Cardiac effects of growth hormone treatment in chronic heart failure: a meta-analysis

CRD summary
The authors concluded that sustained treatment with growth hormone improves several cardiovascular parameters in adults with chronic heart failure, but more randomised evidence is needed. Although these conclusions are supported by the data presented, they fail to reflect that, for a large majority of outcomes, the randomised studies found no evidence of benefit from growth hormone.

Authors' objectives
To evaluate the effect of sustained treatment with growth hormone (GH) in patients with chronic heart failure (CHF).

Searching
MEDLINE, BIOSIS Previews and EMBASE were searched from inception to June 2005; the search terms were reported. There were no language restrictions. Unpublished studies were sought by contacting manufacturers of GH and authors of published studies, and by handsearching abstracts from major cardiology meetings.

Study selection
Studies in which GH was administered for over 1 month to adults with CHF, but without GH deficiency, were eligible. Studies were required to report at least one of the following outcome measures: heart rate, thickness of the interventricular septum or left ventricular (LV) posterior wall, LV end-diastolic diameter, LV end-systolic diameter, LV mass, LV end-systolic wall stress, LV ejection fraction (LVEF), ratio of early to late mitral diastolic flow, isovolumic relaxation time, systemic vascular resistance, New York Heart Association class (NYHA), exercise duration and maximal oxygen uptake (VO₂max). Randomised controlled trials (RCTs) and open studies (not further defined) were eligible.

The characteristics of participants in the included studies varied widely (where stated): their mean age was 32 to 65 years, 0 to 75% were female, and 0 to 100% were ischaemic. Where stated, mean baseline NYHA was 2.8 and LVEF was 25%. The majority of participants were receiving conventional drugs such as diuretics (88%), angiotensin-converting enzyme inhibitors or angiotension II receptor antagonists (94%), and/or beta-blockers (42%).

The weekly target dose of GH in the included studies varied from 7 to 28 units, or 0.14 to 0.25 units/kg. The duration of therapy ranged from 2 to 6 months.

In addition to cardiovascular outcomes, the review reported the incidence of serious adverse events.

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 following aspects of study quality were considered: sample size, design, blinding, statistical methods and losses to follow-up.

Two reviewers independently assessed study quality, with any disagreements resolved by team discussion.

Data extraction
Effect sizes and 95% confidence intervals (CIs) were calculated as follows: for parallel-group trials, the mean difference between the groups in changes from baseline, divided by their pooled variance; for crossover trials, the mean difference between the final score in each period divided by the variance in the placebo period; and for uncontrolled studies, the difference between baseline and end scores, divided by the variance.

Two reviewers independently extracted the data using standardised forms, with any disagreements resolved by team
discussion. Study authors were contacted to obtain unpublished data and/or verify extracted data as required.

Methods of synthesis
Mean differences were meta-analysed to obtain weighted mean differences and standard deviations, from which overall effect sizes and 95% CIs were calculated. Statistical heterogeneity was assessed using the Q test. Where significant heterogeneity was detected, potential causes were evaluated and a random-effects model was used. Potential selection bias (by publication status or type of publication) was assessed using funnel plots, while funnel plot asymmetry was tested by linear regression. Sensitivity analyses were conducted, excluding outliers from the analysis. Subgroup or meta-regression analyses were used to assess the impact on the findings of a range of clinical variables.

Results of the review
Twelve studies (n=195) were included: 8 blinded placebo-controlled RCTs (7 parallel-group, n=159; 1 crossover, n=12) and 4 studies (n=24) described as ‘open’.

The studies were generally of a good quality, with losses to follow-up in only 4 studies (all RCTs).

When RCTs were pooled, a statistically significant effect favouring GH treatment was found for thickness of the interventricular septum (0.43, 95% CI: 0.08, 0.77; 4 RCTs n=102), LV end-systolic wall stress (-0.69, 95% CI: -1.37, -0.02; 5 RCTs n=116) and VO$_2$max (0.62, 95% CI: 0.16, 1.09; 3 RCTs, n=47).

Pooling of all studies resulted in a statistically significant effect favouring GH treatment for the following outcomes (in addition to those above): LV posterior wall, LV end-diastolic diameter, LV end-systolic diameter, LVEF, systemic vascular resistance, NYHA class and exercise duration. There was statistically significant heterogeneity (p<0.05) for the following outcomes: LV posterior wall, LV mass and LVEF.

Funnel plots and linear regression suggested that there might be selection bias for two outcomes: LVEF (p=0.003) and exercise duration (p=0.022).

The results of subgroup and regression analyses were also reported.

In terms of major adverse events, no significant differences were observed between the intervention and placebo groups in the incidence of death, worsening of heart failure or ventricular arrhythmias: 2.8% versus 2.1%, 6.1% versus 9.3% and 2.0% versus 0%, respectively.

Authors’ conclusions
Sustained treatment with GH improves several cardiovascular parameters in adults with CHF. However, more randomised evidence is needed.

CRD commentary
The objectives and inclusion criteria were clear. Relevant sources were searched and efforts were made to retrieve unpublished studies. Steps were taken to minimise error and bias in the validity assessment and data extraction by having more than one reviewer make decisions independently; however, it is not clear whether this also applied to the study selection process. Relevant quality criteria were considered, but few details about the individual studies were reported. The design of the open studies was not clear: these studies were apparently uncontrolled and it is unclear whether it was appropriate to pool their findings with the RCTs. The analyses based solely on RCTs seem more likely to be reliable, but it is difficult to interpret the clinical significance of the positive findings in view of the very large number of outcomes measured, the lack of pre-specified primary outcomes and the small sample sizes. It is also unclear whether the RCT-only analyses were statistically homogeneous. Although the authors’ conclusions are supported by the data presented, they fail to reflect that, for a large majority of outcomes, the randomised studies found no evidence of benefit from GH.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that a large placebo-controlled RCT of long-term high-dose GH is needed, with haematological, morphological and functional outcome measures.

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