Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis
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Authors' objectives
To determine the effect of growth hormone (GH) on short- and long-term growth in children with idiopathic short stature.

Searching
MEDLINE was searched from 1985 to 2000 for articles published in the English language, using the following search terms: ('growth hormone' or 'somatotropin' or 'somatropin' or 'somatrem') plus ('therapy' or 'treatment') plus ('growth' or 'height') plus ('child' or 'adolescent'). The following sources were searched manually: Journal of the American Medical Association, Journal of Pediatrics, Pediatrics and Acta Paediatrica, all from 1996 to 2000; meeting abstract books in these journals and those of the Lawson Wilkins Pediatric Endocrine Society and the Endocrine Society; and the bibliographic references from all the retrieved studies. In addition, pharmaceutical companies were contacted and external experts were asked to review the list of eligible studies.

Study selection
Study designs of evaluations included in the review
Studies that contained at least 5 patients, and obtained a last outcome measure for at least 50% of the original patients, were eligible. Randomised controlled trials (RCTs), non-randomised controlled trials and uncontrolled trials were included.

Specific interventions included in the review
Treatments with biosynthetic GH (not pituitary-derived) in the range of 0.14 to 0.40 mg/kg per week for at least 6 months were eligible.

Participants included in the review
Studies of children with idiopathic short stature (height below tenth percentile for age) were eligible. The participating children had to have the following characteristics: present as GH-naive patients with no previous GH treatment; an absence of classic GH deficiency (peak GH levels of at least 10 microg/L on at least one standard stimulation test); an absence of co-morbid conditions that impair growth; and have had no previous treatment with sex steroids or anabolic agents that potentially affect growth.

Outcomes assessed in the review
Studies that assessed appropriate height outcomes measures such as the growth velocity (as cm or inches per unit time) or height (as SD score or height Z score) were eligible. The actual outcomes assessed in the review were the effect of GH on the short-term (1-year) growth velocity, short-term height SD score, and adult height.

How were decisions on the relevance of primary studies made?
Two reviewers screened all the citation abstracts according to the basic inclusion criteria. Three reviewers then assessed each retrieved study in detail, using a standardised abstraction form to assess the relevance according to the inclusion criteria. They then met to discuss each study and reach consensus. The agreement regarding study inclusion was 92% before the meeting and 100% after.

Assessment of study quality
The authors do not state that they assessed validity.
Data extraction
Three reviewers independently extracted the following data using a standardised form: sample size; mean age; gender distribution; study design (controlled or uncontrolled); baseline pubertal status; growth variables; and growth outcome measures. The primary authors were contacted for clarification of published and unpublished data. Any disagreements were resolved by consensus. Only one abstraction form was filled in for each trial.

Methods of synthesis

How were the studies combined?
The pooled estimates and 95% confidence intervals (CIs) were estimated using random-effects models, with weighting by the reciprocal of their standard errors. The data from the controlled trials and uncontrolled trials were analysed separately. For the controlled trials, the weighted mean pooled differences between the treated and control groups were calculated for each growth variable at baseline, and for short-term (1 year) and long-term (adult height) outcomes. For the uncontrolled trials, the weighted pooled mean estimates for each growth variable before and after treatment were calculated. For each growth variable, two main types of analyses were performed: a pooled estimate across all studies reporting that growth variable (aggregate analysis); and pooling of the baseline growth variable, limited to studies that also reported that variable as an outcome (paired analysis).

How were differences between studies investigated?
Statistical heterogeneity was assessed for each planned meta-analysis. The following analyses were performed to test the robustness of results: analysis limited to RCTs; paired analyses limited to studies reporting baseline and outcome measures for each growth variable; and within-group changes in growth variables from baseline to follow-up. For the controlled and uncontrolled studies, the aggregate effect sizes were recalculated after omitting the study with the largest sample size and, separately, the study with the largest extreme results.

Results of the review
Thirty-eight studies were included: 6 RCTs (239 children), 4 non-randomised controlled trials (195 children) and 28 uncontrolled studies (655 children).

Controlled studies. There was little or no information about the method of randomisation or masking.

Effect of short-term GH therapy on growth velocity.
The baseline pre-treatment growth velocities were similar between the treatment groups. After one year, the growth velocity was significantly greater in the GH-treated group than the control; the pooled difference (6 studies) in growth velocity was 2.86 cm/year (95% CI: 2.13, 3.59). After 2 years, the growth velocity remained greater in the treatment group compared with the control; the pooled difference (2 studies) was 2.36 (plus or minus 0.36) cm/year.

For the RCTs reporting baseline and outcome data, the results were similar; however, after one year the pooled difference was 2.53 cm/year (95% CI: 1.72, 3.35).

The GH-treated group had a significantly greater increment in growth velocity than the untreated group at one year; the pooled change was 3.63 cm/year (95% CI: 3.00, 4.25) for GH therapy versus 0.93 cm/year (95% CI: 0.25, 1.62) for untreated controls.

Effect of short-term GH therapy on height SD score. After 1 year (2 studies, 36 children) the height of GH-treated children was greater than that of untreated children by 0.60 SD (95% CI: 0.26, 0.95).

Effect of GH therapy on adult height (4 controlled studies, 118 children).
GH-treated children reached significantly greater adult height than untreated children after a mean duration of treatment of 5.3 years. The weighted aggregate difference in height was 0.84 SD (95% CI: 0.46, 1.22). The pooled estimate for adult height was -1.51 SDs (95% CI: -1.70, -1.32) for the GH-treated group versus -2.29 SDs (95% CI: -2.63, -1.96) for the control group.
For the 3 paired studies (112 children) reporting the predicted and achieved adult heights, the baseline predictions for adult height were similar. The pooled difference in predicted adult height was 0.13 SD (95% CI: 0.18, 0.44). The actual adult height of the GH-treated group was greater than that for the control group; the gain for the GH-treated group was 0.78 SD (95% CI: 0.35, 1.21), representing a gain of 3.6 to 4.6 cm in height.

Uncontrolled studies.

The growth velocity (14 studies, 218 children) increased significantly from baseline after one year of GH treatment to 7.57 cm/year (95% CI: 6.99, 8.16). The height SDs score (10 studies) increased significantly from -2.62 SDs (95% CI: -2.79, -2.44) at baseline to -2.19 SDs (95% CI: -2.39, -1.99) after one year of GH, to -1.99 SDs after 2 years' GH (4 studies), and to -1.77 after 3 years' GH (6 studies).

The actual adult height achieved after a mean of 4.7 years of GH treatment was greater than that predicted (6 studies): the actual height was -1.62 SDs (95% CI: -1.80, -1.45) while the predicted height was -2.25 SDs (95% CI: -2.74, -1.77), representing a difference of 3.8 to 4.5 cm.

Adverse events.

Mild increases in serum insulin levels and/or the presence of GH antibodies were occasionally reported.

Cost information
A gain of 4 to 6 cm in adult height, together with an average of 5 years' GH therapy beginning at age 10 years, and prices of $11,000 to $18,000 per year, corresponds to more than $35,000 per 2.54 cm gained.

Authors' conclusions
Treatment with GH results in short-term increases in growth for children with idiopathic short stature, while long-term treatment can increase adult height. These results are fundamental to decisions about GH use, and they raise questions about the goals of treatment. The use of GH for idiopathic short stature in clinical practice will depend on its efficacy in promoting growth and the value of this to families, physicians and third-party payers.

CRD commentary
The aims were stated, and the inclusion criteria were defined in terms of the participants, study design, intervention and outcome. The search was adequate: several relevant sources were searched, attempts were made to locate unpublished material, and the methods used to select the studies were described. Restricting eligible studies to those published in the English language may have resulted in the omission of other relevant studies. Validity was not assessed, although only those studies reporting final outcome measures for more than 50% of the study sample were included and the results for controlled studies were presented separately. Relevant data were extracted and tabulated, and the methods used to extract the data were described. Statistical heterogeneity was assessed for each planned meta-analysis that was performed, and additional analyses were conducted to explore the robustness of the results.

The evidence presented tends to support the authors' conclusions, with the caveat that the evidence was based largely on non-randomised studies of unknown quality.

Implications of the review for practice and research
Practice: The authors state that GH therapy augments short- and long-term growth in children with idiopathic short stature, but that these data alone are insufficient to define the clinical value of treatment.

Research: The authors state that further long-term research is needed to identify factors that predict long-term responsiveness to GH therapy in individual children. They also state that future research should address the standardisation of reporting requirements for clinical studies of GH.
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