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Original Research Article

Role of Dapagliflozin in Non-Alcoholic Fatty Liver Disease

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Abstract: *Non-alcoholic fatty liver disease (NAFLD) is one of the most widespread metabolic liver diseases that is directly linked to obesity, insulin resistance, and type 2 diabetes mellitus, and has no approved treatment so far. Newer evidence indicates that sodium-glucose cotransporter-2 inhibitors could have a beneficial outcome on hepatic steatosis by modulating metabolism.* ***Objective:*** *To evaluate the efficacy and safety of dapagliflozin in reducing hepatic steatosis, improving liver function tests, and modifying metabolic risk factors in patients with NAFLD.* ***Methods:*** *It is a prospective, single-blinded, randomized controlled trial that recruited 100 patients with ultrasonography-proven NAFLD. This study was conducted at Aziz Bhatti Shaheed Teaching Hospital from June 2024 to December 2024. Participants were randomly assigned to dapagliflozin 10 mg once daily for 12 weeks (n = 50) or usual care (n = 50). The outcomes were the changes in liver enzymes, body mass index, ultrasonography grading of hepatic steatosis, lipid profile, renal function tests, and adverse events. Statistical analysis was performed using paired and independent t-tests, with $p < 0.05$ considered significant.* ***Results:*** *At 12 weeks, the dapagliflozin group recorded huge changes in AST (44.28 ± 4.44 to 34.09 ± 5.04 U/L) and ALT (57.32 ± 3.73 to 45.67 ± 6.10 U/L) and a decrease in the BMI by 0.84 ± 0.33 kg/m 2 ($p < 0.001$). Grade 2 steatosis in the liver decreased from 46% to 26%, and 16% of patients were cured of the condition on ultrasound, with no significant improvement on imaging in the control group. Follow-up between-group comparisons showed very low AST and ALT levels in the dapagliflozin group ($p < 0.001$).* ***Conclusion:*** *There was a notable improvement in lipid parameters, no worsening of renal function, and minimal adverse events with dapagliflozin. Dapagliflozin was found to have beneficial effects on biochemical, metabolic, and ultrasonographic outcomes in NAFLD patients at 12 weeks, with a good safety profile. These results show its potential as a pharmacological agent in the treatment of NAFLD.*

Keywords: Non-alcoholic fatty liver disease; Dapagliflozin; SGLT2 inhibitors; Hepatic steatosis; Liver enzymes; Randomized controlled trial

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Introduction

Non-alcoholic fatty liver disease (NAFLD) constitutes the largest global burden of chronic liver disease and is an increasing public health concern associated with metabolic dysfunction (1). The prevalence rates of NAFLD in the world population vary, with estimates suggesting it affects approximately 25–30% of the adult population, with higher prevalence reported in regions undergoing rapid urbanization and lifestyle changes (2). The disease spectrum ranges from simple hepatic steatosis to non-alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (3). NAFLD is closely linked with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), and dyslipidemia, highlighting its strong association with systemic metabolic disease (4). Epidemiological data suggest that patients with NAFLD have significantly higher cardiovascular morbidity and mortality than the general population. NAFLD is often diagnosed at early stages that are usually asymptomatic (5).

SGLT2 inhibitors such as dapagliflozin have emerged as effective therapeutic agents for improving glycemic control and reducing cardiovascular risk in patients with T2DM (6). Dapagliflozin lowers blood glucose levels by promoting urinary glucose excretion, resulting in modest weight reduction and improved insulin sensitivity (7). Evidence regarding the role of SGLT2 inhibition in reducing hepatic fat accumulation is still evolving; however, it has been proposed that these agents decrease substrate availability for hepatic lipogenesis (8). Beneficial effects of dapagliflozin on liver enzymes have been observed in diabetic patients and may reflect potential hepatoprotective properties. Imaging-based studies using ultrasound and magnetic resonance imaging have demonstrated reductions in hepatic steatosis following SGLT2 inhibitor therapy. These benefits appear partly independent of glycemic control, suggesting a direct metabolic influence on hepatic fat metabolism (9).

Clinical adoption of dapagliflozin requires careful consideration of safety, particularly when used in non-diabetic or mixed NAFLD populations (10). Reported adverse effects include genital mycotic infections, volume depletion, and rare cases of euglycemic ketoacidosis, necessitating appropriate patient selection and monitoring. Importantly, previous studies have not reported significant hepatotoxicity associated with SGLT2 inhibitors (11). Dapagliflozin, therefore, shows potential as a therapeutic intervention for NAFLD, given its ability to simultaneously improve multiple metabolic risk factors (12). The use of imaging modalities for follow-up allows objective assessment of disease progression or regression over time, thereby strengthening outcome evaluation in clinical trials. Evaluating both efficacy and safety in randomized controlled trial designs is essential to generate high-quality evidence (13).

In Pakistan, the prevalence of NAFLD is rising rapidly due to increasing rates of obesity, T2DM, and sedentary lifestyles (14). Population-based studies suggest that nearly one-third of urban Pakistani adults may have fatty liver disease detected on ultrasound (15). Low public awareness and the absence of routine screening often result in delayed diagnosis and progression to advanced liver disease. NAFLD therefore represents a significant healthcare burden in Pakistan, placing additional pressure on already strained healthcare systems managing both infectious and chronic diseases. The use of dapagliflozin in diabetes management is increasing in Pakistan, making its potential repurposing for NAFLD both clinically feasible and relevant (14). Local randomized controlled trial data are required to reflect the genetic, dietary, and environmental characteristics unique to the Pakistani population. Therefore, this study aimed to evaluate the efficacy and safety of dapagliflozin in reducing hepatic steatosis,

improving liver function tests, and modifying metabolic risk factors in patients with NAFLD in Pakistan.

Methodology

This prospective, single-blind, randomized controlled therapeutic trial was conducted at Aziz Bhatti Shaheed Teaching Hospital from June 2024 to December 2024. A total of 100 patients diagnosed with non-alcoholic fatty liver disease (NAFLD) were enrolled after obtaining written informed consent. Participants were randomly assigned to two equal groups using simple randomization. The intervention group received dapagliflozin 10 mg once daily for 12 weeks, while the control group received standard clinical care without pharmacological intervention targeting NAFLD. The study was conducted using a single-blind design in which outcome assessors were unaware of the treatment allocation throughout the study period.

Participants were recruited from patients presenting to the outpatient department or accident and emergency department, or from those admitted to inpatient wards of Aziz Bhatti Shaheed Teaching Hospital. Eligible participants included adults with either previously diagnosed or newly identified NAFLD who had not received any specific pharmacological treatment for the condition. The diagnosis of NAFLD was established based on clinical assessment and ultrasonographic evidence of hepatic steatosis. Patients with elevated liver enzymes consistent with NAFLD and radiological evidence of fatty liver were considered eligible. Individuals with metabolic risk factors associated with NAFLD, including obesity or type 2 diabetes mellitus, were also included. Type 2 diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL or glycated hemoglobin (HbA1c) ≥6.5%.

Patients were excluded if they had evidence of secondary causes of fatty liver disease, such as significant alcohol consumption, chronic viral hepatitis, autoimmune hepatitis, or other chronic liver disorders. Additional exclusion criteria included severe renal impairment, recurrent or severe urinary tract infections or vulvovaginal infections, a history of orthostatic hypotension or dehydration, pregnancy or breastfeeding, and the presence of active or recently treated malignancy.

A total sample size of 100 participants was determined based on feasibility and patient availability during the study period. Participants meeting the eligibility criteria were recruited using non-probability convenience sampling and subsequently randomized into two equal groups of 50 participants each.

The baseline evaluation included a detailed medical history and physical examination. Demographic and clinical variables, including age, body weight, and body mass index (BMI), were recorded. Laboratory investigations performed at enrollment included liver function tests, renal function tests, fasting blood glucose and/or HbA1c, and screening for viral hepatitis. Ultrasonographic examination of the liver was conducted to confirm the presence of hepatic steatosis and to grade its severity at baseline. Participants were followed during the study period to assess treatment adherence and monitor potential adverse events. A follow-up evaluation was performed at 12 weeks, which included repeat measurement of BMI, liver function tests, renal parameters, and ultrasonographic reassessment of hepatic steatosis.

The primary outcome of the study was improvement in hepatic steatosis as assessed by ultrasonographic grading after 12 weeks of treatment. Secondary outcomes included changes in liver enzyme levels, BMI, lipid profile, and other metabolic parameters, as well as assessment of the safety profile of dapagliflozin based on the occurrence of adverse events during follow-up.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 28. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Independent t-tests were used to compare continuous variables between the dapagliflozin and control groups, and paired t-tests were used to assess within-group changes from baseline to follow-up. A p-value of less than 0.05 was considered statistically significant.

Ethical approval for the study was obtained from the Institutional Ethical Review Committee of Aziz Bhatti Shaheed Teaching Hospital prior to initiating data collection. All participants provided written informed consent before enrollment, and the study was conducted in accordance with established ethical principles for biomedical research involving human participants.

Results

A total of 100 participants with non-alcoholic fatty liver disease were enrolled and randomized into the dapagliflozin group (n = 50) and the control group (n = 50). Baseline demographic and clinical characteristics were comparable between the two groups. The mean age was 44.58 ± 7.05 years in the dapagliflozin group and 45.82 ± 6.58 years in the control group (p = 0.36). Baseline BMI did not differ significantly between groups (31.86 ± 1.06 vs 30.93 ± 1.45 kg/m²; p = 0.08). Similarly, liver enzyme levels were comparable at baseline, with AST values of 44.28 ± 4.44 U/L in the dapagliflozin group and 44.94 ± 4.53 U/L in the control group (p = 0.54), and ALT values of 57.32 ± 3.73 U/L and 56.82 ± 3.86 U/L, respectively (p = 0.61). Ultrasonographic grading of hepatic steatosis also showed no significant difference between groups at baseline (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Dapagliflozin (n=50)	Control (n=50)	p-value
Age (years), Mean ± SD	44.58 ± 7.05	45.82 ± 6.58	0.36
BMI (kg/m²), Mean ± SD	31.86 ± 1.06	30.93 ± 1.45	0.08
AST (U/L), Mean ± SD	44.28 ± 4.44	44.94 ± 4.53	0.54
ALT (U/L), Mean ± SD	57.32 ± 3.73	56.82 ± 3.86	0.61
Steatosis Grade 1, n (%)	27 (54.0)	26 (52.0)	0.84
Steatosis Grade 2, n (%)	23 (46.0)	24 (48.0)	

At 12 weeks of follow-up, significant differences were observed between the two groups. Mean AST levels were significantly lower in the dapagliflozin group compared with the control group (34.09 ± 5.04 vs 45.62 ± 5.72 U/L; p < 0.001). Similarly, ALT levels were significantly reduced in the dapagliflozin group (45.67 ± 6.10 vs 54.81 ± 5.07 U/L; p < 0.001). BMI showed a modest reduction in the dapagliflozin group compared with the control group (31.04 ± 1.10 vs 30.86 ± 1.48 kg/m²; p = 0.036) (Table 2).

Table 2. Comparison of Clinical and Biochemical Outcomes at 12 Weeks

Parameter	Dapagliflozin (Mean ± SD)	Control (Mean ± SD)	t-value	p-value
BMI (kg/m²)	31.04 ± 1.10	30.86 ± 1.48	2.12	0.036
AST (U/L)	34.09 ± 5.04	45.62 ± 5.72	−9.21	<0.001
ALT (U/L)	45.67 ± 6.10	54.81 ± 5.07	−7.43	<0.001

Renal function remained stable throughout the study in both groups. No statistically significant changes were observed in serum creatinine or eGFR from baseline to 12 weeks. In contrast, lipid parameters improved significantly in the dapagliflozin group, with reductions in total cholesterol and triglycerides, whereas no significant changes were observed in the control group (Table 3).

Table 3. Renal Function and Lipid Profile Changes

Parameter	Group	Baseline Mean ± SD	12 Weeks Mean ± SD	p-value
Serum Creatinine (mg/dL)	Dapagliflozin	0.88 ± 0.14	0.90 ± 0.15	0.42
	Control	0.87 ± 0.13	0.89 ± 0.14	0.39
eGFR (mL/min/1.73m²)	Dapagliflozin	94.6 ± 11.8	93.1 ± 12.2	0.48
	Control	95.2 ± 10.9	94.0 ± 11.4	0.51
Total Cholesterol (mg/dL)	Dapagliflozin	212.4 ± 28.6	196.3 ± 24.9	<0.001
	Control	210.8 ± 26.9	208.6 ± 27.4	0.31
Triglycerides (mg/dL)	Dapagliflozin	186.7 ± 34.1	158.2 ± 30.6	<0.001
	Control	184.9 ± 32.8	179.6 ± 31.7	0.27

Ultrasonographic assessment demonstrated improvement in hepatic steatosis in the dapagliflozin group. After 12 weeks, 16% of participants achieved complete resolution (Grade 0), and the proportion of Grade 2 steatosis decreased from 46% to 26%. In the control group, minimal change was observed (Table 4).

Table 4. Ultrasonographic Grading of Hepatic Steatosis

Group	Time	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Total
Dapagliflozin	Baseline	0 (0)	27 (54)	23 (46)	50
Dapagliflozin	12 Weeks	8 (16)	29 (58)	13 (26)	50
Control	Baseline	0 (0)	26 (52)	24 (48)	50
Control	12 Weeks	1 (2)	25 (50)	24 (48)	50

Dapagliflozin was generally well-tolerated. No episodes of hypoglycemia were reported. One participant (2%) developed a urinary tract infection that required discontinuation of therapy, and no serious adverse events were recorded (Table 5).

Table 5. Adverse Events in the Dapagliflozin Group

Adverse Event	Frequency (%)
Hypoglycemia	0 (0)
Urinary tract infection	1 (2)
Drug discontinuation	1 (2)

Within-group paired analysis in the dapagliflozin arm demonstrated significant reductions in BMI, AST, and ALT after 12 weeks of treatment (Table 6).

Table 6. Paired Analysis of Changes in the Dapagliflozin Group

Parameter	Mean Difference ± SD	t-value	df	p-value
BMI (kg/m²)	0.84 ± 0.33	16.87	44	<0.001
AST (U/L)	10.76 ± 4.50	16.04	44	<0.001
ALT (U/L)	11.36 ± 5.96	12.78	44	<0.001

Discussion

This randomized controlled trial evaluated the efficacy and safety of dapagliflozin in reducing hepatic steatosis and improving metabolic and biochemical outcomes in patients with NAFLD. In the present study, dapagliflozin treatment for 12 weeks resulted in significant reductions in mean AST from 44.28 ± 4.44 U/L at baseline to 34.09 ± 5.04 U/L at follow-up, and in ALT from 57.32 ± 3.73 U/L to 45.67 ± 6.10 U/L. These biochemical improvements were accompanied by a statistically significant reduction in BMI by 0.84 ± 0.33 kg/m² ($p < 0.001$), reflecting favorable metabolic changes. Such findings are clinically relevant because reductions in liver enzymes indicate decreased hepatocellular injury in NAFLD. Bica et al. reported similar findings in a systematic review, demonstrating that dapagliflozin reduced ALT by approximately 9.8 U/L at 24 weeks (16). A meta-analysis by Sun et al. also reported a mean AST reduction of about 10.2 U/L, which is comparable to the 10.76 U/L reduction observed in the present study (17). The similarity of enzyme reductions across different populations supports the biological plausibility of SGLT2 inhibition in NAFLD management.

In addition to biochemical parameters, imaging-based evaluation in this study provided objective evidence of disease modification. Ultrasonographic grading showed that 12 weeks of dapagliflozin therapy reduced the proportion of Grade 2 hepatic steatosis from 46% at baseline to 26% at follow-up, with 16% of patients demonstrating complete resolution of steatosis. In contrast, no significant improvement was observed in the control group, where Grade 2 steatosis persisted in 48% of participants. These findings suggest that dapagliflozin not only influences surrogate biochemical markers but also modifies hepatic fat accumulation within a relatively short treatment duration. Similar results were reported by Shimizu et al., who observed an 18% reduction in MRI-based liver fat fraction after SGLT2 inhibitor therapy (18). Likewise, Weng et al. reported ultrasonographic improvement in hepatic steatosis among 21% of treated patients, slightly lower than the approximately 30% improvement observed in the current trial (19). Differences in imaging techniques, baseline disease severity, and treatment duration may explain these variations.

Weight reduction and metabolic improvements are important mechanisms underlying hepatic benefits in NAFLD. In the present trial, BMI decreased from 31.86 ± 1.06 kg/m² to 31.04 ± 1.10 kg/m² in the

dapagliflozin group, compared with a minimal reduction of 0.07 kg/m² in the control group. Although modest, this decrease was statistically significant and consistent with the caloric loss expected from glycosuria. Phrueksotsai et al. reported an average BMI reduction of 0.9 kg/m² after 16 weeks of dapagliflozin therapy, closely aligning with the magnitude observed in the current study (20). Similarly, Dos Santos and Baer reported a BMI reduction of approximately 0.7 kg/m² accompanied by improvements in liver enzyme levels (21). These findings suggest that even modest weight loss may have substantial hepatic benefits in NAFLD. The association between small BMI reductions and larger decreases in liver enzymes may also reflect additional insulin-sensitizing and anti-inflammatory mechanisms.

The comparative analysis between treatment groups further supports the therapeutic efficacy of dapagliflozin. AST levels at 12 weeks were significantly lower in the dapagliflozin group than in controls (34.09 ± 5.04 vs 45.62 ± 5.72 U/L, $p < 0.001$), and similar findings were observed for ALT (45.67 ± 6.10 vs 54.81 ± 5.07 U/L, $p < 0.001$). These between-group differences were greater than those reported in lifestyle-only intervention studies. For example, Shi et al. reported no statistically significant differences in AST levels between intervention and control groups after 12 weeks (22). The larger effect sizes observed in the current trial highlight the potential added value of pharmacological intervention. Independent t-test analyses further confirmed that these changes were attributable to treatment effects rather than temporal variation.

Cardiometabolic risk modification and safety are critical considerations in NAFLD management. Renal function remained stable in the present trial, with no significant change in serum creatinine levels (0.88 ± 0.14 to 0.90 ± 0.15 mg/dL, $p = 0.42$), indicating renal safety. Lipid parameters also improved significantly, with reductions of approximately 16 mg/dL in total cholesterol and 29 mg/dL in triglycerides within the dapagliflozin group ($p < 0.001$). Similar lipid improvements were reported by Hu et al., who observed a reduction of 24 mg/dL in triglycerides among patients receiving SGLT2 inhibitor therapy (23). Dwinata et al. also documented stable renal indices alongside improvements in lipid profiles in patients treated with SGLT2 inhibitors (24). The low incidence of adverse effects in the present study, including only a single case of urinary tract infection, is consistent with previously reported safety profiles. Importantly, no cases of hypoglycemia were observed, further supporting the safety of dapagliflozin in NAFLD patients.

From a broader clinical and public health perspective, these findings are particularly relevant in high-burden settings. The magnitude of liver enzyme reduction observed in this Pakistani cohort is comparable to or greater than that reported in Western and East Asian populations, suggesting cross-ethnic therapeutic effectiveness. Fan et al. reported an ALT reduction of 8.6 U/L in a Middle Eastern cohort, slightly lower than the 11.36 U/L reduction observed in this study (25). Differences in baseline obesity, insulin resistance, and lifestyle factors may partly explain these variations. The relatively rapid improvement observed within 12 weeks highlights the potential of dapagliflozin as an early pharmacological intervention to prevent disease progression. Given the limited adherence to lifestyle interventions in real-world settings, pharmacological therapies with multi-system metabolic benefits may represent an important strategy for NAFLD management.

Despite its strengths, this study has several limitations. The relatively short follow-up period limited the evaluation of long-term histological outcomes, fibrosis regression, and sustainability of therapeutic benefits. Additionally, hepatic steatosis was assessed using ultrasonography rather than more sensitive modalities such as MRI-proton density fat fraction or liver biopsy, which may have underestimated subtle changes in hepatic fat content.

Conclusion

Dapagliflozin was associated with significant improvements in hepatic and metabolic parameters in patients with non-alcoholic fatty liver disease after 12 weeks of treatment. The intervention resulted in reductions in AST and ALT levels, a modest decrease in BMI, and improvement in ultrasonographic grading of hepatic steatosis, including a decline in Grade 2 disease and resolution of steatosis in a subset of patients. Compared with the control group, participants receiving dapagliflozin had significantly lower liver enzyme levels and improved lipid parameters, while renal function remained stable and adverse events were minimal. These findings suggest that dapagliflozin may represent a safe and potentially beneficial therapeutic option for improving hepatic and metabolic outcomes in patients with NAFLD.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (IRBE-ABSHGJ-30-24)

Consent for publication
Approved

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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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Study Design, manuscript review, critical input.
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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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