doi: 10.14744/hf.2024.2024.0047

Efficacy of orlistat for the treatment of metabolic dysfunction–associated steatotic liver disease patients: A systematic review and meta-analysis

Ariyan Ayati[1,*], Iman Elahi Vahed[1,*], Yasaman Rahimi[1,*], Shima Karbasi[2], Ali Safdari[3], Mahkameh Razaghi[4], Aida Bazrgar[5], Melika Arab Bafrani[6], Mohammad Mehdi Mousavi Nasab[1], Masoud Noroozi[7], Shokoofeh Noori[8], Mohammad Rahmanian[9,10]

[1]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [2]Department of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [3]Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran; [4]School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [5]Student Research Committee, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran; [6]Students' Scientific Research Center (SSRC), Tehran University of Medical Sciences, Tehran, Iran; [7]Universal Scientific Education and Research Network (USERN), Tehran, Iran; [8]Department of Clinical Biochemistry, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [9]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran; [10]Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Metabolic dysfunction–associated steatotic liver disease (MASLD) is a persistent hepatic condition linked with cardiovascular disorders and metabolic disturbances. Characterized by inflammation, fat accumulation, and fibrosis within the liver, MASLD can develop into liver cancer and cirrhosis. With a global prevalence of 32.4%, the condition parallels rising obesity rates. Orlistat inhibits lipase enzymes and, therefore, reduces dietary fat absorption, which may benefit MASLD patients. The present systematic review and meta-analysis were performed in accordance with PRISMA guidelines. Searches of PubMed, Scopus, Web of Science, and Embase up to January 2025 were performed using specific keywords and MeSH terms. Bias assessment and data extraction were conducted using Joanna Briggs Institute (JBI) tools independently by two researchers. Statistical analyses were performed with Stata version 14, calculating standardized mean differences, 95% confidence intervals (CI), and heterogeneity (by performing Cochran's Q test and I^2 index). Moreover, meta-regression, subgroup analyses, and sensitivity analyses were conducted. Eleven studies featuring 582 participants were included. Orlistat treatment induced a significant reduction in levels of alanine transaminase (ALT) (SMD = -26.23; 95% CI = -34.70 to -17.76) and aspartate aminotransferase (AST) (SMD = -19.62; 95% CI = -28.33 to -10.92). Furthermore, reductions in HOMA-IR, body mass index, cholesterol, insulin, and waist circumference were observed. The included studies exhibited low to moderate heterogeneity for most outcomes, indicating consistent results across trials. Orlistat significantly improved AST, ALT, and some other metabolic parameters in MASLD patients, suggesting its potential as an additional treatment option. However, the outcome must be interpreted cautiously, considering study heterogeneity. Further high-quality, multicenter research is necessary to confirm these results.

Keywords: Metabolic dysfunction-associated fatty liver disease (MAFLD); metabolic dysfunction–associated steatotic liver disease (MASLD); non-alcoholic fatty liver disease; orlistat; steatosis.

Introduction

Nonalcoholic fatty liver disease (NAFLD) involves a range of chronic hepatic conditions closely associated with various extra-hepatic complications, like cardiovascular disorders and metabolic disturbances. NAFLD is primarily described by the aggregation of fat within the liver, accompanied by fibrosis and inflammation. This condition is prone to progress into more severe hepatic diseases, like cirrhosis and liver cancer.[1,2] Recent progressions have culminated in the utilization of the designation metabolic dysfunction–associated steatotic liver disease (MASLD), which more accurately encapsulates the fundamental metabolic risk determinants contributing to NAFLD. MASLD is delineated by the existence of hepatic steatosis accompanied by one or more metabolic risk factors, encompassing obesity, type 2 diabetes, or dyslipidemia.[3,4] Considering the convergence, these terminologies may be employed interchangeably within populations characterized by metabolic dysfunction, such as individuals with obesity.[5] The global prevalence of MASLD is estimated at 32.4%,[6] paralleling rising obesity rates and associated metabolic complications.[7–9] Although obesity is heterogeneous regarding its etiology, excessive dietary fat consumption is recognized as a significant causative factor in the obesity epidemic.[10] Thus, it seems logical to target dietary fat to reduce body mass index (BMI) and decrease the risk of liver steatosis.

Current management for MASLD is centered on lifestyle modifications and gradual weight loss, causing a decrease in hepatic steatosis and

*The authors contributed equally to the article.

How to cite this article: Ayati A, Vahed IE, Rahimi Y, Karbasi S, Safdari A, Razaghi M, et al. Efficacy of orlistat for the treatment of metabolic dysfunction–associated steatotic liver disease patients: A systematic review and meta-analysis. Hepatology Forum 2025; 6(3):129–136.

Received: October 01, 2024; **Revised:** February 28, 2024; **Accepted:** April 14, 2024; **Available online:** May 22, 2025

Corresponding author: Mohammad Rahmanian, Shokoofeh Noori; SBUMS, Arabi Ave, Daneshjoo Blvd, Velenjak, Tehran, Iran.
Phone: +982122437293; **e-mail:** mmdrahmanian@gmail.com

serum liver enzyme concentrations, coupled with improved hepatic inflammation and fibrosis.[11] Although lifestyle-induced weight loss patterns, such as dietary restriction, seem to be sufficient in some patients, multiple drugs have been evaluated in MASLD patients.[12,13]

Orlistat, a semi-synthetic lipase enzyme inhibitor, is designed to treat obesity by inhibiting the breakdown of long-chain triglycerides, thereby decreasing subsequent absorption of dietary triglycerides in the gastrointestinal lümen.[14,15] In 2018, a meta-analysis encompassing seven trials comprising 330 patients with MASLD revealed that orlistat treatment could decrease BMI and enhance biochemical indicators of liver damage.[16] In recent years, more published trials on orlistat efficacy in MASLD have become available. This study aimed to conduct a thorough analysis of the effectiveness and safety of using the medication orlistat to treat MASLD.

Materials and Methods

Systematic Review Protocol

The protocol for this study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The study protocol has been registered in the PROSPERO database (registration ID: CRD42024610117).

Search Strategy

The search was mainly administered on Scopus, PubMed, Web of Science, and Embase utilizing the following keywords and Boolean operators: "Orlistat," "Xenical," "nonalcoholic fatty liver," "non-alcoholic fatty liver," "non-alcoholic," "fatty," "non-alcoholic fatty liver disease," "nonalcoholic," "fatty liver," and "NAFLD" through May 2024. Additionally, MeSH terms were used for "non-alcoholic fatty liver disease" and "fatty liver" as the primary subject for meta-analysis. A manual search was also administered on Google Scholar to increase sensitivity and to find gray literature. The search was updated in January 2025 using the aforementioned keywords (Fig. 1).

Eligibility Criteria

The titles and abstracts of all articles were reviewed independently by two researchers, without considering time and location limitations. After eliminating duplicate articles, full-text articles were reviewed to identify studies meeting our inclusion criteria, and data from these studies were extracted. The inclusion criteria were studies involving adult patients diagnosed with MASLD based on imaging, biopsy, or established clinical criteria, and randomized or non-randomized controlled trials evaluating the efficacy of Orlistat as a monotherapy. The exclusion criteria were cellular or animal studies, studies using Orlistat in combination with other pharmacological or lifestyle interventions, articles without available full text, cross-sectional studies, editorial letters, case reports, single-arm trials, and systematic reviews. The intervention of interest was Orlistat, administered at standard therapeutic doses, typically 120 mg three times daily, as recommended for managing obesity-related conditions. Comparators included placebo, standard care, or other interventions for MASLD management.

PICO Strategy

Population (P): Patients diagnosed with MASLD/metabolic-associated steatohepatitis (MASH) based on imaging, biopsy, or clinical criteria.

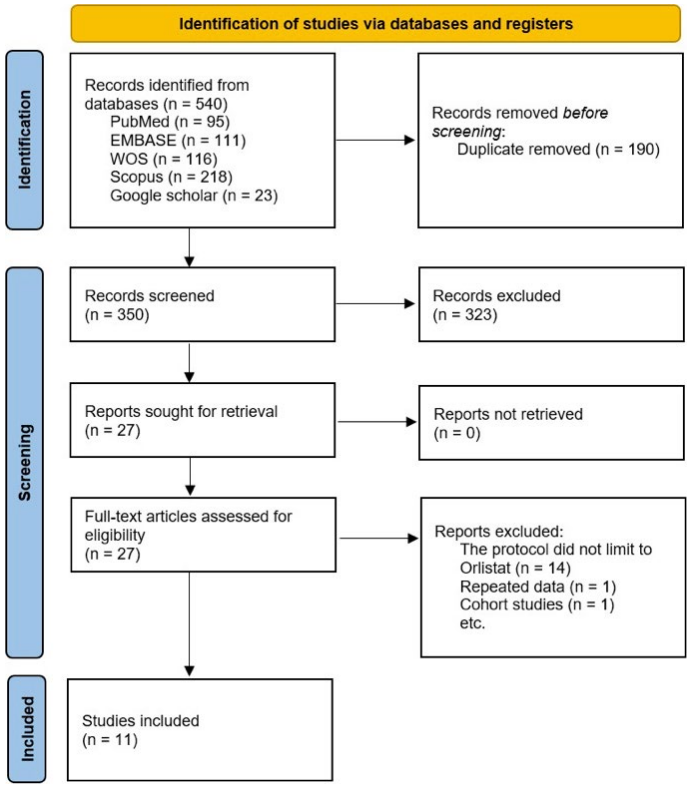

Figure 1. PRISMA flow chart of the screening process.

Intervention (I): Orlistat monotherapy, administered at standard therapeutic doses

Comparator (C): Placebo, standard care, or other MASLD management interventions.

Outcome (O): Changes in liver enzymes (ALT, AST), liver fat content (imaging or biopsy-confirmed), weight loss, and any reported adverse effects.

Data Extraction and Bias Assessment

Two researchers (A.A. and S.K.) independently conducted data extraction (Table 1) and bias assessment (Table S1, Table S2). Extracted information from the studies encompassed general data (first author, year of publication, nation), study characteristics (study design, sample size, follow-up duration), patient characteristics (age, gender, anthropometric indices, insulin levels, glucose, lipid profile, liver function test, diagnostic method), intervention (dosage, duration, dietary regimen), and control (placebo or other interventions). A third investigator (M.R.) resolved any disagreements. Two researchers (A.B. and A.S.) conducted a quality assessment of the included studies independently, and a third researcher (M.R.) resolved and accorded it. Two critical appraisal tools[18]—(i) Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool and (ii) JBI Critical Appraisal Checklist for Randomized Control/Pseudo-Randomized Trials—were allocated to evaluate the quality of the studies based on their study design. These tools were primarily developed for systematic reviews.

Statistical Analysis

Data analysis was done using Stata Ver. 14 software. The standardized mean difference (SMD) was used as the effect size, and a 95% confidence interval (CI) was calculated for the combined results. Hetero-

Table 1. Characteristics of included studies

Author, year	Country	Orlistat N	Placebo N	Females N (%)	Mean age, years	Intervention dose	Comparator	Diagnosis	Duration
Randomized clinical trial									
Zahmatkesh et al.[20]	Iran	27	26	23 (43)	13.76	120 mg daily	Placebo	MASLD	3 months
Feng et al.[21]	China	40	39	23 (29)	47	120 mg TDS	60 g/day of standard meal replacement powder + reduction of 500–1000 kcal/day only by controlling their normal diet	MASLD	6 months
Wasta Esmail et al.[22]	Iraq	25	25	30 (60)	43.3	120 mg daily	Placebo	MASLD	3 months
Ye et al.[23]	China	68	102	54 (32)	45.58	120 mg TDS	Lifestyle intervention in combination with drug therapy	MASLD	6 months
Harte et al.[24]	UK	8	6	8 (57)	50	120 mg BD	Placebo	MASLD	12 months
Harrison et al.[25]	USA	23	18	28 (68.3)	47	120 mg TDS	Diet/Vitamin E	MASLD	9 months
Zelber–Sagi et al.[26]	Israel	21	23	25 (56)	47.7	120 mg TDS	Placebo	MASLD	6 months
Single arm trial									
Iranparvar Alamdari et al.[27]	Iran	45		24 (53.3)	45.8	120 mg TDS		MASLD	3 months
Khazal et al.[28]	Iraq	60		40 (66.6)	48.5	120 mg TDS		MASLD	4 months
Hussein et al.[29]	Israel	16		10 (62)	42	120 mg TDS		MASH	6 months
Harrison et al.[30]	USA	10		6 (60)	54.4	120 mg TDS		MASLD	6 months

MASLD: Metabolic dysfunction–associated steatotic liver disease; USA: United States of America; TDS: Three times daily; BD: Twice daily.

geneity was assessed statistically using Cochran's Q test and I^2 tests. If heterogeneity was present, the appropriate model would be a random-effects model. Heterogeneity intensity was estimated through the I^2 index. If I^2 was less than 25%, the heterogeneity was considered mild; between 25% and 50%, the heterogeneity was moderate; and between 50% and 75%, the heterogeneity was severe. Finally, if the heterogeneity exceeds 75%, it is considered very severe.[19] A statistically significant threshold was considered as a p-value<0.05. Besides subgroup analysis and meta-regression, Egger's regression test was also performed to assess publication bias. Finally, sensitivity analyses were conducted to investigate the magnitude of change in the overall effect size and heterogeneity.[20]

Results

Trial Characteristics

The trial characteristics of the 11 included studies can be found in Table 1. Briefly, seven randomized clinical trials were performed between 2004 and 2023 and encompassed 343 patients in the Orlistat group against 239 participants in the control group of RCTs. Single-arm trials encompassed 141 patients in the Orlistat group. The average age of the subjects varied from 13.76 to 47.7 years, and a majority of them had a 100 percent obesity rate. The timeframe of Orlistat usage in the analyzed studies varied from 3 to 12 months. The studies were conducted across six different countries.

Quality of Included Studies

According to JBI critical appraisal checklists for experimental studies,[18] seven included RCTs (Table S1) and four included single-arm trials (Table S2) had a low risk of bias.

Quantitative Data Synthesis

Alanine transaminase (ALT) levels were reported in six trials and four single-arm trials. Orlistat decreased ALT levels in comparison to the initial measurements significantly, both in an analysis of RCTs (SMD=-6.79; 95% CI=-11.96 to -1.63; I^2=0%, p-value=0.66) and RCTs summed with single-arm trials (SMD=-26.23; 95% CI=-34.70 to -17.76; I^2=97%, p-value = 0.66) (Fig. S1 and Fig. 2). The funnel plot was proven to be symmetrical, and therefore, no publication bias was present (p-value=0.2067) (Fig. S2).

Due to high heterogeneity in the second analysis, a leave-one-out sensitivity analysis and subgroup analysis were performed based on the

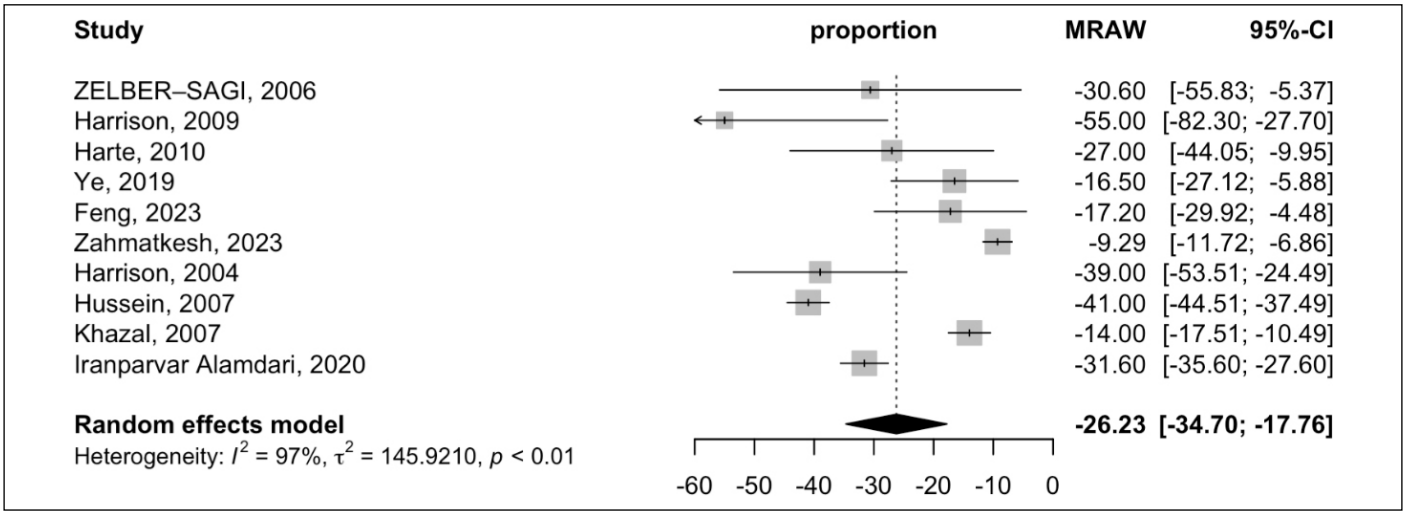

Figure 2. Forest plot describing the connection between ALT concentration in MASLD patients after orlistat administration.

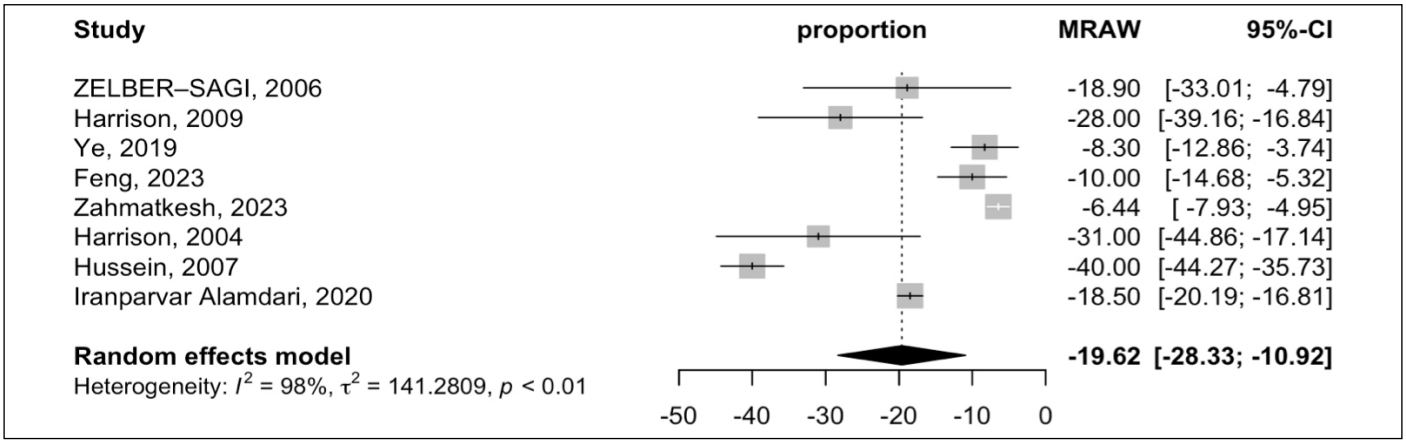

Figure 3. Forest plot describing the connection between AST concentration in MASLD patients after orlistat administration.

age of participants, daily dose of Orlistat, MASLD diagnosis method, and study duration. No study was removed after the sensitivity analysis. ALT changes in both pediatric and adult population studies were significant (Fig. S3), as were all subgroups based on daily doses of Orlistat (Fig. S4). Based on study duration, ALT decreased significantly in subgroups of 4, 6, 9, and 12 months; however, the reduction was not meaningful in the 3-month-long studies (Fig. S5). Finally, for MASLD detection subgroups, biopsy-, MRI–proton density fat fraction (MRI-PDFF)-, and ultrasound-based study results were significant, in contrast with NAFLD activity score (NAS)-based studies (Fig. S6).

Aspartate aminotransferase (AST) levels were reported in five RCTs and three single-arm trials. Orlistat treatment meaningfully reduced AST levels compared to baseline in RCTs (MD=-3.86; 95% CI=-5.64 to -2.08; I^2=0%, p-value=0.74) and in RCTs summed with single-arm trials (SMD=-19.62; 95% CI=-28.33 to -10.92; I^2=98%, p-value<0.01) (Fig. S7 and Fig. 3). No publication bias was present due to the symmetrical funnel plot (Fig. S8) (p-value=0.5172).

Due to high heterogeneity in the latter analysis, a leave-one-out sensitivity analysis and subgroup analysis were performed based on the age of participants, daily dose of Orlistat, MASLD diagnosis method, and study duration. Sensitivity analysis did not detect any study as a source of heterogeneity, and no study was removed. All subgroups in the analyses based on age, dose, and study duration were proven significant (Figs. S9, S10, and S11). However, based on the MASLD detection method, AST changes in NAS-based studies were insignificant, in contrast with ultrasound-, MRI-PDFF-, and biopsy-based studies, in which AST changes were considered significant (Fig. S12).

The effect of Orlistat on alkaline phosphatase (ALP) levels was reported in three RCTs. Orlistat did not change ALP levels significantly compared to baseline (SMD=-0.48; 95% CI=-7.05 to 6.10; I^2=0%, p-value=0.409) (Fig. 4). Publication bias was not considered significant (p-value = 0.2640) (Fig. S13).

The use of Orlistat was associated with an insignificant reduction in fasting blood sugar (FBS) levels relative to baseline values in MASH and MASLD patients (SMD=-0.28; 95% CI=-0.76 to 0.19) (Fig. S14). Between-study heterogeneity was considered high (I^2=77%, p-value<0.01). Additionally, funnel plot asymmetry was proven insignificant, and therefore, publication bias was not present (p-value=0.0947) (Fig. S14).

To reduce heterogeneity, subgroup analysis was conducted based on the daily dose of Orlistat and study durations. Based on the Orlistat dose, the changes in FBS were significant in all subgroups except for the 120 mg-TDS subgroup (Fig. S15). Furthermore, FBS change was significant in 3- and 12-month-long studies, in contrast with 6- and 9-month-long

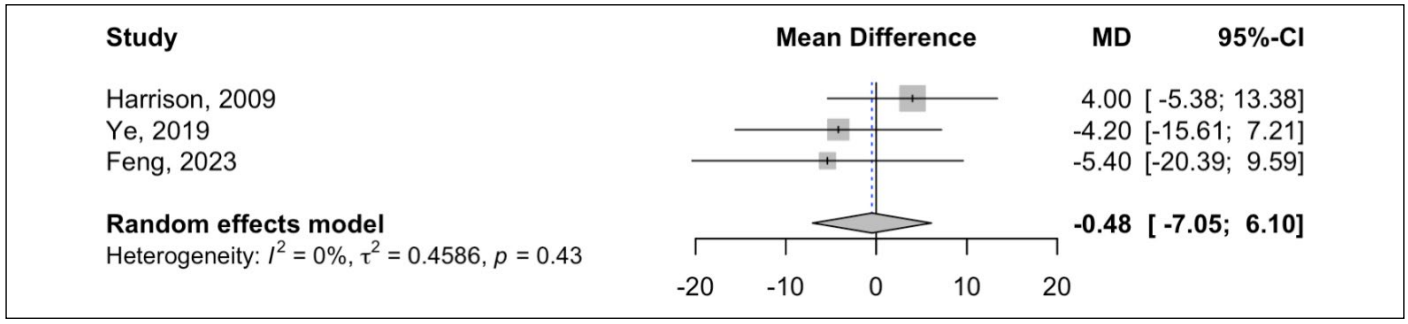

Figure 4. Forest plot describing the connection between ALP concentration in MASLD patients after orlistat administration.

studies, in which FBS change was not considered significant (Fig. S16).

Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) levels were assessed in four studies. In comparison to baseline values, the administration of Orlistat resulted in significantly lower insulin resistance (SMD=-0.67; 95% CI=-0.93 to -0.40; I²=0%, p-value=0.53; Fig. S17). In addition, the funnel plot was proven symmetrical (p-value=0.9920) (Fig. S17).

Information gathered from four studies was used to assess body mass index (BMI) after Orlistat administration. In comparison to the control group, Orlistat treatment reduced BMI significantly (SMD=-1.18; 95% CI=-1.45 to -0.90; I²=0%, p-value=0.71; Fig. S18). The funnel plot was also proven to be symmetrical, and publication bias was therefore absent (p-value=0.7892) (Fig. S18).

The impact of Orlistat administration on triglyceride (TG) levels in six studies was analyzed, and the result was an insignificant change in TG levels due to Orlistat intake (SMD=0.46; 95% CI=-0.64 to 1.56; I²=94%, p-value<0.01) (Fig. S19). Sensitivity analysis detected the study by Feng et al.[21] as a source of heterogeneity, and after its removal, heterogeneity decreased from 94% to 56%, but changes in TG levels were still insignificant (SMD=-0.07; 95% CI=-0.46 to 0.32; I²=56%, p-value=0.06; Fig. S20). The funnel plot was also proven symmetrical (p-value=0.7803) (Fig. S19).

Cholesterol levels were assessed in seven studies before and after Orlistat intake. Our analysis showed that Orlistat did not change cholesterol levels significantly (SMD=-0.11; 95% CI=-0.68 to 0.46; I²=86%, p-value<0.01) (Fig. S21). However, after performing a sensitivity analysis, the study by Feng et al.[21] was removed from this analysis, and alongside a significant reduction in heterogeneity, the results changed (SMD=-0.38; 95% CI=-0.67 to -0.08; I²=34%, p-value=0.18) (Fig. S22). The funnel plot was also proven symmetrical (p-value=0.9139) (Fig. S21).

Analysis of insulin levels in five studies showed that Orlistat treatment caused a slight decrease in insulin levels in MASLD or MASH patients (SMD=-2.33; 95% CI=-3.44 to -1.21; I²=0%, p-value=0.76) (Fig. S23). Funnel plot asymmetry was also proven insignificant (p-value=0.9881) (Fig. S23).

The effect of Orlistat on low-density lipoprotein (LDL) levels was evaluated in six studies. Our analysis demonstrated that Orlistat administration did not significantly influence LDL levels (SMD=-0.55; 95% CI=-1.14 to 0.04; I²=86%, p-value<0.01; Fig. S24). Sensitivity analysis repeatedly found the study by Feng et al.[21] as a source of heterogeneity, and after its removal, the heterogeneity reached 42%; however, the reduction was still insignificant (SMD=-0.24; 95% CI=-0.58 to 0.11; I²=42%, p-value=0.14; Fig. S25). As a result of funnel plot symmetry, publication bias was absent (p-value=0.9139) (Fig. S24).

Table 2. Meta-regression results

Comparison	Age	Gender	BMI
ALT	0.1154	**0.0491**	0.0559
AST	0.2312	**<0.0001**	0.1067
ALP	0.4705	0.1928	0.1925
FBS	0.3522	0.6726	0.5614
HOMA-IR	0.2629	0.6621	0.4055
BMI	0.4791	0.7841	0.3281
TG	0.2455	0.2484	0.8192
Cholesterol	0.2455	0.2484	0.8192
Insulin	0.5421	0.5208	0.9901
LDL	0.9146	0.3520	0.4505
WC	0.7541	0.8350	0.6671
SBP	0.6967	0.5432	0.5581

BMI: Body mass index; ALT: Alanine transaminase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; FBS: Fasting blood sugar; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; TG: Triglyceride; LDL: Low-density lipoprotein; WC: Waist circumference; SBP: Systolic blood pressure.

The effect of Orlistat on waist circumference (WC) in five studies was analyzed. Finally, waist circumference was reduced compared to baseline after Orlistat treatment (SMD=-3.08; 95% CI=-3.94 to -2.22; I²=0%, p-value=0.94) (Fig. S26). The funnel plot was also considered symmetrical (p-value=0.5382) (Fig. S26).

The effect of daily Orlistat intake on systolic blood pressure (SBP) was analyzed in three studies. Orlistat treatment did not yield a statistically significant alteration in SBP compared to the initial measurement (SMD=2.34; 95% CI=-1.11 to 5.79; I²=0%, p-value=0.80) (Fig. S27). Publication bias was absent in this analysis (p-value=0.9139) (Fig. S27).

As sensitivity analyses were performed to assess the robustness of results, data are available within the supplementary material (Tables S3–S8).

Meta-regression analysis was also conducted to explore the potential influence of age, BMI, and sex on the 12 previously specified comparisons by assessing p-values for them.

In more detail, gender structure showed a significant correlation with changes in ALT and AST (Table 2). The rest of the comparisons were insignificant.

Discussion

Orlistat exerts an inhibitory effect on pancreatic and gastric lipases by forming a covalent link with serine residues within their active sites.[14,32–33] As these lipases act as major components of dietary lipid catabolism, inhibiting them will diminish the amount of available free fatty acids in the liver; this will also result in controlled blood pressure.[31,33] Moreover, a recent meta-analysis of seven trials demonstrated that Orlistat administration is beneficial in maintaining uric acid at a low level.[34] Although these findings suggest that Orlistat may be advantageous for MASLD patients' hepatic status, Orlistat usage was also correlated with rare and scattered complications, including several hepatic diseases (e.g., cholestatic hepatitis and subacute liver failure).[32] To gain a better understanding of Orlistat's efficacy, this systematic review and meta-analysis summarized its effects on MASLD and MASH patients. This study encompassed eleven RCTs and single-arm trials with a total of 592 participants. Quantitative synthesis results from the included studies showed that Orlistat treatment significantly improved metabolic and biochemical parameters of liver disease, including ALT, AST, BMI, cholesterol, HOMA-IR, and WC, while other anthropometric and metabolic parameters showed non-significant changes.

Dyslipidemia is recognized as a prominent risk factor for MASLD.[35] Improvement of dyslipidemia is a priority in the supervision of MASLD patients.[36] A meta-analysis of 33 RCTs confirmed a reduction in total cholesterol and TG, which was consistent with our findings.[37] Using meta-regression analysis, they further reported that the lipid-lowering effect of Orlistat may be caused by its concomitant effect on body weight loss.[37] In non-obese subjects, the baseline triglyceride level is a strong indicator of the development and regression of MASLD.[38] Orlistat is a lipase inhibitor that inhibits the hydrolysis of triglycerides and leads to lower fatty acid absorption.[39] Its effects are not limited to liver enzymes and parameters assessed in this analysis; liver fat content, NAS, and NAFLD fibrosis score (NFS) are some other vital scores in evaluating MASLD severity. Orlistat failed to improve NAS and NFS scores in the studies by Harrison et al.,[25] Esmail et al.,[40] and Ali Khan et al.[41] In contrast, the ultrasound properties of the liver improved after Orlistat administration in the studies by Khazal et al.[28] and Ali Khan et al.[41] Liver fat content showed paradoxical results after Orlistat consumption; while in the study by Feng et al.,[21] MRI-PDFF analysis showed significant improvement in the Orlistat group, a whole-liver analysis based on MRI-PDFF in the study by Ye et al.[23] demonstrated that fat content was not altered in the Orlistat group compared to the control group.

Although lifestyle modifications and weight loss are important elements in the management of MASLD, recent advances in pharmacological therapies are reshaping the treatment landscape. Resmetirom, a thyroid hormone receptor-β agonist, has received conditional approval for patients with MASLD and significant fibrosis (F2–F3), showing promise in reducing liver fat and improving histology.[42] Similarly, semaglutide, a GLP-1 receptor agonist, has demonstrated significant weight loss and liver histological improvements, particularly in the ESSENCE-3 trial.[43] These innovations highlight the growing role of pharmacotherapy alongside lifestyle interventions, emphasizing the need for a tailored, multidisciplinary approach to MASLD treatment. In the current study, we focused on the effect of Orlistat on several metabolic parameters. Our analysis demonstrated its significant reduction of ALT, which may be a proper therapeutic pathway, as a reduction of ALT has been shown to be correlated with significant histological improvement in liver biopsies.[44] Additionally, our analysis showed that Orlistat reduced AST levels in MASLD patients. It has been claimed that a reduction in AST is associated with improved liver function and a lower risk of fibrosis and cirrhosis.[45,46] Other improved parameters, like BMI and cholesterol, are also correlated with a lower risk of comorbid conditions such as obesity or metabolic syndrome.[44]

MASLD and metabolic syndrome are strongly connected, with MASLD having a bidirectional relationship with metabolic syndrome.[47,48] Type 2 diabetes, as a main risk factor for MASLD, is correlated with the progression of fibrosis and disease deterioration. It is also associated with liver-related mortality.[49] According to current international clinical practice guidelines, the assessment of insulin resistance is considered a crucial component during the diagnosis and prognosis determination of individuals with MASLD, along with numerous other factors.[50–52] Insulin resistance and subsequent hyperinsulinemia increase free fatty acid delivery and fat accumulation, and stimulate anabolic metabolism.[53] Recently, multiple meta-analyses evaluated the impact of Orlistat on metabolic parameters. Data from Zhou et al.[54] showed that Orlistat treatment is paralleled by a significant reduction in FBS. A meta-analysis on obese and overweight subjects reported that Orlistat significantly improved hemoglobin A1C (HbA1c) and FBS, compared to placebo.[55] Our results further showed improvement in HOMA-IR following Orlistat treatment. Moreover, FBS and insulin levels were significantly improved following the administration of Orlistat.

Despite the similar design of the included studies, heterogeneity was found among studies. The average age of included participants was inconsistent, with a range of 13.76 to 54.4 years, and to resolve this issue, we conducted a meta-regression featuring participants' mean age in the encompassed studies. The results showed that age did not affect alterations in the previously mentioned comparisons. The duration of treatment was not uniform and ranged from three to twelve months in the included studies. Subsequently, a duration-based subgroup analysis was conducted to assess the effect of study duration on our analyses. Moreover, the MASLD detection methods encompassed a range of techniques (e.g., MRI-PDFF, NAS, ultrasound), which could affect our results. Due to this issue, subgroup analyses were performed based on the detection method to minimize the effect.

Finally, our study has some advantages, including the following: strict exclusion and inclusion criteria were used, and only clinical trials were included. We conducted a systematic and comprehensive literature search to reduce bias. However, this study had some limitations, which might affect the generalizability of the study results. The number of studies included in this systematic review and meta-analysis was limited, and a relatively large sample size was not observed within them. These limitations may influence our meta-analysis results. To acquire more robust evidence to guide clinical practice, additional high-quality and multicenter research should be conducted.

Conclusion

In this study, Orlistat's potential for MASLD management was quantitatively analyzed. Orlistat significantly improved AST levels and some metabolic parameters in MASLD patients. It was demonstrated that Orlistat might provide an additional treatment choice for patients with MASLD. These findings need to be interpreted with caution.

Online Appendix File: https://hepatologyforum.org/storage/upload/files/1751633527-appendix-en.pdf.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Author Contributions: Concept – MR; Design – MR; Supervision – SN, MR; Data Collection and/or Processing – IEV, AB, SK, AS, MRaz, YR; Analysis and/or Interpretation – IEV, MN, MAB, MMMN; Literature Search – MR, AA; Writing – AA, YR, MRaz; Critical Reviews – MR, AA.

Peer-review: Externally peer-reviewed.

References

1. Allen AM, Therneau TM, Ahmed OT, Gidener T, Mara KC, Larson JJ, et al. Clinical course of non-alcoholic fatty liver disease and the implications for clinical trial design. J Hepatol 2022;77(5):1237-1245. [CrossRef]
2. Ko JS. [Nonalcoholic fatty liver disease]. Korean J Gastroenterol 2010;56(1):6-14. [CrossRef]
3. Younossi ZM, Paik JM, Stepanova M, Ong J, Alqahtani S, Henry L. Clinical profiles and mortality rates are similar for metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease. J Hepatol 2024;80(5):694-701. [CrossRef]
4. Yilmaz Y. The heated debate over NAFLD renaming: An ongoing saga. Hepatol Forum 2023;4(3):89-91. [CrossRef]
5. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6):1542-1556. [CrossRef]
6. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2022;7(9):851□861. [CrossRef]
7. Li L, Liu DW, Yan HY, Wang ZY, Zhao SH, Wang B. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. Obes Rev 2016;17(6):510-519. [CrossRef]
8. Johnson PC, Cochet AA, Gore RS, Harrison SA, Magulick JP, Aden JK, et al. Early Cardiac Dysfunction in Biopsy-proven Nonalcoholic Fatty Liver Disease. Korean J Gastroenterol 2021;78(3):161-167. [CrossRef]
9. Seval GC, Kabacam G, Yakut M, Seven G, Savas B, Elhan A, Cinar K, et al. The natural course of non-alcoholic fatty liver disease. Hepatol Forum 2020;1(1):20-24. [CrossRef]
10. Duan Y, Zeng L, Zheng C, Song B, Li F, Kong X, et al. Inflammatory Links Between High Fat Diets and Diseases. Front Immunol 2018;9:2649. [CrossRef]
11. Zelber-Sagi S, Ratziu V, Oren R. Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. World J Gastroenterol 2011;17:3377. [CrossRef]
12. Jalili R, Somi MH, Hosseinifard H, Salehnia F, Ghojazadeh M, Makhdami N, et al. The evaluation of effective drugs for the treatment of non-alcoholic fatty liver disease: A systematic review and network meta-analysis. Adv Pharm Bull 2020;10(4):542-555. [CrossRef]
13. Guveli H, Ozlu T, Ersoy Tasar B, Batuhan Kenger E, Kaya E. Sustainability of diet-based moderate calorie restriction among obese patients with metabolic-associated fatty liver disease. Hepatol Forum 2021;2(3):97-101.
14. Guerciolini R. Mode of action of orlistat. Int J Obes Relat Metab Disord 1997;21:S12-S23.
15. Kim WJ. [Current State of Pharmacotherapy in Obesity]. Korean J Gastroenterol 2024;83:94-101. [Korean] [CrossRef]
16. Wang H, Wang L, Cheng Y, Xia Z, Liao Y, Cao J. Efficacy of orlistat in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Biomed Rep 2018;9(1):90-96. [CrossRef]
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg 2010;8(5):336-341. [CrossRef]
18. The Joanna Briggs Institute. Critical appraisal tools - JBI. Available at: http://joannabriggs.org/research/critical-appraisal-tools.html Accessed May 19, 2023.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539-1558. [CrossRef]
20. Zahmatkesh A, Sohouli MH, Shojaie S, Rohani P. The effect of orlistat in the treatment of non-alcoholic fatty liver in adolescents with overweight and obese. Eur J Pediatr 2024;183(3):1173-1182. [CrossRef]
21. Feng X, Lin Y, Zhuo S, Dong Z, Shao C, Ye J, et al. Treatment of obesity and metabolic-associated fatty liver disease with a diet or orlistat: A randomized controlled trial. Am J Clin Nutr 2023;117(4):691-700. [CrossRef]
22. Wasta Esmail VA, Al-Nimer MSM, Mohammed MO. Effects of Orlistat or Telmisartan on the Serum Free Fatty Acids in Non-alcoholic Fatty Liver Disease Patients: An Open-Labeled Randomized Controlled Study. Turk J Gastroenterol 2022;33(5):421-426. [CrossRef]
23. Ye J, Wu Y, Li F, Wu T, Shao C, Lin Y, et al. Effect of orlistat on liver fat content in patients with nonalcoholic fatty liver disease with obesity: assessment using magnetic resonance imaging-derived proton density fat fraction. Therap Adv Gastroenterol 2019;12:1756284819879047. [CrossRef]
24. Harte AL, da Silva NF, Creely SJ, McGee KC, Billyard T, Youssef-Elabd EM, et al. Elevated endotoxin levels in non-alcoholic fatty liver disease. J Inflamm (Lond) 2010;7:15. [CrossRef]
25. Harrison SA, Fecht W, Brunt EM, Neuschwander-Tetri BA. Orlistat for overweight subjects with nonalcoholic steatohepatitis: A randomized, prospective trial. Hepatology 2009;49(1):80-86. [CrossRef]
26. Zelber-Sagi S, Kessler A, Brazowsky E, Webb M, Lurie Y, Santo M, et al. A double-blind randomized placebo-controlled trial of orlistat for the treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2006;4(5):639-644. [CrossRef]
27. Iranparvar Alamdari M, Habibzadeh S, Azami A, Shirinzadeh B, Aslanian R, Yazdanbod K. Efficacy of orlistat in the treatment of patients with non-alcoholic fatty liver. Int J Basic Clin Pharmacol 2020;9(2):296-299. [CrossRef]
28. Khazal FAK. Non-Alcoholic Fatty Liver Disease Responce to Orlistat Therapy in Iraqi Type 2 Diabetic Obese Patients. Iraqi Postgrad Med J 2007;6(4):267-271.
29. Hussein O, Grosovski M, Schlesinger S, Szvalb S, Assy N. Orlistat reverse fatty infiltration and improves hepatic fibrosis in obese patients with non-alcoholic steatohepatitis (NASH). Dig Dis Sci 2007;52(10):2512-2519. [CrossRef]
30. Harrison SA, Fincke C, Helinski D, Torgerson S, Hayashi P. A pilot study of orlistat treatment in obese, non-alcoholic steatohepatitis patients. Aliment Pharmacol Ther 2004;20(6):623-628. [CrossRef]
31. Hall ME, Cohen JB, Ard JD, Egan BM, Hall JE, Lavie CJ, et al. Weight-Loss Strategies for Prevention and Treatment of Hypertension: A Scientific Statement From the American Heart Association. Hypertension 2021;78(5):e38-e50. [CrossRef]
32. Filippatos TD, Derdemezis CS, Gazi IF, Nakou ES, Mikhailidis DP, Elisaf MS. Orlistat-associated adverse effects and drug interactions: a critical review. Drug Saf 2008;31(1):53-65. [CrossRef]
33. Chaikomin R, Russo A, Rayner CK, Feinle-Bisset C, O'Donovan DG, Horowitz M, et al. Effects of lipase inhibition on gastric emptying and alcohol absorption in healthy subjects. Br J Nutr 2006;96(5):883-887. [CrossRef]
34. Noori S, Mirzababaei A, Amini MR, Clark CCT, Mirzaei K. Effect of orlistat on serum uric acid level in adults: A systematic review and meta-analysis of randomised controlled trials. Int J Clin Pract 2021;75(11):e14674. [CrossRef]
35. Méndez-Sánchez N, Cerda-Reyes E, Higuera-de-la-Tijera F, Salas-García AK, Cabrera-Palma S, Cabrera-Álvarez G, et al. Dyslipidemia as a risk factor for liver fibrosis progression in a multicentric population with non-alcoholic steatohepatitis. F1000Res 2020;9:56. [CrossRef]
36. Lu FB, Zheng KI, Rios RS, Targher G, Byrne CD, Zheng MH. Global epidemiology of lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Gastroenterol Hepatol 2020;35(12):2041-2050. [CrossRef]
37. Sahebkar A, Simental-Mendía LE, Reiner Ž, Kovanen PT, Simental-Mendía M, Bianconi V, et al. Effect of orlistat on plasma lipids and body weight: A systematic review and meta-analysis of 33 randomized controlled trials. Pharmacol Res 2017;122:53-65. [CrossRef]
38. Kim NH, Kim JH, Kim YJ, Yoo HJ, Kim HY, Seo JA, et al. Clinical and

metabolic factors associated with development and regression of nonalcoholic fatty liver disease in nonobese subjects. Liver Int 2014;34(4):604-611. [CrossRef]

39. Hamza RZ, Alsolami K. Ameliorative effects of Orlistat and metformin either alone or in combination on liver functions, structure, immunoreactivity and antioxidant enzymes in experimentally induced obesity in male rats. Heliyon 2023;9(8). [CrossRef]
40. Esmail VAW, Mohammed MO, Al-Nimer MSM. Short-term orlistat therapy improves fatty infiltration indices and liver fibrosis scores in patients with non-alcoholic fatty liver disease and metabolic syndrome. Arab J Gastroenterol 2021;22(1):1-5. [CrossRef]
41. Ali Khan R, Kapur P, Jain A, Farah F, Bhandari U. Effect of orlistat on periostin, adiponectin, inflammatory markers and ultrasound grades of fatty liver in obese NAFLD patients. Ther Clin Risk Manag 2017;13:139-149. [CrossRef]
42. Chen VL, Morgan TR, Rotman Y, Patton HM, Cusi K, Kanwal F, et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. Hepatology 2025;81(1):312-320. [CrossRef]
43. Newsome PN, Sanyal AJ, Engebretsen KA, Kliers I, Østergaard L, Vanni D, et al. Semaglutide 2.4 mg in Participants With Metabolic Dysfunction-Associated Steatohepatitis: Baseline Characteristics and Design of the Phase 3 ESSENCE Trial. Aliment Pharmacol Ther 2024;60(11-12):1525-1533. [CrossRef]
44. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77(5):1797-1835. [CrossRef]
45. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease. Obes Facts 2016;9(2):65-90. [CrossRef]
46. Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. J Hepatol 2019;70(3):531-544. [CrossRef]
47. Radu F, Potcovaru CG, Salmen T, Filip PV, Pop C, Fierbin-eanu-Braticievici C. The Link between NAFLD and Metabolic Syndrome. Diagnostics (Basel) 2023;13(4):614. [CrossRef]
48. Hashimoto E, Tokushige K, Ludwig J. Diagnosis and classification of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: Current concepts and remaining challenges. Hepatol Res 2015;45(1):20-28. [CrossRef]
49. Stepanova M, Rafiq N, Makhlouf H, Agrawal R, Kaur I, Younoszai Z, et al. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). Dig Dis Sci 2013;58:3017-3023. [CrossRef]
50. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64(6):1388-1402. [CrossRef]
51. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020;14(6):889-919. [CrossRef]
52. Kiyak A, Elibol S, Barutcu O, Saruc M, Tozun N. Subtracted Adulthood Mass Index - a new index to predict NAFLD risk in non-obese individuals. Hepatol Forum 2021;2(1):26-30. [CrossRef]
53. Palma R, Pronio A, Romeo M, Scognamiglio F, Ventriglia L, Ormando VM, et al. The role of insulin resistance in fueling NAFLD pathogenesis: from molecular mechanisms to clinical implications. J Clin Med 2022;11(13):3649. [CrossRef]
54. Zhou YH, Ma XQ, Wu C, Lu J, Zhang SS, Guo J, et al. Effect of Anti-Obesity Drug on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One 2012;7(6):e39062. [CrossRef]
55. Khera R, Pandey A, Chandar AK, Murad MH, Prokop LJ, Neeland IJ, et al. Effects of Weight-Loss Medications on Cardiometabolic Risk Profiles: A Systematic Review and Network Meta-analysis. Gastroenterology 2018;154(5):1309-1319.e7. [CrossRef]