

Ultrasonographic Outcomes of Ursodeoxycholic Acid Alone and in Combination with Atorvastatin or Ezetimibe in Patients with Asymptomatic Gallbladder Stones: A Comparative Clinical Study

Sepideh Manzori¹, Nima Sheikhi¹ , Hossein Nazarian² , Mehdi Birjandi³ , Saleh Azadbakht^{4*} 

¹ Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran.

² School of Global Studies, Oklahoma State University, Stillwater, Oklahoma, USA.

³ Department of Biostatistics and Epidemiology, Nutritional Health, Lorestan University of Medical Sciences, Khorramabad, Iran.

⁴ Department of Internal Medicine, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran.

***Corresponding author:** Saleh Azadbakht, Department of Internal Medicine, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran. E-mail: Azadbakht.saleh@yahoo.com

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Abstract:

Background: Ursodeoxycholic acid (UDCA) dissolves selected cholesterol gallstones, but treatment response varies. Whether adding cholesterol-lowering agents improves dissolution remains uncertain. This trial compared UDCA alone with UDCA plus atorvastatin or ezetimibe in patients with asymptomatic gallbladder stones.

Methods: In this three-arm randomized clinical trial, 60 participants were assigned to UDCA (600 mg/day) alone, UDCA plus atorvastatin (20 mg/day), or UDCA plus ezetimibe (10 mg/day) for six months. Following one withdrawal, 59 participants were analyzed. Ultrasonographic outcomes included total gallstone length, stone number, and treatment response. Complete response was defined as no visible stones; partial response required a reduction of at least 50% in stone size without complete disappearance.

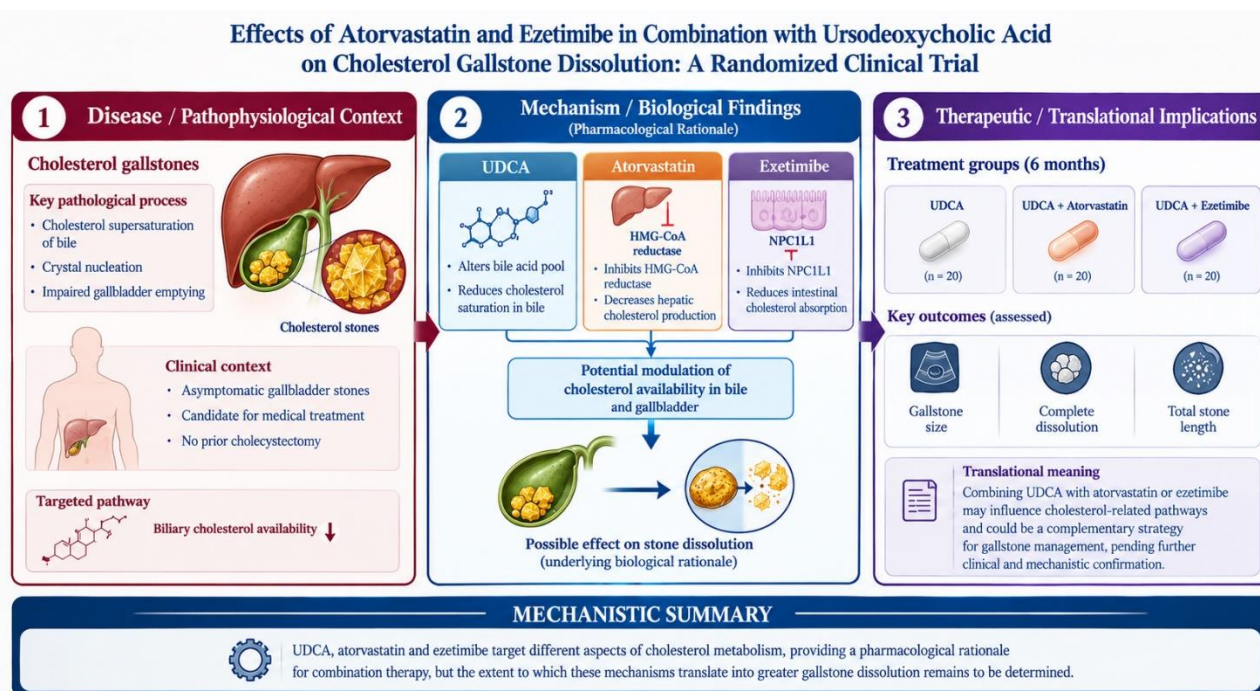
Results: Mean total gallstone length decreased from 21.42 to 12.10 with UDCA alone and from 18.02 to 10.65 with UDCA plus atorvastatin, compared with a reduction from 25.55 to 24.95 with UDCA plus ezetimibe. The reported baseline-adjusted analysis indicated an overall between-group difference ($P = 0.015$). Complete response rates were 47.4%, 60.0%, and 15.0%, respectively. Treatment-response distributions differed among groups ($P = 0.005$), whereas changes in stone number did not ($P = 0.136$). Pairwise comparisons did not establish a significant difference between UDCA alone and UDCA plus atorvastatin.

Conclusion: UDCA alone and UDCA plus atorvastatin showed reductions in mean stone length, whereas the ezetimibe combination had a less favorable descriptive response. Neither combination was established as superior to UDCA alone.

Mechanistic and Translational Relevance: UDCA modifies biliary cholesterol saturation, whereas atorvastatin inhibits cholesterol synthesis and ezetimibe reduces intestinal cholesterol absorption. These distinct mechanisms do not necessarily translate into equivalent improvements in gallstone dissolution.

Keywords: Ursodeoxycholic acid; gallstones; atorvastatin; ezetimibe; gallbladder; ultrasonography





Graphical Abstract: Comparative Ultrasonographic Outcomes of UDCA-Based Regimens for Asymptomatic Gallbladder Stones. Ursodeoxycholic acid (UDCA) is used to promote cholesterol gallstone dissolution by reducing biliary cholesterol saturation. This randomized clinical study evaluated six-month ultrasonographic outcomes of UDCA monotherapy compared with UDCA combined with atorvastatin or ezetimibe in patients with asymptomatic cholesterol gallbladder stones. Among the three regimens, UDCA plus atorvastatin yielded the highest descriptive treatment-response rate, whereas UDCA alone was associated with the greatest mean reduction in total gallstone length. The UDCA–ezetimibe combination showed less favorable results across the principal descriptive outcome measures. Overall, the findings illustrate that a plausible pharmacological rationale does not necessarily translate into superior clinical outcomes, and neither combination demonstrated established superiority over UDCA monotherapy.

Introduction

Gallstone disease is a common hepatobiliary disorder in which cholesterol supersaturation of bile, crystal nucleation, and impaired gallbladder emptying contribute to stone formation and persistence (1). Although many patients remain asymptomatic, gallstones may cause biliary colic, acute cholecystitis, and other complications (2). Management depends on the clinical presentation and characteristics of the stones (2). Expectant management is preferred for most asymptomatic gallstones, while pharmacological dissolution may be considered in selected patients unsuitable for or reluctant to undergo surgery (3). Ursodeoxycholic acid (UDCA) is used to dissolve selected

cholesterol gallstones by reducing cholesterol saturation in bile and modifying the bile acid pool (4). However, treatment selection depends on stone characteristics, and the timing of intervention can influence therapeutic outcomes (5). Complete dissolution is not achieved in every patient, and recurrence may occur after successful treatment (6). These limitations have encouraged interest in additional pharmacological approaches that target cholesterol metabolism and may complement the effects of UDCA. Atorvastatin lowers plasma LDL-cholesterol levels by suppressing hepatic cholesterol production through inhibition of the HMG-CoA reductase enzyme (7, 8). These effects provide a biological rationale for investigating

whether statins can improve UDCA-associated gallstone dissolution. Clinical evidence supporting this approach comes from a study in which simvastatin combined with UDCA improved gallstone dissolution in patients with multiple, but not solitary, gallstones compared with UDCA alone (9). UDCA promotes cholesterol gallstone dissolution by reducing biliary cholesterol saturation and facilitating the gradual solubilization of cholesterol from existing stones (10). Combining UDCA with a statin may therefore offer a complementary approach by targeting biliary cholesterol availability through distinct but potentially convergent pathways. Nevertheless, the extent to which this pharmacological rationale translates into measurable changes in established gallstones remains uncertain.

Ezetimibe acts through a different mechanism by inhibiting the Niemann–Pick C1-like 1 (NPC1L1) transporter and reducing intestinal cholesterol absorption (11). Experimental evidence links biliary cholesterol supersaturation and impaired mucosal cholesterol clearance to gallbladder cholesterol accumulation (12). A previous study reported that ezetimibe reduced biliary cholesterol saturation and delayed cholesterol crystallization (13). However, whether these effects translate into greater dissolution of established gallstones remains unclear. Recent clinical research has continued to investigate adjunctive approaches to UDCA therapy, but the available findings remain preliminary and do not establish whether cholesterol-lowering agents such as statins or ezetimibe provide additional benefits in patients with existing gallstones (10, 14). Comparing these two agents within the same clinical trial also provides an opportunity to examine whether distinct approaches to cholesterol lowering are associated with different patterns of gallstone response. Accordingly, this randomized clinical trial compared UDCA alone with UDCA combined with atorvastatin or ezetimibe in patients with cholesterol

gallstones. The primary objective was to evaluate changes in gallstone size over six months, while complete stone dissolution and other stone-related outcomes were assessed as additional measures of treatment response.

Materials and Methods

Study Design and Setting

This study was conducted as a three-arm, parallel-group randomized clinical trial comparing UDCA alone with UDCA combined with atorvastatin or ezetimibe in patients with asymptomatic gallbladder stones. The intervention period was six months. The study was conducted in Khorramabad, Iran, at Shahid Rahimi Hospital, affiliated with Lorestan University of Medical Sciences. The study protocol was approved by the Ethics Committee of Lorestan University of Medical Sciences (approval No. IR.LUMS.REC.1403.440), and written informed consent was obtained from all participants before enrollment. The trial was registered with the Iranian Registry of Clinical Trials (IRCT) under registration number IRCT20260313068983N1.

Study Population

The study population comprised patients with asymptomatic gallbladder stones who were evaluated for eligibility for pharmacological treatment. Participants were enrolled if they met the prespecified inclusion criteria and had none of the exclusion criteria.

Inclusion criteria were: (1) confirmed gallbladder stones documented by ultrasonography; (2) absence of symptoms attributable to gallstone disease at enrollment; (3) eligibility for medical treatment with ursodeoxycholic acid (UDCA); and (4) provision of written informed consent before participation.

Exclusion criteria were: (1) symptomatic gallstone disease or evidence of acute gallbladder inflammation or other acute biliary complications; (2) a history of cholecystectomy or other treatment

that precluded assessment of gallbladder stones; (3) contraindications to UDCA, atorvastatin, or ezetimibe, as applicable to the assigned treatment; (4) known hypersensitivity to any study medication; and (5) any documented medical condition or concomitant treatment that, according to the original study protocol, precluded participation.

Randomization and Treatment Allocation

A total of 60 participants were planned for enrollment and were randomly assigned in a 1:1:1 allocation ratio to one of three parallel treatment groups: UDCA alone, UDCA plus atorvastatin, or UDCA plus ezetimibe. A computer-generated method was used to randomize participants into the study groups. Treatment assignments were concealed in sequentially numbered, opaque, sealed envelopes until allocation. The envelopes were opened only after eligibility had been confirmed and enrollment completed, thereby preventing advance knowledge of the upcoming treatment assignment. The trial used a blinded design in which participants and personnel responsible for treatment administration were unaware of the assigned treatment. Outcome assessors were also blinded to treatment allocation during the assessment of gallstone-related outcomes. These procedures were intended to reduce the risk of selection and outcome-assessment bias. Following randomization, one participant withdrew from the study and was excluded from the final analysis. Accordingly, 59 participants were included in the reported analysis: 19 in the UDCA group, 20 in the UDCA-plus-atorvastatin group, and 20 in the UDCA-plus-ezetimibe group. The participant who withdrew remained part of the randomized population but was not included in the final analysis. The study flow, including randomization, withdrawal, and the number of participants analyzed in each group, was reported in the CONSORT flow diagram (15).

Interventions

Participants received one of three treatment regimens for six months.

Group 1: UDCA monotherapy. Participants received UDCA at a total daily dose of 600 mg.

Group 2: UDCA plus atorvastatin. Participants received UDCA at a total daily dose of 600 mg combined with atorvastatin at a daily dose of 20 mg.

Group 3: UDCA plus ezetimibe. Participants received UDCA at a total daily dose of 600 mg combined with ezetimibe at a daily dose of 10 mg.

All treatment regimens were administered over the six-month intervention period. Medication doses were specified according to the assigned treatment group. Information on dosing frequency, medication manufacturers, concomitant treatments, treatment adherence, and interruptions or discontinuations was reported only where documented in the original study records. Participants received one of three treatment regimens for six months. The UDCA group received oral UDCA at a total daily dose of 600 mg. The UDCA-plus-atorvastatin group received oral UDCA at 600 mg/day combined with oral atorvastatin at 20 mg/day. The UDCA-plus-ezetimibe group received oral UDCA at 600 mg/day combined with oral ezetimibe at 10 mg/day. Treatment was administered according to the assigned regimen throughout the intervention period. Any additional information regarding dosing frequency, medication manufacturers, concomitant treatments, adherence monitoring, and treatment interruptions was reported according to the original study records.

Outcome Assessment

Study outcomes were assessed at baseline and at the end of the six-month intervention period. Gallstone-related outcomes were evaluated using ultrasonography and included total gallstone length, gallstone number, and treatment response. Lipid-profile parameters were also measured at the two assessment time points.

- Total Gallstone Length

Total gallstone length was assessed by ultrasonography at baseline and after six months of treatment. Measurements recorded at the two time points were used to evaluate changes in gallstone size during the intervention period. The absolute change was calculated as the baseline measurement minus the follow-up measurement, with positive values indicating a reduction in total gallstone length. The measurement unit and the precise method used to derive total gallstone length were based on the original study records.

- Gallstone Number

Gallstone number was assessed by ultrasonography at baseline and at the six-month follow-up. The recorded findings were used to compare stone number before and after treatment. Changes in stone number were analyzed separately from changes in total gallstone length and from the proportion of participants in whom no gallstones were visible at follow-up.

- Treatment Response

Treatment response was evaluated using follow-up ultrasonographic findings. Complete response was defined as the absence of visible gallstones on follow-up ultrasonography. Partial response was defined as a reduction of at least 50% in gallstone size without complete disappearance, whereas nonresponse was defined as a reduction of less than 50%. Response categories were used to summarize the distribution of treatment outcomes in each group.

- Lipid Profile

Lipid-profile parameters were assessed at baseline and after six months of treatment. The evaluated parameters included total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Baseline and follow-up values were compared to evaluate changes in circulating lipid concentrations during treatment. These measurements were considered distinct from direct assessments of

biliary cholesterol composition or gallstone dissolution.

Sample Size

The sample size was calculated a priori using a one-way analysis of variance (ANOVA) framework based on Cohen's effect size (f) to compare the three treatment groups. The calculation was performed using a statistical formula, and the resulting target sample size was 60 participants, with 20 participants allocated to each group. Following randomization, one participant withdrew from the study and was excluded from the final analysis. Consequently, 59 participants were included in the final analysis: 19 in the UDCA group, 20 in the UDCA-plus-atorvastatin group, and 20 in the UDCA-plus-ezetimibe group.

Statistical Analysis

Continuous data were reported as mean $\pm$ standard deviation or median with interquartile range, depending on their distribution. Categorical variables were reported as frequencies and percentages. Between-group differences in continuous outcomes were evaluated using appropriate statistical tests, with baseline-adjusted analysis of covariance (ANCOVA) applied to follow-up gallstone measurements when appropriate. Categorical outcomes were compared using tests selected according to the data structure and expected cell frequencies. Changes in gallstone number and treatment-response categories were analyzed using methods appropriate to the distribution and scale of the variables. When pairwise comparisons were performed, adjustment for multiple testing was applied as appropriate. Within-group changes were distinguished from between-group treatment effects. Results were reported using effect estimates and P values, with 95% confidence intervals provided where available. All statistical analyses were performed using IBM

SPSS Statistics. The statistical significance threshold was set at $P < 0.05$, where applicable.

Result

Comparison of Baseline Demographic and Laboratory Characteristics Among the Study Groups

A total of 59 patients were included in the baseline analysis: 19 in the UDCA group, 20 in the UDCA plus atorvastatin group, and 20 in the UDCA plus ezetimibe group. Overall, 42 patients (71.2%) were women. The proportion of women was 68.4% in the UDCA group, 75.0% in the UDCA plus atorvastatin group, and 70.0% in the UDCA plus ezetimibe group. Pearson's chi-square test showed no significant difference in sex distribution among the three groups ($\chi^2 = 0.226$, $df = 2$, $P = 0.893$). The overall mean age was 45.90 ± 12.13 years. The mean ages were 42.16 ± 12.12 years in the UDCA group, 48.45 ± 10.06 years in the UDCA plus

atorvastatin group, and 46.85 ± 13.71 years in the UDCA plus ezetimibe group. No statistically significant between-group difference in age was reported ($P = 0.248$). The overall mean body mass index (BMI) was 27.53 ± 3.19 kg/m², with group means of 26.61 ± 3.10 , 28.82 ± 3.07 , and 27.13 ± 3.11 kg/m², respectively. The between-group difference in BMI was also not statistically significant ($P = 0.073$). At baseline, no statistically significant between-group differences were reported in total cholesterol (TC), triglycerides (TG), or high-density lipoprotein cholesterol (HDL-C) (all $P > 0.05$). A nominally statistically significant difference was reported in low-density lipoprotein cholesterol (LDL-C) ($P = 0.048$). These findings should be interpreted cautiously because the reported P values have not been independently verified and the handling of multiple comparisons is unclear. Baseline demographic and laboratory characteristics are presented in Table 1.

Characteristic	UDCA (n = 19)	UDCA + atorvastatin (n = 20)	UDCA + ezetimibe (n = 20)	P value
Male	6 (31.6)	5 (25.0)	6 (30.0)	0.893
Female	13 (68.4)	15 (75.0)	14 (70.0)	
Age (years)	42.16 ± 12.12	48.45 ± 10.06	46.85 ± 13.71	0.248
BMI (kg/m ²)	26.61 ± 3.10	28.82 ± 3.07	27.13 ± 3.11	0.073
Total cholesterol (mg/dL)	181.05 ± 32.40	197.10 ± 48.24	168.94 ± 38.56	0.102
Triglycerides (mg/dL)	174.00 ± 69.42	181.85 ± 50.39	138.15 ± 57.68	0.061
LDL-C (mg/dL)	109.21 ± 23.28	125.90 ± 39.64	107.27 ± 34.66	0.048
HDL-C (mg/dL)	42.36 ± 13.06	47.20 ± 14.93	53.33 ± 15.39	0.086

Table 1. Baseline demographic and laboratory characteristics of the study groups. Values are presented as mean $\pm$ standard deviation or number (%), as appropriate. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UDCA, ursodeoxycholic acid. The P value for sex distribution was recalculated using Pearson's chi-square test. The remaining P values are those reported in the thesis and have not been independently verified. Lipid concentrations are expressed in mg/dL, subject to confirmation against the original laboratory records.

Comparison of Total Gallstone Length Before and After Six Months of Treatment Among the Study Groups

At baseline, the mean total gallstone length was 21.42 ± 12.54 in the UDCA-alone group, $18.02 \pm$

13.09 in the UDCA-plus-atorvastatin group, and 25.55 ± 12.34 in the UDCA-plus-ezetimibe group. No statistically significant between-group difference was observed at baseline (one-way ANOVA, $P = 0.180$). After six months, the mean

total gallstone length decreased from 21.42 to 12.10 in the UDCA-alone group and from 18.02 to 10.65 in the UDCA-plus-atorvastatin group. In the UDCA-plus-ezetimibe group, the corresponding mean changed from 25.55 to 24.95. The mean reductions were 9.32, 7.37, and 0.60, respectively. According to the thesis, ANCOVA adjusted for baseline total gallstone length showed an overall between-group difference at follow-up ($F = 4.50$, P

$= 0.015$). Sidak-adjusted post hoc analysis reportedly identified a significant difference between the UDCA-alone and UDCA-plus-ezetimibe groups ($P = 0.016$), whereas the other pairwise comparisons were not statistically significant. These inferential results require confirmation against the original statistical output before the findings are finalized.

Treatment group	Baseline, mean $\pm$ SD	After 6 months, mean $\pm$ SD	Mean reduction, mean $\pm$ SD
UDCA alone (n = 19)	21.42 $\pm$ 12.54	12.10 $\pm$ 16.14	9.32 $\pm$ 9.74
UDCA + atorvastatin (n = 20)	18.02 $\pm$ 13.09	10.65 $\pm$ 16.59	7.37 $\pm$ 9.54
UDCA + ezetimibe (n = 20)	25.55 $\pm$ 12.34	24.95 $\pm$ 16.00	0.60 $\pm$ 7.35

Table 2. Comparison of Total Gallstone Length Before and After Six Months of Treatment. Data are presented as mean $\pm$ standard deviation (SD). Mean reduction was calculated as the baseline value minus the value at six-month follow-up. The measurement unit for total gallstone length should be specified according to the original study records. Baseline values were compared using one-way analysis of variance (ANOVA). The overall between-group difference at follow-up was reportedly assessed using analysis of covariance (ANCOVA), adjusted for baseline values ($F = 4.50$, $P = 0.015$). According to the thesis, Sidak-adjusted post hoc analysis identified a statistically significant difference between the UDCA-alone and UDCA-plus-ezetimibe groups ($P = 0.016$); the other pairwise comparisons were reportedly not statistically significant ($P > 0.05$). The ANCOVA and post hoc results have not been independently verified.

Comparison of Gallstone Number Among the Study Groups

The distribution of gallstone counts before and after six months of treatment is presented in Table 3. At baseline, the proportion of participants with four or more gallstones was 57.9% in the UDCA-alone group, 35.0% in the UDCA-plus-atorvastatin group, and 65.0% in the UDCA-plus-ezetimibe group. At the six-month assessment, no visible gallstones were detected in 9 (47.4%), 11 (55.0%), and 3 (15.0%) participants in the UDCA-alone, UDCA-plus-atorvastatin, and UDCA-plus-ezetimibe groups, respectively. The proportion of participants with four or more gallstones at follow-up was

26.3%, 10.0%, and 55.0%, respectively. Regarding changes in gallstone count, no reduction was observed in 47.4% of participants receiving UDCA alone, 45.0% receiving UDCA plus atorvastatin, and 75.0% receiving UDCA plus ezetimibe. A reduction of four or more stones was observed in 31.6%, 25.0%, and 10.0% of participants, respectively. The thesis reported no statistically significant between-group difference in the distribution of changes in gallstone count ($P = 0.136$). This result should be interpreted cautiously because the original statistical output and participant-level data were unavailable for independent verification.

Variable	UDCA alone (n = 19)	UDCA + atorvastatin (n = 20)	UDCA + ezetimibe (n = 20)
Gallstone count before treatment, n (%)			
1 stone	3 (15.8)	7 (35.0)	1 (5.0)
2 stones	5 (26.3)	4 (20.0)	3 (15.0)
3 stones	0 (0.0)	2 (10.0)	3 (15.0)
≥4 stones	11 (57.9)	7 (35.0)	13 (65.0)
Gallstone count after treatment, n (%)			
No visible stones	9 (47.4)	11 (55.0)	3 (15.0)
1 stone	3 (15.8)	4 (20.0)	2 (10.0)
2 stones	2 (10.5)	2 (10.0)	4 (20.0)
3 stones	0 (0.0)	1 (5.0)	0 (0.0)
≥4 stones	5 (26.3)	2 (10.0)	11 (55.0)
Change in gallstone count, n (%)			
No reduction	9 (47.4)	9 (45.0)	15 (75.0)
Reduction by 1 stone	2 (10.5)	3 (15.0)	1 (5.0)
Reduction by 2 stones	2 (10.5)	2 (10.0)	0 (0.0)
Reduction by 3 stones	0 (0.0)	1 (5.0)	2 (10.0)
Reduction by ≥4 stones	6 (31.6)	5 (25.0)	2 (10.0)
P-value for between-group comparison of change categories	0.136*		

Table 3. Distribution of Gallstone Counts Before and After Six Months of Treatment and Categorical Changes in Gallstone Number. Values are presented as number (percentage). Percentages were calculated using the total number of participants in each treatment group. “No visible stones” indicates that no gallstones were detected at the six-month assessment. Reduction in gallstone count was defined as the baseline count minus the follow-up count. The reported P-value was obtained from the thesis and has not been independently verified; the statistical test and its application should be confirmed against the original analysis output. UDCA, ursodeoxycholic acid.

Comparison of Treatment Response Among the Study Groups

Treatment response at six months differed descriptively among the three study groups (Table 4). Overall, 24 of 59 participants (40.7%) achieved a complete response, 3 (5.1%) achieved a partial response, and 32 (54.2%) had no response. In the UDCA-alone group, complete, partial, and absent responses were observed in 9 (47.4%), 3 (15.8%), and 7 (36.8%) participants, respectively. In the UDCA-plus-atorvastatin group, 12 participants (60.0%) achieved a complete response, while 8 (40.0%) had no response. No partial responses were recorded in this group. In the UDCA-plus-ezetimibe group, 3 participants (15.0%) achieved a complete response, whereas 17 (85.0%) had no response; no

partial responses were recorded. The thesis reported an overall between-group difference in treatment response (Kruskal–Wallis test, $P = 0.005$). Bonferroni-adjusted post hoc comparisons reportedly showed differences between the UDCA-plus-ezetimibe group and each of the other two groups, whereas the UDCA-alone and UDCA-plus-atorvastatin groups did not differ significantly. The pairwise results require confirmation against the original statistical output.

Discussion

In this study, gallstone outcomes differed descriptively among the three treatment groups after six months. Mean total gallstone length decreased in the UDCA-alone and UDCA-plus-atorvastatin

groups, whereas only a small reduction was observed with UDCA plus ezetimibe. Complete response rates were 47.4%, 60.0%, and 15.0%, respectively. However, the reported overall difference in treatment-response distribution does not establish the superiority of UDCA plus atorvastatin over UDCA alone, particularly because the pairwise comparison between these two groups was not statistically significant. Changes in gallstone number also did not differ significantly among the groups. These findings suggest a less favorable response pattern in the UDCA-plus-ezetimibe group, but the reasons for this pattern remain unclear.

Cholesterol gallstone formation is a multifactorial process involving biliary cholesterol supersaturation, cholesterol crystal nucleation and growth, and impaired gallbladder motility (1). Impaired gallbladder emptying, mucin accumulation, and chronic gallbladder inflammation may further contribute to cholesterol gallstone formation (16). UDCA promotes cholesterol gallstone dissolution by reducing cholesterol saturation in bile and changing the composition of the bile acid pool (17, 18). In the UDCA-alone group, mean total gallstone length decreased over six months, and complete dissolution was observed in 47.4% of participants.

Treatment group	Complete response, n (%)	Partial response, n (%)	No response, n (%)	Total, n
UDCA alone	9 (47.4)	3 (15.8)	7 (36.8)	19
UDCA + atorvastatin	12 (60.0)	0 (0.0)	8 (40.0)	20
UDCA + ezetimibe	3 (15.0)	0 (0.0)	17 (85.0)	20
Overall	24 (40.7)	3 (5.1)	32 (54.2)	59

Table 4. Comparison of Treatment Response at Six Months Among the Three Study Groups. Values are presented as number (percentage). Percentages were calculated using the total number of participants in each group. Complete response was defined as the absence of visible gallstones on follow-up ultrasonography. Partial response was defined as a reduction of at least 50% in total gallstone length. All other outcomes were classified as no response. The thesis reported an overall between-group difference using the Kruskal–Wallis test ($P = 0.005$). This result is numerically consistent with an ordinal analysis of the reported response categories, but the original statistical output should be checked to confirm the coding and analytical method. Bonferroni-adjusted pairwise comparisons were reported to show differences between the UDCA-plus-ezetimibe group and each of the other groups, with no statistically significant difference between the UDCA-alone and UDCA-plus-atorvastatin groups; these comparisons have not been independently verified. Abbreviation: UDCA, ursodeoxycholic acid.

The variable response to UDCA is consistent with evidence that medical dissolution therapy is most effective in selected patients with small, non-calcified cholesterol stones and a functioning gallbladder. In its clinical practice guideline, the European Association for the Study of the Liver reported that approximately 63% of appropriately selected patients were stone-free after more than six months of bile acid dissolution therapy, although long-term recurrence remained an important limitation (19). Atorvastatin inhibits HMG-CoA

reductase, a key enzyme in hepatic cholesterol synthesis, and increases hepatic LDL receptor expression (20). However, reductions in circulating LDL cholesterol do not necessarily reflect changes in biliary cholesterol saturation, which also depends on bile acid and phospholipid composition (21). Clinical evidence on combining statins with UDCA is limited and not entirely consistent. In a prospective clinical study, simvastatin plus UDCA was associated with a higher dissolution rate than UDCA alone among patients with multiple stones,

but not among those with solitary stones. In another small randomized study conducted after extracorporeal shock-wave lithotripsy, adding simvastatin did not increase the rate of stone disappearance. These findings suggest that the effect of statin–UDCA combinations may depend on the clinical context and cannot be assumed to apply equally to all statins (9, 22). In the present study, the UDCA-plus-atorvastatin group had a mean reduction in total gallstone length of 7.37 and the highest descriptive proportion of complete responses (60.0%). This response pattern provides a rationale for further investigation of atorvastatin as an adjunct to UDCA, but it does not establish an additional treatment benefit or demonstrate pharmacological synergy. Ezetimibe inhibits the Niemann–Pick C1-like 1 (NPC1L1) transporter and reduces intestinal cholesterol absorption. Experimental studies have suggested that ezetimibe can reduce biliary cholesterol secretion and delay cholesterol crystallization. In a small human study, ezetimibe treatment was associated with reduced biliary cholesterol saturation, but the study did not establish a clinical benefit for gallstone dissolution (13). A subsequent human study involving eight patients also found heterogeneous changes in biliary lipid composition, indicating that the effect of ezetimibe on bile lithogenicity may vary between individuals (23). An important distinction in interpreting these findings is that total gallstone length, gallstone number, and complete dissolution represent different treatment outcomes. A reduction in total gallstone length does not necessarily indicate a reduction in stone number, while the absence of visible stones on follow-up ultrasonography represents a more stringent outcome. In the present study, the overall treatment-response distribution was reported to differ among groups, whereas changes in gallstone number did not differ significantly. These findings should therefore be interpreted as separate aspects of

treatment response rather than as contradictory results.

Limitations

These results should be interpreted in light of several study limitations. First, the sample size was small, with 59 participants distributed across three treatment groups, which limits the precision of the estimates and the ability to detect between-group differences. Second, the six-month follow-up allowed assessment of short-term treatment response but did not establish the durability of dissolution or the risk of subsequent stone recurrence. Third, gallstone composition and biliary biochemical measures were not assessed, limiting the ability to explain the observed differences in response. Finally, the findings should be interpreted within the specific treatment regimens and outcome definitions used in this study and require confirmation in larger clinical trials.

Conclusion

After six months of treatment, the three groups showed different patterns of gallstone response. Although the highest descriptive rate of complete dissolution was observed with UDCA plus atorvastatin, the findings do not establish its superiority over UDCA alone. The less favorable response observed with UDCA plus ezetimibe also requires confirmation in further studies. Larger, adequately powered clinical trials with longer follow-up are needed to determine whether either combination improves gallstone dissolution. The present findings do not support adding atorvastatin or ezetimibe solely for gallstone dissolution.

Mechanistic and Translational Relevance

Cholesterol gallstone dissolution depends not only on circulating cholesterol levels but also on the composition of bile and the conditions that favor cholesterol solubilization. UDCA directly modifies

the biliary environment, whereas atorvastatin and ezetimibe target cholesterol metabolism through different pathways. This distinction provides a pharmacological basis for investigating whether these agents can complement UDCA in patients with established gallstones. In the present study, UDCA combined with atorvastatin showed the highest proportion of complete responses, while UDCA alone produced the greatest mean reduction in total gallstone length. In contrast, the combination of UDCA and ezetimibe was associated with less favorable outcomes across the principal descriptive measures. These findings suggest that interventions targeting different components of cholesterol metabolism may not produce equivalent clinical responses when combined with bile acid therapy. However, because biliary lipid composition and molecular pathways were not directly assessed, the mechanisms underlying these differences remain uncertain. The translational relevance of these findings lies in the distinction between a plausible pharmacological mechanism and a measurable clinical benefit. Although both atorvastatin and ezetimibe influence cholesterol homeostasis, their addition to UDCA cannot be assumed to improve gallstone dissolution solely on mechanistic grounds. The observed response patterns provide a basis for further clinical investigation, particularly studies that combine standardized ultrasonographic assessment with measurements of biliary cholesterol saturation and other relevant metabolic parameters. Such an approach may help clarify whether changes in cholesterol metabolism translate into meaningful improvements in gallstone dissolution.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Sepideh Manzori and Nima Sheikhi contributed to participant recruitment and data collection. Hossein Nazarian conceived the study, developed the methodology, and drafted the initial manuscript. Mehdi Birjandi performed the statistical analyses. Saleh Azadbakht contributed to participant recruitment and data collection, supervised data collection, coordinated study activities, and managed the project. All authors critically reviewed the manuscript, read and approved the final version, and agreed to be accountable for the work.

Ethics Statement

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Artificial Intelligence (AI) Disclosure

Artificial intelligence tools were used exclusively for final language editing and grammatical refinement of the manuscript, with no other AI-assisted activities involved in the research or manuscript preparation.

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