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Somatropin for Growth Hormone Deficiency

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Rapid Review

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Abbreviations

AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
AO-GHD	adult-onset growth hormone deficiency
BMD	bone mineral density
BMI	body mass index
CO-GHD	childhood-onset growth hormone deficiency
DM	diabetes mellitus
DXA	dual-energy X-ray absorptiometry
GH	growth hormone
GHD	growth hormone deficiency
GST	glucagon-stimulation test
IGF-1	insulin-like growth factor-1
IGHD	isolated growth hormone deficiency
ITT	insulin tolerance test
MPHD	multiple pituitary hormone deficiency
PES	Pediatric Endocrine Society
PHD	pituitary hormone deficiency
QoL	quality of life
rhGH	recombinant human growth hormone
SDS	standard deviation score

Key Messages

- We identified 2 evidence-based guidelines that provide recommendations for the clinical management of children and adults with growth hormone deficiency.
- The American Association of Clinical Endocrinologists and American College of Endocrinology guideline provides recommendations on assessment, screening, diagnostic testing, treatment, and monitoring for a range of patients with different causes of adult growth hormone deficiency. The recommendations emphasize accurate diagnosis using appropriate growth hormone cut points for different growth hormone–stimulation tests and careful interpretation of serum growth hormone and insulin-like growth factor-1 levels. Treatment with recombinant human growth hormone should be carried out with consideration of the benefits and risks specific to each individual patient.
- The Pediatric Endocrine Society guideline provides recommendations for the clinical management of children and adolescents with growth failure due to growth hormone deficiency. The guideline lists various conditions for which growth hormone deficiency can be diagnosed by conventional approaches without growth hormone–stimulation testing. The treatment dose of growth hormone should be calculated based on weight and body surface area and not on insulin-like growth factor-1 levels. The guideline highlights that the initial growth hormone dose, subsequent dosing, and discontinuation of pediatric doses should be assessed based on each individual patient.
- Both guidelines recognize the uncertainty of long-term safety (i.e., posttreatment effects) of growth hormone treatment, which is a limitation of both guidelines.

Context and Policy Issues

Growth hormone deficiency (GHD) is characterized by inadequate secretion of growth hormone (GH) from the pituitary gland which affects approximately 1 in 4,000 to 10,000 children worldwide and approximately 1 in 1,600 children in Canada.[1] Adult GHD affects 1 in 3,300 to 5,000 of the population in Europe[2] (Canadian data for adult GHD were not available). GHD can be classified into childhood-onset GHD (CO-GHD) and adult-onset GHD (AO-GHD).[3] CO-GHD can be further categorized as congenital, acquired, or idiopathic.[3] AO-GHD is generally acquired, although it can be a continuation of CO-GHD.[3] The causes of congenital GHD include abnormalities of genes related to GH synthesis and the GH-releasing hormone receptor.[4] The causes of acquired GHD include tumours in the pituitary gland and hypothalamus, surgery or therapeutic radiation of these tumours, meningitis, and brain injury.[4] GHD can occur in isolation or in association with deficiencies of other pituitary hormones.[4]

Children with GHD who are untreated can have shorter-than-average height and delayed puberty.[4] In adults, the disease is characterized by alterations of body composition and bone structure, reduced physical performance, and quality of life (QoL), and unfavourable changes in lipid profile, carbohydrate metabolism, and cardiovascular function, which may cause increased morbidity and mortality.[5] Random measurement of GH level in a blood sample is not sufficient to diagnose GHD because GH levels decline with age, its secretion from the pituitary gland is episodic in a pulsative pattern, and it is modified by age, sex, and body

mass index (BMI).[6] Its diagnosis is based on the combination of direct and indirect criteria, such as body measurements (e.g., age, height, bone age, and height velocity), concentration of insulin-like growth factor-1 (IGF-1), pituitary disease, hypopituitarism, and measurement of GH in response to GH-stimulation testing.[7] There are different GH-stimulation tests available to assess the secretion of GH after pharmacological stimulation. These pharmacological agents or stimulants include GH-releasing hormone, insulin, glucagon, macimorelin, levodopa, clonidine, and arginine. The insulin tolerance test (ITT) is generally accepted as the "gold-standard" test for the assessment of GHD, but it can potentially cause hypoglycemia and is contraindicated in older patients and patients with a history of cardiovascular and cerebrovascular disease or seizures.[8]

Recombinant human GH (rhGH) or somatropin has been used as GH replacement therapy since the 1980s.[5] In Canada, 6 somatropin products (Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, and Norditropin) are available for treatment of GHD in children, and 5 products (Genotropin, Omnitrope, Humatrope, Nutropin, and Saizen) are available for treatment of GHD in adults.[9] The benefits of treatment with GH include a decrease in fat mass and increase in lean mass, increase in bone mineral density (BMD), improvement of QoL, and improvement of several cardiovascular risk factors, such as lipid profile, endothelial function, and cardiovascular inflammatory markers.[5] The most common side effects of GH replacement therapy are swelling due to fluid retention and pain in the joints and muscles.[5] Reducing the GH dose can usually relieve the side effects.[5] There are some concerns regarding long-term outcomes of GH treatment related to an increase in insulin resistance and an increased risk of cancer.[7] It remains to be determined whether GH treatment improves overall mortality, bone fractures, or heart disease.[5]

Because there is a wide range of patients with various causes of GHD, it is important to seek guidance from evidence-based guidelines regarding the identification, diagnosis, and treatment of GHD. The objective of this report is to summarize the recommendations from evidence-based guidelines regarding the diagnosis and treatment of GHD and the monitoring of GH therapy in children and adults.

Research Question

What are the evidence-based guidelines regarding the use of growth hormone therapy for children and adults with growth hormone deficiency?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical

Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were somatropin and GHD. CADTH-developed search filters were applied to limit retrieval to guidelines. The search was completed on June 2, 2023, and was limited to English-language documents published since January 1, 2013.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Adults and children with GHD
Intervention	All somatropin products
Comparator	Not applicable
Outcomes	Recommendations regarding best practices (e.g., dose and timing of treatment, duration of treatment, laboratory cut-offs for eligibility, monitoring treatment response)
Study designs	Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1. Guidelines with unclear methodology were not included in the text, but their characteristics and findings are presented in Appendix 5.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[10] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 90 citations were identified in the literature search. Following screening of titles and abstracts, 72 citations were excluded and 18 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of the potentially relevant articles, 16 publications were excluded for various reasons, and 2 publications met the inclusion criteria and were included in this report. These were 2 evidence-based guidelines. Appendix 1 presents the PRISMA[11] flow chart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

We identified 2 evidence-based guidelines:

- the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guideline by Yuen et al. (2019)[12]
- the Pediatric Endocrine Society (PES) guideline by Grimberg et al. (2016).[13]

The AACE and ACE guideline[12] and PES guideline[13] clearly provided the methods of evidence collection, selection, and synthesis. A systematic search of the literature was conducted from multiple databases. Study selection, data extraction, and quality assessment of the included studies were performed in duplicate. Both guidelines[12,13] used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tool to grade the level of evidence and the strength of recommendations.

- The AACE and ACE guideline[12] rated the level of evidence ranging from strong evidence (1) if the data were derived from randomized controlled trials or a meta-analysis of randomized controlled trials to no evidence (4). The strength of each recommendation was graded based on the level of evidence, ranging from very strong (A) to primarily based on expert opinions (D).
- The PES guideline[13] judged its level of evidence ranging from "high" to "very low," reflecting the reviewers' assessment of the quality of the evidence according to GRADE guidelines. The strength of each recommendation was graded as strong (denoted by "we recommend") or conditional (denoted by "we suggest") in accordance with GRADE guidelines. Recommendations without direct supporting evidence but were important to include in the guideline are marked "ungraded good practice statement."

Both guidelines[12,13] clearly described how the recommendations were developed and evaluated. Additional details regarding the characteristics of the included guidelines are provided in Appendix 2.

Country of Origin

Both guidelines[12,13] were conducted by authors from the US.

Patient Population

- The target populations in the AACE and ACE guideline[12] were adults with GHD and patients with GHD transitioning from pediatric to adult care. The intended users were clinicians involved in the management of GHD in adults and in patients transitioning from pediatric to adult care.
- The target populations of the PES guideline[13] was children and adolescents with growth failure from GHD, idiopathic short stature, or primary IGF-1 deficiency. The intended users were clinicians involved in the management of GHD, idiopathic short stature, or primary IGF-1 deficiency in children and adolescents. Only recommendations related to GHD are presented and discussed in this report.

Interventions and Comparators

Both guidelines[12,13] considered the management of GHD, including diagnosis and treatment with GH replacement therapy.

Outcomes

Both guidelines[12,13] considered all outcomes (e.g., clinical, cost, or QoL) related to the diagnosis and treatment of GHD.

Summary of Critical Appraisal

Both included guidelines[12,13] were explicit in terms of scope and purpose (i.e., objectives, health questions, and populations), and had clear presentation of recommendations (i.e., specific, unambiguous, and easy-to-find key recommendations, with options for managing the different conditions or health issues). The recommendations were arranged by specific clinical questions regarding the identification, diagnosis, and treatment of patients with GHD. In terms of stakeholder involvement, both guidelines[12,13] clearly defined target users and the development groups, but did not report whether the views and preferences of the patients were sought. The methodology for the development of both guidelines[12,13] were robust. Both guidelines[12,13] clearly reported methods for evidence collection, criteria for selection, and methods for evidence synthesis. There were explicit links between the recommendations and the supporting evidence and the methods of formulating the recommendations in both guidelines.[12,13] Both guidelines[12,13] also considered the health benefits and risks of side effects in formulating the recommendations. However, the procedures for updating the guidelines were not reported in both guidelines.[12,13] For applicability, it was unclear in terms of facilitators and barriers to application, advice, and/or tools on how the recommendations can be put into practice, and monitoring or auditing criteria in both guidelines.[12,13] For editorial independence, both guidelines[12,13] reported competing interests of guideline development group members, but did not report if the views of the funding body had any influence on the content of the guidelines. Overall, both guidelines[12,13] were robust in terms of scope and development, rigour of development, and clarity of presentation.

Additional details regarding the strengths and limitations of the included guidelines[12,13] are provided in Appendix 3.

Summary of Findings

Guidelines Regarding the Use of GH Therapy for Children and Adults With GHD

Appendix 4 presents the summary of recommendations from the included guidelines.[12,13]

The guidelines provided recommendations on assessment, screening, diagnostic testing, and treatment for a range of individuals with various causes of adult with GHD[12] or children[13] with GHD. The recommendations were developed based on predefined clinical questions. Recommendations from each guideline are summarized subsequently, with recommendations related to somatropin use reported in more detail.

AACE and ACE Guideline[12] for the Management of GHD in Adults and in Patients Transitioning From Pediatric to Adult Care

The AACE and ACE guideline provides detailed, evidence-based recommendations regarding the identification, diagnosis, and treatment of adults with GHD and young patients with GHD transitioning from pediatric to adult care services. There are differences in the etiology of CO-GHD and AO-GHD in adults who

have been diagnosed with GHD. The transition to adult care services for adolescents with GHD should be facilitated seamlessly so that rhGH replacement therapy in patients with confirmed persistent GHD can be resumed without delay to achieve long-term benefits through adulthood. GH-stimulation testing should be performed to confirm the diagnosis of adult GHD, except for certain GHD subtypes.

Testing should be carried out with a reasonable level of clinical suspicion of GHD using appropriate GH cut points for various GH-stimulation tests to accurately diagnose adult GHD. The ITT remains the gold-standard test for the diagnosis of adult GHD. If the ITT is contraindicated, then the glucagon-stimulation test (GST) or macimorelin-stimulation test should be used instead. Laboratories should standardize and validate their GH and IGF-1 assays because GH cut points and IGF-1 levels are important for the diagnosis and management of GHD.

RhGH replacement therapy should be initiated at low dosages. The suggested starting doses are 0.1 mg/day to 0.2 mg/day for patients with concurrent diabetes mellitus (DM) or previous gestational DM, patients with obesity, or older patients, and 0.4 mg/day to 0.5 mg/day for adults younger than 30 years without DM. For patients who are transitioning to adult care, clinicians should consider restarting rhGH therapy at half the dose used in childhood. After starting rhGH therapy, patients should be followed at 1-month to 2-month intervals, and the rhGH dose should be increased in increments of 0.1 mg/day to 0.2 mg/day based on serum IGF-1 levels. Patients should be followed at 6-month to 12-month intervals during the maintenance period. Several biochemical and cardiovascular parameters should be monitored during the maintenance period. Bone mineral content and BMD should be measured at baseline and at 2-year to 3-year intervals. QoL should also be assessed at baseline and at 12-month intervals during rhGH therapy. Side effects of rhGH replacement are mainly related to fluid retention effects. Treatment with rhGH should be conducted with caution in patients with a strong family history of cancer.

What Is Adult GHD?

Recommendations pertaining to the definition of adult GHD are presented in Appendix 4. In brief, adult GHD can be categorized into CO-GHD and AO-GHD. AO-GHD can be caused by tumours in the hypothalamic-pituitary area or brain injury.

Are There Any Differences Between CO-GHD Versus AO-GHD?

Recommendations related to the differences in etiology between CO-GHD and AO-GHD are presented in Appendix 4.

How Should Pediatric Patients With CO-GHD Be Transitioned to Adult Care Services?

Recommendations of how adolescents with CO-GHD can be transitioned to adult endocrine services are presented in Appendix 4.

What Are the Benefits of Continuing rhGH Replacement in Transition Patients With CO-GHD?

- Adults with CO-GHD caused by structural pituitary or brain tumours should be followed up closely during transition. These patients tend to have low BMD; impaired bone microarchitecture; and abnormal body composition, which may include increased fat mass and decreased lean body

mass; and increased adverse cardiovascular markers **(quality of evidence: strong; strength of recommendation: very strong).**

- It is recommended that rhGH replacement therapy be resumed in patients with confirmed persistent GHD during the transition period after achieving their final height. Evidence suggests that rhGH therapy has the greatest impact on body composition, muscle strength, and cardiovascular risk markers, with less impact on BMD, insulin sensitivity, and QoL **(quality of evidence: strong; strength of recommendation: very strong).**

Who Should Be Tested for Adult GHD?

- Adults with certain GHD subtypes can be diagnosed for GHD without needing to perform GH-stimulation testing, including those with:
  - organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) and biochemical evidence of multiple pituitary hormone deficiencies (MPHDs) (≥ 3 pituitary hormone deficiencies [PHDs]) together with low serum IGF-1 levels (< –2.0 standard deviation score [SDS])
  - genetic defects affecting the hypothalamic-pituitary axes
  - hypothalamic-pituitary structural brain defects **(quality of evidence: weak; strength of recommendation: not strong).**
- Patients with 2 or fewer PHDs should have 1 GH-stimulation test to confirm diagnosis because low serum IGF-1 levels are not sufficient to make a diagnosis of adult GH deficiency **(quality of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: strong).**
- Patients who are transitioning to adult therapy after longitudinal growth is completed should be retested for GHD with GH-stimulation tests after at least 1 month of discontinuation of rhGH therapy if they have any of the following:
  - idiopathic isolated GHD (IGHD)
  - low-normal (between 0 SDS to –2 SDS) serum IGF-1 levels
  - low (< –2 SDS) serum IGF-1 levels **(quality of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: strong).**
- Patients with IGHD who have organic hypothalamic-pituitary disease after longitudinal growth is completed should have GH-stimulation tests depending on the degree of clinical suspicion for GHD. One or 2 GH-stimulation test(s) should be performed if clinical suspicion is high or low, respectively **(quality of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: strong).**
- Most transition patients, especially those with idiopathic IGHD and serum IGF-1 SDS less than 0, should be retested for GHD with GH-stimulation test(s) after longitudinal growth is completed and pediatric rhGH therapy has been discontinued for at least 1 month to continue rhGH replacement therapy in adulthood in **(quality of evidence: strong; strength of recommendation: very strong).**

- Patients with idiopathic IGHD and serum IGF-1 level of 0 SDS or higher do not require retesting and rhGH therapy because these patients are likely to have a normal GH-stimulation test **(quality of evidence: intermediate; downgraded due to inconsistent results; strength of recommendation: not strong).**
- Patients who are transitioning to adult care do not require retesting before continuation of rhGH therapy if they have any of the following:
  - MPHD (≥ 3 PHD) and low serum IGF-1 levels (< −2.0 SDS)
  - genetic defects affecting the hypothalamic-pituitary axes
  - hypothalamic-pituitary structural brain defects **(quality of evidence: intermediate; downgraded due to inconsistent results; strength of recommendation: not strong).**
- Patients undergoing radiation therapy with higher radiation doses and longer duration of radiation therapy should be retested later in the transition period or in adulthood to rule out delayed GHD **(quality of evidence: intermediate; strength of recommendation: strong).**
- Patients with traumatic brain injuries or subarachnoid hemorrhage events should have GH-stimulation testing at least 12 months after the event because these may cause GHD **(quality of evidence: intermediate; strength of recommendation: strong).**

How Should One Test for Adult GHD?

- Perform GH-stimulation test(s), instead of random measurements of serum GH and IGF-1 levels, to confirm the diagnosis of GHD except in certain subpopulations of patients, including those with:
  - organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) who have MPHD (≥ 3 PHDs) and low serum IGF-1 levels (< –2.0 SDS)
  - genetic defects affecting the hypothalamic-pituitary axes
  - hypothalamic-pituitary structural brain defects **(quality of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: strong).**
- Perform GH-stimulation test(s) only after all other PHDs have been optimally replaced with stable hormone doses **(quality of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: not strong).**
- Use the ITT to establish the diagnosis of adult GHD using a peak GH cut point of 5 mg/L. If the test is contraindicated in certain patients, such as older patients and those with seizure disorders, cardiovascular disease, or cerebrovascular disease, then use the GST or the macimorelin test instead **(quality of evidence: strong; strength of recommendation: strong).**
- For the GST, use BMI-appropriate GH cut points to diagnose adult GHD:
  - GH cut point of 3 mcg/L for patients with “normal” weight (BMI < 25 kg/m^2) and with overweight (BMI 25 kg/m^2 to 30 kg/m^2) and with a high pretest probability
  - GH cut point of 1 mcg/L for patients with obesity (BMI > 30 kg/m^2) or with overweight (BMI 25 kg/m^2 to 30 kg/m^2) and with a low pretest probability **(quality of evidence: intermediate; strength of recommendation: strong).**

- For macimorelin-stimulation test, use GH cut point of 2.8 mg/L to diagnose adult GHD **(quality of evidence: intermediate; strength of recommendation: strong).**
- Use the ITT (with a GH cut point ≤ 5.0 mg/L) for patients who are transitioning to adult care. If the test is contraindicated, then use the GST or the macimorelin test instead **(quality of evidence: intermediate; strength of recommendation: not strong).**
- Do not use arginine and levodopa testing because these tests have low sensitivity and specificity and have not been systematically evaluated and validated **(quality of evidence: intermediate; strength of recommendation: strong).**

Why Are Standardized GH and IGF-1 Assays Important in the Management of Adult GHD?

Accurate measurement of serum GH and IGF-1 levels is critical for the management of adult GHD; therefore, it is recommended that all assays should meet the standards provided by the National Institute for Biological Standards and Control. Recommendations pertaining to the importance of the standardization of the GH and IGF-1 assays are presented in Appendix 4.

How Should Initiation and Monitoring of rhGH Replacement Be Undertaken?

- There is no evidence that 1 commercial rhGH product is more advantageous than another **(strength of recommendation: primarily based on expert opinion).**
- Use serum IGF-1 as the biomarker for guiding rhGH dose adjustments **(quality of evidence: strong; strength of recommendation: very strong).**
- Start with a low dose of rhGH and gradually titrate the dose up to normalize serum IGF-1 levels with the aim of minimizing any side effects **(quality of evidence: strong; strength of recommendation: very strong).**
- Target the serum IGF-1 levels within the age-adjusted reference range (IGF-1 SDS between −2 and +2) to achieve clinical response and avoid side effects **(strength of recommendation: primarily based on expert opinion).**
- Initiate rhGH therapy with the following suggested starting doses:
  - 0.1 mg/day to 0.2 mg/day for patients with concurrent DM or previous gestational DM, with obesity, or who are older adults
  - 0.3 mg/day to 0.4 mg/day for adults younger than 30 years without DM and for people on oral estrogen therapy **(quality of evidence: strong; strength of recommendation: very strong).**
- Recommended follow-up intervals and dose increase increments are the following:
  - After starting rhGH therapy: Follow-up at 1-month to 2-month intervals; the dose is increased in increments of 0.1 mg/day to 0.2 mg/day.
  - During maintenance period: Follow-up at 6-month to 12-month intervals.
  - A shorter follow-up time and smaller dose increments can be applied to older patients or those with comorbidities, such as DM **(quality of evidence: strong; strength of recommendation: very strong).**

- Assay the following parameters during the maintenance period at approximately 6-month to 12-month intervals:
  - serum IGF-1
  - fasting glucose
  - hemoglobin A1C
  - fasting lipids
  - BMI
  - waist circumference
  - waist-to-hip ratio
  - serum-free T4
  - hypothalamic-pituitary-adrenal axis **(quality of evidence: intermediate; primarily based on expert opinion; strength of recommendation: not strong).**
- Consider restarting rhGH therapy in transition patients with 50% of the pediatric dose. The dose should be modified based on clinical response, serum IGF-1 levels (not exceeding the upper limit of normal range [IGF-1 > 2 SDS]), side effects, and individual patient considerations **(strength of recommendation: primarily based on expert opinion).**
- Measure the following parameters in transition patients:
  - every year: height, weight, BMI, fasting lipid levels, and waist and hip circumferences
  - every 2 to 3 years: BMD **(strength of recommendation: primarily based on expert opinion).**
- Monitor the following parameters in adults with GHD at 6-month to 12-month intervals because there is increased risk of cardiovascular morbidity and mortality during rhGH therapy:
  - fasting lipids
  - systolic and diastolic blood pressure
  - heart rate
  - electrocardiogram
  - echocardiogram
  - carotid echo-Doppler examinations **(quality of evidence: intermediate; primarily based on expert opinion; strength of recommendation: not strong).**
- Suggest measuring bone mineral content and BMD using dual-energy X-ray absorptiometry (DXA) in adults with GHD before starting rhGH therapy. If the scan is abnormal, repeat the scans at 2-year to 3-year intervals to assess the need for bone treatment **(quality of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: not strong).**
- Perform a baseline MRI before initiating rhGH in patients who underwent surgery for a tumour remnant in the hypothalamic-pituitary region and periodic MRIs during rhGH therapy **(quality**

of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: not strong).

- Consider assessing QoL at baseline and at 12-month intervals during rhGH therapy **(quality of evidence: no evidence; upgraded by consensus based on expert opinion; strength of recommendation: not strong).**
- Consider monitoring glucocorticoid and thyroid hormones before starting and during rhGH therapy because these hormone may be required while on rhGH therapy **(quality of evidence: strong; strength of recommendation: strong).**
- Continue rhGH treatment indefinitely when patients experience beneficial effects on QoL and improvements in biochemistry, body composition, and BMD **(quality of evidence: intermediate; strength of recommendation: strong).**

Can rhGH Be Used During Conception and Pregnancy?

Routine use of rhGH during conception and pregnancy cannot be recommended at this time due to lack of safety data **(quality of evidence: weak; strength of recommendation: not strong).**

What Are the Side Effects of rhGH Replacement?

- Side effects are mainly related to fluid retention and are typically observed during initiation and dose escalation of rhGH. Therefore, lower doses of rhGH are recommended in patients with obesity and older patients who are more susceptible to the side effects of rhGH replacement therapy **(quality of evidence: strong; strength of recommendation: very strong).**
- Avoid using high rhGH doses to minimize the risk of side effects and to maintain target serum IGF-1 levels within the age-adjusted laboratory reference range (IGF-1 SDS between –2 and +2) **(quality of evidence: strong; strength of recommendation: very strong).**

How Safe Is Long-Term rhGH Replacement Therapy?

- Consider using low-dose rhGH therapy and adjusting antidiabetic medications if DM develops during rhGH therapy. Consider discontinuing rhGH therapy and adjusting the doses of antidiabetic therapy if pre-existing DM worsens during rhGH therapy to optimize DM treatment before resuming rhGH therapy **(quality of evidence: strong; strength of recommendation: strong).**
- RhGH therapy is contraindicated in patients with a history of active malignancy (other than basal cell or squamous cell skin cancers) and active proliferative or severe nonproliferative diabetic retinopathy **(quality of evidence: intermediate; strength of recommendation: strong).**
- Treatment with rhGH should be conducted carefully in patients with a strong family history of cancer **(quality of evidence: intermediate; strength of recommendation: strong).**
- For adults with GHD and a history of cancer who wish to start rhGH replacement therapy, low-dose rhGH therapy should only be initiated at least 5 years after cancer remission **(strength of recommendation: primarily based on expert opinion).**
- Although there are no data to suggest that adult rhGH replacement for more than 20 years increases the risk of cancer or accelerates recurrences of tumours in the hypothalamic-pituitary region, long-

term monitoring and standard cancer screening is suggested **(quality of evidence: intermediate; strength of recommendation: strong).**

PES Guideline[13] for GH Treatment in Children and Adolescents With GHD

The PES guideline provides recommendations for the clinical management of children and adolescents with GHD. The guideline begins with a recommendation on the use of GH to treat GHD. Routine cardiac testing, DXA scanning, and measurement of lipid profiles of patients receiving GH treatment are not recommended. GH-stimulation testing should not be the sole diagnostic criterion for GHD, and the test is not needed in certain populations with specific conditions. Laboratories should provide standardized GH assays using standard somatropin. Sex steroid priming before GH-stimulation testing may be considered in prepubertal children. GH treatment should be started with a low dose, although some patients may need higher doses. Serum IGF-1 levels should be used to monitor response to changes in GH dose. GH treatment is continued until the growth rate falls below 2.5 cm/year. Patients should be aware of the potential short-term and long-term adverse effects of GH treatment. Re-evaluate the somatotropic axis in children diagnosed with GHD during the transition period (i.e., from pediatric to adult care).

Efficacy of GH Treatment for GHD

- Use GH to normalize adult height in children and adolescents with GHD **(quality of evidence: high; strength of recommendation: strong).**
- Routine cardiac testing, DXA scanning, and measurement of lipid profiles in children and adolescents treated with GH are not needed **(quality of evidence: low; strength of recommendation: conditional).**

Consideration and Diagnosis of GHD

- Patients with all of the following 3 conditions can be diagnosed for GHD without the need for performing GH-provocative testing (another term for GH-stimulation testing):
  - auxological criteria
  - hypothalamic-pituitary defect
  - deficiency of at least 1 additional pituitary hormone **(quality of evidence: low; strength of recommendation: conditional).**
- Patients with GHD due to congenital hypothyroidism (hypoglycemia, GH levels < 5 mcg/L, ≥ 1 PHD) can be diagnosed without the need for performing GH-provocative testing **(quality of evidence: low; strength of recommendation: conditional).**
- Do not rely on GH-provocative testing as the sole diagnostic criterion for diagnosis of GHD **(quality of evidence: high; strength of recommendation: strong).**
- Laboratories should provide standardized GH assays using a recommended standard method **(quality of evidence: high; strength of recommendation: strong).**
- They suggest using sex steroid priming before performing provocative GH testing in male children older than 11 years and in female children older than 10 years with an adult height prognosis within −2 SD of the reference population mean **(quality of evidence: low; strength of recommendation: conditional).**

- Do not use spontaneous GH secretion in the diagnosis of GHD **(quality of evidence: low; strength of recommendation: conditional).**

Dosing of GH Treatment for Patients With GHD

- GH dosing based on weight and body surface area, not on IGF-1 levels, is recommended in children with GHD **(quality of evidence: moderate; strength of recommendation: strong).**
- The initial GH dose is recommended to be 0.16 mg/kg/week to 0.24 mg/kg/week (22 mcg/kg/day to 35 mcg/kg/day), although some patients may require higher doses **(quality of evidence: low; strength of recommendation: strong).**
- The serum IGF-1 level is recommended to monitor GH dose response. If serum IGF-1 levels rise above the laboratory-defined normal range, a lower GH dose should be considered **(quality of evidence: very low; strength of recommendation: conditional).**
- Do not routinely use higher GH dosing (i.e., 0.7 mg/kg/week) during puberty **(quality of evidence: low; strength of recommendation: strong).**
- Discontinue GH treatment at pediatric doses before the growth velocity reaches between 2 cm/year and 2.5 cm/year. The decision to discontinue GH therapy before reaching this growth rate should be individualized. Bone age was defined as 14 to 15 years for female children and 16 to 17 years for male children. Acromegalic changes should be avoided because these may occur with the use of pediatric GH doses in adolescents with fused epiphyseal plates **(quality of evidence: low; strength of recommendation: strong).**

Safety Issues of GH Treatment for Patients With GHD

- Provide guidance regarding the potential adverse effects of GH treatment, such as intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression **(ungraded good practice statement).**
- Monitor and perform physical examinations in patients receiving GH treatment for the development of intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression; order further testing if needed **(quality of evidence: high; strength of recommendation: strong).**
- Reassess both the adrenal and thyroid axes (i.e., monitor glucocorticoid and thyroid hormones) after initiation of GH therapy in patients with GHD due to MPHD **(quality of evidence: low; strength of recommendation: strong).**
- Monitor glucose metabolism in patients at increased risk for diabetes due to insulin resistance during GH treatment **(ungraded good practice statement).**
- Inform patients receiving GH treatment about the risk of neoplasia and encourage long-term follow-up with their oncologist **(ungraded good practice statement).**
- Share all information regarding GHD caused by primary malignancy among patient, family, oncologist, and treating endocrinologist **(ungraded good practice statement).**
- Wait for 12 months after completion of tumour therapy before initiating GH treatment; the waiting period can vary depending on individual circumstances **(ungraded good practice statement).**

- Provide counselling about the lack of evidence regarding the effect of GH on cancer risk in patients with increased risk of cancer, including patients with neurofibromatosis-1, Down syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome, and Diamond-Blackfan anemia **(ungraded good practice statement).**
- Provide counselling about the unknown long-term risks of neoplasia that are still being studied **(ungraded good practice statement).**
- Inform patients about the uncertainty regarding long-term safety of GH treatment **(ungraded good practice statement).**

Transition Care After Childhood GH Treatment

- Diagnose persistent GHD in patients with MPHD (≥ 3 PHDs) or in patients with GHD caused by genetic mutation or specific pituitary or hypothalamic structural defects except ectopic posterior pituitary defects **(quality of evidence: moderate; strength of recommendation: strong).**
- Re-evaluate the somatotropic axis for persistent GHD in patients with the following:
  - deficiency of only 1 additional pituitary hormone
  - idiopathic IGHD
  - IGHD with or without a small pituitary/ectopic posterior pituitary
  - after irradiation **(quality of evidence: moderate; strength of recommendation: strong).**
- Suggest measuring serum IGF-1 levels as the initial test of the somatotropic axis re-evaluation **(quality of evidence: very low; strength of recommendation: conditional).**
- Use GH-provocative testing to evaluate the function of the somatotropic axis if IGF-I level is low **(quality of evidence: moderate; strength of recommendation: strong).**
- Offer GH treatment to patients with persistent GHD during the transition period because there are benefits of treatment; however, the specific patient population, optimal starting time, and optimal dose are not clear **(quality of evidence: low; strength of recommendation: conditional).**

Limitations

A limitation in both guidelines was that certain recommendations were developed based primarily on consensus from expert opinion of the committee due to a lack of evidence. Further clinical investigation is needed to fill the gaps in the current knowledge base to develop future treatment guidelines. Evidence supporting the recommendations was mostly derived from short-term outcomes because prospective studies for long-term outcomes have more logistical and cost challenges. The lack of correlation between short-term and long-term outcomes creates some uncertainties about certain evidence-based recommendations. Due to variability among patients, recommendations made at the population level may not be optimal for a particular individual. We did not identify any Canadian guidelines for diagnosis and treatment of GHD in children and adults.

Conclusions and Implications for Decision- or Policy-Making

We identified 2 evidence-based guidelines that provided detailed recommendations regarding the identification, diagnosis, and treatment of GHD in adults and children. Both guidelines were developed in the US, therefore their recommendations are applicable to the Canadian clinical context. We also identified a position statement guideline from the Korean Endocrinology Society (KES) and Korean Society of Pediatric Endocrinology (KSPE) regarding the diagnosis and treatment of GHD in adults and children. This guideline was excluded due to unclear methodology. Its recommendations and the rationales for the development of those recommendations are presented in Table 6 in Appendix 5.

The AACE and ACE guideline highlighted the importance of recognizing that CO-GHD and AO-GHD have different etiologies and that the diagnosis of adult GHD using available GH-stimulation tests has several limitations due to intraindividual variability. Criteria for GH-stimulation testing are presented using different BMI-appropriate cut points depending on the type of test and the specific population. Once a correct diagnosis is established, GH treatment should be initiated at low doses and slowly increased to avoid side effects. Treatment should be periodically monitored for both clinical benefits and side effects. Due to the lack of long-term evidence, the effects of GH treatment on cardiovascular disease, fractures, cancer, and mortality remain to be established.

The PES guideline provided recommendations for the clinical management of children and adolescents with GHD. The guideline presented criteria for the diagnosis of GHD in different populations. Diagnosis and treatment of GHD should not be based solely on the results of GH-stimulation testing. Dosing of GH treatment should be based on weight and body surface area. GH treatment should be started with a low dose and be closely monitored for possible treatment-related side effects. The guideline highlighted that the initial GH dose, subsequent dosing, and discontinuation of the pediatric dose should be individualized. Patients and caregivers should be informed regarding potential short-term and long-term side effects of the treatment.

Recommendations of the KES and KSPE position statement guideline are similar but less comprehensive and detailed compared with those in the AACE and ACE guideline and PES guideline regarding diagnosis and treatment of GHD and the benefits and side effects of GH treatment in adults, children, and adolescents. Similar to the other 2 included guidelines, the KES and KSPE guideline highlighted the importance of an accurate diagnosis of GHD and individualized dosing to minimize side effects and maximize clinical benefits. Although the guideline was developed with unclear methodology, it appears the evidence supporting its recommendations was up to date.

All guidelines identified in this report emphasized the lack of long-term outcome data as a limitation, therefore they recommended that side effects and clinical response should be frequently monitored during GH treatment. Certain recommendations were made mainly by expert opinion due to lack of evidence. Those recommendations should be applied with caution until stronger evidence from future studies is available.

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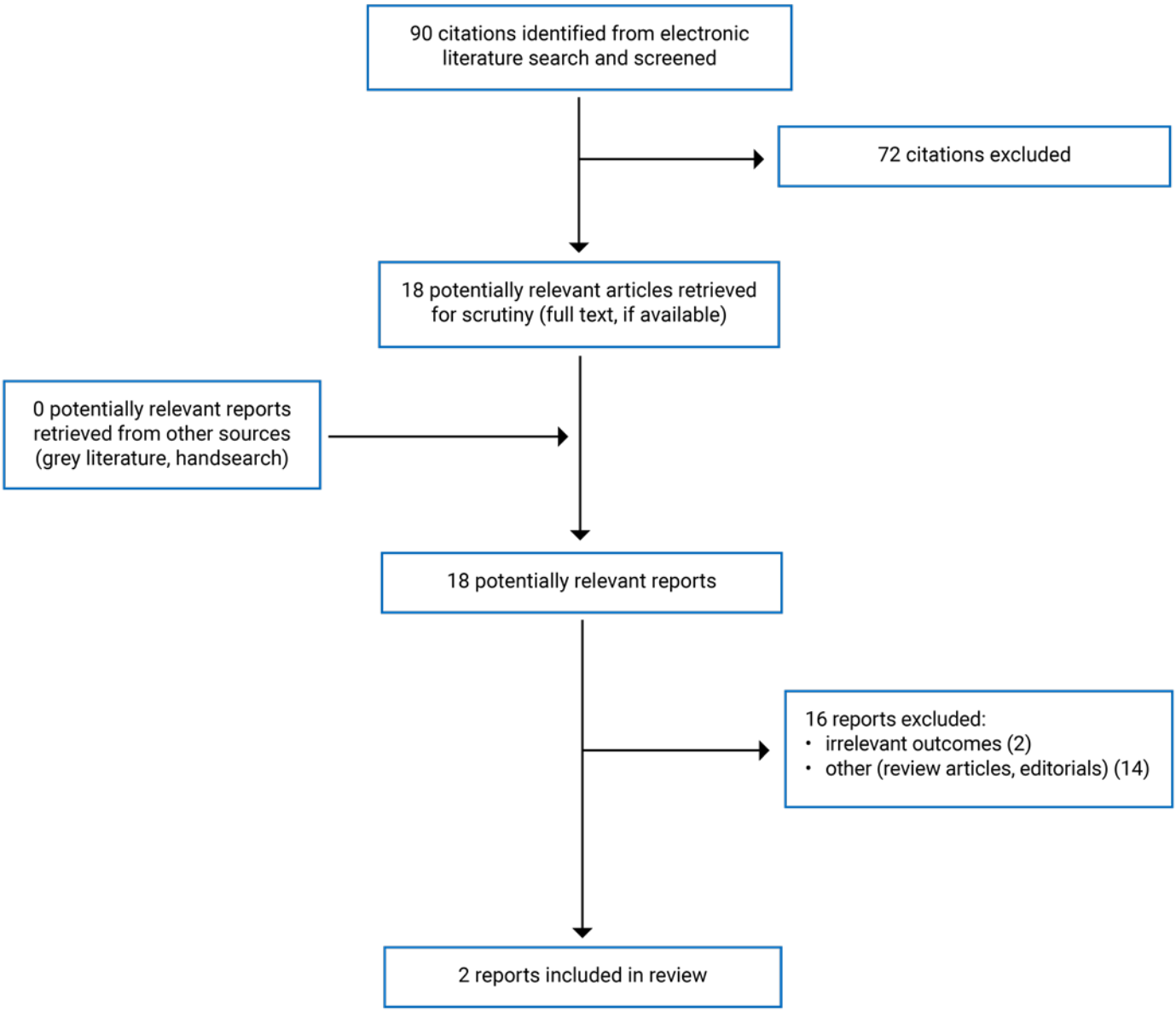
Appendix 1: Selection of Included Publications

Figure 1: Selection of Included Guidelines



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of the Included Guidelines — AACE and ACE Guideline and PES Guideline

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
AACE/ACE, Yuen et al. (2019)[12]						
Intended users: Clinicians involved in the management of GHD in adults and patients transitioning from pediatric to adult care. **Target population**: Adults and patients transitioning from pediatric to adult care with GHD.	Diagnosis of GHD in adults and patients transitioning from pediatric to adult care, and treatment with rhGH	All outcomes related to the diagnosis and treatment of adult GHD.	• Established key research questions. • Systematic search of literature from multiple databases. • Selected study, extract data and assessed the quality of included studies. • Reviewers drafted the recommendations with supporting evidence.	Level of evidence[a] and strength of recommendation[b] were graded using GRADE tool.	Taskforce panel: • Reviewed evidence (using GRADE) • Wrote recommendations and supporting text. • Reviewed, discussed, and integrated into the final document. • Approved by AACE members and credentialed experts in the field for publication and dissemination.	The guideline was reviewed and approved by all primary writers, other invited experts, the AACE Publications Committee, the AACE Board of Directors. The guideline was published in peer-reviewed journal.
PES, Grimberg et al. (2016)[13]						
Intended Users: Clinicians involve in the management of GHD, ISS, or PIGFD in children and adolescents. **Target Population**: Children and adolescents with growth failure from GHD, ISS, or PIGFD.	Diagnosis of GHD, ISS, or PIGFD in children and adolescents, and treatment with GH replacement therapy.	All outcomes related to the diagnosis and treatment of children and adolescents with growth failure from GHD, ISS, or PIGFD.	• Key questions drafted and revised. • Systematic literature search on multiple databases. • Study selection, data extraction and assessment of risk of bias performed in duplicate.	Two reviewers graded the level of evidence (very low, low, moderate, or high) and strength of recommendation[c] according to GRADE guidelines.	Taskforce members (7 pediatric endocrinologists from the US and Canada, and a pediatric bioethicist): • Presented the recommendation and evidence grade for the key question with summary of supporting evidence.	The guideline was published in peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
			• Reviewers drafted the recommendations with supporting evidence.		• Discussed until achieving consensus (defined as at least 6 of the 8 members agreeing on the recommendations).	

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; GH = growth hormone; GHD = growth hormone deficiency; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; ISS = idiopathic short stature; MA = meta-analysis; NMA = network meta-analysis; PES = Pediatric Endocrine Society; PIGFD = primary insulin-like growth factor-I deficiency; RCT = randomized controlled trial.

[a]Levels of evidence: strong evidence = RCT, MA of RCTs; intermediate evidence = MA including nonrandomized prospective or case-controlled studies, NMA, non-RCT, prospective cohort study, retrospective case-control study, nested case-control study, cross-sectional study, epidemiological study, open-label extension study, post hoc analysis study; weak evidence = discovery science, economic study, consecutive case series, since case report, preclinical study, basic research; no evidence = theory, opinion, consensus, review, position, policy, guideline, others.

[b]Strength of recommendation: A = "very strong"; B = "strong"; C = "not strong"; D = "primarily based on expert opinion."

[c]Strength of recommendation: Strong (denoted by "We recommend") or conditional (denoted by "We suggest"). Recommendations without direct supporting evidence were marked as "ungraded good practice statements."

Note: This table has not been copy-edited.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of the AACE and ACE Guideline and PES Guideline Using AGREE II[10]

Item	AACE/ACE, Yuen et al. (2019)[12]	PES, Grimberg et al. (2016)[13]
Domain 1: scope and purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: stakeholder involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear	Unclear
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: rigour of development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes
14. A procedure for updating the guideline is provided.	Unclear	Unclear
Domain 4: clarity of presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes

Item	AACE/ACE, Yuen et al. (2019)[12]	PES, Grimberg et al. (2016)[13]
Domain 5: applicability		
18. The guideline describes facilitators and barriers to its application.	Unclear	Unclear
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Unclear	Unclear
20. The potential resource implications of applying the recommendations have been considered.	Unclear	Unclear
21. The guideline presents monitoring and/or auditing criteria.	Unclear	Unclear
Domain 6: editorial independence		
22. The views of the funding body have not influenced the content of the guideline.	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; AGREE II = Appraisal of Guidelines for Research and Evaluation II; PES = Pediatric Endocrine Society.

Appendix 4: Main Study Findings

Table 4: Summary of Recommendations in the Included Guidelines — AACE and ACE Guideline and PES Guideline

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
AACE/ACE, Yuen et al. (2019)[12]	
1. What is adult GHD?	
"The clinician should consider the possibility of adult GHD in each individual patient with a history of hypothalamic-pituitary disease, as this condition is a well-defined clinical entity that is associated with excess morbidity and mortality." (p. 1194-1195) **Supporting evidence:** Two controlled cross-sectional studies and 1 systematic review provided evidence that GHD may play a role in contributing to the excess morbidity and mortality rates among patients with hypopituitarism.	Quality of evidence: 2 Strength of recommendation: B
"The clinician should be aware that adults can be diagnosed with GHD in childhood (childhood-onset GHD [CO-GHD]) and adulthood (adult-onset GHD [AO-GHD])." (p. 1195) **Supporting evidence:** Two cross-sectional studies, 1 workshop position paper, and 1 retrospective study estimated the prevalence data for CO-GHD and AO-GHD.	Quality of evidence: 2 Strength of recommendation: B
"The most common causes of CO-GHD and AO-GHD are isolated idiopathic GHD and hypothalamic-pituitary tumors and/or their treatment regimens, respectively; hence, the possibility of GHD should be considered in these patients." (p. 1195-1196) **Supporting evidence:** Evidence from a guideline suggests that the most frequent cause of CO-GHD is idiopathic and may not be associated with other PHD, while AO-GHD is most commonly acquired from hypothalamic-pituitary tumours and/or their treatment.	Quality of evidence: Expert opinion Strength of recommendation: B
"Several nontumoral causes of adult GHD (e.g., TBI, subarachnoid hemorrhage, ischemic stroke, and infections in the central nervous system) have been increasingly described in the past decade, and screening may be considered although the accuracy and reliability of GH-stimulation tests for the diagnosis of adult GHD have not been studied extensively in these populations." (p. 1196) **Supporting evidence:** Two narrative reviews, 1 cross-sectional studies, and 3 retrospective studies reported nontumoral causes of hypopituitarism associated with GHD that were previously unrecognized.	Quality of evidence: 2 Strength of recommendation: C
2. Are there any differences between CO-GHD vs. AO-GHD?	

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"It is recommended that clinicians recognize the differences in the etiology of CO-GHD versus AO-GHD as there are differences in the phenotypic features which are due to the fact that CO-GHD occurs during the developmental years and that adults with CO-GHD may have had a longer duration of being GH-deficient than their AO-GHD counterparts." (p. 1196) **Supporting evidence:** Two case-controlled studies, 2 retrospective cohort studies, and 1 RCT provided evidence for the differences between CO-GHD and AO-GHD, and the diagnosis of these 2 types of GHD.	Quality of evidence: 1 Strength of recommendation: A
3. How should pediatric patients with CO-GHD be transitioned to adult care services?	
"Transition is a vulnerable period when adolescents may drop out of follow-up medical care. Pediatricians should start counseling patients and caregivers early about the potential of future transition and collaborate closely with adult endocrinologists closer to the time to facilitate a seamless transition to adult endocrine-care services." (p. 1196) **Supporting evidence:** One narrative review, 2 consensus guidelines, 1 before-and-after study, 1 cost study, and 1 cross-sectional study provided evidence about the transition of pediatric patients with CO-GHD to adult care services, and how transition should be done as seamless as possible to prevent morbidity and mortality and to improve long-term outcomes.	Quality of evidence: 2 Strength of recommendation: C
4. What are the benefits of continuing rhGH replacement in transition patients with CO-GHD?	
"It is recommended that adults with CO-GHD caused by structural pituitary or brain tumors be followed up closely during transition as these patients tend to have lower bone mineral density, impaired bone microarchitecture, and more adverse body composition abnormalities and cardiovascular risk markers than those with AO-GHD." (p. 1197) **Supporting evidence:** One retrospective analysis, 1 case series, 1 case-control study, and 1 RCT provided evidence that young adults with CO-GHD and underlying structural pituitary or brain tumours tend to have low BMD, impaired bone microarchitecture and abnormal body composition more frequently than those with idiopathic GHD. These patients, with abnormal body composition, may have increased in fat mass, decreased lean body mass, and adverse cardiovascular markers. These patients are at risk of not achieving peak bone mass as a consequence of discontinuing rhGH treatment at final height.	Quality of evidence: 1 Strength of recommendation: A
"Resuming rhGH replacement therapy in patients with confirmed persistent GHD during the transition period after achievement of final height is recommended, as most studies have reported long-term improvement in body composition, bone health, quality of life, and lipid metabolism in adulthood." (p. 1197) **Supporting evidence:** Seven RCTs, 1 cross-sectional study, and 3 prospective cohort studies suggested that rhGH therapy has greatest impact on body composition, muscle strength, and cardiovascular risk markers, with less impact on BMD, insulin sensitivity, and QoL. One retrospective analysis and 2 case series suggested that untreated GHD during the transition period can adversely impact somatic and metabolic development.	Quality of evidence: 1 Strength of recommendation: A
5. Who should be tested for adult GHD?	

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"GH-stimulation test/s should only be performed based on the appropriate clinical context of each individual patient with a history suggestive of a reasonable clinical suspicion of GHD, and with the intent to initiate rhGH replacement if the diagnosis is confirmed." (p. 1197) **Supporting evidence:** A case-control study suggested criteria as which patients do not require a GH-stimulation test for the diagnosis of adult with GHD.	Quality of evidence: Expert opinion Strength of recommendation: D
"The diagnosis of adult GHD can be made without the need for performing GH-stimulation testing in certain patient subtypes, such as patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) and biochemical evidence of multiple pituitary hormone deficiencies (MPHD) (≥ 3 pituitary hormone deficiencies [PHD]) together with low-serum IGF-1 levels (< −2.0 standard deviation score [SDS]), genetic defects affecting the hypothalamic-pituitary axes, and hypothalamic-pituitary structural brain defects." (p. 1197) **Supporting evidence:** A case-control study and a guideline suggested types of patients who do not need GH-stimulation test for the diagnosis of adult with GHD.	Quality of evidence: 3 Strength of recommendation: C
"In patients with ≤2 PHD, low-serum IGF-1 levels (<−2.0 SDS) alone are not sufficient to make a diagnosis of adult GHD; clinicians should perform 1 GH-stimulation test to confirm the diagnosis." (P.1197) **Supporting evidence:** This recommendation was supported by evidence from a case-control study and a guideline.	Quality of evidence: 4 Strength of recommendation: B; upgraded by consensus based on expert opinion
"After longitudinal growth is completed in transition patients with idiopathic isolated GHD, those with low-normal (between 0 to −2 SDS) or low (< −2 SDS) serum IGF-1 levels should be retested for GHD with GH-stimulation tests after at least 1 month following discontinuation of rhGH therapy." (p. 1197-1198) **Supporting evidence:** This recommendation was supported by evidence from a case-control study and a guideline.	Quality of evidence: 4 SOR: B; upgraded by consensus based on expert opinion
"After longitudinal growth is completed in transition patients with isolated GHD (IGHD) and the presence of organic hypothalamic-pituitary disease (e.g., craniopharyngioma, pituitary hypoplasia, ectopic posterior pituitary, or previous cranial irradiation), the number of GH-stimulation tests to be undertaken should be guided by the degree of clinical suspicion for GHD. If clinical suspicion is high, 1 GH-stimulation test is sufficient, but if clinical suspicion is low, then a second GH-stimulation test should be performed." (p. 1198) **Supporting evidence:** This recommendation was supported by evidence from a case-control study and a guideline.	Quality of evidence: 4 Strength of recommendation: B; upgraded by consensus based on expert opinion
"To continue rhGH replacement in adulthood, retesting for GHD with GH-stimulation test/s is recommended in most transition patients, especially patients with idiopathic isolated GHD and serum IGF-1 SDS <0, when longitudinal growth is complete, and at least 1 month after discontinuation of pediatric rhGH therapy" (p. 1198) **Supporting evidence:** This recommendation was supported by evidence from a case-control study and a guideline.	Quality of evidence: 1 Strength of recommendation: A

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"Patients with idiopathic IGHD and serum IGF-1 ≥ 0 SDS are likely to have a normal GH-stimulation test; hence, retesting and rhGH therapy in these patients after completion of longitudinal growth are not required." (p. 1198) **Supporting evidence:** Two prospective cohort studies provided evidence to refute retesting and rhGH therapy in patients with idiopathic IGHD and serum IGF-1 ≥ 0 SDS.	Quality of evidence: 2 Strength of recommendation: C; downgraded due to inconsistent results
"Retesting is not required in transition patients with MPHD (≥ 3 PHD) and low-serum IGF-1 levels (< –2.0 SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects, and rhGH therapy may be continued in these patients without interruption." (p. 1198) **Supporting evidence:** A survey study provided evidence to support this recommendation.	Quality of evidence: 2 Strength of recommendation: C; downgraded due to inconsistent results
"The risk for development of persistent GHD after radiation therapy is increased with higher radiation doses and longer duration of time since the therapy. Retesting those patients who initially test as GH-sufficient may be performed later in the transition period or in adulthood to rule out delayed GHD." (p. 1198) **Supporting evidence:** Evidence from 3 cross-sectional studies suggested that retesting should be given to those patients.	Quality of evidence: 2 Strength of recommendation: B
"TBI and subarachnoid hemorrhage are now recognized clinical conditions that may cause GHD, but because GHD may be transient in these patients, GH-stimulation testing should be performed only after at least 12 months following the event." (p. 1198) **Supporting evidence:** Three prospective cohort studies suggested that those patients should have GH-stimulation testing at least 12 months after the events.	Quality of evidence: 2 Strength of recommendation: B
6. How should one test for adult GHD?	
"Random serum GH and IGF-1 levels cannot be used alone to make the diagnosis of adult GHD, and GH-stimulation test/s should be performed to confirm the diagnosis with the exception of certain subpopulations, such as patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) who have MPHD (≥3 PHD) and low serum IGF-1 levels (< –2.0 SDS), patients with genetic defects affecting the hypothalamic-pituitary axes, and patients with hypothalamic-pituitary structural brain defects." (p. 1198) **Supporting evidence:** The recommendation was based on evidence from a previous guideline.	Quality of evidence: 4 Strength of recommendation: B; upgraded by consensus based on expert opinion
"GH-stimulation tests should only be performed after all other PHD have been optimally replaced with stable hormone replacement doses." (p. 1198) **Supporting evidence:** Expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"The insulin tolerance test (ITT) remains the gold-standard test to establish the diagnosis of adult GHD using a peak GH cut-point of 5 mg/L. However, this test is increasingly used less frequently in the U.S. because of safety concerns, laboriousness, potential to cause severe hypoglycemia, and contraindicated in certain patients, such as elderly patients and those with seizure disorders and cardio/cerebrovascular disease. For adults suspected to have GHD and if the ITT is contraindicated or is not feasible to be performed in these patients, the glucagon-stimulation test (GST) and the macimorelin test could be considered as alternative tests." (p. 1198) **Supporting evidence:** Evidence from a case-control study suggested that ITT remains the gold-standard test to establish the diagnosis of adult GHD using a peak GH cut point of 5 mg/L. Another case-control study raised safety concerns of the test for older patients and those with seizure disorders and cardio/cerebrovascular disease. Two prospective cohort studies, 1 RCT, 1 cross-sectional study and 1 preclinical study suggested GST and macimorelin test as alternative tests to ITT.	Quality of evidence: 1 Strength of recommendation: B
"For the GST, we recommend utilizing BMI-appropriate GH cut-points to diagnose adult GHD to reduce the possibility of misclassifying GH-sufficient patients because increased BMI is associated with decreased glucagon-induced GH stimulatory effect. We recommend using the GH cut-point of 3 µg/L for normal-weight (BMI <25 kg/m^2) and overweight (BMI 25 to 30 kg/m^2) patients with a high pretest probability, and a lower GH cut point of 1 µg/L for obese (BMI >30 kg/m^2) and overweight (BMI 25 to 30 kg/m^2) patients with a low pretest probability. In patients with glucose intolerance, the diagnostic accuracy of the GST remains unclear." (p. 1198) **Supporting evidence:** Evidence from a prospective cohort study and a cross-sectional study supported this recommendation.	Quality of evidence: 2 Strength of recommendation: B
"For the macimorelin-stimulation test, the U.S. Food and Drug Administration (FDA) approved this test for use as a diagnostic test for adult GHD in December, 2017, and selected the GH cut-point of 2.8 mg/L to differentiate patients with normal GH secretion from those with GHD. However, it is not yet known whether BMI-adjusted peak GH cut-points for this test are needed for overweight and obese patients." (p. 1198) **Supporting evidence:** Based on data from 2 RCTs, the US FDA approved macimorelin for use as a diagnostic test for adult GHD.	Quality of evidence: 2 Strength of recommendation: B
"For transition patients, a feasible and validated GH-stimulation test has been less well studied. In this patient population, the ITT (using a GH cut-point ≤5.0 mg/L) may be utilized, but if the test is contraindicated or not feasible to be performed, the GST (using a GH cut point of 3 µg/L for normal-weight [BMI <25 kg/ m^2] patients and overweight [BMI 25 to 30 kg/m^2] patients with a high pretest probability, and a lower GH cut point of 1 µg/L for overweight [BMI 25 to 30 kg/m^2] patients with a low pretest probability and obese [BMI >30 kg/m^2] patients) and the macimorelin test (using a GH cut point ≤2.8 mg/L) can be considered as alternative tests." (p. 1199) **Supporting evidence:** One epidemiologic study, 4 cross-sectional studies, and 2 RCTs provided evidence to support these recommendations.	Quality of evidence: 2 Strength of recommendation: C

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"Arginine (ARG) and levodopa (L-DOPA) testing have not been systematically evaluated and validated, and because these tests have low sensitivity and specificity in adults and transition patients with suspected GHD, we do not recommend utilizing these tests." (p. 1199) **Supporting evidence:** Evidence for this recommendation was not reported.	Quality of evidence: 2 Strength of recommendation: B
7. Why are standardized GH and IGF-1 assays important in the management of adult GHD?	
"Substantial heterogeneity exists among currently utilized assays due to different standard preparations for calibration of GH immunoassays and lack of harmonization between various GH assays. It is recommended that laboratories adopt the standards set by the National Institute for Biological Standards and Control and state their methodology of analyses, including reporting serum GH levels in mass units without reliance of conversion factors." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
"It is suggested that all assay manufacturers indicate the validation of their assay, including specification of the GH isoforms detected, analyte being measured, specificities of the antibodies used, and presence or absence of GH–binding protein interference." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
"Differences in serum IGF-1 assay performance should be considered when evaluating and monitoring rhGH therapy in adults with GHD, and, if possible, the same IGF-1 assay should be used for a given patient throughout evaluation for diagnosis and follow-up." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
"Quality-control materials should be used, widely verified, and disseminated among laboratories for uniformity." (p.1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
"Because certain conditions such as DM, malnutrition, chronic liver disease, and renal diseases may lower serum IGF-1 levels that may not be due to GHD, reliable sera from healthy subjects and from such patients should be employed for validation of the assays." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
"Normative IGF-1 assay data should be provided by each laboratory and should include a sufficient random sample of individuals from a wide range of ages to achieve clinical efficacy and minimize the induction of side effects." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"Laboratories, in addition to reporting serum IGF-1 levels, should report IGF-1 SDS values (Z-scores)." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
8. How should initiation and monitoring of rhGH replacement be undertaken?	
"The use of one commercial rhGH product is not suggested over another, as there is no evidence that one rhGH product is more advantageous than another." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: expert opinion Strength of recommendation: D
"It is recommended to use serum IGF-1 as the biomarker for guiding rhGH dose adjustments." (p. 1199) **Supporting evidence:** Evidence from 2 RCTs suggested serum IGF-1 levels can be used as biomarker for rhGH dose adjustment.	Quality of evidence: 1 Strength of recommendation: A
"It is recommended to individualize rhGH dosing independent of body weight, starting with a low dose, and gradually up-titrating the dose to normalize serum IGF-1 levels with the primary aim of minimizing the induction of side effects." (p.1199) **Supporting evidence:** Two cross-sectional studies and 1 prospective cohort study provided evidence to support this recommendation.	Quality of evidence: 1 Strength of recommendation: A
"Serum IGF-1 levels should be targeted within the age-adjusted reference range (IGF-1 SDS between −2 and +2) provided by the laboratory utilized. This decision should consider the pretreatment IGF-1 SDS and the circumstances and tolerability of each individual patient. Because some patients may only tolerate lower rhGH doses frequently limited by side effects, whereas others may require higher rhGH doses to achieve desired clinical effects, the goals of treatment should be the clinical response, avoidance of side effects, and targeting serum IGF-1 levels to fall within the age-adjusted reference range (IGF-1 SDS between −2 and +2)." (p. 1199) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: expert opinion Strength of recommendation: D
"It is recommended to initiate rhGH therapy using low GH dosages (0.1 to 0.2 mg/day) in GH-deficient patients with concurrent DM, obesity, older age, and previous gestational DM to avoid impairment of glucose metabolism. Higher rhGH starting doses (0.3 to 0.4 mg/day) are advised in nondiabetic young adults <30 years of age and women on oral estrogen therapy." (p. 1199) **Supporting evidence:** Two cross-sectional studies and 1 prospective cohort study provided evidence to support this recommendation.	Quality of evidence: 1 Strength of recommendation: A
"After starting on rhGH therapy, it is recommended to follow patients at 1- to 2-month intervals initially, increasing the rhGH dose in increments of 0.1 to 0.2 mg/day based on the clinical response, serum IGF-1 levels, side effects, and individual considerations. Once maintenance doses are achieved, follow-up can be implemented at approximately 6- to 12-month intervals. Shorter follow-up time intervals and smaller dose increments can be implemented especially for the elderly, and	Quality of evidence: 1 Strength of recommendation: A

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
those with other comorbidities, such as DM." (p.1199-1120) **Supporting evidence:** Two cross-sectional studies and 1 prospective cohort study provided evidence to support this recommendation.	
"When maintenance rhGH doses are achieved, the following parameters may be assessed at approximately 6- to 12-month intervals: serum IGF-1, fasting glucose, hemoglobin A1c, fasting lipids, BMI, waist circumference, waist-to-hip ratio, serum-free T4, and the hypothalamic-pituitary-adrenal axis via early morning cortisol or cosyntropin stimulation test, if clinically indicated." (p. 1200) **Supporting evidence:** Evidence primarily came from expert opinion.	Quality of evidence: 2 Strength of recommendation: C; primarily based on expert opinion
"When restarting rhGH therapy in transition patients, resuming rhGH at 50% of the dose used in childhood may be considered. Serum IGF-1 levels should be monitored to avoid exceeding the upper limit of the normal range (IGF-1 >2 SDS). The dose should be modified based on the clinical response, serum IGF-1 levels, side effects, and individual patient considerations." (p.1200) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: expert opinion Strength of recommendation: D
"In transition patients, annual measurements of height, weight, BMI, and waist and hip circumference are recommended, measuring bone mineral density and fasting lipids after discontinuing rhGH therapy as a baseline assessment, and subsequently every 2 to 3 years and every year, respectively." (p. 1200) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: expert opinion Strength of recommendation: D
"Adults with GHD have an increased risk of cardiovascular morbidity and mortality, and currently, there are no definitive outcome data that confirm that treating this condition would mitigate this risk as long-term prospective, controlled clinical trials are still lacking. Therefore, clinicians should monitor cardiovascular parameters at 6- to 12-month intervals and include fasting lipids, systolic and diastolic blood pressure, and heart rate, while more detailed examinations such as electrocardiogram, echocardiogram, and carotid echo-Doppler examinations may be performed if clinically indicated according to local best clinical practice." (p. 1200) **Supporting evidence:** Evidence primarily came from expert opinion.	Quality of evidence: 2 Strength of recommendation: C; primarily based on expert opinion
"Adults with GHD have an increased risk of developing osteopenia and osteoporosis. Measurement of bone mineral content and bone mineral density is suggested in GH-deficient patients before starting rhGH therapy. If the initial bone dual-energy X-ray absorptiometry (DXA) scan is abnormal, clinicians should repeat bone DXA scans at 2- to 3-year intervals to assess the need for additional bone-treatment modalities." (p. 1200) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"Clinicians should perform baseline magnetic resonance imaging (MRI) in patients with any post-surgical tumor remnant in the hypothalamic-pituitary region before initiating rhGH, and periodic MRIs during rhGH therapy." (p. 1200) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
"Because untreated adults with GHD frequently report impaired quality of life (QoL), clinicians should consider assessing baseline QoL using specific Quality of Life in Adult Growth Hormone Deficiency Assessment (QoL-AGHDA) questionnaires before rhGH treatment is commenced, and at 12-month intervals to determine whether there is a change or sustained impact of rhGH therapy on QoL." (p. 1200) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: 4 Strength of recommendation: C; upgraded by consensus based on expert opinion
"Interactions of GH with other pituitary hormone axes may affect glucocorticoid and thyroid hormone requirements; hence, these hormones should be monitored closely, especially before initiation of rhGH therapy, as introduction of these hormones or dose increments may be required while on rhGH therapy. When stable new glucocorticoid and thyroid hormone doses are established, less frequent monitoring may be undertaken, unless symptoms develop or radiotherapy is administered." (p. 1200) **Supporting evidence:** One RCT, 1 review, 5 consecutive case series, 1 prospective cohort study provided evidence for this recommendation.	Quality of evidence: 1 Strength of recommendation: B
"The optimal duration of rhGH replacement therapy remains unclear. If patients on rhGH replacement experience beneficial effects on QoL and objective improvements in biochemistry, body composition, and bone mineral density, rhGH treatment can be continued indefinitely." (p. 1200) **Supporting evidence:** Two post hoc analysis studies, 2 retrospective case-control studies, and 1 open-label extension study provided evidence for this recommendation.	Quality of evidence: 2 Strength of recommendation: B
9. Can rhGH be used during conception and pregnancy?	
"Previous studies support the use of rhGH while seeking fertility, and continuing rhGH during pregnancy does not appear to impact the outcomes of either mother or fetus. However, more data are still needed regarding the safety of rhGH. Routine use of rhGH for conception or continued use during pregnancy in women with GHD cannot be recommended at this present time." (p. 1200) **Supporting evidence:** Inconsistent data from previous studies (narrative reviews, RCTs, basic research, case-control studies, and case report) in terms of the role of rhGH replacement during conception and continuation during pregnancy preclude the recommendation on the use of rhGH in these conditions.	Quality of evidence: 3 Strength of recommendation: C
10. What are the side effects of rhGH replacement?	

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"Side effects are related mainly to fluid retention effects and are typically seen during initiation and dose escalation of rhGH, and generally respond to dose reductions or cessation of therapy. Lower doses of rhGH are recommended in obese and older patients who are generally more susceptible to the side effects of rhGH replacement." (p. 1200-1201) **Supporting evidence:** Evidence from 3 RCTs supported this recommendation.	Quality of evidence: 1 Strength of recommendation: A
"It is recommended to avoid the use of high rhGH doses to minimize the risk of side effects and aim to maintain target serum IGF-1 levels within the age-adjusted laboratory reference range (IGF-1 SDS between −2 and +2)." (p. 1201) **Supporting evidence:** Evidence from 3 RCTs supported this recommendation.	Quality of evidence: 1 Strength of recommendation: A
11. How safe is long-term rhGH replacement therapy?	
"If DM develops during rhGH therapy, or if rhGH therapy is considered in patients with concurrent DM, use of low-dose rhGH therapy, and addition and/or adjustments in antidiabetic medications are suggested. If pre-existing DM worsens while on rhGH therapy, it is reasonable to initiate or increase the doses of antidiabetic therapy or discontinue rhGH therapy and optimize treatment of DM first before considering resuming rhGH therapy in these patients." (p. 1201) **Supporting evidence:** A narrative review, a systematic review and meta-analysis, and a post hoc analysis study provided evidence to support this recommendation.	Quality of evidence: 1 Strength of recommendation: B
"Treatment with rhGH in patients with a history of active malignancy (other than basal-cell or squamous-cell skin cancers) and active proliferative or severe nonproliferative diabetic retinopathy is contraindicated." (p. 1201) **Supporting evidence:** Two epidemiological studies found that secondary neoplasms may occur in some patients, especially in those irradiated for the primary malignancy, the potential risks of worsening or accelerating the course of these malignancies should be weighed against the benefits of treatment with rhGH.	Quality of evidence: 2 Strength of recommendation: B
"Treatment with rhGH should be conducted with caution in patients with a strong family history of cancer." (p. 1201) **Supporting evidence:** Evidence from multiple studies.	Quality of evidence: 2 Strength of recommendation: B
"For adults with GHD and a history of cancer who have expressed a desire to start rhGH replacement therapy, such therapy may be considered based on each individual circumstance, and low-dose rhGH therapy should only be initiated at least 5 years after cancer remission is achieved and after discussion with the patient's oncologist." (p. 1201) **Supporting evidence:** No evidence; expert opinion.	Quality of evidence: expert opinion Strength of recommendation: D
"After over 20 years of adult rhGH replacement, there are no data to suggest that rhGH replacement in adults increases the risk of cancer or accelerates recurrences of tumors in the hypothalamic-pituitary region; however, for the purposes of safety surveillance, continued long-term monitoring and standard cancer screening should still be performed." (p. 1201) **Supporting evidence:** Evidence from multiple studies.	Quality of evidence: 2 Strength of recommendation: B

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
PES, Grimberg et al. (2016)[13]	
1. Efficacy of GH treatment for GHD	
"We recommend the use of GH to normalize AH and avoid extreme shortness in children and adolescents with GHD." (p. 362) **Supporting evidence:** Four GH We recommend the use of GH to normalize AH and avoid extreme shortness in children and adolescents with GHD postmarketing surveillance registries, a population-based registry, a cancer survivor registry, 4 clinic/ hospital-based case series provided data on GH treatment for pediatric GHD.	Quality of evidence: High Strength of recommendation: Strong
"We suggest against routine cardiac testing, dual X-ray absorptiometry (DXA) scanning, and measurement of lipid profiles in children and adolescents treated with GH." (p. 362) **Supporting evidence:** Eighteen studies of different designs had different results regarding cardiac performance, bone density and body composition, and lipid profiles in children with GHD.	Quality of evidence: Low Strength of recommendation: Conditional
2. Consideration and diagnosis of GHD	
"We suggest establishing a diagnosis of GHD without GH provocative testing in patients possessing all of the following three conditions: auxological criteria, hypothalamic-pituitary defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor or irradiation), and deficiency of at least one additional pituitary hormone." (p. 362) **Supporting evidence:** In 2 observational studies of those patients, provocative tests showed GH concentrations very distinct from the normal range such that test precision, reproducibility, and assay performance may not be crucial barriers to precise diagnosis. These tests were not validated on the basis of intervention in an RCT.	Quality of evidence: Low Strength of recommendation: Conditional
"We suggest that GHD due to congenital hypopituitarism be diagnosed without formal GH provocative testing in a newborn with hypoglycemia who does not attain a serum GH concentration above 5 µg/L and has deficiency of at least one additional pituitary hormone and/or the classical imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk)." (p. 362) **Supporting evidence:** Data from 6 observational studies suggested that a GH level (whether random or associated with spontaneous hypoglycemia) that distinguishes infants with GHD from those with GH sufficiency has not been established definitively.	Quality of evidence: Low Strength of recommendation: Conditional
"We recommend against reliance on GH provocative test results as the sole diagnostic criterion of GHD." (p. 362) **Supporting evidence:** One review and 4 observational studies showed that although very low peak levels on provocative testing are consistent with severe GHD, the threshold test result that distinguishes normal from partial GHD that was responded to treatment has not been established. Data from 1 observational study and 1 large registry-based study showed that the results from provocative tests using different agents were inconsistent. These results also suggested imperfect reproducibility of the	Quality of evidence: High Strength of recommendation: Strong

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
same test in the same patient. Four observational studies showed that GH responses to provocative testing depends on BMI and that GH response to stimulation is considerably lower in children with obesity.	
"Given the large discrepancies between GH assays, we recommend that institutions require laboratories to provide harmonized GH assays using the somatropin standard, IRP IS 98/574, 22k rhGH isoform, as recommended by the 2006 and 2011 consensus statements, and the published commutability standards." (p. 363) **Supporting evidence:** Evidence from 2 consensus statements and 6 observational studies provided evidence to support this recommendation.	Quality of evidence: High Strength of recommendation: Strong
"We suggest sex steroid priming prior to provocative GH testing in prepubertal boys older than 11 and in prepubertal girls older than 10 years with AH prognosis within −2 SD of the reference population mean in order to prevent unnecessary GH treatment of children with constitutional delay of growth and puberty." (p. 363) **Supporting evidence:** Data from 3 observational studies suggested that GH testing should be preceded by brief treatment with sex steroids. Best available evidence exists for male children; evidence extrapolated for female children.	Quality of evidence: Low Strength of recommendation: Conditional
"We recommend against the use of spontaneous GH secretion in the diagnosis of GHD in a clinical setting." (p. 363) **Supporting evidence:** Five observational studies measuring spontaneous GH secretion in the diagnosis of GHD has serious limitations. Data from 3 other observational studies were inconsistent.	Quality of evidence: Low Strength of recommendation: Strong
3. Dosing of GH treatment for patients with GHD	
"We recommend the use of weight-based or body surface area (BSA)-based GH dosing in children with GHD." (p. 363) **Supporting evidence:** Seventeen studies demonstrating the positive effects of GH on achieved AH have overwhelmingly used weight-based or BSA-based dosing. IGF-1-based dosing was not recommended because there are no published AH data using this method. The target IGF-1 level has not been established to optimize the balance between AI gain, potential risks, and cost.	Quality of evidence: Moderate Strength of recommendation: Strong
"We recommend an initial GH dose of 0.16–0.24 mg/kg/week (22–35 µg/kg/day) with individualization of subsequent dosing." (p. 363) **Supporting evidence:** The body of evidence concerning the effect of different GH dosing regimens on AH outcomes came from 18 reports of registry- or population-based studies, analysis of potential variables that may affect AH in patients enrolled in registries, and nonrandomized or randomized trials with low patient numbers. In studies reporting AH, the majority of patients were administered GH doses between 0.18 and 0.24 mg/kg/week and multivariate analysis of the data did not consistently reveal a correlation between higher dosing and a greater AH.	Quality of evidence: Low Strength of recommendation: Strong

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"We suggest measurement of serum IGF-I levels as a tool to monitor adherence and IGF-I production in response to GH dose changes. We suggest that the GH dose be lowered if serum IGF-I levels rise above the laboratory-defined normal range for the age or pubertal stage of the patient." (p. 363) **Supporting evidence:** Data from 1 RCT suggested that serum IGF-1 concentration is a useful biomarker of GH exposure both in diagnosis and treatment monitoring. However,	Quality of evidence: Very low Strength of recommendation: Conditional
"During puberty, we recommend against the routine increase in GH dose to 0.7 mg/kg/week in every child with GHD." (p. 363) **Supporting evidence:** The FDA approved higher GH dosing (0.7 mg/kg/week) during puberty based on results of an RCT. However, the study was not adequately powered to detect potential serious side effects. Three other RCTs comparing pubertal doses lower than 0.7 mg/kg/week to standard dosing found no differences in clinical outcomes between groups. An observational study using multiple linear regression analysis of data from KIGS database revealed that gender, age at puberty onset, and height at puberty onset were associated more strongly with pubertal growth than was GH dose. There is a concern of undesirable risk of harm to patients receiving 0.7 mg/kg/week.	Quality of evidence: Low Strength of recommendation: Strong
"We recommend that GH treatment at pediatric doses not continue beyond attainment of a growth velocity below 2–2.5 cm/year. The decision to discontinue pediatric dosing prior to attainment of this growth velocity should be individualized." (p. 363) **Supporting evidence:** Across 14 studies describing the effect of GH on the outcome of AH, growth rates used to define near-AH and consideration of GH discontinuation varied from 0.5 to 3 cm/year, with the majority of studies using rates between 2 and 2.5 cm/year. Definition by bone age also varied across studies, with 14 to 15 years used for female adolescents and 16 to 17 years used for male adolescents.	Quality of evidence: Low Strength of recommendation: Strong
4. Safety issues of GH treatment for patients with GHD	
"We recommend that prospective recipients of GH treatment receive anticipatory guidance regarding the potential adverse effects of intracranial hypertension, slipped capital femoral epiphysis (SCFE), and scoliosis progression." (p. 363)	Ungraded good practice statement.
"We recommend monitoring of GH recipients for potential development of intracranial hypertension, SCFE, and scoliosis progression by soliciting pertinent history and performing a physical examination at every follow-up clinic visit; further testing should be pursued if indicated." (p. 363) **Supporting evidence:** Four observational studies and 1 RCT provided incidence rates of intracranial hypertension, SCFE, and scoliosis progression associated with GH therapy.	Quality of evidence: High Strength of recommendation: Strong
"We recommend re-assessment of both the adrenal and thyroid axes after initiation of GH therapy in patients whose cause of GHD is associated with possible multiple pituitary hormone deficiencies (MPHD)." (p. 363) **Supporting evidence:** Data from 2 observational studies suggested association of adrenal insufficiency and GH treatment rather than causality. A review pointed out that GH can lower free T4 concentrations by increasing the peripheral deiodination of T4 to T3.	Quality of evidence: Low Strength of recommendation: Strong

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
"We recommend discussion about and monitoring of glucose metabolism of GH recipients who are at increased risk for diabetes due to insulin resistance." (p. 364)	Ungraded good practice statement.
"Counseling prospective recipients of GH treatment regarding the risk of neoplasia, we recommend informing at-risk patients about available data and encourage long-term follow-up with their oncologist." (p. 364)	Ungraded good practice statement.
"For children with acquired GHD due to effects of a primary malignancy, we recommend shared decision-making that involves the patient, family, oncologist, and treating endocrinologist. Before initiation of GH treatment, we recommend sharing with families the most recent data about risks, including the potential effect of GH treatment on the timing of second neoplasm occurrence." (p. 364)	Ungraded good practice statement.
"For GH initiation after completion of tumor therapy with no evidence of ongoing tumor, a standard waiting period of 12 months to establish "successful therapy" of the primary lesion is reasonable but can also be altered depending on individual patient circumstances." (p. 364)	Ungraded good practice statement.
"In the rare situation where a child with GHD has an accompanying condition with intrinsic increased risk for malignancy (e.g., neurofibromatosis-1, Down syndrome, Bloom syndrome, Fanconi anemia, Noonan syndrome, and Diamond-Blackfan anemia), we recommend providing counseling regarding the lack of evidence concerning GH effect on malignancy risk in these groups." (p. 364)	Ungraded good practice statement.
"For children considered not to be at risk, we recommend that counseling includes information about the unknown long-term (i.e., posttreatment) risks of neoplasia still being studied." (p. 364)	Ungraded good practice statement.
"We recommend that prospective recipients of GH treatment be informed about the uncertainty regarding long-term safety (posttreatment adverse effects in adulthood)."	Ungraded good practice statement.
5. Transition care after childhood GH treatment	
"We recommend that patients with multiple (≥ 3) pituitary hormone deficiencies regardless of etiology, or GHD with a documented causal genetic mutation or specific pituitary/hypothalamic structural defect except ectopic posterior pituitary, be diagnosed with persistent GHD." (p. 364) **Supporting evidence:** Thirteen studies provided definition of MPHD and described persistent GHD associated with MPHD. Adolescents with MPHD or a structural defect (except ectopic posterior pituitary) have a nearly 100% fail rate on provocative testing.	Quality of evidence: Moderate Strength of recommendation: Strong
"We recommend re-evaluation of the somatotropic axis for persistent GHD in persons with GHD and deficiency of only one additional pituitary hormone, idiopathic isolated GHD (IGHD), IGHD with or without a small pituitary/ectopic posterior pituitary, and in patients after irradiation." (p. 364) **Supporting evidence:** Four observational studies showed that individuals with GHD and deficiency of only one additional	Quality of evidence: Moderate Strength of recommendation: Strong

Recommendation and supporting evidence	Quality of evidence and strength of recommendations[a]
pituitary hormone may or may not have persistent GHD upon testing. Two observational studies found that the development of GHD after radiation treatment was dose and time dependent.	
"We suggest that measurement of the serum IGF-1 concentration be the initial test of the somatotropic axis if re-evaluation of the somatotropic axis is clinically indicated." (p. 364) **Supporting evidence:** Four studies suggested that individuals diagnosed with idiopathic IGHD have a high likelihood of retesting sufficient on GH-provocative testing. Six studies showed that many adolescents with an IGF-I level greater than 0 SD will have normal results on provocative testing, but the absolute IGF-I cut-off value below which children retest as having persistent GHD varies between studies and, thus, is not clear. Those studies also suggested that a normal IGF-I level does not preclude the need for provocative GH testing.	Quality of evidence: Very low Strength of recommendation: Conditional
"We recommend GH provocative testing to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-I level." (p. 364) **Supporting evidence:** The ITT has been validated for the diagnosis of adult GHD (2 studies) and persistent GHD in the transition period (3 studies). Arginine- L -dopa testing has not been systematically tested in the transition population and in adults poorly predicts GHD (1 study). Glucagon-stimulation testing is a promising alternative for provocative testing in adults (2 studies) but has not been specifically tested in the transition period.	Quality of evidence: Moderate Strength of recommendation: Strong
"We suggest that GH treatment be offered to individuals with persistent GHD in the transition period. There is evidence of benefit; however, the specifics of the patient population that benefits, the optimal time to reinitiate treatment, and the optimal dose are not clear." (p. 364) **Supporting evidence:** Six studies discussed the biochemical aspects of young adults with childhood-onset GHD. Three RCTs found that GH treatment in young adults with persistent GHD increased bone mineral density, normalized IGF-I levels, and improved lipid profiles from baseline. Another RCT did not demonstrate, after 2 years of GH treatment, a difference in bone mineral density or lipids from baseline, compared to nontreated GHD patients or compared to normal controls. The optimal GH dose during the transition period was unclear (2 RCTs).	Quality of evidence: Low Strength of recommendation: Conditional

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; AGHDA = Adult Growth Hormone Deficiency Assessment; AH = adult height; AO = adult onset; ARG = arginine; BMD = body mass density; BSA = body surface area; CO = childhood onset; DM = diabetes mellitus; DXA = dual X-ray absorptiometry; GH = growth hormone; GHD = growth hormone deficiency; GST = glucagon-stimulation test; IGF-1 = insulin-like growth factor-1; IGHD = isolated growth hormone deficiency; IRP IS = International Reference Preparation international standard; ITT = insulin tolerance test; L = DOPA = levodopa; MPHD = multiple pituitary hormone deficiencies; NA = not applicable; NR = not reported; PES = Pediatric Endocrine Society; PHD = pituitary hormone deficiencies; QoL = quality of life; RCT = randomized controlled trial; rhGH = recombinant human growth hormone; SCFE = slipped capital femoral epiphysis; SD = standard deviation; SDS = standard deviation score; TBI = traumatic brain injury.

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Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

This is a position statement with unclear methodology. Its characteristics and findings are presented in Table 5 and Table 6, respectively.

Table 5: Characteristics of the KES and KSPE Guideline With Unclear Methodology

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
KES/KSPE, Kim et al. (2020)[14]						
Intended users: Clinicians involved in the management of GHD in adults and children/ adolescents. **Target population**: Adults and children/ adolescents with GHD	Diagnosis of GHD in adults and children/ adolescents, and treatment with GH replacement therapy.	All outcomes related to the diagnosis and treatment of adult GHD.	NR	Each recommendation was graded based on the level of evidence.[a]	Panel of experts: • Discussed the literature. • Recommendations were made by consensus.	Unclear

GH = growth hormone; GHD = growth hormone deficiency; KES = Korean Endocrine Society; KSPE = Korean Society of Pediatric Endocrinology; NR = not reported.

[a]Recommendation level:

(A) When there is a clear rationale for the recommendations: When manifold randomized controlled trials that can be generalized because they have sufficient test or meta-analysis results support a recommendation.

(B) When there is a reliable basis for the recommendations: When reasonable grounds support this through well-performed cohort studies or patient—control group studies.

(C) When there is a possible basis for the recommendations: When relevant grounds are seen through randomized clinical studies or case reports and observational studies carried out in a small institution, despite their inherent unreliability.

(D) Expert recommendations: There is no basis to support the recommendations, but they are supported by expert opinion or expert clinical experience.

Table 6: Summary of Recommendations in the KES and KSPE Guideline With Unclear Methodology

Recommendation and rationale	Level of recommendation[a]
KES/KSPE, Kim et al. (2020)[14]	
1. Diagnosis of GHD in adults	
"The insulin tolerance test is recommended as the standard test for diagnosing GH deficiency." (p. 276) **Rationale**: GH deficiency is diagnosed through GH-stimulation tests such as the ITT, the GHRH, arginine, glucagon, levodopa, and clonidine stimulation tests. There is no single gold-standard test, but the ITT is a major GH-stimulation test.	B
"When GH deficiency is suspected, but an ITT is contraindicated, two or more GH stimulation tests (GHRH, arginine, glucagon, levodopa, or clonidine stimulation tests) should be administered." (p. 276) **Rationale**: Since ITT causes hypoglycemia, it is contraindicated in older patients and patients with a history of epilepsy or cardiovascular disease due to its risks. Even healthy individuals should be continuously monitored during ITT. In obese patients with insulin resistance, a greater dose of insulin is injected to induce hypoglycemia, and this process increases the risk of delayed hypoglycemia. ITT is also difficult to replicate since the response to ITT varies from occasion to occasion in healthy individuals. The response to ITT also depends on the menstrual cycle.	B
"GH deficiency cannot be ruled out even if IGF-1 levels are normal. However, low serum IGF-1 levels may be indicative of GH deficiency in individuals who do not have a history of poorly controlled diabetes, chronic liver disease, or treatment with oral contraceptives." (p. 277) **Rationale**: GH deficiency cannot be ruled out even when serum IGF-1 levels are normal. Higher BMIs are associated with a weaker GH response and increased IGF-1 levels. However, if a patient with a high BMI has a low IGF-1 level, it can be considered as GH deficiency.	C
"GH deficiency can be diagnosed without GH stimulation testing when the typical clinical characteristics of GH deficiency are present, accompanied by deficiencies in three or more pituitary hormones with low serum IGF-1 levels." (p. 277) **Rationale**: GH-stimulation tests can be omitted if there are abnormally low levels of 3 or more pituitary hormones and IGF-1 levels are low (at least 2.0 standard deviations lower than normal), if the patient has a structural hypothalamic-pituitary condition, if the patient has a genetic condition that impacts the hypothalamic-pituitary axis, and if there is a structural lesion in the hypothalamus or pituitary gland.	B
"Repeated GH stimulation testing should be performed in patients with childhood-onset GH deficiency if they do not have a proven genetic cause of GH deficiency or irreversible damage." (p. 277) **Rationale**: When patients with idiopathic child-onset GH deficiency are re-evaluated in adulthood, most show normal GH secretion.	B
"Adult patients with irreversible pituitary damage should not regularly receive repeated GH stimulation tests." (p. 277) **Rationale**: GH deficiency due to structural conditions, including tumours, surgery, radiation, and genetic disorders, do not improve in adulthood, so GH-stimulation tests is not needed to be repeated in such patients.	B
2. Treatment of GHD in adults	

Recommendation and rationale	Level of recommendation[a]
"Unless contraindicated, GH therapy is recommended for patients with GH deficiency. GH therapy should start from a low dose, considering the patient's age, sex, and estrogen levels." (p. 278) **Rationale**: Patients should be started on low doses since side effects are dose-dependent. Side effects are more frequent in older patients, patients with obesity, and female patients, but subside after the dose is lowered.	A
"Clinical improvements, side effects, and targeting serum IGF-1 levels within the age-adjusted reference range should be considered when adjusting the GH dose." (p. 278) **Rationale**: GH secretion decreases with age, and the side effects of GH are more common in older patients. Therefore, the appropriate therapeutic levels of GH are lower in older individuals and higher in younger individuals. The dosage should be increased by 0.1 to 0.2 mg/day (0.4 to 0.8 IU/day) monthly or bimonthly, and the maintenance level should be determined based on an evaluation of the patient's clinical response, side effects, and the normal range of IGF-1 levels for the patient's age group.	A
"During the adjustment period, IGF-1 levels should be monitored monthly or bimonthly. Once the maintenance level is determined, IGF-1 levels should be monitored around twice per year. monitoring should include an evaluation of the patient's clinical response, side effects, and IGF-1 levels." (p. 278) **Rationale**: These recommendations are based on empirical experience. Although it is unclear precisely how long GH should be administered, if there is no clear response to GH replacement after at least 1 year, treatment can be suspended.	B
3. Diagnosis and treatment of growth hormone deficiency in children and adolescents	
"Two or more GH stimulation tests should be administered when GH deficiency is suspected in children." (p. 279) **Rationale**: Childhood-onset GH deficiency may be a long-lasting endocrine condition, starting in childhood and continuing into adulthood. Diagnostic workup of childhood-onset GH deficiency include auxology, bone age view, measurement of IGF-1 and IGF binding protein 3, GH-stimulation tests, brain imaging and, genetic tests if needed. GH-stimulation test is one of the most important diagnostic tools, but it is also intrusive and is accompanied by a risk of side effects [43]. The validity and reproducibility of GH-stimulation tests have also been called into question. Therefore, to diagnose GH deficiency, 2 or more GH-stimulation tests should be administered.	A
"Repeated GH stimulation tests are not required in GH patients with pituitary lesions or a proven genetic cause of GH deficiency." (p. 279) **Rationale**: Patients with structural lesions in the hypothalamus or pituitary gland or other structural problems, such as tumours, have a high risk of persistent GH deficiency. Several genetic defects may also lead to an irreversible GH deficiency. Therefore, GH-stimulation tests do not need to be repeated in patients with definite genetic or structural pituitary abnormalities.	C
"GH replacement should be continued in children and adolescents until the epiphyseal plates close or their full height is reached." (p. 280) **Rationale**: The benefits of GH replacement during the transition period of adolescence are widely recognized. Childhood-onset GH deficiency contributes to low bone mass and an increased risk of fracture in adulthood. Therefore, GH replacement should be maintained until either the epiphyseal plates close or the final height is reached, since there are various benefits besides height gain.	C

Recommendation and rationale	Level of recommendation[a]
"GH replacement should be resumed as soon as possible in patients with GH deficiency during adolescence." (p. 280) **Rationale**: It is widely known that appropriate GH replacement during the transition period of adolescence is necessary. The purpose of GH replacement during this transition period is to maintain the continuity of hormonal care and to prevent health problems. If GH replacement is discontinued in such patients, it should be resumed as soon as possible.	B
4. Benefits of growth hormone treatment	
"GH treatment improves body composition, exercise capacity, and bone mineral density in patients with GH deficiency." (p. 280) **Rationale**: GH deficiency can cause decreased bone mineral density, muscle strength, and exercise capacity, deterioration in memory, decreased physical activity and vitality, lethargy, difficulty in concentration, and sleep disorders. Patients also are exposed to a high risk of cardiovascular disease due to central obesity, dyslipidemia, or insulin resistance. Several studies consistently reported that GH treatment had the significant effect on body composition including decrease in fat mass and increase in muscle mass. Significant improvements in bone mineral density in response to GH treatment were reported among males and patients with severe bone loss. Even in patients without a history of osteoporosis, GH treatment prevented fractures.	A
"GH treatment lowers the risk of cardiovascular disease in patients with GH deficiency, but there is insufficient evidence regarding its effects on mortality reduction." (p. 280) **Rationale**: GH deficiency increases the risk of cardiovascular disease via its negative effects on metabolic parameters, such as abdominal obesity, insulin resistance, and deterioration of lipid panels, and increases in various inflammatory markers. A meta-analysis also found that GH replacement reduced the mortality rate among male patients with hypopituitarism. However, the mortality improvement is lower for women than for men, and the question of whether GH replacement can fully restore the long-term negative effects of GH deficiency on cardiovascular risk factors remains.	B
"GH treatment improves quality of life in patients with GH deficiency." (p. 281) **Rationale**: Studies measuring the quality of life among adult patients diagnosed with GH deficiency using various tools in comparison to that of healthy adults found significantly poorer results for sleep, social integration, and physical activity among patients with GH deficiency, and their physical health negatively influenced their occupational status and daily life	A
5. Risks and side effects of growth hormone treatment	
"GH treatment is contraindicated in patients with an active malignancy (other than basal cell or squamous cell skin cancers)." (p. 281) **Rationale**: Theoretically, the increased activity of the IGF-1 axis resulting from GH treatment can exacerbate malignant tumours, as GH and increased IGF-1 levels are independently associated with the development of various malignant tumours.	A
"Changes in blood glucose levels should be observed during the course of GH treatment in patients with diabetes mellitus, who may require their antidiabetic medication to be adjusted." (p. 281) **Rationale**: GH and IGF-1 independently influence insulin resistance and insulin secretion by pancreatic Beta-cells. Both increased and decreased	B

Recommendation and rationale	Level of recommendation[a]
GH and IGF-1 levels can cause abnormalities in blood glucose levels. The elevated blood glucose levels present in patients with acromegaly and the increased insulin resistance in patients with GH deficiency are clinically observed.	
"Thyroid and adrenal gland function should be monitored during GH treatment in patients with hypopituitarism." (p. 281) **Rationale**: It is common for patients with GH deficiency to have other manifestations of hypopituitarism, and thyroid and adrenal gland function—even if they are initially normal—should be monitored during GH treatment.	B

GH = growth hormone; GHD = growth hormone deficiency; GHRH = growth hormone-releasing hormone; IGF-1 = insulin-like growth factor-1; ITT = insulin tolerance test.

[a]Recommendation level:

(A) When there is a clear rationale for the recommendations: When manifold randomized controlled trials that can be generalized because they have sufficient test or meta-analysis results support a recommendation.

(B) When there is a reliable basis for the recommendations: When reasonable grounds support this through well-performed cohort studies or patient—control group studies.

(C) When there is a possible basis for the recommendations: When relevant grounds are seen through randomized clinical studies or case reports and observational studies carried out in a small institution, despite their inherent unreliability.

(D) Expert recommendations: There is no basis to support the recommendations, but they are supported by expert opinion or expert clinical experience.

Guidelines and Recommendations

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