

Growth Hormone Treatment

Ali Talea

Pediatric Endocrinologist

Metabolic Disorder Research Center

Molecular-cellular Endocrinology & Metabolism
Research Institute

Tehran University of Medical Sciences

Approved Indications

- ❖ Growth hormone deficiency in children and adolescents
- ❖ Growth hormone deficiency in adults
- ❖ Idiopathic short stature syndrome
- ❖ Small for gestational age
- ❖ SHOX (short stature homeobox-containing gene) deficiency
- ❖ Chronic renal failure in pre-transplantation children
- ❖ Prader-Willi syndrome, Turner syndrome, Noonan syndrome
- ❖ Therapy of infantile hypoglycemia
- ❖ Central nervous system tumor treated with radiation
- ❖ Short-bowel syndrome

History of growth hormone therapy

- ❖ 1985 Growth Hormone therapy
- ❖ 1993 Chronic renal insufficiency
- ❖ 1996 Adult growth hormone deficiency
- ❖ 1997 Turner syndrome
- ❖ 2000 Prader-Willi syndrome
- ❖ 2001 Small for gestational age
- ❖ 2003 Idiopathic short stature
- ❖ 2006 homeobox-containing gene deficiency
- ❖ 2007 Noonan syndrome



SPECIAL ARTICLE

UPDATE OF GUIDELINES FOR THE USE OF GROWTH HORMONE IN CHILDREN: THE LAWSON WILKINS PEDIATRIC ENDOCRINOLOGY SOCIETY DRUG AND THERAPEUTICS COMMITTEE

THOMAS A. WALTON, MD, SUSAN R. ROSE, MD, PHOEBUS COHEN, MD, ALAN D. ROGOL, MD, PhD, PHILIPPE BAREGLIAUX, MD, ROSALIND BROWN, MD, DANNA S. HADDIN, MD, STEPHEN F. KHR, MD, PhD, MARGARET LAWSON, MD, SALLY RADZICKI, MD, STEPHEN M. ROSENTHAL, MD, LAWRENCE SILVERMAN, MD, AND PHILLIS SPEER, MD

The Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee guidelines for the use of growth hormone were first published in 1983, near the end of the era of human pituitary-derived growth hormone (GH), and again in 1995, a decade after the introduction of recombinant human (rh)GH.¹ The Lawson Wilkins Pediatric Endocrine Society also endorsed an international consensus document led by the Growth Hormone Research Society published in 2000.² This report serves to update those guidelines with an emphasis on new recommendations. The recommendations included here are limited primarily to the use of GH in infants, children, and adolescents.

FDA-APPROVED USES OF GH

Recombinant human GH has replaced human pituitary-derived GH, which should no longer be used because of the risk of contamination with the Jakob-Creutzfeldt prion. By 1995, the Food and Drug Administration (FDA) had approved GH therapy for short stature in the following conditions for which efficacy has been shown and much experience has been gained:

1. Growth hormone deficiency (GHD)/insufficiency
2. Chronic renal insufficiency posttransplantation
3. Turner syndrome

Since 1995, the FDA has approved GH for five additional indications:

1. Adults with GHD
2. Adults with AIDS wasting
3. Short stature from Prader-Willi syndrome (PWS)
4. Children with a history of intrauterine growth restriction (small for gestational age [SGA]) who have not reached a normal height range by age 2 years
5. Children with idiopathic short stature who are >2.25 SD below the mean in height and who are unlikely to catch up in height.

DIAGNOSIS OF GHD

The diagnoses of Turner syndrome, PWS, chronic renal insufficiency, and SGA are generally straightforward based on genetic testing, renal function, and/or birth data coupled with auxology. However, considerable variability exists in the diagnosis of GH deficiency, which remains a clinical challenge.^{3,4} This is related to the continuum between severe GHD

FDA	Food and Drug Administration	IGF-1	Insulin-like growth factor 1
GH	Growth hormone	IGFBP-3	Insulin-like growth factor-binding protein-3
GHD	Growth hormone deficiency	PWS	Prader-Willi syndrome
GHRH	Growth hormone releasing hormone	SGA	Small for gestational age
HIV	Human immunodeficiency virus		

From Division of Pediatric Endocrinology, State University of New York at Stony Brook, Stony Brook, Division of Pediatric Endocrinology, Schneider Children's Hospital, NYU School of Medicine, New Hyde Park, New York; Division of Pediatric Endocrinology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Division of Pediatric Endocrinology, David Geffen School of Medicine at UCLA, Los Angeles; Department of Pediatrics, University of California San Francisco, San Francisco, California; Department of Pediatrics, University of Virginia, Charlottesville, Virginia; Division of Endocrinology, The Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts; Department of Pediatrics, University of Texas Southwestern, Dallas, Texas; Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, Arkansas; Division of Endocrinology and Metabolism, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; Section of Pediatric Endocrinology, Department of Pediatrics, The University of Chicago, Chicago, Illinois; and Children's Medical Center Atlanta Health System, Marietta, Georgia.

Submitted for publication Oct 4, 2000; revision received Jan 26, 2001; accepted Apr 13, 2001.

Address requests to Thomas A. Walton, MD, Chief, Division of Pediatric Endocrinology, State University of New York, Stony Brook, NY 11794-5011. E-mail: twalton@stonybrook.edu. [J Pediatr 2002;141:415-21.]

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0022-3476/2002/\$30.00 + 0
10.1067/j.peds.2002.3476.01.00244-4

Guidelines from PES (last one 2003)

GH is indicated in children with a clinical picture of GHD who fail GH stimulation tests. In addition, a trial of GH therapy is warranted in children who may have atypical GHD with unexplained short stature and the following clinical findings:

- Height >2.25 SD below the mean for age or >2 SD below the midparental height percentile**
- Growth velocity <25 th percentile for bone age**
- Bone age >2 SD below the mean for age**
- Low serum IGF-1 and/or IGFBP-3**
- Other clinical features suggestive of GHD**



More from PES

SPECIAL FEATURE

Clinical Review

The Role of Recombinant Human Insulin-Like Growth Factor-I in Treating Children with Short Stature

Paulo F. Collett-Solberg and Madhusmita Misra, on behalf of the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society

Evidence Acquisition: We used the Entrez-PubMed search engine to conduct a review of publications addressing IGF-I deficiency, the use of rhIGF-I, and treatment for short stature.

Conclusion: The use of rhIGF-I is justified in conditions approved by the Food and Drug Administration. Until more substantial data become available, the use of rhIGF-I outside Food and Drug Administration recommendations should only be investigational. (*J Clin Endocrinol Metab* 93: 10–18, 2008)

Growth Hormone Deficiency in Children

- ❖ Two (2) pharmacologic provocation tests (insulin, clonidine, arginine, levodopa, glucagon) with a result < 10 ng/mL
- ❖ Patients who do not meet stimulation test criteria < 10 ng/mL on both tests or whose stimulation tests are discordant can be approved for a 6 month trial of growth hormone if the other criteria for growth hormone deficiency have been met and both IGF-1 and IGFBP-3 levels are below the normal range for gender and age
- ❖ Diagnosis by a pediatric endocrinologist
- ❖ The patient's baseline height must be > 2 standard deviations [SD] below the mean for gender and age (which corresponds to < 2.3 percentile)
- ❖ Growth rate is such that the patient is unlikely to attain an adult height in the normal range - 59 inches for girls and 63 inches for boys (ie, growth velocity below the 25th percentile or, alternatively, in children aged < 3 years, pretreatment growth velocity < 7 cm per year and for children aged 3 years and older growth velocity < 4 cm per year measured accurately for at least one year)

Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature: A Summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop

P. Cohen, A. D. Rogol, C. L. Deal, P. Saenger, E. O. Reiter, J. L. Ross, S. D. Chernausek, M. O. Savage, and J. M. Wit on behalf of the 2007 ISS Consensus Workshop participants

Department of Pediatric Endocrinology (P.C.), Mattel Children's Hospital at University of California, Los Angeles, Los Angeles, California 90095; Department of Pediatrics (A.D.R.), University of Virginia, and OOR Consulting, Charlottesville, Virginia 22911; Endocrinology Service (C.L.D.), Sainte-Justine Hospital, Montreal, Quebec, Canada H3T 1C5; Department of Pediatrics (P.S.), Albert Einstein College of Medicine, Bronx, New York 10467; Baystate Children's Hospital (E.O.R.), Tufts University School of Medicine, Springfield, Massachusetts 01199; Department of Pediatrics (J.L.R.), Thomas Jefferson University, Philadelphia, Pennsylvania 19107; Department of Pediatrics (S.D.C.), University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104; Centre for Endocrinology (M.O.S.), the London School of Medicine and Dentistry, London E1 2AQ, United Kingdom; and Department of Pediatrics (J.M.W.), Leiden University Medical Center, 2300 RC Leiden, The Netherlands

Objective: Our objective was to summarize important advances in the management of children with idiopathic short stature (ISS).

Participants: Participants were 32 invited leaders in the field.

Evidence: Evidence was obtained by extensive literature review and from clinical experience.

Consensus: Participants reviewed discussion summaries, voted, and reached a majority decision on each document section.

Conclusions: ISS is defined auxologically by a height below -2 sd score (SDS) without findings of disease as evident by a complete evaluation by a pediatric endocrinologist including stimulated GH levels. Magnetic resonance imaging is not necessary in patients with ISS. ISS may be a risk factor for psychosocial problems, but true psychopathology is rare. In the United States and seven other countries, the regulatory authorities approved GH treatment (at doses up to $53 \mu\text{g/kg}\cdot\text{d}$) for children shorter than -2.25 SDS, whereas in other countries, lower cutoffs are proposed. Aromatase inhibition increases predicted adult height in males with ISS, but adult-height data are not available. Psychological counseling is worthwhile to consider instead of or as an adjunct to hormone treatment. The predicted height may be inaccurate and is not an absolute criterion for GH treatment decisions. The shorter the child, the more consideration should be given to GH. Successful first-year response to GH treatment includes an increase in height SDS of more than 0.3 – 0.5 . The mean increase in adult height in children with ISS attributable to GH therapy (average duration of 4 – 7 yr) is 3.5 – 7.5 cm. Responses are highly variable. IGF-I levels may be helpful in assessing compliance and GH sensitivity; levels that are consistently elevated (>2.5 SDS) should prompt consideration of GH dose reduction. GH therapy for children with ISS has a similar safety profile to other GH indications. (*J Clin Endocrinol Metab* 93: 4210–4217, 2008)

0021-9726/08/9315-0010

Printed in U.S.A.

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doi: 10.1210/enc.2008-0509 Received March 4, 2008. Accepted August 27, 2008.

First Published Online September 9, 2008

Abbreviations: CDGP, Constitutional delay of growth and puberty; GnRH, GnRH analog; ISS, idiopathic short stature; SDS, sd score.

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J Clin Endocrinol Metab. 2008; 93:4210–4217.

Investigation of the GH Secretion

Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature. *J Clin Endocrinol Metab.*2008;93:4210–4217.

- ❖ GHD must be excluded to make a diagnosis of ISS
- ❖ Majority: Short, with normal height velocity, no bone age delay and a plasma IGF-I level above the mean does not require GH testing
- ❖ Minority: GH testing irrespective of IGF-I levels
- ❖ The choice of GH stimuli is country-dependent, as is the decision to prime with sex steroids
- ❖ Traditionally, a peak GH < 10 ng/mL = GHD, but new GH standards and assay methodologies may require a downward adjustment of the lower limit
- ❖ Assessing spontaneous GH secretion not indicated

Criteria for Treating Children with ISS

Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature. *J Clin Endocrinol Metab.*2008;93:4210–4217.

- ❖ Auxological: FDA approved < -2.25 SDS (1.2 percentile)
- ❖ Expert opinions range from - 2 SDS to – 3 SDS
- ❖ Optimal age for initiating treatment is 5 years to early puberty
- ❖ There are no accepted biochemical criteria for initiating GH
- ❖ Psychological: weigh the degree of short stature and the coping capacity of the child

Care of the Child with SGA

CONSENSUS STATEMENT: Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society

P. E. Clayton, S. Cianfarani, P. Czernichow, G. Johannsson, R. Rapaport, and A. Rogol

University of Manchester (P.E.C.), Manchester M13 9PL, United Kingdom; "Tor Vergata" University (S.C.), 00133 Rome, Italy; Robert Debre Hospital (P.C.), 75019 Paris, France; Sahlgrenska University Hospital (G.J.), SE-41345 Gothenburg, Sweden; Mount Sinai School of Medicine (R.R.), New York, New York 10029; and University of Virginia (A.R.), Charlottesville, Virginia 22911

Objective: Low birth weight remains a major cause of morbidity and mortality in early infancy and childhood. It is associated with an increased risk of health problems later in life, particularly coronary heart disease and stroke. A meeting was convened to identify the key health issues facing a child born small for gestational age (SGA) and to propose management strategies.

Participants: There were 42 participants chosen for their expertise in obstetrics, perinatal and neonatal medicine, pediatrics, pediatric and adult endocrinology, epidemiology, and pharmacology.

Evidence: Written materials were exchanged, reviewed, revised, and then made available to all. This formed the basis for discussions at the meeting. Where published data were not available or adequate, discussion was based on expert clinical opinions.

Consensus Process: Each set of questions was considered by all and then discussed in plenary sessions with consensus and unresolved issues identified. The consensus statement was prepared in plenary sessions and then edited by the group chairs and shared with all participants.

Conclusions: The diagnosis of SGA should be based on accurate anthropometry at birth including weight, length, and head circumference. We recommend early surveillance in a growth clinic for those without catch-up. Early neurodevelopment evaluation and interventions are warranted in at-risk children. Endocrine and metabolic disturbances in the SGA child are recognized but infrequent. For the 10% who lack catch-up, GH treatment can increase linear growth. Early intervention with GH for those with severe growth retardation (height sd score, < -2.5 ; age, 2–4 yr) should be considered at a dose of 35–70 $\mu\text{g/kg/d}$. Long-term surveillance of treated patients is essential. The associations at a population level between low birth weight, including SGA, and coronary heart disease and stroke in later life are recognized, but there is inadequate evidence to recommend routine health surveillance of all adults born SGA outside of normal clinical practice. (*J Clin Endocrinol Metab* 92: 804–810, 2007)

LOW BIRTH WEIGHT remains a major cause of morbidity and mortality in early infancy and childhood throughout the world (1). In addition, being born small has been associated with increased mortality from a wide range of disorders, in particular coronary heart disease (CHD) and stroke (2). For children born small for gestational age (SGA), it is important to integrate such data into their health-care management. Therefore, a meeting was convened in Manchester, United Kingdom, in February 2006, with representation from pediatric endocrine societies and the Growth Hormone Research Society, to examine current data relevant to the early, mid-, and long-term outcome of children born SGA. This statement presents a summary of key

health issues and proposed management of these children while recognizing topics that require further investigation.

Definition

The definition of SGA is not straightforward. It requires the following: 1) accurate knowledge of gestational age (ideally based on first trimester ultrasound exam), 2) accurate measurements at birth of weight, length, and head circumference, and 3) a cutoff against reference data from a relevant population. This cutoff has been variably set at the 10th centile, 3rd centile, or at less than -2 sd from the mean (~ 2 nd centile) (3). We recommend that SGA should be defined as a weight and/or length less than -2 sd because this will identify the majority of those in whom ongoing growth assessment is required.

Babies can then be subclassified into SGA for weight, SGA for length, or SGA for both weight and length (3). Additionally, those SGA babies who have small head circumference should be recognized. This subclassification may help in understanding the mechanisms and implications of being born SGA.

First Published Online January 2, 2007

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HPA, hypothalamic-pituitary-adrenal; IUGR, intrauterine growth retardation; SDS, sd score; SGA, small for gestational age.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

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Consensus Statement

- Diagnosis should be based on accurate anthropometry at birth
- At-risk children: early neurodevelopment evaluation and intervention
- Endocrine and metabolic disturbances are infrequent
- 10% lack “catch-up” growth
- GH therapy can increase linear growth in those lacking catch-up growth
- For severe growth retardation (-2.5 SD, 2–4 yr), start GH at 35–70 $\mu\text{g/kg/d}$
- SGA associated with coronary disease and stroke later in life
- Presently, inadequate evidence to recommend routine surveillance outside normal clinical practice

SGA = small for gestational age.

IUGR

❖ Definition

- Birth weight below 10 % for gestational age
- Birth weight or length at least - 2 SD < mean

❖ 85-90% catch up growth in the 1st or 2nd year of life

❖ Remaining 10-15% are eligible for GH treatment

❖ Child must be at least two years old

Care of Turner Syndrome (Led from the NIH)

CLINICAL PRACTICE GUIDELINE

Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group

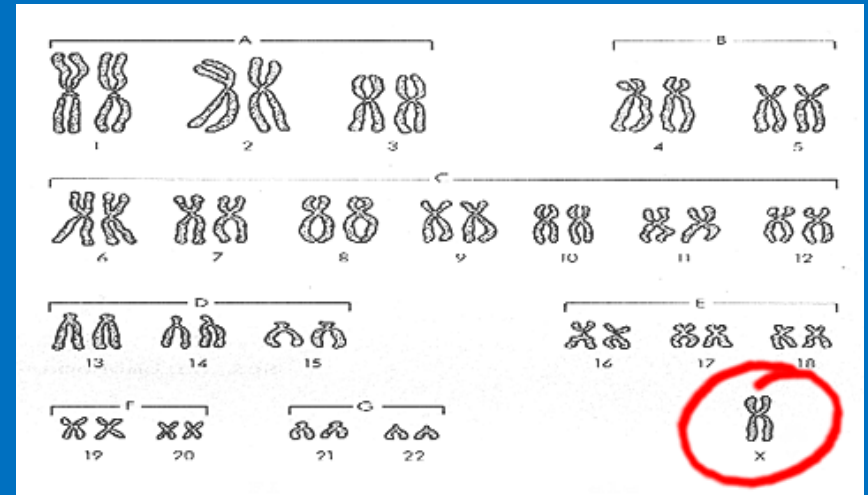
Carolyn A. Bondy for the The Turner Syndrome Consensus Study Group*

Evidence: The study group used peer-reviewed published information to form its principal recommendations. Expert opinion was used where good evidence was lacking.

Consensus: The study group met for 3 d to discuss key issues. Breakout groups focused on genetic, cardiological, auxological, psychological, gynecological, and general medical concerns and drafted recommendations for presentation to the whole group. Draft reports were available for additional comment on the meeting web site. Synthesis of the section reports and final revisions were reviewed by e-mail and approved by whole-group consensus.

Turner's Syndrome

- ❖ Evidence of IGF-1 resistance
- ❖ Haploinsufficiency of one copy of SHOX gene
- ❖ Absence of normal pubertal estrogen induced increase in endogenous GH secretion



The Latest Workshop: Prader-Willi Syndrome (PWS)

J Clin Endocrin Metab. First published ahead of print March 29, 2013 as doi:10.1210/jc.2012-3888

Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome

Cheri L Deal,¹ Michèle Tony², Charlotte Höybye³, David B. Allen⁴,
Maïthé Tauber⁵, Jens Sandahl Christiansen⁶, and
the 2011 GH in PWS Clinical Care Guidelines Workshop Participants.^a

Objective:

- Compose recommendations for the use of rhGH in children and adult patients with PWS

Recommendations:

- Consideration of rhGH treatment should be made in patients with genetically confirmed PWS in conjunction with dietary, environmental, and lifestyle interventions
 - Cognitive impairment should not be a barrier to treatment
 - Risk/benefit information should be part of informed consent
 - GH Dose should be adjusted to maintain IGF-I levels within the normal range (<-2SDS)

Noonan syndrome

- ❖ Is an autosomal dominant disorder that shares clinical features with TS, including growth retardation usually in the absence of GH deficiency
- ❖ A recent 3 year controlled trial showed a mean increase in growth rate from a baseline of 4.4 cm/year to 8.4, 6.2, and 5.8 cm/year during years 1, 2, and 3 of GH therapy respectively
- ❖ Others report that initial GH-induced growth acceleration is followed by a waning of effect with long-term therapy; in a small group of 10 patients, a mean increment in final height of only 3.1 cm was observed

CRF & GH

- ❖ Poor nutrition, anemia, and chronic metabolic acidosis contribute to the growth failure
- ❖ Elevated GH level, exaggerated responses to provocative stimuli, depressed serum IGF-1 levels, and increased levels of IGF-1 binding protein (in particular IGFBP-1) suggest resistance to the action of GH
- ❖ A randomized, double-blind, placebo-controlled study of 125 prepubertal growth-retarded children with CRF revealed first-year (10.7 ± 3.1 cm/yr) and second-year (7.8 ± 2.1 cm/yr) growth rates in the GH-treated group that were significantly greater than those seen in the placebo group
- ❖ In general, responsiveness to GH appears to be inversely related to the degree of renal function impairment and metabolic compromise
- ❖ Growth failure due to CRF is an approved indication for GH therapy

Skeletal dysplasia & GH

- ❖ Growth response to GH is generally less than that observed in children treated for classic GH deficiency and declines after initial acceleration
- ❖ Reports of response to GH are variable
- ❖ Some data indicate little change in growth rate, even when higher than conventional dosages are used
- ❖ More recent studies suggest that GH therapy can increase growth rate and height z-score in a dose-dependent manner without significant side effects
- ❖ Effects on ultimate height remain unknown

Achondroplasia

- ❖ Autosomal Dominant Disorder.
- ❖ Affects about 1 in 25,000 people.
- ❖ About 98% of those with achondroplasia have a point mutation in the FGFR3 gene at 4p16.3 that encodes fibroblast growth factor receptor 3.

Hypophosphate Rickets & GH

- ❖ In normal kidneys, GH increases renal phosphate retention
- ❖ Consequently, GH has been administered to poorly growing children with X-linked hypophosphatemic rickets
- ❖ In a recent study reporting final height outcome, GH therapy combined with conventional treatment resulted in a change in height SD score in six children with XHR (mean baseline -3.4 , mean post-treatment, -2.4) whereas no change in height SD score was observed in six XHR patients not treated with GH
- ❖ Phosphate retention, bone markers, and radial bone mineral density increased only in the GH-treated group
- ❖ Additional long-term studies are needed to verify the value of long-term GH therapy for patients with this disorder

Glucocorticoid-Treated Children

- ❖ Early studies, implementing relatively low dosage and infrequent administration of GH, demonstrated marginal and inconsistent beneficial effects
- ❖ Subsequent investigations of daily GH therapy for children with stable GC-treated illness or who had undergone renal transplantation show more consistent resumption of normal growth velocity during 1–3 years of treatment.
- ❖ Responsiveness to GH appears greatest in those on moderate-dosage GC regimens with stable, nonarthritic underlying disease.
- ❖ Persistence of disease activity and higher GC dosage (e.g., prednisone dosage >0.35 mg/kg/day) interfere with GH responsiveness

DOSAGE & ADMINISTRATION

- ❖ Should be administered subcutaneously
- ❖ Pediatric GHD: 0.024 to 0.034 mg/kg/day
- ❖ Noonan syndrome: Up to 0.066 mg/kg/day
- ❖ Turner syndrome: 0.067-0.09 mg/kg/day
- ❖ SGA: 0.035 Up to 0.067 mg/kg/day
- ❖ Prader-Willi syndrome: 0.035 mg/kg/day
- ❖ Chronic renal insufficiency: 0.045-0.050
- ❖ Adult GHD: 0.004-0.016 mg/kg/day

Starting GH Replacement

- ❖ Start with a low dose
 - subcutaneously at bedtime
- ❖ Monitor response carefully
 - clinically and biochemically
- ❖ Increase dose slowly
 - no more frequently than at monthly intervals

Response to GH Treatment

- ❖ Successful 1st year response: delta height SDS > 0.3 ; a HV increment > 3 cm/year; HVSDS $> +1$
- ❖ Emerging tools: prediction modeling/specific charts
- ❖ Serial IGF-I to assess efficacy, safety and compliance, and as tool for adjusting the GH dose
- ❖ No other biochemical tests are routinely recommended in GH-treated ISS patients
- ❖ If after 1-2 years, plus higher doses of GH, growth rate is still inadequate, GH should be stopped and alternative therapies could be entertained

GH Treatment Adjustment Strategies

Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature. *J Clin Endocrinol Metab.*2008;93:4210–4217.

- ❖ Dosage is usually selected and adjusted by weight
- ❖ If the growth response is considered inadequate, the dose may be increased
- ❖ There are no definitive data concerning the long-term safety of doses higher than 70 mcg/kg/day in ISS
- ❖ IGF-I levels may be helpful in assessing compliance and GH sensitivity; levels that are consistently elevated (>2.5 SDS) should prompt consideration of GH dose reduction

Monitoring Treatment Efficacy - Initial Assessment

❖ Baseline

- History from patient and partner (including quality of life)
- Examination (including weight & girth) & biochemical investigations (IGF-1, lipids, TFT)
- If possible, body composition & bone density by DEXA
- MRI (or CT) if past or present pituitary pathology

Duration of GH Treatment

Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature. *J Clin Endocrinol Metab.*2008;93:4210–4217.

Two schools of thought:

1. Treatment should stop when near adult height is achieved (HV < 2 cm/year, and/or BA > 16- boys / 14- girls).
2. Therapy can be discontinued when height is in the “normal” adult range (> – 2 SDS), or as in Australia, the 10th percentile or the 50th percentile

Stopping therapy is influenced by patient/family satisfaction and cost-benefit analysis

BA = bone age.

Criteria for Discontinuation GH Therapy

- ❖ Unless the patient requests to D/C therapy early or there are financial issues, side effects, etc., GH therapy is continued to near-final height.
- ❖ It is my practice to D/C therapy after we document a linear growth velocity of <0.5 cm every 3 months over 2 successive visits, assuming good compliance with therapy.
- ❖ We also document a near-mature/mature bone age.
- ❖ All GH deficient patients undergo repeat GH testing after a washout period, following D/C of GH.

Continuation Criteria for hGH RX in Children

- ❖ Increased growth rate by two cm over baseline in first year or one cm over baseline in 6 months for those patients undergoing a 6-month trial
- ❖ Continued growth rate exceeds 2.5 cm/year
- ❖ For treatment of growth hormone deficiency child's height remains below median adult height (5'10" for males, 5'5" for females) and mid-parental height
- ❖ For non-growth hormone deficiency treatment, the child's height continues to be >2.25 standard deviations below the normal adult height for gender (5' 3" for a male, 4' 11" for a female)

Consensus Guidelines for Adult GHD & Transition-Age Patients

CONSENSUS STATEMENT

Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society for Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia

Ken K Y Ho on behalf of the 2007 GH Deficiency Consensus Workshop Participants
c/o Growth Hormone Research Society, Medical Department M, Aarhus University Hospital, DK-8000 Aarhus, Denmark
(Correspondence should be addressed to K K Y Ho; Email: k.ho@arvan.org.au)

Abstract

Objective: The GH Research Society held a Consensus Workshop in Sydney, Australia, 2007 to incorporate the important advances in the management of GH deficiency (GHD) in adults, which have taken place since the inaugural 1997 Consensus Workshop.
Method: Two commissioned review papers, previously published Consensus Statements of the Society and key questions were circulated before the Workshop, which comprised a rigorous structure of review with breakout discussion groups. A writing group transcribed the summary group reports for drafting in a plenary forum on the last day. All participants were sent a polished draft for additional comments and gave signed approval to the final revision.
Conclusion: Testing for GHD should be extended from hypothalamic-pituitary disease and cranial irradiation to include traumatic brain injury. Testing may indicate isolated GHD; however, idiopathic isolated GHD occurring *de novo* in the adult is not a recognized entity. The insulin tolerance test, *or* combined administration of GHRH with arginine or growth hormone-releasing peptide, and glucagon are validated GH stimulation tests in the adult. A low IGF-1 is a reliable diagnostic indicator of GHD in the presence of hypopituitarism, but a normal IGF-1 does not rule out GHD. GH status should be reevaluated in the transition age for continued treatment to complete somatic development. Interaction of GH with other axes may influence thyroid, glucocorticoid, and sex hormone requirements. Response should be assessed clinically by monitoring biochemistry, body composition, and quality of life. There is no evidence that GH replacement increases the risk of tumor recurrence or *de novo* malignancy.

European Journal of Endocrinology 157 1–7

Introduction

Growth hormone deficiency (GHD) is a well-recognized clinical entity in the adult. It causes abnormalities in substrate metabolism, body composition, physical, and psychosocial function, which improve with GH replacement. In April 1997, the GH Research Society (GRS) convened an international workshop that formalized Consensus Guidelines for the Diagnosis and Treatment of Adults with GHD, which were widely adopted internationally by the health authorities and professional societies (1). The GRS convened a second international workshop on March 13–15, 2007 in Sydney, Australia, to review and incorporate important advances that have occurred in the last 10 years. The GRS invited leading experts in the field and related

professional societies, all of whom contributed to the updated Consensus.

The 2007 Workshop was structured in terms of format and discussions using the 1997 document as a template and produced this comprehensive statement that integrates new recommendations to those generated in 1997. The reader is encouraged to read the first document for further details (1).

Two discussion documents were commissioned for the workshop: one on the diagnosis and the other on the therapy of adults with GHD. These two review papers will be published separately (2, 3). Two previously published Consensus Statements for the GRS, the initial 1997 document (1) and another on the management of the GH-treated adolescent in the transition to adult care (4), along with the two commissioned reviews were

- Appropriate patients should undergo repeat GH testing at least one month after discontinuation of GH treatment
- In patients with CO GHD
 - Before the age of 20 years, the need for continuation of GH replacement should be evaluated following completion of statural growth
 - At approximately 25 years of age, a second re-investigation can be considered in those with CO-isolated idiopathic GHD
- Repeat GH testing is not required in patients with
 - Transcription factor mutations (eg, POU1F1 [Pit-1], PROP-1, HESX-1, LHX-3, LHX-4)
 - >3 pituitary hormone deficits
 - Isolated GHD associated with identified mutation (eg, GH-1, GHRH-R)

Adults with Growth Hormone Deficiency

- ❖ Pharmacologic provocation tests (insulin, clonidine, arginine, levodopa, glucagon) with a result <10 ng/ml with RIA (Radioimmunoassay) or <2.5 ng/ml with IRMA (Immunoradiometric assay)
- ❖ Hypothalamic or pituitary disease
- ❖ Significant clinical symptoms related to growth hormone deficiency such as fatigue, poor endurance, poor sense of well being persist despite maximizing treatment of other hormonal disorders, mood disorders, and medical illness
- ❖ Patient has multiple pituitary hormone deficiencies resulting from structural hypothalamic/pituitary disease, radiation, defined CNS pathology, cranial radiation, trauma, pituitary surgery, or genetic defect affecting the GH axis with low IGF-1 and low IGFBP-3

Side Effects

- ❖ **More common:**
- ❖ Abnormal or decreased touch sensation
- ❖ Blurred vision
- ❖ Burning,crawling,itching,numbness, prickling,pins and needles,or tingling feeling
- ❖ Dizziness
- ❖ Ear infection or other ear problem,pounding
- ❖ Nervousness
- ❖ Headache
- ❖ Slow or fast beat,chest pain, Gynecomastia

Side Effects

- ❖ **Rare:**
- ❖ Abdominal pain or bloating
- ❖ Changes in vision
- ❖ Depression of skin at place of injection
- ❖ Severe headache
- ❖ Limp
- ❖ Nausea and vomiting
- ❖ Pain and swelling at place of injection
- ❖ Pain in hip or knee
- ❖ Skin rash or itching, Nevi growth
- ❖ Significant adverse drug reactions rare

Contraindications

- ❖ Active malignancy
- ❖ Proliferative or pre-proliferative diabetic retinopathy
- ❖ Acute Critical illness
- ❖ Children with prader-Willi syndrome who are severely obese or have severe respiratory impairment-reports of sudden death
- ❖ Children with closed epiphyses
- ❖ Known hypersensitivity to somatropin or excipients

WARNINGS & PRECAUTIONS

- ❖ Acute critical illness
- ❖ Prader-Willi syndrome
- ❖ Neoplasm
- ❖ Impaired Glucose Tolerance and diabetes
- ❖ Intracranial Hypertension
- ❖ Fluid Retention
- ❖ Hypothyroidism
- ❖ Slipped Capital Femoral Epiphysis
- ❖ Progression of preexisting Scoliosis
- ❖ Pancreatitis

Adverse side effects of GH therapy

- ❖ Recombinant biosynthetic GH preparations are highly purified and free of contaminants
- ❖ The possibility of viral transmission through GH has been virtually eliminated
- ❖ Antigenicity of GH preparations is also low, although GH antibodies can be detected in 10–30% of treated children. With rare exceptions (less than 0.1%), these antibodies do not impede effects of GH

GH Treatment and Intercurrent Illness

- ❖ No data to support discontinuation of GH replacement treatment during illness
- ❖ Risk of hypoglycemia should be considered in children with GH deficiency who discontinue GH treatment
- ❖ GH-IGF system is dysregulated in critical illness
- ❖ GH deficiency, is frequently part of a more extensive pituitary deficiency including adrenocortical deficiency, which should be considered during critical illness in such patients

Adverse effects of GH treatment

- ❖ In first 8 weeks – **Benign Intracranial Hypertension** Has been reported in 1 in 1000 children receiving GH treatment
 - due to the increase in salt and water retention
 - complain of headache, loss of vision, nausea or vomiting.
 - resolves rapidly when growth hormone treatment is stopped
 - GH can usually then be restarted at a lower dose, and the dose slowly increased without further problems
 - Fundoscopic examination should be performed before initiation of GH treatment and repeated when clinically indicated

Epidemiological Data

GH Replacement and Cancer Risk

- No data to suggest that IGF-I and IGFBP-3 modulate cancer risk in GH-treated patients
- Patients with previous malignancies or history of radiation therapy carry significant risk for recurrence and second malignancy
- Recommend measurement of serum IGF-I levels in patients receiving GH treatment; place of regular IGFBP-3 monitoring is not defined
- Recommend that IGF-I level be maintained within appropriate age- and gender-related normal range in GH-deficient adults during long-term therapy

Safety - GH Therapy in Children

Malignancy Risk

- ❖ Certain patient groups who receive GH treatment carry an intrinsic risk of developing malignancies, including those with Neurofibromatosis type 1, Fanconi anemia, Downs and Bloom syndromes.
 - Although no evidence that GH replacement poses increased cancer risk, *such children be carefully monitored* with regard to tumor formation

Safety - GH Therapy in Children

Malignancy Risk

All subjects who have had a malignancy and received treatment for it are at risk for a second malignancy.

- No evidence that GH treatment increases risk of this process based on limited data available
- No evidence that *de-novo* cancer and leukemia are increased in GH recipients
- In view of continuing evolution of oncology treatments, ongoing surveillance of GH recipients with appropriate age-related controls is important

Is GH mitogenic ??

- ❖ In 1988, reports from Japan describing leukemia in GH-treated children raised concern about malignancy
- ❖ Any possible increased incidence of leukemia appears limited to those patients with known risk factors, and due to the small numbers of events in such patients, it remains impossible to determine any contribution of GH therapy
- ❖ With regard to non-leukemia cancers, a retrospective analysis of large post-marketing database found no evidence of an increased risk of developing an extracranial, nonleukemia neoplasm in GH-treated patients

Is GH mitogenic ??

- ❖ No reports have associated GH therapy with an increased incidence of tumor recurrence
- ❖ A lack of reliable knowledge about the natural history of recurrence of these tumors, however, supports a cautious interpretation of such data.
- ❖ Most recurrences occur within the first 2 years of treatment, and most endocrinologists defer institution of treatment until a year of stable remission has passed.
- ❖ No study to date has directly compared the incidence of new second tumors in those receiving GH

Safety - GH Therapy in Children

Malignancy Risk

Children receiving GH, who have had a malignancy, account for approximately 20% of patients enrolled in international databases.

- Existing evidence does not indicate that GH treatment will increase tumor recurrence in those successfully treated for their primary lesion
- In patients who have been rendered GH deficient by tumor and/or its treatment, timing of initiation of GH treatment must be decided on basis of individual case, once tumor treatment is completed and condition is in remission

Safety - GH Replacement in Glucose Metabolism

- ❖ Prevalence of diabetes mellitus (DM) increased in hypopituitary adults
- ❖ Metabolic actions of GH include insulin antagonism
- ❖ *Thus*, recommend that glucose metabolism be assessed in all patients before and during GH replacement
- ❖ DM (or impaired glucose tolerance) not a contraindication to GH replacement; care of diabetes in GH-replaced adults should follow standard guidelines, but intensified monitoring of metabolic control is advocated in early phase of GH replacement of such patients

Safety - GH Therapy in Children

Glucose Metabolism

- ❖ Reduction of insulin sensitivity is physiologic effect of GH, however, glucose homeostasis is maintained in vast majority of patients
- ❖ Most available surveillance data do not demonstrate increased incidence of diabetes, either type 1 or type 2, associated with GH treatment
- ❖ There are, however, subgroups of patients inherently at risk of developing diabetes - these should be carefully monitored

Safety - GH Therapy in Children Skeletal Disorders

- ❖ Some underlying disorders that are treated with GH therapy can be associated with slipped capital femoral epiphysis, scoliosis and avascular necrosis
- ❖ No evidence these conditions are caused by GH treatment; however, scoliosis may be exacerbated when growth is accelerated

Safety - GH Therapy in Children

Interaction with Other Hormones

- ❖ No compelling evidence that GH treatment has any adverse effect on pubertal development and gonadal function
- ❖ GH can affect metabolism of thyroid hormones and cortisol

Safety - GH Replacement in Interaction with Other Hormones

- ❖ Growth hormone increases extrathyroidal conversion of T_4 to T_3 - thyroid function should be monitored in all patients
- ❖ GH may decrease serum total cortisol concentrations by decreasing circulating cortisol binding globulin

Safety - GH Replacement in Interaction with Other Hormones

- ❖ Even though clinical implications for these observations are uncertain, increased awareness of glucocorticoid status is recommended in all patients
- ❖ Possibility that overt ACTH insufficiency may be unmasked during GH replacement (as a result of inhibition of 11 β HSD1) should be considered

Conclusion-1

Growth hormone therapy has many advantages including:

- ❖ Improves linear growth
- ❖ Body composition changes producing a reduction in total and visceral fat and increase in lean body mass
- ❖ Improvement in CV function and lipids
- ❖ Improves Quality of life
- ❖ Increases bone mineral density
- ❖ Improves memory, alertness, and concentration

Conclusion -2

- ❖ GH has been approved for many conditions including: growth hormone deficiency, CRF,
- ❖ Turner Syndrome, PWS,SGA, ISS, AIDS wasting and Noonan Syndrome
- ❖ Increased frequency of GH administration improves
- ❖ growth rate, suggesting the so-called pulsing
- ❖ message of GH to its target cells
- ❖ Nocturnal administration mimics physiological GH secretion may add to efficacy
- ❖ The effect of GH wanes with time
- ❖ First year of treatment usually produces the greatest growth increment

