Role of Growth Hormone Therapy in Metabolic-Dysfunction-Associated Steatotic Liver Disease: A Systematic Review and Meta-Analysis

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Abstract

Multiple observation studies and meta-analysis have linked growth hormone (GH) deficiency with metabolic-dysfunction-associated steatotic liver disease (MASLD). No meta-analysis has analysed the efficacy and safety of GH therapy on different aspects of MASLD. We undertook this meta-analysis to address this gap in knowledge. Electronic databases were searched for RCTs involving patients with MASLD receiving GH therapy. Primary outcome was to evaluate changes in radiologic measures of MASLD (magnetic resonance spectroscopy (MRS) and ultrasonography) and liver enzymes. Secondary outcomes were to evaluate alterations in body composition parameters [dual-energy X-ray absorptiometry (DXA)], lipids, glycaemia and side effects. From initially searched 1047 articles, data from three RCTs (120 patients) which fulfilled all criteria were analysed. After 6 months of GH therapy in MASLD, the per cent reduction in intrahepatic lipid (MRS) was significantly higher with GH as compared to placebo [MD -5.85% (95%CI:-11.41– -0.30); $P = 0.04$; $I^2 = 63\%$]. Visceral adipose tissue (VAT) area reduction (DXA) was significantly higher with GH [MD-9.94 cm^2 (95%CI:-19.04– -0.84); $P = 0.03$; $I^2 = 0\%$]. Serum insulin-like growth factor-1 (IGF-1) was significantly raised in MASLD patients receiving GH as compared to placebo [MD +166.86 ng/ml (95%CI: 79.19–254.53); $P < 0.0.001$; $I^2 = 90\%$]. High-sensitivity C-reactive protein (hsCRP) was significantly lower in patients receiving GH [MD -0.89 mg/L (95%CI:-1.40–-0.38); $P = 0.0.0006$; $I^2 = 0\%$]. Patients receiving GH had similar changes in triglycerides [MD-1.06 mg/L (95%CI:-20.45–18.34); $P = 0.91$; $I^2 = 15\%$] and fasting glucose [MD -0.56 mg/L (95%CI:-4.67–3.55); $P = 0.79$; $I^2 = 39\%$]. Gamma-glutamyl transpeptidase was significantly lower in patients receiving GH [MD -7.86 U/L (95%CI:-12.46–-3.27); $P = 0.0008$; $I^2 = 0\%$]. No increase in new-onset hypothyroidism was noted [OR 5.49 (95%CI: 0.25–121.18); $P = 0.28$]. Short-term 6-month GH therapy in MASLD is associated with a significant reduction in intrahepatic lipid content, visceral adiposity, GGT and hsCRP without any increased occurrence of dysglycaemia or hypothyroidism.

Keywords: Adult growth hormone deficiency, growth hormone, long-acting growth hormone, meta-analysis

Introduction

Daily growth hormone (GH) injections have been shown to reverse many of the metabolic consequences of people living with adult growth hormone deficiency (AGHD) like increased visceral adiposity (intra-abdominal fat mass), decreased lean (muscle) mass, associated with increased insulin resistance and metabolic syndrome (MetS).[1] In a systematic review and meta-analysis (SRM), we documented that even once weekly, long-acting growth hormone use was associated with a significant reduction in visceral adipose tissue (VAT),

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with efficacy and side effect profiles comparable to daily GH injections.[2]

Metabolic-dysfunction-associated steatotic liver disease (MASLD) is perhaps one of the most common complications of MetS, believed to be affecting nearly one-third of the global population.[3] The exponential increase in the twin problem of obesity and diabetes (diabesity) will have a major role in the worsening global pandemic of MASLD in the next 15 years.[4] Management of MASLD consists of lifestyle interventions to achieve weight reduction, intensive cardiovascular risk factor modification, and liver-directed pharmacotherapy. Currently, there are no approved treatments for MASLD. Several anti-diabetic, anti-obesity and lipid-modifying medications are being evaluated for managing MASLD. Some studies have suggested the role of pioglitazone, ursodeoxycholic acid and vitamin E in managing MASLD. Promising agents under evaluation for MASLD include obeticholic acid (OCA) (farnesoid X receptor agonist), saroglitazar (dual peroxisome proliferator-activated receptor (PPAR)-γ,α agonist), elafibranor (dual PPAR γ,δ agonist), glucagon-like peptide-1 receptor agonists (GLP1RAs) (semaglutide and liraglutide), twincretin tirzepatide, fibroblast growth factor analogues and resmetirom which is a once-daily, orally administered, liver-targeted and small-molecule thyroid hormone receptor (THR) activator. Resmetirom is 28 times more specific for THR-β than THR-α.[5]

GH deficiency has been linked with MASLD. In a recently published meta-analysis, Kong *et al*.[6] reported that the prevalence of MASLD in people with GH deficiency was 51% compared to 32.4% of global prevalence in the general population. Authors reported that patients with GH deficiency have a 4.27 times odds ratio of developing MASLD as compared to people without GH deficiency.[6] Kong *et al*.[6] reported that the prevalence of non-alcoholic steatohepatitis (NASH) in patients with GH deficiency was 18% as compared to 1.33-5.4% in people without GH deficiency. Hence, it may be hypothesised that since GH deficiency is associated with MASLD, GH therapy may have a role in improving MASLD. Recently, many RCTs have been published evaluating the role of GH therapy in MASLD.[7-9] However, a literature search reveals that, to date, no SRM has been published holistically evaluating the efficacy and safety of GH therapy in MASLD. We undertook this study to address this gap in knowledge.

Methods

This meta-analysis was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), the filled checklist of which can be found at the end of the manuscript.[10] The predefined protocol is registered with PROSPERO, having registration number CRD42023479669. As ethical approval already exists for individual studies included in the meta-analysis, no separate approval was required for this study.

The patient, intervention, control, outcome and study type (PICOS) criteria were used to screen and select the studies for this meta-analysis, with patients (P) being people living with MASLD; intervention (I) being use of GH injections for treating MASLD; control (C) being patients either on placebo or any other medication approved for managing MASLD; outcomes (O) being evaluated were impact on radiologic (magnetic resonance spectroscopy (MRS) and ultrasonography) and biochemical assessment tools for MASLD, body composition parameters [lean mass, fat mass, VAT, subcutaneous adipose tissue and total adipose tissue] and adverse events; and (S) being studies included which were RCTs. Only patients with MASLD were considered. Patients with other forms of liver disease, like alcoholic liver disease, viral hepatitis-induced liver disease, hemochromatosis and Wilson's disease, were excluded. Only those studies that had two arms were included, in which one arm received GH therapy, and the other arm received a placebo or any other approved medication for MASLD.

Primary outcome was to evaluate changes in radiologic (MRS and ultrasonography) and liver enzyme parameters. Secondary outcomes were to evaluate alterations in body composition parameters, lipids, glycaemia and side effects. Analysis was performed based on whether the control group received an active comparator (approved medicine for MASLD) – labelled here as the active control group or a placebo – labelled as a passive control group.

A detailed electronic database of Medline (Via PubMed), Embase (via Ovid SP), Cochrane Central Register of Controlled Trials (CENTRAL) (for trials only), ctri.nic.in, clinicaltrials.gov, global health and Google Scholar were searched using a Boolean search strategy: (growth hormone) AND (fatty liver).

Data extraction was carried out independently by two authors using standard data extraction forms. In cases where more than one publication of a single study group was found, results were grouped together, and relevant data from each report were used in the analyses. Patient characteristics from the different studies included in the analysis were noted in a tabular form. All disagreements were resolved by the third and fourth authors.

Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 (The Cochrane Collaboration, Oxford, UK) software. The different types of bias looked for have been elaborated previously in a previous meta-analysis.[11]

For continuous variables, the outcomes were expressed as mean differences (MD). Conventional units were used for analysis. For dichotomous outcomes (treatment success) results were expressed as risk ratios with 95% confidence intervals (CI). For adverse events, results were expressed as absolute risk differences after treatment. RevMan 5.4 was used for comparing MD of the different primary and secondary

outcomes between the GH therapy and the control groups. Heterogeneity was initially assessed using forest plots for the primary and secondary outcomes. Subsequently, heterogeneity was analysed using the chi^2 test on *N*-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test.[12] The details of the assessment and interpretation of heterogeneity have already been elaborated elsewhere.[11]

An overall grading of the evidence related to each of the primary and secondary outcomes of the meta-analysis was performed using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach.[13] The details of how grading of the study results was performed and how the summary of findings table was developed [Table 1] have been elaborated elsewhere.[11] Publication bias was assessed by plotting the funnel plot, which specifically targets small study bias, in which small studies tend to show larger estimates of effects and greater variability than larger studies.[12] The presence of one or more of the smaller studies outside the inverted funnel plot was taken as evidence of the presence of significant publication bias.[14]

Data was pooled as random effect model for the analysis of primary and secondary outcomes. The outcomes were expressed as 95% CI. Forest plots were plotted using RevMan 5.4 software, with the left side of the graph favouring GH therapy for MASLD and the right side of the graph favouring control. $P < 0.05$ was considered statistically significant.

Results

A total of 1,047 articles were found after the initial search [Figure 1]. Thirty-two duplicates were removed. Following the screening of the titles, the number of articles was reduced to 222. After a detailed screening of the abstracts, the number of articles was reduced to 25, whose full texts were evaluated in detail [Figure 1]. Finally, data from three RCTs that fulfilled all the criteria were analysed in this meta-analysis.[7-9] The baseline characteristics of the study participants are elaborated in Supplementary Table 1. In the study by Dichtel *et al.*,[7] GH starting doses were 0.2 mg/day in men and 0.3 mg/day in women. In the study by Xue *et al.*,[8] GH was started at a dose of 0.033 mg/kg/day. In the study by Pan *et al.*,[9] GH was started at a dose of 0.5 mg/day. GH dose titration was performed in all studies based on IGF-1 levels on follow-up.

Risk of bias in the included studies

The summaries of the risk of bias of the three studies included in the meta-analysis have been elaborated in Supplementary Figure 1a and b. Random sequence generation, incomplete outcome data (attrition bias) and selective reporting (reporting bias) were judged to be at low risk in all three studies (100%). Selection bias, performance bias and detection bias were at low risk in one out of three studies (33%). Source of funding, especially pharmaceutical, authors from the pharmaceutical organisations and conflict of interests were looked in the "other bias" section. Other biases were judged to be high risk in two of the studies (67%).

Effect of GH on hepatic lipid content and body composition parameters

After 6 months of clinical use in patients with MASLD, per cent reduction in intrahepatic lipid as determined by MRS was significantly higher with GH as compared to placebo [MD -5.85% (95% CI: -11.41 – -0.30); $P = 0.04$; $I^2 = 63\%$ (moderate heterogeneity (MH)); $n = 59$; Figure 2a]. Dichtel *et al.*[7] showed that intrahepatic lipid (proton density fat fraction) reduction was significantly higher with GH as compared to placebo [MD -3% (95% CI: -5.12 – -0.88);

Table 1: Summary of findings of the key outcomes of this systematic review and metanalysis

Outcomes	Anticipated absolute effects* (95% CI)		№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo (6-months)	Risk with growth hormone		
Body mass index	The mean body Mass Index was 36.3 kg/m^2	MD 0.89 lower (2.64 lower to 0.86 higher)	61 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
Visceral adipose tissue area (DXA)	The mean visceral adipose tissue area (DXA) was 147.4 cm^2	MD 9.94 lower (19.04 lower to 0.84 lower)	59 (2 RCTs)	⊕⊕⊕⊕ High
Total body lean mass (DXA)	The mean total body lean mass (DXA) was 59.5 kg	MD 0.99 lower (3.82 lower to 1.83 higher)	59 (2 RCTs)	⊕⊕⊕◯ Moderate[c]
Intrahepatic lipid (MRS)	The mean intrahepatic lipid (MRS) was 16.4%	MD 5.85 lower (11.41 lower to 0.3 lower)	59 (2 RCTs)	⊕⊕⊕◯ Moderate[d]
Fasting glucose	The mean fasting Glucose was 90 mg/dl	MD 0.25 lower (3.28 lower to 2.79 higher)	105 (3 RCTs)	⊕⊕⊕⊕ High
GGT	The mean GGT was 33.75 U/L	MD 7.86 lower (12.46 lower to 3.27 lower)	64 (2 RCTs)	⊕⊕⊕⊕ High

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); CI: confidence interval; MD: mean difference; [a]. Heterogeneity I^2=79%; [b]. Heterogeneity I^2=51%; [c]. Heterogeneity I^2=77%; [d]. Heterogeneity I^2=63%; DXA: dual-energy X-ray absorptiometry; MRS: magnetic resonance spectroscopy; GGT: gamma-glutamyl transpeptidase. GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

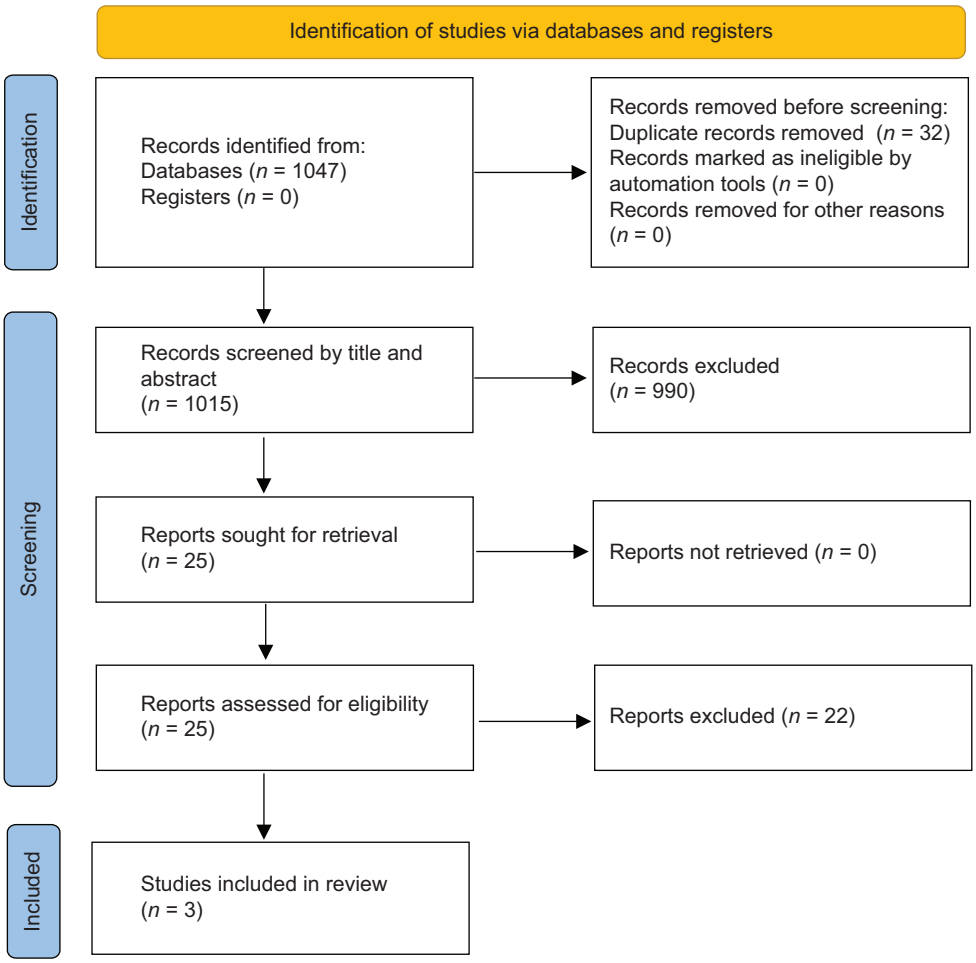

Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis. RCT: randomised controlled trial

P = 0.005]. After 6 months, in patients with MASLD, *VAT area reduction as determined using dual-energy X-ray absorptiometry (DXA) was* significantly higher with GH as compared to controls [MD -9.94 cm^2 (95% CI: -19.04 – -0.84); *P* = 0.03; I^2 = 0% (low heterogeneity (LH)); *n* = 59 Figure 2b]. Total body lean mass [MD -0.99 kg (95% CI: -3.82 – 1.83); *P* = 0.49; I^2 = 77% (MH); *n* = 59] was not significantly different after 6 months of GH therapy as compared to placebo.

Effect of GH on anthropometry

Six-month GH therapy in MASLD was not associated with any significant difference in BMI [MD -0.89 kg/m^2 (95% CI: -2.64 – 0.86); *P* = 0.32; I^2 = 79% (MH); *n* = 61 Figure 2c] and waist circumference [MD -4.58 cm (95% CI: -12.45 – 3.3); *P* = 0.25; I^2 = 66% (MH); *n* = 61 Figure 2d] as compared to placebo.

Effect of GH on serologic and hormonal parameters

After 6 months therapy, serum insulin-like growth factor-1 (IGF-1) was significantly raised in MASLD patients receiving GH as compared to placebo [MD +166.86 ng/ml (95% CI: 79.19 – 254.53); *P* < 0.0.001; I^2 = 90% (considerable heterogeneity (CH)); *n* = 105 Figure 3a].

IGF-1 Z was significantly higher in patients receiving GH as compared to placebo [MD 1.40 (95% CI: 1.10 – 1.70); *P* < 0.0.001; I^2 = 0% (low heterogeneity (LH)); *n* = 61 Figure 3b]. High-sensitivity C-reactive protein (hsCRP) was significantly lower in patients receiving GH as compared to placebo [MD -0.89 mg/L (95% CI: -1.40 – -0.38); *P* = 0.0006; I^2 = 0% (low heterogeneity (LH)); *n* = 105, Figure 3c].

Safety

After 6 months of therapy, patients receiving GH had similar changes in triglycerides [MD -1.06 mg/L (95% CI: -20.45 to 18.34); *P* = 0.91; I^2 = 15% (LH); Figure 4a], low-density lipoprotein cholesterol (LDL-C) [MD -8.65 mg/L (95% CI: -18.23 to 0.93); *P* = 0.08; I^2 = 26% (LH); Figure 4b], high-density lipoprotein cholesterol (HDL-C) [MD 1.63 mg/L (95% CI: -1.41 to 4.67); *P* = 0.29; I^2 = 48% (MH); Figure 4c], fasting plasma glucose [MD -0.56 mg/L (95% CI: -4.67 to 3.55); *P* = 0.79; I^2 = 39% (LH); Figure 4d] and alanine transaminase [MD -7.45 U/L (95% CI: -15.24 to 0.35); *P* = 0.06; I^2 = 66% (MH); Figure 4e] as compared to placebo. Gamma-glutamyl transferase was significantly lower in patients receiving GH as compared to placebo [MD -7.86 U/L (95% CI: -12.46 to -3.27); *P* = 0.0008; I^2 = 0% (LH); Figure 4f]. Patients receiving GH had a similar incidence of new-onset hypothyroidism as compared to placebo OR 5.49 (95% CI: 0.25 – 121.18); *P* = 0.28]. The summary

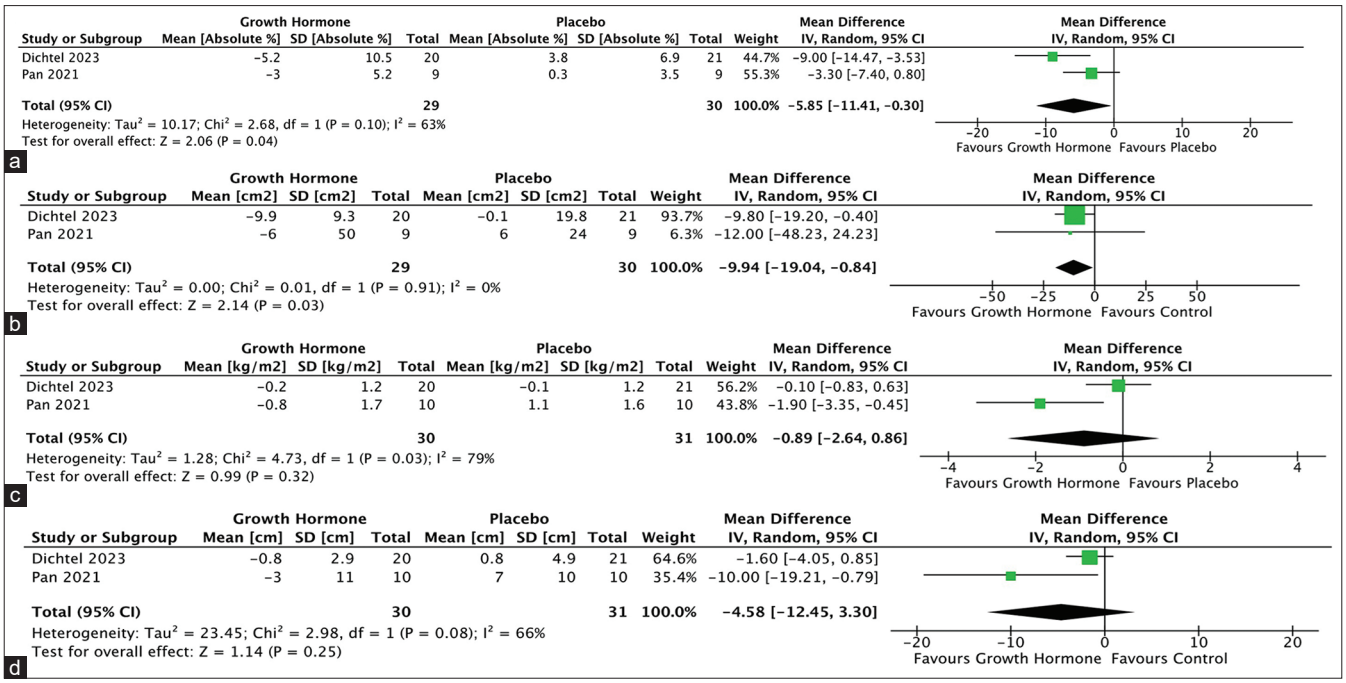

Figure 2: Forest plot highlighting the impact of growth hormone therapy as compared to placebo therapy on (a) intrahepatic lipid as determined by magnetic resonance spectrometry (MRS); (b) visceral adipose tissue area as determined by dual-energy X-ray absorptiometry (DXA) (c) body mass index (d) waist circumference

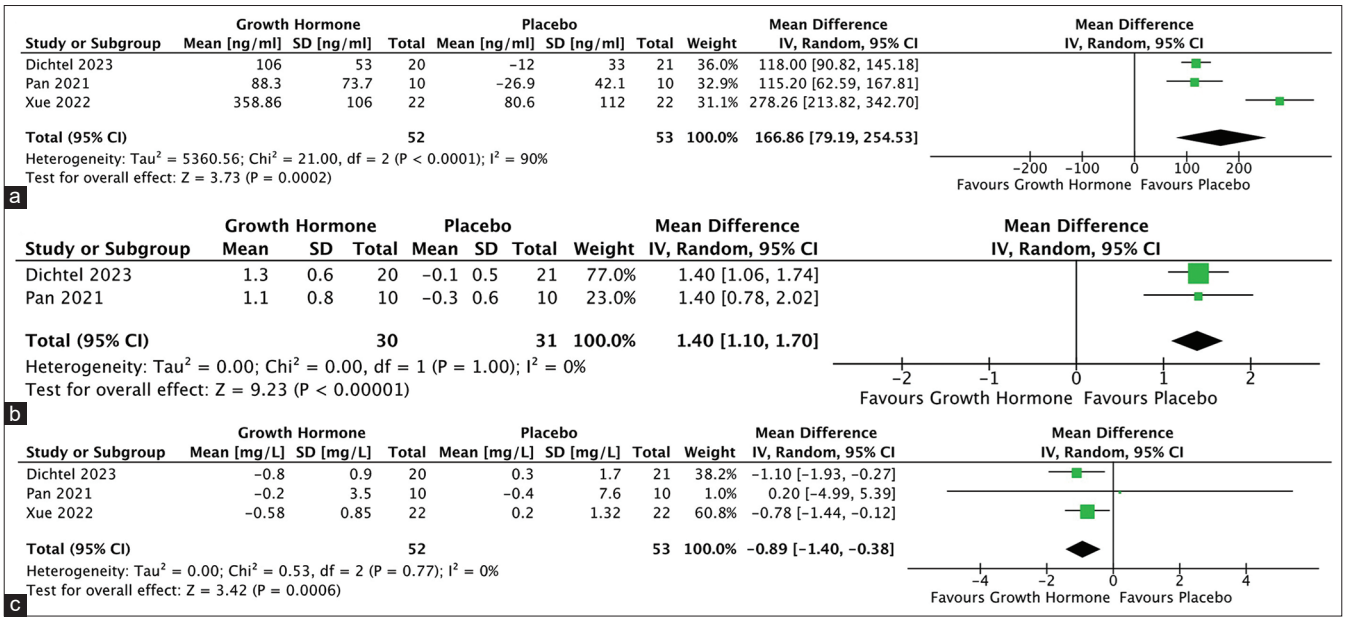

Figure 3: Forest plot highlighting the impact of growth hormone therapy as compared to placebo (a) insulin-like growth factor-1 (IGF-1); (b) IGF-1 Z scores; (c) High-sensitivity C-reactive protein

of findings of the key outcomes of this SRM has been elaborated in Table 1. Publication bias have been elaborated in Supplementary Figure 2.

Discussion

This is the first SRM to evaluate the efficacy and safety of GH therapy for managing MASLD. Our analysis showed that short-term GH therapy for 6 months in patients with MASLD was associated with a significant reduction in hepatic fat content as estimated using MRS. An overall significant reduction in visceral fat was noted, as estimated using DXA. These findings align closely with the "twin cycle hypothesis" emphasising the importance of significant reduction in visceral fat, especially hepatic for the resolution of metabolic syndrome. This reduction is especially critical for remission of recent onset

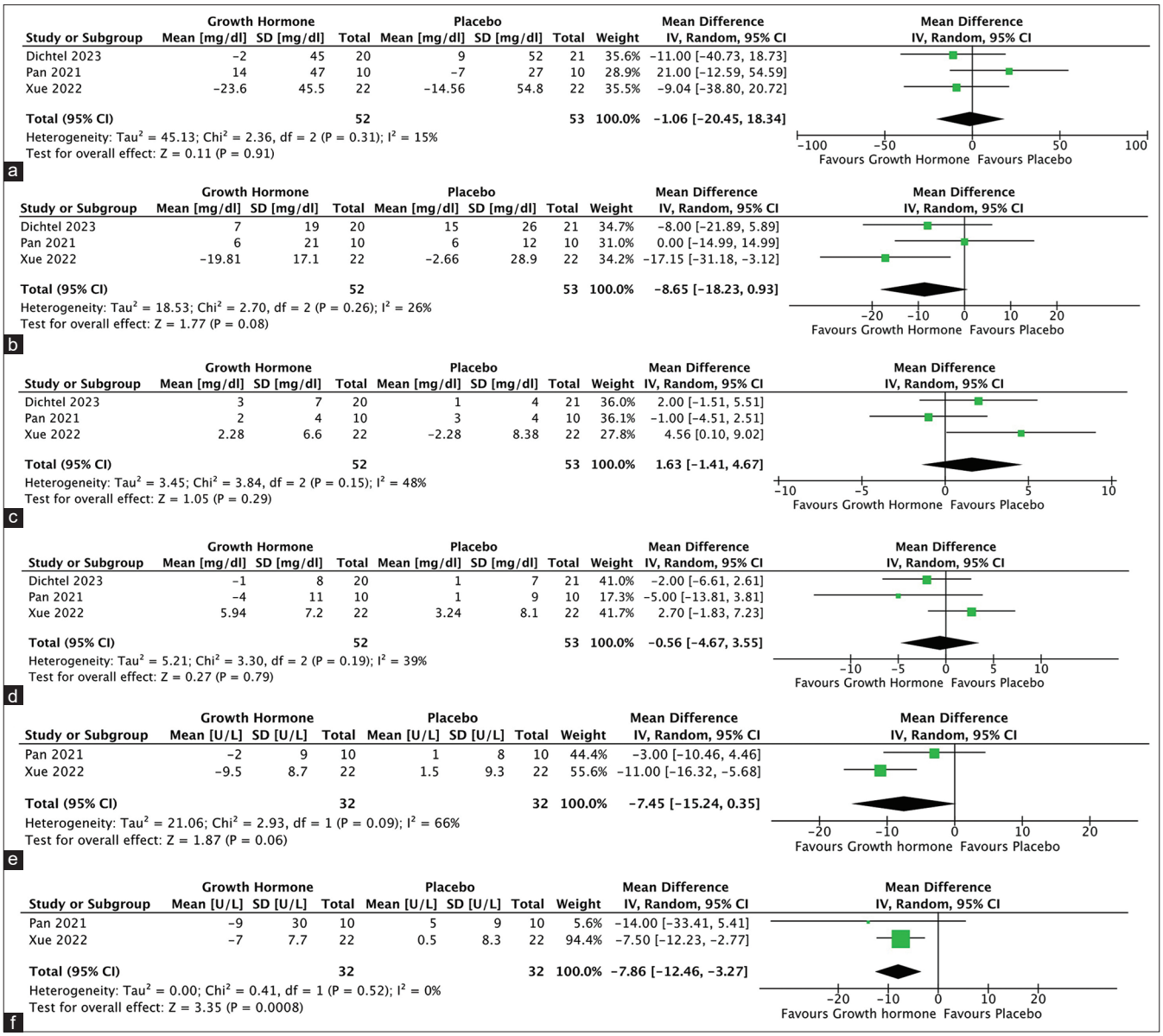

Figure 4: Forest plot highlighting the impact of growth hormone therapy as compared to placebo on (a) triglycerides; (b) low-density lipoprotein cholesterol (LDL-C); (c) high-density lipoprotein cholesterol (HDL-C); (d) fasting plasma glucose (FPG); (e) alanine transaminase; (f) gamma-glutamyl transferase

type 2 diabetes in individuals with diabesity.[15] A significant reduction in serologic markers of MASLD like GGT (mean reduction -7.86 U/L) was also noted. A reduction in alanine aminotransferase was also noted (mean reduction -7.45 U/L) with approached statistical significance. A beneficial impact on reduction in systemic inflammation was also noted, as documented by reduction in circulating levels of hsCRP.

As expected, GH therapy was associated with a significant increase in absolute circulating levels as well as Z scores of IGF-1. It was reassuring to see that short-term GH therapy in MASLD (a cohort of patients who are already at a high risk of T2DM) was not associated with an increased risk of new-onset diabetes or dysglycaemia and hypothyroidism. This is likely due to the overall benefits of the treatment in visceral adiposity and the low dose of GH used. GH therapy for short stature in children (at much higher doses) has been linked with dysglycaemia and new-onset hypothyroidism.[2]

The precise pathophysiological mechanism underlying the effectiveness of short-term GH treatment in MASLD remains incompletely understood. However, a potential explanation is as follows: IGF-1 has been demonstrated as a protective factor against MASLD, playing a pivotal role in preventing the development of MASLD.[16] Secondly, it is suggested that GH could contribute to the improvement of hepatic steatosis by positively influencing lipid metabolism.[17] GH might play a role in ameliorating hepatocyte steatosis by inhibiting de novo lipogenesis through the downregulation of carbohydrate-responsive element-binding protein and fatty acid synthase.[18]

One notable limitation of this SRM is the limited number of studies and patients included in the analysis. This limitation may have contributed to the observed lack of statistical significance concerning the reduction in alanine aminotransferase levels. Secondly, liver biopsies were not performed in the studies. Despite these limitations, the SRM exhibits strengths in showcasing that, even within a relatively small cohort of patients with MASLD, a 6-month course of GH therapy yielded significant reductions in hepatic and visceral adiposity, coupled with improvements in serologic markers of MASLD. This SRM underscores the critical need for larger RCTs involving more substantial cohorts of patients and extended follow-up durations, evaluating the impact of GH therapy on improving MASLD in patients diagnosed with AGHD, followed by an extension to encompass individuals with MASLD more broadly. To conclude, it may be said that short-term 6-month GH therapy in MASLD is associated with a significant reduction in intrahepatic lipid content, visceral adiposity, GGT and hsCRP without any increased occurrence of dysglycaemia or hypothyroidism.

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None.

Authors' contribution

The study was conceptualized by DD. Literature search was done by LN, RM and AKH. Data entry was done by SB and AJ. Data analysis and graphs generation was done by DD, LN and AKH. All authors contributed equally to the manuscript preparation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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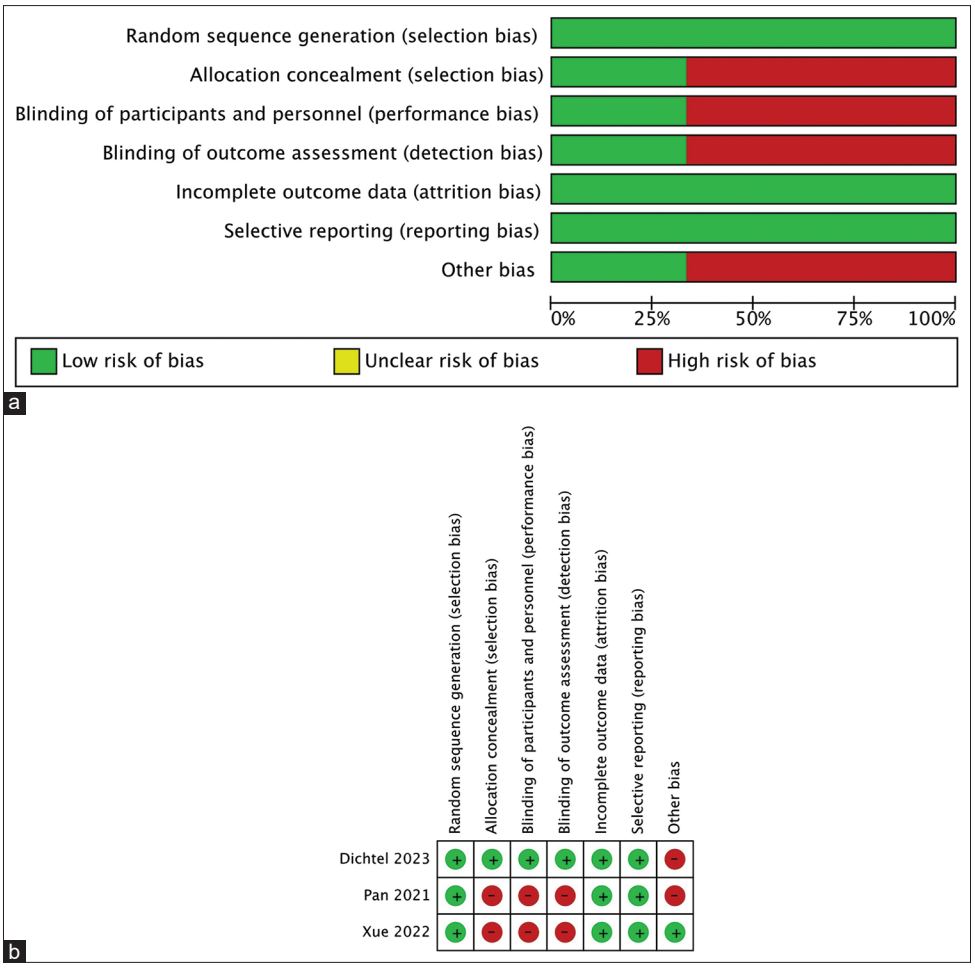
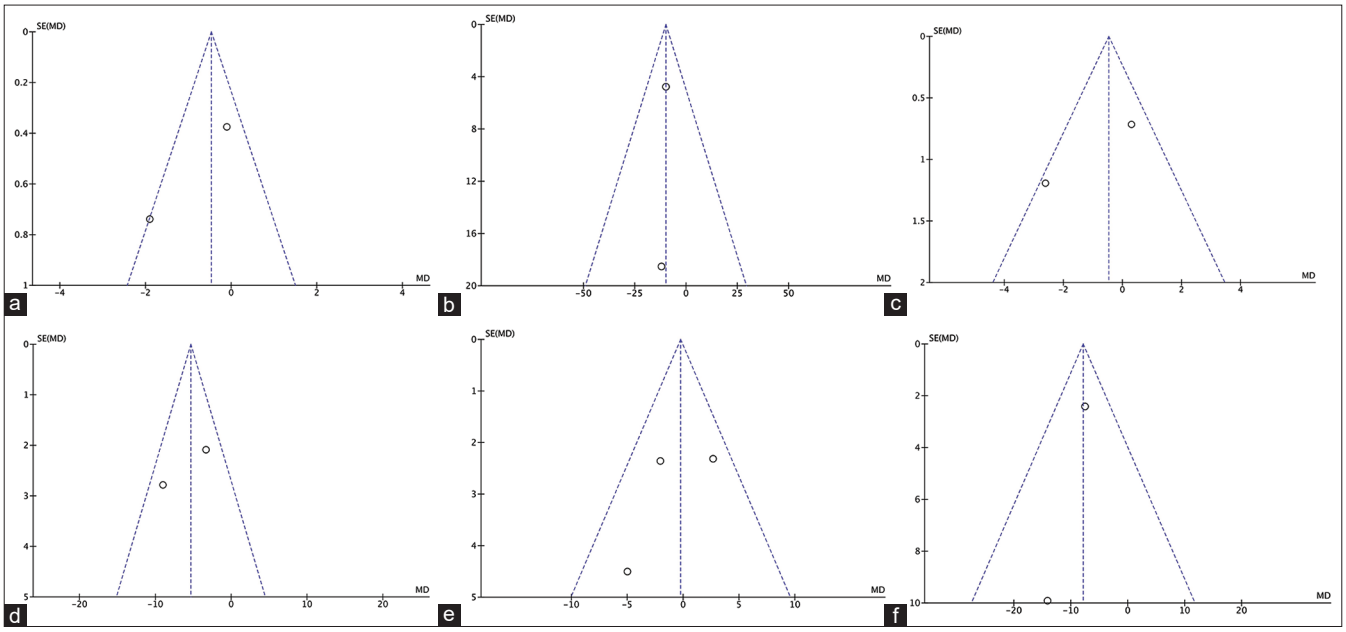


Supplementary Figure 1: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Supplementary Figure 2: Funnel plots to look at the presence of publication bias for the following outcomes comparing growth hormone to placebo (a) body mass index; (b) visceral adipose tissue area estimated using dual-energy X-ray absorptiometry (DXA); (c) total body lean mass (DXA); (d) Intrahepatic lipid using magnetic resonance spectroscopy (MRS); (e) Fasting glucose (f) Gamma-glutamyl transpeptidase (GGT)

Supplementary Table 1: Profile of patients analysed in the different randomised controlled trials in this meta-analysis

	Dichtel *et al*[7]		Xue *et al*[8]		Pan *et al*.[9]	
	GH group (*n*=26)	Placebo group (*n*=26)	GH group (*n*=22)	Placebo group (*n*=22)	GH group (*n*=13)	Placebo group (*n*=11)
Age (years)	46.1±11.8	45.8±12.5	12.04±1.56	11.48±1.78	25±3	23±4
Males	13 (50%)	13 (50%)			8 (61.5%)	5 (45.4)
BMI (kg/m^2)	33.6±5.1	32.3±6.3	2.56±0.65*	2.75±0.61*	40.5±6.6	39.3±7.3
Intrahepatic lipid (%)	24.7±14.8	18.3±13.8	-	-	12.1±7.2	10.4±7.6
Total body fat (%)	37.6±7.2	36.9±6.5	-	-		
Total lean body mass (kg)	60.7±14.1	56.8±12.4	-	-	61.5±7.6	59.7±10.5
ALT (IU/L)	34±17	40±57	24.5 (14.75,46.0)**	26.53 (17.00,60.25)**	29±22	27±13
AST (IU/L)	24±8	25±16	25.50 (22.00,29.75)**	24.50 (21.50,34.25)**	24±15	21±3
Peak stimulated GH (ng/ml)	7.9±4.2	10.4±7.3	-	-	-	-
IGF-1 Z-score	0.0±0.6	-0.1±0.7	-	-	-0.7±0.6	-0.3±0.4
HbA1C (%)	5.5±0.3	5.4±0.2	-	-	-	-
Fasting glucose (mg/dl)	86±8	83±8	93.06±7.02	93.24±6.84	87±10	84±8
Total cholesterol (mg/dl)	184±26	189±26	176.72±23.2	172.47±37.51	-	-
Triglycerides (mg/dl)	131±70	129±42	116.92 (74.4, 165.63)**	107.17 (81.49, 139.95)**	110±50	98±31
HDL Cholesterol (mg/dl)	46±11	46±10	47.95 (41.38,54.14)**	46.40 (41.38,52.98)	42±7	40±6
LDL Cholesterol (mg/dl)	113±23	119±25	104.8±17.4	103.63±30.55	103±33	96±39
GH therapy regimen	GH starting doses were 0.2 mg/day in men and 0.3 mg/day in women. Dose titrations were performed based on IGF-1 levels by the unblinded study monitor at the 1-month, 2-month and 3 month visits.		Daily dose of GH was 0.1 IU/kg (0.033 mg/kg). GH doses were adjusted based on weight levels and IGF-1 level at these visits.		GH was started at a dose of 0.5mg daily & adjusted according to IGF-1 z-score at 2, 4, 6, 12 and 18 weeks to reach a target z-score between 0–2. A 20% dose increase was performed for any rhGH-treated subject with IGF-1 z-score ≤0. Conversely, a 20% decrease was performed for any rhGH-treated subject with IGF-1 z-score >2.	

Normally distributed continuous variables have been expressed as mean±standard deviation; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; GH: growth hormone; IGF-1: Insulin-like growth factor 1; HbA1C: Glycated haemoglobin; *BMI in standard deviation score; **Median (Inter-quartile range)