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Original Article

Atorvastatin versus tetrahydrolipstatin in male patients with dyslipidemia: A systematic review and meta-analysis

[Atorvastatina frente a tetrahidrolipstatina en pacientes varones con dislipidemia: Una revisión sistemática y meta-análisis]

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Abstract

Context: Atorvastatin is typically used in the treatment of dyslipidemia. However, the interest in using anti-obesity medications such as orlistat has grown rapidly as obesity is one of the variables associated with dyslipidemia.

Aims: To synthesize the findings from previous studies published to date on the potential effects of atorvastatin and tetrahydrolipstatin (orlistat) on the levels of serum LDL.

Methods: A systematic review and meta-analysis of research reports and RCTs about atorvastatin and orlistat on LDL levels from articles published in Medline, PubMed, and Scopus from 2012 to 2022 were conducted using PRISMA and RevMan 5.4 software.

Results: From 9 final included articles, 6 focused on atorvastatin and 3 on orlistat. Five papers on atorvastatin reported a significant decrease in LDL level, whereas only 2 from orlistat papers. There is a significant decrease in LDL level associated with Atorvastatin treatment (p = 0.04, CI = 1.58, 56.81, I^2 = 99%), but not with orlistat (p = 0.05, CI = 0.10, 17.69, I^2 = 93%).

Conclusions: Here, it is shown that atorvastatin instead of orlistat has a significant effect on decreasing LDL serum levels in dyslipidemia patients.

Keywords: atorvastatin; dyslipidemia; obesity; orlistat; tetrahydrolipstatin.

Resumen

Contexto: La atorvastatina se utiliza habitualmente en el tratamiento de la dislipidemia. Sin embargo, el interés por utilizar medicamentos contra la obesidad, como el orlistat, ha crecido rápidamente, ya que la obesidad es una de las variables asociadas a la dislipidemia.

Objetivos: Sintetizar los hallazgos de estudios previos publicados hasta la fecha sobre los efectos potenciales de la atorvastatina y la tetrahidrolipstatina (orlistat) en los niveles de LDL sérico.

Métodos: Se realizó una revisión sistemática y un meta-análisis de informes de investigación y ECA sobre atorvastatina y orlistat en los niveles de LDL de artículos publicados en Medline, PubMed y Scopus desde 2012 hasta 2022 utilizando PRISMA y el software RevMan 5.4.

Resultados: De 9 artículos finales incluidos, 6 se centraron en atorvastatina y 3 en orlistat. Cinco artículos sobre atorvastatina informaron de una disminución significativa del nivel de LDL, mientras que sólo 2 de los artículos sobre orlistat. Existe una disminución significativa del nivel de LDL asociada al tratamiento con atorvastatina (p = 0,04; IC = 1,58; 56,81; I^2 = 99%), pero no con orlistat (p = 0,05; IC = 0,10; 17,69; I^2 = 93%).

Conclusiones: Aquí se demuestra que la atorvastatina en lugar del orlistat tiene un efecto significativo en la disminución de los niveles séricos de LDL en pacientes con dislipidemia.

Palabras Clave: atorvastatina; dislipidemia; obesidad; orlistat; tetrahidrolipstatina.

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INTRODUCTION

Dyslipidemia is a primary risk factor for cardiovascular diseases (CVD), with the main target of therapy to reduce the levels of blood low-density lipoprotein (LDL). A study by Grundy et al. (2019) that was conducted on a sample population in Western Europe and North America reported that the atorvastatin treatment (80 mg, 1 dose per day) has yet succeeded in reducing the level of LDL serum among adult men and women with dyslipidemia. On the other hand, a study reported that orlistat (120 mg, 3 times per day), which is generally used as an anti-obesity agent, could lower the LDL level serum in adult men and women patients (Alanazi et al., 2022).

It has been reported that atorvastatin can lower the cholesterol level by inhibiting HMG-CoA reductase that lowers mevalonate and other isoprenoid metabolites, which in turn decreases the LDL serum level (Morofuji et al., 2022; Tien et al., 2023). On the other hand, orlistat (tetrahydrolipstatin) has been reported to inhibit gastric and pancreatic lipases by forming a covalent bond with the active serine residue site, thus preventing fat absorption (Bénarouche et al., 2014; Nasri et al., 2019).

Previous studies have analyzed the use of tetrahydrolipstatin (orlistat) as an anti-obesity agent to lower the level of LDL serum and reduce the risk of obesity (Bessesen and Van Gaal, 2018). Since the 1990s, orlistat has been recommended for the treatment of obesity due to its beneficial role, especially in the management of obesity-associated dyslipidemia (Kotseva et al., 2017). Additionally, orlistat is a potent and temporary inhibitor of gastric and pancreatic lipases that can lower fat absorption by 30% (Sahebkar et al., 2017). It has been shown that orlistat reduces total serum cholesterol levels and low-density lipoprotein cholesterol (LDL-C) (Kwon et al., 2022).

In addition, dyslipidemia is associated with the prevalence of obesity, especially central or abdominal obesity, although not all patients with dyslipidemia are considered obese. Currently, the gold-standard treatment for dyslipidemia is a statin regimen. These uncertainties raise the following question: In men suffering dyslipidemia, is a single treatment of atorvastatin compared to tetrahydrolipstatin effective at decreasing LDL serum level? In this study, the authors review the use of atorvastatin as an HMG Co-A reductase inhibitor that can reduce the levels of serum LDL (Reiner et al., 2016) and compare it with orlistat as a specific and long-acting inhibitor of gastrointestinal lipases (Kwon et al., 2022).

MATERIAL AND METHODS

Search strategy

To identify relevant articles, this study conducted an extensive literature search in the Medline, PubMed, and Scopus databases. All publications between 2012 and 2022 were included in this study. The following search terms were used: tetrahydrolipstatin OR orlistat AND atorvastatin AND dyslipidemia OR hyperlipidemia AND man OR men OR male. With a quick scan of the content, if the title and abstract of an article were relevant to this study, the article would be retained for further consideration.

Search methods for identification of studies

In collaboration with authoritative university lecturers, the authors employed a methodical search strategy with pertinent keywords. According to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (Higgins et al., 2019), this search method was developed using the PICO (Patient, Intervention, Comparison, Outcome) framework as Patient/problem: Male patients suffering from dyslipidemia, Intervention: Atorvastatin, Comparison: Tetrahydrolipstatin (orlistat), Outcome: Decreased levels of serum LDL.

Data collection and analysis

Study selection

Articles from the literature search were downloaded. After removing duplicates, two impartial reviewers examined the titles and abstracts. In order to select articles according to the eligibility criteria, the authors read the full text of articles that seemed relevant. The PRISMA flowchart was used to illustrate the basis for exclusion following full-text reading as well as the details of the approach. The authors would have a discussion if any disagreements arose. From a total of 366 articles identified from the literature search, nine articles met the inclusion criteria and were assessed for eligibility. From a total of nine studies, three studies investigated the capacity of orlistat to reduce the levels of serum LDL, while six studies investigated the capacity of atorvastatin to reduce the levels of serum LDL (Fig. 1).

Study design and population

From a total of nine studies included in this systematic review, eight used a randomized controlled trial (RCT) design, and one used a cross-sectional design. The studies were published between 2012 and 2022. For atorvastatin (459 participants) and orlistat

(237 participants), the sample sizes ranged from 25 (Joyeux-Faure et al., 2014) to 130 (Hing Ling et al., 2012) participants. The key characteristics of the studies included in this systematic review are presented in Tables 1 and 2 alongside the Jadad score (Jadad et al., 1996), JBI's critical appraisal (Moola et al., 2020), and the like.

Inclusion criteria

All eligible studies met the following inclusion criteria: (1) using a randomized controlled trial (RCT), cohort, or cross-sectional study design; (2) involving male subjects with a mean age between 45 and 64 years; (3) focusing only on human patients; and (4) written in English. Other studies were excluded due to the following criteria: (1) focusing on animal subjects, (2) using a clinical trial study design, and (3) discussing diseases other than dyslipidemia.

Data extraction and quality assessment

Each author was assigned with several articles to examine. All authors had a discussion to settle any disagreements. Subsequently, the name of the first author, year of publication, ethnicity, sample size, number of participants who used atorvastatin and tetrahydrolipstatin (orlistat), demographic data (including sex, age, and body mass index/BMI), and lipid profile (low-density lipoprotein/LDL-C) were extracted from all articles included in this study. Tables containing information about the characteristics of the studies were made using Microsoft Word following data retrieval and documentation. In addition, information about the authors and publication, as well as the year, sex, age, number of occurrences, intervention, mean, and standard deviation, was extracted from the studies. Finally, the potential for bias in the studies was assessed using the Jadad score for RCTs and the JBI's critical appraisal checklist for cross-sectional studies.

Statistical evaluation

Cochran's Q-test and the I^2 index were used to measure the heterogeneity of the studies (Von Hippel, 2015). The results of the Fisher z-transformation were derived from a fixed effect model ($I^2 < 50\%$) or a random effect model ($I^2 > 50\%$) (Dettori et al., 2022). Additionally, RevMan 5.4 was used to perform statistical analysis. Continuous data were calculated and shown as mean differences, while dichotomous data were generated and given risk ratios. The outcome measure and meta-analysis were combined with an analysis of specific subgroup considerations to investigate the treatment effects more thoroughly. A 95% confidence interval (CI) was used to represent the degree of uncertainty of the effects. Funnel plots and fail safe-N were used to assess publication bias using JASP software (version 0.18.1) (Berkhout et al., 2023; Juandi and Tamur, 2021).

RESULTS

Study selection

Initially, 366 papers were acquired; however, 62 articles remained after 42 were eliminated due to duplication, and 20 studies were determined to be unrelated to the current meta-analysis. Initially, 366 papers were acquired; however, 62 articles remained after 42 were eliminated due to duplication, and 20 studies were determined to be unrelated to the current meta-analysis. There are 20 articles left after carefully examining the titles and abstracts. 12 of these 20 papers were not retrieved for a variety of reasons, including review (42 articles), clinical trial (110 articles), irrelevant study design (101 articles), and abstract only (10), among others. Furthermore, a thorough analysis of eligibility was conducted using 20 papers. Eight publications were left after eligibility was determined after 12 articles were rejected for various reasons, including the fact that two articles were not conducted on humans, five involved additional interventions, and five did not (Agrawal et al., 2018; Alanazi et al., 2022; Blom et al., 2014; Hing Ling et al., 2012; Jin et al., 2021; Joyeux-Faure et al., 2014; Roth et al., 2012; Shirai et al., 2018; Werida et al., 2021) (Fig. 1).

Study characteristics

Nine articles were included, with 696 subjects in the treatment group. One of the selected articles was cross-sectional, and the others were randomized controlled trials. In addition, three articles received orlistat, while six articles received atorvastatin therapy. Men between the ages of 40 and 60 made up the study's subject population. Additionally, identification was based on comparing LDL levels before and after therapy (Tables 1 and 2).

Risk of bias in studies

The potential for bias in the 8 studies was assessed using the Jadad score for RCTs and 1 using the JBI's critical appraisal checklist for cross-sectional studies (Table S1). Funnel plot and fail safe N were used to assess publication bias using JASP software (version 0.18.1). The funnel plots for atorvastatin showed symmetrical results, which indicated no publication bias (Fig. 2). The results of the fails-safe N value calculation also showed no publication bias (n value = 76481). On the other hand, funnel plots for orlistat showed asymmetrical results, which indicated publication bias (Fig. 3), and the fails-safe N value calculation showed publication bias (n value = 5.469×10^7).

Table 1. Main characteristics of studies on atorvastatin for meta-analysis.

No.	Author(s)	Study design	Jadad score	Mean age (male)	LDL – baseline (mg/dL)			LDL – after treatment (mg/dL)		
					Mean	SD	Total	Mean	SD	Total
1	(Agrawal et al., 2018)	RCT	5	59.05 ± 10.25	136.43	18.81	120	64.18	17.58	109
2	(Blom et al., 2014)	RCT	7	58.4 ± 8.7	96.2	13.3	73	104.6	3.7	73
3	(Joyeux-Faure et al., 2014)	RCT	7	51 ± 12	160.0	67.0	25	88.0	30.0	25
4	(Hing Ling et al., 2012)	RCT	7	59.7	119.01	15.52	130	107.81	15.52	125
5	(Roth et al., 2012)	RCT	7	55.3 ± 10.3	121.2	18.1	31	103.8	14.6	31
6	(Werida et al., 2021)	RCT	7	54.38 ± 5.84	116.67	26.52	80	99.46	20.53	80

Table 2. Main characteristics of studies on orlistat for meta-analysis.

No.	Author(s)	Study design	Jadad score	Mean age (male)	LDL – baseline (mg/dL)			LDL – after treatment (mg/dL)		
					Mean	SD	Total	Mean	SD	Total
1	(Alanazi et al., 2022)	Cross-sectional	JBI's Critical Appraisal = Eligible	53.65 ± 0.8	124.19	2.32	100	108.72	1.55	100
2	(Jin et al., 2021)	RCT	5	40.053 ± 8.107	121.41	45.62	37	123.69	31.03	32
3	(Shirai et al., 2018)	RCT	7	45.1	124.0	18.7	100	118.0	0.1	94

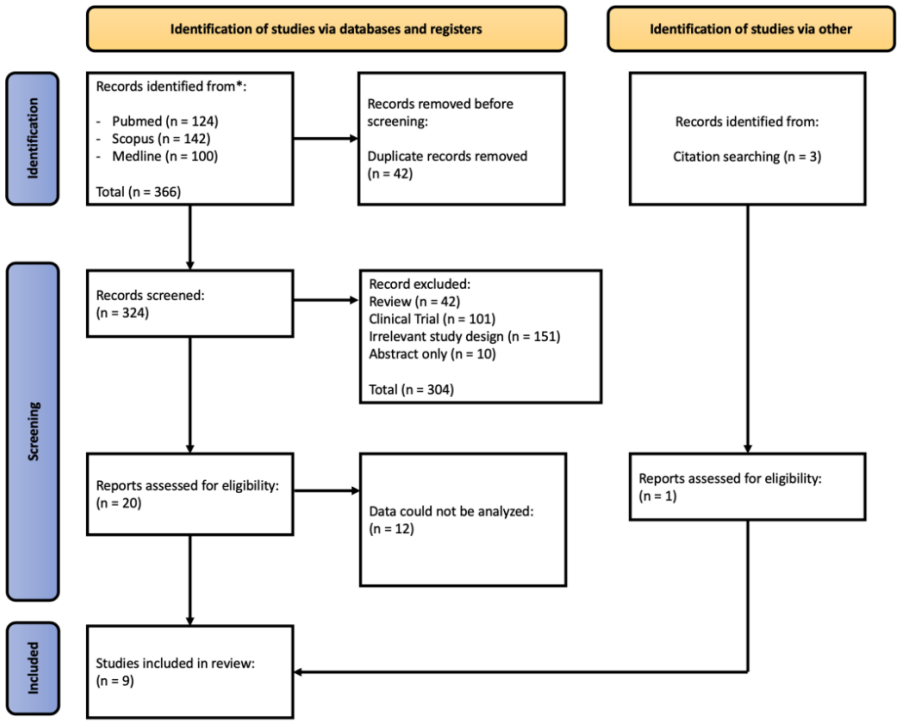

Figure 1. PRISMA flowchart of this systematic review and meta-analysis.

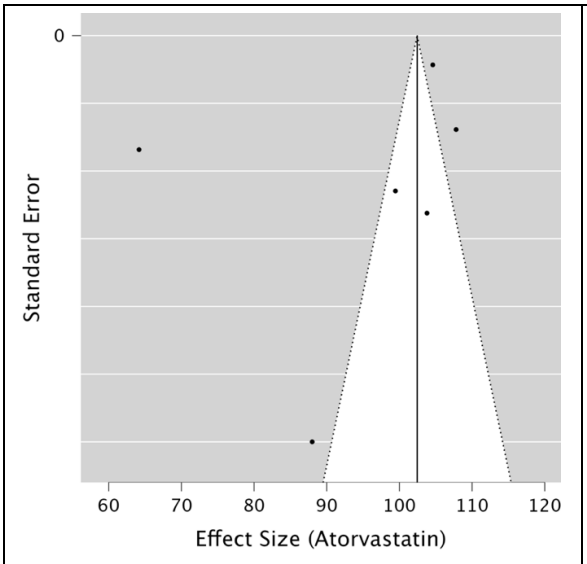

Figure 2. Funnel plots of trials included in the meta-analysis of the effect of atorvastatin on reducing LDL serum levels.

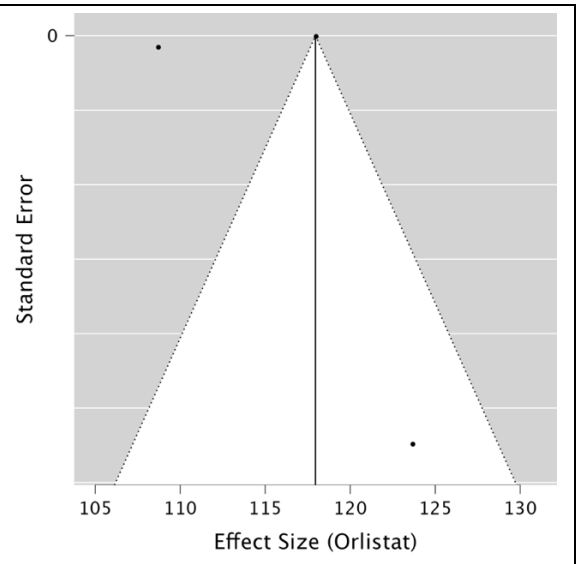

Figure 3. Funnel plots of trials included in the meta-analysis of the effect of orlistat on reducing LDL serum levels.

Results of individual studies of atorvastatin

According to a study by Agrawal et al. (2018), atorvastatin 40 mg results in mean LDL cholesterol reductions of 47.18 ± 20.81 and 50.03 ± 18.06, respectively, during 3 and 6-month follow-ups. While atorvastatin 80 mg causes LDL reductions of 50.11 ± 15.85 and 52.30 ± 13.72. A non-significant difference between the two doses was found when they were compared ($p = 0.118$ and $p = 0.149$, respectively). This study found that both atorvastatin dosages (40 and 80 mg) are equally effective in reducing dyslipidemia.

According to research by Blom et al. (2014), the overall least-squares mean (± SEM) reduction in LDL cholesterol from baseline in the evolocumab group was 57.0 ± 2.1% ($p<0.001$) among the 901 patients included in the primary analysis. The mean reduction was 55.7 ± 4.2% for patients receiving diet-only back-

ground therapy, 61.6 ± 2.6% for those receiving 10 mg of atorvastatin, 56.8 ± 5.3% for those receiving 80 mg of atorvastatin, and 48.5 ± 5.2% for those receiving 80 mg of atorvastatin and 10 mg of ezetimibe ($p<0.001$ for all comparisons). Apolipoprotein B, non-high-density lipoprotein cholesterol, lipoprotein (a), and triglyceride levels were all markedly lowered by evolocumab treatment. In patients with a variety of cardiovascular risks, evolocumab added to diet alone, low-dose atorvastatin, or high-dose atorvastatin with or without ezetimibe significantly lowered LDL cholesterol levels at 52 weeks.

In research published in 2014, Joyeux-Faure et al. (2014) randomized 51 individuals with severe obstructive sleep apnea (OSA). After 12 weeks of atorvastatin treatment, total and LDL cholesterol levels considerably decreased ($p = 0.0001$), whereas HDL cholesterol remained stable in comparison to the placebo group. A three-month course of atorvastatin did not enhance endothelial function or lessen the onset of atherosclerosis, although it did lower blood pressure and enhance lipid profiles.

According to a study by Hing Ling et al. (2012), switching to ezetimibe/simvastatin had a statistically significant positive impact on LDL-C (-26.81 vs. -11.81 %), total cholesterol (-15.97 vs. -7.73%), non-HDL-C (-22.50 vs. -10.88%), Apo B (-17.23 vs. -9.53%), and Apo A-I (2.56 vs. -2.69%), but not on HDL-C, triglycerides, or hs-CRP (all $p\leq0.002$). After switching to ezetimibe/simvastatin as opposed to doubling the atorvastatin dose, significantly more participants attained LDL-C 1.81 mmol/L (29 vs. 5%), 2.00 mmol/L (38 vs. 9%), or 2.59 mmol/L (69 vs. 41%) (all $p = 0.001$). Between treatment groups, the overall safety profile seems to be generally comparable. Switching to a combination of ezetimibe/ simvastatin 10/40 mg provided significantly greater LDL-C lowering and greater achievement of LDL-C targets in high-cardiovascular-risk subjects with hypercholesterolemia who had already been treated with atorvastatin 20 mg but not at LDL-C 2.59 mmol/L. This was in comparison to doubling the atorvastatin dose to 40 mg. In general, both therapies were well received.

In a 2012 study by Roth et al. (2012), the least-squares mean (± SEM) percent reduction in LDL cholesterol from baseline was found to be 73.2 ± 3.5 with 80 mg of atorvastatin plus SAR236553, as opposed to 17.3 ± 3.5 with 80 mg of atorvastatin plus placebo ($p<0.001$) and 66.2 ± 3.5 with 10 mg of atorvastatin plus SAR236553. All of the patients who received SAR236553 achieved LDL cholesterol levels of less than 100 mg/dL, compared to 52% of those who received 80 mg of atorvastatin plus placebo, and at least 90% of the patients who received SAR236553 achieved LDL cholesterol levels of less than 70 mg/dL (1.8 mmol/L), compared to 17% of those who received 80 mg of atorvastatin plus placebo. A considerably higher reduction in LDL cholesterol was seen with SAR236553 added to either 10 mg or 80 mg of atorvastatin in a randomized trial involving patients with primary hypercholesterolemia than with 80 mg of atorvastatin alone.

According to a study by Werida et al. (2021), using ROSUVA vs. ATORVA led to a significant ($p<0.001$) decrease (compared with baseline, respectively) in HbA1c% (9.13 vs. 2.35%), LDL-C (22.23 vs. 14.75%), triglycerides (13.56 vs. 8.21%), total cholesterol (16.10 vs. 10.81%), atherogenic index (18.08 vs. 10.97%), hs-CRP (23.51 vs. 18.96%), sortilin (33.33 vs. 15.08%), and leptin (31.81 vs. 23.17%) but increased adiponectin (97.99 vs. 76.47.1%) and HDL-C (76.47 vs. 0.21%). ROSUVA is more effective at lowering cholesterol levels, reducing the atherogenic index, and controlling inflammatory biomarkers in type 2 diabetes (T2D) patients who have dyslipidemia. However, in patients with dyslipidemic T2D, both statins are equally effective as cardioprotective medications.

Results of individual studies of orlistat

In a study by Alanazi et al. (2022), the orlistat group demonstrated a significant improvement ($p<0.05$) in triglycerides, total cholesterol, LDL/HDL ratio, and LDL cholesterol. In contrast, BMI and systolic blood pressure did not significantly differ between the orlistat and placebo groups. The results of this investigation showed that orlistat can dramatically improve lipid profiles. The study also found that orlistat might not significantly decrease blood pressure and BMI without significant lifestyle modifications.

Jin et al. (2021) examined the gut microbiota and short-chain fatty acid (SCFA) characteristics of obese individuals from Xinjiang, northwest China, a region with a multiethnic culture and distinctive lifestyle. The study also explored the potential microbes that respond to a 12-week course of orlistat and ezetimibe medication in a randomized controlled open-label trial setting. According to the findings, geography and eating habits significantly impacted how much the gut microbiota contributed to obesity. Waist circumference, total triglyceride, and fasting blood glucose all fell considerably after orlistat therapy, whereas ezetimibe significantly reduced total triglyceride, total cholesterol, and low-density lipoprotein cholesterol (LDL-C).

According to a study by Shirai (2018), orlistat 60 mg was given three times daily for 24 weeks to participants in Japan who were at risk for metabolic illnesses because of an excessive buildup of visceral fat.

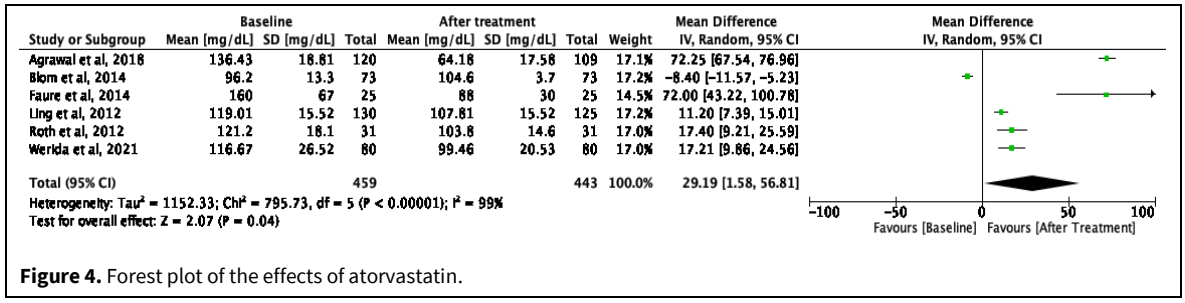

Figure 4. Forest plot of the effects of atorvastatin.

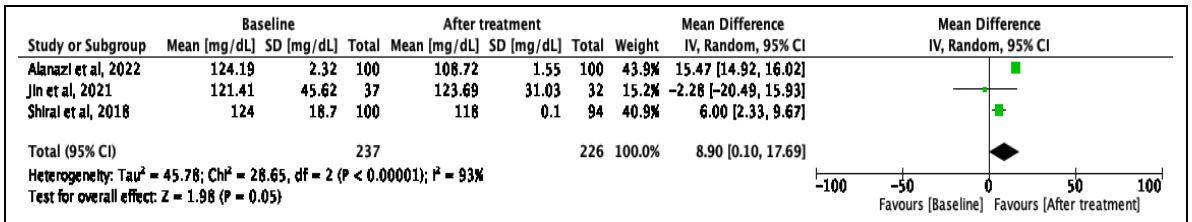

Figure 5. Forest plot of the effects of orlistat.

The usage of orlistat may lessen the buildup of visceral fat and the danger of developing metabolic illnesses brought on by obesity, as seen by the significant reductions in visceral fat area and waist circumference that were seen with an acceptable safety profile. In the orlistat and placebo groups, respectively, the changes in these parameters from the initial assessment (mean ± SD) to the most recent assessment were as follows: Total cholesterol decreased from 4.5 ± 21.7 mg/dL (p = 0.007) and 5.1 ± 18.9 mg/dL (p = 0.003), LDL cholesterol decreased from -6.0 ± 18.6 mg/dL (p<0.001) and 2.0 ± 19.6 mg/dL (p = 0.095), HDL cholesterol increased from 3.4 ± 6.2 mg/dL (p<0.001) and 4.9 ± 6.4 mg/dL (p<0.001), and triglycerides decreased from -4.6 ± 37.6 mg/dL (p = 0.144) and -2.5 ± 58.4 mg/dL (p = 0.104). However, other factors linked to metabolic disorders, such as blood glucose, HbA1c, systolic blood pressure, and diastolic blood pressure, fluctuated within normal ranges over the course of the trial and did not demonstrate any appreciable alterations.

Results of syntheses

Association of atorvastatin with decreased serum LDL

The results of a random effects model suggested that atorvastatin in patients with dyslipidemia decreased the levels of serum LDL by 29.19 points (95% CI [1.58, 56.81]; p = 0.04). This suggested that consuming atorvastatin had a significant relationship with a decrease in the levels of serum LDL. In addition, it was found that this study is heterogeneous (I^2 = 99%). The results of the analysis are presented in Fig. 4.

Association of orlistat with decreased serum LDL

The results of a random effects model suggested that consuming orlistat as a treatment for dyslipidemia had no significant relationship with a decrease in the levels of serum LDL by 8.90 points (95% CI [0.10, 17.69]; p = 0.05). However, it was found that this study is not heterogeneous (I^2 = 93%). The results of the analysis are presented in Fig. 5.

Reporting biases

The data analysis revealed that there were different numbers of papers between atorvastatin and orlistat for lowering LDL serum levels, with atorvastatin having more findings. Comparing their LDL serum levels can have an impact on data analysis if it appears that using one of them is more successful than using the other. Different frequency outcomes can occur from using different numbers of divisors. Despite these variations, they had little impact on the systematic review's overall findings.

DISCUSSION

The International Atherosclerosis Society has developed guidelines for the treatment of dyslipidemia. According to the panel, non-high-density lipoprotein cholesterol is the main atherogenic lipoprotein. Two types of prophylaxis exist, namely primary and secondary, both of which have atherogenic lipoprotein levels. The guidelines focus on lifestyle changes to lower atherogenic lipoprotein in primary prophylaxis, while medication therapy is only recommended for those at a higher risk. The estimation of lifetime risk is based on variations in the baseline population risk in different countries or areas. On the other hand, sec-

ondary prophylaxis focuses on using cholesterol-lowering medications to achieve normal levels of atherogenic lipoprotein (Grundy et al., 2014). In addition, other organizations and institutions have given recommendations for managing dyslipidemia. Even though they share a lot of characteristics, they have marked differences. To develop consensual guidelines for the patients of dyslipidemia in clinical medicine, the National Lipid Association (NLA) established a panel of experts. The recommendations made by the panel of experts of the NLA address the following issues: background and conceptual framework; screening and classification of the levels of lipoprotein lipid in adults; targets for intervention or treatment in dyslipidemia; management of atherosclerotic cardiovascular disease; atherogenic risk factors; and targets for lifestyle and drug treatments (Jacobson et al., 2015).

Several diseases, such as central obesity, insulin resistance, hypertension, and dyslipidemia, are examples of metabolic syndrome characterized by impaired metabolic balance (Fujioka, 2015; Laksana et al., 2021). The burden of cardiovascular disease will undoubtedly increase as the frequency of metabolic syndrome increases (Kalanjati et al., 2021). The key characteristics of metabolic syndrome are obesity and dyslipidemia. Both conditions can be accompanied by dysfunction of adipose tissue (AT), which is influenced by the pathogenic processes triggering this syndrome (Fairuz et al., 2021). The current list of approved medications for dyslipidemia and obesity includes sibutramine, diethylpropion, ezetimibe, naltrexone, niacin, resin, fibrate, statin, and orlistat. These medications can alter the intricate metabolic, inflammatory, atherogenic, insulin-sensitive, and adipogenesis pathways (Dias et al., 2018). Meanwhile, the current pharmacological choices for weight loss are phentermine (advised for short-term use only), phentermine and topiramate extended-release capsules, orlistat, naltrexone/bupropion, lorcaserin, and liraglutide 3.0 mg. Currently, naltrexone/bupropion, liraglutide 3.0 mg, and orlistat are all permitted in Europe. Compared to placebo, all the aforementioned drugs are effective in weight loss (Fujioka, 2015).

Research shows that obesity is strongly associated with a higher risk of metabolic disorders such as non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and dyslipidemia. Due to an imbalance between energy expenditure and food intake, obesity is caused by an abnormal buildup of adipose tissue. Adipose tissue is now understood as an endocrine organ and the primary location for storing extra energy from food consumption. Adipocytokines, sometimes called adipokines, are a group of bioactive molecules produced by the growth of adipose tissue that influence various physiological processes in many organs and cause persistent inflammation. Although the exact processes are unknown, excess adipose tissue leads to dysregulation of the synthesis or secretion of certain adipokines (Jung and Choi, 2014; Pranoto et al., 2023).

According to this meta-analysis, orlistat was not significantly associated with a decrease in the levels of serum LDL ($\beta = 8.90$; 95% CI [0.10, 17.69]; $p = 0.05$; $I^2 = 93\%$). However, the results suggested that atorvastatin in patients with dyslipidemia caused a decrease in the levels of serum LDL serum by 29.19 points (95% CI [1.58, 56.81]; $p = 0.04$). In other words, this study revealed a significant relationship between consuming atorvastatin and the levels of serum LDL. Therefore, although atorvastatin and orlistat are recommended for the treatment of patients with dyslipidemia, the authors argue that both have different mechanisms (Fig. 6). On the other hand, variability between publications was frequently nevertheless large ($I^2 > 50\%$). Several other potential sources of variability, including the nation of origin, the population, the methodology, dose of orlistat and atorvastatin, the instrument, and the unit of LDL serum level, might produce variations in magnitude or the opposite direction of an impact. As a result, subgroup analysis and random-effects models were run (Von Hippel, 2015).

Orlistat blocks gastric and pancreatic lipases, which are essential for the breakdown of dietary fat. Therefore, orlistat can reduce weight by 3% and improve glucose intolerance as well as parameters of lipids such as total cholesterol and LDL serum. However, it is interesting to note that orlistat cannot reverse adipocyte hypertrophy (Heck et al., 2000). Orlistat has been promoted as an intestinal lipase inhibitor for the treatment of obesity. It is used in conjunction with a hypocaloric diet. Moreover, weight loss induced by orlistat is also associated with a slight increase in blood pressure, the levels of serum LDL, glycemic index, and the onset of diabetes. Orlistat is considered safe and rarely causes adverse side effects such as severe renal and liver disorders. Treatment compliance is challenging, nevertheless, due to a high prevalence of gastrointestinal side effects (Sumithran and Proietto, 2014).

Recent studies have reported that orlistat, a reversible inhibitor of stomach and pancreatic lipases, is well known for its ability to fight obesity and protect against free radicals. In cardiovascular diseases, cholesterol intermediates and metabolites serve a variety of crucial roles. An experiment demonstrated the influence of orlistat on sterol metabolism in obese and overweight individuals following weight loss in week 12. In week 12, the metabolic profiles of serum sterol, free cholesterol, sitosterol, 7a-hydroxycholesterol

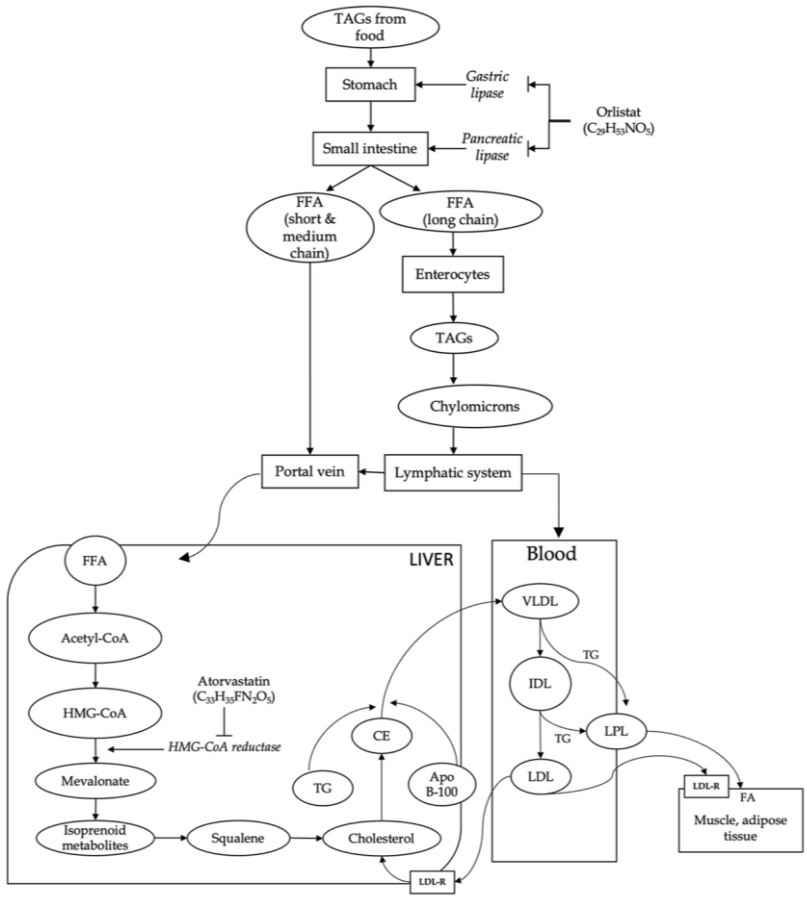

Figure 6. Simplified illustration of the different mechanisms between atorvastatin and orlistat to inhibit cholesterol biosynthetic pathway (from digestion, absorption, and transport).

(Heck et al., 2000; Zhang et al., 2020a).

TAGs: Triacylglycerols; FFA: Free Fatty Acid; HMG-CoA: β-Hydroxy β-methylglutaryl-Coenzim A; TG: Triglycerides; CE: Cholesterol Ester; ApoB-100: Apolipoprotein B-100; VLDL: Very-Low-Density Lipoprotein; IDL: Intermediate-Density Lipoprotein; LDL: Low-Density Lipoprotein; LDL-R: LDL Receptor; LPL: Lipoprotein Lipase; FA: Fatty Acid.

(7a-OHC), and 7b-OHC were significantly lower in the experimental group. Additionally, lower metabolic ratios of sitosterol, 7a-OHC, and cholesterol were observed in the experimental group (Kwon et al., 2022).

On the other hand, atorvastatin blocks the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Statin stimulates the expression of LDL receptors in the liver, lowering total cholesterol and increasing LDL catabolism. This leads to decreases in LDL (21-55%) and TG (6–30%), as well as an increase in HDL (2–10%). With a surface under the cumulative ranking (SUCRA) score of 76.7%, atorvastatin comes in second place regarding LDL-C reduction behind resuvastatin (Zhang et al., 2020a).

Furthermore, statin significantly reduces basal cholesterol release and content from adipocytes, while AT serves as a buffer for plasmatic cholesterol. In fact, statin can reverse basal cholesterol release from adipocytes, but it cannot reverse apoA-1-stimulated cholesterol release or apoE secretion from adipocytes. On the other hand, pitavastatin increases HSL expression in mature adipocytes, boosting lipolysis, lowering lipid buildup, inhibiting adipocyte hypertrophy, and increasing the proportion of small adipocytes. Additionally, regression of epicardial AT volume occurs with intensive atorvastatin therapy. Statin appears to boost the expression of LPL mRNA in preadipocytes and the activity of LPL in 3T3-L1 preadipocytes and adipocytes. These effects decrease TG and VLDL levels and are mediated by various transcription factors, including SREBP and PPAR (Bencharif et al., 2010; Dias et al., 2018).

In overweight or obese individuals, orlistat medication increases the metabolism of oxysterol. The positive changes in oxysterol are maintained for six months following the end of medication. Therefore, by modulating oxysterol, orlistat can play a crucial role in developing atherosclerosis and endothelial

dysfunction. Adults consuming orlistat have been shown to experience significant reductions in cholesterol, sitosterol, and the metabolic ratio of sitosterol following weight loss. Consequently, orlistat can be a potential additional treatment for hypercholesterolemia (Kwon et al., 2022).

Before recommending the results to healthcare professionals, some limitations of this meta-analysis should be highlighted and considered. We still found high heterogeneity across studies, however, meta-analyses comparing the use of atorvastatin and orlistat have not been conducted previously (Mihaylova et al., 2012; Nikniaz et al., 2023; Zhang et al., 2020a; Zhou et al., 2012). Future studies are expected to report more on the effectiveness of orlistat use in patients with obesity associated with dyslipidemia in various other countries around the world.

CONCLUSION

According to the systematic review and meta-analysis, atorvastatin is strongly associated with lower levels of serum LDL in patients with dyslipidemia. The capacity of orlistat to reduce the levels of serum LDL is lower than that of atorvastatin, one of the statin derivatives, in treating dyslipidemia. This could be attributed to the different action mechanisms of orlistat as a medication. In other words, consuming orlistat does not immediately reduce the levels of serum LDL despite the fact that obesity is one of the variables associated with dyslipidemia. Furthermore, it is necessary to conduct additional research regarding the effects of atorvastatin and orlistat on patients with dyslipidemia supported by a balanced diet and frequent exercise. By reducing LDL levels and managing obesity, orlistat may be able to become a solution to the potentially increasing prevalence of metabolic syndrome.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Hasan NA	Kalanjati VP	Purwantari KE	Abdurachman A	Mifftahussurur M
Concepts or ideas	x	x			
Design	x	x	x	x	
Definition of intellectual content	x	x	x	x	x
Literature search	x	x	x	x	x
Experimental studies	x	x	x	x	x
Data acquisition	x	x	x	x	x
Data analysis	x	x	x	x	x
Statistical analysis	x	x	x	x	
Manuscript preparation	x	x	x	x	x
Manuscript editing	x				
Manuscript review	x	x	x	x	x

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Supplementary data

Table S1. Supplementary data.

No.	Author	Study design	Country	Gender (age, year old)	Jadad score	Treatment	Diagnosis	Follow up (week)	Outcome evaluated	Method of measurement
1	Agrawal et al. (2018)	RCT	India	Male (20-90)	5	Atorvastatin 40 mg, 80 mg	Dyslipidemia	24	LDL-c, HDL-c, TG	Blood serum
2	Blom et al. (2014)	RCT	South Africa, Czech Republic, United States	Male (18-75)	7	Atorvastatin 10 mg and 80 mg	Hyperlipidemia	52	TC, HDL-c, LDL-c, VLDL-c, apo-B, ratio of TC to HDL cholesterol, ratio of apo-B to apo-A1, and the levels of lipoprotein(a) and TG	Blood serum (ultracentrifugation) ELISA
3	Faure et al. (2014)	RCT	France and Switzerland	Male (54 ± 11)	7	Atorvastatin 40 mg	Dyslipidemia	12	Glucose level, LDL-c, TG, Insulin level, hs-CRP, urinary leukotriene E4 (LTE4)	Blood serum
4	Ling et al. (2012)	RCT	United States, Malaysia, Hungary, Poland, Spain, Romania, Costa Rica, Guatemala, Latvia, Peru, Estonia, and Israel	Male (18-79)	7	Atorvastatin 40 mg	coronary heart disease (CHD) with primary hypercholesterolemia	6	LDL-c, TC, Non-HDL-c, Apo-B, Apo-A1, hs-CRP	Blood serum
5	Roth et al. (2012)	RCT	United States	Male (18-75)	7	Atorvastatin 80 mg	hypercholesterolemia	8	LD-c, TC, HDL-c, TG, ratio of apo-B to apo-A1	Blood serum ELISA
6	Werida et al. (2021)	RCT	Egypt	Male (median = 55)	7	Atorvastatin 40 mg	type II diabetes with dyslipidemia	24	HbA1c, LDL-C, TG, TC, atherogenic index, hs-CRP, sortilin, leptin levels	Blood serum ELISA
7	Alanazi et al. (2022)	Cross-sectional	Saudi Arabia	Male (40-65)	7	Orlistat 120 mg 3x/d	Type 2 diabetes mellitus and dyslipidemia	24	LDL-c, HDL-c, TC, LDL/HDL ratio, and TG, BMI and systolic blood pressure	Blood serum
8	Jin et al. (2021)	RCT	China	Male (26-71)	5	Orlistat 120 mg 3x/d	overweight or obesity and dyslipidemia	12	fasting blood, LDL-c, HDL-c, γ-GT, ALT, and ALB, body weight, BMI, waist circumference, hip circumference, fasting blood glucose, total triglyceride, total cholesterol,	Blood serum
9	Shirai et al. (2018)	RCT	Japan	Male (27-59)	7	Orlistat 60 mg 3x/d	Obesity	24	HbA1c, LDL-c, HDL-c, and TG	Blood serum