A Systematic Review of the Impact of Growth Hormone Therapy on Final Adult Height of Children with Idiopathic Short Stature

Tawfik Muammar[1] Muna Alhasaeri[2]

[1] Department of Pediatric Endocrinology, Imperial College London Diabetes Centre, Abu Dhabi, United Arab Emirates
[2] Department of Injectables and Research, Everlast Wellness Health Centre, Abu Dhabi, United Arab Emirates

Address for correspondence Tawfik Muammar, MBBCh, DCH, MSc, MRCPCH, CCT, Department of Pediatric Endocrinology, Imperial College London Diabetes Centre, Al Khaleej Al Arabi Street, P.O. Box 48338, Abu Dhabi, United Arab Emirates (e-mail: tmuammar@yahoo.co.uk).

J Diabetes Endocrine Practice 2024;7:25–34.

Abstract

Introduction This review aims to systematically determine the effect of growth hormone (GH) therapy on adult height of children and adolescents with idiopathic short stature (ISS).

Methods A systematic review was conducted to assess the effectiveness of GH therapy in children with ISS. Databases like ProQuest Central, journal @ Ovoid, EBSCOhost Medline Complete, Oxford University Press Journals, KB + JISC Collections Elsevier Science Direct Freedo, and BMJ, and cross-referencing of bibliographies were searched electronically. The randomized trials from 1989 to January 2023 were retrieved. Randomized trials with final adult height measurements and fit the inclusion criteria (height >2 standard deviation [SD] score below the mean with no comorbid conditions that would impair growth, peak growth hormone responses >10 µg/L, no previous history of GH therapy) were included in this review. The exclusion criteria are nonrandomized trials; trials include causes of short stature other than ISS, and studies include interventions other than GH and gonadotropin-releasing hormone analog (GnRH-a). A structured approach to the critical appraisal program by Oxford was used to analyze and extract the data.

Results The study reviewed 14 eligible randomized trials, which recruited 2,206 assessable children for analysis. Seven trials compared different GH doses, four trials compared GH therapy with controls, and three trials compared a combination of GH and GnRH therapy with GH alone. Apart from one study, the overall dropout rate was not high. The high percentage of boys was a potential source of heterogeneity between trials. The change in height (HT)-SD score was 1.06 ± 0.30 and 0.18 ± 0.27 with treatment and control children, respectively, and the difference is statistically significant ($p < 0.001$). The overall mean height gain was 5 cm (0.84 SD score) more in treated children. The height velocity was found to be decreased significantly ($p < 0.001$) in the second and third years of treatment in the GH + GnRH-a treated group from 7 cm/year during the first year of treatment to 5.4 cm during the second year and

Keywords
- short stature
- idiopathic short stature
- GH therapy
- r-hGH therapy
- combined GH with GnRH-a
- systematic review

DOI https://doi.org/10.1055/s-0043-1778678.
ISSN 2772-7653.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

4.9 cm/year during the third year. They also found that using a higher dose of GH at 9 mg/m^2/week leads to approximately 7 cm mean final height gain; however, lower dose regimens are less effective.

Conclusion Although the magnitude of the effectiveness of GH therapy is, on average, less than that achieved in other conditions for which GH is licensed, GH therapy seems to be effective in children with idiopathic short stature, and it reduces the deficit in height as adults. Moreover, the effect seems to be dose-dependent, with better results at high GH doses, and the response variability is seen in different individuals. The use of combined GH with GnRH therapy needs to be balanced with their side effects.

Introduction

Short stature is the most common cause of referral to pediatric endocrinologists[1,2] A height above two standard deviations (SDs) below the mean height of a reference population matched for age, pubertal stage, and sex is the definition of short stature.[2,3] Based on this definition, 95% of the general population fall within two SDs of the mean of a normal distribution; hence, 2.5% is considered short.[3]

Several conditions can lead to short stature and impaired linear growth. However, most short children do not fit into any of the causes.[4] Therefore, short stature can be idiopathic due to an endocrine disorder or secondary to systemic disease like chronic kidney disease.[5]

Idiopathic short stature (ISS) is defined as a height of less than −2 SDs of the corresponding average height for the same sex, age, and population in the absence of any causes of growth disorders like systemic, nutritional, endocrine, or chromosomal abnormalities.[6] Therefore, children with short stature will be classed as having ISS after completing a diagnostic investigation.[7] ISS describes a heterogeneous group of short children who are growth hormone (GH)-sufficient and have normal birth weight. This definition causes many short children to remain without a definitive underlying cause and hence are labeled as ISS.[1,2,8] ISS also includes children with familial short stature and constitutional delay of growth and puberty (CDGP).

Although it is usually accepted that, on average, children with ISS will achieve adult height below the parental target height,[9] ISS has emotional and socioeconomic impacts.[10] In some countries, short stature is considered a disability causing physical challenges; for example, "dwarfism" of any type is one of the conditions under the Americans with Disabilities Act.[11]

GH treatment of ISS was approved by the US Food and Drug Administration (FDA). In 2003, expanding the GH treatment eligibility to 1.2% of the US population.[12] The Growth Hormone Research Society and the International Societies of Paediatric Endocrinology proposed warranted consideration for the treatment of children with ISS whose heights were less than −2.0 SD scores (SDS). They had a predicted height of less than −2.0 SD or more than 2.0 SDS below their mid-parental target height.[13]

ISS was the first FDA indication that emphasized height as the eligibility criterion for treatment rather than underlying pathology.[12]

However, the European Agency for the Evaluation of Medicinal Products Europe is yet to approve using GH for ISS because available data is affected by several biases, including using a wide variety of doses and relatively small study cohorts.[14]

GH is an expansive biotechnology originally designed for treating GH deficiency,[13] and increasing growth to achieve an adult height within the target height range for the individual is the primary treatment goal.[15,16] The expansion of GH therapy to include ISS is facilitated by pediatric endocrinologists and supported by the producing companies.[13] In response, the insurance industry has imposed progressive restrictions on GH treatment coverage over the last 10 years. Moreover, the psychological burden caused by anxiety about the side effects and pain caused by daily GH injections have also led to low patient satisfaction.[17] In addition, a high economic burden is caused by the high cost of GH treatment worldwide.[18]

It is assumed that (1) severe short stature requires treatment in children because it is considered a disabling condition; (2) GH increases final adulthood and improves the quality of life (QoL); and (3) GH is safe for children with ISS. However, due to a shortage of evidence, each of the assumptions' validity and value are being challenged. An increasingly honest and evidence-based appraisal of GH treatment's risks, benefits, value, and costs is highly required.[15,18] There is also a considerable debate about using such an expensive therapy in otherwise healthy short children to increase their height by just 2.5 to 5.0 cm (1 -to 2 inches).[19] However, some studies showed improvement in QoL in short children by using GH therapy.[20] The guidelines-developing process published by the Pediatric Endocrine Society (PES) revealed some fundamental questions about hGH treatment that still need evidence-based answers. An hGH treatment of ISS continues to inspire debate due to weak supporting evidence for treatment benefits and philosophical disagreements between the involved parties. The gaps related to diagnostic limitations, long-term post-treatment safety, and appropriate outcome measures of hGH therapy persist. The current healthcare constraints and the persisting gaps move the situation to more restraints instead of expiation. Therefore, the current practice guidelines by PES

for hGH treatment are even more conservative than previous guidelines.[13] This clearly explains the necessity of our systematic review, which will be examined for all randomized controlled trials (RCTs) published up to January 2023, where the potential implications for clinical practice, patient outcomes, and decision-making will be discussed.

Materials and Methods

The Study Question

What is the impact of GH therapy on the final adult height of children with ISS in terms of effectiveness and safety?

Aims and Objectives

1. A clear and comprehensive overview of the available data in this systematic review will explore the effect of GH on the final height of children diagnosed with ISS.
2. The review will also find out the effect of combining gonadotropin-releasing hormone analog (GnRH-a) with GH therapy on the final height of children with ISS compared to GH alone and the cost-effectiveness of long-term use of expensive therapy.
3. To provide evidence-based information that guides and helps pediatric endocrinologists and policymakers make appropriate decisions when managing children with ISS.

Background and Justification

The process by which this systematic review was carried out will be discussed by the author under the following headings: Ethics, data source, and search strategy, inclusion and exclusion criteria, methods of searching, study selection and data extraction; studies excluded data analysis and critical appraisal, risk of bias assessment.

Search Strategy

The Medical Subject Headings (MeSH) were used in the literature search and are expressed in the Boolean search format, as shown below.

#1 "idiopathic short stature" OR "short stature" OR "Growth Disorders" OR "growth disorder" OR "growth retardation" Dwarfism OR "growth impairment" OR "Failure to Thrive"
#2 "Growth hormone" OR "growth hormone therapy" OR "recombinant growth hormone" OR "Genotropin" OR "Somatropin" OR 'Somatrem" OR "Norditropin"
#3 #1 AND #2
#4 A combinations of keywords and MeSH terms were adopted for each database.
#5 Limits to human studies and the English language were applied.

Inclusion and Exclusion Criteria

(i) Study design: All RCTs reporting the outcomes of interest were included. (ii) Participants: This review targeted ISS children aged between 2 and 18 years with a height of more than two SDs below the corresponding average height for a given sex, age, and population. No restrictions were imposed on the sex or race of the patients. (iii) Interventions: Only studies that included GH therapy or a combination of GH and GnRH as an intervention were included. (iv) Outcome measures: final adult height. We have excluded the following: (i) Studies done on short-term causes other than ISS were excluded. (ii) Studies with any other intervention, other than GH therapy or a combination of GH with GnRH, were excluded. iii) Children with known chronic diseases that might affect growth rate. iv) Short stature due to specific pathologies, such as skeletal deformities, achondroplasias, or GH deficiency. (v) Articles with insufficient information or where the full texts cannot be accessed were also excluded. (vi) Nonrandomized trials were also excluded. (vii) The literature search was restricted to English-language articles, and papers in other languages were excluded because the author can only read English. The transition was considered money and time-consuming.

Methods of Searching

The search was done in three main ways: electronic, hand, and reference searching. Electronic searches were conducted for the last 33 years (between 1989 and January 2023). The databases (shown in ►**Table 1**) included national and international comprehensive online collections of medical journals, journals targeting health professionals and researchers, and the largest collections of online journals, research resources, and books covering health. The full texts were searched where possible; however, when it was not possible, abstracts rather than the title alone were searched as the title may need more information. Searching for a reference list can be a good source of related papers and provide the project with valuable information.[22] However, only six papers were relevant and duplicates

Table 1 List of the database searched and the number of article retrieved

Database	Number of articles retrieved
ProQuest Central	110
journal @ Ovoid	77
EBSChost Medline Complete	67
IntegraConnect Journals	65
DeGryter Journals (NIESG)	39
Oxford University Press Journals	32
EBSCOhost Academic Search Complete	30
KB + JISC Collections Elsevier Science Direct Freedo	23
DOAJ Directory of Open Access Journals	18
Single Journals	17
Publicity available content	16
Wiley Online Library	14
Spinger Journals	11
Spinger link Journals	6
BMJ	3
Total	528

of the original search. The search terms were developed using the keywords, alternatives, or related words referring to the study question. The search terms included: idiopathic short stature, ISS, short stature, growth disorders, growth retardation, dwarfism, growth impairment or failure to thrive; GH, GH therapy, recombinant GH, r-hGH, Genotropin, Somatropin, Somatrem or Norditropin; Effect, effectiveness, Impact, Effect on final height, Impact on final height, final adult height.

Study Selection and Data Extraction

All studies on the effectiveness of GH in ISS were identified and imported. Duplicate, unrelated studies, and studies not fulfilling the inclusion criteria were excluded. Full-text were reviewed before final inclusion. Fourteen relevant randomized studies were included in this review, and the researcher collected the outcome measures data independently. Each study was assessed carefully against the inclusion and exclusion criteria before selection; this has led to the identification of the relevant data. A descriptive analysis of each study was conducted. The age group of the patients, percentage of males, GH dose used, duration, side effects, and effect of treatment on final height were the key variables extracted from each study. All relevant information is summarized in ►**Table 2**. The following studies were excluded because they were not randomized trial.[23–30] The literature selection process is illustrated and reported in the flow diagram depicted in ►**Fig. 1**.

Data Analysis/Critical Appraisal

The studies included in this review were very heterogeneous; therefore, a descriptive analysis of individual studies was carried out.

Risk of Bias Assessment

Although all included one reviewer assessed studies, the reviewer worked independently and assessed the risk of bias, any inconsistency, imprecision, and publication bias for each included study. A measurement tool to assess systematic reviews (AMSTAR 2) was the main tool used to assess the risk of bias in this review.[31] For studies where full text was unavailable, the reviewer searched other sources but was unsuccessful.

Quality Assessment

This review has included RCTs only as it owns a "high quality" rating, and this allows the decision makers and healthcare professionals to draw causal inferences linking interventions (GH or GH +GnRH therapy) and outcomes (Effect on final adult height) with protection against bias. Desirable effects can include beneficial health outcomes regarding satisfactory height gain, reducing the burden on the families and physicians, and cost savings for the insurers and healthcare facilities. Undesirable effects can include harm in terms of side effects of GH, affected patient compliance, and medication expenses. The review recommendation strength reflects the degree of confidence that the desirable effects of a recommendation outweigh the undesirable effects. The Endocrine Society classified scientific trials into two grades (strong and weak) of recommendation and categorized the quality of the evidence into four categories (high, moderate, low, and very low).[32] On this basis, a grading was assigned to each of the fourteen RCTs. The Oxford quality scoring system (also known as the Jadad scale) was used in this review to assess the quality of RCTs.[33] The primary efficacy outcome measure was the difference in adult height between treated and untreated groups.

Results

Background Details for Papers Retrieved

In total, 469 potentially relevant articles were initially identified after a literature search for clinical studies on the effect of GH therapy on final adult height in children with ISS. Eight duplicates were excluded, and on the basis of abstract screening for eligibility, a further 479 were excluded due to their irrelevance. Then, the full texts of 37 papers were thoroughly screened, and a further 23 articles were excluded. Finally, there were 14 RCTs (►**Table 2**) that fulfilled the inclusion criteria of this study. This involved a total of 2206 assessable children for analysis, and all trials were published from 1989 to 2022. Only one study included a placebo-control group.[34]

Characteristics of the Qualified Trials

Characteristics of the fourteen qualified RCT trials are provided in ►**Table 2**. Four trials compared GH therapy with controls, seven trials compared different GH doses, and three trials compared a combination of GH and GnRH therapy with GH alone.

Dropout/Withdrawal from the Study

The highest dropout was shown in[34] Leschek et al study in which 65% of the participants were in the placebo group, and 40% were in the GH-treated children. In the McCaughey et al study,[35] the dropout rate was 17% (5 patients out of 41) and 11% in van Gool et al study,[36] while the smallest dropout rate (4.5%) was reported by Yuan et al.[37] In one study by Benabbad et al, the initial protocol of the trial included a control (no treatment) group, but this was stopped due to recruitment issues.[38] Apart from one study, the overall dropout rate needed to be higher.

Effectiveness of GH Therapy

Short-duration studies compared different doses of GH therapy.[39,40] These studies showed better growth rate results of high GH therapy doses than smaller doses; however, early induction of puberty and acceleration of bone age due to high-dose GH treatment may limit the potential therapeutic benefit of this regimen in ISS.

Although studies combined GH and GnRH-a showed some effect on increasing the final adult height. However, given the lengthy, expensive treatment regimen and the possible adverse effect on peak bone mineralization in males compared to its modest height gain results, it cannot be considered a routine treatment for children with ISS[36]

Table 2 Characteristics of qualified randomized trials in this systematic review

Study and year	Patient no.		Mean age at start ± SD		Males %		Pubertal status at baseline	GH dose, mg/kg/week/frequency, injections/week	Mean duration of therapy (years)	Mean (SD) height at base line treated/control	Mean (SD) adult height	Difference (case–control) in adult height (SD score)	Multicenter (MC)/ multi dose (MD)
	GHT	C	GHT	C	GHT	C							
Yuan et al 2022[37]	351	118	5.8 ± 1.51	6.0 ± 1.67	62.2%	63%	Prepubertal	0.05 mg/kg /day	2.0	105.75 ± 7.91 / 106.81 ± 8.81	NA	NA	MC
Bennabbad et al 2018[38]	45	43	12.1	12.1	42.2%		II/III	0.05 mg/kg /day	2.4	NA	NA	NA	–
Counts et al 2015[43]	316 (202 FBD; 114 StD)	NA	NA	NA	71.8%	NA	Prepubertal	0.18 or 0.24 mg/ kg/wk	4	NA	NA	NA	MC/MD
Albertsson-Wikland et al 2008[41]	81 (31 LD; 50 HD)	45	11.7 ± 1.4		NA	NA	Prepubertal	0.033 or 0.067	5.6	−2.84/−2.76	−1.6/ −2.2	1.24(0.82)/ 0.4(0.62)	MC
van Gool et al 2007[36]	11 ISS	10 ISS	–	–	54.5%	50%	G2-3 /B2-3	0.05 mg/kg /day	3	NA	NA	NA	MC
Kamp et al 2006[52]	12 ISS	11 ISS	9.43 ± 2.4	NA	50%	45%	G2 or 3 / B2 or 3	0.05 mg/kg /day	3	NA	NA	NA	MC
Wit et al 2005[40]	78 LD (0.24); 83 HD, 78 LD then HD (0.37)	NA			66%	NA	Prepubertal	0.24 and 0.37 mg/kg/wk	2	NA	NA	NA	MC / MD
Leschek et al 2004[34]	37	31	12.7 ± 1.4		78%	77.4%	30% prepubertal	0.037	4.4	−2.7/−2.8	−1.77/ −2.34	0.93(0.75)/ 0.46(0.23)	–
Wit et al 2002[42]	58 (24 LD; 34 HD)	34	10.5 ± 2.0		59%		Prepubertal	6 mg/m^2/wk & 9 mg/m^2/wk	6.5	NA	NA	NA	MD
Hintz et al 1999[51]	80	41	10.4 ± 1.8 boys 9.7 ± 2.1 girls		71%	NA	Peri pubertal	0.3 mg/kg/wk	5.5–6.0	−2.7 /–	NA	NA	MC / MD
Rekers-Mombarg et al 1998[45]	223	229	>5 and <10 years old (girls), <12 years (boys).		NA	NA	Prepubertal	0.2 and o.3 mg/kg/wk	4.8	NA	NA	NA	MC / MD
mcCauglhey, et al, 1998[53]	8	6	6.24	6.14	All girls	All girls	Prepubertal	0.04 mg/kg/day	6.2	−2.52/−2.55	−1.14/ −2.37	1.38/0.18 (0.7/0.4)	–
Barton et al 1995[39]	20 (10 in each treated group)	9	NA	NA	60% and 100%	88%	Prepubertal	20 or 40 IU/m^2/ wk groups	2	NA	NA	NA	MD
Genentech Collaborative study group 1989[50]	85	63	9.5 ± 2.4	9.4 ± 1.9	74%	73%	Prepubertal	0.1 mg/kg three times a week	1	NA	NA	NA	MC
Total	1566	640											

Abbreviations: C, control group; FBD, formula-based dose; GHT, growth Hormone treated group; HD, high dose; LD, low dose; SD, standard dose; ISS, idiopathic short stature.

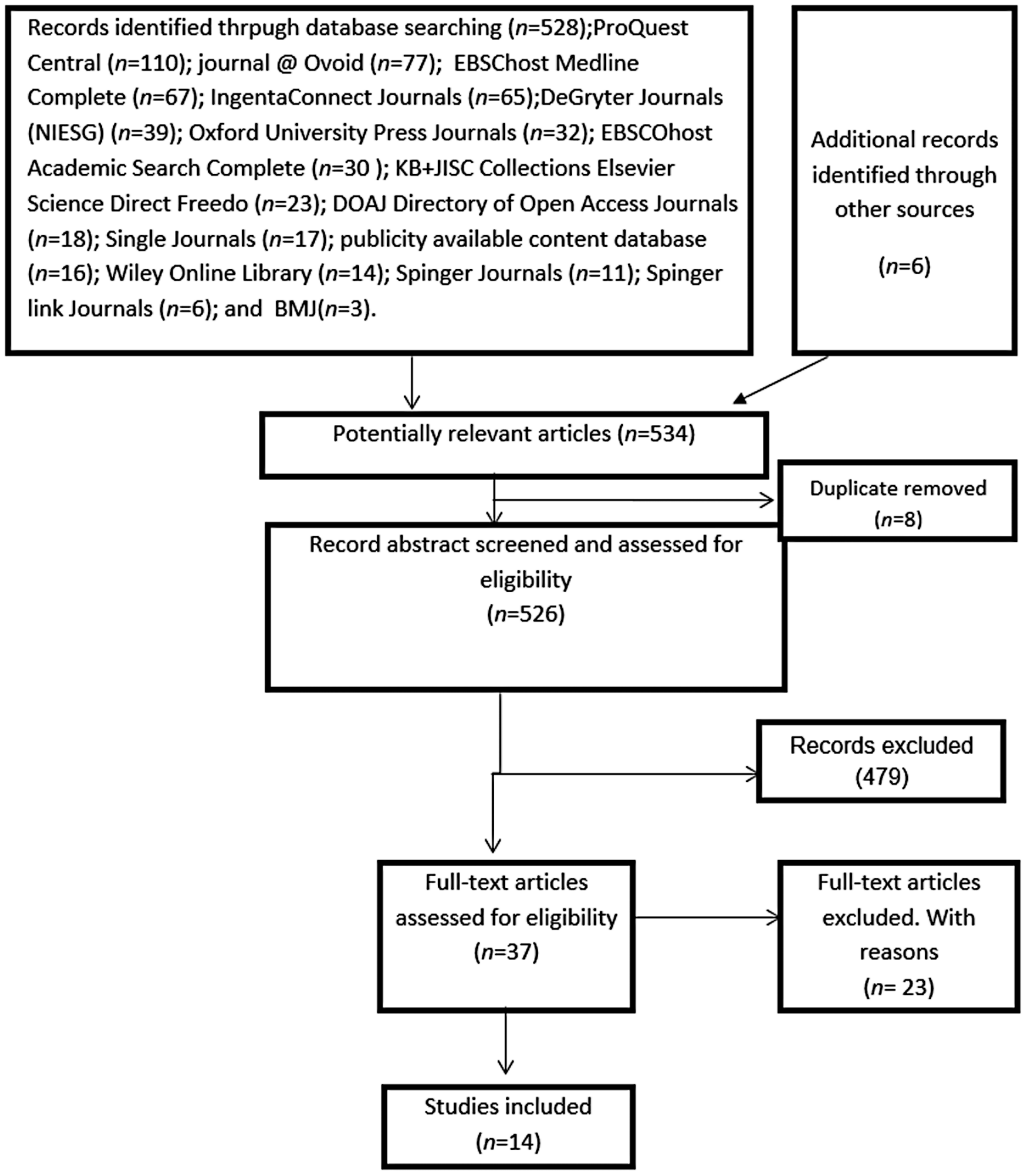

Fig. 1 A flowchart diagram for the literature identification and selection process.

Outcomes

The effectiveness of GH is the primary outcome measure of interest of this review, and it is defined as post-treatment height changes in growth-related anthropometric indicators, such as adult height or predicted adult height. Therefore, all studies in which the effectiveness of GH therapy for ISS children and adolescents was conducted were included in this review. Finding out if combining GH with GnRH-a is more effective than GH therapy alone is the secondary outcome and cost-effectiveness of long-term use of expensive therapy.

Quality of Evidence and Strength of Recommendation

The evidence provided in this heterogeneous review is moderate-to-high quality, with some low-quality studies. There is a lack of detail on the randomization procedure and high variability in some studies[34] where the whole study population comprised only 68 children: 49 treated children (18 with low dose and 31 with high dose GH) and 19 controls could have affected the results of the study. McCaughey et al's trial was classed as low-quality evidence because of the small population (seven treated and six randomized untreated girls).[35]

Discussion

Out of the 14 RCTs, seven trials studied the dose–response relationship and its effect on the final adult height; three studies compared the effect of a combination of GH with GnRH-a versus GH only, and four studies compared the effect of GH therapy versus untreated control groups.

The studies compared the effect of different doses of GH which have established that there was a dose–response relationship for the effect of GH therapy on the height velocity (HV) and final height in children with ISS. A greater velocity and final height increase were produced by the dose

of 0.37 mg/kg per week, which is more than the dose of 0.24 mg/kg per week. As a result of this increase in height, the final height for most patients receiving high doses was within the normal adult range compared to those receiving smaller doses.[39,40] Children with ISS have a better growth response to GH therapy, especially if treated at a younger age. Although the response to GH therapy in those children is dose-dependent, the magnitude of height gain is not solely dependent on the GH dose. Other factors influencing the growth response include delayed bone age or age at treatment height velocity (HV).[42,43] This difference in response between treated groups was more obvious during the first year of treatment[41] and height deficits in comparison to mid-parental height.[35,42] Even after adjustment for growth changes in the control subjects, the magnitude of HV is substantial[42] Although the interindividual variation in growth response is considerable, GH therapy effectively increases HV into adult height.[35,42,43] The effectiveness of combination therapy (GnRH-a + GH) in the treatment of children with ISS was examined in three RCTs.[36,38,43] These trials found that combination therapy was shown to be slightly effective in increasing the final height of children with ISS. However, this effectiveness could have been more evident when compared with GH-only treated groups. It was also noted that factors like intervention duration, sample size, study type, and boys percentage might have affected the results.

The marked male predominance in most studies reflects the referral pattern to specialist growth clinics. However, one RCT recruited girls only[35] has shown that girls with ISS may respond well to the early start of GH treatment, while untreated short normal girls may not reach predicted or targeted adult height.

The short-duration studies have compared different doses of GH therapy and showed better growth rate results of high GH therapy doses than smaller doses.[39,40] However, long-duration studies showed that the early benefits or caring from GH therapy is lost during puberty.[27]

Regarding adverse events, there were fewer serious adverse effects noted in GH alone therapy compared to a combination of GH and GnRH-a (26.1 and 15.6%, respectively).[38] The combination of GnRH-a with GH was also associated with increased serious adverse events, including fracture rate.[38] Decrease in height SDS gain was noted in patients treated with a combination of GH and GnRH-a[38] and this was also observed when GnRH-a was used alone during puberty.[44] Increases in final height and HV in children with ISS are found to be dose-dependent,[40] where the growth and final adult height prognosis improved slightly more with a high rhGH therapy than with smaller doses when treated for 4 years. However, on average, bone age advanced 4.8 years during this period; therefore, any effect on final adult height will probably be modest.[45]

GH dosage of 0.33 mg/kg/week has an average increase of 7 cm in FAH and more if BA is considerably delayed. However, the effect of small doses of GH (0.17–0.21 mg/kg/wk) on FH of children with ISS is limited to approximately 3 cm even if the dose was increased by 50 to 100% after one or a few years. Therefore, treatment of children with ISS with smaller doses of GH is not recommended.

In this review, three trials reported the long-term effect of GH therapy in children with ISS, and they were carried out up to adulthood.[34,35,41] Although none of the three studies was a high-quality evidence RCT, one trial reported a dose-dependent effect of GH therapy on adult height.[41]

Statistical comparison of NAH SDS between the groups in the study by Benabbad et al.[38] was not possible due to premature discontinuation of treatments. Mean NAH SDS was similar in the two groups despite the fact that patients treated with the combination group more slowly than those receiving GH alone during the first 3 years of treatment. Apart from the potential effect of GnRH on bone fracture incidence, there were no new GH-related safety concerns identified.[38]

Some studies reported that the average annual cost of GHT is about €20 000 ($27 000, £17 000) per year of treatment, and this is correspondent to approximately €27 000 per gained centimeter.[46,47] Therefore, cost is an important factor to consider when using GH. Moreover, evidence from some studies suggests that there may be an increased human burden of any cause in children with short stature, and parents of those children may experience poorer QoL. Potential improvements in this burden and QoL could be gained by improving final adult height.[11] However, more research is required in this area.

Strengths and Limitation of the Review

The strengths of this systematic review are: (i) a relatively large sample size (2206 enrolled, out of which 1566 were treated and 640 untreated), (ii) comprehensive exploration of the heterogeneous trials, (iii) including of the wide range of height-related indexes, and (iv) it answers a specific question of high importance. However, limitations of this review are as follows: 1. As in any systematic review, one potential limitation is the pooling of studies with heterogeneous populations. However, strict review procedures and entry criteria for the analyses were instituted to exclude studies in patients with known causes of short stature.

2. Potential limitation involves the effect of dropouts on the validity of their findings in some studies. 3. There is a high chance of false-positive results in some studies due to their small sample size. 4. There was a lack of final height measurement for many randomized patients in some studies.[40] 5. High dropout rate in some studies could lead to dropout bias.[34] 6. Randomization was not stratified in some studies, which might cause a selection bias. 7. The review has included early trials from 1989, and as the diagnosis of ISS has become more accurate by using more advanced genetic-related techniques. Gene mutation-inducing bone maldevelopment cannot be fully separated from ISS in some early-year trials included in this review. and finally (8) the power to detect significance needed to be increased in some analyzed subgroups due to the small sample size in some studies.

Safety and Potential Harms of GH Therapy

Some serious adverse side effects have led to discontinuation of the GH therapy occurred in some studies, like slipped femoral

epiphysis, impaired glucose tolerance with glycosylated hemoglobin of 6.3% and the third adverse event was intra-abdominal desmoplastic small cell tumor in a 12-year-old boy after 6.5 years of GH treatment at 0.24 mg/kg per week (the only patient died 4 years after discontinuation of the study despite surgery and chemotherapy),[40] Other adverse events are Persistent migraine (one patient on GH+ leuprorelin), scoliosis (four patients), and bone fracture, which was more in the combination group than in GH alone and impaired glucose tolerance.[38] Counts et al have also reported scoliosis (6.1% in the individualized dose group vs. 6.8% in the standard-dose group) and headaches (11.6% vs. 8.5%).[43]

Most other adverse events were not serious and included infection, pharyngitis, and flu syndrome, with no significant differences among doses in the groups.

Other side effects like reduced tolerance during oral glucose tolerance tests, fasting hyperinsulinemia, and impaired fasting glucose (insulin resistance) have also been described. Although metabolic memory could predispose these children to a long-term increased risk of type II diabetes, all minor effects mentioned above were reversible after discontinuation of therapy.

There is an occasional increase of insulin-like growth factor-I (IGF1) concentrations (which are dose-dependent) reaching values above the 3 SDS as reported by Albertsson-Wikland et al.[41] The antiapoptotic and mitogenic actions of insulin-like growth factor-I (IGF1) create a theoretical risk of malignancy, and the association of high levels of IGF-I with an increased risk of carcinogenesis has been shown. However, there is no evidence for an increased risk of malignancy. Therefore, the potential relationships among GH therapy, insulin-like growth factor-I levels, and neoplasia require long-term surveillance after treatment.[48]

Other mild-to-moderate side effects like elevated thyroid-stimulating hormone (4 children), scoliosis (3 children), elevated blood glucose level and rash (2 children each), and hypersensitivity and hypothyroidism (1 child each) were also seen. The numbers of subjects with high IGF-1 SDS more than +2 noted in the control and treatment groups at week 52 were 2 (1.7%) and 154 (42.5%), respectively. The number of subjects detected with antidrug antibodies at baseline was 0 (0.0%), 5 (1.4%) at week 26, and 10 (2.8%) at week 52.[37]

Conclusion

However, on average the effect of GH is less than that achieved in children with other conditions like GH deficiency.[49] Treatment with GH seems to be effective in children with ISS, and it reduces the deficit in height as adults. Moreover, the effect seems to be dose-dependent with better results at high GH doses and the response variability is seen in different individuals. The combined therapy of GH with GnRH is found to augment the effect of GH alone; however, their use needs to be balanced with the side effects. Treatment of ISS children with a high dose of GH is more effective than the smaller doses regimen. However, a balance between this positive effect and possible harm due to GH side effects needs to be carefully considered.

The current review findings supported by high-quality evidence from randomized, double-blind, placebo-controlled trials[34] indicate that GH therapy can increase adult height up to the achievement of adult height and showed that GH therapy increases adult height in prepubertal children with ISS.

High doses of r-hGH may result in a greater short-term acceleration in growth rate than "standard" dose therapy of children with ISS, without an excessive advance in bone age, and represented the optimal growth-promoting dose for children with ISS.[39,40] However, long-duration studies showed that the early benefits or caring from GH therapy are lost during puberty.[27]

This study also provided the best estimate of the height increase expected from GH treatment. However, given the lengthy, intensive, and expensive treatment regimen and the possible adverse effect on peak bone mineralization in males compared to its modest height gain results, a combination of GH plus GnRH-a cannot be considered a routine treatment for children with idiopathic short stature.[36]

GH treatment has shown a positive effect on growth in children with ISS in the short term was well tolerated with no safety issues.[35,37,50] Long-term treatment of children with ISS administration with GH can increase final adult height to a level above the PAH and the adult height of untreated control children.[34,51] However, a more cost-effective growth improvement in patients with ISS was provided by individualized, formula-based GH dosing than generalized fixed doses.[43]

Recommendations and Implications for Clinicians and Policymakers

This is the first systematic review that includes such a good number of RCTs only (14 RCTs with 2206 participants). Therefore, the results of this study can provide a guide to pediatric endocrinologists to make evidence-based decisions when managing children with ISS; it will also help the insurers to understand the logic behind treating these children with an expensive medication like GH.

The results of this review may have potential implications for health policies and clinical practice. Most of the previous and current ongoing debate about GH use in children with ISS have centered around the magnitude of GH therapy's effect on the final adult height. Based on the included RCTs, the current findings indicate that long-term GH therapy can increase the final height of children with ISS and partially reduce the height deficit in those children.

As pediatric endocrinologists, we always have to ask ourselves this difficult question of the ethical and cost-effectiveness of these ISS children treated with GH.

Pediatric endocrinologists and policymakers need to address the value of the height gained and its clinical importance in relation to treatment goals in children with ISS. Other important factors like adverse effects, cost of therapy, the impact of the height gained on psychosocial and physical wellbeing, and patients' expectations should be considered when deciding GH therapy for ISS children in practice. Moreover, the cost–benefit ratio should always be considered for GH therapy.

Cost-effectiveness, psychological Impact, pressure from surrounding society, involvement of insurers, social class, and

economic status of the country all play an important role when it comes to GH therapy, and the weight of each factor may differ from one country to another and from patient to another; therefore, the recommendations cannot be generalized, and discussion of healthcare providers with parents, considering our evidence may help to take the appropriate decision.

Further discussion on the implications of the findings for clinical practice, patient management, and future research directions would be beneficial.

It is also recommended that children and their parents should receive counseling and monitoring for slipped capital femoral epiphysis (SCFE), potential intracranial hypertension, scoliosis progression, and diabetes development before starting hGH therapy.

Compliance with Ethical Principles

This study is a systematic review, and the data of individual patients will not be included. Therefore, approval was optional. To ensure transparency and accuracy of the review, it was conducted under the guidance of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Standards[21]

Authors' Contribution

All the authors have contributed equally.

Funding and Sponsorship

None.

Conflict of Interest

None declared.

References

1 Ho KK2007 GH Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol 2007;157(06):695–700
2 Growth Hormone Research Society GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 2000;85(11):3990–3993
3 WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006;95(S 450):76–85
4 Bang P. Statement 3: a low serum IGF-I Level in idiopathic short stature patients indicates partial GH insensitivity. Pediatr Endocrinol Rev 2008;5(suppl 3):841–846
5 Wit JM, Clayton PE, Rogol AD, Savage MO, Saenger PH, Cohen P. Idiopathic short stature: definition, epidemiology, and diagnostic evaluation. Growth Horm IGF Res 2008;18(02):89–110
6 Rosenfeld RG. Molecular mechanisms of IGF-I deficiency. Horm Res 2006;65(suppl 1):15–20
7 Bonert VS, Melmed S. Growth hormone. The Pituitary. 4th ed. Academic Press; 2017:85–127
8 Pedicelli S, Peschiaroli E, Violi E, Cianfarani S. Controversies in the definition and treatment of idiopathic short stature (ISS). J Clin Res Pediatr Endocrinol 2009;1(03):105–115
9 Luo ZC, Albertsson-Wikland K, Karlberg J. Target height as predicted by parental heights in a population-based study. Pediatr Res 1998;44(04):563–571
10 Zlotkin D, Varma SK. Psychosocial effects of short stature. Indian J Pediatr 2006;73(01):79–80
11 Backeljauw P, Cappa M, Kiess W, et al. Impact of short stature on quality of life: a systematic literature review. Growth Horm IGF Res 2021;57-58:101392
12 Grimberg A, Kanter GP. US growth hormone use in the idiopathic short stature era: trends in insurer payments and patient financial burden. J Endocr Soc 2019;3(11):2023–2031
13 Grimberg A, Allen DB. Growth hormone treatment for growth hormone deficiency and idiopathic short stature: new guidelines shaped by the presence and absence of evidence. Curr Opin Pediatr 2017;29(04):466–471
14 Ariza-Jimenez AB, Leiva Gea I, Martinez-Aedo Ollero MJ, Lopez-Siguero JP. Isolated growth hormone deficiency and idiopathic short stature: Comparative efficiency after growth hormone treatment up to adult height. J Clin Med 2021;10(21):4988
15 Grimberg A, DiVall SA, Polychronakos C, et al; Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016;86(06):361–397
16 Huh K, Park MJ. Questionnaire-based analysis of growth-promoting attempts among children visiting a university growth clinic. Clin Exp Pediatr 2009;52(05):576–580
17 Deodati A, Cianfarani S. Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review. BMJ 2011;342:c7157
18 Allen DB. Growth promotion ethics and the challenge to resist cosmetic endocrinology. Horm Res Paediatr 2017;87(03):145–152
19 Bolin K, Sandin R, Koltowska-Häggström M, Loftus J, Prütz C, Jonsson B. The cost-effectiveness of growth hormone replacement therapy (Genotropin®) in hypopituitary adults in Sweden. Cost Eff Resour Alloc 2013;11(01):24
20 Geisler A, Lass N, Reinsch N, et al. Quality of life in children and adolescents with growth hormone deficiency: association with growth hormone treatment. Horm Res Paediatr 2012;78(02):94–99
21 Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(04):264–269, W64
22 Whiting LS. Systematic review protocols: an introduction. Nurse Res 2009;17(01):34–43
23 Hughes IP, Harris M, Choong CS, et al; Australasian Paediatric Endocrine Group (APEG) Growth hormone regimens in Australia: analysis of the first 3 years of treatment for idiopathic growth hormone deficiency and idiopathic short stature. Clin Endocrinol (Oxf) 2012;77(01):62–71
24 Schena L, Meazza C, Pagani S, et al. Efficacy of long-term growth hormone therapy in short non-growth hormone-deficient children. J Pediatr Endocrinol Metab 2017;30(02):197–201
25 Hou L, Liang Y, Wu W, Lin HH, Luo XP, Ying YQ. Comparison of the efficacy and safety of recombinant human growth hormone in treating idiopathic short stature and growth hormone deficiency in children. Growth Horm IGF Res 2020;53-54:101331
26 Wu D, Chen RM, Chen SK, et al. Final adult height of children with idiopathic short stature: a multicenter study on GH therapy alone started during peri-puberty. BMC Pediatr 2020;20(01):138
27 Hindmarsh PC, Brook CG. Final height of short normal children treated with growth hormone. Lancet 1996;348(9019):13–16
28 Reiter EO. A brief review of the addition of gonadotropin-releasing hormone agonists (GnRH-Ag) to growth hormone (GH) treatment of children with idiopathic growth hormone deficiency: previously published studies from America. Mol Cell Endocrinol 2006;254-255:221–225

29 Pasquino AM, Pucarelli I, Roggini M, Segni M. Adult height in short normal girls treated with gonadotropin-releasing hormone analogs and growth hormone. J Clin Endocrinol Metab 2000;85(02):619–622
30 Lazar L, Levy S, Oron T, et al. The beneficial effect of combined GH/GnRHa therapy in increasing adult height outcome in children with ISS. J Clin Endocrinol Metab 2019;104(08):3287–3295
31 Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008
32 Swiglo BA, Murad MH, Schünemann HJ, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab 2008;93(03):666–673
33 Mohsina S, Gurushankari B, Niranjan R, Sureshkumar S, Sreenath GS, Kate V. Assessment of the quality of randomized controlled trials in surgery using Jadad score: where do we stand? J Postgrad Med 2022;68(04):207–212
34 Leschek EW, Rose SR, Yanovski JA, et al; National Institute of Child Health and Human Development-Eli Lilly & Co. Growth Hormone Collaborative Group. Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2004;89(07):3140–3148
35 McCaughey ES, Mulligan J, Voss LD, Betts PR. Randomised trial of growth hormone in short normal girls. Lancet 1998;351 (9107):940–944
36 van Gool SA, Kamp GA, Visser-van Balen H, et al. Final height outcome after three years of growth hormone and gonadotropin-releasing hormone agonist treatment in short adolescents with relatively early puberty. J Clin Endocrinol Metab 2007;92(04):1402–1408
37 Yuan J, Fu J, Wei H, et al. A randomized controlled phase 3 study on the efficacy and safety of recombinant human growth hormone in children with idiopathic short stature. Front Endocrinol (Lausanne) 2022;13:864908
38 Benabbad I, Rosilio M, Tauber M, et al; Phoenix Study Group. Growth hormone in combination with leuprorelin in pubertal children with idiopathic short stature. Endocr Connect 2018;7 (05):708–718
39 Barton JS, Gardineri HM, Cullen S, Hindmarsh PC, Brook CGD, Preece MA. The growth and cardiovascular effects of high dose growth hormone therapy in idiopathic short stature. Clin Endocrinol (Oxf) 1995;42(06):619–626
40 Wit JM, Rekers-Mombarg LT, Cutler GB Jr, et al. Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. J Pediatr 2005;146(01):45–53
41 Albertsson-Wikland K, Aronson AS, Gustafsson J, et al. Dose-dependent effect of growth hormone on final height in children with short stature without growth hormone deficiency. J Clin Endocrinol Metab 2008;93(11):4342–4350
42 Wit JM, Rekers-Mombarg LTMDutch Growth Hormone Advisory Group. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. J Clin Endocrinol Metab 2002;87 (02):604–611
43 Counts DR, Silverman LA, Rajicic N, et al. A 4-year, open-label, multicenter, randomized trial of Genotropin® growth hormone in patients with idiopathic short stature: analysis of 4-year data comparing efficacy, efficiency, and safety between an individualized, target-driven regimen and standard dosing. Horm Res Paediatr 2015;84(02):79–87
44 Guaraldi F, Beccuti G, Gori D, Ghizzoni L. Management of endocrine disease: Long-term outcomes of the treatment of central precocious puberty. Eur J Endocrinol 2016;174(03):R79–R87
45 Rekers-Mombarg LTM, Massa GG, Wit JM, et al; European Study Group Participating Investigators. Growth hormone therapy with three dosage regimens in children with idiopathic short stature. J Pediatr 1998;132(3 Pt 1):455–460
46 Maiorana A, Cianfarani S. Impact of growth hormone therapy on adult height of children born small for gestational age. Pediatrics 2009;124(03):e519–e531
47 Baxter L, Bryant J, Cave CB, Milne R, and Cochrane Metabolic and Endocrine Disorders Group. Recombinant growth hormone for children and adolescents with Turner syndrome. Cochrane Database Syst Rev 2007;2010(01):CD003887
48 Allen DB. Growth hormone post-marketing surveillance: safety, sales, and the unfinished task ahead. J Clin Endocrinol Metab 2010;95(01):52–55
49 Dahlgren J. Growth outcomes in individuals with idiopathic short stature treated with growth hormone therapy. Horm Res Paediatr 2011;76(suppl 3):42–45
50 Genentech Collaborative Study Group. Idiopathic short stature: results of a one-year controlled study of human growth hormone treatment. J Pediatr 1989;115(5 Pt 1):713–719
51 Hintz RL, Attie KM, Baptista J, Roche AGenentech Collaborative Group. Effect of growth hormone treatment on adult height of children with idiopathic short stature. N Engl J Med 1999;340 (07):502–507
52 Kamp GA, Mul D, Waelkens JJJ, Jansen M, Delemarre-Van De Waal HA, et al. A randomized controlled trial of three years growth hormone and gonadotropin-releasing hormone agonist treatment in children with idiopathic short stature and intrauterine growth retardation. J Clin Endocrinol Metab 2001;86(07): 2969–2975
53 McCaughey ES, Mulligan J, Voss LD, Betts PR. Growth and metabolic consequences of growth hormone treatment in prepubertal short normal children. Archives of disease in childhood 1994;71 (03):201–206

