REVIEW ARTICLE

Ursodeoxycholic Acid's Effectiveness in the Management of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis

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Received on: 08 April 2024; *Accepted on*: 10 May 2024; *Published on*: 12 June 2024

Abstract

Aim: This meta-analysis's objective was to assess the effectiveness of ursodeoxycholic acid (UDCA) in the management of nonalcoholic fatty liver disease (NAFLD).

Methods: Electronic databases like PubMed, Embase, Scopus, and Cochrane Library were thoroughly looked for randomized controlled trials determining ursodeoxycholic acid's (UDCAs) effectiveness on the serum liver function tests in NAFLD patients. After screening, seven randomized controlled trials were incorporated overall. Utilizing a fixed effects model, quantitative data synthesis was performed in R version 4.3.1.

Results: The meta-analysis showed significant reductions in alanine transaminase (ALT) ($p \leq 0.0001$), aspartate transaminase ($p = 0.0009$), and gamma-glutamyl transferase (GGT) ($p \leq 0.0001$) after UDCA therapy. However, significant reductions in bilirubin ($p = 0.6989$) and alkaline phosphatase (ALP) ($p = 0.1172$) levels were not noted. Sensitivity analysis by removing the studies with some concerns of bias was successful in demonstrating a remarkable reduction in heterogeneity for aspartate transaminase and ALP, which was also observed while performing the subgroup analyses via dosage.

Conclusion: Ursodeoxycholic acid was beneficial in patients diagnosed with NAFLD as it significantly reduced aspartate transaminase, ALT and GGT levels. However, more randomized controlled trials are required to be conducted in the future to increase the certainty of the evident findings.

Clinical significance: This meta-analysis strengthens the evidence about the reductions in AST, ALT, and GGT levels observed with ursodeoxycholic acid therapy in NAFLD patients by pooling the data together from the latest RCTs thus proving its hepatoprotective effects which can be beneficial in preventing the associated complications.

Keywords: Meta-analysis, Nonalcoholic fatty liver disease, Systematic review, Ursodeoxycholic acid.

Euroasian Journal of Hepato-Gastroenterology (2024): 10.5005/jp-journals-10018-1434

Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by macrovesicular steatosis that affects at least 5% of hepatocytes, without any identifiable secondary cause. This condition encompasses a range of disorders that span from simple nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis.[1] On a global scale, NAFLD has become the principal cause of chronic liver disease.[2]

Patients diagnosed with NAFLD exhibit an elevated likelihood of end-stage liver disease, hepatocellular carcinoma (HCC),[3] and liver-related mortality.[2] The presence of fibrosis is deemed a crucial indicator of unfavorable consequences in NAFLD as opposed to the histological characteristics of NASH.[4]

However, the involvement of the liver is merely a single element of the multifaceted manifestation of NAFLD. It is noteworthy that cardiovascular diseases are the number one cause of mortality among individuals with NAFLD. Liver-related mortality is only the third most prevalent cause of death.[5]

Ursodeoxycholic acid (UDCA) has proven to be known for being hepatoprotective in NAFLD. Ursodiol as UDCA is commonly known, is a bile acid that comprises 3% of the bile pool and possesses hydrophilic properties. Its efficacy in reducing cholestasis has been established in various studies.[6] The hypothesized mechanism of action of ursodiol is it reduces the amount of hydrophobic bile acids in the hepatobiliary system, thereby mitigating the risk of hepatotoxicity. Additionally, it has been hypothesized that ursodiol exhibits immunomodulatory and antiapoptotic properties, rendering it a potential adjunctive therapy for acute or chronic graft vs host disease (GVHD) of the liver.[7]

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How to cite this article: Patel VS, Mahmood SF, Bhatt KH, *et al*. Ursodeoxycholic Acid's Effectiveness in the Management of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. Euroasian J Hepato-Gastroenterol 2024;14(1):92–98.

Source of support: Nil

Conflict of interest: None

Currently, the aforementioned agent is utilized for the dissolution of gallstones in specific patients.[8]Additionally, the use of UDCA has been established for the management of hepatobiliary disorders, including primary biliary cirrhosis (PBC).[9.] However, its effectiveness in the treatment of ailments such as hepatitis B and C virus infections or pediatric cholestasis, such as extrahepatic biliary atresia or primary sclerosis cholangitis, remains to be established.[10–12]

This meta-analysis has been structured with the purpose of addressing several key objectives.

- It aims to conduct a rigorous systematic review of relevant studies that have investigated the use of UDCA in NAFLD's management.
- It seeks to undertake a quantitative evaluation of the collected data from these studies to evaluate the impact of UDCA on bilirubin levels, liver enzymes, and other pertinent clinical endpoints.
- It intends to explore potential sources of heterogeneity among the selected studies and to evaluate the accuracy of the data obtained.
- It looks to provide a synthesized conclusion on the UDCA's significance in managing NAFLD and to address the consequences for the clinical approach and future research goals.

Materials and Methods

This systematic review and meta-analysis were carried out as per the PRISMA Guidelines 2020.[13] Prior to the stage of data extraction, a protocol was registered on PROSPERO (registration number: CRD42023463029)

Data Sources and Search Strategy

Four of our reviewers independently searched through electronic databases PubMed Central, Embase, Scopus, and Cochrane Library to retrieve Randomized Controlled Trials (RCTs) published up to 25 June 2023. The search was confined to studies that were issued in English. The search was performed utilizing the following keywords: (Nonalcoholic Fatty Liver disease OR Nonalcoholic steatohepatitis) AND (Ursodeoxycholic acid OR Ursodiol) AND (Randomized Controlled Trial)

Study Selection Criteria

Clinical trials that met the criteria listed below were included:

1. Study design: Randomized Controlled Trials.
2. All RCT participants to be >18 years of age (population)
3. All patients should be diagnosed with NAFLD (population)
4. The intervention group received UDCA alone (intervention)
5. The control group that received placebo (Comparison)
6. Studies which measured outcomes in the form of alanine transaminase (ALT) and aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin not mandatory. (Outcome)

We excluded studies that were:

1. Non-human trials.
2. Non-English.
3. Including pregnant or <18-year-old patients.
4. Without any control group.
5. Unavailable in full-text form with only abstracts accessible.

Data Screening and Extraction

Three reviewers (VP, DJ, and MG) worked independently and thoroughly screened the titles, abstracts, and entire articles based on the inclusion/exclusion criteria. Any disagreement over a study's eligibility was settled by consensus. Data were retrieved and later tabulated, recording the following key information: First author, study design, year of publication, number of participants in total as well as the number of individually enrolled in the intervention vs control group, duration of intervention, the dosage of UDCA, geographical region where the RCT was conducted, age of patients, number of patients lost to follow-up in total, in addition to the ones lost in follow-up in intervention vs control group and serum levels of hepatic parameters in mean ± SD/SE (standard deviation/standard error) pre-and post-treatment.

Quality Assessment

Risk of bias assessment was independently conducted utilizing the Cochrane Collaboration's tool (RoB2 tool)[14] and evaluated the subsequent domains: bias arising from the randomization process; bias due to deviations from intended intervention; bias due to missing outcome data; bias in measurement of the outcome; bias in selection of the reported result; and overall bias.

Statistical Analysis

We utilized R version 4.3.1 (Posit team (2023). RStudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA.) to analyze continuous variables in our study. When data was initially provided as mean ± SE, we transformed it into mean ± SD. The findings of our meta-analysis were presented as standardized mean difference (SMD)[15] along with a 95% confidence interval (CI). A fixed-effect model was applied for analysis. Standardized mean difference values were not considered statistically significant when $p > 0.05$, whereas SMD values were considered statistically significant when $p < 0.05$. Additionally, we conducted I-square (I^2) tests to assess statistical heterogeneity among the studies we analyzed. Statistical heterogeneity was considered substantial if I^2 >60%, moderate if I^2 30–60%, and low if <30%.[16] The possible causes of heterogeneity were explored using sensitivity analysis, which was performed according to the risk of bias and by using a random-effects model when needed. To explore variations among the studies, subgroup analyses according to the intervention duration and dosage of UDCA were conducted.

Results

Study Selection Process and Study Characteristics

The study selection process is portrayed through the PRISMA flow diagram[13] in Figure 1. The preliminary search yielded a total of 178 studies including 98 from PubMed, 22 from Embase, 33 from Scopus, and 25 from Cochrane Library. After removing 56 duplicate records, the remaining 122 records were reviewed for title and abstract. About 98 studies were excluded upon initial screening. Subsequently, after reading the entire text of each study, 14 more studies were excluded due to a different study design, insufficient data, and lack of a control group. Ultimately, 7 studies were incorporated into this meta-analysis.

Encompassing 760 patients in all from the seven selected RCTs, consisting of 379 in the intervention and 381 participants in the placebo groups. Out of which 94 patients were lost to follow-up or were not able to complete the trials for various reasons. The

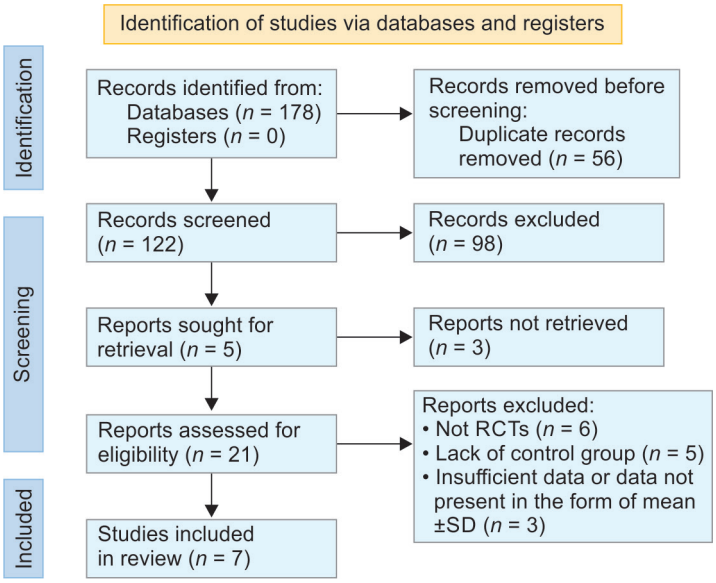

Fig. 1: PRISMA flow diagram demonstrating study selection process

Table 1: Study characteristics

Author; year	*Country*	*Duration*	*Dosage*	*Treatment*	*No. of participants at the start of the trial*	*No. of participants that completed the trial*
Ratziu et al., 2011[17]	France	12 months	28–35 mg/kg/d	UDCA	60	55
				Placebo	66	61
Leuschner et al., 2010[18]	Germany, Greece	18 months	23–28 mg/kg/d	UDCA	95	78
			23–28 mg/kg	Placebo	91	82
Lindor et al., 2004[19]	United States, Canada	2 years	13–15 mg/kg/d	UDCA	78	55
				Placebo	86	64
Mojtahedi et al., 2023[20]	Iran	3 months	5–10 mg/kg/d	UDCA	30	30
				Placebo	30	30
Elhini et al., 2022[21]	Egypt	6 months	5–10 mg/kg/d	UDCA	87	80
				Placebo	80	80
Santos et al., 2003[22]	Brazil	3 months	10 mg/kg/d	UDCA	15	14
				Placebo	15	14
Méndez-Sánchez et al., 2004[23]	Mexico	1.5 months	13–17 mg/kg/d	UDCA	14	12
				Placebo	13	11

study characteristics of the seven selected RCTs are presented in Table 1 and Supplementary Table 1. This meta-analysis comprises studies from all around the globe, spanning across France,Germany, Greece, United States, Canada, Iran, Egypt, Brazil and Mexico.[17–23] Included trials have treatment duration ranging from 45 days to 2 years. The total daily dose of UDCA varied from 5–10 to 28–35 mg/kg/day across the included studies.

Risk of Bias Assessment

The Cochrane Collaboration Risk of Bias tool[14] was utilized for the evaluation of all potential sources of bias. According to the Cochrane Statement of Risk of Bias,[14] each domain was deemed low, with some concerns or a high risk of bias. 7 studies[17–23] were evaluated out of which five studies were of low concern[17–20,23] and two were deemed with some concerns[21,22] (Fig. 2).

Meta-analysis

In comparison to the control group ($n = 351$), our meta-analysis showed a significant effect of ursodeoxycholic acid in reducing the serum alanine aminotransferase (ALT) ($n = 341$; SMD = –1.05 at 95% CI [–1.22 to –0.89], $p < 0.0001$, $I^2 = 91.9\%$ and aspartate aminotransferase (AST) levels in the intervention group SMD = –0.26, 95% CI [–0.41 to –0.11], $p = 0.0009$, $I^2 = 70.7\%$) (Figs 3 and 4). Similarly, its impact on the gamma-glutamyl transferase (GGT) levels was significant too (SMD = –0.66, 95% CI [–0.83 to –0.48], $p \leq 0.0001$). (Fig. 5). However, ALP and total bilirubin in the experimental groups were not found to be significant [SMD = –0.14, 95% CI (–0.32 to 0.04), $p = 0.12$; and SMD = 0.05, 95% CI (–0.19 to 0.28), $p = 0.7$, respectively]. There was a high heterogeneity noted which is often biased when the number of included studies is small.[24]

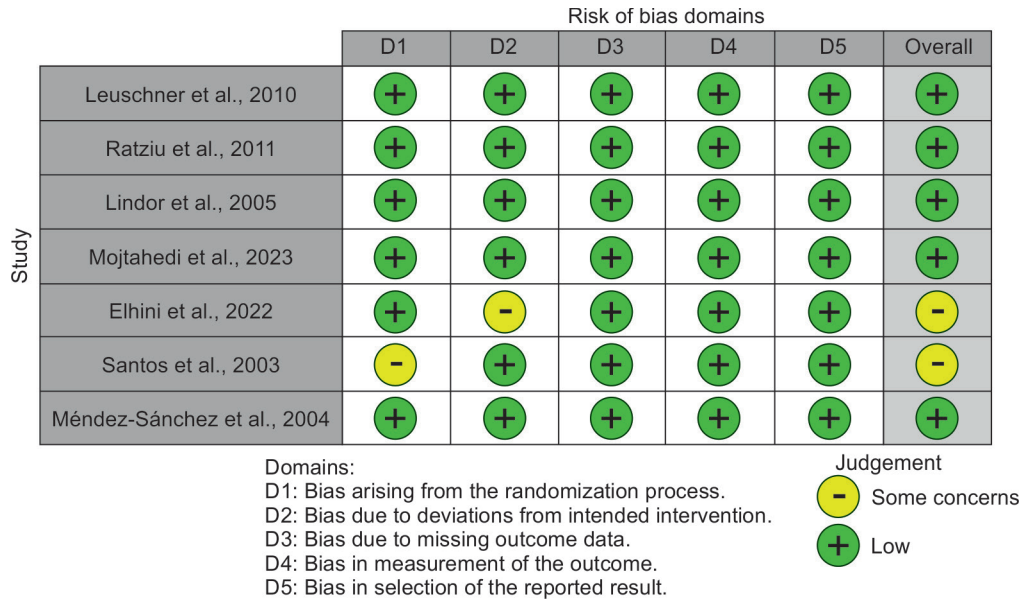

Fig. 2: Risk of bias assessment according to Cochrane guidelines

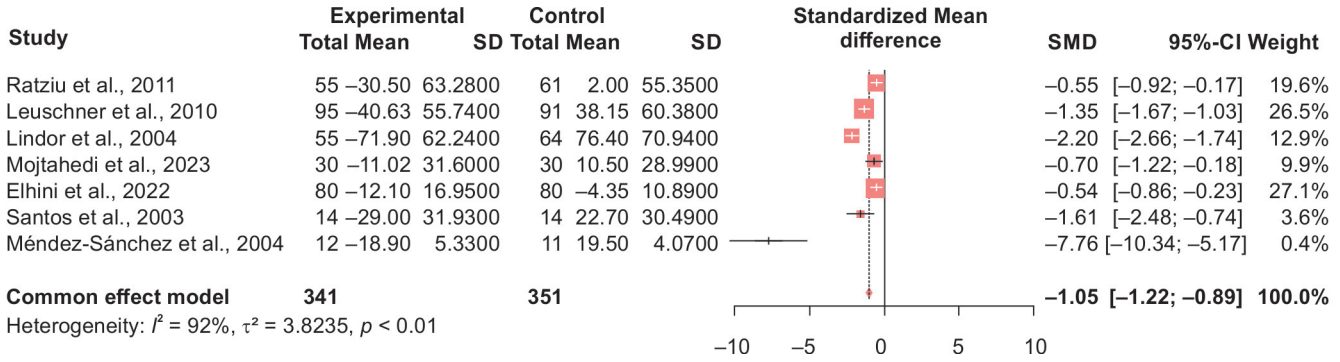

Fig. 3: Forest plot comparing the ALT values of intervention (UDCA) and control group

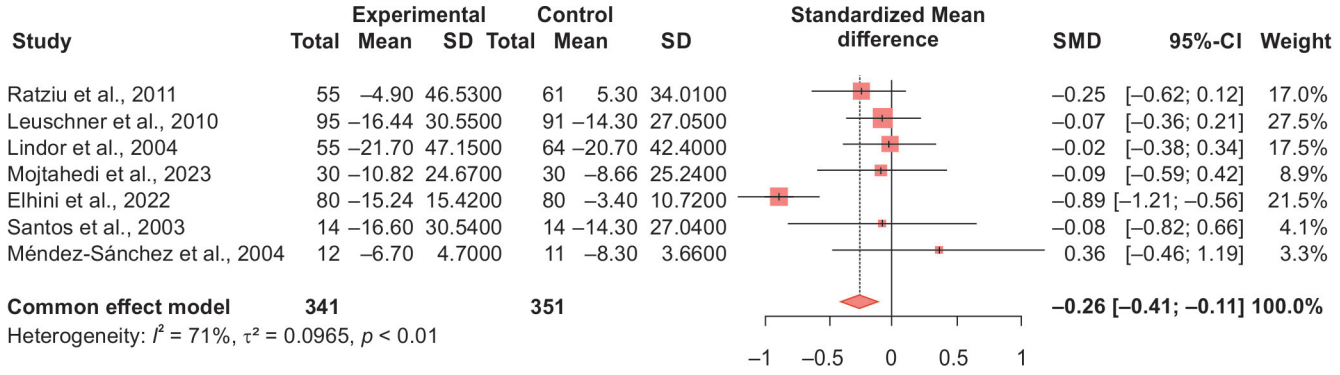

Fig. 4: Forest plot comparing the AST values of intervention (UDCA) and control group

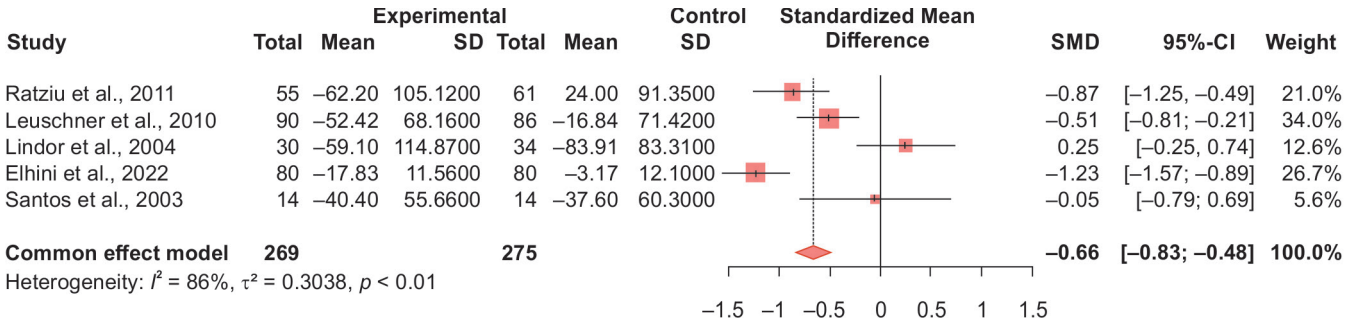

Fig. 5: Forest plot comparing the GGT values of intervention (UDCA) and control group

Subgroup Analyses

Subgroup analyses stratified by the duration of intervention (>6 months[17–19] and ≤6 months)[20–23] and dosage of the regimen (>20 mg/kg/day[17,18] and ≤20 mg/kg/day)[19–23] were performed. The results of which are portrayed in Supplementary Table 2. The results indicated that a treatment duration of >6 months did not show a reduction in ALT, AST, ALP, and bilirubin levels. However, there was a significant reduction in ALT, AST, ALP, GGT, Bilirubin levels when the duration of intervention was less than 6 months. Furthermore, subgroup analysis by dosage regimen showed no significant reductions for any hepatic parameters other than ALT and GGT. However, GGT values always showed significant reductions no matter how it was subgrouped. Additionally, a substantial decrease in heterogeneity was observed when grouping the studies for AST and ALP parameters.

Publication Bias

Visual assessment of funnel plots revealed potential publication bias for ALT, AST, and ALP, as an asymmetry was noted. Although an evident symmetry was observed in the funnel plots of GGT and bilirubin. However, owing to the quantity of studies in this meta-analysis being small, the results can be considered inconclusive.[25]

Discussion

Nonalcoholic fatty liver disease is a chronic condition that affects roughly a quarter of adults globally.[26] With such an incidence rate, our purpose is to study the possible advantages of UDCA therapy for individuals with NAFLD. This meta-analysis probed the effects of UDCA therapy, evaluating its impact on five key parameters: ALT, AST, GGT, ALP, and bilirubin. Elevated AST and ALT values are indicators of hepatocellular injury and indicate hepatic cell membrane damage.[27] Gamma-glutamyl transferase is found in both liver and biliary epithelial cells and has been shown to be a definite indicator of hepatobiliary disorders. Meanwhile, ALP levels might indicate liver illness or bone development difficulties.[28] Bilirubin is a byproduct of hemoglobin breakdown, and its elevated concentration often parallels hepatocyte injury, resulting in jaundice.[29]

Nonalcoholic fatty liver disease is often associated with hypertension, hyperlipidemia, type 2 diabetes, visceral obesity, and insulin resistance.[30] These complications often result in the emergence of new long-term health issues, adversely affecting patients' overall quality of life. Ursodeoxycholic acid is a bile acid that is formed during metabolism by gut bacteria, has been proven to be an effective non-surgical approach for treating cholesterol gallstones and PBC.[31] A recent study has demonstrated a significant decline in total cholesterol levels among patients, especially in those with PBC, after UDCA therapy.[32] With its remarkable potential for treating chronic liver diseases, such as PBC[33–35] and NASH,[18,36,37] UDCA is now being considered a viable therapy option. UDCA has a number of therapeutic benefits, including the ability to prevent cell death, reduce TNF-α (Tumor necrosis factor) levels in the circulation, alleviate endoplasmic reticulum stress, and enhance the liver's insulin sensitivity. These characteristics imply that UDCA may be useful in treating NASH.[38] It has been discovered that administering UDCA to PBC patients decreases the levels of liver damage markers in their blood. This advantageous impact is thought to be due to UDCA's ability to protect liver cells, prevent cell death, and combat oxidative stress, making it a good immune system regulator.[39] Another potential benefit is that UDCA therapy lowers inflammation by protecting liver cells from necrosis,[40] thereby lowering the local inflammatory response. UDCA is thought to minimize oxidative stress in liver cells by boosting the amounts of protective chemicals like glutathione and thiol-containing proteins like metallothionein.[41] Furthermore, it may inhibit liver cell death by minimizing mitochondrial membrane depolarization and decreasing the generation of dangerous reactive oxygen species.[42] Furthermore, UDCA has anti-inflammatory properties in the liver by decreasing NF-β (nuclear factor)-dependent transcription via glucocorticoid receptor activation.[43]

Ursodeoxycholic acid is usually well tolerated and has a low toxic level. The only recorded adverse effect is diarrhea, which is estimated to affect fewer than 5% of individuals.[44–46] It is recommended to take ursodeoxycholic acid with meals to improve absorption since it stimulates the gallbladder to release bile acids.[47]

In this meta-analysis, we observed statistically significant findings for ALT, AST, and GGT after performing our analysis using a fixed-effect model. This implies that the administration of UDCA to the experimental group had an impact, leading to reduction in ALT, AST, and GGT levels in comparison with the control group. However, it's essential to take into account that these changes come with a degree of high heterogeneity. Conversely, things differ for ALP and bilirubin. In our study, the changes found for these two parameters turned out to be statistically insignificant.

When we performed a subgroup analysis based on the dose and duration of treatment, we found that the dose of UDCA had no significant influence on AST and ALP results. In other words, the dose of UDCA did not influence its effectiveness in reducing these liver markers. The findings of our subgroup analysis based on treatment duration were intriguing. We observed that treatment durations of more than 6 months had insignificant results, but those of less than 6 months had significant outcomes. This demonstrates

that the duration of treatment has minimal influence on how UDCA affects liver parameters. Or this could just be a consequence of the subgrouping of studies and not necessarily indicate anything. It should be noted, however, that our study encountered difficulties owing to the high heterogeneity in treatment duration. This might be a drawback of our study, and as a consequence, we cannot say with conviction that treatment duration has no influence on UDCA's efficacy in lowering hepatic markers.

It is crucial to highlight that our meta-analysis does have some limitations. The levels of ALT, AST, and GGT were significantly reduced, although there was also a lot of heterogeneity. This degree of heterogeneity is frequently seen when the total number of research taken into consideration is limited.[24] So, we decided to do a sensitivity analysis to overcome this constraint. We selectively eliminated two studies from our analysis due to their significant potential for bias. What is remarkable is that after these studies were eliminated, we saw a considerable improvement. The heterogeneity in the AST and ALP values improved and reached zero. Additionally, we discovered that upon grouping the studies by dosage, for AST and ALP, there was an improvement in heterogeneity.

A few meta-analyses have been already conducted on this topic.[48,49] The addition of two more recent studies, Mojtahedi et al.[20] and Elhini et al.,[21] both published within the past 2 years, distinguishes our study. Their inclusion has significantly improved the overall results. These studies show that UDCA can reduce ALT levels while simultaneously also improving AST and GGT parameters.

Conclusion

After comprehensively combining the latest data from multiple studies on UDCA's effectiveness on liver markers in NAFLD patients, we concluded that UDCA was beneficial in not only effectively reducing the ALT levels but also the AST and GGT levels, which as far as we know has not previously been successfully established in other meta-analysis. However, more RCTs are required to increase the certainty of results, especially regarding the duration of UDCA and if longer duration means much more effective reductions in liver function parameters.

Clinical Significance

In the context of NAFLD management, the profound reductions observed in lowering ALT, AST, and GGT levels with UDCA therapy advocate its role as a promising adjunctive therapy in NAFLD patients. While lifestyle changes are the traditional treatment for NAFLD, they have their own limitations that can be addressed using UDCA as an adjuvant. Which owing to its antioxidant properties has been proven favorable in the management of dyslipidemia and in decreasing the risk of atherosclerotic cardiovascular disease in NAFLD patients.

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Supplementary Materials

All the supplementary materials are available online on the website of www.EJOHG.com.

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