Cardiac effects of growth hormone in adults with growth hormone deficiency: a meta-analysis

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CRD summary
This review evaluated the effect of growth hormone treatment on the structure and function of the heart in adults with growth hormone deficiency. The authors concluded that growth hormone significantly improves some measures of mass, thickness and volume of the heart. The conclusion needs cautious interpretation because different types of studies were combined and their quality was unclear.

Authors' objectives
To evaluate the cardiac effects of growth hormone (GH) treatment in adults with growth hormone deficiency (GHD).

Searching
MEDLINE, EMBASE and Biosis Previews were searched from inception to 2002. There was no language restriction.

Study selection
Study designs of evaluations included in the review
The authors initially stipulated that blind placebo-controlled randomised trials (RCTs) were eligible for inclusion, but because few studies were found they widened the inclusion criteria to encompass 'open' studies as well. The RCTs included in the review were of either a parallel or crossover design. The design of the 'open' studies was not stated.

Specific interventions included in the review
Studies of GH treatment were eligible for inclusion. Comparative studies had to be placebo controlled. In the included studies, the target GH dose ranged from 0.03 to 0.5 IU/kg per week and the treatment duration ranged from 3 to 36 months.

Participants included in the review
Studies in people aged over 17 with GHD and a GH peak of less than 5 microg/L were eligible for inclusion. In most of the included studies GHD was diagnosed by the insulin tolerance test. The proportion of women in the included studies ranged from zero to 50%. Two thirds of the included studies reported the proportion of participants with adult-onset GHD, which ranged from zero to 100%.

Outcomes assessed in the review
Studies eligible for inclusion were those that used 2-dimensional echocardiography for cardiopulmonary investigation and reported left ventricular (LV) mass, interventricular septum thickness (IVS), LV posterior wall, LV end-systolic and -diastolic diameters, stroke volume, ratio of E-wave and A-wave peak velocities of the mitral flow profile (E/A), isovolumic relaxation time, or fractional shortening.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The assessment of study quality was based on design, blinding, loss to follow-up and statistical methods, including whether the data were analysed on an intention-to-treat basis. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.
Data extraction
Data were extracted using a standard form, possibly by two reviewers who resolved any disagreements by discussion. Outcome data extracted for the treatment and control groups in each study were the baseline and follow-up mean values and standard deviation (SD) or standard error. For parallel RCTs, the mean change from baseline to follow-up in each group was used to calculate the effect size (ES) by subtracting the mean change in the placebo group from the mean change in the GH group. For crossover trials, the ES was the difference in the mean change between each period. For open studies, mean differences between baseline and follow-up were used. A standard formula was used to calculate the LV mass from IVS, LV end-diastolic diameter and LV posterior wall. Where necessary, the variance of changes in means was estimated from other data or figures. The loss to follow-up for each outcome was also extracted.

Methods of synthesis
How were the studies combined?
A pooled ES and 95% confidence interval (CI) were calculated for each outcome using a meta-analysis weighted by the inverse variance. A positive ES was defined as an increase with GH treatment, and a negative ES as a decrease. Analyses were conducted using a fixed-effect model and were repeated using a random-effects model if the ES was significant.

A meta-analysis of available data was also used to quantify the difference in the mean change between groups or periods for each outcome as a weighted mean difference (WMD) and SD.

Publication bias was assessed using funnel plots and regression methods.

How were differences between studies investigated?
Heterogeneity in the ES was examined using a Q test. A sensitivity analysis was undertaken by omitting particular studies from the meta-analyses. Subgroup analyses and weighted meta-regression were used to explore the effects of dose, duration, insulin-like growth factor (IGF-I) and study design on the findings.

Results of the review
Sixteen studies were included: 7 parallel RCTs (n=269), 2 crossover RCTs (n=31) and 7 open studies (n=168).

The studies were judged to be of a good quality generally; the main concern was the loss to follow-up. There was no evidence of publication bias.

Treatment with GH showed a significant increase in LV mass (ES 0.23, 95% CI: 0.06, 0.41; WMD 10.8 g, SD 9.3), LV end-diastolic diameter (ES 0.31, 95% CI: 0.15, 0.47; WMD 1.34 mm, SD 1.13) and stroke volume (ES 0.48, 95% CI: 0.22, 0.74; WMD 10.3 mL, SD 8.7), with no statistically significant heterogeneity between the studies. There was a significant increase in IVS (ES 0.18, 95% CI: 0.05, 0.32; WMD 0.28 mm, SD 0.38) and LV posterior wall (ES 0.15, 95% CI: 0.01, 0.29; WMD 0.98, SD 0.22), but also significant heterogeneity. In a subgroup analysis of ES that included only controlled trials, only LV posterior wall and stroke volume were significant.

The subgroup analysis of high-target and low-target GH dose studies showed a significant ES for LV mass, IVS and LV end-diastolic diameter with high doses, but only for LV mass with low doses. A dose-effect relationship could not be confirmed by regression because the data were limited. A subgroup analysis according to IGF-I increase also suggested a dose-effect relationship, the pooled ES being significant for IVS, LV end-diastolic diameter and stroke volume in studies with high increases in IGF-I (greater than 300% median increase) but not in studies with lower increases.

The analyses conducted showed no statistically significant difference in LV end-systolic diameter, E/A, isovolumic relaxation time, or fractional shortening.

Authors' conclusions
The authors concluded that in adults with GHD, GH has a significant positive effect on LV mass, IVS, LV posterior wall, LV end-diastolic diameter and stroke volume, but not on systolic parameters.
CRD commentary
The inclusion criteria were clear and the post hoc change with regard to study design was explicit. The search, which was poorly reported, might have included literature other than that retrieved from the databases searched. Steps might have been taken to minimise bias and errors in the data extraction, quality assessment and, perhaps, the study selection processes, but again the procedures were poorly reported. The methods of analysis were sound but pooling different study designs is questionable. There were insufficient individual study details to enable an independent judgment of the appropriateness of pooling. The subgroup analyses were not shown or reported sufficiently for an independent interpretation. The evidence presented generally supports the authors’ conclusions, but a more cautious interpretation is warranted because the conclusions are based largely on a pooled analysis of studies of various designs and uncertain quality.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.