Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis


CRD summary
The review found that growth hormone (GH) therapy in adults with GH deficiency reduced weight and body fat, and increased lean body mass, oedema and joint stiffness. Limitations of the review process and reporting, and the presence of significant publication bias for the main outcomes, mean that the results should be interpreted with caution.

Authors' objectives
To evaluate the efficacy and safety of growth hormone (GH) in adult patients with GH deficiency.

Searching
MEDLINE, EMBASE, The Cochrane Library, Web of Science, Scopus, PsycINFO and CINAHL were searched to April 2011 for published articles. Reference lists of identified studies were reviewed for additional studies. Experts were contacted to request information on potentially eligible published and unpublished trials.

Study selection
Randomised, placebo-controlled trials of GH in adult patients with GH deficiency, which lasted for at least three months, were eligible for inclusion. Studies of patients with conditions associated with GH deficiency, such as obesity, were excluded. Efficacy outcomes eligible for inclusion were health-related quality of life, changes in body composition, BMI and skeletal mass. Safety outcomes were clinically significant hyperglycaemia, hypertension, dyslipidaemia, clinically significant oedema, joint stiffness, carpal tunnel syndrome, cardiovascular events and tumour occurrence or recurrence.

Included studies were of GH (synthetic or recombinant human GH) in patients with child or adult onset growth hormone deficiency, or multi-pituitary hormone deficiency. The method for diagnosing hormone deficiency varied across studies. GH dosages and regimens were given in the review. The duration of treatment ranged from three weeks to 24 months; follow-up ranged from three to 24 months. Where reported, participant age ranged from 17 to 79 years (or if reported, the mean age ranged from 23.8 to 68 years) and the proportion of males ranged from 0 to 100%. Baseline insulin-like growth factor 1 (IGF-1) levels ranged from 1.24 to 381ug/L, where reported. Reported side-effects were recorded. Quality of life was measured with a variety of different outcome measures. Approximately half of the included studies were funded at least in part by a for-profit organisation.

Two reviewers independently selected studies for the review; disagreements were resolved by consensus or arbitration.

Assessment of study quality
Two reviewers used the GRADE approach to independently assess study levels of evidence. Disagreements were resolved by consensus or arbitration. Brief details of loss to follow-up, blinding, methods of randomisation and allocation concealment were given in the review.

Data extraction
Mean differences between GH and placebo groups were calculated for continuous outcomes. For dichotomous outcomes, the number of events in each group was extracted and used to calculate the risk ratios (RR) with 95% confidence intervals (CI). Authors were contacted if clarification of published data was needed.

Two reviewers extracted the data; disagreements were resolved by consensus or arbitration.

Methods of synthesis
The data were combined using DerSimonian and Laird random-effects models. For continuous outcomes, weighted mean differences (WMD) with 95% confidence intervals were calculated. For dichotomous outcomes, pooled risk ratios with 95% confidence intervals were calculated. Publication bias was assessed using funnel plots. Heterogeneity
was assessed using $I^2$. A priori subgroup analyses assessed the effect of: the degree of loss to follow-up; the quality of the allocation concealment and child versus adult onset of disease. Post-doc meta-regression was used to assess the effect of GH dose, baseline IGF-1 and duration of GH treatment.

Meta-analysis was not possible for the quality of life outcomes; results were reported as significant or not for each outcome per trial.

Results of the review
The review included 54 studies (3,438 patients). Only ten of these trials had over 100 patients. The overall quality of the studies was fair. There was significant evidence of publication bias for the following outcomes: weight, lean body mass and carpal tunnel syndrome.

Quality of life: Five out of sixteen trials found that GH was associated with a statistically significant improvement in at least one quality of life measure compared with placebo.

Body composition: GH was associated with a reduction in body weight (WMD -2.31kg, 95% CI -2.66 to -1.96) with no evidence of heterogeneity. There was an increase in lean body mass (WMD 1.38kg, 95% CI 1.10 to 1.65) but heterogeneity for this outcome was not reported. It was not clear how many studies these analyses were based on. GH was associated with a reduction in body fat content (WMD -2.56kg, 95% CI -2.97 to -2.16) based on 30 comparisons in 29 trials (1,207 patients). This analysis showed significant heterogeneity between studies, $I^2=73.7\%$. Meta-regression showed that some of this heterogeneity was due to differences in follow-up, baseline IGF-I and GH dose. GH did not significantly affect BMI or bone mineral density.

Adverse effects: GH was associated with a higher risk of oedema (RR 6.07, 95 %CI 4.34 to 8.84) and joint stiffness (RR 4.17, 95% CI 1.40 to 12.38). There were no significant effects of GH on other safety outcomes, although subgroup analyses showed that excluding the study which did not report allocation concealment resulted in a pooled risk ratios for carpal tunnel syndrome of 5.83 (95% CI 1.30 to 26.06).

Authors’ conclusions
Growth hormone (GH) treatment in adults with GH deficiency reduced weight and body fat and increased lean body mass, oedema, joint stiffness and, probably, quality of life.

CRD commentary
The review addressed a clear question, with well-defined inclusion criteria. Several databases were searched in an attempt to identify all relevant studies, including sources of unpublished studies, but there was evidence of publication bias in the results. No language restrictions appeared to have been applied, which reduced the potential for language bias. Two reviewers performed the study selection, data extraction and validity assessment, which reduced the potential for reviewer bias and error.

The quality of the included trials was assessed, but this was not sufficiently reported in detail. Adequate details of the included trials were provided. Appropriate methods were used to pool the results and to investigate statistical heterogeneity. The results of the meta-regression did not allow the reader to assess the direction of effect of the explanatory variables on the pooled outcomes. The quality of life results were not pooled and were synthesised only using a vote-counting approach, which relied too heavily on statistical significance. For some outcomes, insufficient details of the results were provided in the review. The authors acknowledged some limitations of the review, such as the potential for outcome reporting bias and heterogeneity in the quality of life measures.

Limitations of the review process and reporting, and the presence of significant publication bias for the main outcomes, meant that the results should have been interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice, but did state that the clinical implications of the reported reductions in weight and body fat content in GH deficient adults were unknown.

Research: Further RCTs, either placebo-controlled or comparisons of GH to other active treatments, of homogenous groups of GH deficient patients with long-term follow-up were required to assess mortality, cardiovascular events,
fractures and quality of life.

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