Effects of recombinant human growth hormone therapy in obesity in adults: a metaanalysis

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CRD summary
The authors concluded that recombinant human growth hormone therapy was associated with a reduction in total and visceral adiposity, an increase in lean body mass and favourable changes in lipid profile, but not in overall body weight. Given the uncertainty around the quality of included studies and the suitability of the analyses, the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the effectiveness and safety of recombinant human growth hormone (rhGH) in patients with obesity not associated with distinct clinical syndromes or classical endocrinopathies.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched from inception until December 2007 for articles in any language. Search terms were reported. Reference lists of retrieved articles and review articles were handsearched.

Study selection
Studies of recombinant human growth hormone in obese adults with at least five participants and lasting for more than two weeks were eligible for inclusion. Studies of children, adolescents, lean elderly or participants with growth hormone deficiency, syndromic obesity, HIV lipodystrophy or classical endocrinopathies were excluded. Outcomes eligible for inclusion were body weight, body mass index, waist to hip ratio, fat mass, percentage of weight lost as fat, lean body mass, visceral adipose tissue area, subcutaneous adipose tissue area, thigh muscle area, resting energy expenditure, respiratory quotient, systolic and diastolic blood pressure, serum concentrations of IGF-1, leptin, fasting lipid profile, fasting plasma glucose, insulin, glycosylated haemoglobin (HbA1c) and the homeostasis model assessment index of insulin resistance (HOMA-1R).

Included studies were of recombinant human growth hormone in dosages ranging from 2 mg/week to 41 mg/week administered daily or every other day compared to placebo in participants with a mean body mass index ranging from 28 to 42 kg/m². In 15 studies participants were also placed on a hypocaloric diet. In four studies participants were also given an exercise regime. The mean age of participants ranged from 25.4 years to 67.5 years. Reported side effects were recorded. The duration of included studies ranged from three weeks to 72 weeks.

The authors stated neither how the studies were selected for the review nor how many reviewers performed the study selection.

Assessment of study quality
Two reviewers evaluated study quality according to inclusion and exclusion criteria, study design, randomisation, blinding, definition of endpoints, adequacy of follow up, data analysis and presentation. The reviewers did not use a scoring system.

Data extraction
Mean differences between intervention and placebo conditions were calculated for each continuous outcome. For dichotomous outcomes, the number of events in each group was extracted and used to calculate the odds ratios with 95% confidence intervals. The change in serum IGF-1 was calculated as a fold increase over baseline. Two reviewers extracted the data.

Methods of synthesis
The results were combined in a DerSimonian and Laird random-effects model. For continuous outcomes, a weighted mean difference (WMD) with 95% CI was calculated. The studies were weighted according to the inverse of the
variance. Standardised mean differences were also calculated with 95% confidence intervals. Pooled odds ratios with 95% confidence intervals were calculated for dichotomous outcomes. Statistical heterogeneity was assessed using the Cochran Q and I² statistic. Subgroup and meta-regression analyses were conducted to investigate the role of potential covariates. Publication bias was assessed using funnel plots and the trim and fill method.

**Results of the review**

Twenty four articles were included for the review (n=539): 16 double blind randomised controlled trials (n=438); one single blind randomised controlled trial (n=20); one randomised controlled trial (n=14); one double-blind crossover trial (n=9); four crossover trials (n=38); and one prospective placebo-controlled trial (n=20). The quality of included studies was reported to be good, but detailed information about individual studies was not provided. No evidence of publication bias was found.

The use of recombinant human growth hormone was associated with a significant reduction in: waist to hip ratio (five studies, n=137, weighted mean difference -0.01, 95% confidence interval -0.02, -0.001, p=0.027); fat mass (15 studies, n=325, weighted mean difference -0.9, 95% confidence interval: -1.3, -0.4, p<0.001); percentage of fat mass (13 studies, n=245, weighted mean difference -1.95% confidence interval: -1.3, -0.7, p<0.001); and visceral adipose tissue area (eight studies, n=190, weighted mean difference -22.8, 95% confidence interval: -39.8, -5.7, p=0.009) compared to placebo.

The percentage of weight lost as fat (six studies, n=72, weighted mean difference 0.15, 95% confidence interval: 0.10, 0.19, p<0.001) and the lean body mass (16 studies, n=332, weighted mean difference 1.8, 95% confidence interval: 0.6, 2.9, p=0.003) increased significantly with the use of recombinant human growth hormone compared to placebo.

The use of recombinant human growth hormone was associated with significant decreases in total cholesterol (13 studies, n=317, weighted mean difference -7, 95% confidence interval: -11, -3, p=0.001) and in low-density lipoprotein (nine studies, n=249, weighted mean difference -9, 95% confidence interval: -13, -5, p<0.001) compared to placebo.

Serum IGF-1 (20 studies, n=410, weighted mean difference 171, 95% confidence interval: 131, 212, p<0.001), fasting glucose (16 studies, n=324, weighted mean difference 3, 95% confidence interval: 1.6, p=0.004) and insulin concentration (14 studies, n=286, weighted mean difference 1.9, 95% confidence interval: 0.2, 3.7, p=0.037) all rose significantly with the use of recombinant human growth hormone compared to placebo.

There was no evidence of statistical heterogeneity for most outcomes; exceptions were IGF-1 and insulin concentration (both p<0.001). There were no significant differences between recombinant human growth hormone and placebo in body weight, body mass index, subcutaneous adipose tissue area, thigh muscle area, resting energy expenditure, respiratory quotient, systolic blood pressure, diastolic blood pressure, leptin, high-density lipoproteins, triglycerides, glycosylated haemoglobin or homeostasis model assessment index of insulin resistance.

The use of recombinant human growth hormone was associated with significantly increased risk of arthralgias (seven studies, n=169; odds ratio 6, 95% confidence interval: 1.9, 18.6, p=0.002), paresthesias (five studies, n=124; odds ratio 6.5, 95% confidence interval: 1.5, 27.3, p=0.011) and oedema (11 studies, n=305; odds ratio 5, 95% confidence interval: 2.4, 10.5, p<0.001). There were no incidents of study related deaths. There was no evidence of statistical heterogeneity.

Results of the meta-regression analyses were also reported

**Authors’ conclusions**

Recombinant human growth hormone therapy was associated with a significant reduction in total and visceral adiposity, an increase in lean body mass and favourable changes in lipid profile. It did not affect overall body weight. The use of recombinant human growth hormone was also associated with increases in fasting plasma glucose and insulinemia.

**CRD commentary**

The review addressed a clear question with well-defined inclusion criteria for intervention, participants and outcomes. Inclusion criteria for study design were not stated. Several relevant databases were searched for articles in any language, thereby minimising the risk of language bias. No attempts appeared to be made to identify unpublished data, however,
Publication bias was assessed and no evidence of it found. It was unclear whether appropriate steps were taken in the review process to minimise the risk of reviewer error and bias. Although study quality was assessed, the results were not reported in detail, so it was not possible for the reader to ascertain the quality of the included studies. It was unclear whether appropriate steps were taken combining parallel and crossover study designs in the pooling of results, therefore, the findings may be unreliable. Given the uncertainty around the quality of included studies and the suitability of the analyses, the reliability of the authors’ conclusions is unclear.

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

*Practice:* The authors stated that the observed effects were small and did not justify the use of recombinant human growth hormone given the high dosages used and the high cost of recombinant human growth hormone.

*Research:* The authors stated that further long-term adequately powered studies of the safety and efficacy of recombinant human growth hormone in obese adults were needed, particularly in relation to cardiovascular risk and glucose homeostasis. In future studies, participants should be carefully monitored and recombinant human growth hormone should be titrated to maintain serum IGF-1 levels within the age and gender-adjusted reference range.

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