EFFECTS OF RECOMBINANT HUMAN GROWTH HORMONE THERAPY IN OBESITY IN ADULTS - A META-ANALYSIS

Short title: Growth hormone therapy in obesity

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PRECIS: rhGH therapy decreases visceral adiposity, increases lean body mass and improves lipid profile in obese adults, without inducing weight loss

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ABSTRACT

**Objective:** To conduct a meta-analysis of human studies examining the efficacy and safety of recombinant human growth hormone (rhGH) as therapy for obesity in adults.

**Design:** A thorough search of the literature (including MEDLINE, EMBASE and the Cochrane Register) was performed for pertinent studies, which were analyzed and subsequently synthesized in a comprehensive meta-analysis.

**Results:** Administration of rhGH led to significant changes in body composition (weighted mean difference (95 % CI)), including fat mass (-0.9 kg (-1.3, -0.4)), percent body fat (-1% (-1.3, -0.7)), lean body mass (1.8 kg (0.6, 2.9)), visceral adipose area (-22.8 cm² (-39.8, -5.7)) and lipid profile, including total cholesterol (-7 mg/dl (-11, -3)) and LDL-cholesterol (-9 mg/dl (-13, -5)). There were increases in fasting plasma glucose (3 mg/dl (1, 6)) and insulin 1.9 mcU/ml (0.2, 3.7)). The latter finding was found only in shorter-term studies. Adverse effects included (OR, (95 % CI)) arthralgias (6 (1.9, 18.6)), peripheral edema (5, (2.4, 10.5)) and paresthesias (6.5 (1.5, 27.3)).

**Conclusions:** Our meta-analysis suggests that rhGH therapy leads to decrease in visceral adiposity and increase in lean body mass as well as beneficial changes in lipid profile in obese adults, without inducing weight loss. Administration of rhGH was associated with increases in fasting plasma glucose and insulinemia. As the rhGH doses used in many studies were supraphysiologic, future studies of longer duration, using carefully titrated rhGH protocols, will be needed in order to fully establish the effects of rhGH therapy in obesity, including effects on cardiovascular morbidity and mortality.
Abbreviations: BMI: body mass index; BW: body weight; CI: confidence interval; DBP: diastolic blood pressure; FG: fasting glucose; FM: fat mass; GH: growth hormone; rhGH: recombinant human growth hormone; GHRH: growth hormone releasing hormone; HDL-C: high density lipoprotein cholesterol; HOMA IR: homeostasis model assessment of insulin resistance; IGF-I: insulin-like growth factor I; LBM: lean body mass; LDL-C: low density lipoprotein cholesterol; LP (a): lipoprotein (alpha); REE: resting energy expenditure; RQ: respiratory quotient; SBP: systolic blood pressure; ST: subcutaneous adipose tissue; TC: total cholesterol; TG: total cholesterol; TM: thigh muscle area; VAT: visceral adipose tissue; WHR: waist to hip ratio; WLF: weight lost as fat

Key-words: Growth hormone, meta-analysis, obesity
Introduction

Obesity is associated with a major increase in morbidity and mortality (1). As the prevalence of obesity has been rapidly increasing, particularly in western countries, so has the unmet medical need for effective therapies for this condition. Despite major progress in our understanding of mechanisms involved in weight regulation, currently available medical therapies are of limited efficacy and uncertain long-term safety.

The endogenous secretion of growth hormone (GH) is decreased in obesity (2). Although the lipolytic and anabolic effects of GH are well-established, the pathophysiologic role of GH in obesity remains uncertain (2, 3).

The effects of recombinant human growth hormone (rhGH) in obesity and its associated cardio-metabolic risk factors, including body composition, lipid profile, blood pressure and glycemia, have been examined in several studies, leading to conflicting results (4).

In the current study we have conducted a comprehensive meta-analysis of clinical studies examining the efficacy and safety of rhGH therapy in patients with “simple” obesity (not associated with distinct clinical syndromes or classical endocrinopathies).

Methods

Studies

We searched 3 computerized databases for pertinent articles, including MEDLINE (PubMed), EMBASE, and the Cochrane Register of Controlled Trials. We used the keywords growth hormone (GH), somatotropin, somatropin, somatotrophin, somatrophin, obesity, adiposity and the Boolean functions AND, OR during searches. Study searches were not limited by language and included all available data from the day of the inception of each database until December 2007. We also searched the reference list of all published original articles we found, as well as several review articles for additional references.

We considered all human studies examining the efficacy and safety of rhGH administration in obese adult subjects. Publications arising from the same study group on the same patient cohort were considered as a single study for the purpose of analysis. We excluded studies of children or adolescents, healthy (lean) elderly, patients with GH deficiency, syndromic obesity (including Turner syndrome and Prader-Willi syndrome), HIV lipodystrophy or classical endocrinopathies (including Cushing’s syndrome), as the pathophysiology is different and the effects of rhGH may vary considerably in these populations. We also excluded very small studies (enrolling less than 5 subjects) or short-term studies (lasting for 2 weeks or less), which examined short-term metabolic effects of rhGH.

Data analysis

All studies included in the meta-analysis were reviewed by the 2 authors who extracted data on study design, year of publication, age and gender distribution of study subjects, baseline body mass index (BMI), rhGH target dose, duration and dosing regimen for rhGH used in each study, diet and additional medications prescribed and number of patients withdrawn. Study quality was examined by the 2 authors with regards to inclusion and exclusion criteria, study design, randomization, blinding, definition of endpoints, adequacy of follow-up, data analysis and presentation. However, studies were not scored for quality.

In the present meta-analysis we evaluated clinical endpoints, including body weight, BMI, waist to hip ratio (WHR), body composition (fat mass and lean body mass (LBM), visceral and subcutaneous adipose tissue area, thigh muscle area), blood pressure and calorimetry (resting energy expenditure (REE) and respiratory quotient (RQ)). We also examined endpoints based on laboratory data, including serum concentrations of insulin-like growth factor I (IGF I), leptin, fasting lipid profile, fasting plasma glucose (FPG), insulin, glycosylated hemoglobin (HbA1c) and the homeostasis model assessment index of insulin resistance (HOMA). Safety endpoints reported include arthralgias, paresthesias, peripheral edema,
glycemia as well as deaths and reasons for withdrawal from study. We recorded the change in serum IGF I during therapy (reported as fold increase over baseline) when available.

**Data synthesis**

The possibility of publication bias was investigated by examining the symmetry of funnel plots as well as Duval and Tweedie’s trim and fill analysis. In addition, we examined the presence of heterogeneity between studies using the Cochran Q test and the I^2 index (5). Subgroup analysis was pursued if heterogeneity was present (Q test p-value < 0.05) in order to investigate its origin.

In the present meta-analysis we employed a random effects (DerSimonian-Laird) model to estimate weighted mean differences for each endpoint examined, calculated as the mean difference between the 2 groups (rhGH-treated minus placebo). Use of the random effects model assumes that the true treatment effect may vary between studies and is therefore more conservative and appropriate to use when studies of different design and duration of follow-up are pooled (6). Each study was weighted by the inverse of its variance. We subsequently estimated the weighted mean differences between rhGH-treated and placebo groups and calculated the 95 % confidence interval (95 % CI) for each endpoint of interest. Standardized mean differences and the 95 % CI were similarly estimated. In addition, the odds ratio (OR) and 95 % CI were estimated for binary outcomes.

Using a mixed effects model, subgroup analysis was then conducted to investigate the origin of heterogeneity between studies and examine the modifying role of study-level covariates, including population age, gender, baseline BMI, rhGH dose, duration of rhGH therapy, increase in serum IGF I during therapy, diet and presence of glucose intolerance, on rhGH treatment effects. Meta-regression analysis was used to further investigate the association between these study-level covariates and rhGH treatment effects.

All statistical analyses were conducted using the statistical package Comprehensive Meta-Analysis (version 2.2.046, 2007, Biostat, Inc, Englewood, NJ). P values less than 0.05 were considered significant. Data are presented as mean ± SD, mean and 95 % CI, or mean and range, as appropriate.

**Results**

Our searches identified 2362 articles (Fig. 1). A total of 2325 publications were excluded for several reasons, including study type (animal, review, or non-interventional), population (GH deficiency, Prader-Willi syndrome, Turner syndrome, Cushing’s syndrome, HIV lipodystrophy, healthy elderly), small sample size (less than 5 subjects) or short duration (2 weeks or less). Of the remaining 37 publications, 13 articles included data from non-unique study cohorts and were therefore not considered as individual studies, leaving 24 articles describing separate study cohorts, which formed the basis of the present meta-analysis (Fig. 1) (7-30).

There were 18 randomized, parallel placebo-controlled studies (17 of which were double-blind), 5 cross-over placebo-controlled studies and 1 prospective placebo-controlled study (Table 1). These studies were thought to be of good quality, based on inclusion and exclusion criteria, definition of endpoints, follow-up, data analysis and presentation.

The clinical characteristics of study patients are shown in Table 1. There were a total of 539 subjects in 24 studies. Sixty-two subjects withdrew from participation, leaving 477 subjects who completed their study, whose data were reported in individual studies as well as the present meta-analysis. Mean age for study participants ranged between 25.4 to 67.5 years (median: 38 years), and their mean BMI ranged between 28 to 42 kg/m^2. Ten studies included only women and 4 studies included only men. Four studies enrolled subjects with glucose intolerance or type 2 diabetes mellitus.

Study subjects were allocated to rhGH therapy or placebo, administered daily or every other day, according to each study protocol. Treatment duration ranged between 3 to 72 weeks (median 11.5 weeks). A hypocaloric diet with or without exercise was prescribed to study subjects in 15 studies.

Body composition was estimated by different methods. Among 16 studies reporting data on LBM, dual energy X ray absorptiometry (DXA) was used in 8 studies, electrical bioimpedance in 5 studies, total
body potassium counting in 2 studies and hydrostatic weighing in 1 study. Among 15 studies reporting
data on total fat mass, DXA was used in 9 studies, electrical bioimpedance in 2 studies, total body
potassium counting in 2 studies, and hydrostatic weighing in 2 studies. Visceral and subcutaneous adipose
tissue areas as well as thigh muscle area were measured by computerized tomography.

No evidence of relevant publication bias was identified by examining the symmetry of funnel plots
as well as Duval and Tweedie’s trim and fill analysis (data not shown). As shown in Tables 2 and 3, the
results of Q test and $I^2$ index suggested that data were likely heterogeneous with regards to treatment
effects on several endpoints, including body weight, BMI, REE, RQ, systolic blood pressure (SBP),
diastolic blood pressure (DBP), IGF I, FPG and fasting insulin. The presence of heterogeneity further
justified the choice of the random effects model for pooling data and was subsequently explored in
appropriate subgroup analyses.

Efficacy endpoints

The results of the meta-analysis are summarized in Tables 2 and 3. These include weighted mean
differences between rh-GH- treated and placebo groups for each endpoint analyzed, as well as the 95 %
CI and P values.

We found a significant decrease in WHR, fat mass, percent body fat and visceral adipose tissue area,
as well as a significant increase in the percent weight lost as fat, in subjects allocated rhGH therapy
compared to those who received placebo (Table 2). There was a significant increase in LBM as well as a
(statistically non-significant) trend towards increase in thigh muscle area in rhGH-treated subjects
compared to placebo (Table 2). There were no significant differences in rhGH treatment effects on indices
of body adiposity and LBM across studies using different methods to estimate body composition (data not
shown).

There were no significant differences in body weight, BMI, subcutaneous fat area, REE, RQ, SBP
and DBP between rhGH-treated and placebo-treated subjects.

There were significant decreases in total and LDL cholesterol in rhGH-treated subjects compared
with controls (Table 3). In addition, there was a non-statistically significant decrease in serum leptin.
There were no significant changes in HDL cholesterol, LP(a) or serum triglycerides found between the 2
groups.

As anticipated, there was a significant increase in serum IGF I in rhGH-treated subjects (Table 3). In
addition, there was a small, but statistically significant, increase in fasting glucose and insulin
concentrations in rhGH-treated subjects compared with controls (Table 3). There were no significant
differences in HbA1c or HOMA-IR between the 2 groups.

On meta-regression analysis we found a positive association between LBM and rhGH dose (beta
coefficient: 0.089, 95 % CI: 0.045, 0.132, P<0.0001) and a positive association between fasting insulin
and rhGH dose (beta coefficient: 0.374, 95 % CI: 0.218, 0.531, P<0.0001). We also found a positive
association between fasting glucose and increase in serum IGF I during rhGH therapy (beta coefficient:
5.280, 95 % CI: 2.813, 7.748, P<0.0001).

Additional meta-regression analyses suggested a negative association between LDL cholesterol and
rhGH dose (beta coefficient: -0.267, 95 % CI: -0.462, -0.072, P=0.0073) as well as a negative association
between fasting insulin and duration of rhGH therapy (beta coefficient: -1.123, 95 % CI: -1.807, -0.440,
P=0.0013).

Subgroup analysis

To investigate sources of heterogeneity, we explored the possibility that study level covariates,
including age, gender, baseline BMI, rhGH dose and duration, diet, presence of glucose intolerance, and
serum IGF I increase on therapy, may influence rhGH treatment effects in study subgroups. We found
that age, rhGH dose and duration of treatment, as well as IGF I increase during treatment may influence
some of rhGH treatment effects.
We found that BMI decreased in response to rhGH therapy in studies of younger subjects (below median age, 38 yr); mean BMI difference (95 % CI): -1.15 kg/m$^2$ (-1.69, -0.60) in studies of younger subjects, versus 0.05 kg/m$^2$ (-0.03, 0.13) in studies of older subjects, P<0.001.

The dose of rhGH therapy had an effect on BMI, fasting insulin and serum IGF I. We found that BMI decreased in response to rhGH therapy in studies where higher target rhGH dose was used (above median dose, 31.1 units/week (10.4 mg/wk)); mean BMI difference: -1.18 kg/m$^2$ (-1.74, -0.62) in studies with rhGH dose above median, versus 0.05 kg/m$^2$ (-0.03, 0.13) in studies with rhGH dose below median, P<0.001. Fasting serum insulin increased in response to rhGH therapy in studies with rhGH dose above median; mean serum insulin difference: 3.5 mcU/ml (1.6, 5.6) (25.4 pmol/L (11.2, 39.6)) in studies with rhGH dose above median, versus -0.1 mcU/ml (-2.3, 2.1) (-0.7 pmol/L (-16.2, 14.8)) in studies with rhGH dose below median, P=0.015. Serum IGF I showed a trend towards a greater increase in response to rhGH therapy in studies with rhGH dose above median; mean serum IGF I difference: 202 µg/L (154, 249) (26.30 nmol/L (10.40, 24.70)) in studies with rhGH dose above median, versus 135 µg/L (80, 190) (17.55 nmol/L (10.40, 24.70)) in studies with rhGH dose below median, P=0.070.

The duration of rhGH therapy had an effect on total cholesterol and fasting serum insulin. Total cholesterol decreased in response to rhGH therapy of longer duration (above median, 11.5 weeks); mean total cholesterol difference: -8 mg/dl (-10, -6) (-0.21 mmol/L (-0.26, -0.16)) in studies with rhGH duration above median, versus 7 mg/dl (-5, 20) (0.18 mmol/L (-0.13, 0.52)) in studies with rhGH duration below median, P=0.014. Fasting serum insulin increased in response to rhGH therapy of shorter duration (below median); mean fasting serum insulin difference: 3.1 mcU/ml (1.4, 4.8) (22.3 pmol/L (9.9, 34.6)) in studies with rhGH duration below median, versus -0.6 mcU/ml (-2.9, 1.7) (-4.4 pmol/L (-20.8, 12.0)) in studies with rhGH duration above median, P=0.011.

The increase in serum IGF I during rhGH therapy had an effect on FPG. We found an increase in FPG in response to rhGH therapy associated with serum IGF I increase above median (two fold increase); mean FPG difference: 6 mg/dl (3, 8) (0.33 mmol/L (0.16, 0.44)) in studies with serum IGF I increase above median, versus 1 mg/dl (-2, 4) (0.06 mmol/L (-0.11, 0.22)) in studies with serum IGF I increase below median, P=0.022.

Safety endpoints

There were no study-related deaths reported. One male subject with known hypertension withdrew at 8 months from study because of cerebral hemorrhage (15). Reported side-effects included arthralgias, peripheral edema and paresthesias. We found significant increases in the OR for these 3 adverse effects in response to rhGH therapy (Table 4). Data on glucose homeostasis have been presented in Table 3.

Discussion

We have performed a meta-analysis of clinical studies examining the efficacy and safety of rhGH in obesity. This therapy may have beneficial effects on body composition, including a decrease in body fat and increase in LBM. In addition, rhGH therapy may improve body fat distribution, leading to a decrease in WHR and visceral adiposity. We also found that rhGH therapy may favorably affect lipid profile, leading to a decrease in total and LDL cholesterol. These benefits occurred regardless of concurrently recommended diet. However, these effects appear to be quantitatively small and would not justify a clinically relevant role for rhGH therapy in the treatment of visceral adiposity, particularly in view of the supraphysiologic rhGH dose used in many studies as well as the high cost of rhGH therapy. In addition, it is currently unknown whether the positive effects of rhGH therapy would translate into decreased cardiovascular morbidity and mortality in obese subjects.

Our findings suggest that rhGH therapy does not lead to significant weight loss in the obese. However, it is possible that rhGH therapy may lead to a decrease in BMI in younger subjects. As this finding was found on subgroup analysis, it should be interpreted with caution and would therefore require confirmation in future studies.
Overall, these data are consistent with the findings of GH administration to experimental animals, and likely reflect the lipolytic and anabolic (protein-sparing) effects of GH (31-34).

Similar mechanisms may apply to human obesity as well. Both spontaneous and evoked GH secretion is reduced in obese humans (35, 36). However, the pathophysiologic role of GH in obesity is not well established. Adults with growth hormone deficiency (GHD) have abnormalities in body composition, exercise tolerance, lipid profile, and increased cardiovascular risk, and show favorable effects in response to rhGH replacement (37-39). In aggregate, available data suggest a relevant role of GH in the regulation of body composition and cardiometabolic risk in adults with GHD and likely in obesity as well.

Any benefits of rhGH therapy should be viewed in the context of possible risks. The dose of rhGH administered in many studies was clearly supraphysiologic (median dose: 31.1 units/wk (10.4 mg/wk)). Not surprisingly, our data showed a clear association of rhGH therapy with arthralgias, peripheral edema and paresthesias, all well-established side-effects of rhGH administration (37, 38). In addition, there was a small increase in FPG and fasting insulinemia. The latter appeared to be mitigated in longer studies, perhaps reflecting improvement in visceral adiposity and insulin resistance, as has also been suggested in adults with GHD (37, 38). As relatively few studies included data on insulin resistance and overall glycemia, the effects of rhGH therapy on glucose homeostasis in obesity require further evaluation in long-term studies. To minimize risks, future studies of rhGH therapy in obesity should include careful monitoring and rhGH titration to maintain serum IGF I within the age and gender adjusted reference range.

A limitation of our study is the lack of data on cardiovascular morbidity, predicated by the lack of pertinent data in primary studies of rhGH therapy in obesity. Adequately powered, long-term studies are required in order to fully evaluate the risks and benefits of rhGH therapy in obesity, including its effects on cardiovascular risk in this population.

Stimulation of endogenous GH secretion by administration of GH releasing hormone (GHRH) or other GH secretagogues might also be effective in reducing visceral adiposity and improve cardiometabolic risk in obesity, as has been demonstrated in patients with HIV lipodystrophy (40). Since feedback inhibition of GH secretion by IGF I remains intact in subjects administered GHRH, this therapy may avoid GH excess and decrease overall risks associated with stimulation of somatotrophic axis. However, establishing the risks and benefits of this therapy in obesity will require further study.

In conclusion, the findings of the present meta-analysis suggest that rhGH therapy in obesity leads to a decrease in total and visceral adiposity, an increase in LBM and favorable changes in lipid profile, but does not affect overall body weight. However, the dose of rhGH administered in many studies was clearly supraphysiologic. Larger studies are needed to evaluate the effects of rhGH therapy on cardiovascular risk. Careful titration of rhGH dose to maintain serum IGF I in the reference range will be needed to minimize adverse effects of rhGH therapy, including hyperglycemia and hyperinsulinemia.
REFERENCES


8. Albert SG, Mooradian AD 2004 Low-dose recombinant human growth hormone as adjuvant therapy to lifestyle modifications in the management of obesity. J Clin Endocrinol Metab 89:695-701


dehydrogenase type 1 but has no effect upon fat mass in patients with simple obesity. J Clin Endocrinol Metab 88:2113-8


Figure Legend

**FIG. 1:** Results of searches for pertinent studies to be included in the meta-analysis
**TABLE 1.** Patient characteristics of studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>First author, yr</th>
<th>Study design</th>
<th>Age (yr)</th>
<th>Gender (%F/M)</th>
<th>BMI / % over IBW</th>
<th>No. of subjects</th>
<th>No. withdrawn</th>
<th>Approximate mean target rhGH dose [IU/wk (mg/wk)]</th>
<th>Concurrent Diet/ Exercise</th>
<th>Duration of therapy (weeks)</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clemmons et al, 1987 (10)</td>
<td>PC, crossover</td>
<td>34.4 (23 - 50)</td>
<td>62.5/37.5</td>
<td>23 - 67% over IBW</td>
<td>8</td>
<td>NR</td>
<td>67 (22.3)</td>
<td>Mild hypocaloric diet</td>
<td>3</td>
<td>%BF, BW, IGF-1, TBF</td>
</tr>
<tr>
<td>Snyder et al, 1988 (23)</td>
<td>PC</td>
<td>20 - 54</td>
<td>80/20</td>
<td>30 - 67% over IBW</td>
<td>20</td>
<td>NR</td>
<td>67 (22.3)</td>
<td>Moderate hypocaloric diet</td>
<td>11</td>
<td>%BF, BW, FG, FI, HDL, IGF-1, TBF, TC</td>
</tr>
<tr>
<td>Snyder et al, 1989 (24)</td>
<td>PC, crossover</td>
<td>21 - 49</td>
<td>100/0</td>
<td>32 - 75% over IBW</td>
<td>11</td>
<td>NR</td>
<td>67 (22.3)</td>
<td>VLCD</td>
<td>5</td>
<td>%BF, BW, FG, FI, FW, IGF-1, TBF</td>
</tr>
<tr>
<td>Snyder et al, 1990 (25)</td>
<td>PC, cross over</td>
<td>28.6 (18 - 37)</td>
<td>100/0</td>
<td>33 - 83% over IBW</td>
<td>8</td>
<td>NR</td>
<td>123 (41)</td>
<td>VLCD</td>
<td>5</td>
<td>%BF, BW, FG, FI, FW, IGF-1, TBF</td>
</tr>
<tr>
<td>Skaggs et al, 1991 (22)</td>
<td>R, DB, PC</td>
<td>36 ± 6.92</td>
<td>100/0</td>
<td>138 - 226% over IBW</td>
<td>12</td>
<td>NR</td>
<td>30 (10)</td>
<td>None</td>
<td>4</td>
<td>%BF, BW, FFM, FM, IGF-1, TBF, V02 MAX</td>
</tr>
<tr>
<td>Richelsen et al, 1994 (19)</td>
<td>DB, PC, cross-over</td>
<td>32 ± 8.68</td>
<td>100/0</td>
<td>34.5 ± 3.94</td>
<td>9</td>
<td>0</td>
<td>38 (12.7)</td>
<td>None</td>
<td>5</td>
<td>BMI, BW, FG, FI, FM, HDL, IGF-1, LBM, REE, RQ, TC, TG, TMA, TP, VAT, TBF</td>
</tr>
<tr>
<td>Drent et al, 1995 (11)</td>
<td>R, DB, PC</td>
<td>39.1± 7.9(GH)</td>
<td>87/13</td>
<td>35.1 ± 2.3 (GH)</td>
<td>20</td>
<td>5</td>
<td>42 (14)</td>
<td>VLCD</td>
<td>8</td>
<td>BW, DBP, FG, FI, FM, IGF-1, LBM, SBP, TBF</td>
</tr>
<tr>
<td>Snyder et al, 1995 (26)</td>
<td>Prospective,</td>
<td>39 (25-49)</td>
<td>NR</td>
<td>32 - 71% over</td>
<td>11</td>
<td>NR</td>
<td>62 (20.7)</td>
<td>Moderate</td>
<td>4</td>
<td>%BF, BW, FG, FI, FM, FW, IGF-1</td>
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<tr>
<td>Study</td>
<td>Treatment</td>
<td>Baseline</td>
<td>Initial Weight</td>
<td>Change</td>
<td>BMI</td>
<td>Weight</td>
<td>IGF-1</td>
<td>LDL</td>
<td>HDL</td>
<td>TG</td>
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<tr>
<td>Johannsson et al, 1997</td>
<td>R, DB, PC</td>
<td>58.1±4.9</td>
<td>0/ 100</td>
<td>30.1±2.8 (GH)</td>
<td>30</td>
<td>1</td>
<td>20 (6.7)</td>
<td>None</td>
<td>36</td>
<td>BMI, BW, DBP, FG, FFM, FL, HDL, IGF-1, L, LDL, LPa, REE, SCA, TBF, TC, VAT</td>
</tr>
<tr>
<td>Thompson et al, 1998</td>
<td>R, DB, PC</td>
<td>69 ± 7 (GH)</td>
<td>100/ 0</td>
<td>30.7±2.3 (GH)</td>
<td>16</td>
<td>2</td>
<td>42 (14)</td>
<td>Mild hypocaloric diet; endurance exercise / weight training</td>
<td>12</td>
<td>%BF, BW, ECF, FFM, FM, HDL, IGF-1, LDL, REE, TBF, TC, VO2 MAX</td>
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<tr>
<td>Tagliaferri et al, 1998</td>
<td>R, SB, PC</td>
<td>25.4±4.78</td>
<td>100/ 0</td>
<td>35.9±1.56 (GH)</td>
<td>20</td>
<td>NR</td>
<td>57 (19)</td>
<td>VLCD</td>
<td>4</td>
<td>BMI, BW, IGF-1, LBM, L, REE, TBF, TG, TC</td>
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<tr>
<td>Kim et al, 1999 (16)</td>
<td>R, DB, PC</td>
<td>37.5±31 (GH)</td>
<td>91/ 9</td>
<td>29.4±9.68 (GH)</td>
<td>24</td>
<td>0</td>
<td>9 (3)</td>
<td>Mild hypocaloric diet</td>
<td>12</td>
<td>%BF, FFA, FW, IGF-1, LBM, SCA, TBF, TMA, VAT</td>
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<tr>
<td>Richelsen et al, 2000</td>
<td>R, DB, PC</td>
<td>35.3±10.7 (GH)</td>
<td>100/ 0</td>
<td>42.4±7 (GH)</td>
<td>18</td>
<td>NR</td>
<td>32 (10.7)</td>
<td>VLCD</td>
<td>4</td>
<td>%BF, BMI, BW, FFM, FL, HDL, IGF-1, LBM, L, REE, RQ, TBF, TC, TG, VO2 MAX</td>
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<td>Vestergaard et al, 2000</td>
<td>R, DB, PC</td>
<td>33.8±9.4 (GH)</td>
<td>100/ 0</td>
<td>41.1±6.3 (GH)</td>
<td>20</td>
<td>3</td>
<td>33 (11)</td>
<td>VLCD</td>
<td>8</td>
<td>BW, IGF-1, LBM, TBF</td>
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<tr>
<td>Nam et al, 2001 (17)</td>
<td>R, DB, PC</td>
<td>47.3±18.6 (GH)</td>
<td>40/ 50</td>
<td>28±7.8 (GH)</td>
<td>18</td>
<td>0</td>
<td>11 (3.7)</td>
<td>Mild hypocaloric diet</td>
<td>12</td>
<td>FG, FL, FW, HBA1C, HDL, IGF-1, LBM, LDL, SCA, TBF, TC, TMA, VAT</td>
</tr>
<tr>
<td>Tomlinson et al, 2003</td>
<td>R, DB, PC</td>
<td>38.8±12.88 (GH)</td>
<td>54/ 46</td>
<td>35.2±3.64 (GH)</td>
<td>24</td>
<td>5</td>
<td>8 (2.7)</td>
<td>None</td>
<td>32</td>
<td>BMI, IGF-1, LBM, TBF, TC, WHR</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Gender</td>
<td>Baseline</td>
<td>Baseline (P)</td>
<td>Baseline (male)</td>
<td>Baseline (female)</td>
<td>Study Intervention Details</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------</td>
<td>--------</td>
<td>----------</td>
<td>-------------</td>
<td>----------------</td>
<td>------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herrmann et al, 2004</td>
<td>R, DB, PC</td>
<td>0/100</td>
<td>55 ± 6</td>
<td>54.3 ± 4.6</td>
<td>54.4 ± 5.7 (P)</td>
<td>54.3 ± 2.5 (P)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albert et al, 2004 (8)</td>
<td>R, DB, PC</td>
<td>74/26</td>
<td>54.4 ± 5.7 (P)</td>
<td>35 ± 6 (GH)</td>
<td>36.6 ± 4.6 (GH)</td>
<td>37.3 ± 5.4 (P)</td>
<td>Mild hypocaloric diet and exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sartorio et al, 2004 (21)</td>
<td>R, PC</td>
<td>1/00</td>
<td>68.2 ± 3.3 (GH)</td>
<td>66.5 ± 4.1 (P)</td>
<td>39.5 ± 3.3 (GH)</td>
<td>38.9 ± 2.6 (P)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Franco et al, 2005 (12)</td>
<td>R, DB, PC</td>
<td>0/100</td>
<td>57.3</td>
<td>58.2 (GH)</td>
<td>30 ± 3.12 (GH)</td>
<td>30 ± 3.57 (P)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahn et al, 2006 (7)</td>
<td>R, DB, PC</td>
<td>50/50</td>
<td>53.7 ± 7.2</td>
<td>53.1 ± 7.2</td>
<td>28.3 ± 4.1 (GH)</td>
<td>28.1 ± 3 (P)</td>
<td>Mild hypocaloric diet and 200 kcal/day exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halpern et al, 2006 (13)</td>
<td>R, DB, PC</td>
<td>0/100</td>
<td>54.2 ± 7.1 (P)</td>
<td>35.9 ± 7.48 (GH)</td>
<td>39.2± 5.6 (GH)</td>
<td>38.4± 7 (P)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atallah et al, 2007 (9)</td>
<td>R, DB, PC, 2x2 factorial</td>
<td>34/66</td>
<td>55.1 ± 10.5 (GH)</td>
<td>55.1 ± 8.5 (P)</td>
<td>37.4± 8.1 (GH)</td>
<td>34.5± 5.8 (P)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pasarica et al, 2007 (18)</td>
<td>R, DB, PC</td>
<td>0/100</td>
<td>47.87 ± 8.02 (GH)</td>
<td>50.33 ± 6.98 (P)</td>
<td>32.9 ± 2.8 (GH)</td>
<td>32.3 ± 2.6 (P)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data shown as mean ± SD or mean (range)

Abbreviations: % BF: percent body fat; BW: body weight; BMI: body mass index; DB: double blind; DBP: diastolic blood pressure; DM: diabetes mellitus; FFM: fat free mass; FG: fasting glucose; FI: fasting insulin; FW: fraction of weight lost as fat; HOMA IR: homeostasis model assessment of insulin resistance; IGF1: serum insulin-like growth factor 1; IBW: ideal body weight; LBM: lean body mass; L: serum leptin; Lp(a): Lipoprotein (a); NR: none reported; PC: placebo controlled; R: randomized; RQ: respiratory quotient; REE: resting energy expenditure; SBP: systolic blood pressure; SCA: subcutaneous adipose tissue area; SB: single blind; TBF: total body fat; TC: total cholesterol; TG: triglycerides; TMA: thigh muscle area; VAT: visceral adipose tissue area; VLCD: very low calorie diet; VO2 max: maximal oxygen uptake; WC: waist circumference; WHR: waist to hip ratio
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Weighted mean difference</th>
<th>95 % CI</th>
<th>P value</th>
<th>Number of studies</th>
<th>Number of subjects (GH)</th>
<th>Number of subjects (placebo)</th>
<th>Total number of subjects</th>
<th>Q test P value</th>
<th>I² index</th>
<th>Global effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td>0.33</td>
<td>-0.44, 1.09</td>
<td>0.403</td>
<td>20</td>
<td>207</td>
<td>213</td>
<td>420</td>
<td>0.021</td>
<td>43 %</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.3</td>
<td>-1.0, 0.4</td>
<td>0.432</td>
<td>12</td>
<td>151</td>
<td>134</td>
<td>285</td>
<td>0.004</td>
<td>59 %</td>
<td></td>
</tr>
<tr>
<td>WHR</td>
<td>-0.01</td>
<td>-0.02, -0.001</td>
<td>0.027</td>
<td>5</td>
<td>65</td>
<td>72</td>
<td>137</td>
<td>0.838</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>FM (kg)</td>
<td>-0.9</td>
<td>-1.3, -0.4</td>
<td>&lt;0.001</td>
<td>15</td>
<td>160</td>
<td>165</td>
<td>325</td>
<td>0.632</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>% FM</td>
<td>-1</td>
<td>-1.3, -0.7</td>
<td>&lt;0.001</td>
<td>13</td>
<td>127</td>
<td>118</td>
<td>245</td>
<td>0.886</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>% WLF</td>
<td>0.15</td>
<td>0.10, 0.19</td>
<td>&lt;0.001</td>
<td>6</td>
<td>36</td>
<td>36</td>
<td>72</td>
<td>0.129</td>
<td>41 %</td>
<td></td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>1.8</td>
<td>0.6, 2.9</td>
<td>0.003</td>
<td>16</td>
<td>167</td>
<td>165</td>
<td>332</td>
<td>0.417</td>
<td>3 %</td>
<td></td>
</tr>
<tr>
<td>VAT (cm²)</td>
<td>-22.8</td>
<td>-39.8, -5.7</td>
<td>0.009</td>
<td>8</td>
<td>97</td>
<td>93</td>
<td>190</td>
<td>0.984</td>
<td>6 %</td>
<td></td>
</tr>
<tr>
<td>ST (cm²)</td>
<td>2.2</td>
<td>-2.6, -2.7</td>
<td>0.363</td>
<td>7</td>
<td>97</td>
<td>93</td>
<td>190</td>
<td>0.947</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>TM (cm²)</td>
<td>8.8</td>
<td>-1.4, 19.1</td>
<td>0.092</td>
<td>5</td>
<td>55</td>
<td>51</td>
<td>106</td>
<td>0.998</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>REE (kcal/24 h)</td>
<td>115</td>
<td>-33, 262</td>
<td>0.127</td>
<td>7</td>
<td>94</td>
<td>87</td>
<td>181</td>
<td>&lt;0.001</td>
<td>93 %</td>
<td></td>
</tr>
<tr>
<td>RQ</td>
<td>-0.02</td>
<td>-0.05, 0.004</td>
<td>0.102</td>
<td>3</td>
<td>25</td>
<td>27</td>
<td>52</td>
<td>0.049</td>
<td>67 %</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>4.6</td>
<td>-7.0, 16.2</td>
<td>0.437</td>
<td>4</td>
<td>55</td>
<td>53</td>
<td>108</td>
<td>&lt;0.001</td>
<td>88 %</td>
<td></td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>1.4</td>
<td>-3.7, 6.4</td>
<td>0.591</td>
<td>5</td>
<td>71</td>
<td>67</td>
<td>138</td>
<td>0.006</td>
<td>72 %</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: BMI: body mass index; BW: body weight; CI: confidence interval; DBP: diastolic blood pressure; FM: fat mass; LBM: lean body mass; REE: resting energy expenditure; RQ: respiratory quotient; SBP: systolic blood pressure; ST: subcutaneous adipose tissue area; TM: thigh muscle area; VAT: visceral adipose tissue area; WHR: waist-to-hip ratio; WLF: weight lost as fat.
TABLE 3. Results of meta-analysis of rhGH therapy in obese adults, including laboratory endpoints (serum IGF-I, leptin, lipid profile and glucose homeostasis).

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Weighted mean difference</th>
<th>95% CI</th>
<th>P value</th>
<th>Number of studies (GH)</th>
<th>Number of subjects (placebo)</th>
<th>Total number of subjects</th>
<th>Q test P value</th>
<th>I² index</th>
<th>Global effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF I (µg/L)</td>
<td>171</td>
<td>131, 212</td>
<td>&lt;0.001</td>
<td>20</td>
<td>204</td>
<td>410</td>
<td>&lt;0.001</td>
<td>85 %</td>
<td></td>
</tr>
<tr>
<td>LEPTIN (µg/L)</td>
<td>-1.8</td>
<td>-4.1, 0.5</td>
<td>0.130</td>
<td>4</td>
<td>57</td>
<td>51</td>
<td>108</td>
<td>0.477</td>
<td>0 %</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>-7</td>
<td>-11, -3</td>
<td>0.001</td>
<td>13</td>
<td>164</td>
<td>153</td>
<td>317</td>
<td>0.379</td>
<td>7 %</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>-9</td>
<td>-13, -5</td>
<td>&lt;0.001</td>
<td>9</td>
<td>130</td>
<td>119</td>
<td>249</td>
<td>0.244</td>
<td>22 %</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>-0.4</td>
<td>-3, 2</td>
<td>0.779</td>
<td>11</td>
<td>139</td>
<td>124</td>
<td>263</td>
<td>0.105</td>
<td>37 %</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>1</td>
<td>-9, 11</td>
<td>0.811</td>
<td>14</td>
<td>177</td>
<td>168</td>
<td>345</td>
<td>0.281</td>
<td>16 %</td>
</tr>
<tr>
<td>LPa (g/L)</td>
<td>0.02</td>
<td>-0.03, 0.07</td>
<td>0.330</td>
<td>3</td>
<td>43</td>
<td>46</td>
<td>89</td>
<td>0.707</td>
<td>0 %</td>
</tr>
<tr>
<td>FG (mg/dl)</td>
<td>3</td>
<td>1, 6</td>
<td>0.004</td>
<td>16</td>
<td>166</td>
<td>158</td>
<td>324</td>
<td>0.002</td>
<td>57 %</td>
</tr>
<tr>
<td>INSULIN (mcU/ml)</td>
<td>1.9</td>
<td>0.2, 3.7</td>
<td>0.037</td>
<td>14</td>
<td>146</td>
<td>140</td>
<td>286</td>
<td>&lt;0.001</td>
<td>76 %</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.1</td>
<td>-0.2, 0.03</td>
<td>0.125</td>
<td>5</td>
<td>69</td>
<td>60</td>
<td>129</td>
<td>0.922</td>
<td>0 %</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.6</td>
<td>-1.6, 0.4</td>
<td>0.236</td>
<td>3</td>
<td>54</td>
<td>44</td>
<td>98</td>
<td>0.124</td>
<td>52 %</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; FG: fasting plasma glucose; HbA1c: glycosylated hemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; HOMA IR: homeostasis model assessment of insulin sensitivity; IGF-I: insulin-like growth factor I; LDL-C: low-density lipoprotein cholesterol; LP(a): lipoprotein (alpha); TC: total cholesterol; TG: (serum) triglycerides
SI unit conversion factors: IGF I: 0.13 x µg/L = nmol/L; cholesterol: 0.026 x mg/dl = mmol/L; triglycerides: 0.011 x mg/dl = mmol/L; glucose: 0.055 x mg/dl = mmol/L; insulin: 7.175 x mcU/ml = pmol/L
TABLE 4. Results of meta-analysis of adverse effects of rhGH therapy in obese adults.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OR</th>
<th>95 % CI</th>
<th>P value</th>
<th>Number of studies</th>
<th>Number of subjects (GH)</th>
<th>Number of subjects (placebo)</th>
<th>Total number of subjects</th>
<th>Q test P value</th>
<th>I² index</th>
<th>Global effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias</td>
<td>6</td>
<td>1.9, 18.6</td>
<td>0.002</td>
<td>7</td>
<td>17/86</td>
<td>1/83</td>
<td>169</td>
<td>0.997</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>Paresthesias</td>
<td>6.5</td>
<td>1.5, 27.3</td>
<td>0.011</td>
<td>5</td>
<td>12/63</td>
<td>0/61</td>
<td>124</td>
<td>0.853</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>5</td>
<td>2.4, 10.5</td>
<td>&lt;0.001</td>
<td>11</td>
<td>44/153</td>
<td>10/152</td>
<td>305</td>
<td>0.753</td>
<td>0 %</td>
<td>0.01 0.1 1 10 100</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; OR: odds ratio.
Search terms: Growth hormone (GH), somatotropin, somatotrophin, obesity, adiposity

2315 articles excluded (animal studies, reviews; also excluded: GH deficiency, Prader-Willi syndrome, HIV lipodystrophy, Cushing’s syndrome, Turner Syndrome, children, adolescents, healthy elderly)

47 articles

8 articles excluded (short duration)
2 articles excluded (small sample size)

37 articles

13 articles not separately considered (reporting same study populations as those included in meta-analysis)

24 studies included in meta-analysis