frontiers in Endocrinology

ORIGINAL RESEARCH
published: 29 November 2021
doi: 10.3389/fendo.2021.726172

RETRACTED: Effect of Weekly Long-Acting Growth Hormone Replacement Therapy Compared to Daily Growth Hormone on Children With Short Stature: A Meta-Analysis

Liyan Ma[1†], *Liangyi Li*[2†], *Wen Pan*[3], *Congfu Huang*[4], *Limei Liu*[1] and *Xiaoxiao Zhang*[5,6*]

[1] Department of Pediatrics, General Hospital of Ningxia Medical Univeristy, Yinchuan, China, [2] Department of Endocrinology, Second Affiliated Hospital of Fujian Medical University, Quanzhou, China, [3] Department of General Internal Medicine, Qingdao Fuwai Cardiovascular Hospital, Qingdao, China, [4] Department of Pediatrics, Longgang District Maternity & Child Healthcare Hospital, Shenzhen, China, [5] Department of Pediatrics, Chongqing Jiangbei Hospital of Traditional Chinese Medicine, Chongqing, China, [6] Department of Child Healthcare, Longgang District Maternity & Child Healthcare Hospital, Shenzhen, China

Background: We performed a meta-analysis to evaluate the efficacy and safety of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature.

Methods: A systematic literature search up to April 2021 was performed and 11 studies included 1,232 children with short stature treated with growth hormone replacement therapy at the start of the study; 737 of them were using weekly long-acting growth hormone replacement therapy and 495 were using daily growth hormone. They were reporting relationships between the efficacy and safety of long-acting growth hormone replacement therapy and daily growth hormone in children with short stature. We calculated the odds ratio (OR), and mean difference (MD) with 95% confidence intervals (CIs) to assess the efficacy and safety of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature using the dichotomous or continuous method with a random or fixed-effect model.

Results: Long-acting growth hormone replacement therapy had significantly lower height standard deviation scores chronological age (MD, –0.10; 95% CI, –0.13 to –0.08, p <0.001), and insulin-like growth factor binding protein-3 (MD, –0.69; 95% CI, –1.09 to –0.30, p <0.001) compared to daily growth hormone in children with short stature.However, growth hormone replacement therapy had no significantly difference in height velocity (MD, –0.09; 95% CI, –0.69–0.5, p = 0.76), height standard deviation scores bone age (MD, –0.04; 95% CI, –0.10–0.02, p = 0.16), insulin-like growth factor 1 standard deviation scores (MD, 0.26; 95% CI, –0.26–0.79, p = 0.33), and incidence of adverse events (OR, 1.16; 95% CI, 0.90–1.50, p = 0.25) compared to daily growth hormone in children with short stature.

OPEN ACCESS

Edited by:
Luca Persani, Istituto Auxologico Italiano (IRCCS), Italy

Reviewed by:
Luiz Augusto Casulari, University of Brasilia, Brazil
Mauro Antonio Czepielewski, Federal University of Rio Grande do Sul, Brazil

***Correspondence:**
Xiaoxiao Zhang
zhangxiaoxiao_16@sina.com

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Pituitary Endocrinology, a section of the journal Frontiers in Endocrinology

Received: *16 June 2021*
Accepted: *08 November 2021*
Published: *29 November 2021*

Citation:
Ma L, Li L, Pan W, Huang C, Liu L and Zhang X (2021) Effect of Weekly Long-Acting Growth Hormone Replacement Therapy Compared to Daily Growth Hormone on Children With Short Stature: A Meta-Analysis. Front. Endocrinol. 12:726172. doi: 10.3389/fendo.2021.726172

Conclusions: Long-acting growth hormone replacement therapy had significantly lower height standard deviation scores chronological age, and insulin-like growth factor binding protein-3 compared to daily growth hormone in children with short stature. However, growth hormone replacement therapy had no significant difference in height velocity, height standard deviation scores bone age, insulin-like growth factor 1 standard deviation scores, and incidence of adverse events compared to daily growth hormone in children with short stature. Further studies are required to validate these findings.

Keywords: children with short stature, long-acting growth hormone, daily growth hormone, height velocity, chronological age, bone age, insulin-like growth factor 1

BACKGROUND

Growth hormone replacement therapy was first shown to cure growth hormone insufficiency in the late fifties (1). Growth hormone was manufactured by recombinant DNA technique in the early eighties, which increased its possible usages (2). The growth hormone usage has been accepted by the Food and Drug Administration in idiopathic short stature (3). Randomized controlled trials have shown that everyday recombinant human growth hormone can improve height velocity and efficiently progress body composition in subjects with idiopathic short stature (4–6). The use of growth hormone in cancer survivors and short children with RASopathies, chromosomal breakage syndromes, or DNA-repair disorders should be carefully evaluated owing to an increased risk of recurrence, primary cancer, or second neoplasia in these individuals (7). Early growth hormone replacement therapy was limited to two or three intramuscular injections weekly, which were rapidly substituted by subcutaneous injections every day due to the added suitability. Many studies have demonstrated that subcutaneous injections every day are effective as the early treatments of growth hormone insufficiency in terms of producing insulin-like growth factor 1 and encouraging linear growth (8, 9). However, the need for injections every day causes non-compliance, higher health care costs, and reduced efficiency (10). This causes a decrease in height velocity in subjects with poor compliance (10, 11). Multiple characteristic problems occur in the long-term administration of growth hormone therapy that can decrease their effectiveness. Some of the recognized problems for long-term adherence comprise the injections method, the injection difficulty, pain produced by the injections, the device type used for the injections, parental apparent benefits and formulary changes, and many others (10, 11). The creation of pens, needle-free strategies, and infusion pumps with their limited applications helped in recovering compliance (12). Presently, oral administration is not similarly effective as injections in clinical practice (12). Many long-acting growth hormone formulae that need one injection every week, 2 weeks, or month have been developing offering a potential substitute to accomplish similar effectiveness and safety (13). Compared to daily recombinant human growth hormone treatment, a long-acting growth hormone treatment needs one injection every week can probably save almost 300 injections year, and can also offer better suitability, tolerance, and compliance than daily injections (14). To maximize the growth effects of growth hormone treatment and its other physiological benefits, there have been many different advanced pharmaceutical tools used to improve the growth hormone preparations (15–17). The six types of long-acting growth hormone formulae that have been studied are pegylated molecules, depot formulae, growth hormone molecules bound to albumin, prodrug formulae, growth hormone molecules bound to Fab antibodies, and growth hormone synthesis proteins (18). However, long-acting growth hormone effectiveness and safety in children with short stature is still conflicting. As an outcome, this meta-analysis aimed to generate efficacy and safety of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature.

METHODS

The present study followed the meta-analysis of studies in the epidemiology statement (19), which was performed following an established protocol.

Study Selection

Included studies were that with statistical measures of association (odds ratio [OR], mean difference [MD], frequency rate ratio, or relative risk, with 95% confidence intervals [CIs]) between the efficacy and safety of long-acting growth hormone replacement therapy and daily growth hormone in children with short stature.

Human studies only in any language were considered. Inclusion was not restricted by study size or type. Publications excluded were review articles and commentary and studies that did not supply a degree of relationship. **Figure 1** shows the whole study process.

The articles were included in the meta-analysis when the next inclusion criteria were met:

1. The study was a randomized control trial or retrospective study.
2. The target population is children with short stature treated with growth hormone replacement therapy.

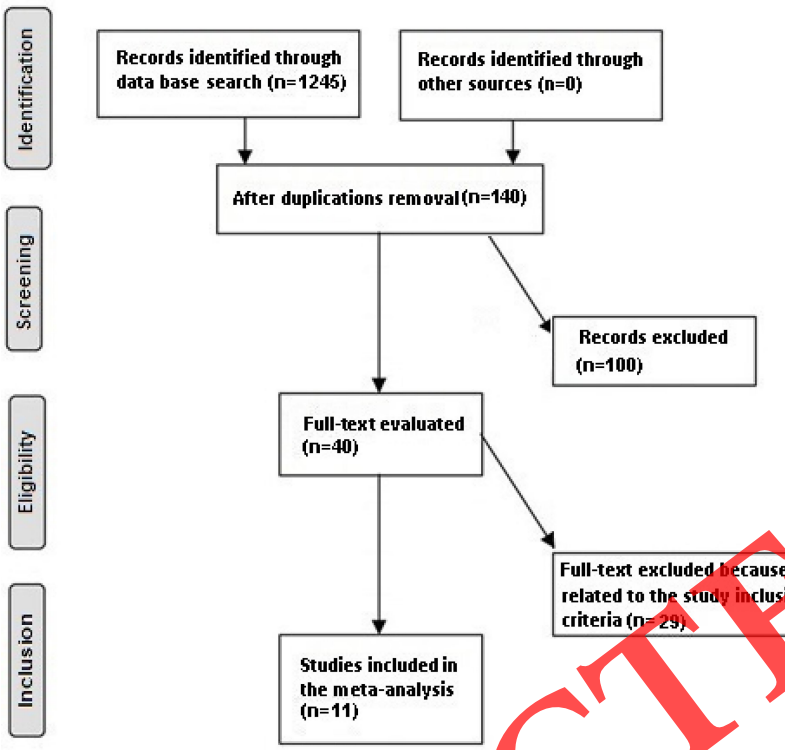

FIGURE 1 | Diagram of the study process.

3. The intervention program was growth hormone replacement therapy.
4. The study included comparisons between the long-acting growth hormone replacement therapy and daily growth hormone.

The exclusion criteria were:

1. Studies that did not determine efficacy and safety of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature.
2. Studies with growth hormone replacement therapy in children with short stature.
3. Studies did not focus on the effect of comparative results.

Identification

A search protocol strategy was organized according to the PICOS principle (20) as follows: P (population): children with short stature treated with growth hormone replacement therapy; I (intervention/exposure): growth hormone replacement therapy; C (comparison): the long-acting growth hormone replacement therapy and daily growth hormone; O (outcome): change in the height velocity, height standard deviation scores chronological age, height standard deviation scores bone age, insulin-like growth factor 1 standard deviation scores, insulin-like growth factor binding protein-3, and incidence of adverse events in children with short stature treated with growth hormone replacement therapy; and S (study design): no restriction (21).

First, a systematic search was conducted in OVID, Embase, Cochrane Library, PubMed, and Google scholar till April 2021, by a blend of keywords and related words for the children with short stature, long-acting growth hormone, daily growth hormone, height velocity, chronological age, bone age, insulin-like growth factor 1, insulin-like growth factor binding protein-3, and incidence of adverse events as shown in **Table 1**. All selected studies were gathered in an EndNote file, duplicates were removed, and the title and abstracts were revised to eliminate studies that did not report a relationship between the efficacy and safety of long-acting growth hormone replacement therapy and daily growth hormone in children with short stature. The remaining articles were revised for related information.

Screening

Data were abbreviated based on the following: study associated and subject associated features onto a homogeneous form, the primary author last name, study period, publication year, country, the studies region, and design of the study; type of the population, the total number and subjects number, demographic data and clinical and treatment features; the evaluation period associated with measurement, quantitative method and qualitative method of assessment, source of information, and outcomes' assessment; and statistical analysis MD or relative risk, with 95% CI of relationship among the efficacy and safety of long-acting growth hormone replacement therapy and daily growth hormone in children with short stature (22). If a study

TABLE 1 | Search strategy for each database.

Database	Search strategy
Pubmed	#1 "children with short stature"[MeSH Terms] OR "long-acting growth hormone"[All Fields] OR "daily growth hormone"[All Fields] OR " insulin-like growth factor binding protein-3"[All Fields] #2 "height velocity"[MeSH Terms] OR "children with short stature"[All Fields] OR "insulin-like growth factor 1"[All Fields] OR "chronological age"[All Fields] OR " bone age"[All Fields] OR " incidence of adverse events "[All Fields] #3 #1 AND #2
Embase	'children with short stature'/exp OR 'long-acting growth hormone'/exp OR 'daily growth hormone'/exp OR ' insulin-like growth factor binding protein-3'/exp #2 'height velocity'/exp OR 'insulin-like growth factor 1'/exp OR 'chronological age'/exp ' bone age'/exp OR OR ' incidence of adverse events '/exp #3 #1 AND #2
Cochrane library	#1 (children with short stature):ti,ab,kw OR (long-acting growth hormone):ti,ab,kw OR (daily growth hormone):ti,ab,kw OR (insulin-like growth factor binding protein-3):ti,ab,kw (Word variations have been searched) #2 (height velocity):ti,ab,kw OR (insulin-like growth factor 1):ti,ab,kw OR (chronological age):ti,ab,kw OR (bone ag):ti,ab,kw OR (incidence of adverse events):ti,ab,kw (Word variations have been searched) #3 #1 AND #2

fit for inclusion based upon the above-mentioned principles, data were extracted individually by two authors. In case of discrepancy, the corresponding author gave a final choice. When there were diverse data from a study, the data were extracted separately. For the bias risk in the studies: each study was assessed using two authors who individually evaluated the methodological quality of the selected studies. We used the "risk of bias tool" from the RoB 2: A revised Cochrane risk-of-bias tool for randomized trials to evaluate methodological quality (23). In terms of the evaluation criteria, each study was valued and allocated to one of the next three risks of bias: low: if all quality criteria were met; unclear or moderate: if one or more of the quality criteria were partly met or unclear, or high: if one or more of the criteria were not met, or not included. Any discrepancies were addressed by a reassessment of the original article.

Eligibility

The main result concentrated on measuring the efficacy and safety of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature. An assessment of the effects of efficacy and safety of long-acting growth hormone replacement therapy and daily growth hormone in children with short stature was extracted forming a summary.

Inclusion

Sensitivity analyses were limited only to studies reporting the relationship between the efficacy and safety of long-acting growth hormone replacement therapy and daily growth hormone in children with short stature. For subcategory and sensitivity analysis, we compared long-acting growth hormone replacement therapy to daily growth hormone treatment.

Statistical Analysis

The dichotomous or continuous method with random-effect or fixed-effect models was used to calculate the odds ratio (OR) or mean difference (MD) and 95% CI. We used the Chi-square test to perform biological heterogeneity analyses between different studies. We calculated the I^2 index; the I^2 index is from 0 to 100%. Values of about 0, 25, 50, and 75% indicate no, low, moderate, and high heterogeneity, respectively (24). When I^2 was higher than 50%, we chose the random effect model; when it was lower than 50%, we used the fixed-effect model. A subgroup analysis was performed by stratifying the original evaluation per liver cancer and chemotherapy different outcomes as described before. In this analysis, a p-value for differences between subgroups of <0.05 was considered statistically significant. Publication bias was evaluated quantitatively using the Egger regression test (publication bias considered present if $p \geq 0.05$), and qualitatively, by visual examination of funnel plots of the logarithm of ORs or MDs *versus* their standard errors (SE) (22). All p-values were 2-tailed. All calculations and graphs were performed using Reviewer manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

A total of 1,245 unique studies were identified, of which 11 studies (between 2012 and 2021) fulfilled the inclusion criteria and were included in the study (25–35).

The 11 studies included 1,232 children with short stature treated with growth hormone replacement therapy at the start of the study; 737 of them were using weekly long-acting growth hormone replacement therapy and 495 were using daily growth hormone. All studies evaluated the efficacy and safety of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature.

The study size ranged from 25 to 440 children with short stature treated with growth hormone replacement therapy at the start of the study. The details of the 11 studies are shown in **Table 2**. Ten studies reported data stratified to height velocity; seven studies reported data stratified to height standard deviation scores chronological age; five studies reported data stratified to height standard deviation scores bone age; six studies reported data stratified to insulin-like growth factor 1 standard deviation scores; two studies reported data stratified to insulin-like growth factor binding protein-3; and 10 studies reported data stratified

TABLE 2 | Characteristics of the selected studies for the meta-analysis.

Study	Country	Total	High-dose long-acting growth hormone every week	Growth hormone every day
Péter (24)	Multicenter	51	39	12
Hwang (25)	Korea	60	30	30
Khadilkar (26)	Multicenter	178	91	87
Zelinska (27)	Multicenter	52	41	11
Chatelain (28)	Multicenter	25	12	13
Luo (29)	China	440	291	149
Hwang (30)	Korea	42	14	28
Qiao (31)	China	98	49	49
Sävendahl (32)	Multicenter	59	45	14
Maniatis (33)	USA	161	105	56
Bright (34)	Germany	66	20	46
	Sum	**1,232**	**737**	**495**

to the incidence of adverse events. Several studies adjusted data stratified analysis based on the dose given and were extracted separately. Their comparison results are shown in **Figures 2**–**7**.

Long-acting growth hormone replacement therapy had significantly lower height standard deviation scores chronological age (MD, −0.10; 95% CI, −0.13 to −0.08, p <0.001) with low heterogeneity (I^2 = 23%), and insulin-like growth factor binding protein-3 (MD, −0.69; 95% CI, −1.09 to −0.30, p <0.001) with low heterogeneity (I^2 = 38%) compared to daily growth hormone in children with short stature as shown in **Figures 2** and **6**.

However, growth hormone replacement therapy had no significantly difference in height velocity (MD, −0.09; 95% CI, −0.69–0.5, p = 0.76) with high heterogeneity (I^2 = 83%), height standard deviation scores bone age (MD, −0.04; 95% CI, −0.10–0.02, p = 0.16) with low heterogeneity (I^2 = 38%), insulin-like growth factor 1 standard deviation scores (MD, 0.26; 95% CI, −0.26–0.79, p = 0.33) with high heterogeneity (I^2 = 92%), and incidence of adverse events (OR, 1.16; 95% CI, 0.90–1.50, p = 0.25) with no heterogeneity (I^2 = 0%) compared to daily growth hormone in children with short stature as shown in **Figures 1**, **3**–**5**, **7**.

Selected studies stratified analysis that adjusts for children age, and ethnicity was not performed since no studies reported or adjusted for these factors.

Based on the visual examination of the funnel plot as well as on quantitative measurement by the Egger regression test, there was no indication of publication bias (p = 0.86). Though, most of the comprised studies were evaluated to be of a low methodological quality. All studies did not have selective reporting bias, and no articles had incomplete result data and selective reporting.

DISCUSSION

This meta-analysis study based on 11 studies included 1,232 children with short stature treated with growth hormone replacement therapy at the start of the study; 737 of them were using weekly long-acting growth hormone replacement therapy and 495 were using daily growth hormone (25–35).

Long-acting growth hormone replacement therapy had significantly lower height standard deviation scores chronological age, and insulin-like growth factor binding protein-3 compared to daily growth hormone in children with short stature.

However, long-acting growth hormone replacement therapy had no significant difference in height velocity, height standard deviation scores bone age, insulin-like growth factor 1 standard

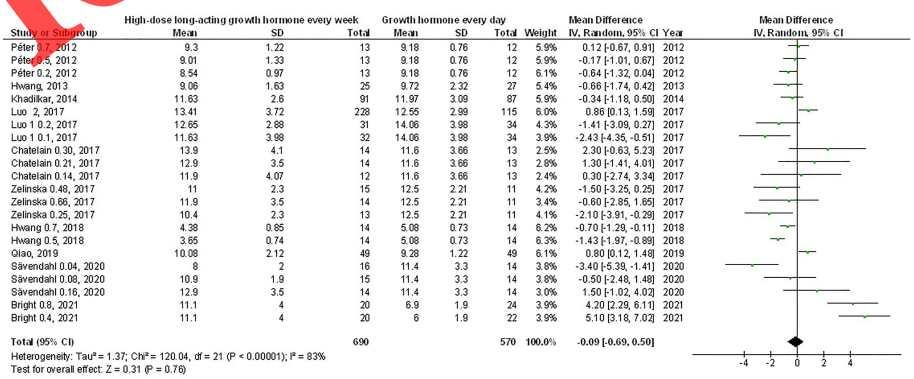

FIGURE 2 | Forest plot of the change in height velocity in long-acting growth hormone replacement therapy compared to daily growth hormone.

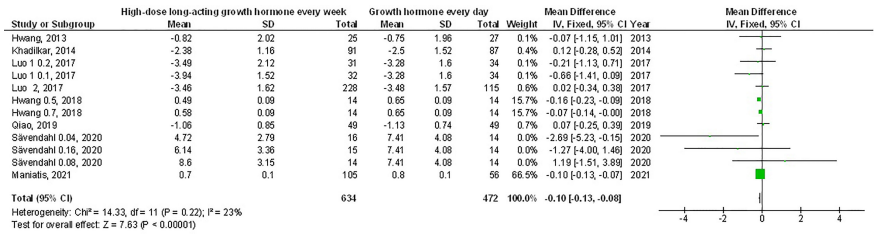

FIGURE 3 | Forest plot of the change in height standard deviation scores chronological age in long-acting growth hormone replacement therapy compared to daily growth hormone.

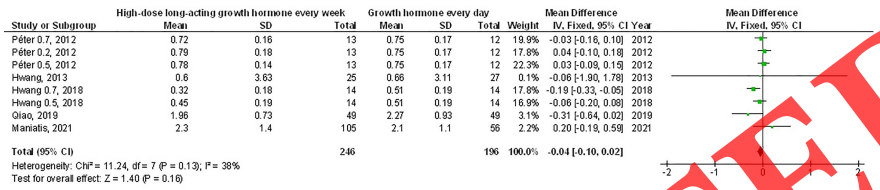

FIGURE 4 | Forest plot of the change in height standard deviation scores bone age in long-acting growth hormone replacement therapy compared to daily growth hormone.

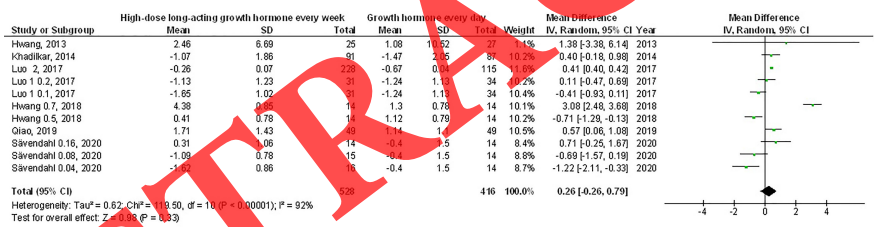

FIGURE 5 | Forest plot of the change in insulin-like growth factor 1 standard deviation scores in long-acting growth hormone replacement therapy compared to daily growth hormone.

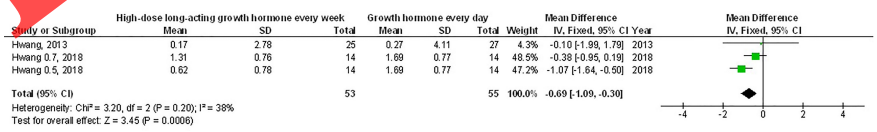

FIGURE 6 | Forest plot of the change in insulin-like growth factor binding protein-3 in long-acting growth hormone replacement therapy compared to daily growth hormone.

deviation scores, and incidence of adverse events compared to daily growth hormone in children with short stature (25–35). However, the analysis of outcomes should be done with caution because of the small sample size of most of the selected studies in our meta-analysis (eight studies out of 11 <100 subjects); proposing the need for more studies to confirm these results or possibly to significantly affects confidence in the outcome assessment, e.g., height standard deviation scores bone age comparison with its relatively low p-value = 0.16.

The insulin-like growth factor 1 standard deviation scores levels shown in these trials were within the normal range. Earlier studies have also shown a rise of serum insulin-like growth factor

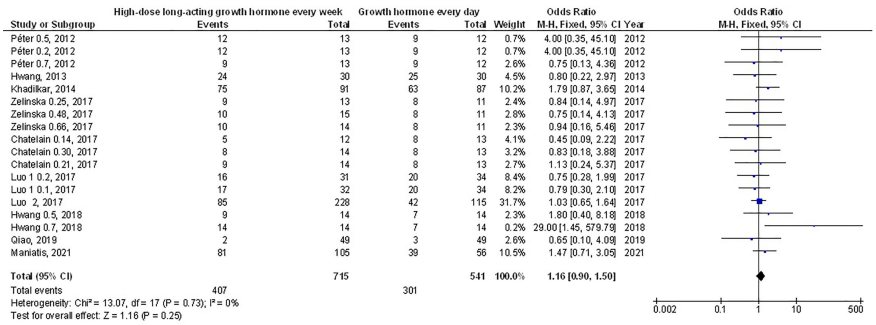

FIGURE 7 | Forest plot of the incidence of adverse events in long-acting growth hormone replacement therapy compared to daily growth hormone.

1 levels after long-acting growth hormone therapy, but the mean insulin-like growth factor 1 standard deviation scores levels were all preserved within +2 standard deviation values (36–38). This result may be associated with the slow release property of long-acting growth hormone, which encourages liver-production of insulin-like growth factor 1. There was a significant rise in the free insulin-like growth factor 1 level, which represents its biological activity after growth hormone therapy. As an outcome, the level of free insulin-like growth factor 1 is a good predictor of recombinant human growth hormone management response (39). Guidelines established by the Pediatric Endocrine Society in 2016 suggested that determining the serum insulin-like growth factor 1 levels could be used to monitor patient compliance and the production of insulin-like growth factor 1 when the growth hormone dose is changed. The growth hormone dose is ought to be reduced if the levels of serum insulin-like growth factor 1 are exceeding the laboratory-defined upper limit of the normal range for the age or stage of puberty of the subject (40). The Growth Hormone Research Society states that there is no evidence that after long-acting growth hormone injection, the impact of possible supra-physiological and continued insulin-like growth factor 1 level is related to an increased risk of adverse side effects (15). However, men in the highest quartile of plasma insulin-like growth factor 1 levels indicated a higher risk of prostate cancers compared with men in the lowest quartile (41). Also, insulin-like growth factor 1 levels in the highest tertile or quintile were related to a higher risk of breast cancer or colorectal cancer (42, 43). Moreover, high insulin-like growth factor 1 standard deviation scores during growth hormone therapy are associated with the risk of diminished insulin sensitivity (44). So, management with growth hormone needs close monitoring of the insulin-like growth factor 1 levels. Long-acting growth hormone formulae vary in the induction kinetics of serum insulin-like growth factor 1. Studies require considering the pharmacokinetics and pharmacodynamics of each formula for assessing the clinically ideal time point to determine insulin-like growth factor 1 levels (15). Also, the ideal dose and the frequency of administration of long-acting growth hormone with diverse mechanisms should be measured based on the insulin-like growth factor 1 levels.

The adverse events related to long-acting growth hormone treatment were numerous, e.g., injection site pruritus, arthralgia, hematoma, hematuria, adrenal insufficiency, erythema, anemia, abnormal liver function test results, peripheral edema, hypothyroidism, pyrexia, rash, headache, and vomiting. These adverse events were generally mild, and none of the adverse events caused subject withdrawal. The most frequently described adverse events in subjects taking long-acting growth hormone therapy were injection site pruritus, anemia, hypothyroidism, pyrexia, rash, headache, and vomiting (25–35).

Long-acting growth hormone replacement therapy had no significant difference in height velocity, height standard deviation scores bone age, insulin-like growth factor 1 standard deviation scores, and incidence of adverse events compared to daily growth hormone in children with short stature; suggesting that both are equivalent. However, the significant difference found in height standard deviation scores chronological age, and insulin-like growth factor binding protein-3 should be further studied since the number of studies used to determine these significant differences were small. This meta-analysis showed the relationship between the efficacy and safety of long-acting growth hormone replacement therapy and daily growth hormone in children with short stature. However, further studies are needed to validate these potential relationships. Also, further studies are needed to deliver a clinically meaningful difference in the results. These studies must comprise larger with more homogeneous samples. This was also suggested before in a similar meta-analysis study that showed a similar effect of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature treated with growth hormone replacement therapy (45). Well-conducted studies are also required to evaluate these factors and the combination of different subject-level data, children's age, and ethnicity; since our meta-analysis study could not answer whether they are related to the outcomes. In summary, long-acting growth hormone replacement therapy had significantly lower height standard deviation scores chronological age, and insulin-like growth factor binding protein-3 compared to daily growth hormone in children with short stature. However, growth hormone replacement therapy had no significant difference in

height velocity, height standard deviation scores bone age, insulin-like growth factor 1 standard deviation scores, and incidence of adverse events compared to daily growth hormone in children with short stature. Further studies are required to validate these findings.

Limitations

There may be selection bias in this study because many studies selected were excluded from the meta-analysis. However, the excluded studies did not fulfill the inclusion criteria of our meta-analysis. Also, whether the results are associated with age and ethnicity or not could not be answered. The study designed to evaluate the relationship between the efficacy and safety of weekly long-acting growth hormone replacement therapy compared to daily growth hormone in children with short stature was based on data from previous studies, which might cause bias induced by incomplete details. The meta-analysis was based on a small number of studies (11 studies); eight studies were small, ≤100. Variables including children's age, ethnicity, and nutritional status of subjects were also the possible bias-inducing factors. Some unpublished articles and missing data might lead to a bias in the pooled effect. Subjects were using different treatment schedules, dosages, and health care systems. Lastly, none of the selected studies showed data on thyroid function, so the meta-analysis of this result was not accessible. The selected studies included patients with short stature, but they did not define properly which criteria were used to conceptualize short stature. The inclusion or exclusion criteria of the selected studies also did not mention information on whether or not patients with genetic syndromes were included, whether systemic diseases were excluded, and whether patients with idiopathic short stature, short family stature, or constitutional short stature were included. These criteria vary widely in the populations studied. It is not recorded whether or not patients with growth hormone deficiency were included, either isolated or associated with multiple pituitary deficiencies. The impact of puberty and hormone replacement with glucocorticoids and sex steroids was also not assessed in most of the selected studies to the extent that did not allow us to analyze its effect in our metal analysis. Final we height was not evaluated properly in the selected studies, an outcome that should always be the consistent objective of studies involving growth.

CONCLUSIONS

Long-acting growth hormone replacement therapy had significantly lower height standard deviation scores chronological age, and insulin-like growth factor binding protein-3 compared to daily growth hormone in children with short stature. However, growth hormone replacement therapy had no significant difference in height velocity, height standard deviation scores bone age, insulin-like growth factor 1 standard deviation scores, and incidence of adverse events compared to daily growth hormone in children with short stature. Further studies are required to validate these findings. However, the analysis of outcomes should be done with caution because of the small sample size of most of the selected studies in our meta-analysis; proposing the need for more studies to confirm these results or possibly to significantly affects confidence in the outcome assessment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Conception and design: XZ. Administrative support: All authors. Provision of study materials or subjects: All authors. Collection and assembly of data: JC, LL, WP, CH, and LL. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Raben M. Treatment of a Pituitary Dwarf With Human Growth Hormone. *J Clin Endocrinol Metab* (1958) 18(8):901–3. doi: 10.1210/jcem-18-8-901
2. Flodh H. Human Growth Hormone Produced With Recombinant DNA Technology: Development and Production. *Acta Paediatrica* (1986) 75:1–9. doi: 10.1111/j.1651-2227.1986.tb10356.x
3. Richmond E, Rogol AD. Current Indications for Growth Hormone Therapy for Children and Adolescents. *Curr Indications Growth Hormone Ther* (2010) 18:92–108. doi: 10.1159/000316130
4. Hodson EM, Willis NS, Craig JC. Growth Hormone for Children With Chronic Kidney Disease. *Cochrane Database Syst Rev* (2012) 2:1–59. doi: 10.1002/14651858.CD003264.pub3
5. Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, et al. Clinical Effectiveness and Cost-Effectiveness of Growth Hormone in Adults in Relation to Impact on Quality of Life: A Systematic Review and Economic Evaluation. *Health Technol Assess* (2002) 6(19):1–96.
6. Cave CB, Bryant J, Milne R. Recombinant Growth Hormone in Children and Adolescents With Turner Syndrome. *Cochrane Database Syst Rev* (2003) 1:1–29. doi: 10.1002/14651858.CD003887
7. Boguszewski CL, Boguszewski M. Growth Hormone's Links to Cancer. *Endocr Rev* (2019) 40(2):558–74. doi: 10.1210/er.2018-00166
8. Laursen T, Gravholt CH, Heickendorff L, Drustrup J, Kappelgaard A-M, Jørgensen JO, et al. Long-Term Effects of Continuous Subcutaneous Infusion Versus Daily Subcutaneous Injections of Growth Hormone (GH) on the Insulin-Like Growth Factor System, Insulin Sensitivity, Body Composition, and Bone and Lipoprotein Metabolism in GH-Deficient Adults. *J Clin Endocrinol Metab* (2001) 86(3):1222–8. doi: 10.1210/jc.86.3.1222
9. Jørgensen JO, Møller N, Lauritzen T, Christiansen JS. Pulsatile Versus Continuous Intravenous Administration of Growth Hormone (GH) in GH-Deficient Patients: Effects on Circulating Insulin-Like Growth Factor-I and Metabolic Indices. *J Clin Endocrinol Metab* (1990) 70(6):1616–23. doi: 10.1210/jcem-70-6-1616
10. Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, Robinson E, et al. Non-Compliance With Growth Hormone Treatment in Children is Common and

Impairs Linear Growth. *PloS One* (2011) 6(1):e16223. doi: 10.1371/journal.pone.0016223
11. Kapoor RR, Burke S, Sparrow IA, Hughes DB, Dunger KK, Ong CL, et al. Monitoring of Concordance in Growth Hormone Therapy. *Arch Dis Childhood* (2008) 93(2):147–8. doi: 10.1136/adc.2006.114249
12. Aguiar-Oliveira MH, Meneguz-Moreno RA, Nascimento-Junior AC. News Options and Preparations in Growth Hormone Therapy. *Arquivos Brasileiros Endocrinologia Metabologia* (2008) 52(5):917–24. doi: 10.1590/S0004-27302008000500024
13. Boguszewski CL. Update on GH Therapy in Adults. *F1000Research* (2017) 6:1–13. doi: 10.12688/f1000research.12057.1
14. Saenger PH, Mejia-Corletto J. Long-Acting Growth Hormone: An Update. *Adv Ther Pediatr Endocrinol Diabetol* (2016) 30:79–97. doi: 10.1159/000439333
15. Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BM, Boguszewski MC, Casanueva FF, et al. Growth Hormone Research Society Perspective on the Development of Long-Acting Growth Hormone Preparations. *Eur J Endocrinol* (2016) 174(6):C1.
16. Høybye C, Cohen P, Hoffman AR, Ross R, Biller BM, Christiansen JS, et al. Status of Long-Acting-Growth Hormone Preparations—2015. *Growth Hormone IGF Res* (2015) 25(5):201–6.
17. Sprogøe K, Mortensen E, Karpf DB, Leff JA. The Rationale and Design of TransCon Growth Hormone for the Treatment of Growth Hormone Deficiency. *Endocr Connections* (2017) 6(8):R171–81. doi: 10.1530/EC-17-0203
18. Yuen KC, Miller BS, Biller BM. The Current State of Long-Acting Growth Hormone Preparations for Growth Hormone Therapy. *Curr Opin Endocrinol Diabetes Obes* (2018) 25(4):267–73. doi: 10.1097/MED.0000000000000416
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-Analysis of Observational Studies in Epidemiology: A Proposal for Reporting. *JAMA* (2000) 283(15):2008–12. doi: 10.1001/jama.283.15.2008
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring Inconsistency in Meta-Analyses. *Bmj* (2003) 327(7414):557–60. doi: 10.1136/bmj.327.7414.557
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *J Clin Epidemiol* (2009) 62(10):e1–34.
22. Gupta A, Das A, Majumder K, Arora N, Mayo HG, Singh PP, et al. Obesity is Independently Associated With Increased Risk of Hepatocellular Cancer–related Mortality. *Am J Clin Oncol* (2018) 41(9):874–81. doi: 10.1097/COC.0000000000000388
23. Collaboration, C. *RoB 2: A Revised Cochrane Risk-of-Bias Tool for Randomized Trials* (2020). Available at: http://bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials (Accessed December 6, 2019).
24. Sheikhbahaei S, Trahan TJ, Xiao J, Taghipour M, Mena E, Connolly RM, et al. FDG-PET/CT and MRI for Evaluation of Pathologic Response to Neoadjuvant Chemotherapy in Patients With Breast Cancer: A Meta-Analysis of Diagnostic Accuracy Studies. *Oncologist* (2016) 21(8):931–9. doi: 10.1634/theoncologist.2015-0353
25. Péter F, Bidlingmaier M, Savoy C, Ji H-J, Saenger PH. Three-Year Efficacy and Safety of LB03002, a Once-Weekly Sustained-Release Growth Hormone (GH) Preparation, in Prepubertal Children With GH Deficiency (GHD). *J Clin Endocrinol Metab* (2012) 97(2):400–7. doi: 10.1210/jc.2011-2234
26. Hwang JS, Lee HS, Chung WY, Han H-S, Jin D-K, Kim H-S, et al. Efficacy and Safety of LB03002, a Once-Weekly Sustained-Release Human GH for 12-Month Treatment in Korean Children With GH Deficiency. *Eur J Endocrinol* (2013) 169(2):179–85. doi: 10.1530/EJE-13-0148
27. Khadilkar V, Radjuk KA, Bolshova E, Khadgawat R, El Kholy M, Desai M, et al. 24-Month Use of Once-Weekly GH, LB03002, in Prepubertal Children With GH Deficiency. *J Clin Endocrinol Metab* (2014) 99(1):126–32. doi: 10.1210/jc.2013-2502
28. Zelinska N, Iotova V, Skorodok J, Malievsky O, Peterkova V, Samsonova L, et al. Long-Acting C-Terminal Peptide–Modified hGH (MOD-4023): Results of a Safety and Dose-Finding Study in GHD Children. *J Clin Endocrinol Metab* (2017) 102(5):1578–87. doi: 10.1210/jc.2016-3547
29. Chatelain P, Malievskiy O, Radziuk K, Senatorova G, Abdou MO, Vlachopapadopoulou E, et al. A Randomized Phase 2 Study of Long-Acting TransCon GH vs Daily GH in Childhood GH Deficiency. *J Clin Endocrinol Metab* (2017) 102(5):1673–82. doi: 10.1210/jc.2016-3776
30. Luo X, Hou L, Liang L, Dong G, Shen S, Zhao Z, et al. Long-Acting PEGylated Recombinant Human Growth Hormone (Jintrolong) for Children With Growth Hormone Deficiency: Phase II and Phase III Multicenter, Randomized Studies. *Eur J Endocrinol* (2017) 177(2):195–205. doi: 10.1530/EJE-16-0905
31. Hwang JS, Lee HS, Lee K-H, Yoo H-W, Lee D-Y, Suh B-K, et al. Once-Weekly Administration of Sustained-Release Growth Hormone in Korean Prepubertal Children With Idiopathic Short Stature: A Randomized, Controlled Phase II Study. *Hormone Res Paediatrics* (2018) 90(1):54–63. doi: 10.1159/000489262
32. Qiao Y, Wang Z, Han J, Li G. Use of PEGylated Recombinant Human Growth Hormone in Chinese Children With Growth Hormone Deficiency: A 24-Month Follow-Up Study. *Int J Endocrinol* (2019) 2019:1–8. doi: 10.1155/2019/1438723
33. Sävendahl L, Battelino T, Brod M, Højby M, Rasmussen R, Horikawa RV, et al. Once-Weekly Somapacitan vs Daily GH in Children With GH Deficiency: Results From a Randomized Phase 2 Trial. *J Clin Endocrinol Metab* (2020) 105(4):e1847–61. doi: 10.1210/clinem/dgz310
34. Maniatis A, Nadgir U, Hofman P, Saenger P, Chertok E, Aghajanova E, et al. Lonapegsomatropin (TransCon hGH) in Children With Growth Hormone Deficiency: Efficacy and Safety of Up to 2 Years of Treatment. *Presented at ENDO* (2021) 2021:1–6.
35. Bright GM, Do M-HT, McKew JC, Blum WF, Thorner MO, et al. Development of a Predictive Enrichment Marker for Oral GH Secretagogue LUM-201 in Children With Growth Hormone Deficiency. *J Endocr Soc* (2021) 5. doi: 10.1210/jendso/bvab030
36. Fisher DM, Rosenfeld RG, Jaron-Mendelson M, Amitzi L, Koren R, Hart G. Pharmacokinetic and Pharmacodynamic Modeling of MOD-4023, a Long-Acting Human Growth Hormone, in Growth Hormone Deficiency Children. *Hormone Res Paediatrics* (2017) 87(5):324–32. doi: 10.1159/000470842
37. Battelino T, Rasmussen MH, De Schepper J, Zuckerman-Levin N, Gucev Z, Sävendahl L, et al. Somapacitan, a Once-Weekly Reversible Albumin-Binding GH Derivative, in Children With GH Deficiency: A Randomized Dose-Escalation Trial. *Clin Endocrinol* (2017) 87(4):350–8. doi: 10.1111/cen.13409
38. Bidlingmaier M, Kim J, Savoy C, Kim MJ, Ebrecht N, de la Motte S, et al. Comparative Pharmacokinetics and Pharmacodynamics of a New Sustained-Release Growth Hormone (GH), LB03002, Versus Daily GH in Adults With GH Deficiency. *J Clin Endocrinol Metab* (2006) 91(8):2926–30. doi: 10.1210/jc.2006-0514
39. Wacharasindhu S, Aroonparkmongkol S, Srivuthana S. Measurement of IGF-1, IGFBP-3 and Free IGF-1 Levels by ELISA in Growth Hormone (GH) Deficient Children Before and After GH Replacement. *Asian Pacific J Allergy Immunol* (2002) 20(3):155.
40. Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, et al. 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. *Hormone Res Paediatrics* (2016) 86(6):361–97. doi: 10.1159/000452150
41. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma Insulin-Like Growth Factor-I and Prostate Cancer Risk: A Prospective Study. *Science* (1998) 279(5350):563–6. doi: 10.1126/science.279.5350.563
42. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, et al. Prospective Study of Colorectal Cancer Risk in Men and Plasma Levels of Insulin-Like Growth Factor (IGF)-I and IGF-Binding Protein-3. *J Natl Cancer Inst* (1999) 91(7):620–5. doi: 10.1093/jnci/91.7.620
43. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating Concentrations of Insulin-Like Growth Factor I and Risk of Breast Cancer. *Lancet* (1998) 351(9113):1393–6. doi: 10.1016/S0140-6736(97)10384-1
44. Witkowska-Sedek E, Labochka D, Stelmaszczyk-Emmel A, Majcher A, Kucharska A, Sobol M, et al. Evaluation of Glucose Metabolism in Children With Growth Hormone Deficiency During Long-Term Growth Hormone Treatment. *J Physiol Pharmacol* (2018) 69(2):219–30.
45. Yang Y, Bai X, Yuan X, Zhang Y, Chen S, Yang H, et al. Efficacy and Safety of Long-Acting Growth Hormone in Children With Short Stature: A Systematic Review and Meta-Analysis. *Endocrine* (2019) 65(1):25–34. doi: 10.1007/s12020-019-01950-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in

this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.