Growth hormone therapy in congestive heart failure due to left ventricular systolic dysfunction: a meta-analysis
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CRD summary
This review concluded that recombinant human growth hormone had some benefit in people with heart failure due to left ventricular dysfunction, but increased left ventricular mass. Evidence came from a mix of small controlled and uncontrolled studies. The controlled studies showed little treatment effect, which suggests that the conclusions should be treated with extreme caution.

Authors' objectives
To assess the effects of exogenous recombinant human growth hormone (rhGH) in people with congestive heart failure caused by systolic dysfunction.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched to June 2006. Search terms were reported. No language restrictions were applied. Reference lists of identified studies and reviews were checked.

Study selection
Studies that examined the effects of rhGH in adults with congestive heart failure caused by systolic dysfunction were eligible for inclusion. Studies that lasted only several hours were excluded. Studies with fewer than five participants were excluded. Outcomes of interest were clinical outcomes (exercise duration, New York Heart Association (NYHA) class, heart rate, systolic and diastolic blood pressure), haemodynamic variables (cardiac output, systemic vascular resistance) and echocardiographic indices (left ventricular mass, interventricular septum thickness, posterior wall thickness), systolic function (left ventricular end-diastolic dimension (EDD), end systolic dimension (ESD), left ventricular ejection fraction (LVEF), end-systolic wall stress (ESS)) and diastolic function (isovolumic relaxation time and early to atrial wave (E/A) ratio). Changes in serum insulin like growth factor 1 (IGF-1) level and safety endpoints (death, congestive heart failure exacerbation, ventricular tachycardia) were reported.

In the included studies aetiology of congestive heart failure was dilated or ischaemic cardiomyopathy, Chagas’ disease, hypertension and Becker muscular dystrophy. Mean age of participants ranged from 28 to 65 years. More men than women were included. Mean NYHA class was 2.5 (0.5 standard deviation) and mean LVEF was 25.7% (4.75 standard deviation). rhGH was given subcutaneously daily or every other day at a dosage of seven to 56 units per week. Participants were also took standard medications for congestive heart failure. Duration of therapy was from one to six months.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Quality was assessed in terms of inclusion and exclusion criteria, definitions of endpoints, randomisation, blinding, follow-up, data analysis and presentation.

The authors did not state how many reviewers performed quality assessment.

Data extraction
The authors did not state how outcome data were extracted for the review.

Methods of synthesis
Standardised mean differences (SMD) and 95% CIs and weighted mean differences (WMD) and 95% CI were
calculated for each outcome using a random-effects model.

Statistical heterogeneity was assessed with the Cochran Q test and investigated by subgroup analyses based on study design (controlled, uncontrolled) and duration of therapy (up to three months, more than three months). Sensitivity analyses were performed by removal of studies responsible for asymmetry in funnel plots. Metaregression was used to examine the association between rhGH effects on increase in IGF-1 and cardiovascular efficacy endpoints.

Publication bias was assessed using funnel plots and calculation of fail-safe n.

Results of the review
Fourteen studies (212 people) were included: six were placebo controlled parallel RCTs (139 participants); one was a crossover RCT (12 participants); one was a placebo controlled non-RCT (20 participants); and six were uncontrolled studies (41 participants). Study size ranged from five to 50 participants. All were considered good quality in terms of inclusion/exclusion criteria, adequacy of follow-up, data analysis and presentation, but no further details were provided. Most studies had no withdrawals; four studies had between one and five withdrawals.

There was a discrepancy between statistics used in the text (WMD) and forest plots (SMD) and we have used those reported in the forest plots.

There was evidence of heterogeneity for the outcomes exercise duration, NYHA class, systolic blood pressure, left ventricular mass, EDD, ESD, LVEF, ESS and E/A ratio. For most of these statistical heterogeneity could be explained by study design (controlled versus uncontrolled). Funnel plots showed evidence of publication bias for the outcomes cardiac output, EDD and LVEF. For all outcomes fail safe n ranged from two to 62 studies.

Compared to placebo, treatment with rhGH showed an increase in exercise duration (SMD 1.9 minutes, 95% CI 1.1 to 1.27 minutes; six studies), decrease in NYHA class (SMD -0.9, 95% CI -1.5 to -0.3; seven studies), increase in maximum oxygen uptake (SMD 2.1 mL/kg/min, 95% CI 1.2 to 3; four studies) and increase in LVEF (SMD 4.3% 95% CI 2.2 to 6.4; 13 studies). There were also improvements in cardiac output (SMD 0.4L/min, 95% CI 0.1 to 0.6; six studies) and systemic vascular resistance (SMD -177 dyn.s/cm$^5$, 95 CI -279 to -74; four studies). Other effects were: left ventricular mass, interventricular septum thickness, posterior wall thickness and decreases in EDD, ESD and ESS. There were no significant effects on heart rate, systolic and diastolic blood pressure, isovolumic relation time and E/A ratio.

Sensitivity analyses did not significantly alter the findings.

For safety endpoints, there was an increased risk of ventricular arrhythmia with rhGH (p=0.48). There was no statistical difference in risk of death or congestive heart failure exacerbations between those on rhGH and placebo.

Subgroup analyses showed contradictory findings between controlled and uncontrolled studies and between shorter and longer term studies (see paper for details), which suggested that study design and treatment duration may have influenced some of the treatment effects.

Metaregression showed a significant association between an increase in IGF-1 and a decrease in NYHA class and increases in LVEF and left ventricular mass, but no association between IGF-1 and exercise duration.

Authors' conclusions
There was some evidence of benefit from rhGH in people with congestive heart failure due to left ventricular systolic dysfunction, which included beneficial effects on clinical and haemodynamic endpoints and systolic cardiac function. An increase in left ventricular mass raised concerns about long-term effects. There was a need for further research to fully elucidate the efficacy and safety of rhGH therapy in this patient population.

CRD commentary
The aims of the review were clearly stated in terms of inclusion criteria for participants, treatment and outcomes. The search covered several relevant sources without language restrictions. There was some evidence of publication bias
according to funnel plots. Methods of study selection, data extraction and quality assessment were not described and it was not possible to say whether efforts were made to eliminate reviewer error or bias. Quality was assessed, but details were not presented and so it was difficult to comment on the quality of included data. Statistical heterogeneity was present and attributed mainly to differences in study design and treatment duration. The included studies were a mixture of controlled and uncontrolled trials and it may not have been appropriate to combine these results. In subgroup analyses there was no evidence of any effect in the controlled studies (generally considered to be a better quality design than uncontrolled studies). Study sizes were small.

Given potential for bias in the review and the limitations with the included studies, the authors’ conclusions about efficacy of rhGH in patients with congestive heart failure should be interpreted with extreme caution; their recommendation for further research seems appropriate.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that there was a need for larger RCTs of longer treatment duration to assess safety and efficacy of rhGH in people with congestive heart failure. These should include assessment of any effects on left ventricular mass and development of arrhythmias. Cost-benefit analysis was needed.

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