Level II-2}

c. Carbohydrate metabolism

Studies have shown that fasting insulin was significantly increased at 12 months and returned to baseline between 24 and 36 months of rhGH therapy. All PWS children receiving rhGH therapy had normal levels of insulin, glucose, insulin to glucose ratio and HOMA-IR during the entire study.^{120, Level II-2; 121, Level II-3}

However, in the KIGS database (n= 22), one patient developed impaired glucose tolerance (IGT) and another T2DM when their weights increased rapidly over six months (gained >10 kg). In the patient with IGT, glucose levels normalised after weight reduction.^{122, Level II-1}

d. Scoliosis

The prevalence of scoliosis in children with PWS is high (37.5%) and increases with age.^{123, level II-3} However, the prevalence of scoliosis is not higher in PWS patients receiving rhGH therapy.^{124, Level III; 125, Level II-2} Many children with scoliosis (13%) had undergone brace treatment or surgery.^{123, level II-3}

In local setting, PWS are generally very obese with high risk of central apnoea at presentation. rhGH dose based on their body weight is likely to be very high and hence very expensive.

Recommendation

rhGH therapy should not be given to children with PWS. **(Grade C)**

3.7 NOONAN SYNDROME

Noonan Syndrome (NS) is a multiple congenital abnormality syndrome characterised by short stature, mental retardation, distinctive facial appearance, congenital heart defects, thoracic deformities and cryptorchidism. The incidence of NS is estimated to be between 1:1000 and 1:2500 live births. It is a hereditary autosomal dominant disorder but 60% of the cases are sporadic. Mutation of PTPN11 gene accounts for approximately 50% of all cases.^{126, Level II-3; 127, Level II-3; 128, Level II-2}

3.7.1 Outcome of rhGH Therapy

a. Final height

FH gain was variable with rhGH therapy in Noonan patients. Some rhGH-treated NS patients had no or only small increases in final adult height. The poor FH may be partly explained by PTPN11 gene mutation which is associated with lower basal height and possibly poor response.^{129, Level III}

In the KIGS Database (n=402) of patients treated with rhGH therapy for 4 to 12 years, the median increment in final height was 0.6 SDS.^{127, Level II-3} In an uncontrolled study of 29 patients (22 patients had PTPN11 mutation) using high dose of 0.05 mg/kg/day over 3.0 to 10.3 years, mean height gain was 1.3 SDS (range from +0.2 to +2.7).^{126, Level II-3}

3.7.2 Adverse Reactions

NS patients with hypertrophic cardiomyopathy may be at risk from rhGH therapy because of the effect of rhGH on cardiac muscle mass. These patients have generally been excluded from trials of rhGH therapy.^{126, Level II-3; 128, Level II-2} Possible abnormal anabolic effects of rhGH on myocardial thickness are not confirmed, and none of the rhGH-treated NS patients develop hypertrophic cardiomyopathy.^{128, Level II-2}

In local setting, rhGH cannot be recommended for short children with Noonan syndrome in view of the high dose and cost, a wide variation of growth response and the uncertainty of rhGH on cardiovascular safety.

Recommendation

rhGH therapy should not be given to children with Noonan syndrome.
(Grade C)

3.8 RUSSELL-SILVER SYNDROME

The incidence of Russell-Silver Syndrome (RSS) is 1:100,000 live births. Key features of RSS include intrauterine cum postnatal growth retardation, triangular facies and limb asymmetry. There is a tendency for fasting hypoglycaemia in early childhood and genital dysmorphism (cryptorchidism, hypospadias and hypogonadism).

3.8.1 Growth Response with GH Therapy

Recent data suggested that RSS exhibit abnormal pulsatility of GH secretion. There were very few studies on RSS. In an earlier review it was suggested that FH outcome can be improved by using pharmacological doses of rhGH. However the number of RSS patients was very small.^{130, Level III; 131, Level III} Height gain (+1.3 SD) was the same in SGA and RSS, but final adult height is lower in RSS as they were shorter at baseline.^{132, Level III}

Recommendation

rhGH should not be given to children with Russell-Silver syndrome. (Grade C)

3.9 SKELETAL DYSPLASIA

The incidence of skeletal dysplasia is at least 30 - 45 in every 100,000 newborn. Skeletal dysplasia comprises a large and heterogeneous group of disorders affecting the development of the skeleton. Achondroplasia (ACH) and hypochondroplasia (HCH) are the most common. ACH has an estimated incidence of about 4 - 5 per 100,000.^{133, level III; 134, level II-3} ACH is characterized by short-limb dwarfism, a relative macrocephaly with prominent forehead, midfacial hypoplasia, lumbar lordosis and a trident configuration of hands and hydrocephalus.

In addition to prepubertal growth failure, ACH patient have decreased pubertal growth spurt. The FH in untreated ACH is 131.5 and 125 cm for boys and girls respectively.^{135, level III} HCH is phenotypically milder than ACH with a FH of 145.0 to 165.0 cm in untreated boys and 133.4 to 150.6 cm in untreated girls.^{134, level II-3}

3.9.1 Goals of GH Treatment

First year response to rhGh therapy is typically a 2 - 3 cm increase in growth velocity in prepubertal children with skeletal dysplasia, or a height gain of 0.5 SDS or less from a baseline level of -4 to -5 SDS.

rhGH therapy for up to five years in ACH can produce a total height gain of about 1 SDS. However, FH data is lacking. The body proportion (trunk to leg length ratio) does not seem to be affected by rhGH therapy.^{133, level III;}

rhGH therapy is unlikely to improve the height of ACH to within normal range for the population. On the contrary, rhGH therapy can worsen scoliosis during pubertal growth and also the stature. Surgical limb lengthening is a better alternative for these patients.^{135, level III}

The height improvement was much greater in HCH than in ACH. With three years of rhGH therapy, the mean increase in height SD for ACH was negligible (-0.2 SD to 0.1 SD) but was better in HCH (1.2 SD to 2.6 SD).^{134, level II-3}

Recommendation

rhGH therapy should not be used for skeletal dysplasia. **(Grade C)**

4. USE OF GROWTH HORMONE IN TRANSITION PATIENT

The primary goal of rhGH therapy in children is to achieve a final height (FH) which is consistent with the target height (TH). It is a common practice to discontinue rhGH therapy after attainment of FH when growth is completed. This period of adolescence after attainment of FH until 6 to 7 years later (approximately from 17 to 25 years old) is termed the transition period. This period encompasses a broad set of physical and psychosocial changes.^{136, level III}

The new goal of rhGH therapy in the transition period is normalisation of metabolism and improvement in quality of life.

4.1 WHO SHOULD CONTINUE GH THERAPY?

It has been reported that 71.9% of childhood-onset growth hormone deficient (COGHD) children continue to be GHD in adult life and are likely to require further rhGH therapy.^{137, level II-2} However, a substantial proportion of children with isolated IGHD recover normal GH reserve by the time FH is attained^{138, level II-1; 139, level II-3} especially in those who were previously diagnosed to have partial GH deficiency.^{140, level II-3} Patients with MPPHD, with or without structural pituitary or peri-pituitary disease^{141, level II-3; 138, level II-1} and/or previous cranial radiation therapy are more likely to have ongoing GHD.^{139, level II-3} Studies also found that in the presence of two or more additional hormones deficiency (≥ 3 pituitary hormones deficiency), all patients had a pathological GH response during re-testing.^{142, level II-2; 138, level II-1} A prospective study on adults with a history of either adult-onset hypothalamic-pituitary disease or COGHD demonstrated that the positive predictive values (PPVs) for GH deficiency in these subjects with three and four pituitary hormones deficiency were 96% and 99% respectively.^{142, level II-2}

In those who had been exposed to cranial irradiation (median dose 58 Gy) during childhood, it was demonstrated that 48% did not fulfill the biochemical criteria (peak stimulated GH < 3 mcg/L) for rhGH replacement in adulthood.^{143; level II-2} It was also found that location of the ectopic posterior pituitary at the median eminence and absence of a visible stalk on MRI were predictors of severe GHD. However, only 61% of patients with COGHD and the above abnormal MRI findings remain severely GHD in adulthood. All of those with associated MPPHD continued to have severe GHD in adulthood.^{141, level II-3; 144, level II-2}

The AACE 2009 guidelines recommend that all patients with COGHD should be re-evaluated using a GH stimulation test at completion of

growth except those with organic causes of hypothalamic-pituitary disease, presence of at least three pituitary hormones deficiency and serum IGF-1 below the given laboratory reference range of <-2 SD. Repeat screening for GH deficiency should be performed by paediatric endocrinologists at least one to three months after cessation of rhGH therapy.^{145, level III}

Recommendation

All patients with COGHD should be re-tested at completion of growth **EXCEPT** for those with:

- organic hypothalamic-pituitary disease

AND

- ≥ 3 pituitary hormone deficiencies

AND

- serum IGF-1 below -2 SD

(Grade C)

4.2 RE-TESTING OF GHD PATIENTS

There are scarce data regarding the optimal pharmacologic agent for GH stimulation test in the transition period. The functional dynamics of GH secretion are different in growing children and in those who have reached FH, leading to different definitions of GHD in children and in young adults. The committees from various established consensus guidelines have recommended ITT as the standard test to re-evaluate GH reserve in adolescents during the transition period.^{145, level III; 146, Level III; 136, level III, 42, level III} A mean peak GH response to ITT in those with high probability of permanent GH deficiency was significantly lower compared to controls.^{147, Level II-2}

A Consensus Statement (2007) has recommended a peak stimulated GH cut-off of less than 6 mcg/L for the diagnosis of permanent GH deficiency in young adults with COGHD.^{146, Level III} However, the accuracy of ITT was recently evaluated and the best diagnostic accuracy was found to be 5.62 mcg/L or less.^{148, level II-1} The glucagon test has been shown to be as good as the ITT in assessing GH reserve in hypopituitary adults.^{149, level II-2; 150, level II-2} A case-control study demonstrated that glucagon test reliably identified patients with GH deficiency using a cut-off peak stimulated GH of 3 mcg/L with a sensitivity and specificity of 97% and 88% respectively.^{149, level II-2} It was also demonstrated that serum IGF-1 in a patient who has discontinued rhGH treatment may be helpful in identifying persistent GH deficiency. However, serum IGF-1 may not fall below normal levels until six months after rhGH therapy is discontinued.^{144, level II-3} Various studies

showed different IGF-1 cut-off points for persistent GH deficiency i.e. -1.7 SDS¹⁴⁷, level II-2, <-2 SDS¹³⁷, level II-2 and ≤ -2.83 SDS.¹⁴⁸, level II-1

Insulin tolerance test (ITT) is the preferred stimulatory test to re-assess patients with COGHD during the transition period.

A peak stimulated GH value of 5.6 mcg/L or less in response to ITT has the best accuracy for diagnosing permanent GH deficiency.

Glucagon test is a good alternative to ITT.

Recommendation

ITT should be used to re-test COGHD patients during transition period. **(Grade B)**

4.3 DOSE OF GH

In a large RCT of young adults with GH deficiency randomised to rhGH doses of 25 mcg/kg/day (paediatric dose), 12.5 mcg/kg/day (adult dose) or no GH treatment, there were no treatment differences between the two rhGH doses but there was significant improvement when compared to the control in body composition in the rhGH arms compared to the placebo arm. This study also suggested that dose requirements may have to be adjusted for gender, as females requiring a higher dose to normalise IGF-1 than males.¹⁵¹, level 1

Using the same cohort of patients to study the effect of rhGH therapy on bone, it was shown that there were no significant changes in bone turnover markers, bone mineral content (BMC) and BMD between the 2 rhGH doses but significant improvement as compared with the control. However, this study favoured the lower paediatric dose for bone mass accumulation as the higher paediatric dose in GHD young adults causes a predominant bone resorption over bone formation.¹⁵², level 1

In an earlier smaller RCT, comparing outcomes of two years treatment with rhGH (12.5 or 25.0 mcg/kg/d) and placebo, the LBM and FM changed from baseline to the end point exhibited a significant dose dependency. Improvement in LBM, FM and spine BMD was significantly better with the higher dose.¹⁵³, level 1

The American Association of Clinical Endocrinologists (AACE) 2009 guidelines recommend that the starting dose of rhGH in transition should be approximately 50% of the dose between the paediatric dose required for growth and the adult dose.¹⁴⁵, level III

Recommendation

The starting dose of rhGH that should be given during transition period is 0.0125 - 0.0250 mg/kg/day. **(Grade C)**

The dose of rhGH should be adjusted to maintain normal serum IGF-1 level. **(Grade A)**

4.4 BENEFITS OF TREATMENT

Studies had shown improvement in body composition and lipid profiles in young adults but not muscle strength with rhGH therapy during the transition period.^{Carroll 154 PV et al 2004, level II-2; Hulthen 155 L et al 2001, level II-2, Vahl 156 N et al 2000, level I; Johannsson 157 G et al 1999, level II-2} rhGH treatment in GHD adolescents did not show any effect in terms of cardiac mass and function.^{Lanes 158 R et al 2001, level II-2}

As for QoL in COGHD patients, results showed that overall baseline QoL was not compromised in severely GHD patients during the transition period but dimensions related to age-specific psychological problems were significantly worse than healthy subjects and appeared to positively respond to rhGH therapy.^{159, level 1}

In a large RCT, it was shown that there was an increase in total BMD in the rhGH-treated versus the untreated GHD adolescents after two years.^{152, level 1} Similarly, in a large multicentre RCT, results showed that there was a significant improvement in lumbar spine BMD in those treated compared to the untreated.^{160, level 1} Another study documented that areal bone mineral density (aBMD) continued to accrue in untreated patients with GH deficiency after two years at a slightly but significantly lower rate than those treated.^{161, level 1}

However, smaller studies did not demonstrate any benefit to BMD, lipid metabolism, body composition, cardiac function, muscle strength and QoL with rhGH therapy during the transition period.^{162, level II-2; 163, level I}

Many studies have shown an improvement in body composition, lipid profile, bone mineral density and QoL in rhGH-treated GHD adolescents during transition period.

5. GROWTH HORMONE DEFICIENCY IN ADULTS

5.1 CLINICAL FEATURES OF ADULT WITH GH DEFICIENCY SYNDROME

Adults with GH deficiency present with a wide spectrum of clinical presentation and is termed as GH deficiency syndrome. However the features are not pathognomonic and may overlap with a variety of other conditions.

Table 1: Clinical Features of Syndrome of Adult GH Deficiency

Symptoms	Signs
<ul style="list-style-type: none"> • Increased body fat • Reduced muscle bulk • Reduce strength and physical fitness • Reduced sweating • Impaired psychological well-being • Depressed mood • Anxiety • Reduced physical stamina • Reduced vitality and energy • Increased social isolation 	<ul style="list-style-type: none"> • Overweight • Increased adiposity especially abdominal • Poor muscular development • Reduced exercise performance • Thin, dry skin • Depressed affect

* Adopted from Ho K 2006. Growth Hormone deficiency in Adults. *Endocrinology* 2006. 5th edition; 755-765.

Untreated GH deficiency in adults is associated with increased morbidity and mortality.^{164, level II-2; 165, level II-2} The syndrome is associated with increased risk for cardiovascular mortality, osteopenia, fracture rates, fat mass and decreased muscle mass. There is also a greater propensity for dyslipidaemia with increased total and LDL cholesterol, and reduced HDL cholesterol.^{145, level III} Successful rhGH replacement treatment ameliorates many symptoms of GH deficiency syndrome.^{166, level III} GHD adults are associated with reduced bone density and osteoporosis. COGHD results in reduced bone density in adult life.^{167, level II-2} and subjects with adult onset GH deficiency have an increased prevalence of fractures.^{168, level II-2} The KIMS database of GHD adult showed that the majority (60 - 70%) of patients had additional pituitary hormones deficiency primarily gonadotropin, TSH and ACTH deficiency. Posterior pituitary deficiency was less common (22%).^{169, level II-3}

Recommendation

Regular monitoring of the cardiovascular parameters including lipid profiles, blood pressure and fasting glucose should be done. **(Grade C)**

GHD adults should:

- be regularly monitored for the cardiovascular parameters including lipid profiles, blood pressure and fasting glucose **(Grade C)**
- undergo DEXA scan **(Grade C)**
- be screened for other pituitary hormone deficiencies and if present, be optimally treated as well **(Grade A)**

5.2 AETIOLOGY

A large number of different aetiologies contribute to GH deficiency in adulthood. Frequent causes include previous hypothalamic–pituitary disease, such as pituitary adenoma, craniopharyngioma, cranial irradiation, head trauma/vascular injury and infiltrative disease. COGHD also contributes to growth deficiency in adulthood. Idiopathic GH deficiency may also occur in some cases.

The KIMS global surveillance database of adult GHD patients showed that the most common causes of GH deficiency were pituitary adenoma, idiopathic GH deficiency and craniopharyngiomas which collectively contributed to 60 - 70% of all cases.^{170, level II-3; 169 G, level II-3} Other causes of GHD adults include non-pituitary brain tumours and irradiation (7.0%), traumatic brain injury/TBI (3.1%), postpartum pituitary necrosis (2.9%) and lymphocytic hypophysitis (0.9%).

GH deficiency has also been found to occur in one third of patients who have undergone cranial irradiation for non-pituitary brain tumours^{171, Level III} and two-thirds of patients with childhood onset acute lymphoblastic leukaemia (ALL).^{172, level II-2}

At least 25% of TBI survivors developed one or more pituitary hormone deficiencies. Most cases of post-traumatic hypopituitarism remain undiagnosed and untreated in clinical practice. In a recent systematic review, up to one third of TBI patients were diagnosed to have GH deficiency. In the majority of patients, the condition was transient and only 16% of the cases had persistent deficiency at 6 - 12 months of follow up.^{173, level I} It was recommended that screening for GH deficiency is appropriate 6 to 12 months after the head trauma in moderate to severe head cases.^{174, level III}

Recommendation

GH deficiency should be excluded in adult patients with clinical features of GH deficiency AND one of the following:

- hypothalamic-pituitary disease,
- previous cranial irradiation
- traumatic brain injury (**Grade B**)

In the absence of hypothalamic-pituitary disease, screening for GH deficiency is not recommended in adults. (**Grade C**)

5.3 DIAGNOSIS

The diagnosis of GH deficiency in adults should ideally be based on correct identification of clinical features in individuals at risk of GH deficiency and biochemical confirmation. The diagnosis of GHD is confirmed by performing stimulation tests. Commonly used tests are ITT, glucagon stimulation test, arginine with/without growth hormone releasing hormone (GHRH) (ARG plus GHRH) test. Comparison of these different diagnostic tests has shown that the ITT and ARG plus GHRH tests were better to differentiate between GHD patient from normal persons.^{175, level III} In the KIMS global database of adult GHD, these two stimulation tests were the most commonly used.^{169, level II-3} However, GHRH is not available in Malaysia.

The cut off value to diagnose GH deficiency in adults is GH level that is less than 5.1 mcg/l. This value will provide 96% sensitivity and 92% specificity. The GH assay used for this particular cut off is an immunochemiluminometric assay.^{175, level III} If a patient has three or four pituitary hormone deficiencies in addition to a low IGF-1 level (below -2 SD), in the absence of conditions that lower IGF-1, the probability of GH deficiency being documented on stimulation testing is more than 90% and thus stimulation test is necessary to make the diagnosis.^{142, level II-3} In most circumstances, the biochemical diagnosis of GH deficiency in an adult would require only one stimulation test.^{176, level III}

ITT is contraindicated in patients with electrocardiographic evidence or history of ischaemic heart disease or in patients with seizure disorders.^{166, Level III} Since ITT can cause seizures,^{177, level III} it might be prudent to avoid it in patients with a history of previous stroke as well. In such patients where the ITT is undesirable or contraindicated, a reliable alternative GH stimulation test is the glucagon stimulation test (GST) for the following reasons: 1) accurate and reliable discrimination between

normal and true GH deficiency, 2) availability, 3) reproducibility, 4) safety and 5) lack of influence by gender, or hypothalamic cause of GHD.^{178; level III}

Insulin Tolerance Test (ITT) is the **gold standard** for diagnosing adult GH deficiency.

Recommendation

ITT should be avoided in patients with one or more of the following:

- History of seizures
- History of strokes
- Presence of coronary artery disease.
- >55 years of age (**Grade C**)

Glucagon stimulation test is an alternative in patients who are unsuitable for ITT. (**Grade C**)

Patients with irreversible hypothalamic-pituitary lesions and with evidence of at least three pituitary hormone deficiencies and serum IGF-1 levels below the age- and sex-appropriate reference range are deemed GH deficient and do not require GH stimulation test. (**Grade C**)

5.4 BENEFITS

There are protean clinical manifestations of GH deficient syndrome for which the appropriate management is GH replacement. However, not all subjects with GH deficiency has the GHD syndrome.^{176, level III} The benefits of GH replacement are well documented and many of the metabolic and body composition improvement may have a positive impact on the cardiovascular risk that GH deficient adult. The indications and the positive impact are discussed in the sections below.

Recommendation

rhGH should only be prescribed to patients with clinical features suggestive of adult GH deficiency **AND** biochemically proven GH deficiency. (**Grade C**)

5.4.1 Psychological well-being

Patients with GH deficiency have been shown to have a reduced sense of well-being. The majority of studies showed that adults with hypopituitarism of both childhood and adult onset have a diminished

QoL in comparison with the normal population. Reductions in physical and mental energy, dissatisfaction with body image and poor memory have been reported most consistently.^{179, level I; 180, level II-3; 181, level III}

GH replacement in GHD adults has improved QoL, especially in the domain of energy level, self-esteem, attention and memory. There is considerable social impact with fewer days of sick leave.^{179, level I; 182, level III; 180, level II-3; 183, level II-I; 184, level II-2; 181, level III}

Both generic and GHD-specific tests usually indicate that rhGH replacement therapy enhances QoL. Quantitative indices of QoL are increased within 1 - 3 months in most patients, although some individuals require longer treatment duration (6 months) before improvements are noted.^{182, level III} Some patients show definite benefit after receiving rhGH therapy but in others improvements were either limited or none. The degree of improvement in QoL is generally proportional to the deviation from normality at the outset but shows no correlation with the degree of improvement in IGF-1 levels in practice. If the QoL of the patients is normal at baseline, no improvement will be seen with rhGH therapy.^{181, level III}

Methods for assessing the QoL in adult with GH deficiency:

- Generic Questionnaires such as Nottingham Health Profile, Psychological General Health Well-being Schedule and General Health Questionnaire
- Disease-Specific Questionnaire such as Quality of Life-Adult with GH deficiency Assessment, GH deficiency Questionnaire

Recommendation

A QoL questionnaire should be administered before beginning GH replacement as psychological well-being is the most compelling indication for GH replacement in adults with GH deficiency. **(Grade C)**

Adults with GH deficiency on GH replacement should be evaluated using the QoL questionnaire at 6 to 12-monthly intervals to document the effects of GH on their psychological well being. **(Grade C)**

5.4.2 Body Composition

There is a reduction of total body fat mass (FM) after rhGH replacement and the magnitude of FM reduction is dose dependent^{185, level III; 186, level II-2; 187, level II-I} This FM reduction is accompanied by a parallel increase in fat free mass (FFM) which follows the same rhGH dose trend.^{185, level III} The reduction in whole body FM with rhGH replacement is due mainly to a marked decrease in central and

visceral fat in GHD subjects.^{185, level III; 188, level II; 186, level II-2; 189, level II-2; 190, level II-1} rhGH replacement has been shown to have greater reduction in central adipose tissue as compared to peripheral adipose tissue.^{188, level III; 189, level II-2; 187, level II-1} These body composition changes were more pronounced for young and lean subjects.^{185, level III} The increase in the FFM was reflected by an increase in muscle power in these subjects.^{191, level III} While the increase in FFM was seen within a month of rhGH replacement, the increase in muscle strength was only seen after 6 - 12 months of rhGH replacement. This lag in the functional improvement may be due to initial improvement in muscle tissue hydration.^{185, level III}

Recommendation

GHD adults who are undergoing rhGH replacement should have their body composition such as BMI and waist circumference measured regularly. **(Grade C)**

5.4.3 Cardiovascular Risk

Patients with GH deficiency have been shown to have an increased cardiovascular morbidity and mortality. There is also an associated increase in cardiovascular risk markers similar to that observed in Insulin Resistance Syndrome (IRS) namely, central obesity, elevated triglyceride (TG) and reduced HDL cholesterol levels.^{192, level I; 185, level III} Higher incidence of diabetes and hypertension has also been reported in GHD adults.^{193, level II-2; 194, level II-2} Furthermore, doppler ultrasound measurement has shown an increased carotid intima-media thickness (IMT) in GHD adults indicating the presence of atherosclerosis.^{184, level II-3}

Replacement with rhGH in GHD adults has shown a reduction in fat mass particularly in centrally distributed fat mass. There is also an improvement in lipid level with a reduction in the total cholesterol and LDL cholesterol levels.^{192, level I; 180, level II-3; 185, level III} The effects of GH replacement on insulin resistance and glucose tolerance is highly dependent on the dose of rhGH used and the susceptibility of the patient to develop diabetes such as underlying obesity, family history of diabetes and previous history of gestational diabetes. It is therefore important that susceptible patients to diabetes mellitus are given a very low dose of rhGH at initiation of therapy (i.e. 0.1 to 0.2 mg/day) and that the dose then is slowly increased based on the clinical response as there may be an initial deterioration of insulin sensitivity with rhGH replacement in the first three months but insulin sensitivity returns to baseline levels with longer duration of rhGH replacement.^{185, level III} In a study on a group of leaner (BMI: 22.8) and younger (age:29.5) COGHD

adults, an improvement of insulin sensitivity was seen.^{195, level II-2}

Longer term studies of five years duration have also demonstrated a significant reduction in IMT suggesting a reversal of the atherosclerotic process.^{196, level II-2; 184, level II-3} However, no data is available yet to show a reduction of cardiovascular events or mortality as the number of GHD adults on sufficient long duration of GH replacement is still relatively small.

Recommendation

GHD adults who are undergoing GH replacement should have their cardiovascular parameters monitored, in addition to body composition measurements. **(Grade C)**

5.4.4 Bone Density

Adults with GH deficiency are associated with reduced bone density and osteoporosis. COGHD results in reduced bone density in adult life^{167, level II-1} and subjects with adult onset GH deficiency have an increased prevalence of fractures.^{168, level II-1}

There are studies showing that treating GHD adults with rhGH replacement improved BMD as assessed by dual energy x-ray absorptiometry scan (DEXA scan) which is more pronounced in males and in those with lower initial BMD.^{191, level III; 194, Level II-2}

Recommendation

GHD adults should undergo DEXA scan prior to starting GH replacement. **(Grade B)**

- If the initial bone density is abnormal, repeat DEXA scan is recommended at 1 - 3 years intervals to assess the need for additional anti-osteoporosis treatment. **(Grade C)**

5.5 DOSAGE

The rhGH dosage should be individualised, independent of body weight and increased slowly to the minimal dose that normalises serum IGF-I level without untoward side effects. In older patients, lower starting dose should be used for replacement.^{145, level I; 197, level I; 198, level II-1}

The dose of rhGH is initiated at 0.1 - 0.2 mg daily for men and 0.2 - 0.3 mg daily for women. At each visit, the rhGH dose is increased by 0.1 to 0.2 mg until the maintenance dose is reached based on clinical

response, IGF-1 levels and limited by the occurrence of side effects.
199, level III

Recommendation

rhGH dose for replacement in GHD adults should be individualised independent of body weight. **(Grade A)**

The starting dose of rhGH is 0.1 mg daily for men and 0.2 mg daily for women. The dose is increased by 0.1 mg or 0.2 mg to achieve a maintenance dose based on clinical response, IGF-1 levels, and side effects. **(Grade C)**

5.6 SAFETY

5.6.1 Common Adverse Effects

In short term RCTs, the most common reported adverse events related to rhGH therapy were oedema, arthralgia and muscle weakness.^{197, level I; 200, level I} Similarly, a three-year RCT reported that adverse events related to fluid retention are fairly common which include arthralgia (30.6%), myalgia (13.5%), peripheral oedema (12.6%), paresthesia (9.0%), carpal tunnel syndrome (7.2%), generalised oedema (7.2%) and hypoaesthesia (5.4%). These events were not associated with increase in IGF-1 levels.^{201, level I} Data from the KIMS Pfizer International Metabolic Database reported that 18% of patients developed fluid retention.^{202, level II-3}

Fluid-related adverse effects such as arthralgia, myalgia and peripheral oedema are common in rhGH replacement therapy.

5.6.2 Risk of Tumour Recurrence

Three observational studies had shown that rhGH replacement therapy had no significant effect on tumour regrowth.^{203, level II-2; 204, level II-2; 205, level II-2}

In a long-term study by Arnold et al. involving 130 patients with non-functioning pituitary adenoma treated by surgical removal, rhGH treatment was not a significant independent predictor of recurrence.^{203, level II-2}

rhGH in GHD adults does not increase recurrence of hypothalamic-pituitary tumours.

5.6.3 Risk of New Malignant Disease

A prospective longitudinal study of rhGH therapy in hypopituitary males of more than 50 years old demonstrated no change in serum prostate specific antigen (PSA).^{206, level II-2} The KIMs database also showed no evidence of rhGH therapy increasing the risk of developing malignant neoplasms.^{202,level II-3}

When comparing 1, 411 hypopituitary adults without rhGH replacement (mean age of 56.9 year) and 289 hypopituitary patients on long-term GH replacement (mean age of 47.6 year and mean duration of GH treatment of 60 months) with the normal population, malignancies were increased in those hypopituitary patients without rhGH replacement. However in patients on rhGH replacement, the overall mortality and the rate of malignancies were similar to the normal population.^{207, level II-2}

rhGH replacement in GHD adults does not increase the risk of new malignant tumours.

6. USE OF GH IN NON-GHD ADULTS

6.1 BURNS PATIENTS

Three RCT conducted in Shriners Hospitals for Children of Texas on the use of low dose rhGH (0.05 mg/kg body weight) in 178 severely burned children (Total Body Surface Area Burn >40%, age below 18 years) showed that rhGH significantly increased body composition (Height, Bone Mineral Content, Lean Body Mass and weight); cardiac function in the treatment group compared to the placebo group ($12\% \pm 24$ vs $1\% \pm 20$). Strength measurements showed significant improvement at 12 months. The number of reconstructive procedures from hospital discharge to the end of the study period was significantly lower in the rhGH group compared to the placebo group (1.8 ± 1.3 vs 4.1 ± 2.5).^{208, level I} Data is still limited for the use of rhGH therapy in children with burns.

There is no retrievable evidence regarding the usefulness of rhGH therapy in burns in adult patients.

Recommendation

rhGH therapy for burns in children should only be limited to research purposes. **(Grade B)**

rhGH therapy should not be used for burns in adults. **(Grade C)**

6.2 CRITICALLY ILL PATIENTS

Two RCT clearly demonstrated that the administration of high doses of rhGH therapy to critically ill patients receiving prolonged intensive care was associated with increased morbidity and mortality.^{209, level I}

However, two smaller studies using short-term, low-dose rhGH in surgical patients showed protein sparing benefits of rhGH supplementation with no major adverse effects apart from hyperglycaemia.^{210, level I; 211, level I}

Recommendation

rhGH therapy should not be used in critical illness. **(Grade A)**

6.3 FIBROMYALGIA

A narrative review of 26 papers suggested that pituitary function was normal in fibromyalgia patients. The therapeutic efficacy of supplemental

rhGH therapy in fibromyalgia requires further study before any further recommendations can be made.^{212, level III}

In a small non-placebo RCT using rhGH as concomitant treatment in severe fibromyalgia associated with low IGF-1 levels, the therapy group showed a 60% reduction in the mean number of tender points compared to the control group (3.25 ± 0.8 vs 8.25 ± 0.9). Similar improvements were observed in FIQ score and EQ-VAS scale. The findings suggested that there may be an advantage of using rhGH therapy in a subset of severe fibromyalgia patients with low IGF-1 serum levels.^{213, level I} Further randomised placebo-controlled studies would be useful to evaluate the place of rhGH therapy in fibromyalgia.

Recommendation

rhGH therapy should not be used for routine treatment of fibromyalgia. It may be considered in patients with low IGF-1 levels. **(Grade A)**

6.4 ANTI-AGEING THERAPY IN HEALTHY ELDERLY

There are physiological changes in GH levels with age. The safety, efficacy and role of rhGH in healthy elderly individual's remains controversial and the use of rhGH therapy as an anti-ageing agent in Europe and United States has not been approved. Published literature evaluating rhGH therapy and ageing in the healthy elderly are limited. Studies have generally been non-randomised, small, of short duration and using only limited surrogate parameters such as body composition.

Liu H et al. 2007 published a systematic review which included 31 articles involving a total of 220 participants. rhGH therapy was associated with small changes in body composition with a reduction in overall fat mass (-2.10 kg, 95% CI -2.80 to -1.35) and an increase in lean body mass (2.10 kg, 95% CI 1.30 to 2.90). rhGH therapy had no significant effect on other outcomes such as serum lipid levels or bone density. There was no evidence to show that the effects of GH on body composition resulted in a change in muscle strength, maximal oxygen uptake during exercise or an improvement in function. Study participants were elderly with a mean age of 69 ± 6 years and overweight (mean body index 28 ± 2 kg/m²). Treatment dose (mean 14 ± 7 mcg per kg body weight) and duration (mean 27 ± 16 weeks) were varied. There was an increased rate of adverse events, with rhGH-treated subjects being more likely to experience oedema, arthralgia, carpal tunnel syndrome, gynaecomastia as well as an increased risk of diabetes and impaired fasting glucose.

²¹⁴, Level I

A recent systematic review also showed no definite evidence that rhGH therapy benefited elderly non-GHD individuals.^{215, level II-2} There is no data available to suggest that rhGH therapy benefits cognition in the healthy adult population.

Recommendation

rhGH should not be used as an anti-ageing therapy. **(Grade A)**

6.5 SPORTS

Exogenous rhGH therapy has been touted as an athletic performance enhancer for many years and its use for such a purpose has been banned by professional sports regulatory authorities.

Liu H et al., in 2008, published a systematic review of 44 articles on the effects of GH on athletic performance. Overall, 303 subjects received rhGH therapy. They were young (mean age of 27 ± 3 years), lean (mean BMI of 24 ± 2 kg/m²) and physically fit (mean maximum oxygen uptake of 51 ± 8 ml/kg/minute). GH dosage varied (mean dose of 36 ± 21 mcg/kg/day) as did treatment duration (mean of 20 ± 18 days). The review found that although exogenous GH was associated with an increase in lean body mass (mean of 2.1 kg, 95% CI 1.3 to 2.9), there was no significant improvement in actual strength and exercise capacity. In fact, two out of three studies that measured exercising lactate levels showed significantly higher exercising lactate levels in rhGH-treated subjects suggesting that GH therapy may worsen exercise capacity. rhGH treated subjects were more frequently experiencing adverse events such as soft tissue oedema and fatigue compared to those not treated with GH.^{216, level I}

Recommendation

rhGH therapy should not be used to enhance athletic performance. **(Grade A)**

6.6 INFERTILITY

There are no studies that have looked at the use of rhGH alone in infertile women with normal pituitary function. Most evidence has looked at rhGH as an adjunct to other treatments for infertility.

A Cochrane systematic review of nine RCT by Harper K et al in 2003 specifically looked at the use of rhGH therapy to improve outcomes of in-vitro fertilisation (IVF) in women. This review found no evidence that

routine addition of GH to IVF increased the livebirth rate. It also showed an improvement only in those who had previously responded poorly to IVF (OR=4.37, 95% CI 1.06 to 18.01).^{217, level I}

The other systematic review looked at various therapeutic options available for women who had previously responded poorly to IVF. Five of the six studies using rhGH therapy showed no significant improvement in measures of fertility (such as serum oestradiol, duration of follicular phase, number of oocytes and pregnancy rate). The single study which favoured the addition of GH was small and used historical controls.^{218, level II-I}

Recommendation

rhGH therapy should not be used in the treatment of infertile women with normal pituitary function. **(Grade B)**

6.7 OBESITY

It is known that the endogenous secretion of GH in obese individuals is decreased although the exact physiological role of GH in obesity is unclear.

A recent meta-analysis of 24 RCTs looked at the efficacy and safety of rhGH therapy in simple adult obesity (i.e. not associated with distinct clinical syndromes). Treatment with very high dosages of rhGH therapy led to very small improvement in waist-hip ratio and fat mass in subjects treated with rhGH therapy compared to placebo. There were no significant differences in body weight, BMI, subcutaneous fat area, resting energy expenditure, respiratory quotient and blood pressure. However, there were significant increase in adverse events associated with rhGH therapy including arthralgia, paraesthesias and oedema. The beneficial effects appear to be quantitatively small and would not justify a clinically relevant role for rhGH therapy in obesity.^{219, level I}

Recommendation

rhGH therapy should not be used in the treatment of simple adult obesity. **(Grade A)**

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Appendix 1

SEARCH TERMS

The following MeSH terms or free text terms were used either singly or in combination:

“growth hormone deficiency” AND “traumatic brain injury, “cranial irradiation”, “neonatal hypoglycaemia”, “auxology”, “breech delivery”, “cleft palate”, “solitary central incisor”, “micropenis, “histiocytosis X, “craniopharyngioma”, “clinical features”, “pitfalls” AND “growth hormone deficiency diagnosis”, “Dwarfism”, “Pituitary diagnosis”[MeSH] AND “pitfalls in diagnosis”, “Growth Hormone stimulation test” AND “precise”, “Growth Hormone stimulation test” AND “accuracy”, “insulin tolerance test” AND “accuracy”, “Growth Hormone stimulation test” AND “gold standard”, “Growth Hormone stimulation test” AND “sensitivity”, “growth hormone deficiency” AND “goal of treatment”, “objective of treatment”, “final height”, “body composition”, “heart”, “bone mineral density”, “malignancy”, “scoliosis”, “slipped capital femoral epiphysis”, “growth hormone” AND “benign Intracranial Hypertension”, “Growth Hormone therapy” AND “Diabetes Mellitus”, “Growth Hormone deficient” AND “cost-benefit”, “growth hormone deficiency” AND “when to start”, “age starting treatment “treatment for young children”, “treatment in Growth Hormone deficiency” AND “dosing”, “treatment” AND “dose”, “growth hormone deficiency” AND “near final height”, “growth hormone deficient children” AND treatment AND “daily injection”, “children with growth hormone deficiency” AND “growth hormone dose through puberty”, “growth hormone therapy” AND “insulin growth factor based dosing”, “growth hormone deficient children” AND “somatropin treatment”, “children with growth hormone deficiency” AND “use of gonadotropin releasing hormone agonist at puberty”, “children with growth hormone deficiency” AND “combination of LHRH analogue at puberty”,

“growth hormone deficiency” AND “monitoring”, “IGF-1”, “bone age monitoring”, “growth hormone treatment” AND “impaired glucose tolerance”, “growth hormone deficient” AND “benefit” AND “growth hormone therapy”, “growth hormone deficiency” AND “growth hormone therapy” AND “children”, “growth hormone insufficiency” AND “Growth Hormone treatment”, “Growth Hormone deficiency” AND “Final Height”, “Adult height”, “Body composition”, “bone mineral density”, “bone markers”, “heart”, quality of life”, “Growth Hormone”[Mesh] AND “adverse effects”, “Growth Hormone”[Mesh] AND “Risk”[Mesh], “Growth Hormone” AND “cancer”, “malignancy”, “scoliosis”, “slipped capital femoral epiphysis”, “Benign Intracranial Hypertension” “Pseudotumour

cerebri", "Diabetes Mellitus", "skin", "Turner syndrome" AND "final adult height", "Turner syndrome" AND "somatotropin therapy" AND "final adult height", "45,X" AND "somatotropin therapy" AND "final adult height", "Genetic short stature" AND "Growth Hormone therapy" AND "height gain", "SGA" AND "Growth Hormone somatotropin therapy" AND "final adult height", "SGA" AND "Growth Hormone therapy" AND "final adult height", "IUGR" AND "Growth Hormone therapy" AND "final adult height", "IUGR" AND "no Growth Hormone therapy" AND "final adult height", "IUGR" AND "final adult height", "IUGR" AND "improving short stature" "Chronic Renal Failure" AND "Growth Hormone therapy" AND "final adult height", "ESRF" AND "somatotropin therapy" AND "final adult height", "Renal insufficiency" AND "Growth Hormone therapy" AND "final adult height", "Prader-Willi Syndrome" AND "GH therapy" AND "improving short stature", "Prader-Willi Syndrome" AND "Growth Hormone therapy" AND "improving body composition", "Familial short stature" AND "Growth Hormone therapy" AND "final adult height", "Genetic short stature" AND "Growth Hormone therapy" AND "final adult height", "Familial short stature" AND "Growth Hormone therapy" AND "improving short stature", "Genetic short stature" AND "Growth Hormone therapy" AND "improving short stature", "Familial short stature" AND "Growth Hormone therapy" AND "height gain", "Genetic short stature" AND "Growth Hormone therapy" AND "height gain" "Russell Silver syndrome" AND "GH therapy", "Russell Silver syndrome" AND "Growth Hormone therapy" AND "improving short stature", "Russell Silver syndrome" AND "Growth Hormone therapy" AND "growth velocity", "Russell Silver syndrome" AND "short stature", "Russell Silver syndrome" AND "Growth Hormone therapy", "Hypochondroplasia" AND "Growth Hormone therapy" AND "improving short stature", "Hypochondro-plasia" AND "Growth Hormone therapy" AND "height gain", "Hypochondro-plasia" AND "no Growth Hormone therapy" AND "final adult height", "Noonan syndrome" AND "Growth Hormone therapy" AND "Short stature", "Noonan syndrome" AND "Growth Hormone therapy" AND "Growth velocity", "Noonan syndrome" AND "Growth Hormone therapy" AND "improving short stature", "Noonan syndrome" AND "Growth Hormone therapy" AND "final adult height", "Noonan syndrome" AND "Growth Hormone therapy".

etiology AND "adult growth hormone deficiency", "Causality"[Mesh] AND "Human Growth Hormone"[Mesh], "cause" AND "growth hormone deficiency", "clinical practice guideline" AND "growth hormone deficiency", "guideline" AND "growth hormone deficiency", "Cause" AND "growth hormone deficiency", "Symptom" AND "growth hormone deficiency", "pituitary *adenoma" AND "growth hormone deficiency", "pituitary microadenoma" AND "growth hormone deficiency", "pituitary

macroadenoma" AND "growth hormone deficiency", "pituitary *adenoma" AND "GH deficiency", *adenoma AND "GH deficiency", "Prevalence" AND "growth hormone deficiency", "Diagnosis" AND "growth hormone deficiency", "Indications" AND "growth hormone treatment", "Indication" AND "growth hormone replacement", "Treatment" AND "growth hormone deficiency", "GHD adults", "GH therapy", "psychological well being", "Quality Of Life", "body composition", "cardiovascular risk", "diabetes", "bone", "growth hormone" (therapy or treatment) AND "growth hormone deficiency" AND "dose", "growth hormone" (therapy or treatment)", "growth hormone" (therapy or treatment) AND "growth hormone deficiency" AND (risk OR side effects), "growth hormone" (therapy or treatment) AND "growth hormone deficiency" AND (risk OR side effects), "growth hormone" AND "short and long term side effects", "Side effect* AND "growth hormone therapy", "Risk", "growth hormone deficiency" AND "treatment" AND "diabetes risk" OR "malignancy risk", "adult growth hormone deficiency" AND "replacement" AND "tumor regrowth OR recurrence", "rhGH therapy in growth hormone deficiency adult" AND "cancer", "Growth hormone" AND "ageing", "growth hormone cognition or cognitive function", "growth hormone memory", "growth hormone dementia", "growth hormone therapy" and "burn and catabolic state", "growth hormone therapy" and "burn", "growth hormone in critical care", "growth hormone in fibromyalgia", "growth hormone therapy" AND "athletics", "growth hormone therapy" AND "infertility", "conception", "in vitro fertilization", "growth hormone therapy" AND "obesity"

Appendix 2

CLINICAL QUESTIONS

A. Use of rhGH in Children

1. Who should be investigated for GH deficiency (GHD)?
2. How is GHD diagnosed in children?
3. What are the pitfalls in the diagnosis of GHD?
4. How should children with GHD be treated?
5. What is the goal of treatment in terms of height achievement and optimisation of other deficiencies such as body composition?
6. What is the starting dose and adverse events of the treatment?
7. How long the treatment should be given?
8. How should GH therapy be monitored?
9. What are the benefits of GH therapy?
10. What are the risks of GH therapy?
11. Is there a role of GH therapy in non-GHD children?
 - Turner syndrome
 - Small for Gestational Age
 - Idiopathic short stature
 - Familial/genetic short stature
 - Chronic renal failure
 - Prader Willi syndrome
 - Noonan syndrome
 - Russell-Silver syndrome
 - Skeletal dysplasia such as achondroplasia and hypochondroplasia
12. How should these non-GHD children be treated?
 - What is the goal of treatment?
 - What is the starting dose and adverse events?
 - How long the treatment should be given?
 - How should they be monitored?

B. Use of rhGH in Transition Period

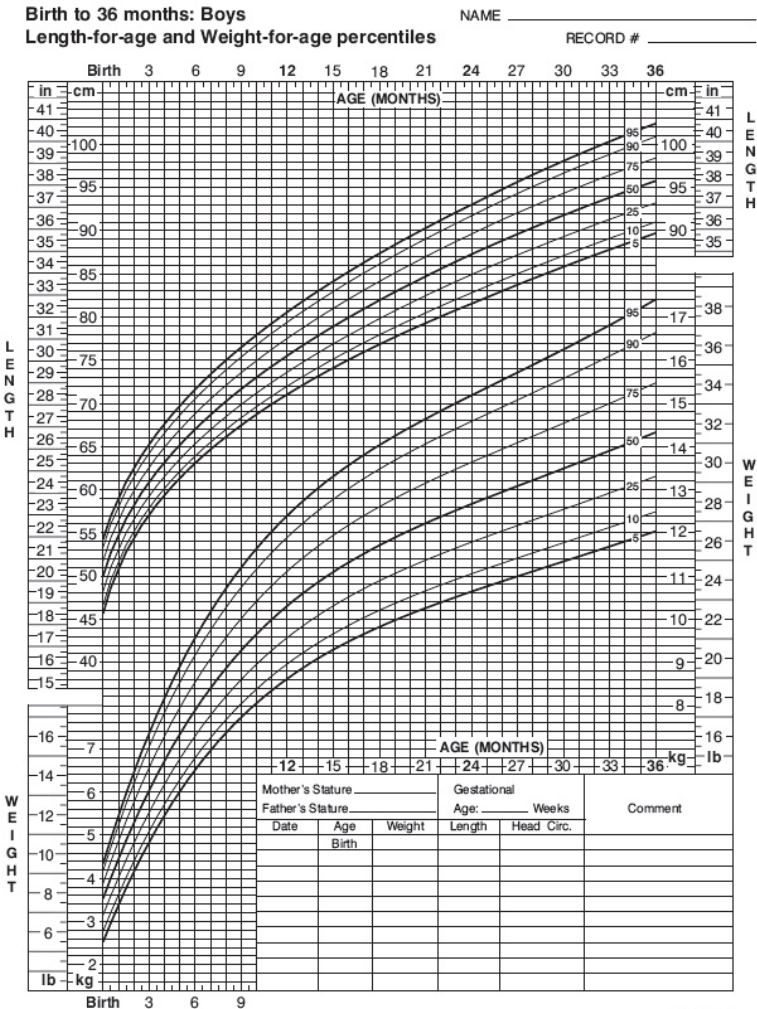
13. Who should continue rhGH therapy during the transition period?
14. How to select them during the transition period?
15. How to re-start rhGH therapy?
16. How should rhGH therapy be monitored?
17. What are the benefits of rhGH therapy?

C. Use of rhGH in Adults

18. Who are at risk for GHD in adults?
 - Hypothalamic pituitary dysfunction
 - Intracranial diseases (non-pituitary causes)
 - Childhood onset GHD
19. What tests should be used to diagnose GHD and what are criteria to make the diagnosis?
 - IGF-1
 - Growth hormone
 - Dynamic testing
20. What are the indications for growth hormone replacement therapy in GHD adults?
21. What are the benefits of GH therapy in GHD adults?
 - Psychological well-being
 - Body composition change
 - Cardiovascular risk
 - Bone health
22. What treatment regime should be used and how should these be monitored?
23. What are the short term and long term risks of rhGH therapy in GHD adults?
24. Are there other indications for rhGH therapy?
 - Burns
 - Critically ill
 - Fibromyalgia
 - Anti-aging in healthy elderly
 - Athletic performance
 - Infertility
 - Obesity

Appendix 3

National Child Health Statistic (NCHS) Growth Chart for Boys 0 to 36 months



Published May 30, 2000 (modified 4/20/01).
 SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>



Appendix 3 (cont...)

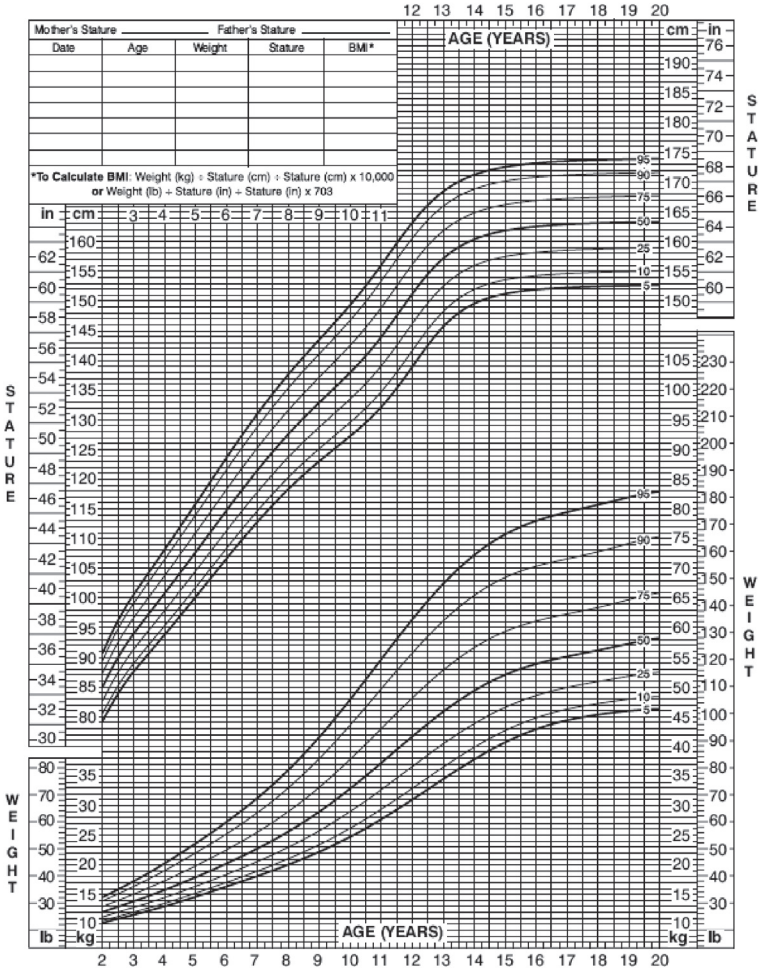
National Child Health Statistic (NCHS) Growth Chart for Girls 2 to 20 years

2 to 20 years: Girls

NAME _____

Stature-for-age and Weight-for-age percentiles

RECORD # _____



Published May 30, 2000 (modified 11/21/00).
 SOURCE: Developed by the National Center for Health Statistics in collaboration with
 the National Center for Chronic Disease Prevention and Health Promotion (2000).
<http://www.cdc.gov/growthcharts>



Appendix 4

SUGGESTED GROWTH HORMONE DOSAGES AND SIDE EFFECTS

Drug	Recommended Dose In Paediatrics	Recommended Dose In Adults	Side Effects	Caution
<p>Growth Hormone (GH)</p>	<p>To be given subcutaneously</p> <ul style="list-style-type: none"> • Pediatric GHD : 0.025 to 0.050 mg/kg/day • Turner syndrome : 0.045 to 0.055 mg/kg/day 	<p>The starting dose of GH is 0.1–0.2 mg daily for men and 0.2–0.3 mg daily for women.</p> <p>The GH dose is increased by 0.1 mg (men) or 0.2 mg (women) until the maintenance dose is achieved based on clinical response, IGF-1 levels, and limited by the occurrence of side effects.</p>	<p>Children: arthralgia, benign intracranial hypertension, glucose intolerance, peripheral oedema, hypertriglyceridaemia, intracranial tumour, lipomatrophy, leukaemia, meningioma, muscle pain, scoliosis progression, slipped capital femoral epiphysis</p> <p>Adults: ALT increased, AST increased, arthralgia, back pain, carpal tunnel syndrome, diaphoresis, dizziness, fatigue, glucose intolerance, hypertension, paresthesia, peripheral oedema, skeletal pain, stiffness in extremities,</p>	<p>Neoplasm: Monitor patients with pre-existing tumours for progression or recurrence. Increased risk of a second neoplasm in childhood cancer survivors treated with GH in particular meningiomas in patients treated with radiation to the head for their first neoplasm.</p> <p>Impaired Glucose Tolerance and Diabetes Mellitus: May be unmasked. Periodically monitor glucose levels in all patients. Doses of concurrent antihyperglycaemic drugs in diabetics may require adjustment.</p> <p>Intracranial Hypertension: Exclude preexisting papilloedema. May develop, usually reversible after discontinuation or dose reduction.</p>

Drug	Recommended Dose In Paediatrics	Recommended Dose In Adults	Side Effects	Caution
				<p>Fluid Retention: (eg. oedema, arthralgia, carpal tunnel syndrome, especially in adults). May occur frequently. Reduce dose as necessary.</p> <p>Hypothyroidism: May first become evident or worsen.</p> <p>Slipped Capital Femoral Epiphysis: May develop. Evaluate children with the onset of a limp or hip/knee pain.</p> <p>Progression of Preexisting Scoliosis: May develop.</p> <p>Acute critical illness</p>

Source:

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LIST OF ABBREVIATIONS (alphabetical order)

AACE	American Association of Clinical Endocrinologists
aBMD	areal Bone Mineral Density
ACTH	Adrenocorticotropin Hormone
ARG	Arginine
AST	Arginine Stimulation Test
BFM	body fat mass
BMI	body mass index
BMD	bone mineral density
CA	chronological age
CNS	Central Nervous System
COGHD	Childhood Onset Growth Hormone Deficient
CT	Computed Tomography
DEXA	Dual Energy X-ray Absorptiometry
EMH	Ectopic posterior pituitary, Missing stalk and Hypoplastic anterior pituitary
FH	Final height
FFM	fat free mass
FM	fat mass
FSH	Follicle Stimulating Hormone
GCS	Glasgow Coma Scale
GH	Growth Hormone
GHD	Growth Hormone Deficient
GHRH	Growth Hormone Releasing Hormone
GST	Glucagon Stimulation Test
HDL	High Density Lipoprotein
HV	Height Velocity
ISS	Idiopathic Short Stature
IRS	Insulin Resistant Syndrome
ITT	Insulin Tolerance Test
LDL	Low Density Lipoprotein
LH	Luteinising Hormone
MPH	Mid-parental Height
MPHD	Multiple Pituitary Hormone Deficient
MRI	Magnetic Resonance Imaging
NCHS	National Child Health Statistics
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
QoL	Quality of Life
RCT	Randomised Clinical Trial
rhGH	recombinant human Growth Hormone
SD	Standard Deviation
SDS	Standard Deviation Score
TBI	Traumatic Brain Injury
TG	Triglyceride
TH	Target Height
TS	Turner Syndrome
TSH	Thyroid Stimulating Hormone
vBMD	volumetric Bone Mineral Density

PROPOSED CLINICAL AUDIT INDICATORS FOR QUALITY MANAGEMENT

Percentage of GHD patients treated with GH = $\frac{\text{No. of GHD patients treated with GH}}{\text{No. of GHD patients diagnosed}} \times 100\%$

Percentage of TS referred to paediatric endocrinologist before 6 years old = $\frac{\text{No. of TS referred to paediatric endocrinologist at age <6 years}}{\text{No. of TS referred to paediatric endocrinologist}} \times 100\%$

* Percentage of re-evaluation of COGHD patients at transition period = $\frac{\text{*No. of COGHD patients re-evaluated at/after completion of growth}}{\text{*No. of COGHD patients at/after completion of growth}} \times 100\%$

** after exclusion of COGHD due to hypothalamic pituitary disease with ≥ 3 pituitary hormone deficiency & IGF-1 below -2 SD*

Appropriate use of GH therapy in adults = $\frac{\text{No. of patients on GH therapy who had ITT done}}{\text{Total no. of patients treated with GH}} \times 100\%$

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