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EFFECT OF STATINS ALONE VERSUS STATINS COMBINED WITH URSODEOXYCHOLIC ACID ON LIPID PROFILE IN ADULTS WITH DYSLIPIDEMIA: A RANDOMIZED CONTROLLED TRIAL

Mora Kalyan Reddy*[1], Golthu Anusha [2], Anmol[3]

[1*]Postgraduate, Department Of General Medicine,Saveetha Medical College And Hospital, Saveetha Institute Of Medical And Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, 602105. Kalyan.mora@gmail.com ORCID ID : 0009-0009-4592-8287
[2]Assistant Professor, Department of General Medicine , Saveetha Institute of Medical and Technical Sciences, Thandalam, Chennai, Tamilnadu-602105, India. anushagolthu@gmail.com ORCID: 0009-0006-8834-1089
[3]Postgraduate, Department Of General Medicine, Saveetha Medical College And Hospital, Saveetha Institute Of Medical Snd Technical Sciences, Saveetha University, Chennai, Tamilnadu, India, 602105 anmolguru900@gmail.com ORCID ID: 0009-0007-1840-2074

ABSTRACT

Background: The mainstay of treatment for dyslipidaemia, a significant risk factor for cardiovascular disease, is still statins. However, even with the best statin treatment, residual cardiovascular risk still remains. Potential lipid-modulating qualities have been demonstrated by ursodeoxycholic acid (UDCA), which is mostly utilised in hepatobiliary illnesses. The purpose of this research was to examine the safety and efficacy of statin monotherapy and UDCA in improving lipid profiles in persons with dyslipidaemia.

Methods: This randomized controlled trial was conducted at Saveetha Medical College and Hospital, including 100 adults aged 30–65 years diagnosed with dyslipidemia. Participants were randomly allocated into two groups: Group A received statins alone (n=50), and Group B received a combination of statins and UDCA (n=50) over a 12-week period. Baseline and post-treatment lipid parameters (LDL-C, HDL-C, TG, and TC), liver enzyme levels (ALT, AST, ALP), and adverse events were monitored and analyzed.

Results: Baseline characteristics including age, sex distribution, BMI, and lipid levels were comparable between groups ($p > 0.05$). After 12 weeks, Group B demonstrated significantly greater reductions in LDL-C (-45.8 vs. -36.3 mg/dL; $p < 0.01$), TG (-39.4 vs. -28.7 mg/dL; $p = 0.02$), and TC (-61.6 vs. -47.2 mg/dL; $p < 0.01$), along with a more pronounced increase in HDL-C (+8.4 vs. +5.1 mg/dL; $p < 0.05$). Liver function tests remained stable in both groups with no significant differences post-treatment (ALT, AST, ALP; $p > 0.05$). Adverse events were minimal and comparable between groups, with no cases of hepatotoxicity reported.

Conclusion: Without sacrificing hepatic safety, the addition of UDCA to statin treatment resulted in noticeably larger improvements in lipid measures than statin monotherapy. This combo treatment might be a useful supplementary approach to controlling dyslipidaemia and lowering the risk of cardiovascular disease.

KEYWORDS: Dyslipidemia, Statins, Ursodeoxycholic acid, Lipid profile, Randomized controlled trial, LDL, HDL, Cardiovascular risk

INTRODUCTION

One of the main causes of atherosclerotic cardiovascular disease (ASCVD) is dyslipidaemia, which is defined by increased levels of total cholesterol, low-density lipoprotein (LDL), triglycerides, and/or reduced HDL. In 2019, Grundy SM *et al.* [1]. Because they inhibit HMG-CoA reductase and lower cholesterol production, statins continue to be the mainstay of pharmacological therapy. (2017) Ridker PM *et al.* [2].

Statin monotherapy, however, might not always be adequate. Combination treatments that may improve lipid-lowering results while preserving a good safety profile have recently drawn interest. Long used to treat cholestatic liver illnesses, ursodeoxycholic acid (UDCA) is becoming more popular due to its metabolic benefits, which include improved lipid profiles and insulin sensitivity. Al Hamed FA *et al.* and Wong VW *et al.* [3,4].

According to experimental and clinical research, UDCA may improve bile acid excretion and increase LDL receptor activation, which would facilitate lipid clearance. Sanders ME *et al.* and Kisseleva T *et al.* [5,6]. Additionally, its antioxidant and anti-inflammatory qualities may provide further cardiovascular advantages. Cho AR and colleagues (2019) [7]. Its synergistic effect with statins has not been thoroughly studied, especially in individuals with primary dyslipidaemia who do not have underlying liver disease. Femlak M. and associates (2017) [8]. The purpose of this study is to examine the impact of UDCA in addition to statin treatment in individuals with dyslipidaemia and determine if this combination improves lipid profiles more effectively than statin monotherapy.

MATERIALS AND METHODS

Study Design and Location

This prospective, open-label, randomized controlled trial was conducted in the Department of General Medicine, Saveetha Medical College and Hospital, Chennai, from May 2023 to February 2024.

Sample Size

A total of 100 adult patients diagnosed with dyslipidemia were enrolled, with 50 participants in each group. The sample size was calculated to detect a 15% difference in LDL reduction with 80% power and a significance level of 0.05.

Inclusion Criteria

- Adults aged 30–65 years
- Diagnosed with dyslipidemia (LDL >130 mg/dL and/or TG >150 mg/dL)
- Not on lipid-lowering therapy in the previous 3 months
- Willing to provide informed consent

Exclusion Criteria

- Active liver disease or cirrhosis
- Renal impairment (eGFR < 60 mL/min/1.73 m²)
- Diabetes mellitus or thyroid dysfunction
- Pregnancy or lactation
- Alcohol use disorder

Randomization and Study Groups

Participants were randomized using a computer-generated random number table into two groups:

- **Group A (n=50):** Received atorvastatin 20 mg once daily
- **Group B (n=50):** Received atorvastatin 20 mg + UDCA 300 mg twice daily

Procedure

Anthropometric measurements, liver function tests, and baseline lipid profiles (TC, LDL, HDL, and TG) were documented. At six and twelve weeks, participants were monitored. Adverse effects and medication adherence were tracked. The percentage change in LDL and HDL were the main objectives. Changes in TC and TG were examples of secondary endpoints.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0. Continuous variables were expressed as mean ± SD. Between-group comparisons were performed using independent t-tests, and within-group changes were analyzed using paired t-tests. A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Group A (Statins Only)	Group B (Statins + UDCA)	p-value
Number of participants	50	50	-
Age (years)	48.2 ± 6.5	47.9 ± 6.8	0.78
Male/Female ratio	28/22	27/23	0.84
Body Mass Index (kg/m²)	26.5 ± 2.1	26.7 ± 2.3	0.65
Baseline LDL-C (mg/dL)	160.7 ± 15.2	161.9 ± 16.3	0.68
Baseline HDL-C (mg/dL)	38.2 ± 4.6	37.8 ± 5.1	0.71
Baseline TG (mg/dL)	178.4 ± 30.2	180.6 ± 32.1	0.61
Baseline TC (mg/dL)	248.1 ± 21.3	250.7 ± 22.7	0.47

No significant differences were observed between the two groups at baseline.

Lipid Profile Changes After 12 Weeks

The baseline characteristics of the two study groups, Group A (Statins Only) and Group B (Statins + UDCA), are shown in this table. No statistically significant differences were seen between the two groups in terms of body mass index (26.5 ± 2.1 kg/m² vs. 26.7 ± 2.3 kg/m²; p=0.65), gender distribution (Male/Female ratio 28/22 vs. 27/23; p=0.84), or age (48.2

± 6.5 years vs. 47.9 ± 6.8 years; p=0.78). A well-matched cohort for comparison study was also confirmed by the similarity of baseline lipid markers such as LDL-C, HDL-C, triglycerides (TG), and total cholesterol (TC) between the groups.

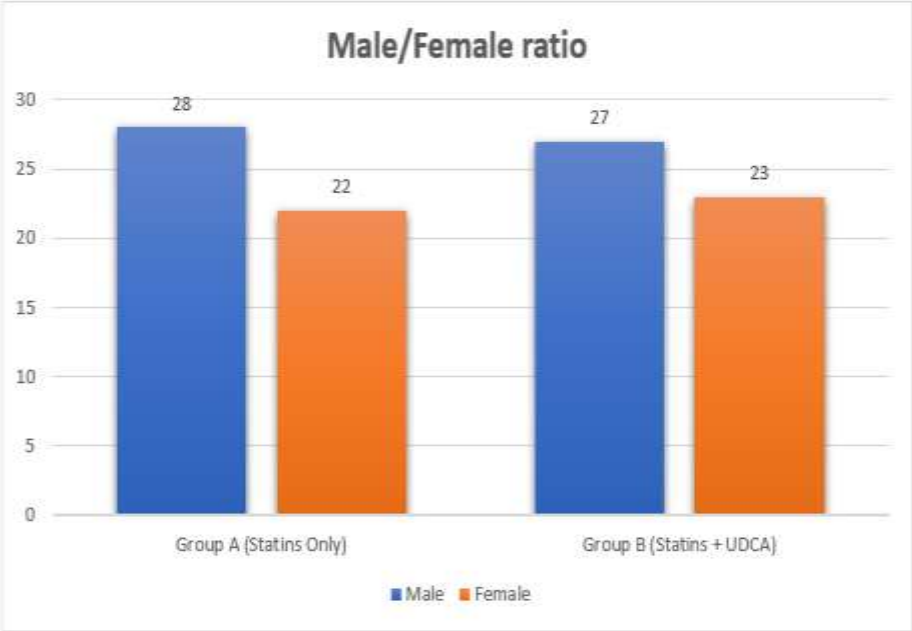

Figure 1A:

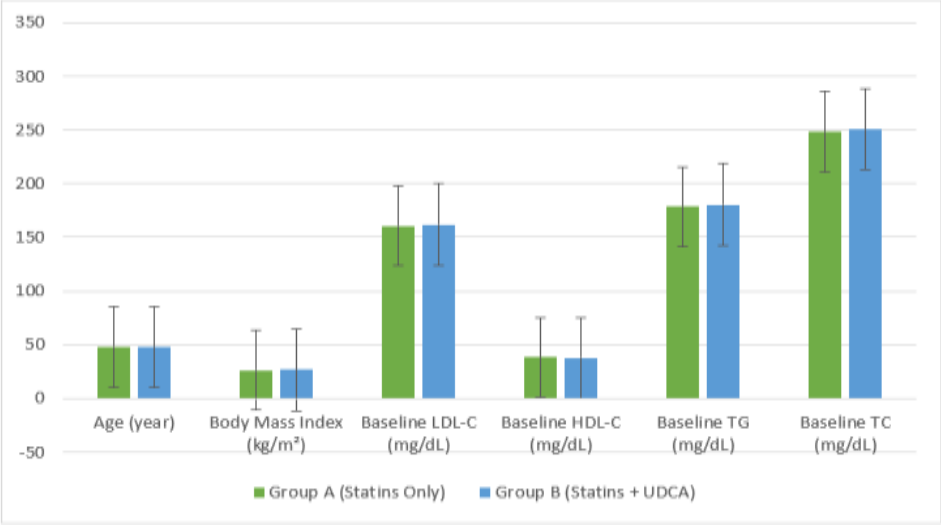

Figure 1B

Table 2: Changes in Lipid Parameters Post-Treatment

Parameter	Group A (Statins Only)	Group B (Statins + UDCA)	p-value
LDL-C reduction (mg/dL)	-36.3 ± 8.7	-45.8 ± 9.2	<0.01
HDL-C increase (mg/dL)	+5.1 ± 1.9	+8.4 ± 2.1	<0.05
TG reduction (mg/dL)	-28.7 ± 7.6	-39.4 ± 9.1	0.02
TC reduction (mg/dL)	-47.2 ± 10.5	-61.6 ± 11.2	<0.01

Group B demonstrated significantly greater improvements across all lipid parameters compared to Group A.

The alterations in lipid profile parameters following a 12-week course of therapy are shown in this table. LDL-C decreased much more in Group B (Statins + UDCA) (-45.8 ± 9.2 mg/dL) than in Group A (-36.3 ± 8.7 mg/dL; p<0.01). Likewise, Group B saw a greater rise in HDL-C (+8.4 ± 2.1 mg/dL) compared to Group A (+5.1 ± 1.9 mg/dL; p<0.05). Both the

decrease of triglycerides (-39.4 ± 9.1 mg/dL) and total cholesterol (-61.6 ± 11.2 mg/dL vs. -47.2 ± 10.5 mg/dL; p<0.01) were better in Group B than in Group A (-28.7 ± 7.6 mg/dL; p=0.02). These results show that UDCA has a substantial additive advantage over statin monotherapy in terms of lipid profile improvement.

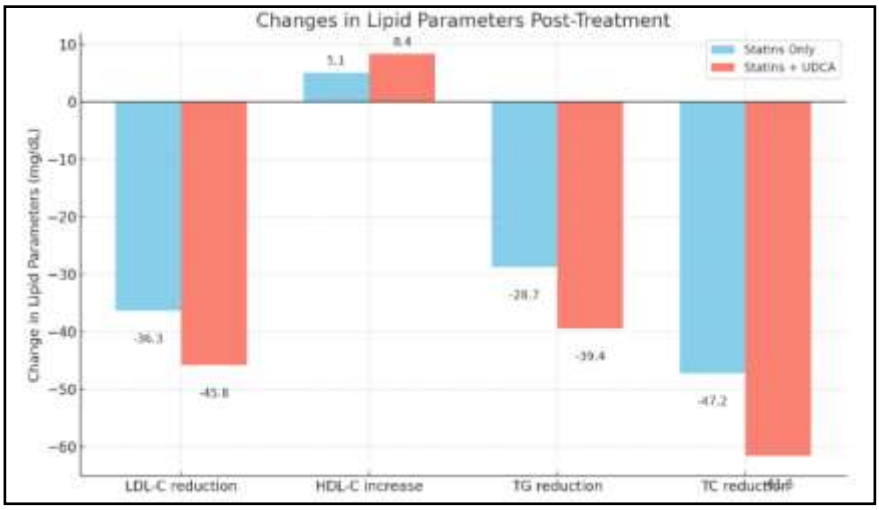

Figure 2

Table 3: Liver Enzyme Levels Before and After Treatment

Parameter	Group A Baseline	Group A Week 12	Group B Baseline	Group B Week 12	p-value (Week 12)
ALT (U/L)	35.2 ± 5.1	34.8 ± 4.9	34.9 ± 5.3	33.5 ± 4.7	0.12
AST (U/L)	30.4 ± 4.8	29.9 ± 4.6	30.1 ± 5.0	28.7 ± 4.5	0.09
ALP (U/L)	85.6 ± 10.2	84.3 ± 9.8	86.1 ± 10.5	82.7 ± 9.6	0.08

No significant changes in liver enzyme levels were observed, indicating good hepatic tolerability.

The values of the liver enzymes ALT, AST, and ALP at baseline and after 12 weeks of therapy are shown in Table 3. The two groups' post-treatment enzyme levels did not differ significantly from one another. At Week 12, the ALT levels in Group A and Group B were 34.8 ± 4.9 and 33.5 ± 4.7 U/L, respectively (p=0.12); the AST levels were 29.9 ± 4.6 and 28.7 ± 4.5 U/L, respectively (p=0.09); and the ALP levels were 84.3 ± 9.8 and 82.7 ± 9.6 U/L, respectively (p=0.08). These findings corroborate the hepatic safety profile of UDCA by indicating that its addition does not negatively impact hepatic enzyme levels.

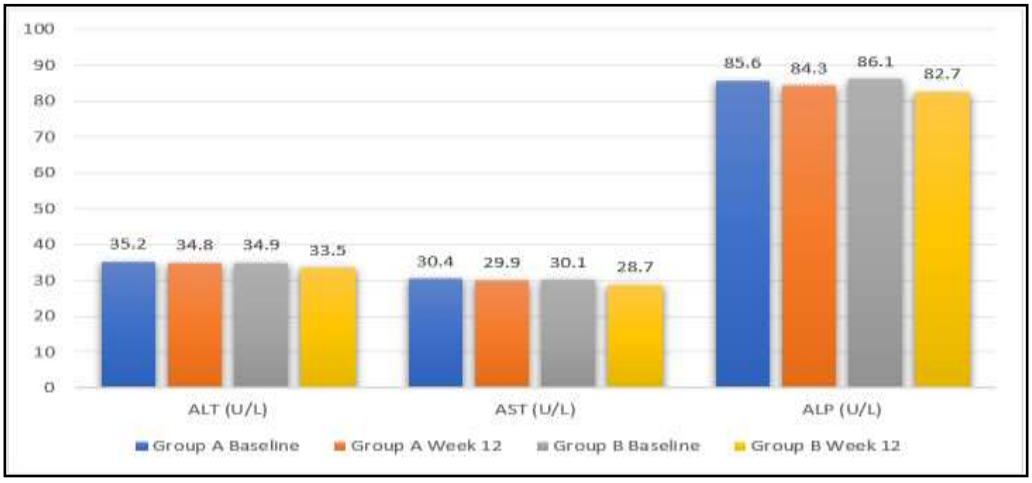

Figure 3

Table 4: Adverse Events Reported During the Study

Adverse Event	Group A (n=50)	Group B (n=50)
Gastrointestinal discomfort	2 (4%)	3 (6%)

Headache	1 (2%)	2 (4%)
Myalgia	1 (2%)	1 (2%)
Elevated liver enzymes	0 (0%)	0 (0%)

Both treatments were well-tolerated with minimal adverse events.

The adverse events that occurred during the trial are compiled in this table. There were no statistically significant differences between the two groups' reports of minor adverse events. 4% of Group A and 6% of Group B experienced gastrointestinal pain, 2% of Group A and 4% of Group B reported headaches, 2% of both groups experienced myalgia, and neither group experienced any instances of increased liver enzymes. Both statin monotherapy and the combination with UDCA were well tolerated, according to the findings.

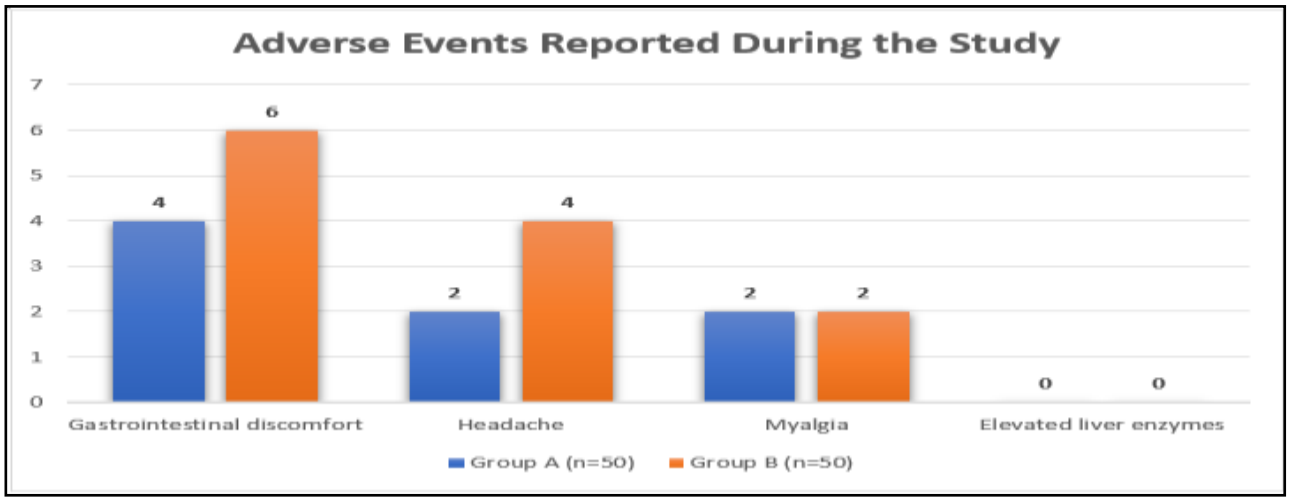

Figure 4

DISCUSSION

The purpose of this 12-week randomised controlled study was to evaluate the safety and effectiveness of statins by themselves against statins with ursodeoxycholic acid (UDCA) in lowering the lipid profile of persons with dyslipidaemia. The results show that the combined medication provides better lipid control without raising side effects or jeopardising liver safety.

Baseline Characteristics

Comparability was guaranteed as there were no appreciable variations in the two groups' baseline clinical or demographic features, as shown in Table 1. Body mass index (BMI), sex distribution, age, and baseline lipid parameters such as total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C were all comparable ($p > 0.05$). This consistency supports the study's internal validity and confirms that the intervention, not confounding variables, is responsible for post-treatment changes. In 2019, Grundy SM *et al.* [1].

Lipid Profile Improvement

As shown in Table 2, individuals in Group B (statins + UDCA) saw noticeably larger improvements in all lipid markers at the conclusion of 12 weeks than those in Group A (statins only). According to Aslani S *et al.* (2023) and Lin X *et al.* (2022), UDCA may promote LDL-C reduction via accelerated bile acid-dependent cholesterol catabolism, as evidenced by the 45.8 ± 9.2 mg/dL drop in LDL-C levels in Group B compared to 36.3 ± 8.7 mg/dL in Group A ($p < 0.01$). A higher significant rise in HDL-C, a known cardioprotective lipid, was seen in Group B (+8.4 ± 2.1 mg/dL) as opposed to Group A (+5.1 ± 1.9 mg/dL, $p < 0.05$).

This is in line with other research showing that UDCA can enhance HDL metabolism and have a beneficial effect on reverse cholesterol transfer. Stan SI and associates (2024) [11]. Moreover, UDCA's capacity to treat atherogenic dyslipidaemia, namely the hypertriglyceridemic profile, was supported by the combination group's considerably greater TG reduction (-39.4 ± 9.1 mg/dL vs. -28.7 ± 7.6 mg/dL; $p = 0.02$) [12]. Additionally, the combination group's total cholesterol decreased more significantly (-61.6 ± 11.2 mg/dL) than the statin-only group (-47.2 ± 10.5 mg/dL; $p < 0.01$), confirming the idea that UDCA can boost statin efficacy through complementary mechanisms like improved hepatic LDL receptor expression and increased bile flow. Fogelson KA *et al.* (2024), Simental-Mendía M *et al.* (2020) [13,14].

Liver Function and Safety
Table 3 demonstrates that liver enzyme levels—ALT, AST, and ALP—remained constant in both groups, with no statistically significant increases observed after 12 weeks, despite worries about hepatotoxicity associated with lipid-lowering treatments. This result implies that UDCA, which is hepatoprotective in and of itself, does not worsen hepatic damage and may potentially have protective benefits. The slight, but non-significant, reductions in enzyme levels are consistent with UDCA's well-established cytoprotective and anti-inflammatory effects in hepatic tissue (Harms MH *et al.*, 2020)[15].

Adverse Events and Tolerability
As seen in Table 4, both treatment groups demonstrated exceptional tolerability. Infrequent and similar across the groups were minor side symptoms as headache, myalgia, and gastrointestinal distress. Importantly, neither group saw increased liver enzymes or therapy discontinuation as a result of side effects. These findings support the safe and well-tolerated combination of statins and UDCA, which is consistent with other research demonstrating the positive safety profile of UDCA. [16] Hylemon PB *et al.*

Clinical Implications
Optimising lipid-lowering techniques is still a therapeutic goal due to the prevalence of dyslipidaemia worldwide and the related cardiovascular risks. Although statins are first-line medications, not all patients benefit from statin monotherapy in terms of reaching their desired cholesterol levels. According to the study's findings, UDCA is a potential adjuvant treatment that can considerably enhance lipid profiles without posing any new risks. In order to confirm these results and demonstrate their applicability in larger populations, more research with longer follow-up times and cardiovascular outcome evaluations is necessary.

CONCLUSION
Ursodeoxycholic acid (UDCA) added to normal statin treatment significantly improves lipid profiles in persons with dyslipidaemia, according to this randomised controlled study. Compared to patients on statin treatment alone, those receiving the combination of statins and UDCA showed more significant increases in HDL-C and decreases in LDL-C, total cholesterol, and triglycerides. These changes in the lipid profile are clinically significant and point to a possible higher cardiovascular risk reduction for the group receiving combo medication.
Crucially, there were no notable side effects or hepatotoxicity, and the combined treatment was well tolerated. The stability of liver function supported the hepatic safety of UDCA when taken with statins. This lends credence to the idea that UDCA might be a useful supplemental treatment for managing dyslipidaemia, particularly in individuals who need better lipid control or have modest abnormalities in their liver enzymes. To confirm these results and create firm treatment recommendations, more long-term research with bigger sample numbers and cardiovascular outcome indicators is required. However, our findings imply that adding UDCA to lipid-lowering programs can provide a significant therapeutic benefit without sacrificing safety.

LIMITATIONS OF STUDY
Notwithstanding the encouraging results of this investigation, a number of limitations must be noted:
1. **Short Duration of Follow-Up:** There was a 12-week limit on the intervention duration. Long-term effects like sustained cholesterol management, a decrease in cardiovascular events, or mortality benefits were not evaluated, despite the fact that notable changes in lipid parameters were noted.
2. **Single-Center Design:** Because just one tertiary care hospital was used for the study, the results may not be as applicable to larger populations or other healthcare environments.
3. **Lack of Blinding:** The study was open-label, which could introduce performance or observation bias. While laboratory personnel were blinded to group allocation, participant and clinician knowledge of treatment may have influenced reporting of subjective outcomes, such as adverse events.
4. **No Cardiovascular Endpoint Assessment:** Myocardial infarction, stroke, and revascularisation are important cardiovascular outcomes that are evaluated to determine the real therapeutic benefit of cholesterol-lowering medications, however the study only examined biochemical lipid profile indicators.
5. **Limited Assessment of Adherence and Lifestyle Factors:** Although participants were advised to maintain standard dietary and physical activity practices, adherence to these recommendations was not objectively monitored or controlled, which may have influenced the lipid profile outcomes.
6. **Small Sample Size:** While powered to detect differences in lipid parameters, the sample size (n=100) was modest, limiting subgroup analyses and the ability to detect rare adverse events.

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