# The Effects of Testosterone Replacement Therapy in Adult Men With Metabolic Dysfunction-Associated Steatotic Liver Disease: A Systematic Review and Meta-analysis

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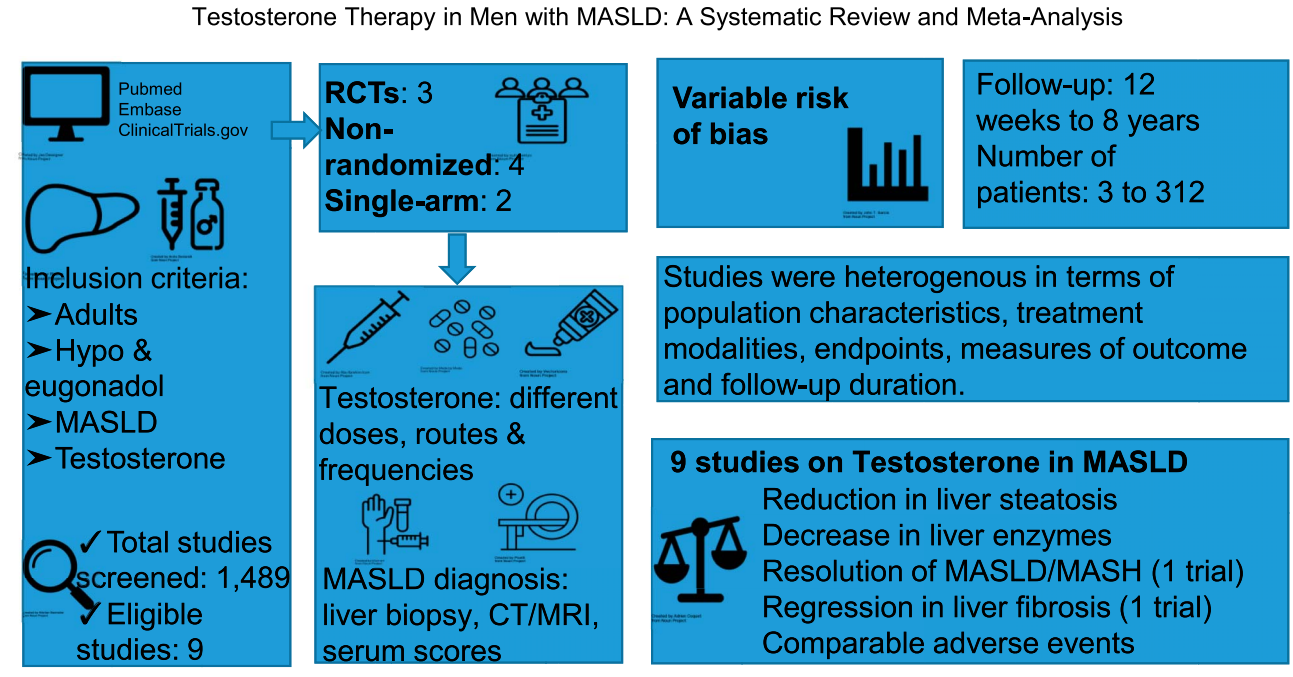
INTRODUCTION: **Sex steroids modulate metabolic dysfunction-associated steatotic liver disease (MASLD) pathobiology. We hypothesized that testosterone treatment (TT) modulates progression of MASLD and performed a systematic review to evaluate the efficacy of TT on liver steatosis and fibrosis.**

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REVIEW ARTICLE

METHODS: **We searched PubMed and Embase from inception until November 2023. We screened 1,489 studies and identified 9 eligible studies. We assessed risk of bias for randomized trials using RoB-2 "Cochrane risk of bias tool for randomized trials," nonrandomized studies using ROBINS-I tool "Risk of Bias In Nonrandomized Studies—of Interventions," and Murad's tool for single-arm studies. We pooled estimates using RevMan 5.**

RESULTS: **Three randomized controlled trialsl, 4 nonrandomized studies, and 2 single-arm studies were identified. The population of interest comprised men with MASLD. TT was administered at varying doses, routes, and frequencies, with follow-up ranging from 12 weeks to 8 years. Liver fibrosis and steatosis were assessed using liver biopsy in 3 studies, CT/MRI in 5, and serum scores in 2. All studies provided evidence of reduction in liver steatosis with TT compared with no TT. In addition, the LiFT (randomized controlled trials) trial demonstrated a resolution of MASLD/ metabolic dysfunction-associated steatohepatitis and a regression in liver fibrosis. TT led to decrease in liver enzymes. Studies were heterogenous in terms of population characteristics, treatment modalities, endpoints, and follow-up. Adverse events were comparable between the 2 groups.**

DISCUSSION: **TT is a promising treatment option for men with MASLD and low testosterone. It may improve liver steatosis and reduce liver fibrosis. Large, double-blinded randomized placebo-controlled trials are needed.**

**KEYWORDS:** testosterone; MASH; MASLD; NASH; NAFLD

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/CTG/B218

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## INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease, is characterized by the excessive accumulation of fat in the liver, affecting 30% of the global population (1,2). Despite the benign nature of MASLD, it does progress to metabolic dysfunction-associated steatohepatitis (MASH), previously known as non-alcoholic steatohepatitis (NASH), in about 20%–30% of patients. MASH is characterized by inflammation in both the lobular and portal areas, hepatocyte ballooning, and fibrosis (3). MASH can progress to cirrhosis and hepatocellular carcinoma.

Metabolic syndrome stands out as a significant risk factor for the onset of liver disease, encompassing factors such as obesity, elevated blood glucose, cholesterol, triglyceride levels, and excess adipose deposition around the waist (4). Sex hormones, particularly estrogens and androgens, also play a role in the risk of liver disease development. Epidemiological studies have highlighted genetic sex and age as crucial factors for MASLD, with postmenopausal women being twice as susceptible as premenopausal women—a trend consistent with a protective role for estrogens. However, the underlying mechanisms remain understudied (5). In men, testosterone deficiency has been linked to the accumulation of visceral adiposity, insulin resistance, and metabolic syndrome (6).

Despite the increasing global burden of MASLD, only one medication, resmetirom (an oral thyroid hormone receptor-beta agonist) has recently received accelerated approval by the Food and Drug Administration (FDA) for the treatment of adults with noncirrhotic MASH with moderate to advanced liver fibrosis (7–9). The process of drug development in this field has been notoriously challenging, leading to the term "MASLD/MASH graveyard" (10). The FDA endpoints for late-stage development in clinical trials for MASH concentrate on histological criteria, specifically aiming for MASH resolution without worsening of fibrosis or an improvement of at least one fibrosis stage without worsening of steatohepatitis. The approach to managing MASLD primarily involves lifestyle modifications and weight loss. As an example, resmetirom has been approved for use in conjunction with diet and exercise. Various drugs with diverse mechanisms of action are also currently undergoing phase 2 and 3 development for the treatment of this metabolic liver disease and may soon be integrated into clinical practice. Studied drugs include peroxisome proliferator-activated receptors, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and farsenoid X receptor agonists (11).

Numerous studies have explored the relationship between TT and MASLD/MASH. Below, we present our unique systematic review evaluating the effectiveness and safety of testosterone treatment in the management of MASLD or MASH in adult men.

## METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (12) for the reporting of this systematic review, and a protocol was registered in PROSPERO (registration ID: CRD42024504883).

### Search strategy and data sources

We systematically searched the published literature in PubMed and Embase from inception till November 2023 for studies assessing the outcomes of testosterone use in patients with MASLD. In addition, we searched manually for registered clinical trials on ClinicalTrials.gov. A full search strategy can be found in Supplementary 1 (see Supplementary Digital Content, http://links.lww.com/CTG/B218).

### Eligibility criteria

Pairs of independent reviewers (M.M., N.M., M.A., and H.K.) screened the title and abstract and the full text of all the identified

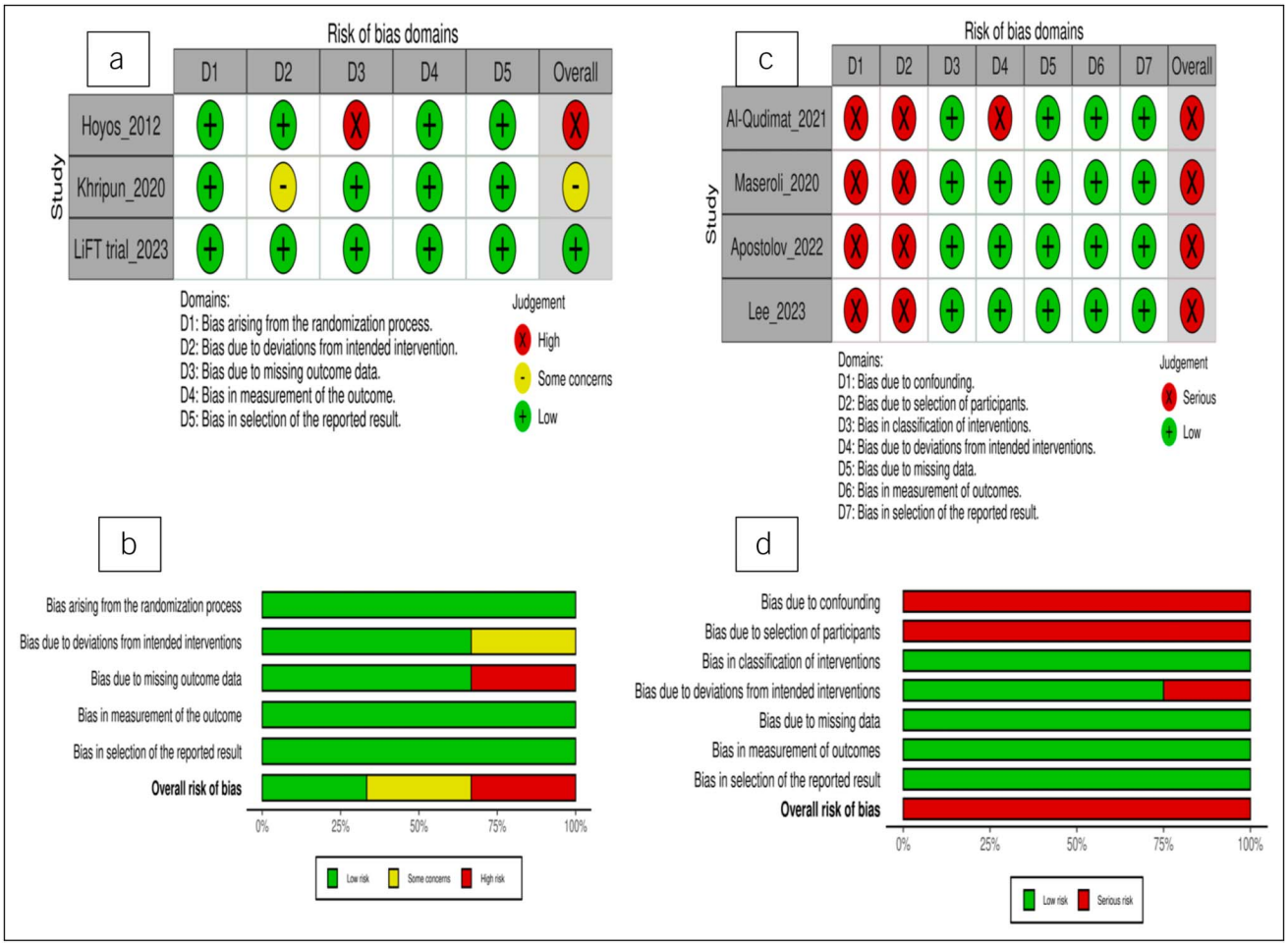


**Figure 1.** Quality assessment. (**a, b**) Risk-of-bias graph and summary according to revised Cochrane risk-of-bias tool for randomized trials (RoB 2). (**c, d**) Risk-of-bias graph and summary according to the Risk of Bias In Nonrandomized Studies—of Interventions (ROBINS-I) assessment tool.

citations using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to assess their eligibility. Disagreements between the reviewers were resolved by a third reviewer.

Patients were eligible if they were adults (>18 years) with or without hypogonadism and had MASLD. We excluded studies assessing the outcomes of testosterone use in patients with alcoholic liver disease, liver cirrhosis, or liver cancer. The intervention of interest was testosterone treatment regardless of the dose, route, formulation, and duration. Studies assessing testosterone alone or comparing it with a placebo were eligible; this means we included randomized controlled trials (RCTs), nonrandomized comparative studies (NRS), and noncomparative observational studies. We excluded case reports, conference abstracts, and any study about basic research in animals.

### Data extraction and synthesis

Pairs of reviewers (M.M., N.M., M.A., and H.K.) extracted data using a standardized spreadsheet in Microsoft Excel (Microsoft Corp, Redmond, WA) with 1 primary extractor and 1 secondary reviewer assigned to each tool. Disagreements were discussed among the reviewers to reach a consensus. For each study, we extracted the following: data related to the study (author, year of publication, and study design); study population (number of patients, age, sex, hypogonadal or not, and diagnostic criteria of MASLD); intervention (testosterone dose, route, formulation, and duration of treatment); outcomes (histological, radiological, and laboratory efficacy outcomes and adverse events); and follow-up duration. We summarized the extracted data from all studies in tables using Microsoft Word (Microsoft Corp, Redmond, WA).

### Risk of bias

For evaluation of risk of bias, reviewers used Version 2 of the Cochrane risk-of-bias tool for randomized trials (https://methods.cochrane.org/bias/), Risk of Bias In Nonrandomized Studies—of Interventions (https://methods.cochrane.org/bias/), and Murad's tool (13) for evaluating RCTs, observational comparative studies, and noncomparative studies, respectively.

### Statistical analysis

We performed statistical pooling of estimates across studies using Review Manager 5 through a random-effects model because of the clinical and methodological heterogeneity across studies. For continuous variables, the pooled estimates were presented as the mean difference (MD) (95% confidence interval [CI]). When data were reported as medians with ranges or interquartile ranges in the studies, we used Hozo's method to convert the medians to

**Table 1. Testosterone treatment vs no testosterone in adult men with MASH/MASLD**

| Author, year | Study design | Diagnosis | Population | Testosterone | TT (n) | No TT (n) | Outcomes | Follow-up duration |
|---|---|---|---|---|---|---|---|---|
| Comparative studies | | | | | | | | |
| LiFT trial, 2023 | RCT | Biopsy-proven MASH | Hypogonadal and eugonadal | LPCN 1144, 450 mg TU daily, oral | 18 | 19 | Hepatic steatosis, hepatic fibrosis, liver enzymes, and adverse events | 36 wk |
| Hoyos, 2012 | RCT | MASLD (CT) | Hypogonadal | Reandron, 1,000 mg TU, IM at 0, 6 and 12 wk | 33 | 34 | Hepatic steatosis, liver enzymes, and adverse events | 18 wk |
| Khripun, 2020 | RCT | MASLD (MRI) | Hypogonadal | AndroGel, 1% T gel, 50 mg daily, transdermal | 30 | 30 | Hepatic steatosis, liver enzymes, and adverse events | 6 mo |
| Al-Qudimat, 2021 | NRS | FL | Hypogonadal | 1,000 mg TU parenteral, every 12 wk, after initial 6-wk interval | 312 | 184 | Hepatic steatosis, liver enzymes, and adverse events | 8 yr |
| Lee, 2023 | NRS | MASLD (CT) | Hypogonadal | AndroGel, 1% T gel, transdermal, 5 g daily titrated to maintain serum T | 23 | 19 | Hepatic steatosis | 12 mo |
| Maseroli, 2020 | NRS | FLI and biopsy | Hypogonadal | 1,000 mg TU, IM, every 12 wk, after initial 6-wk interval | 15 | 46 | Hepatic steatosis | Mean 30 wk |
| Apostolov, 2022 | NRS | MASLD (MRI) | Hypogonadal | 1,000 mg TU, IM, at 0, 6, 18, and 30 wk | 20 | 19 | Hepatic steatosis and liver enzymes | 40 wk |
| Noncomparative studies | | | | | | | | |
| Terepins, 2021 | Single arm study | Biopsy-proven MASH | Hypogonadal | LPCN 1144, 450 mg TU daily, oral | 3 | NA | Hepatic steatosis and hepatic fibrosis | 52 wk |
| Albhaisi, 2020 | Single arm study | MASLD (MRI) | Hypogonadal | LPCN 1144, 450 mg TU daily, oral | 21 | NA | Hepatic steatosis, liver enzymes, and adverse | 16 wk |

CT, computed tomography; FLI, Fatty Liver Index; IM, intramuscular; LPCN: orally bioavailable prodrug of bioidentical endogenous testosterone; MASLD, metabolic dysfunction-associated steatotic liver disease; NRS, nonrandomized study; RCT, randomized controlled trial; T, testosterone; TT, testosterone treatment; TU, testosterone undecanoate.

means to include the studies in the meta-analysis (14). For dichotomous variables, we used relative risk (95% CI). However, when the number of events included zeros in both arms, we used risk difference (95% CI) to account for these studies in pooled estimates (15).

It was not feasible to conduct a formal publication bias assessment using funnel plots because of the small number of studies (Figure 1).

## RESULTS

### Search results and characteristics of included studies

Our search retrieved 2,317 records from searching electronic databases and websites. After title and abstract screening, we retrieved and assessed 93 full-text articles for eligibility. Among them, 84 articles were excluded, and 9 were reviewed in detail and included in this systematic review (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram; see supplementary 1, Supplementary Digital Content, http://links.lww.com/CTG/B218).

We identified 3 RCTs, 4 nonrandomized controlled studies, and 2 single-arm studies. Among these, 3 studies were conducted at multiple centers in the United States, 2 in Australia, 1 in Germany and Qatar, and 1 in each of Italy, Russia, and the United Kingdom. All the studies included were conducted between 2012 and 2023. Comparative studies compared testosterone treatment with either no intervention or placebo. Three studies enrolled patients with biopsy-proven MASLD/MASH, 5 studies enrolled patients with imaging-defined MASLD/MASH, and 2 involved patients with biochemical evidence of MASLD/MASH Fatty Liver Index (FLI). Most studies had a small sample size (fewer than 35 individuals per treatment arm, except for 1 study with 312 individuals). The follow-up period ranged from 16 weeks to 8 years. Among the included studies, 3 reported the use of parenteral testosterone undecanoate, 3 reported the use of LPCN 1144 (an oral prodrug of bioidentical testosterone), 1 trial used Reandron (parenteral testosterone in castor oil), and 2 studies used AndroGel (testosterone gel). A summary of the characteristics of the included studies is available in Table 1.

### Assessment of risk of bias

According to the Cochrane ROB-2 tool, one trial had a low risk of bias (LiFT trial), one had some concerns (Khripun et al), and one had a high risk of bias (Hoyos et al [16]). The primary concern was related to the missing data domain, specifically related to the loss of follow-up (16). Using the ROBINS-I assessment tool, the risk of bias in the nonrandomized studies was serious because of selection bias and confounding (17–19). Figure 1 provides a summary of quality assessment domains, along with authors' judgments and justifications.

### Efficacy outcomes

All included studies reported on hepatic steatosis. Overall, these studies showed improvement in hepatic steatosis with testosterone treatment. Below, we categorized studies based on histologic, imaging, and biochemical diagnostic modalities used to assess steatosis.

### Histopathology

Maseroli et al (17) demonstrated that the mean MASLD activity score was significantly lower in the testosterone treatment group at 3.37 (2.9–3.38) compared with 4.65 (4.39–4.92) in the untreated group ($P < 0.05$). Similarly, the mean steatosis score was lower in the testosterone group (1.5 vs 2.13) ($P < 0.05$) (17). In the Terepins trial, fatty liver grade changed from 2 to 1 in the 3 subjects treated with LPCN 1144 after 52 weeks (20).

### Magnetic resonance imaging

Two RCTs (Lift trial, Khripun et al) reported on the hepatic fat fraction based on MRI. TT treatment resulted in a significant decrease in hepatic fat fraction when compared with placebo, with an MD (95% CI) in change from baseline of −6.66% (−8.92, −4.41). Although the route of TT differed between the 2 trials, the effect of TT on hepatic fraction was comparable. Figure 2 presents a forest plot illustrating the change in hepatic fraction on MRI from individual trials and the pooled estimate.

In the study by Apostolov et al (19), at week 40, subjects receiving parenteral testosterone had a median reduction in absolute liver fat as seen by MRI by 3.5% (interquartile range [IQR] 2.9%–6.4%) compared with an increase of 1.2% in the placebo arm ($P < 0.001$). After controlling for baseline liver fat, it was observed that testosterone treatment was associated with a 39.3% relative reductive in liver fat (95% CI, $P < 0.001$). Albhaisi et al (21) observed an improvement in hepatic fat content in 17 of 21 (81%) subjects treated with LPCN 1144 and a mean decrease of 4.04% in hepatic fat from baseline (21).

### Computed tomography

Hoyos et al (16) assessed hepatic steatosis using CT imaging and observed that testosterone treatment reduced liver fat by 0.11 Hounsfield units (HU) from baseline compared with 0.05 HU in the placebo group ($P = 0.03$) (16). Considering a diagnosis of MASLD based on CT criteria of liver HU <40 or liver-to-spleen ratio of <1, Lee et al (22) found that liver HU < 40 occurred in 16/65 (24.62%) from 23/71 (32.3%) subjects in the AndroGel group compared with 13/53 (24.53%) from 19/69 (27.5%) subjects in the placebo group ($P = 0.21$). They also observed that the odds ratio of liver-to-spleen ratio < 1 occurred in 11/52 (21.15%) from 12/55 (21.82%) in the treatment group compared with 14/46 (30.43%) from 13/62 (20.97%) in the placebo group ($P = 0.69$) (22).

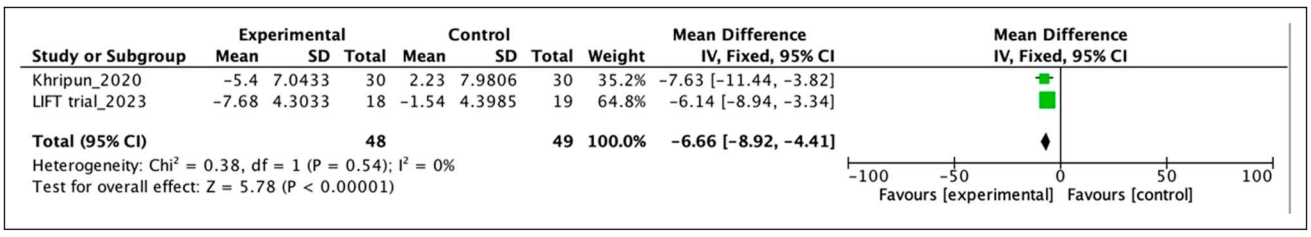


Figure 2. Forest plot of changes in hepatic fat fraction on MRI.

### Fatty Liver Index

Two nonrandomized studies reported on the change in FLI. The decrease in FLI was greater in the TT than in the placebo arm with an MD (95%CI) of −14.94 (−42.82, 12.94). It is worth mentioning that there is inconsistency in the results of the 2 studies. In the study by Al-Quidmat et al (18), the follow-up duration was 8 years versus 30 weeks in the study by Maseroli et al (17). In Maseroli et al (17), the FLI at baseline was the same for both arms, at 99, whereas in Al-Qudimat et al (18), the FLI was higher in the TT compared with placebo, at 83.7 and 68.81, respectively. The aforementioned factors could explain the inconsistency in the results between the 2 studies. Figure 3 presents a forest plot illustrating the change in FLI from individual studies along with the pooled estimate.

### Resolution of MASH/MASLD

Two studies reported on the resolution of MASH/MASLD. In the LiFT trial, resolution of MASH, defined as overall histopathologic improvement without worsening of liver fibrosis, was observed in 7 of 13 individuals (53.8%) in the LPCN 1144-treated subjects, compared with 1 of 11 individuals (9.1%) in the placebo group with an relative risk (RR) (95%CI) of 5.92 (0.85–41.02). The sample size and number of events were very small leading to a wide CI. Albhaisi et al (21) observed MASLD resolution, defined as a reduction in steatosis to <5% on MRI, in 10 of 21 subjects treated with testosterone (46.7%) .

### Hepatic fibrosis

Two studies reported on hepatic fibrosis, both using biopsy, and both demonstrating improvement. The LiFT trial demonstrated fibrosis improvement, defined as a regression of 1 stage or more, in 12 of 15 subjects treated with LPCN 1144 (80%), compared with 5 of 15 subjects receiving placebo (33.3%) with an RR (95% CI) of 1.77 (0.74–4.23). The small sample size and number of events led to a wide CI. The Terepins trial showed a mean change in central fibrosis of 2.75 in the 3 subjects treated with testosterone after 52 weeks (20).

### Liver enzymes

Three RCTs (n = 164) reported the mean change from baseline for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the TT and placebo arms, 2 RCTs (n = 97) for gamma-glutamyl transferase (GGT), and 1 RCT (n = 37) for alkaline phosphatase (ALP). Testosterone resulted in a greater decrease in all liver enzymes when compared with placebo.

The pooled estimates for change from baseline in AST, ALT, GGT, and ALP were greater in the TT arm than in the placebo arm, with an MD (95% CI) of −6.10 (−13.92, 1.73), −8.48 (−17.36, 0.40), −8.46 (−16.20, −0.72), and −6.20 (−13.11, 0.71), respectively (Figure 4). Data on liver enzymes from the NRS and single-arm studies are provided in Supplementary 2 (see Supplementary Digital Content, http://links.lww.com/CTG/B218).

### Testosterone safety profile

Four comparative studies reported on the safety profile and adverse events in patients receiving testosterone treatment. The pooled estimates from 3 RCTs show no significant difference in the rate of adverse events in patients receiving TT and those receiving placebo, with a risk difference (95% CI) of −0.03 (−0.14, 0.08).

Figure 5 presents a forest plot displaying the event rates from individual studies and the pooled estimates for adverse events.

None of the studies reported any cases of prostate cancer in either the TT or placebo arms. In the LiFT trial, there was 1 event of benign prostate hyperplasia in the placebo arm, and 1 of 18 patients in the TT arm experienced an elevation in prostate specific antigen (PSA). Another study (Hoyos et al [16]) reported a higher MD in PSA between the TT and placebo groups, with an MD (95% CI) of 0.24 (0.10–0.38).

Two RCTs and 1 NRS reported on the rates of myocardial infarction. The pooled estimates from the 2 RCTs indicate higher rates of myocardial infarction in the TT arm, with a relative risk (95% CI) of 3.12 (0.34,29.01). The number of events is very small, resulting in a wide CI. In the study by Al-Qudimat et al (18), the rates of myocardial infarction-related mortality were lower in the TT arm, with an RR (95%) of 0.23 (0.08, 0.63). However, this finding is based on a nonrandomized study with selection bias and confounding factors.

Rates of new-onset hypertension were higher in the TT arm, with RR (95% CI) of 3.17 (0.36–27.27) from the Lift trial. Blood pressure was also higher in the TT group when compared to the placebo arm, with an MD (95% CI) of 2.3 (−3 to 7.6) mm Hg (Hoyos et al [16]). Figure 6 shows a forest plot illustrating the event rates from individual studies and the pooled estimates for myocardial infarction.

Interestingly, none of the studies reported any event of hepatic adenoma or hepatocellular carcinoma in either the TT or placebo arms.

## DISCUSSION

To the best of our knowledge, this systematic review is the first to summarize and analyze the available evidence on the effects of testosterone treatment in men with MASLD/MASH. Our systematic review encompassed 9 studies, including 3 RCTs, 4 nonrandomized studies, and 3 single-arm studies, using testosterone for the treatment of MASLD or MASH, as defined by liver biopsy, CT, magnetic resonance, or FLI endpoints. In this systematic review, several key observations were made. Testosterone exhibited superiority over no treatment/placebo in improving individual histologic features of MASLD (steatosis), MASH

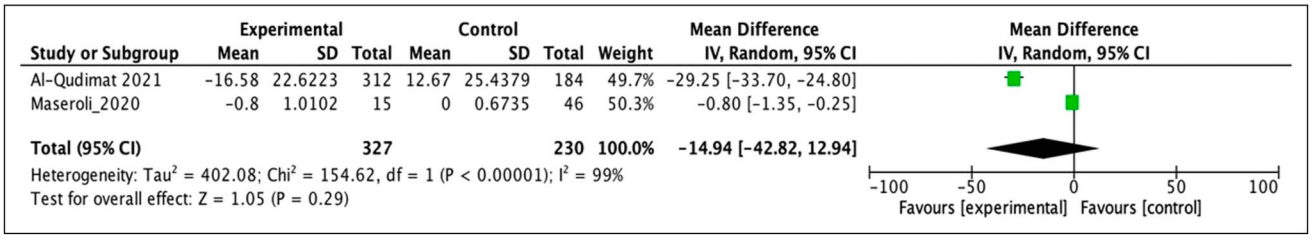


Figure 3. Forest plot of changes in FLI.

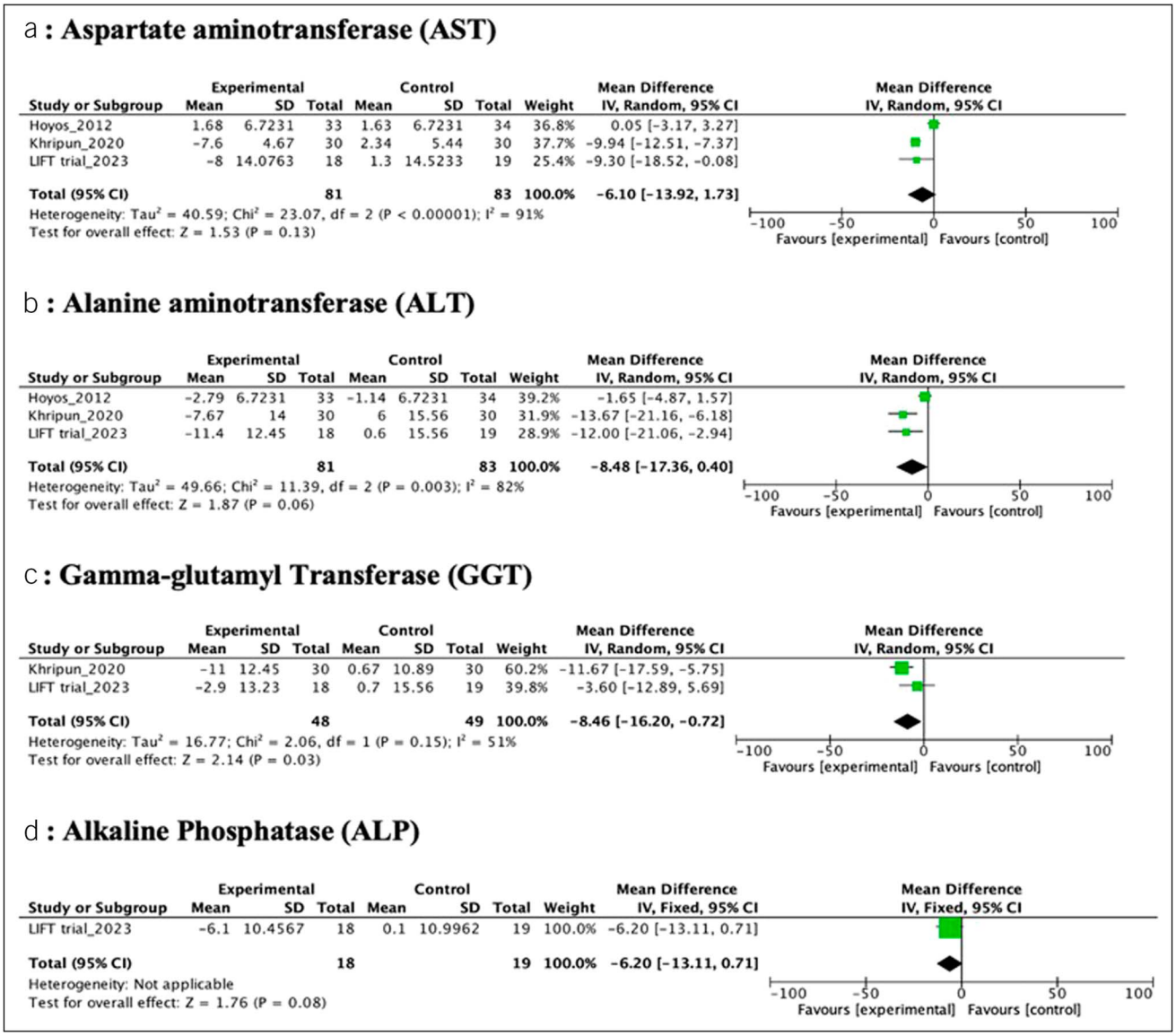


Figure 4. Forest plots illustrating the change from baseline in AST, ALT, GGT, and ALP from individual studies and the pooled estimates.

(fibrosis), or achieving resolution of MASLD/MASH. Moreover, compared with no treatment/placebo, testosterone seemed to improve ALT, GGT, ALP, and AST.

Interestingly, similar results were observed in both the RCTs and observational studies regarding the improvement of liver fibrosis, steatosis, resolution of MASLD/MASH, and liver enzymes, despite significant heterogeneity in study designs and outcome endpoints among the included studies. Design features contributing to this heterogeneity include variations in treatment (dosage, frequency, and administration route), patient

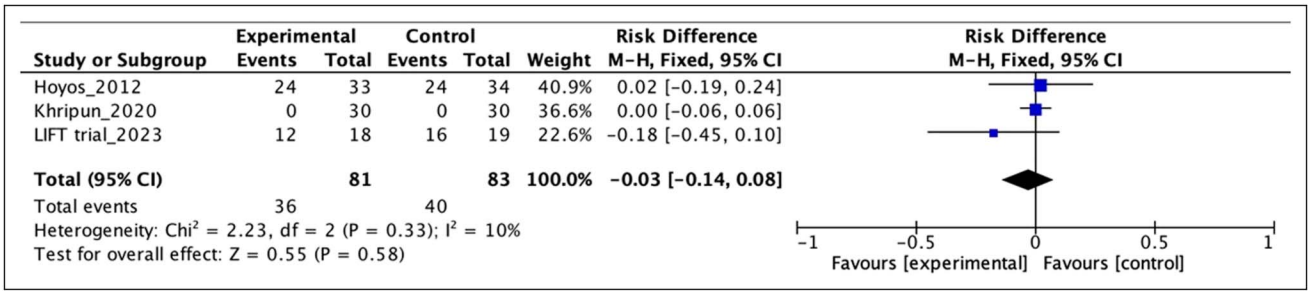


Figure 5. Forest plot of event rates and pooled estimates for adverse events.

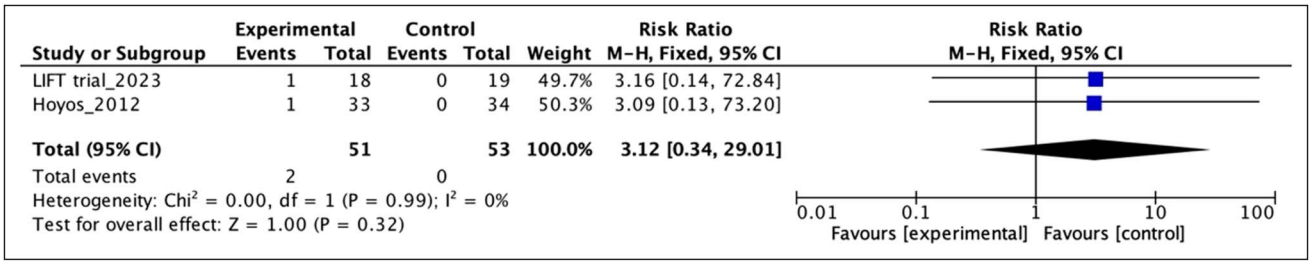


**Figure 6.** Forest plot of event rates and pooled estimates for myocardial infarction.

population (hypogonadal vs eugonadal), methods used for diagnosing patients with MASLD/MASH (histology, imaging, and biochemical tests), differences in the timing of outcome assessment, and duration of follow-up. In addition, the sample sizes were generally small across the different studies, and various modalities were used to assess liver fibrosis and steatosis, including histopathology and imaging techniques. Another aspect relevant to the observational studies is the elevated risk of confounding bias and participant selection bias.

Although preliminary hepatoprotective results were observed across the different trials, the underlying biochemical mechanisms remain to be elucidated. Hypogonadism emerges as a risk factor for the development of MASLD and that is supported by multiple pieces of evidence. In fact, low total testosterone and sex hormone-binding globulin levels were associated with an increased likelihood of metabolic syndrome and MASLD, irrespective of insulin resistance and cardiovascular risk factors (23). In addition, results from preclinical studies suggest that testosterone exerts its antiobesity effects by activating the androgen receptor pathway, inhibiting the expansion of visceral fat deposition, as well as insulin and leptin resistance, ultimately limiting lipogenesis in the liver and adipose tissues (23–25). In fact, adipose tissue plays a critical role in the progression of MASLD. Notably, the extent of fibrosis in adipose tissue correlates with the degree of fibrosis in the liver, further highlighting the close relationship between adipose dysfunction and liver disease progression (26). Moreover, a literature review has shown that testosterone replacement therapy in hypogonadal men with metabolic syndrome has beneficial effects on cardiovascular risk factors and improved liver enzymes (27,28). The limitations preventing its broader clinical use include a potential increase in prostate cancer, cardiovascular diseases, obstructive sleep apnea, and erythrocytosis (29).

Lifestyle interventions, comprising hypocaloric diets, exercise, and weight loss, are recommended as the primary treatment for MASLD/MASH (30). Pharmacotherapies for liver disease should be reserved for patients with advanced liver disease, such as those with biopsy-confirmed MASH and fibrosis. In recent years, there has been a significant increase in drug development for MASH, with numerous investigational drugs targeting various pathways including obeticholic acid, chemokine receptor inhibitors, thyroid hormone receptor-β agonists, lipid metabolism modulators, and antifibrotic drugs. Recently, resmetirom (an oral thyroid hormone receptor-beta agonist) received accelerated approval by the FDA for the treatment of adults with noncirrhotic MASH with moderate to advanced liver fibrosis. It would be important to evaluate the real-world impact of individuals with MASH fibrosis (9). Current guidelines recommend pioglitazone for adults with biopsy-confirmed MASH, with or without diabetes (31–33). Vitamin E is recommended for nondiabetic adults with biopsy-proven MASH. New classes of medications, such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, are also being evaluated for the treatment of MASLD/MASH fibrosis (34). The results of this systematic review provide new evidence to support testosterone replacement as a potential treatment for MASLD/MASH. However, given the limited number of controlled trials assessing the efficacy of testosterone in the treatment of MASLD/MASH, we believe that there is insufficient evidence to definitely confirm its effectiveness for this indication. Adverse events such as polycythemia, hypertension, and elevated PSA levels might preclude its wider clinical use. Longer and larger RCTs are needed to further corroborate the possible beneficial effects of testosterone.

This systematic review has several strengths. It stands as the first comprehensive systematic review to compile and assess all clinical studies concerning the effects of testosterone treatment in patients with MASLD/MASH. Our findings highlight the potential benefits of testosterone for patients with MASLD, including improvement in liver steatosis, fibrosis, resolution of MASLD/MASH, and reduction in liver enzymes. There are some limitations to consider in this systematic review mainly related to the significant heterogeneity across study designs, interventions (testosterone, Reandron, LPCN 1144, and AndroGel), intervention routes (oral, topical, and parenteral), doses and durations, and outcome assessments. These factors limit the comparability of published studies. An additional limitation is the small number of patients in both arms leading to imprecision.

In conclusion, testosterone treatment shows potential as an effective intervention for enhancing liver parameters and histopathologic endpoints in patients with MASLD/MASH. Nonetheless, recommending testosterone for patients with MASLD/MASH at this stage would be premature because of existing limitations in evidence. Therefore, further high-quality trials are essential to expand our understanding of TT benefits in this context. Anticipated results from ongoing clinical trials are expected to provide additional insights into the efficacy of testosterone in managing MASLD/MASH.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Wing-Kin Syn, MD, PhD.
**Specific author contributions:** M.M.: conceptualization, investigation, methodology, validation, data curation, writing-original draft. H.K.: conceptualization, investigation, methodology, validation, data curation. M.A., N.M.: investigation, validation, writing-original draft. I.M.: investigation, visualization. W.-K.S.: conceptualization, writing-review and editing, supervision.
**Financial support:** None.
**Potential competing interests:** None.

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