Systematic review: the safety and efficacy of growth hormone in the healthy elderly


CRD summary
This review concluded that limited randomised controlled trials suggest that growth hormone is associated with small changes in body composition and increased rates of adverse effects; as such it cannot be recommended as an anti-aging therapy. This was generally a well-conducted review and the authors’ cautious conclusions seem appropriate.

Authors' objectives
To determine the efficacy and safety of growth hormone (GH) in the healthy elderly.

Searching
MEDLINE and EMBASE were searched for studies published in English until November 2005; the search terms were reported. The bibliographies of articles identified from the search were checked for additional studies.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that evaluated at least 10 participants were eligible for inclusion.

Specific interventions included in the review
Studies that compared injectable GH therapy with no GH therapy, or injectable GH plus lifestyle interventions (exercise with or without diet) with lifestyle interventions alone, were eligible for inclusion. Trials had to provide GH for 2 weeks or more to be included. Studies that only evaluated GH-releasing factor, other GH secretagogues, or insulin-like growth factor-1 were excluded. The GH interventions varied across the included studies. The initial daily dose of GH ranged from 1.7 to 43 microg/kg body weight (mean 14.3), while the final daily dose ranged from 1.7 to 25 microg/kg (mean 11.2). Treatment duration ranged from 2 to 52 weeks (mean 26.6). All trials that incorporated a lifestyle intervention included an exercise programme with at least 3 sessions per week. The majority of these incorporated resistance training in their exercise protocols; one study also incorporated a concurrent low-calorie, low-fat diet.

Participants included in the review
Studies of participants living in the community, with a mean age of 50 years or more and a body mass index (BMI) of 35 kg/m2 or less, were eligible for inclusion. Studies that explicitly included patients with diabetes mellitus, cardiac disease, thyroid disease, osteoporosis or cancer were excluded, as were studies that looked at specific clinical populations (e.g. participants with GH deficiency, HIV wasting syndrome, renal failure or critical illness). The participants in the included studies had a mean age of 68 years and were overweight (mean BMI 27kg/m2). Thirty-three per cent of the participants were women.

Outcomes assessed in the review
Studies had to provide data on at least one clinical outcome of interest (body composition, strength or functional capacity, bone dynamics, cardiovascular risk factors, insulin resistance markers, quality of life or depression scales, or adverse events) to be included in the review.

How were decisions on the relevance of primary studies made?
One author reviewed the titles and abstracts of articles identified from the search and retrieved potentially relevant studies. Two physicians independently reviewed each study.

Assessment of study quality
Studies were assessed according to eight criteria: quality of randomisation; use of a placebo; allocation concealment; eligibility criteria specified; blinding of the participants and clinicians; point estimates and variability presented; intention-to-treat analysis performed. Two reviewers independently assessed the validity of the studies.
Data extraction
Two reviewers independently extracted the data onto pre-tested extraction forms. If the studies provided insufficient data for analysis, mentioned results but did not provide them, or presented data graphically, authors were contacted for additional data. Data on fat-free mass and lean body mass were combined to form one category of lean body mass. A change score was calculated for each clinical outcome in each trial, calculated as the outcome at the end of the trial minus the outcome at the start of the trial. If studies reported standard errors they were converted to standard deviations. For studies that did not report the variance of an outcome at the end of the trial minus that at the start of the trial, it was calculated (details provided). The proportions of adverse events among study participants who received or did not receive GH therapy were calculated for each adverse event.

Methods of synthesis
How were the studies combined?
Change scores were used to calculate the weighted mean difference (WMD) for each efficacy outcome. WMDs were pooled in a meta-analysis using the DerSimonian and Laird inverse variance-weighted random-effects model. The mean proportions of participants experiencing each of the adverse events across the studies were calculated. Publication bias was assessed using funnel plots for each clinical outcome.

How were differences between studies investigated?
Heterogeneity was assessed using the I-squared statistic. For body composition outcomes, sources of heterogeneity were investigated in subgroup analyses: separate summary effect sizes were calculated for studies of groups receiving and not receiving GH; studies of GH plus lifestyle interventions versus studies of lifestyle interventions alone; studies in which researchers administered GH for less than 26 weeks versus those in which GH was administered for 26 weeks or more; studies that only evaluated men versus those that only evaluated women. Sensitivity analyses were carried out by removing each study individually to evaluate its effect on the results, and by altering the correlations between the mean baseline and mean end-of-trial measures.

Results of the review
Eighteen RCTs (n=508) were included in the review.

No study met all of the quality criteria. The numbers of quality criteria fulfilled ranged from 3 to 7 out of 8. Study sizes were small (mean 28 participants) and some had high drop-out rates.

The funnel plots did not suggest the presence of publication bias.

Efficacy.
There was no statistically significant difference in weight loss between participants who did and did not receive GH. Participants who received GH showed a significant reduction in fat mass (-2.08 kg, 95% confidence interval, CI: -2.80, -1.35) and increase in lean body mass (2.13 kg, 95% CI: 1.32, 2.94) relative to participants not receiving GH.

There was no significant difference in body composition outcomes between participants receiving GH with and without a lifestyle intervention. Based on one study, participants treated with GH alone showed a significant 2.2-kg reduction in lean body mass compared with participants who received exercise therapy alone. However, the decrease in fat mass did not differ between the groups.

There were no significant differences in body composition outcomes between studies that administered GH for 26 weeks and those that administered it for less than 26 weeks. When only those studies administering GH therapy for at least 12 or 26 weeks were analysed, the results did not change. Women treated with GH showed no significant increase in lean body mass, but a borderline statistically significant decrease in fat mass, compared with women not treated with GH. Men treated with GH showed significant improvements in body mass and fat mass.

There was no statistically significant difference in total cholesterol levels between groups after adjustment for decrease in fat mass. There were no statistically significant differences between treatment groups for any other outcomes.

The included studies for measures of weight and fat mass showed little heterogeneity, whereas those for lean body mass...
did show heterogeneity (I-squared 41%). Heterogeneity for this outcome was particularly high for studies that evaluated women, provided GH alone without lifestyle intervention, or provided GH therapy for 26 weeks or more. The I-squared statistic was greater than 50% for femoral neck bone density and for triglyceride, fasting glucose and fasting insulin levels.

Safety.

Participants receiving GH had significantly higher rates of adverse events (including soft tissue oedema, carpal tunnel syndrome, arthralgias and gynaecomastia) than those not receiving GH. Women receiving GH were more likely to experience oedema than men receiving GH. Higher rates of glucose metabolism-related adverse events were reported in participants receiving GH compared with those not receiving GH, but this finding was not statistically significant.

Results of the sensitivity analyses were also reported.

**Authors' conclusions**

The RCTs of GH therapy in the healthy elderly are limited but suggest that it is associated with small changes in body composition and increased rates of adverse effects. Given this evidence, GH cannot be recommended as an anti-aging therapy.

**CRD commentary**

The authors set out a clear objective, and inclusion criteria were defined for the participants, interventions, outcomes and study design. Two appropriate databases were searched. However, the search was restricted to studies published in English, which increases the risk of relevant studies being missed. Publication bias was assessed but not detected. Validity was assessed using appropriate criteria and measures were taken to reduce the risk of error and bias at all stages of the review process. The statistical methods used to pool the studies appeared appropriate; however, the included studies were small, which suggests that the analyses might have been underpowered. Statistical heterogeneity was assessed, and possible causes were investigated. This was generally a well-conducted review; the authors’ cautious conclusions and acknowledgement of the limitations of the evidence seem appropriate.

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

Practice: The authors stated that GH cannot be recommended for use in the healthy elderly.

Research: The authors stated the need for further research to assess the differential effects of exercise and GH on body composition measures.

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