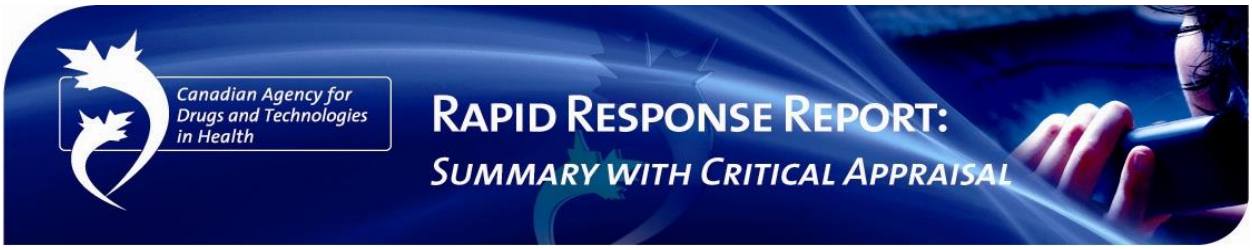

TITLE: Human Growth Hormone Treatment for Adult Growth Hormone Deficiency: A Review of the Clinical Effectiveness, Safety, Cost-Effectiveness, and Guidelines

DATE: 13 March 2015

CONTEXT AND POLICY ISSUES

Human growth hormone (HGH) is produced in the pituitary and effects a wide range of biological processes including lipid, carbohydrate, and bone metabolism, in addition to growth promotion to full adult height.[1] There are a number of medical conditions that can ultimately result in growth hormone deficiency (GHD). These include nonfunctioning pituitary adenoma (NFPA),[2-9] functioning adenoma,[2] craniopharyngioma,[2,3,7-9] cerebral malignancy,[2] empty sella,[3,6,8] traumatic brain injury,[5] acromegaly,[4] idiopathic hypopituitarism,[6,8,9] supra sellar cyst,[6,8] congenital,[2] Sheehan's syndrome,[9] pituitary tumours,[10] pituitary apoplexy,[7] pituitary abscess,[7] lymphocytic hypophysitis,[7] and others.[2,6,8] Pituitary destruction is the outcome of radiotherapy and/or surgical intervention for some of these conditions which then produces GHD in these patients.[8] Estimates from the UK suggest a GHD prevalence of 1 in 2700 adults, and between 1 in 3500 and 1 in 4000 children.[11,12]

In adults, untreated GHD is associated with increased risk of cardiovascular mortality as compared to age-matched controls.[9,10,13] It has also been established that GHD patients have significant differences in clinical parameters such as body mass index (BMI),[1,9] endothelial function,[9] inflammatory markers,[9] insulin sensitivity,[5] insulin resistance,[10] bone mineral density,[1,14,15] dyslipidemia,[1,2,10] visceral adiposity,[10] glucose intolerance,[10] hypertension,[10] cardiac abnormalities,[10] and others.[10] It is therefore thought that these differences, indicating a higher risk of cardiovascular disease (CVD), are the major determinant of increased cardiovascular mortality of GHD patients.[10]

The severity of GHD is arbitrarily defined by peak serum levels of GH in response to various pharmacological stimuli. For example, while some studies define severe GHD as a peak serum GH response of less than 3 µg/L upon an insulin tolerance test,[2,5] others define severe GHD as a peak GH serum response of less than 9 µg/L upon a growth hormone releasing hormone (GHRH) plus arginine test.[10] In addition to a peak serum GH response definition, some studies also include an impaired quality of life (QoL) in the definition of severe GHD.[6,8]

Many studies have investigated the effect of HGH replacement (GHR) therapy on these clinical parameters in GHD patients.[15] Concerns of serious adverse events of long-term GHR therapy in adults include increased glucose intolerance, hypothalamic/pituitary tumour recurrence, and other cancers.[13]

Pediatric GHD can also be treated with GHR therapy with the primary goal of growth promotion to achieve final adult height. As the primary treatment goals differ for adult and pediatric patients, the transition to final adult height represents a juncture for GHD reassessment.[13]

The purpose of this report is to retrieve and review the existing evidence of clinical effectiveness, safety, and cost-effectiveness of GHR therapy in patients with severe GHD due to pituitary destruction 25 years of age and older. This report also aims to retrieve and review existing guidelines for GHD due to pituitary destruction in patients 25 years of age and older. The final purpose of this report is to retrieve and review GHR therapy guidelines for pediatric GHD patients who have attained final adult height.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of human growth hormone for the treatment of severe growth hormone deficiency due to pituitary destruction in patients 25 years of age and older?

2. What is the cost effectiveness of human growth hormone for the treatment of severe growth hormone deficiency due to pituitary destruction in patients 25 years of age and older?

3. What are the evidence-based guidelines regarding the use of human growth hormone for the treatment of severe growth hormone deficiency due to pituitary destruction in patients 25 years of age and older?

4. What are the evidence-based guidelines regarding discontinuing human growth hormone treatment in patients with growth hormone deficiency who have attained their final adult height?

KEY FINDINGS

No evidence for human growth hormone effectiveness on direct patient health outcomes for adult patients aged 25 years or older with growth hormone deficiency due to pituitary destruction was identified. A limited quality evidence consensus from non-randomized studies was suggestive that growth hormone deficient patients of mixed etiology, aged 25 years and older experienced a subjectively measured increase in quality of life during growth hormone replacement therapy. Collectively two randomized controlled trials and 18 non-randomized studies otherwise found no consistent evidence of impacts on a wide range of cardiovascular risk factors with growth hormone replacement therapy in growth hormone deficient patients of mixed etiology. A lack of quantitative adverse event evidence was identified. No cost-effectiveness evidence or guidelines were identified for growth hormone replacement therapy in adult patients aged 25 years or older with growth hormone deficiency due to pituitary destruction. Guidelines were identified that had strong evidence-based recommendations

regarding the confirmation of adult growth hormone deficiency in patients treated with human growth hormone during childhood and transitioning into full adult height.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and February 5, 2015.

Selection Criteria and Methods

One reviewer screened titles and abstracts and a second reviewer verified the selection and subsequently screened the full-text articles and selected studies based on the criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1 - Q3: Adult patients (≥25 years) with severe growth hormone deficiency due to pituitary destruction Q4: Patients with growth hormone deficiency
Intervention	Human growth hormone
Comparator	Any
Outcomes	Q1: Clinical effectiveness and safety - not any subgroups of patients that would benefit from HGH Q2: Cost effectiveness Q3+Q4: Guidelines and recommendations
Study Designs	Health Technology Assessments (HTA)/Systematic review (SR)/Meta-analysis (MA); Randomized controlled trials (RCTs); non-randomized studies (NRSs); Economic evaluations; and Guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, were published in a language other than English, or were published prior to 2007.

Critical Appraisal of Individual Studies

The quality of the included systematic review (SR) was assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.[16] The quality of the non-randomized prospective studies (NRSs) included in this report was assessed using the Downs and Black checklist.[17] Critical appraisal of the included guideline used the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.[18] For all critical appraisals the strengths and limitations were described narratively instead of assigning a numerical score.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search strategy identified 373 articles. One reviewer conducted an initial screen which was verified by a second reviewer. Following screening titles and available abstracts, 34 potentially relevant full-text articles in addition to 20 potentially relevant reports from the grey literature were selected for full-text review. Upon review of the 54 full-text articles, the 43 reports were excluded. Twenty-three reports were excluded for an irrelevant population, four examined an irrelevant intervention, one was excluded as it was included in a selected SR, seven reports were duplicates, and eight articles were review articles or editorials. One SR and nine NRSs were retrieved and met the selection criteria (Table 1). No relevant heath technology assessments, meta-analyses, or randomized controlled trials (RCTs) were identified. No evidence-based guidelines were identified that included recommendations specific to patients with severe GHD due to pituitary destruction. One evidence-based guideline for discontinuation of HGH treatment in patients with GH deficiency subsequent to attainment of final adult height met the inclusion criteria. No cost-effectiveness studies were identified examining HGH treatment of severe growth hormone deficiency due to pituitary destruction in patients 25 years of age and older.

Summary of Study Characteristics

The characteristics of the included SR, non-randomized prospective studies (NRS), and guidelines are available in Appendix 2.

One SR met the selection criteria and is included in this report.[15] This review includes two RCTs and nine NRSs that focused on analysis of elderly GHD patients over 60 years old. The two RCTs enrolled 65 patients and the NRSs enrolled 469 patients in total. One RCT and six NRSs in the SR, were published prior to 2007. The intervention in the included studies was GH replacement therapy (GHR) as compared to placebo in the RCTs, while in the NRSs clinical outcomes were prospectively examined and compared to baseline data before initiation of GH replacement therapy. This SR reported GHR therapy clinical efficacy on CVD risk factors, metabolic parameters, anthropometry, bone parameters, cognitive function, quality of life (QoL) and adverse events.[15]

Nine NRSs are included in this report. One additional NRS identified by the literature search was captured in the selected SR and therefore excluded to avoid over representation of the data. The number of enrolled GHD patients in each study ranged from 6 to 161.[2,5] The follow-up times of the prospective studies ranged from three months to five years.[2-10] All of the studies examined GHD patients over 25 years of age as determined by the defined patient inclusion criteria or enrolled patient characteristic data. One study reported baseline mean patient age with standard deviation in the youngest treatment group as 46 ± 11 years,[4] while another reported a mean age of 47.0 ± 3.9 years.[7] It is possible that these studies included patients under the age of 25 years. The remaining studies reported age ranges of 40 to 70 years,[2] 26 to 65 years,[3] 40 to 59 years,[5] 25 to 50 years,[8,10] 30 to 53 years,[9] and 26 to 60 years.[6]

All of the included studies had patient inclusion criteria for the severity of GHD. Severe GHD was defined as a peak serum GH response of less than or equal to 3 µg/L upon glucagon stimulation and an impaired quality of life (QoL) by Assessment of Growth Hormone Deficiency in Adults (AGHDA) score greater or equal to 11,[6] a GH response of less than or equal to 9 µg/L

upon glucagon stimulation and an AGHDA score greater than or equal to 11,[8] a GH response of less than 9 µg/L following a GHRH plus arginine test,[10] a peak serum GH response of less than 3 µg/L following an insulin tolerance test (ITT) and glucagon stimulation and less than 9 µg/L following a GHRH plus arginine test.[5] One study's criteria for severe GHD was dependent on BMI with severe GHD defined as a peak serum GH response of less than 11µg/L for normal BMI, less than 8 µg/L for overweight patients, and less than 4.2 µg/L for obese patients following a GHRH plus arginine test.[3] One study defined severe GHD as a peak serum GH of less than 4 µg/L and a IGF-1 standard deviation score (SDS) of less than 1.5 following a GHRH plus arginine test.[4] The remaining three studies did not use the term severe GHD, however the patient inclusion criteria contained requirements that fit the definition of severe GHD as defined in the other included studies of this report.[2,7,9] One of these studies defined GHD as a peak serum GH less than 3 µg/L,[2] and another defined as less than or equal to 5 µg/L after an ITT.[7] The final study that did not define severe GHD, included patients with a peak serum GH of less than 3 µg/L after an ITT and glucagon stimulus.[9]

The initial diagnosis leading to GHD in patients followed for these studies included nonfunctioning pituitary adenoma (NFPA),[2-9] functioning adenoma,[2] craniopharyngioma,[2,3,7-9] cerebral malignancy,[2] empty sella,[3,6,8] traumatic brain injury,[5] acromegaly,[4] idiopathic hypopituitarism,[6,8,9] supra sellar cyst,[6,8] congenital,[2] Sheehan's syndrome,[9] pituitary tumours,[10] pituitary apoplexy,[7] pituitary abscess,[7] lymphocytic hypophysitis,[7] in addition to undefined causes labeled as 'others.'[2,6,8] Without exception these patients of mixed etiology were considered equivalent within each study and separate analyses of patients with different initial causes of GHD were not available.

All studies examined growth hormone replacement (GHR) therapy in GHD patients. Four studies reported using GH without identification of the manufacturer,[3,4,6,8] four reported use of Genotropin (Pfizer, Skokie, IL, USA),[2,5,9,10] one reported use of Norditropin (Novo, Princeton, NJ, USA),[2] and one study reported use of Eutropin (LG Life Sciences, New Delhi, India).[7] Six studies started GHR at a fixed dose and then adjusted to achieve an IGF-1 level found in matched controls or reference levels.[2,4,6,8-10] One study had individualized dosing but did not report how the dose was determined.[3] One study used a target IGF-1 level below the 50th percentile for the respective age-related range with the hypothesis that this low GH dose may improve insulin sensitivity and glucose metabolism.[5] One study used a fixed dose of 4µg/kg/day.[7] Most studies also reported the concurrent use of other hormone replacements.[2-10] One study was identified that included a placebo control,[7] three studies compared GHR therapy at follow-up as compared to baseline,[5,6,8] and three trials examined GHD patients before and after GHR compared to data from a population of healthy matched controls.[2,3,9] One study examined three patient groups. One group was cured acromegaly patients that received GHR therapy, the second group was cured acromegaly patients that refused GHR therapy, and the final group was NFPA patients that received GHR therapy after surgery. The stated purpose of this study was to compare GHR therapy in cured acromegaly patients to NFPA patients after surgery, therefore the NFPA patients receiving GHR therapy served as a control in this study.[4] One study compared GHD patients that received GHR therapy to GHD patients that did not receive GHR therapy due to medical reasons and patient refusal. This study also compared outcomes to a sex and age matched healthy control group.[10]

All studies examined the quantitative effects of GHR therapy on glucose metabolic parameters and other cardiovascular disease (CVD) risk factors. None of the included studies, however, reported any direct impacts of GHR therapy on patient health apart from quality of life (QoL). All of the studies examined at least one parameter of glucose metabolism and endocrine function in

GHR patients. These parameters included serum glucose,[2-7,9,10] IGF-1,[2,4-10] insulin levels,[3,5-7,9] insulin resistance,[3-7,10] insulin sensitivity,[3,5] insulin tolerance,[9] and HbA1c.[3,4] Other CVD risk factors were examined as outcomes in eight studies and included lipid profiles,[2-7,9,10] blood pressure (BP),[2,3,7,9,10] and C-reactive protein levels.[5,9] Furthermore, outcomes of anthropometry and body composition were also assessed in eight studies and included body mass index (BMI),[2-9] waist circumference,[2-9] weight,[3,4,7,8] height,[3,4,7] waist to hip ratio (WHR),[5,6,9] body fat percentage (BF%),[3,4,6,7,9] fat mass,[5-7,9] and lean mass.[5,6,9] Five studies included outcomes of QoL,[3,4,6-8] and two reported adverse events.[4,7] One study hypothesized that GHR may alter GHD patient energy intake and/or energy expenditure and therefore examined outcomes of resting energy expenditure, respiratory quotient, voluntary activity, caloric intake, and hunger.[8] Three studies hypothesized that GHR may have beneficial effects on other markers of CVD risk that have been reported to be linked to untreated GHD.[3,9,10] These studies therefore examined outcomes of fibrinolytic markers,[9] soluble adhesion molecules,[9] artery intima-media thickness,[9,10] and epicardial fat thickness.[3]

The included guidelines from the American Association of Clinical Endocrinologists were published in 2009 and contained guidelines on many aspects of GHR therapy in GHD patients. These recommendations included seven relevant to GHR therapy patients with childhood onset GHD transitioning to adult height. The recommendations graded from A to D and were associated with a level of evidence rated from 1 to 4. The method of assignment for the levels of evidence and the corresponding recommendation grades are outlined in Appendix 2, Table A2.3. The reported target audience of these guidelines was physicians who prescribe GH, endocrinologists, other unspecified specialists, general internists, primary care physicians, endocrine nurses, and physician extenders who care for GHD patients on GH therapy.[13]

Summary of Critical Appraisal

The SR included in this report had significant limitations. The SR lacked quantification of conclusions and did not report on, or discuss the statistical significance of the findings in the included studies. Some findings were referred to as significant changes or differences but it was not clear if this meant statistically significant. There was no critical assessment of the included studies and an examination of publication bias was not presented. While the criteria for study inclusion did not include GHD severity, all patients were described as diagnosed with severe GHD. Strengths of the included SR included an outline for the methodology of data extraction, literature search, and criteria for study inclusion and exclusion. The data extraction was performed independently by two reviewers, and the literature search terms and queried databases were comprehensive. A flowchart of study inclusion and exclusion provided some information for the reasons for study exclusion and a table of study characteristics and findings were provided. The SR had a well-defined research objective focused on GHR therapy of the elderly and included a statement of no conflicts of interest (COIs). Adverse event data from the included studies was examined and a brief discussion on the limitations of the SR added to its strengths. A summary of the critical appraisal of the included SR is presented in Appendix 3, Table A3.1.

All of the included individual NRSs had the following strengths: a stated objective, well-described interventions, tabulated patient characteristics, a description of statistical methods, and predefined outcomes.[2-8,10] One study had findings that were not clearly interpreted.[9] Appropriate patient inclusion and exclusion criteria was described in seven studies,[2,3,5,7-10] while two studies had patient inclusion criteria but did not have pre-defined exclusion criteria.[4,6] It was unclear if patients were lost to follow-up in four studies,[3-5,9] while three studies provided some

description of the patients that were lost to follow-up,[2,6,10] and one study clearly had no patients lost to follow-up.[7] In one study not all patients participated in all outcome assessments and no description was provided to indicate how this may have biased the study results.[8] Four studies contained a statement that there was no potential COI,[2,3,7,10] while four studies acknowledged financial support from industry.[4,5,8,9] One study did not provide a COI statement.[6] The GHD patient population in eight studies was of mixed etiology, and no subgroup analyses were presented.[2,4-10] The remaining study did not report the initial cause of GHD in the patient population.[3] One study used a placebo control, and was single blinded, however patients had statistically significant baseline differences in outcomes of total cholesterol and triglycerides complicating the interpretation of findings.[7] Three studies had a baseline measurement as the only control,[5,6,8] while two studies had a control group from a healthy matched population cohort using data from a single time point.[2,3] Two studies had GHD patient control groups, however these patients had either refused treatment or did not receive GHR therapy for medical reasons which may have introduced bias.[4,10] One study had no baseline data and included only one time point for treated patients and a matched healthy population cohort.[9] Two studies had data on adverse events.[4,7] The sample size in six studies was fewer than 20 patients,[3,5-9] and none of the studies conducted a statistical power calculation. Critical appraisal of the included NRSs is summarized in Appendix 3, Table A3.2.

The included guidelines provided graded recommendations and associated the recommendations with a level of supporting evidence. The guidelines provided a discussion of the evidence on which the recommendations are based along with citing the evidence used. The target audience for the guidelines was explicitly stated; however, the guideline development methodology was lacking detail, with a general methodology provided in separate sources. There was no information on the literature search and selection methods used in the guidelines. The guidelines were authored with acknowledged potential COIs. Limited information was provided on updating the guidelines, on stakeholder involvement in the guideline development process, and on limitations of the guidelines.[13]

Summary of Findings

Main study findings and authors' conclusions of the included SR and NRSs are summarized in Appendix 4.

The included SR found evidence from an RCT that GHR therapy in the elderly resulted in decreased LDL, increased HDL, and an increased resting heart rate. A decrease in total cholesterol was observed in the RCT and two NRSs. One NRS included in the SR reported increased osteocalcin and calcium in ten patients. Another NRS examined 58 GHD patients and found a decrease in urinary cAMP levels with GHR therapy. Observed effects on body composition in one RCT and three NRSs were increased lean body mass and decreased body fat. The consensus of five NRSs that examined 400 GHD elderly patients was that GHR therapy increased QoL scores. All other findings were inconsistent between included studies or there was no effect of GHR therapy on examined outcomes. Adverse events in these elderly populations were related to glucose metabolism, in addition to cerebrovascular events and neoplasms. Prior to GH dose optimization, adverse events included fluid retention and carpal tunnel syndrome. One RCT included in the SR examined 34 patients and reported no significant differences in the occurrence of adverse events as compared to a placebo control group.[15]

Of the nine individual NRSs identified for this review, there were no outcomes with consistent statistically significant findings except for studies that examined subjective measurements of

QoL in GHD patients who received GHR therapy. Five studies found statistically significant improvements in QoL as compared to baseline.[3,4,6-8] One of the studies however also observed a statistically significant QoL improvement in healthy controls over the same period,[4] while another found that the relative percentage change between treatment and placebo groups was not significant.[7]

Six of the included studies found increased IGF-1 upon GHR therapy.[2,4-6,8,10] Of the two studies that did not observe an increase in IGF-1, one had a follow-up of 12 weeks,[7] while the other did not have a baseline comparison.[9] Serum glucose level outcomes provided no consistent evidence of efficacy. The most common finding was that GHR therapy had no statistically significant effect,[3-5,9] however, between the remaining studies that examined serum glucose levels, contradicting statistically significant differences were reported.[2,5,6,10] Insulin resistance, reported as homeostasis model assessment (HOMA), increased in one study after six months of GHR therapy,[6] decreased in another study after five years,[10] and two studies did not observe any statistically significant change.[4,7] One study compared treated GHD patients to a healthy matched control group and did not find a difference between the two groups with regards to insulin resistance.[9] Another study examined glucose metabolism in more detail and observed statistically significant improvements in glucose metabolism after 24 and 48 weeks of GHR therapy in six severe GHD patients.[5] Insulin sensitivity reported as quantitative insulin sensitivity check index (QUICKI) transiently increased at six months in one study.[3]

Triglyceride (TG) levels were found to be greater than healthy controls in three studies,[2,7,9] decreased with GHR therapy in two studies,[7,10] and no statistically significant differences were observed in three studies.[3,5,6] Two studies observed a statistically significant decrease in total cholesterol levels over three[4] and five years.[10] The remaining four studies that examined changes in total cholesterol did not observe a statistically significant reduction in total cholesterol,[3,5-7] including in GHD patients followed for one year.[3] A statistically significant decrease in serum LDL levels was observed in one study,[6] but two other studies did not observe a statistically significant difference.[5,7] Another study that examined serum LDL found a statistically significant decrease in serum LDL in cured acromegaly GHD patients receiving GHR therapy, but not in cured acromegaly GHD patients that refused GHR therapy, or GHD patients with previous NFPA receiving GHR therapy.[4] One study found no difference in LDL and HDL levels between treated GHD patients and healthy controls.[9] Two studies observed an increase in average HDL levels,[5,10] one observed a statistically significant decrease in HDL levels over six months,[6] while the four remaining studies looking at HDL levels as an outcome did not observe a statistically significant difference.[2-4,7] None of the included NRSs that examined BP observed statistically significant differences between groups.[2-4,9] Two studies examined physical cardiac measurements in GHD patients undergoing GHR therapy. One study observed decreased epicardial fat thickness,[3] and the other observed decreased right and left carotid artery intima-media thickness (IMT).[10] Decreased WHR was observed in one studies,[6] while another found that treated GHD patients still had a higher WHR than healthy matched controls.[9] The other studies examining WHR did not find any effect of GHR therapy in this population.[5] Body fat decreased in two studies,[3,4] while two others observed no effect.[6,9] It was widely found that GHR therapy had no statistically significant effect on waist circumference,[2-7] fat mass,[5,6,9] or lean mass.[5,6,9] One study observed some benefits of GHR therapy in GHD patients related to voluntary activity and appetite.[8]

One study stated that no side effects were recorded throughout the three year study period.[4] Another NRS reported one instance of arthralgia as a significant adverse event in the 14 severe GHD patients in the treatment arm and no arthralgia in the placebo group.[7] Additionally this

NRS observed three patients who developed self-limiting pedal edema, and two who developed mild diffuse headache. Both of these side-effects were reported to have resolved in a short time.[7] The two largest NRSs identified did not report adverse effects,[2,10] however one reported that 19 of 142 patients did not complete five years of GHR therapy due to death (n = 5), malignancy (n =2), increased prostate specific antigen (n = 1), weight increase (n = 1), carpal tunnel syndrome (n = 2), as well as lack of subjective benefit (n = 4), and follow-up in other centers (n =2).[2] The frequency of these events were not reported nor compared to the sex and age-matched healthy controls.[2]

The identified guidelines contained seven recommendations relevant to patients with childhood onset GHD transitioning to full adult height. These recommendations are quoted in their entirety in Appendix 4, Table A4.3. Four recommendations were assigned a grade A and based upon a level of evidence of 1. The first recommended that HGH only be prescribed to childhood-onset GHD patients who now exhibit symptoms consistent with adult GHD. The second recommended that GH status be reconfirmed after final adult height is achieved and after discontinuing GHR therapy for one month, in order to ascertain endogenous GH levels before transitioning to being treated as an adult GHD patient. This recommendation also included diagnoses for which discontinuation of GHR therapy and retesting is not required. The third recommendation, also assigned a grade A and based upon a level of evidence of 1, recommended the ITT for establishing a diagnosis of adult GHD, with acceptable alternatives being the GHRH plus arginine test, the glucagon test, and, rarely, the arginine test alone. The final recommendation assigned a grade A and based upon a level of evidence of 1 recommended that for patients with childhood hypothalamic GHD the GHRH plus arginine test may be misleading and therefore recommended an ITT or glucagon test. Based upon an evidence level of 2 and graded B, the AACE provided two recommendations for diagnoses where GHR therapy should be discontinued after final adult height is achieved, and recommended that similar cut points be used for GH stimulation testing in transition patients as would be applicable in adults. The final relevant recommendation was graded C and based on a level of evidence of 3. This recommendation stated that the HGH dose upon restarting GHR therapy should be approximately 50% of the dose between the pediatric doses required for growth and the adult dose.[13]

Limitations

All of the identified studies enrolled GHD patients of mixed etiology and separate analyses for patients with GHD due to pituitary destruction were not provided. In addition, the definition of severe GHD was inconsistent amongst the included studies. Two included NRSs reported only a mean age with standard deviation for enrolled patients. These studies may include some patients under the age of 25.[4,7] While the evidence identified represents evaluation of a wide survey of CVD risk factors in GHR therapy patients, no evidence was identified of the clinical effectiveness of GHR therapy in terms of direct health impacts for GHD patients. Evidence for the safety of GHR therapy was insufficient for quantitative conclusions.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited conclusions can be drawn from the evidence identified in this report. Two RCTs were identified by the included SR, but studies in the SR were not assessed for quality. These two RCTs enrolled a total of 65 elderly patients with severe GHD, about half of which were randomized to receive placebo. One RCT found no differences in cognition, HbA1c, insulin, or serum glucose with GHR therapy as compared to placebo. The other RCT found decreased

total cholesterol, decreased LDL, and decreased LDL/HDL ratio with GHR therapy as compared to placebo.[15] The NRSs, identified here and in the included SR, were also of a relatively small size and some were also over a short follow-up that may limit the applicability of the findings to long-term GHR therapy. No studies examined direct patient health outcomes of GHR therapy on adult patients aged 25 years and older with GHD due to pituitary destruction. The most consistent evidence and direct patient outcome examined came from a total of nine NRSs, examining 520 severe GHD patients of mixed etiology, in which improvements in QoL measurements were observed with GHR therapy as compared to baseline.[3,4,6-8,15] QoL in these studies was determined by either QoL-Assessment of Growth Hormone Deficiency in Adults (AGHDA) score[6-8,15] or Questions on life-hypopituitarism (QoL-H) score,[3,4] both of which are self-administered subjective questionnaires. One of these NRSs also observed QoL improvements in scores of healthy controls,[4] and another NRS observed improvements in the placebo control group scores,[7] adding uncertainty to these findings. One study observed some benefits in voluntary activity levels and appetite in GHR treated GHD patients which may be related to QoL scores.[8] There was also some consistent evidence that GHR therapy increased IGF-1 levels, however since IGF-1 levels were used to optimize GH dose this finding has limited relevance to clinical effectiveness.[2,4-6,8,10] All remaining examined outcomes of GHR therapy in severe GHD patients were not affected or statistically significant findings were contradictory between the included studies. Randomized controlled trials enrolling a number of patients sufficient to detect the anticipated differences with longer follow-up times are needed in order to demonstrate confidence of significant benefit of GHR therapy in severe GHD patients. It has been reported however that ethical considerations may prevent such trials.[10,11,19]

One RCT included in the SR mentioned adverse events and observed no differences between placebo and GHR therapy groups.[15] The remainder of reported adverse event evidence identified was not quantitative. Adverse events included cerebrovascular events, neoplasms, fluid retention, carpal tunnel syndrome, arthralgia, self-limiting pedal edema, and mild diffuse headache.[2,7,10,15] The two largest NRSs identified did not report adverse effects or direct patient health outcomes,[2,10] however one did report that 13 of 142 patients did not complete 5 years of GHR therapy due to death, malignancy, increased prostate-specific antigen, carpal tunnel syndrome, and weight increase. The frequency of these events was not compared to the sex and age-matched healthy controls.[2] Based on the identified evidence, conclusions regarding the safety of GHR therapy in patients 25 years and older with GHD due to pituitary destruction are not possible.

Seven recommendations from one identified guideline were identified for GHD patients transitioning to full adult height. Recommendations of the highest grade suggested prescribing GH only to patients who are confirmed to retain clinical features of adult GHD after full adult height is attained. It was recommended to use ITT as confirmation, or less ideally, the GHRH plus arginine, glucagon, or, rarely, the arginine test alone. The strongest recommendations also included diagnoses for which confirmation of GHD is not required, and recommendations with less supporting evidence included diagnoses that do not require GHR therapy after full height is achieved. While no peak serum GH levels were recommended to confirm GHD, it was recommended that the same levels are used to confirm adult GHD in these transitioning patients. Finally the guidelines recommended a starting HGH dose for these patients of approximately 50% of the pediatric dose.[13]

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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AGHD	Assessment of Growth Hormone Deficiency in Adults
BC	body composition
BEL	best evidence level
BF%	body fat percentage
BF	body fat
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CRP	C-reactive protein
CHF	congestive heart failure
COI	conflict of interest
CVD	cardiovascular disease
DM	diabetes mellitus
FFM	fat-free mass
GH	growth hormone
GHD	growth hormone deficient
GHRH	growth hormone releasing hormone
HDL	high density lipoprotein
HGH	human growth hormone
HOMA	homoeostasis model assessment
IGF-1	insulin-like growth factor 1
IMAT	intermuscular adipose tissue
IMT	intima-media thickness
LBM	lean body mass
LDL	low density lipoprotein
MS	metabolic syndrome
NFPA	nonfunctioning pituitary adenoma
NRS	non-randomized study
PTH	parathyroid hormone
QoL	quality of life
QUICKI	quantitative insulin sensitivity test
RCT	randomized controlled trial
SAT	subcutaneous adipose tissue
SD	standard deviation
SDS	standard deviation score
SEM	standard error mean
SSD	statistically significant difference
TFEQ	three factor eating questionnaire
TG	triglyceride
VAT	visceral adipose tissue
WHR	waist to hip ratio

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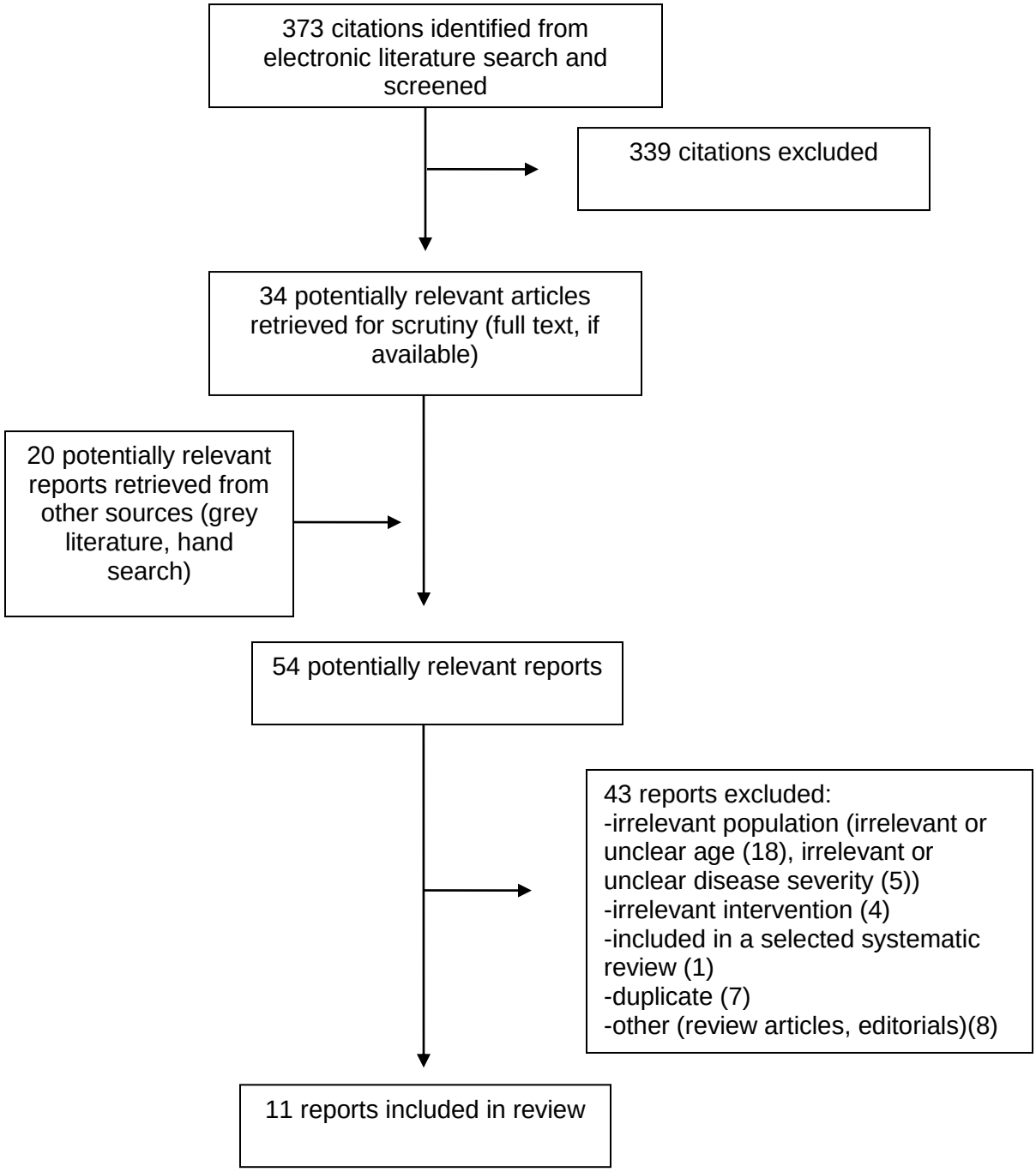
APPENDIX 1: Selection of Included Studies



APPENDIX 2: SUMMARY OF STUDY CHARACTERISTICS

Table A2.1: Summary of Study Characteristics of Included SR

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
Systematic Review				
Kookshoorn et al., 2011[15]				
SR: (2 RCTs, 9 NRSs)	Elderly (> 60 years) GHD patients RCTs (n = 65), NRS = 469)	HGH	Placebo (RCTs) Baseline data (NRSs)	• Endocrine evaluation - IGF-1 SDS, GHRH, ITT • Cardiovascular risk factors - Lipid profiles, BP, cardiac function • Anthropometry - Body weight, height, WHR, BMI • Bone parameters - BMD, osteocalcin, calcium, PTH, urinary cAMP • QoL • Cognitive function • Adverse events

BC=body composition; **BMD**=bone mineral density; **BMI**=body mass index; **BP**=blood pressure; **cAMP**=cyclic adenosine monophosphate; **GHD**=growth hormone deficient; **GHRH**=growth hormone releasing hormone; **ITT**=insulin tolerance test; **NRS**=non-randomized prospective studies; **PTH**=parathyroid hormone; **QoL**=quality of life; **RCT**=randomized controlled trial; **SDS**=standard deviation score; **SR**=systematic review; **WHR**=waist to hip ratio

Table A2.2: Summary of Study Characteristics of Included Non-Randomized Studies

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
Claessen et al., 2014[2]				
Prospective cohort controlled and observational study Yearly follow-up of 5 years	GHD patients (n = 161); Female (n = 72), age range (40 - 70 years), all treated with surgery and or radiotherapy, NFPA (n = 67), functioning adenoma (n = 52), craniopharyngioma (n = 12), cerebral malignancy (n = 2), congenital (n = 6), other (n = 22) Peak serum GH <3µg/L ITT Exclusion: age >70, age <40, started HGH after 2007	HGH (starting dose 0.2mg/day then adjusted monthly for 6 months to achieve target IGF-1) Dosages of other hormonal replacement therapy was monitored and adjusted as required Patients also treated with lipid-lowering and antihypertensive Rx according to discretion of attending physician	• Baseline • General population from the Leiderdorp cohort; age range (45 - 65)	• Endocrine evaluation - Serum glucose, IGF-1 • Cardiovascular risk factors - Lipid profile, BP, MS • Anthropometry - BMI, waist circumference
Ferrante et al., 2013[3]				
Prospective cohort controlled and observational study Follow-up of 6 and 12 months	GHD patients (n = 18); Female (n = 8), mean age 48, age range 26 - 65 years, NFPA (n = 8), craniopharyngioma (n = 6), empty sella (n = 3) Severe GHD defined as peak serum GH <11µg/L for normal BMI, <8µg/L for overweight, <4.2µg/L for obese patients following GHRH+Arg test Exclusion: age > 65 years, Hx CVD, DM, CHF, Hx malignancy, Hx acromegaly,	HGH (starting mean dose 0.23 ± 0.08 mg, 6 month mean dose 0.29 ± 0.1mg, 12 month mean dose 0.34 ± 0.1mg) Upon request conventional stable hormone replacement for other pituitary hormone deficiencies	• Baseline • Healthy matched controls (n = 18)	• Endocrine evaluation - Serum glucose, HbA1c - Insulin level, resistance (HOMA) and sensitivity (QUICKI) • Cardiovascular risk factors - Epicardial fat thickness, BP, lipid profile • Anthropometry - Weight, height, waist circumference, BMI • BC - BF% • QoL

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
	childhood onset GHD			
Giavoli et al., 2012[4]				
Prospective, three arm, open-label, non-randomized study Follow-up of 36 months	Adult GHD patients (n = 42); cured acromegaly (n = 22), operated NFPA (n = 20) IGF-1 < -1.5 SD score Severe GHD defined as peak serum GH < 4µg/L and IGF-1 < 1.5 SDS following GHRH+Arg test Exclusion: age > 65 years, Hx CVD, DM, CHF, Hx malignancy, Hx acromegaly, childhood onset GHD	A) HGH in cured acromegaly (n = 10) (0.2mg/d for males, 0.3mg/d for females, then titrated for individual IGF-1 levels) When necessary stable conventional hormone replacement for other pituitary hormone deficiencies	B) cured acromegaly w/o HGH (n = 12) (refused treatment) C) HGH in GHD patients operated for NFPA (n = 20)	• Endocrine evaluation - IGF-1 levels, serum glucose, HbA1c, insulin resistance (HOMA) • Cardiovascular risk factors - Lipid profile • Anthropometry - Weight, height, waist circumference, BMI • BC - BF% • QoL • Adverse events
Arafat et al., 2010[5]				
Prospective observational study Follow-up of 24 and 48 weeks	Adult GHD patients (n = 6); Male (n = 4), age range 40 - 59 years, NFPA (n = 4), traumatic brain injury (n = 2) Severe GHD defined as peak serum GH <3µg/L ITT, <3µg/L glucagon, and <9µg/L GHRH+Arg test Exclusion: DM, CVD, uncontrolled hypertension, malignancy, pregnancy, hepatic or renal impairment	Self-administered HGH (0.003 mg/kg/day, mean dose 0.3 ± 0.004mg/day) titrated after 4 weeks to maintain IGF-1 levels below 50th percentile Stable hormone replacement as appropriate	Baseline	• Endocrine evaluation - IGF-1 levels, serum glucose - Insulin resistance, sensitivity, secretion and clearance - Serum creatinine, uric acid, and protein • Cardiovascular risk factors - Lipid profile • Anthropometry - Waist circumference, WHR, BMI • BC - Truncal fat mass, truncal lean mass

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
Deepak et al., 2010[6]				
Prospective observational study Follow-up of 6 months	Adult severe GHD patients (n = 15); (26 - 60) Female (n = 4) NFPA (n = 7), Empty sella (n = 2), Idiopathic hypopituitarism (n = 2), supra sellar cyst (n = 2), others (n = 2) Severe GHD defined as peak serum GH ≤3µg/L following glucagon stimulus and impaired QoL (AGHDA ≥ 11) Exclusions: No predefined criteria, however, 2 patients excluded for poor venous access, 1 due to 'technical problems' and 1 exclusion for Langerhans Cell Histiocytosis	HGH (dose titrated to clinical response and IGF-1) Other hormone replacements where required	Baseline	• Endocrine evaluation - IGF-1 levels, serum glucose - Insulin levels, insulin resistance (HOMA) • Cardiovascular risk factors - Lipid profile -Inflammatory markers (hs-CRP, IL-6, TNF-α) • Anthropometry - Waist circumference, WHR, BMI • BC - BF%, fat mass, fat free mass • QoL
Dutta et al., 2010[7]				
Single blinded, Non-randomized controlled clinical trial Follow-up of 12 weeks	Adult male GHD patients (n = 26); mean age 47.0 ± 3.9 years, clinically nonfunctioning pituitary tumour (n = 16), craniopharyngioma (n = 3), pituitary apoplexy (n = 4), pituitary abscess (n = 2), lymphocytic hypophysitis (n = 1) Peak serum GH ≤5µg/L ITT Exclusions: acromegaly, recent	HGH (4µg/kg/day), (n = 14) Other hormone replacements where required	Placebo (n = 12)	• Endocrine evaluation - IGF-1 levels, serum glucose, cortisol - Insulin levels, insulin resistance (HOMA) • Cardiovascular risk factors - Lipid profile, BP • Anthropometry - Waist circumference, height, weight, BMI • BC

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
	surgery, active malignancy, significant residual pituitary tumour			- BF%, Total BF • Hand grip strength • QoL • Adverse events
Deepak et al., 2008[8]				
Prospective observational study Follow-up of 6 months	Adult GHD patients (n = 19); (25 - 50 years) NFPA (n = 7), Craniopharyngioma and Rathke cyst (n = 3), Empty sella (n = 2), Idiopathic hypopituitarism (n = 2), supra sellar cyst (n = 2), Others (n = 3) Severe GHD defined as peak serum GH ≤ 9µg/L following glucagon stimulus and impaired QoL (AGHDA ≥ 11) Exclusions: type 2 DM, no mood or appetite altering medications, no Hx eating disorders	HGH (0.3mg/day titrated to clinical response and IGF-1) follow-up of 6 months after dose established Other hormone replacements as required	Baseline	• Endocrine evaluation - IGF-1 level and SDS score • Resting Energy Expenditure, Respiratory quotient, Activity, • Caloric Intake - Total Calories, Carbohydrates, Fat, Protein • Hunger score, satiety score, TFEQ, ad libitum energy intake • Anthropometry - Weight, waist circumference, BMI • QoL
Colao et al., 2008[10]				
Prospective, open, non-randomized, cohort controlled study Follow-up of 5 years	Adult GHD patients (n = 44); (25 - 50 years), males (n = 44), BMI < 30kg/m^2, all had surgery for pituitary tumours Severe GHD defined as peak serum GH <9µg/L following GHRH+Arg Exclusions: familial or personal Hx CVD, Rx known to interfere with glucose or lipid metabolism or BP, Hx	A) HGH (mean dose 6µg/kg/day) (n = 22) Other hormone replacements where required	B) GHD patients with no HGH treatment (n = 13) (medical reasons and patient refusal of HGH) C) Sex and age-matched healthy controls (same exclusion criteria) (n = 35)	• Endocrine evaluation - IGF-1 levels SDS, serum glucose, insulin resistance (HOMA) • Cardiovascular risk factors - Carotid artery IMT, BP, lipid profile

Study Design	Population (sample size)	Intervention	Comparator(s)	Outcomes
	HGH treatment			
Gomez et al., 2007[9]				
Prospective cohort controlled study Patients on HGH average of 4.1 years	Adult GHD patients (n = 20); males (n = 10), (30 - 53 years) NFPA (n = 10), Craniopharyngioma (n = 4), Idiopathic hypopituitarism (n = 2), Sheehan's syndrome (n = 4) Peak serum GH <3µg/L following ITT and glucagon stimulus Exclusions: age under 30 years, age over 55 years, Hx smoking, hypertension, DM or family Hx DM, abnormal resting ECG, premature vascular disease, chronic disease, risk factors for endothelial dysfunction, BMI under 22 kg/m^2 , BMI over 32 kg/m^2	HGH (average starting dose 0.24 ± 13 mg/day, average final dose 0.24 ± 13 mg/day), titrated to clinical response and IGF-1 target Other hormone replacements as required	Healthy control group matched for age, and BMI (n = 25) with same exclusion criteria as intervention group	• Endocrine evaluation - IGF-1 levels, serum glucose - Insulin levels, ITT • Cardiovascular risk factors - Lipid profile, BP • Fibrinolytic markers, soluble adhesion molecules, inflammatory cytokines • Endothelial function • Anthropometry - Waist circumference, weight, WHR, BMI • BC - BF%, Total BF, fat free mass, total water

AGHD=Assessment of Growth Hormone Deficiency in Adults; **BF%**=body fat percentage; **BF**=body fat; **BMI**=body mass index; **BP**=blood pressure; **CVD**=cardiovascular disease; **CHF**=congestive heart failure; **DM**=diabetes mellitus; **FFM**=fat-free mass; **GHD**=growth hormone deficient; **GHRH**=growth hormone releasing hormone; **HGH**=human growth hormone; **HOMA**=homoeostasis model assessment; **IMAT**=intermuscular adipose tissue; **IMT**=intima-media thickness; **MS**=metabolic syndrome; **NFPA**=nonfunctioning pituitary adenoma; **QoL**=quality of life; **QUICKI**=quantitative insulin sensitivity test; **SAT**=subcutaneous adipose tissue; **SDS**=standard deviation score; **TFEQ**=three factor eating questionnaire; **VAT**=visceral adipose tissue; **WHR**=waist to hip ratio;

Table A2.3: Summary of Study Characteristics of Included Guidelines

Origin, Publication Date	Interventions of Interest	Evidence Levels and Recommendation Grading	Target Population
AACE 2009[13]			
American Association of Clinical Endocrinologists, Endocrine Practice, USA, September/October 2009	GHR therapy in GHD patients	Evidence Levels 1 - 4 **1.** Well conducted SRs, MAs, or RCTs **2.** NRS or limited level 1 studies **3.** Other evidence (case reports, series, limited level 2 evidence) or RCT with ≥ 1 major limitations or ≥ 3 minor limitations **4.** Expert opinion Recommendations graded A - D **A.** Strong evidence- benefit outweighs risk **B.** Intermediate evidence - second-line therapy **C.** "No objection" to recommending or continuing use **D.** Not recommended	Physicians who prescribe HGH, endocrinologists and other specialists, general internists, primary care physicians, endocrine nurses, physician extenders who care for GHD patients on GH therapy
GH=human growth hormone; **GHD**=growth hormone deficiency; **HGH**=human growth hormone; **MA**=meta-analysis; **NRS**=non-randomized prospective study; **RCT**=randomized controlled trial; **SR**=systematic review			

APPENDIX 3: Summary of Critical Appraisal

Table A3.1: Critical Appraisal Summary for included SR using AMSTAR tool.[16]

Strengths	Limitations
Systematic Review	
Kookshoorn et al., 2011[15]	
• Literature search, inclusion, exclusion methodology provided • Data extraction methodology provided • Flowchart of study inclusion and exclusion • Research objective defined • Tabulated study characteristics • Statement of no COI • Examination of reported adverse event data • Discussion of limitations	• No assessment of study quality • No examination of publication bias • No reporting or discussion of statistical significance of reported results of studies • Criteria does not include disease severity definition however this information was tabulated for each study and all patients were described as diagnosed with severe GHD • Limited quantified conclusions
COI=conflict of interest; **GHD**=growth hormone deficiency	

Table A3.2: Critical Appraisal Summary for included Trials using Downs and Black checklist for NRSs.[17]

Strengths	Limitations
Non-Randomized Studies	
Claessen et al., 2014[2]	
• Objective clearly stated • Outcomes clearly described and defined in Methods • Five-year follow-up • Well described intervention • Patient inclusion/exclusion criteria described • Patient characteristics tabulated • Patients lost to follow-up described • Clearly described findings • Statistical methods described and used appropriately • QoL data reported • Statement of no COI	• Patients mixed population and a significant number with an unreported reason for pituitary surgery or radiotherapy • Control group was a general matched population cohort and control samples were from a single time • No data on adverse events • No blinding • ITT analysis not possible
Ferrante et al., 2013[3]	
• Clearly stated objective • Outcomes clearly described and defined • Well described intervention • Blinded assessment • Patient inclusion/exclusion criteria described • Patient characteristics tabulated • Clearly described findings • Statistical methods described and used appropriately • QoL data reported • Statement of no COI	• Initial cause of GHD in patients not described • Control group was a healthy matched population cohort and control samples were from a single time • No mention if patients lost to follow-up • No data on adverse events • Very small sample size
Giavoli et al., 2012[4]	
• Objective stated • Outcomes clearly described and defined • Control patients from the same population (not randomized) • Well described intervention • Patient inclusion criteria described • Patient characteristics tabulated • Statistical methods described and used appropriately • Clearly described findings • Adverse events mentioned • QoL data reported	• Mixed patient population of previous acromegaly and previous NFPA • Controls were GHD patients who refused treatment - reasons not reported • No blinding • Some statistically significant differences between patient groups at baseline • No mention of patients lost to follow-up • Industry funding of study
Arafat et al., 2010[5]	
• Objective clearly stated • Outcomes clearly described and defined • Well described intervention • Patient inclusion/exclusion criteria described • Patient characteristics tabulated	• Mixed patient population of previous NFPA and traumatic brain injury • Baseline data as only control • No blinding • Very small sample size

Strengths	Limitations
Non-Randomized Studies	
• Limitations described • Clearly described findings • Statistical methods described and used appropriately	• No mention if patients lost to follow-up • Industry funding of study • No adverse event data
Deepak et al., 2010[6]	
• Objective clearly stated • Outcomes clearly described and defined • Well described intervention • Patient characteristics tabulated • Patient inclusion criteria described • Statistical methods described and used appropriately • Patients lost to follow-up described • Clearly described findings • QoL data reported	• Mixed GHD patient population of previous NFPA, empty sella, idiopathic hypopituitarism, supra sellar cyst (unknown etiology), and others • Baseline data as control • No blinding • Very small sample size • No COI statement • No adverse event data
Dutta et al., 2010[7]	
• Objective clearly stated • Outcomes clearly described and defined • Well described intervention • Patient characteristics tabulated • Patient inclusion criteria described • Statistical methods described and used appropriately • No patients lost to follow-up • Placebo controlled • Single blind design • Clearly described findings • Adverse event data reported • QoL data reported • Statement of no COI	• Mixed GHD patient population of nonfunctioning pituitary tumour, pituitary apoplexy, pituitary abscess, lymphocytic hypophysitis, and craniopharyngioma • Statistically significant differences between patient groups at baseline • Non-randomized • Small sample size • No discussion of limitations
Deepak et al., 2008[8]	
• Objective clearly stated • Outcomes described • Well described intervention • Patient characteristics tabulated • Patient inclusion criteria described • Statistical methods described and used appropriately • QoL data reported • Clearly described findings	• Mixed GHD patient population of previous NFPA, empty sella, idiopathic hypopituitarism, supra sellar cyst (unknown etiology), craniopharyngioma and Rathke cyst, and others • Baseline data as only control • Some patient-reported and subjective outcomes • Not all patients participated in all outcome assessments • Small sample size • No discussion of limitations • No adverse event data • Industry funding of study

Strengths	Limitations
Non-Randomized Studies	
Colao et al., 2008[10]	
• Objective clearly stated • Outcomes described • Well described intervention • Patient characteristics tabulated • Patient inclusion/exclusion criteria described • Flow chart of patient eligibility, enrollment, and exclusion • Clearly described findings • 5 year follow-up (healthy controls also followed for 5 years) • Statistical methods described and used appropriately • Some discussion of limitations • Patients lost to follow-up described • Statement of no COI	• Second control group did not receive HGH for medical reasons • No adverse event data
Gomez et al., 2007[9]	
• Objective clearly stated • Outcomes clearly described and defined • Well described intervention • Patient characteristics tabulated • Patient inclusion criteria described • Statistical methods described and used appropriately	• Mixed GHD patient population of previous NFPA, idiopathic hypopituitarism, craniopharyngioma and Sheehan's syndrome • No baseline data • Industry funding of study • No adverse event data reported • Small sample size • No mention if patients lost to follow-up • Findings difficult to interpret
BMI=body mass index; **COI**=conflict of interest; **GH**=growth hormone; **GHD**=growth hormone deficiency; **NFPA**=nonfunctioning pituitary adenoma	

Table A3.3: Critical Appraisal Summary for Guidelines using AGREE II[18]

Strengths	Limitations
AACE 2009[13]	
• Graded recommendations • Recommendations linked to supporting level of evidence • Discussion on evidence containing citations • Target audience described	• Some authors with potential COIs • Guideline development methodology including literature search and selection methods absent • Limited information on update process • Limited stakeholder representation • No discussion of limitations
AACE=American Association of Clinical Endocrinologists; **COI**=conflict of interest	

APPENDIX 4: Summary of Findings

Table A4.1: Summary of Main Findings and Author's Conclusions of SR

Main Findings	Author's Conclusions
Kookshoorn et al., 2011[15]	
Cardiovascular Risk Factors and Lipid Profile (2 RCT, 7 NRS) (n = 460) Total cholesterol - decreased by 4-8% (1 RCT, 2 NRS) (n = 105) LDL - decreased by 11-16% (1 RCT) (n = 31) HDL - increased by 17% (1 RCT) (n = 31) TG - unaffected (3 NRS) (n = 324) BMI - unaffected (2 NRS) (n = 35) WHR - decreased (3 NRS) (n = 270), no effect (2 NRS) (n = 75) BP - no effect (1 RCT) (n = 31), transient decrease (1 NRS) (n = 10), decreased diastolic BP only (3 NRS) (n = 324) Heart rate - increased at rest (1 RCT) (n = 31) Cardiac structural and functional parameters - No effect (1 RCT) (n = 31) Cardiac Events - No data **Bone Parameters** (3 NRS) (n = 69) BMD - no effect (2 NRS) (n = 41) Osteocalcin - increased (1 NRS) (n = 10) Calcium - increased (1 NRS) (n = 10) PTH - no effect (1 NRS) (n = 10), decreased (1 NRS) (n = 58) cAMP - decreased (1 NRS) (n = 58) Bone Formation Markers - increased (1 NRS) (n = 31) Fracture Incidence - No data **Body Composition** (1 RCT, 5 NRS) (n = 213) BC - no effect (4 NRS) (n = 45) LBM - increased by 2-5% (1 RCT, 2 NRS) (n = 67), effect dependent on continued HGH (1 NRS) (n = 12) BF - decreased by 7-10% (1 RCT, 2 NRS) (n = 67), effect dependent on continued HGH (1 NRS) (n = 12) **QoL -** increased (5 NRS) (n = 400) **Cognitive Function** - no effect (1 NRS) (n = 34) **Muscle Strength** (1 NRS) (n = 24) Only observed transient improvement in knee flexor strength however HGH protected from most age-related decline in muscle performance and neuromuscular function. **Adverse Effects** Glucose metabolism, Cerebrovascular events, Neoplasms (1 NRS) (n = 125) No significant differences from placebo (1 RCT) (n = 34)	"HGH replacement in elderly subjects with GHD decreases LDL cholesterol levels and improves QoL, but the effects on other parameters are not unequivocal." (pp. 657) "… the question remains whether the treatment with HGH is clinically relevant in elderly, and especially very old, patients with GHD." (pp. 663)

Main Findings	Author's Conclusions
Fluid retention before dose optimization (1 NRS) (n = 12) Carpal Tunnel Syndrome before dose optimization (1 NRS) (n = 58)	

BC=body composition; **BF**=body fat; **BMD**=bone mineral density; **BMI**=body mass index; **BP**=blood pressure; **GHD**=growth hormone deficiency; **HDL**=high density lipoprotein; **LBM**=lean body mass; **LDL**=low density lipoprotein; **NRS**=non-randomized prospective study; **PTH**=parathyroid hormone; **QoL**=quality of life; **RCT**=randomized controlled trial; **TG**=triglyceride; **WHR**=waist hip ratio

Table A4.2: Summary of Main Findings and Author's Conclusions of NRSs

Main Findings	Author's Conclusions
Non-Randomized Studies	
Claessen et al., 2014[2]	
IGF-1 SDS (mean(IQR)) (p<0.001) All GHD patients Baseline -1.30(-2.43, 0.16) 5 years 0.47(-0.50, 1.93) Males Baseline -1.17(-2.17, 0.92) 5 years 0.42(-0.43, 2.03) Females Baseline -1.63(-3.04, 0.47) 5 years 0.51(-0.57, 1.71) **Prevalence Ratio (PR) of MS in GHD patients receiving HGH for 5 years vs the general population control (NCEP-ATP III criteria)** (PR(95% CI)) (p < 0.01) **Adjusted for age, sex, and BMI (PR > 1 more prevalent in GHD patients on HGH)** Fasting glucose 0.5(0.4-0.7) Triglycerides 2.0(1.7-2.3) HDL-C 1.8(1.5-2.2) Blood pressure no SSD Waist no SSD MS 1.3(1.1-1.5) Fasting glucose (mmol/L) Baseline 4.8 ± 0.8 5 years 5.2 ± 1.6 (p<0.001 vs Baseline) Control 5.5 ± 1.1 (p<0.01 vs 5 years) Triglycerides (mmol/L) - no SSD with HGH treatment 5 years 1.9 ± 0.9 Control 1.2 ± 0.8 (p<0.01 vs 5 years) HDL-C (mmol/L) Baseline 1.4 ± 0.4 5 years 1.5 ± 0.5 (p<0.001 vs Baseline) Control 1.6 ± 0.5 (p<0.05 vs 5 years) Systolic blood pressure (mmHg) - no SSD with HGH treatment 5 years 135.7 ± 17.6 Control 130.4 ± 16.9 (p<0.01 vs 5 years) Waist circumference (cm) - no SSD with HGH treatment 5 years 97.2 ± 11.8 (p<0.001 vs Baseline) Control 91.2 ± 12.8 (p<0.01 vs 5 years)	"…despite 5 years of HGH replacement, GHD patients still have a different metabolic profile and a higher MS proportion than the general population. These differences were independent of BMI and resemble the metabolic profile of untreated GHD patients. This emphasizes the need for further study to establish whether HGH replacement is actually beneficial in the long-term, adequately incorporating the cost-effectiveness, QoL, and the potential negative effects of GH/IGF1 on cancer, longevity, and cardiovascular risk." (pp. 270)

Main Findings	Author's Conclusions
Non-Randomized Studies	
Ferrante et al., 2013[3]	
Outcomes with demonstrated SSD only (p < 0.05) BF (mean ± SD) (p<0.05) Baseline 35.2 ± 6.3 kg/m^2 12 months 31.8 ± 6.1 kg/m^2 Insulin (mean ± SD) (p<0.05) Baseline 7.4 ± 4.1 µIU/mL 6 months 10.8 ± 5.6 µIU/mL 12 months no SSD w/ Baseline HOMA-IR (mean ± SD) (p<0.05) Baseline 1.6 ± 1.1 6 months 2.4 ± 1.5 12 months no SSD w/ Baseline QUICKI (mean ± SD) (p<0.05) Baseline 0.37 ± 0.03 6 months 0.34 ± 0.03 12 months no SSD w/ Baseline Echocardiographic epicardial fat thickness (mean ± SD) Baseline 9.8 ± 2.8mm* 6 months 7.0 ± 2.3mm** 12 months 5.9 ± 3.1mm** Control population 8.0 ± 3.0mm * (p < 0.05 vs controls) ** (p < 0.01 vs Baseline) QoL (QLS-H self-administered questionnaire (z-score)) (p < 0.01) Baseline -1.5 ± 1.1 12 months -0.7 ± 1.4 No SSDs observed in BMI, waist circumference, BP, glucose, HbA1c, total cholesterol, HDL, or TG.	"…echocardiographic measurement of epicardial fat thickness may represent a valuable and easy marker of visceral fat changes during HGH replacement treatment in patients with adult-onset GHD and may represent, along with IGF-I, quality of life and body composition a useful parameter in evaluating the efficacy of HGH therapy in these patients. These findings need to be expanded in larger and longer follow-up studies." (pp. 464)
Giavoli et al., 2012[4]	
Group A (A): Acromegalics on HGH (n = 10) Group B (B): Acromegalics not treated (n = 12) Group C (C): NFPA on HGH (n = 20) **Outcomes with demonstrated SSD only (p < 0.05) follow up 36 months** BF% (%) (mean ± SD) A Baseline 35.7 ± 5.2%	"… in GHD acromegalics HGH therapy improved body composition, lipid profile and quality of life as in patients with GHD and previous non-

Main Findings		Author's Conclusions
Non-Randomized Studies		
A 12 months	31.7 ± 2.4%*	functioning pituitary adenoma." (pp. 3987) "Long-term follow-up in wide groups of patients is necessary both to confirm efficacy and safety of HGH and eventually to find any clinical or metabolic deterioration in untreated patients, suggesting the opportunity to start HGH substitution." (pp. 3987) **Adverse Events:** "No side effects were recorded throughout the study period." (pp. 3986)
A 36 months	30.9 ± 2.6%*	
C Baseline	36.9 ± 9.9%	
C 12 months	33.5 ± 9.7%*	
C 36 months	31.6 ± 9.2%*	
<u>IGF-1(SDS) (mean ± SD)</u>		
A Baseline	-2.2 ± 0.5	
A 12 months	0.0 ± 0.9*	
A 36 months	0.0 ± 0.5*	
B Baseline	-1.6 ± 0.8**	
B 12 months	-1.7 ± 0.5**	
B 36 months	-2.2 ± 0.5**	
C Baseline	-2.3 ± 0.5	
C 12 months	0.0 ± 0.5*	
C 36 months	0.0 ± 0.6*	
<u>Total cholesterol (mg/dL) (mean ± SD)</u>		
A Baseline	231 ± 19	
A 12 months	208 ± 14*	
A 36 months	199 ± 39*	
B Baseline	188 ± 35**	
B 12 months	197 ± 36	
B 36 months	191 ± 36	
C Baseline	216 ± 29	
C 12 months	199 ± 33*	
C 36 months	200 ± 34*	
<u>LDL (mg/dL) (mean ± SD)</u>		
A Baseline	150 ± 16	
A 12 months	130 ± 14*	
A 36 months	118 ± 38*	
B Baseline	112 ± 29**	
C Baseline	140 ± 39	
<u>QoL (QLS-H scores) (mean ± SD)</u>		
A Baseline	-1.9 ± 0.9	
A 12 months	-0.9 ± 1.2*	
A 36 months	-0.8* †	
B Baseline	-0.4** †	
B 12 months	-0.4 †	
B 36 months	-0.6 †	
C Baseline	-1.5 ± 1.1	
C 12 months	-0.7 ± 1.4*	
C 36 months	-0.8* †	

Main Findings	Author's Conclusions
Non-Randomized Studies	
* p < 0.018 vs baseline ** p < 0.018 B vs A and C † value estimated from graph No SSDs observed in BMI, Waist circumference, serum glucose, insulin, insulin resistance (HOMA), HbA1c, HDL, or BP.	
Arafat et al., 2010[5]	
Outcomes with demonstrated SSD only (p < 0.05) IGF-1(SDS) (mean ± SEM) Baseline 86.2 ± 5.1 24 weeks 154.8 ± 9.3* 48 weeks 148.7 ± 6.3* Blood glucose at 120min (mmol/L) (mean ± SEM) Baseline 7.9 ± 0.6 24 weeks 6.3 ± 0.4* 48 weeks 6.5 ± 0.5* HDL-cholesterol (mmol/L) (mean ± SEM) Baseline 1.14 ± 0.2 24 weeks 1.20 ± 0.24* 48 weeks 1.29 ± 0.19* * p < 0.05 vs baseline Statistically significant improvements in insulin secretion and clearance were also observed in these patients at 24 and 48 weeks of HGH therapy as compared to baseline. No SSDs observed in BMI, waist circumference, WHR, fat mass, lean mass, creatinine, uric acid, serum protein, serum glucose, insulin, C-peptide, total cholesterol, LDL, TG and C-reactive protein.	"Our data indicate that long-term low-dose growth hormone treatment may improve insulin sensitivity and whole-body glucose metabolism in adults with severe growth hormone - deficiency." (pp. 1304)
Deepak et al., 2010[6]	
Outcomes with demonstrated SSD only (p < 0.05) IGF-1(SDS) (median(IQR)) (p < 0.0001) Baseline -0.6(-0.86 to -0.43) 6 months 0.39 (0.19 to 0.5) IGF-1 level (mean ± SD) (p < 0.0001) Baseline 13.0 ± 4.6nmol/L 6 months 28.1 ± 5.7nmol/L QoL (AGHDA score) (mean ± SD) (p < 0.0001) decrease was an improvement	"…it is likely that the favourable effects of GHR on four well known CV risk markers (hs-CRP, LDL-C, HDL-C and WHR), accompanied by a considerable increase in voluntary physical

Main Findings		Author's Conclusions
Non-Randomized Studies		
Baseline 6 months <u>Glucose (mean ± SD) (p = 0.003)</u> Baseline 6 months <u>Insulin (mean ± SD) (p = 0.03)</u> Baseline 6 months <u>HOMA-IR (mean ± SD) (p = 0.02)</u> Baseline 6 months <u>WHR (mean ± SD) (p = 0.01)</u> Baseline 6 months <u>LDL-C (mean ± SD) (p = 0.03)</u> Baseline 6 months <u>HDL-C (mean ± SD) (p = 0.02)</u> Baseline 6 months <u>hs-CRP (Ln mean ± SD) (p < 0.0001)</u> Baseline 6 months No SSDs observed in weight, BMI, waist circumference, BF, fat mass, lean mass, total cholesterol, TG	16 ± 1.7 7 ± 1.3 4.6 ± 0.1mmol/L 5.1 ± 0.1mmol/L 9.4 ± 8.1µU/mL 12.1 ± 9.2µU/mL 1.2 ± 1.0 1.5 ± 1.1 0.94 ± 0.04 0.92 ± 0.04 3.4 ± 0.9mmol/L 2.9 ± 0.7mmol/L 1.3 ± 0.2mmol/L 1.2 ± 0.2mmol/L 1.21 ± 0.9 0.27 ± 0.9	activity brought about with GHR … will help to improve the cardio-metabolic risk profile of hypopituitary adults." (pp. 224) "… there remains a high prevalence of obesity in this population and given the worsening of insulin sensitivity in the short term with GHR, monitoring and aggressive treatment of established CV risk factors is essential to reduce premature atherosclerotic CVD in this patient population." (pp. 220)
Dutta et al., 2010[7]		
<u>Outcomes with demonstrated SSD only (p < 0.05)</u> <u>TG (mean ± SEM)</u> Treatment Baseline Treatment 12 weeks Placebo Baseline Placebo 12 weeks <u>Cortisol (mean ± SEM)</u> Treatment Baseline Treatment 12 weeks Placebo Baseline	 181.93 ± 16.71mg/dL 158.86 ± 17.34mg/dL* 170.75 ± 14.27mg/dL** 169.58 ± 12.05mg/dL 280.28 ± 256.43nmol/L 172.23 ± 162.73nmol/L* 484.42 ± 346.42nmol/L	"Short term GH therapy in patients with AGHD only resulted in improvement in serum triglycerides. Improvement in other parameters like body composition,

Main Findings		Author's Conclusions
Non-Randomized Studies		
Placebo 12 weeks	435.40 ± 139.58nmol/L**	muscle strength, QOL score and insulin glucose homeostasis probably requires longer duration of GH therapy." (pp. 673)
<u>QoL (mean ± SEM)</u>		
Treatment Baseline	11.79 ± 9.34	
Treatment 12 weeks	42.21 ± 7.32 *	
Placebo Baseline	30.50 ± 10.14 **	
Placebo 12 weeks	46.08 ± 8.77*	
Relative percentage QoL change between groups was not significant.		
<u>Adverse Events:</u> "GH replacement therapy was well tolerated in the present study with arthralgia being the only significant adverse event. Three patients developed self-limiting pedal edema and two had mild diffuse headache, and all resolved within a short time as reported by others." (pp. 673)		
* p < 0.05 12 week vs Baseline ** p < 0.05 Placebo vs Treatment		
No SSDs observed in height, weight, BMI, waist circumference, BF, glucose, total cholesterol, LDL, HDL, insulin resistance (HOMA), IGF-1, cortisol, QoL, or isometric hand grip strength.		
Deepak et al., 2008[8]		
<u>Outcomes with demonstrated SSD only (p < 0.05)</u>		"GHR in AGHD significantly improves voluntary physical activity and quality of life. Following GHR, subjects experience greater 'state' (physiological) hunger, reductions in eating disinhibition and hunger susceptibility, but no effects on calorie intake or macronutrient choice were detected." (pp. 622)
<u>IGF-1(SDS) (median(IQR)) (p < 0.0001)</u>		
Baseline	-0.65(-0.7 to -0.4)	
6 months	0.36(0.1 to 0.5)	
<u>IGF-1 level (mean ± SD) (p < 0.0001)</u>		
Baseline	14.1 ± 5.6nmol/L	
6 months	29.8 ± 7.0nmol/L	
<u>QoL (AGHDA score) (mean ± SD) (p < 0.0001) decrease was an improvement</u>		
Baseline	16.5 ± 6.2	
6 months	9.1 ± 6.5	
<u>Voluntary Activity (mean ± SD) (p < 0.007)</u>		
Baseline	1881.5 ± 1413.1Units	
6 months	3319.9 ± 2078.9Units	
<u>TFEQ score disinhibition domain (mean ± SD) (p = 0.02)</u>		
Baseline	7.2 ± 3.2	
6 months	6 ± 2.5	
<u>TFEQ score susceptibility to hunger domain (mean ± SD) (p = 0.001)</u>		

Main Findings				Author's Conclusions
Non-Randomized Studies				
Baseline	6.8 ± 2.8			
6 months	4.6 ± 2.7			
No SSDs observed in resting energy expenditure, respiratory quotient, total calories, or TFEQ score restraint domain.				
Colao et al., 2008[10]				
Group A (A): GHD patients on HGH (n = 22) Group B (B): GHD patients not treated (n = 13) Group C (C): Healthy male matched (sex, age, BMI) controls (n = 35) **Outcomes with demonstrated SSD only (p < 0.05) - Five year follow-up** IGF-1(SDS) (mean ± SD)				"Severely hypopituitary GHD men have more frequently increased IMT at common carotid arteries and IRS than controls. After 5 years, only in GH replaced patients, IMT and prevalence of IRS decreased." (pp. 3416)
	Baseline	5 years	p	
A	-2.00 ± 0.73	0.88 ± 0.19*	<0.0001	
B	-1.51 ± 0.82	-1.41 ± 0.92	0.52	
C	0.80 ± 0.45	0.71 ± 0.48*	0.35	
Serum IGF-1 levels (µg/L) (mean ± SD)				
	Baseline	5 years	p	
A	51.8 ± 49.4	232.3 ± 39.3*	<0.0001	
B	80.3 ± 45.0	87.5 ± 59.3	0.52	
C	244.6 ± 47.3	225.2 ± 52.2*	0.085	
Right carotid artery IMT (mm) (mean ± SD)				
	Baseline	5 years	p	
A	0.85 ± 0.24	0.76 ± 0.23*	<0.0001	
B	0.86 ± 0.26	0.88 ± 0.26	0.22	
C	0.63 ± 0.07	0.66 ± 0.07*†	<0.0001	
Left carotid artery IMT (mm) (mean ± SD)				
	Baseline	5 years	p	
A	0.83 ± 0.16	0.73 ± 0.16*	<0.0001	
B	0.87 ± 0.22	0.88 ± 0.21	0.95	
C	0.63 ± 0.07	0.66 ± 0.07*†	<0.0001	
Mean carotid artery IMT (mm) (mean ± SD)				
	Baseline	5 years	p	
A	0.84 ± 0.20	0.75 ± 0.20*	<0.0001	
B	0.87 ± 0.23	0.88 ± 0.23	0.19	
C	0.63 ± 0.07	0.66 ± 0.07*†	<0.0001	
Mean carotid artery IMT (mm) (mean ± SD)				
	Baseline	5 years	p	
A	0.84 ± 0.20	0.75 ± 0.20*	<0.0001	
B	0.87 ± 0.23	0.88 ± 0.23	0.19	

Main Findings				Author's Conclusions
Non-Randomized Studies				
C	0.63 ± 0.07	0.66 ± 0.07*†	<0.0001	
Prevalence of insulin resistance syndrome (%)				
	Baseline	5 years	p	
A	12 (60)	4 (25)	0.028	
B	8 (54)	3 (23)	0.24	
C	2 (6)	6 (17)	0.26	
Total blood cholesterol levels (mmol/L) (mean ± SD)				
	Baseline	5 years	p	
A	6.2 ± 1.0	4.4 ± 0.3	<0.0001	
B	5.7 ± 1.1	5.1 ± 0.8	0.033	
C	4.7 ± 0.6	4.9 ± 0.5	0.079	
HDL cholesterol levels (mmol/L) (mean ± SD)				
	Baseline	5 years	p	
A	1.1 ± 0.2	1.4 ± 0.2	<0.0001	
B	1.1 ± 0.2	1.2 ± 0.1	0.033	
C	1.4 ± 0.2	1.4 ± 0.2	0.16	
TG levels (mmol/L) (mean ± SD)				
	Baseline	5 years	p	
A	1.6 ± 0.3	1.2 ± 0.3	<0.0001	
B	1.7 ± 0.2	1.4 ± 0.2	0.002	
C	1.2 ± 0.3	1.3 ± 0.2	0.036	
Fasting blood glucose levels (mmol/L) (mean ± SD)				
	Baseline	5 years	p	
A	5.5 ± 0.6	5.0 ± 0.5	0.036	
B	5.4 ± 0.5	5.1 ± 0.5	0.38	
C	4.7 ± 0.6	5.2 ± 0.6	0.003	
HOMA index (mean ± SD)				
	Baseline	5 years	p	
A	3.8 ± 1.2	2.5 ± 0.6	0.0001	
B	3.9 ± 1.2	3.3 ± 1.3	0.79	
C	1.6 ± 0.7	2.3 ± 1.3	0.021	
Use of lipid-lowering drugs (%) (mean ± SD)				
		5 years		
A		34.3%		
B		92.3%‡		
C		13.6%		
Use of glucose-lowering drugs (%) (mean ± SD)				
		5 years		

Main Findings		Author's Conclusions
Non-Randomized Studies		
A	31.4%	
B	69.2%‡	
C	22.7%	
Use of anti-hypertensive drugs (%) (mean ± SD)		
	5 years	
A	20.0%	
B	61.5%‡	
C	4.5%	
* p < 0.01 vs B 5 years † p < 0.01 vs A 5 years ‡ p < 0.0001 vs A 5 years		
Gomez et al., 2007[9]		
Outcomes with demonstrated SSD only (p < 0.05)		"In this study we have demonstrated in adults with GH deficiency under GH substitution elevation of E-selectin concentrations that may correlate with potential endothelial dysfunction suggesting that the protective effect of GH in these patients may be enhancing other mechanisms." (pp. 55)
Hip/waist ratio (mean ± SD) (p = 0.012)		
Control	0.86 ± 0.08	
Treated	0.92 ± 0.04	
Basal C-peptide (mean ± SD) (p = 0.015)		
Control	0.68 ± 0.18nmol/L	
Treated	1.03 ± 0.39nmol/L	
E-selectin (mean ± SD) (p = 0.0001)		
Control	10.7 ± 6.2µg/L	
Treated	22.5 ± 11.4µg/L	
TG (mean ± SD) (p = 0.0001)		
Control	0.83 ± .29mmol/L	
Treated	1.6 ± 0.3mmol/L	
No SSDs observed in BMI, WHR, BP, fat mass, lean mass, BF, serum glucose, insulin resistance (HOMA), total cholesterol, HDL, LDL, fibrinogen, endothelial and inflammatory parameters apart from E-selectin, or IGF-1		

AGHD=adult growth hormone deficiency; **BF**=body fat; **BMD**=bone mineral density; **BMI**=body mass index; **BP**=blood pressure; **CRP**=C-reactive protein; **HDL**=high density lipoprotein; **HGH**=human growth hormone; **HOMA**=homoeostasis model assessment; **IGF-1**=insulin-like growth factor; **IMT**=intima-media thickness; **IQR**=interquartile range; **GH**=growth hormone; **GHR**=growth hormone replacement; **LBM**=lean body mass; **LDL**=low density lipoprotein; **MS**=metabolic syndrome; **NFPA**=non-functioning pituitary adenoma; **PR**=prevalence ratio; **PTH**=parathyroid hormone; **QoL**=quality of life; **QLS-H**=quality of life questionnaire **QUICKI**=quantitative insulin sensitivity test; **SD**=standard deviation; **SDS**=standard deviation score; **SEM**=standard error mean; **SSD**=statistically significant difference; **TG**=triglyceride; **TFEQ**=three factor eating questionnaire; **WHR**=waist hip ratio

Table A4.3: Summary of Recommendations of Included Guidelines.

AACE 2009[13]
• "GH should only be prescribed to patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD" **(Grade A; BEL 1)**. (pp. 6) • "Patients with childhood-onset GHD (COGHD) previously treated with GH replacement in childhood should be retested after final height is achieved and GH therapy discontinued for at least 1 month to ascertain their GH status before considering restarting GH therapy. Exceptions include those with known mutations, those with embryopathic/congenital defects, those with irreversible hypothalamic-pituitary structural lesions, and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off GH therapy." **(Grade A; BEL 1).** (pp. 6) • "The preferred GH stimulation test to establish the diagnosis of adult GHD in patients with COGHD is the insulin tolerance test (ITT). Acceptable alternative stimulation tests include the GHRH+arginine (ARG) test, the glucagon test, and, rarely, the ARG test alone." **(Grade A; BEL 1).** (pp. 7) • "In patients with hypothalamic GHD, eg, idiopathic isolated GHD of childhood, the GHRH+ARG test may be misleading; hence, an ITT or glucagon stimulation test should be used." **(Grade A; BEL 1).** (pp. 7) • "For childhood GH treatment of conditions other than GHD, such as Turner's syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved." **(Grade B; BEL 2).** (pp. 6) • "Similar cut points for GH stimulation testing in the transition patients coming off GH therapy are applicable as for adults." **(Grade B; BEL 2).** (pp. 7) • "On restarting GH therapy, the starting dose of GH in transition patients should be approximately 50% of the dose between the pediatric doses required for growth and the adult dose." **(Grade C; BEL 3).** (pp. 7)
BEL=best evidence level; **GH**=growth hormone; **GHD**=growth hormone deficiency; **GHRH**=growth hormone releasing hormone; **IGF-1**=insulin-like growth factor 1;