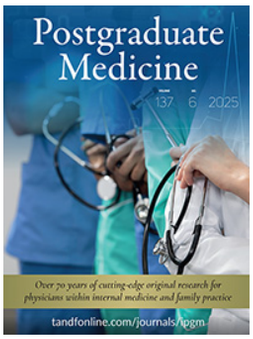


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# Effects of low-dose growth hormone treatment on obesity: a meta-analysis of randomized controlled trials

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**Abstract**

**Background:** Growth hormone (GH) reduces visceral adiposity, increases lean body mass, and improves the lipid profile in obese adults. However, high-dose GH regimens have been associated with frequent adverse effects. The efficacy and safety of low-dose GH treatment in obese individuals without GH deficiency remain unclear. This study aims to evaluate the effects of recombinant human growth hormone (rhGH) on body composition, lipid profile, glucose metabolism, and adverse events in this population..

**Methods:** A systematic review and meta-analysis were conducted in accordance with the PRISMA statement. PubMed, Cochrane Library, and EMBASE databases were systematically searched up to December 2024. Eligible studies included randomized controlled trials (RCTs) involving obese individuals without GH deficiency, with at least one endpoint related to body composition, lipid profile, or glucose metabolism. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, #CRD42023464234).

**Results:** A total of 10 RCTs involving 420 participants were included. The mean age of participants ranged from 18 to 65 years, and treatment durations varied from 4 to 72 weeks. Low-dose rhGH therapy resulted in a significant reduction in visceral adipose tissue (SMD: -0.34, 95%CI: -0.57 to -0.12, p=0.003) and a significant increase in thigh muscle area (MD: 6.33 $cm^2$, 95%CI: 1.72 to 10.95, p=0.007) compared to placebo. Additionally, fasting glucose levels were modestly elevated (MD: 4.18 mg/dL, 95%CI: 0.68 to 7.67, p=0.02). No serious adverse events were reported in association with low-dose rhGH treatment across the included studies.

**Conclusions：** Low-dose rhGH therapy significantly reduces visceral fat and enhances thigh muscle mass in obese individuals without GH deficiency. These findings suggest that low-dose rhGH may offer therapeutic potential for sarcopenic obesity, warranting further investigation in larger, longer-term studies.

**Keywords：** recombinant human growth hormone; low-dose; obesity; overweight; visceral adipose tissue; thigh muscle.

## 1. Introduction

According to the World Obesity Atlas 2025, the number of adults with obesity is expected to increase by over 115% between 2010 and 2030, rising from 524 million to 1.13 billion [1]. Obesity is typically caused by an imbalance between calorie intake and energy expenditure. Indeed, the causes of obesity are complex; abnormal hormone secretion often occurs and may play a causal role in the development of obesity and its associated chronic diseases[2]. For example, the secretion of growth hormone (GH) is suppressed in patients with obesity [3].

Studies have demonstrated that GH secretion is markedly reduced in obese individuals and that there is a strong inverse relationship with the accumulation of visceral adipose tissue (VAT) [4]. This decline in GH secretion has been linked to increased deposition of ectopic fat, particularly in the liver and muscles [5]. Moreover, the expansion of adipose tissue mass or accumulation of ectopic lipids can impair skeletal muscle protein synthesis [6,7]. Consequently, these metabolic alterations further disrupt the body composition balance and exacerbate metabolic dysfunction in obese individuals.

Recombinant human growth hormone (rhGH) has emerged as a promising therapeutic agent for the treatment of obesity. Evidence suggests that rhGH treatment reduces visceral adiposity, augment lean body mass (LBM), and improves lipid profiles in adults with obesity[8]. Additionally, rhGH exhibits anti-inflammatory effects[9], which may be particularly beneficial given that obesity and related conditions-such as metabolic syndrome, type 2 diabetes, and prediabetes—are characterized by chronic inflammatory burden [10-13]. Despite these potential benefits, high-dose rhGH regimens (>0.1 mg/kg) used in prior studies have been associated with frequent adverse reactions, including edema, arthralgia, hypertension, and glucose intolerance[14-16], thereby limiting their clinical utility in obesity management. In contrast, low-dose rhGH (0.1–0.5 mg/day) has been recommended for replacement therapy in adult GH deficiency, with dose adjustments based on clinical response, adverse effects, and serum insulin-like growth factor-1 (IGF-1) levels[17]. To objectively evaluate the effects of rhGH in modern treatment paradigms, we systematically reviewed recent randomized controlled trials (RCTs) examining low-dose rhGH in obesity. Although several studies have reported reductions in VAT with low-dose rhGH[4,18-20], findings regarding its impact on muscle mass, lipid profiles, and glucose

metabolism remain inconsistent [4,18,19]. To address these gaps and to clarify the therapeutic potential and safety of low-dose rhGH in obese individuals without GH deficiency, we conducted a global meta-analysis of selected RCTs.

## 2. Materials and methods

### *2.1. Search strategy*

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (PRISMA 2020) [21]. To identify relevant studies, we performed a comprehensive search in three electronic databases including PubMed, Cochrane library, and EMBASE. The search terms used were (low dose growth hormone OR low dose GH OR low dose recombinant human growth hormone OR low dose rhGH) AND (obesity OR adiposity) AND "randomized controlled trial" covering the period from the day of the inception of each database until 31 December, 2024. Additionally, we manually reviewed the reference lists of the included studies to ensure that all relevant studies were identified.

### *2.2. Eligibility criteria*

To be eligible for inclusion, trials in this study must be randomized controlled trials in population with obesity, the endpoint of the trials must include at least one of the following parameters including lean body mass(LBM), thigh muscle area(TMA), VAT, subcutaneous adipose tissue(SAT), body weight(BW), body mass index(BMI), total cholesterol(TC), triglycerides(TG), high density lipoprotein cholesterol(HDL-C), high density lipoprotein cholesterol(LDL-C), fasting glucose, 2h glucose, homeostasis model assessment of insulin resistance (HOMA-IR) or IGF-1. We excluded duplicated trials, trials focusing on GH deficient population, or specific disease population (HIV, Prader Willi syndrome, pediatric, diabetes, or morbidly obese), outcome data cannot be precisely extracted.

### *2.3. Data extraction and quality control*

Data were extracted from selected publications by two authors (F.S. and Y. J.) and crosschecked, B.G. was involved in resolving the disagreements between the two authors. The information collected from the selected publications included the study design, details of the intervention and control groups, sample size, number of participants in each group, sex and age of the participants, baseline measurements, growth hormone dosage, treatment duration, and the study endpoints. To assess the quality of the included trials, two independent reviewers used the Cochrane Collaboration's tool to evaluate the following domains: sequence generation, incomplete outcome data, allocation concealment, blinding of subjects (if applicable), blinding of outcome assessment (if applicable), selective outcome reporting, and other potential sources of bias [22].

### *2.4. Statistical analysis*

Statistical analyses were undertaken using Review Manager 5.4 which is a tool developed by the Cochrane Collaboration. Continuous measurements were treated as quantitative data, and mean differences (MD) with 95% confidence intervals were calculated to compare changes in outcomes between intervention and control groups. When outcome measurements utilized incompatible units that prevented direct conversion, we employed standardized mean differences (SMDs) accompanied by 95% confidence intervals for pooled analysis. For handling missing standard deviation data in baseline-to-follow-up change measurements, we implemented Cochrane Handbook [23], protocols by first seeking available statistical parameters - including confidence intervals, standard errors, or t/P values. When these parameters were unavailable, we estimated missing values through correlation coefficients calculated from baseline standard deviation data obtained from comparable studies in the same research domain.

In our meta-analysis, we applied a random-effects model to obtain a relatively conservative finding when the $I^2$ test detected significant heterogeneity statistically ($I^2 > 50\%$, $p < 0.05$). A fixed-effects model was otherwise applied if no significant heterogeneity was detected. Pooled mean differences were calculated based on raw mean differences and are reported as inverse- variance weighted averages with 95% confidence intervals (CI). To quantify heterogeneity the $I^2$ statistic was calculated, and Cochran's Q-test was applied.

### *2.5. Ethical approval*

Ethics approval was not required because all data used in this study were collected from previous published studies and were anonymous.

## 3.Results

### *3.1. Study Selection and Characteristics of the Included Trials*

A total of 1,599 articles were identified in the initial database search, comprising 711 articles from PubMed and 888 from the Cochrane Library and EMBASE. The search process is illustrated in Fig. 1. After removing 1,147 duplicate or non-randomized studies, 452 articles were screened for eligibility. Further exclusions were made based on predefined criteria, including studies lacking evaluable endpoints, those involving diseased, adolescent, or healthy populations, trials without control groups, and studies with unextractable endpoints or other ineligibility factors. Finally, ten RCTs were included in this meta-analysis. [4,18-20,24-29].

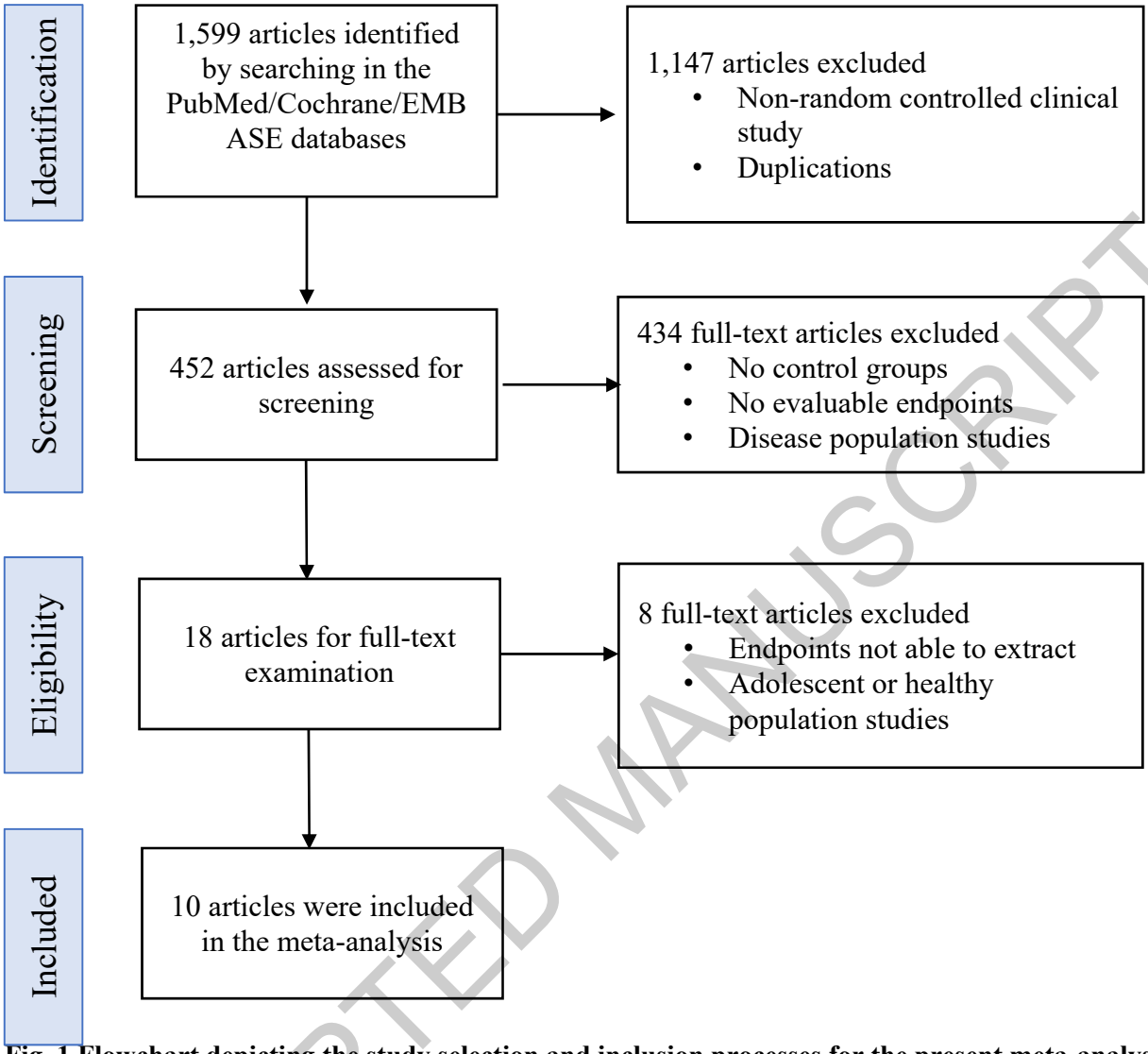


**Fig. 1 Flowchart depicting the study selection and inclusion processes for the present meta-analysis**

### *3.2. Studies Characteristics*

The mean age of the participants ranged from 18 to 65 years. The treatment groups received rhGH at varying dosages, whereas the control group received a placebo (Table 1). The treatment durations varied across trials, ranging from 4 to 72 weeks. The included trials were published between 1997 and 2023. Body composition was assessed using compute tomography, dual-energy X-ray absorptiometry, and bioimpedance analysis.

**Table 1. Selected trials for the present meta-analysis**

| Author | Year | Sample size (Male/Female) | | Age (Male/Female) | | rhGH dosage | Treatment duration | Included outcomes | Body mass index |
|---|---|---|---|---|---|---|---|---|---|
| | | Study | Control | Study | Control | | | | |
| Johannsson et al.[26] | 1997 | 16/NA | 14/NA | 58.3 | 57.9 | 9.5ug/kg/d (0.03IU/kg/d) The dose was reduced by half in the event of side effects. | 36 weeks | BMI, FFM, VAT, TC, TG | 25–35 kg/m$^2$ |
| Kim et al.[27] | 1999 | 1/11 | 1/11 | 35.2 | 37.5 | 0.03 IU/kg$^*$ /d | 12 weeks | LBM, TMA, VAT, SAT | GH: 29.4kg/m$^2$ Placebo: 28.2kg/m$^2$ |
| Richelsen et al.[29] | 2000 | NA/8 | NA/10 | 35 | 35 | 0.03IU/kg$^*$ /d in wk 1, 0.04IU/kg$^*$ /d in wk 2, 0.06IU/kg$^*$ /d in wk 3, 0.08IU/kg$^*$ /d in wk 4. the total daily dose | 4 weeks | BW, BMI, TC, TG, HDL | GH: 42.4 kg/m$^2$ Placebo: 41.76 kg/m$^2$ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | never exceeded 6 IU | | | |
| Vestergaard et al.[28] | 2000 | NA/10 | NA/10 | 33 | 34 | 0.03IU/kg*/d in wk 1, 0.04IU/kg*/d in wk 2, 0.06IU/kg*/d in wk 3, 0.08IU/kg*/d in wk 4-8. Total daily dose was restricted to a maximum of 6 IU and was reduced in case of side effects | 8 weeks | BW, LBM | GH: 41.1 kg/m$^2$ Placebo: 40.6 kg/m$^2$ |
| Franco et al.[4] | 2005 | NA/20 | NA/20 | NA/58 | NA/57 | 0.13 mg/d at initial 0.27 mg/d after 2 wk, 0.4 mg/d after 4 wk, 0.53 mg/d after 5 wk, 0.67 mg/d after 6 wk. The dose was | 48 weeks | BW, VAT, LBM,TMA, FPG, 2h PG, HOMA-IR | GH: 30.6 kg/m$^2$ Placebo: 30.0 kg/m$^2$ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | reduced by half in the event of fluid-related side effects. | | | |
| Albert et al.[24] | 2007 | 23 | 17 | 35(female) 37(male) | | 0.2mg/d in mo 1; 0.4mg/d for men, 0.6mg/d for women in mo 2. . | 24 weeks | BMI, BW, TC, TG, HDL, LDL | GH: 35.9 kg/m$^2$ Placebo: 36.9 kg/m$^2$ |
| Pasarica et al.[25] | 2007 | 15/NA | 15/NA | 48 | 50 | 2.5μg/kg/d in wk 1; 5.0μg/kg/d in wk 2; 7.5μg/kg/d in wk 3; 10μg/kg/d in wk 4-26. | 24 weeks | FPG, TG | GH: 32.9 kg/m$^2$ Placebo: 32.3 kg/m$^2$ |
| Bredella et al.[19] | 2012 | NA/39 | NA/40 | NA/36 | NA/36 | 0.5mg/d at 6 wk.; 1.7mg/d at 6 mo. 4 mg/kg at initial. IGF1 level target: in the upper normal age | 24 weeks | VAT, SAT, LBM, TMA, TC, TG, HDL, LDL, FPG, 2h PG, HOMA-IR | GH: 34.8 kg/m$^2$ Placebo: 34.9 kg/m$^2$ |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | appropriate range. | | | |
| Bredella et al.[18] | 2013 | 32/NA | 30/NA | 32/NA | 34/NA | 0.2mg/d at 3 wk; 0.5mg/d at 6 wk; 0.8mg/d at 9 wk; 1.0mg/d at 3 mo; 1.1mg/d at 6 mo. Starting GH dose: 2ug/kg per day. IGF-1 level target: in the upper normal | 24 weeks | BW, BMI, VAT, SAT, LBM, TMA, FPG, 2h PG, HOMA-IR | GH: 36.4 kg/m$^2$ Placebo:37.7 kg/m$^2$ |
| Dichtel et al.[20] | 2022 | 21/18 | 20/18 | 47 | 49 | 0.51±0.06 mg/d 0.3 mg/day in women and 0.2 mg/day in Men at initial. The GH dose was titrated upward by 0.1 to 0.2 mg/day. IGF-1 level target: the | 72 weeks | VAT, LBM, FPG, 2h PG, HOMA-IR | GH: 33.0 kg/m$^2$ Placebo: 33.1 kg/m$^2$ |

| | | | |
|---|---|---|---|
| | | upper quartile of normal for age. | |

* Ideal body weight

NA: not applicable; wk: week; mo: month; BMI: body mass index; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; FPG: fasting plasma glucose; PG: plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; LBM: lean body mass; TMA: thigh muscle area; BW: body weight; TC: total cholesterol; TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; CT: computerized tomography; DXA: dual-energy X-ray absorptiometry; FM: fat mas

### *3.3. Quality Evaluation*

The methodological quality of the 10 included studies (1997-2022) was assessed using Cochrane Risk of Bias Assessment Tool. For random sequence generation, 9 studies used computer randomization or random number tables, indicating a low risk of bias. Regarding allocation concealment, none of the 10 studies described specific protocols, resulting in high or unclear risk of bias. In terms of blinding implementation, 9 studies adopted a double-blind design, whereas one study did not mention blinding (e.g., Albert 2007), posing a high risk of bias. Data integrity was generally good across all studies, with attrition rates below 10% and the use of intention-to-treat analysis, reflecting a low risk of bias. However, selective reporting was a concern, as nine studies did not publicly pre-register their protocols, indicating a high risk of bias. The remaining studies reported results consistent with their protocols, suggesting a low risk of bias in this regard (Figure S1A-B).

### *3.4. Effects of rhGH on Body Composition*

#### *3.4.1. VAT*

In six eligible trials (n=158 for rhGH and n=154 for placebo), the effect of rhGH on VAT was evaluated. Meta-analysis revealed that rhGH treatment significantly reduced VAT compared to the placebo group (SMD: -0.34, 95% CI: -0.57 to -0.12, $p$ = 0.003), with no heterogeneity observed among the studies ($I^2$ = 0%, $p$ = 0.72).

#### *3.4.2. SAT*

Four eligible trials (n=103 for rhGH and n=102 for placebo) assessed the impact of rhGH on SAT. Results showed no significant reduction in SAT area (MD: -8.35 $cm^2$, 95% CI: -45.76 to 29.07, $p$ = 0.66), and no heterogeneity was detected ($I^2$ = 0%, $p$ = 0.95).

#### *3.4.3. LBM*

Data from seven eligible trials (n=168 for rhGH and n=164 for placebo) indicated that rhGH treatment increased LBM by 0.80 kg (95% CI: -0.09 to 1.69, $p$ = 0.08) compared to placebo, although this difference was not statistically significant. No heterogeneity was observed among the studies ($I^2$ = 0%, $p$ = 0.48).

*3.4.4. TMA*

Four eligible trials (n=103 for rhGH and n=102 for placebo) examined the effect of rhGH on TMA. Results demonstrated a significant increase in TMA with rhGH treatment (MD: 6.33 $cm^2$, 95% CI: 1.72 to 10.95, $p$ = 0.007), with no heterogeneity across studies ($I^2$ = 0%, $p$ = 0.77) (Fig. 2).

***3.5. Subgroup Analyses by Treatment Duration***

Subgroup analyses were conducted to evaluate the effects of rhGH on body composition based on treatment duration. VAT: Analyses were divided into two subgroups: 12–24 weeks (three trials: n=83 for rhGH and n=82 for placebo) and >24 weeks (three trials: n=75 for rhGH and n=72 for placebo). In the >24-week subgroup, rhGH treatment was associated with a significant reduction in VAT (SMD: -0.49, 95% CI: -0.82 to -0.17, $p$ = 0.003), with no heterogeneity ($I^2$ = 0%, $p$ = 0.65). In contrast, no significant difference was observed in the 12–24-week subgroup (SMD: -0.21, 95% CI: -0.52 to 0.10, $p$ = 0.18) (Figure. S2C). TMA: Subgroups were defined as 12–24 weeks (three trials: n=83 for rhGH and n=82 for placebo) and >24 weeks (one trial: n=20 for rhGH and n=20 for placebo). In the 12–24-week subgroup, rhGH treatment led to a significant increase in TMA (MD: 7.94 $cm^2$, 95% CI: 2.37 to 13.51, $p$ = 0.005), with no heterogeneity ($I^2$ = 0%, $p$ = 0.95). However, no significant difference was observed in the >24-week subgroup (MD: 2.8 $cm^2$, 95% CI: -5.45 to 11.05, $p$ = 0.51) (Figure. S2B). LBM and SAT: No significant differences were observed in LBM or SAT across different treatment duration subgroups (Figure. S2A, D).

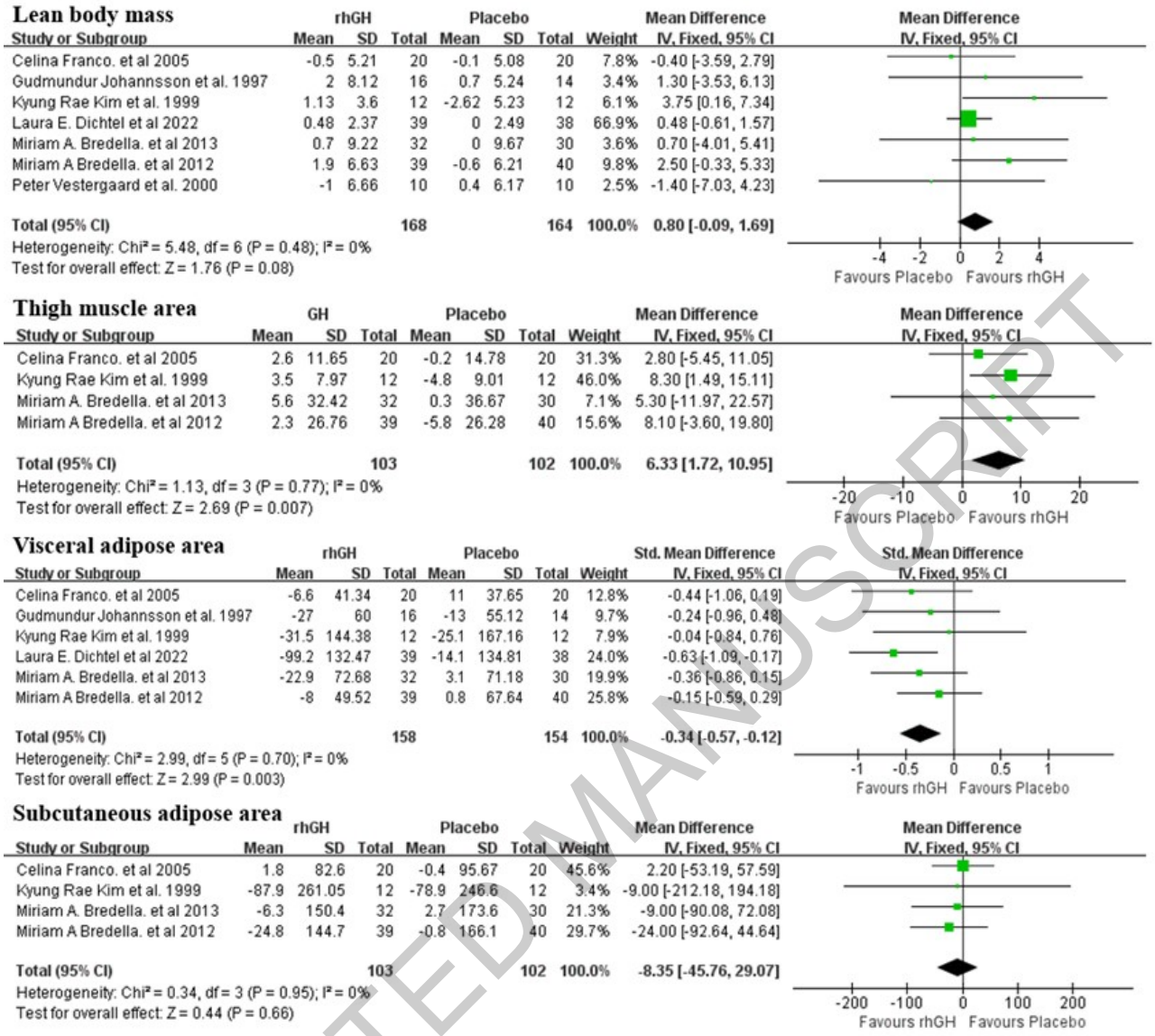


**Fig. 2 Forest plot of randomized controlled trials investigating the effects of rhGH on visceral adipose tissue area, subcutaneous adipose tissue, lean body mass and thigh muscle area.** GH: growth hormone; SD：standard deviation; IV: information value; CI: confidence interval; df: degree of freedom; z: z-score



### *3.6. Effects of rhGH on BW and BMI*

Five eligible trials (n=93 for rhGH and n=87 for placebo) demonstrated that rhGH treatment resulted in a non-significant decrease in BW by 2.01 kg (95% CI: -5.80 to 1.79, $p$ = 0.30), with no heterogeneity observed

among the studies ($I^2$ = 0%, $p$ = 0.84). Similarly, four eligible trials (n=79 for rhGH and n=71 for placebo) showed that rhGH treatment led to a non-significant reduction in BMI by 0.75 kg/m² (95% CI: -2.29 to 0.78, $p$ = 0.34) compared to the placebo group, with no significant heterogeneity ($I^2$ = 0%, $p$ = 0.92) (Fig. 3).

### *3.7. Subgroup Analyses by Treatment Duration*

Subgroup analyses based on treatment duration revealed no significant differences in BW or BMI between the rhGH treatment and placebo group across different treatment durations (Figure S3A,B).

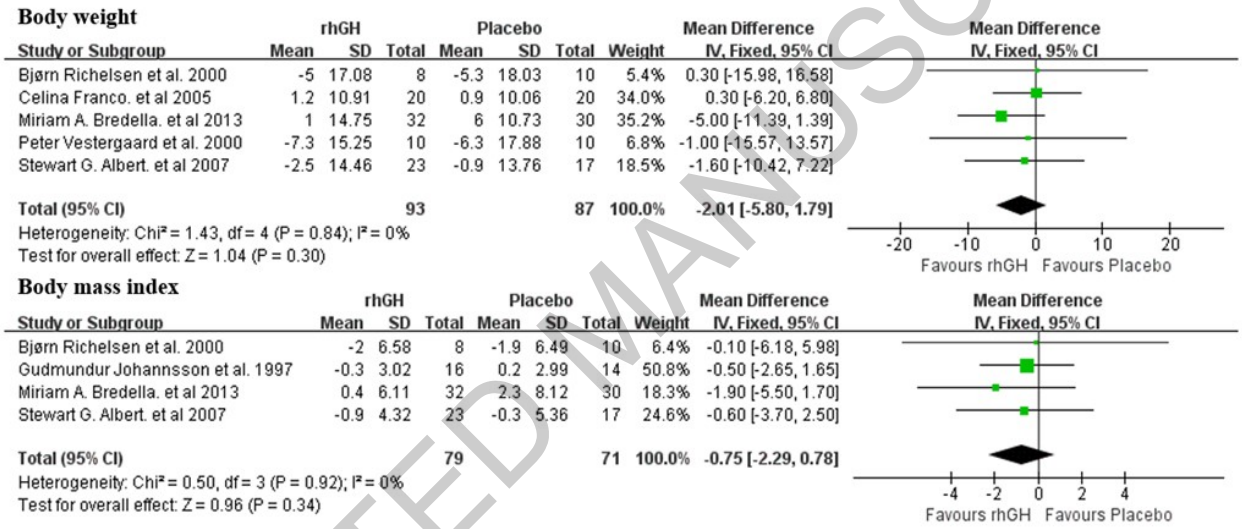


**Fig. 3 Forest plot of randomized controlled trials investigating the effects of rhGH on body weight and body mass index.** GH: growth hormone; SD：standard deviation; IV: information value; CI: confidence interval; df: degree of freedom; z: z-score

### *3.8. Effects of rhGH on Lipid Profiles*

*3.8.1. TC*

rhGH treatment demonstrated a non-significant reduction in TC compared with the placebo group (SMD: -0.27, 95% CI: -0.54 to 0.01, $p = 0.06$) in five eligible trials (n=106 for rhGH and n=101 for placebo), with no heterogeneity observed among the studies ($I^2 = 0\%$, $p = 0.61$).

*3.8.2. TG*

Similarly, six eligible trials (n=98 for rhGH and n=99 for placebo) reported a non-significant decrease in TG with rhGH treatment (SMD: -0.18, 95% CI: -0.47 to 0.10, $p = 0.53$), and no heterogeneity was detected ($I^2 = 0\%$, $p = 0.65$).

*3.8.3. HDL-C*

Four eligible trials (n=90 for rhGH and n=87 for placebo) showed that rhGH treatment resulted in a non-significant elevation in HDL-C levels (SMD: 0.03, 95% CI: -0.27 to 0.32, $p = 0.85$), indicating no clinical significance. No significant heterogeneity was observed among the studies ($I^2 = 0\%$, $p = 0.84$).

*3.8.4. LDL-C*

Three eligible trials (n=82 for rhGH and n=77 for placebo) reported a non-significant decrease in LDL-C levels with rhGH treatment (SMD: 0.18, 95% CI: -0.49 to 0.13, $p = 0.26$). No significant heterogeneity was observed among the studies ($I^2 = 0\%$, $p = 0.76$) (Fig. 4).

***3.9. Subgroup Analyses by Treatment Duration***

Subgroup analyses based on treatment duration revealed no significant differences in lipid profiles between the rhGH treatment and placebo groups across various treatment durations (Figure S4A-D).

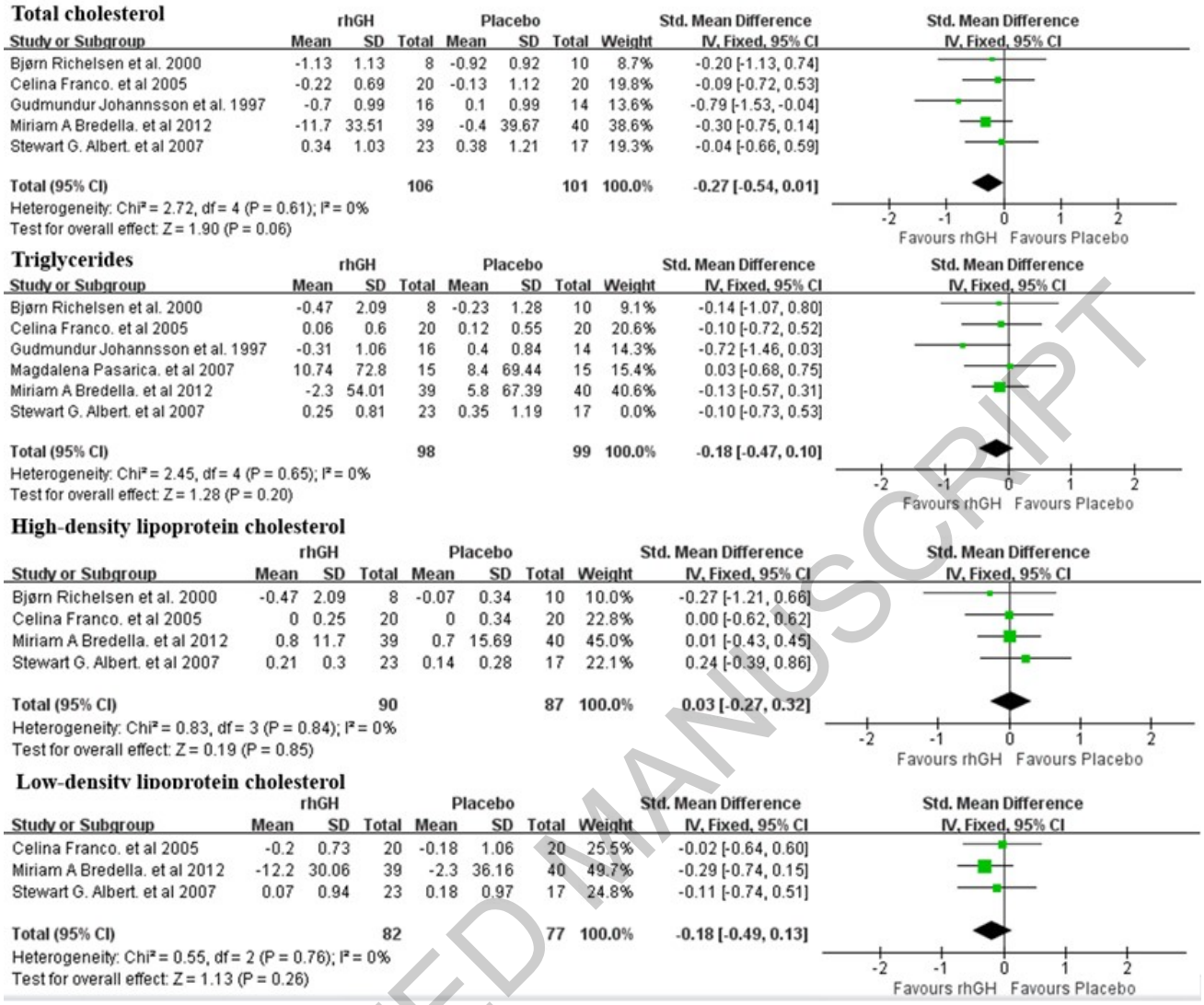


**Fig. 4 Forest plot of randomized controlled trials investigating the effects of rhGH on lipid profile.** GH: growth hormone; SD：standard deviation; IV: information value; CI: confidence interval; df: degree of freedom; z: z-score

### *3.10. Effects of rhGH on Glycemic Parameters*

#### *3.10.1. Fasting Glucose*

Based on data from five eligible trials (n=145 for rhGH and n=143 for placebo), rhGH treatment was associated with a significant increase in fasting glucose by 4.18 mg/dL (95% CI: 0.68 to 7.67, $p$ = 0.02). However, significant heterogeneity was observed among the studies ($I^2$ = 66%, $p$ = 0.02).

*3.10.2. 2h Glucose*

Four eligible trials (n=130 for rhGH and n=128 for placebo) reported the effect of rhGH on 2-hour postprandial glucose levels. Results showed a non-significant increase of 5.71 mg/dL (95% CI: -1.67 to 13.08, $p = 0.13$), with no heterogeneity detected ($I^2 = 0\%$, $p = 0.63$).

*3.10.3. HOMA-IR*

Data from four eligible trials (n=114 for rhGH and n=107 for placebo) indicated that rhGH treatment increased HOMA-IR by 0.44 (95% CI: -0.19 to1.06, $p = 0.17$), though this difference was not statistically significant. No heterogeneity was observed among the studies ($I^2 = 0\%$, $p = 0.47$) (Fig. 5).

***3.11. Subgroup Analyses by Treatment Duration***

Subgroup analyses were conducted to evaluate the effects of rhGH on glycemic parameters based on treatment duration. The subgroups were defined as 12–24 weeks and >24 weeks. Fasting Glucose: In the 12–24-week subgroup (three trials: n=86 for rhGH and n=85 for placebo), rhGH treatment led to a significant increase in fasting glucose by 5.99 mg/dL (95% CI: 0.52 to 11.47, $p = 0.02$), with significant heterogeneity observed ($I^2 = 74\%$, $p = 0.02$). In contrast, no significant change was observed in the >24-week subgroup (two trials: n=59 for rhGH and n=58 for placebo)：MD 1.66 mg/dL, 95% CI: -1.61to 4.92, and heterogeneity was not significant ($I^2 = 14\%$, $p = 0.28$) (Figure. S5A). 2h Glucose and HOMA-IR: Subgroup analyses revealed no significant differences in 2-hour postprandial glucose or HOMA-IR between the rhGH treatment and placebo groups across different treatment durations (Figure S5B, C).

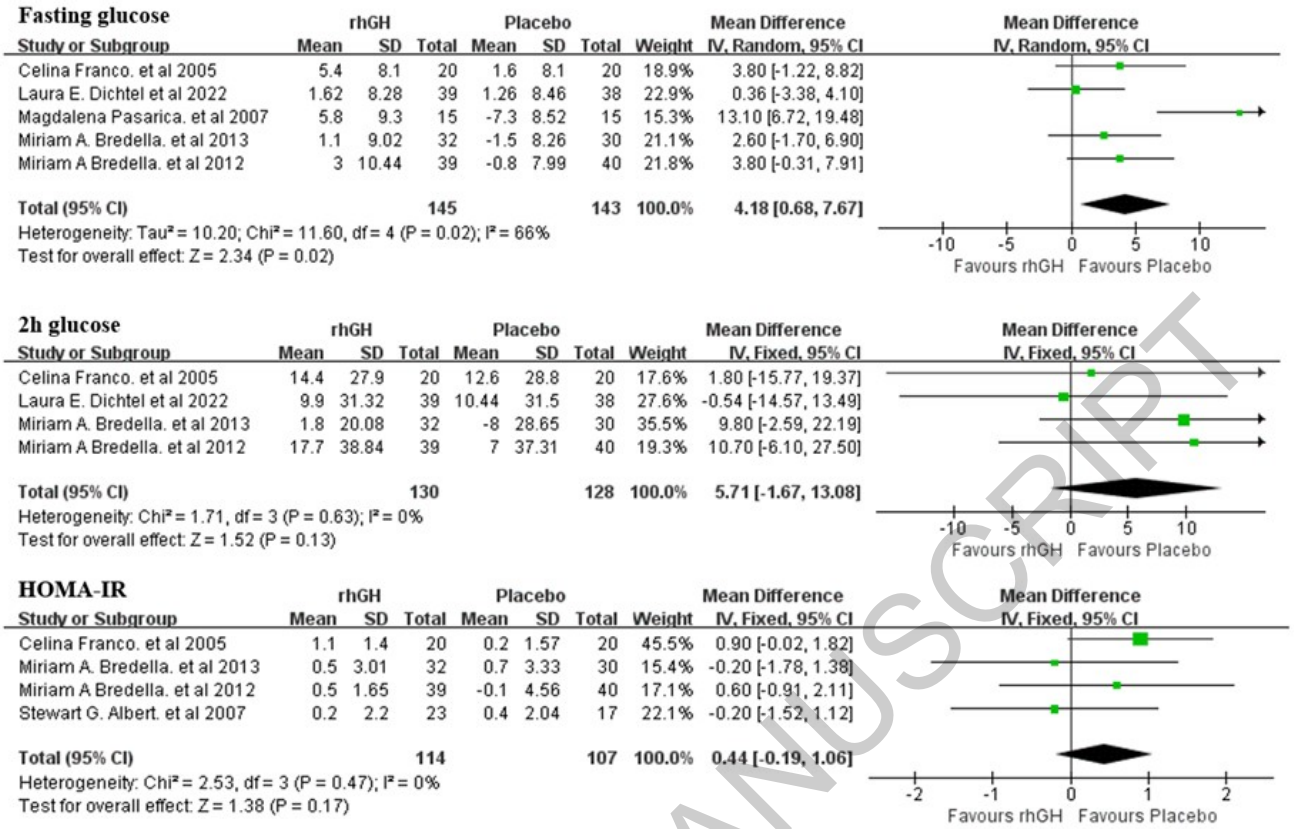


**Fig. 5 Forest plot of randomized controlled trials investigating the effects of rhGH on fasting glucose, 2h glucose and HOMA-IR.** GH: growth hormone; SD： standard deviation; IV: information value; CI: confidence interval; df: degree of freedom; z: z-score

### *3.12. Subjects Reporting Adverse Events During the Drug Treatment Period*

No serious adverse events related to the rhGH treatment were reported in any of the included studies. However, rhGH treatment was associated with a significant increase in joint pain and discomfort (OR, 2.55, 95% CI: 1.28 to 5.09). Other reported side effects included edema, headache, muscle aches, nasal congestion, back pain, and injection site discomfort or bruising in a few studies (Table S1).

## Discussion

In this meta-analysis of RCTs, we evaluated the effects of low-dose rhGH therapy in obese individuals. Our results demonstrated that low-dose rhGH treatment significantly reduced VAT and increased TMA, with only a minor elevation in fasting blood glucose levels. No significant effect was observed on HOMA-IR compared to the control group. However, low-dose rhGH therapy did not significantly affect the SAT, lipid profiles, BW, or BMI. Although rhGH treatment is associated with a slight increase in joint pain or discomfort, no serious adverse events related to rhGH have been reported across the studies.

Since the 1980s, several studies have explored the potential of rhGH as a treatment for obesity [15]. Kavya et al. conducted a meta-analysis of clinical studies between 1988 to 2006, evaluating the efficacy and safety of rhGH as a therapeutic option for obesity in adults[8]. Their findings suggested that rhGH treatment not only reduced VAT, but also increased LBM, similar to our results. However, unlike in our study, they reported beneficial effects on lipid profiles. Two factors may account for these discrepancies. First, dose differences: A previous meta-analysis included studies involving higher rhGH doses (mean target dose: approximately 22.3–41 mg/week)[15,30]. The highest rhGH dose was 1.7mg/day in the studies we included[19]. High-dose rhGH may enhance lipid metabolism improvements, but low-dose regimens have been increasingly recommended in recent years owing to preserved GH and IGF-1 sensitivity in obese populations [17,31], Studies have revealed that GH and IGF-1 sensitivity are preserved in population with obesity [32,33] . In addition, low-dose GH could reduce the risk of GH-related side effects, such as edema, arthralgia, and glucose intolerance compare to high-dose GH. Second, regarding population heterogeneity, the meta-analysis conducted by Kavya et al. included individuals with simple obesity and those with comorbidities such as diabetes or metabolic syndrome [33-35]. The complex interplay between GH, insulin resistance, and glucose metabolism in these populations may influence the therapeutic effects of rhGH[36].

GH plays a dominant role in lipolysis during fasting and postabsorptive states [37]. The effect of rhGH in reducing VAT has been demonstrated in numerous studies in both GH deficient and obese individuals. The efficacy of rhGH in reducing VAT has been consistently demonstrated in multiple studies involving both GH-deficient individuals and those with obesity [4,18-20,38]. The anabolic effects of GH are primarily mediated by the hepatic and peripheral production of IGF-1, a critical regulator of muscle growth, differentiation, and

regeneration[39]. In obesity, both spontaneous and stimulated GH secretion are blunted[3,40]. Notably, elevated portal insulin levels in obese individuals promote hepatic IGF-1 production while suppressing the formation of IGF-binding protein-1, resulting in bioactive IGF-1 levels comparable to those in normal-weight individuals [41]. In contrast to with circulating IGF-1 patterns, skeletal muscle IGF-1 concentrations are significantly reduced in obese individuals compared to their lean counterparts [42]. Acute GH administration induced 23% increase in muscle IGF-1 mRNA expression [43]. Notably, prolonged fasting and elevated serum GH levels failed to produce significant alterations in muscular IGF-1 mRNA expression in both obese and non-obese populations [43]. These findings suggest that the tissue production of IGF-1 is enhanced only when GH levels are raised to supraphysiological, rather than physiological levels. Our results further indicate that low-dose GH treatment can effectively reduce VAT while increasing thigh muscle area in obese individuals, highlighting its potential therapeutic benefits in modulating body composition.

Sarcopenic obesity, a subtype characterized by increased adiposity and muscle loss, exacerbates the adverse effects of sarcopenia in older adults [44]. Contemporary anti-obesity pharmacotherapies, such as semaglutide and tirzepatide, have demonstrated superior efficacy in weight reduction and cardiovascular risk mitigation. For instance, semaglutide achieved a weight loss of 15.3 kg (14.9%) in the STEP-1 trial, while tirzepatide resulted in a 22.1 kg (20.9%) reduction in the SURMOUNT-1 trial [45,46], However, these therapies may also reduce muscle mass during weight loss: semaglutide was associated with a 6.92 kg (13.2%) reduction in lean mass in the STEP-1 trial, and tirzepatide with a 5.67 kg (10.9%) reduction in the SURMOUNT-1 trial [47,48]. The long-term implications of these effects in obese individuals at risk of sarcopenia require ongoing evaluation [49,50]. Currently, there is a lack of effective therapies for sarcopenic obesity. While lifestyle interventions, including calorie restriction and physical activity, are mainstays of management [44]. Given the potential benefits of GH therapy in reducing VAT and increasing muscle mass, further investigation into the efficacy and safety of GH alone or in combination with GLP-1 agonists is warranted in individuals with sarcopenic obesity.

This meta-analysis represents the first comprehensive synthesis of low-dose rhGH treatment in RCTs involving obese individuals without GH deficiency. A key strength of this study lies in its conclusion that

low-dose rhGH therapy significantly increases TMA in this population. However, this study had several limitations. First, owing to the limited clinical attention given to low-dose rhGH in obesity treatment, the number of available studies and their sample sizes were limited. This precludes definitive conclusions regarding the efficacy across age, sex, and obesity subtypes. Second, there is inconsistency in the exact dosing regimens of low-dose rhGH across studies, which may influence the generalizability of the findings. Since the 2011 Endocrine Society (ES) and 2019 American Association of Clinical Endocrinologists (AACE) guidelines for adult growth hormone deficiency recommend starting with low-dose GH (0.1 mg/d)[17,51], more evidence-based studies in obese populations are needed to establish uniform standards. Regarding the safety of low-dose GH use, our study found a slight increase in fasting blood glucose, which was evident in the 12 to 24 -week treatment subgroup but not in the >24-week subgroup. Additionally, no differences were observed in 2-hour blood glucose or HOMA-IR. The transient increase in fasting blood glucose without corresponding changes in insulin sensitivity metrics suggests that elevated fasting glucose levels may reflect early-phase activation of hepatic gluconeogenesis mediated by GH-induced lipolysis. Meanwhile, preserved postprandial glucose homeostasis indicates compensatory β -cell adaptation. We speculate that these changes may be related to long-term improvements in body composition and glycemic benefits[52,53]. However, the analysis of fasting blood glucose revealed high heterogeneity among studies (overall: $I^2$ = 66%, p = 0.02; 12- to 24-week subgroup: $I^2$ = 74%, p = 0.02). Lastly, the current study cannot directly assess the cardiovascular benefits of GH therapy. However, reductions in visceral fat and increases in muscle mass may contribute to indirect cardiovascular benefits[54,55]. Therefore, the long-term effects of GH treatment require further confirmation through more studies.

## 5. Conclusion

The effect of low-dose rhGH treatment on improving body composition in individuals with obesity is expected. This meta-analysis indicated a definite reduction in visceral fat and an increase in thigh muscle. We have provided valuable insights into the potential benefits of low-dose rhGH therapy. Since low-dose rhGH therapy can lead to a reduction in adiposity and an increase in muscle protein synthesis, we postulate that rhGH still holds promise for treating sarcopenic obese patients. Further research is warranted to gain a more

comprehensive understanding of the potential benefits and limitations associated with rhGH treatment in sarcopenic obesity.

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**Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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