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ORIGINAL RESEARCH

Effectiveness of SGLT2 Inhibitors on Hepatic Steatosis and Inflammatory Markers in Diabetic Patients with MAFLD

[1]Dr. Tanzeem, [2]Dr. Khudabakash N

[1]Department of Medicine, SRM Trichy Medical College, Trichy, India
[2]Department of Medicine, Tagore Medical College, Chennai, India

Corresponding Author
Dr. Khudabakash N
Department of Medicine, Tagore Medical College, Chennai, India
Email: drkhudabaksh50@gmail.com

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ABSTRACT

Background: Metabolic-related fatty liver disease (MAFLD) usually presents together with type 2 diabetes mellitus (T2DM), with subsequent advancing hepatic steatosis and increased systemic inflammation. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are a new group of glucose-lowering drugs, have proven extensive cardiometabolic benefits. Nonetheless, their distinct effects on hepatic fat accumulation as well as on inflammatory markers among T2DM subjects with MAFLD remain less comprehensively understood. **Methods:** In this 24-week, prospective, randomized trial, 120 adult subjects with T2DM and imaging-confirmed MAFLD received either empagliflozin 10 mg/day or dapagliflozin 10 mg/day (as an add-on to current antidiabetic therapy) or continued on standard care alone. Hepatic steatosis was measured by the controlled attenuation parameter (CAP) with a FibroScan device at the beginning of the study and at week 24. Biochemical markers of hepatic function (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and inflammation (C-reactive protein [CRP] and interleukin-6 [IL-6]) were assessed at both visits. **Results:** Patients in the SGLT2 inhibitor arm showed a remarkable reduction in CAP readings, representing a mean reduction of 35 dB/m ($p<0.01$), suggesting enhanced hepatic steatosis. Concomitant reductions in levels of ALT, AST, CRP, and IL-6 were also noted ($p<0.05$ for each) versus the control arm. Furthermore, patients on SGLT2 inhibitors had modest but significant improvements in glycemic control and body weight. No severe adverse events were noted. **Conclusion:** In more than 24 weeks, the addition of an SGLT2 inhibitor to usual diabetes care considerably improved liver fat content and inflammatory markers in T2DM and MAFLD patients. These results highlight the dual benefit potential of SGLT2 inhibitors in improving metabolic profiles and providing hepatoprotective effects in this high-risk patient group.

Keywords: SGLT2 inhibitors, metabolic-associated fatty liver disease, type 2 diabetes mellitus, hepatic steatosis, inflammation, empagliflozin, dapagliflozin

INTRODUCTION

Metabolic-associated fatty liver disease (MAFLD), previously classified in the spectrum of nonalcoholic fatty liver disease (NAFLD), is now becoming the most prevalent chronic liver disease globally [1]. Its prevalence has a close connection with the increase in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome. MAFLD is defined as hepatocellular lipid accumulation and can lead to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma [2]. Notably, individuals with MAFLD and coincident T2DM also exhibit a heightened risk of cardiovascular sequelae and worse prognosis of liver disease [3]. For these reasons, it is increasing in interest to delineate treatment methods that target the metabolic derangements and the liver injury at the same time.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors like empagliflozin, dapagliflozin, and canagliflozin lower hyperglycemia through urinary glucose excretion. Aside from their antihyperglycemic properties, SGLT2 inhibitors have other favorable effects, such as weight reduction, blood pressure lowering, and cardiovascular benefits [4,5]. Since inflammation is central in the pathogenesis of steatosis and the development of advanced fibrosis, treatments that can reduce systemic and hepatic inflammation are highly attractive in patients with MAFLD [6]. While recent data support the hypothesis that SGLT2 inhibitors improve liver enzymes and decrease steatosis, data continue to develop,

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particularly as to whether their influence extends to inflammatory markers including CRP and IL-6 [7]. Furthermore, pathophysiological pathways through which the agents would decrease hepatic steatosis through enhanced insulin sensitivity, decreased lipogenesis, or lessened inflammation are as yet only incompletely defined [8].

Considering the increasing burden of MAFLD and its robust correlation with poor hepatic and cardiovascular outcomes in T2DM, it is crucial to investigate new therapies that target both glycemic control and liver disease. The current study sought to assess the effect of SGLT2 inhibitor treatment on hepatic steatosis and systemic inflammatory markers in patients with T2DM and MAFLD. We predicted that SGLT2 inhibitor-treated patients would have substantial reductions in liver steatosis and systemic inflammatory markers versus those treated with conventional antidiabetic therapy. The findings of this study may inform a more holistic management of MAFLD, providing insight into the therapeutic value of SGLT2 inhibitors for reversing early liver damage and preventing the progression of chronic liver disease.

MATERIALS AND METHODS

Study Design and Participants

This study was a 24-week, prospective, randomized, controlled trial performed at a single tertiary care center. Adult patients aged 35–70 years with a known diagnosis of T2DM for at least one year were screened for inclusion. Eligibility criteria included: (1) poorly controlled T2DM (HbA1c 7.0–10.0%) despite stable antidiabetic therapy for the previous three months; and (2) a diagnosis of MAFLD confirmed by ultrasound-based controlled attenuation parameter (CAP) ≥ 248 dB/m on FibroScan. Exclusion criteria comprised significant alcohol consumption (>20 g/day for women, >30 g/day for men), known chronic liver diseases other than MAFLD, severe renal impairment (eGFR <45 mL/min/1.73 m^2), and use of SGLT2 inhibitors in the preceding six months.

Randomization and Intervention

Eligible participants (n=120) were randomized using a computer-generated sequence to either the SGLT2 inhibitor group or the control group in a 1:1 allocation. The SGLT2 inhibitor group received once-daily oral empagliflozin 10 mg or dapagliflozin 10 mg, based on physician discretion and patient tolerance, added to their background antidiabetic regimen. The control group continued on standard of care treatments (metformin, sulfonylureas, or DPP-4 inhibitors as applicable). Both groups received lifestyle modification advice, including a standardized dietary plan and exercise guidance.

Data Collection and Assessments

Baseline demographic and clinical data were collected, including age, sex, body mass index (BMI), and duration of T2DM. Laboratory tests, including fasting plasma glucose (FPG), HbA1c, alanine aminotransferase (ALT), aspartate aminotransferase (AST), CRP, and IL-6, were performed at baseline and week 24. Hepatic steatosis was quantified by CAP measured via transient elastography (FibroScan, Echosens). Body weight and blood pressure were recorded during each clinic visit.

Outcome Measures

The primary outcome was the change in CAP values from baseline to week 24. Secondary outcomes included changes in ALT, AST, CRP, and IL-6, as well as glycemic parameters (FPG, HbA1c), BMI, and adverse events. Safety assessments included evaluation of genitourinary infections, hypoglycemic episodes, and any serious adverse events.

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp.). Normality was tested using the Shapiro-Wilk test. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range) based on distribution. Between-group comparisons were performed using the independent samples t-test or Mann-Whitney U test, as appropriate. Within-group comparisons from baseline to study endpoint were conducted using paired t-tests or Wilcoxon signed-rank tests. Categorical variables were compared using the Chi-square test. A two-sided p-value <0.05 was considered statistically significant.

All participants provided written informed consent, and the study was approved by the Institutional Ethics Committee. The trial adhered to the principles of the Declaration of Helsinki.

RESULTS

Overview of Findings

A total of 120 patients were enrolled and randomized equally into two groups: SGLT2 inhibitor group (n=60) and control group (n=60). Four patients in the control group and three in the SGLT2 inhibitor group were lost to follow-up, leaving 113 patients who completed the 24-week study. Baseline characteristics, including age, sex distribution, BMI, and duration of diabetes, were comparable between the two groups (Table 1).

In summary, the SGLT2 inhibitor group demonstrated clinically and statistically significant improvements in hepatic steatosis, as evidenced by CAP reduction. Furthermore, the treatment group exhibited favorable changes in inflammatory markers and glycemic parameters over the 24-week intervention period.

Primary Outcome: Hepatic Steatosis

At baseline, the mean CAP values were 290.3 ± 32.5 dB/m in the SGLT2 inhibitor group and 292.6 ± 34.1 dB/m in the control group, with no significant difference (p=0.64). After 24 weeks, the SGLT2 inhibitor group showed a mean reduction of 35.2

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dB/m ($p<0.01$ from baseline), whereas the control group showed a modest reduction of 10.1 dB/m ($p=0.08$ from baseline). Between-group comparison revealed that the reduction in CAP was significantly greater in the SGLT2 inhibitor group ($p<0.01$). These findings suggest that SGLT2 inhibitors may attenuate hepatic steatosis, potentially through weight loss, improved insulin sensitivity, and reduced lipogenesis (Figure 1).

Inflammatory Markers

Serum CRP levels decreased from 6.8 ± 1.6 mg/L to 4.9 ± 1.4 mg/L ($p<0.05$) in the SGLT2 inhibitor group, but only from 6.6 ± 1.7 mg/L to 5.9 ± 1.6 mg/L in the control group ($p=0.10$), indicating a more prominent anti-inflammatory effect of SGLT2 inhibition. IL-6 levels showed a similar pattern, with a significantly greater decline in the intervention group ($p<0.05$ for between-group difference). Serum ALT and AST levels showed meaningful reductions in the SGLT2 inhibitor group compared to minimal changes in the control group (Table 2, Figure 2).

Glycemic Control and Other Parameters

HbA1c decreased by an average of 0.6% (from 8.3% to 7.7%) in the SGLT2 inhibitor group and by 0.2% in the control group (from 8.2% to 8.0%; $p<0.05$ for between-group difference). Body weight declined by 2.4 ± 1.0 kg in the SGLT2 inhibitor group, whereas the control group showed a mean reduction of 0.5 ± 0.8 kg ($p<0.01$ for between-group comparison). Blood pressure also improved more significantly in the intervention group (Table 3).

No serious adverse events were reported in either group. Minor genitourinary infections were noted in four patients receiving SGLT2 inhibitors, and two patients in the control group experienced hypoglycemic episodes requiring dose adjustments. Overall, the therapy was well tolerated.

Table 1. Baseline Characteristics of Study Participants

Variable	SGLT2 Inhibitor Group (n=60)	Control Group (n=60)	p-value
Age (years)	55.2 ± 9.8	56.1 ± 8.9	0.60
Male, n (%)	35 (58)	33 (55)	0.72
BMI (kg/m^2)	29.4 ± 2.5	29.2 ± 2.7	0.80
Duration of T2DM (yrs)	8.3 ± 3.1	7.9 ± 3.4	0.55
HbA1c (%)	8.3 ± 0.6	8.2 ± 0.7	0.65
CAP (dB/m)	290.3 ± 32.5	292.6 ± 34.1	0.64
ALT (U/L)	50.4 ± 10.5	51.2 ± 11.2	0.70
AST (U/L)	45.1 ± 9.8	46.3 ± 9.2	0.58

Table 2. Changes in Liver Enzymes and Inflammatory Markers at Week 24

Parameter	SGLT2 Inhibitor Group	Control Group	Between-Group p-value
ALT (U/L)	−9.8 ($p<0.01$ vs BL)	−2.4 ($p=0.12$ vs BL)	0.01
AST (U/L)	−7.2 ($p<0.01$ vs BL)	−1.8 ($p=0.20$ vs BL)	0.02
CRP (mg/L)	−1.9 ($p<0.05$ vs BL)	−0.7 ($p=0.10$ vs BL)	0.04
IL-6 (pg/mL)	−1.6 ($p<0.05$ vs BL)	−0.4 ($p=0.23$ vs BL)	0.03

Abbreviations: BL, baseline.

Table 3. Secondary Metabolic Outcomes at Week 24

Outcome	SGLT2 Inhibitor Group	Control Group	p-value
HbA1c (%)	7.7 ± 0.5	8.0 ± 0.6	<0.05
FPG (mmol/L)	7.2 ± 0.8	7.8 ± 0.9	<0.05
Weight (kg)	−2.4 ± 1.0	−0.5 ± 0.8	<0.01
SBP (mmHg)	−8.5 ± 4.1	−3.2 ± 3.5	<0.05
DBP (mmHg)	−5.4 ± 3.2	−2.1 ± 2.9	<0.05

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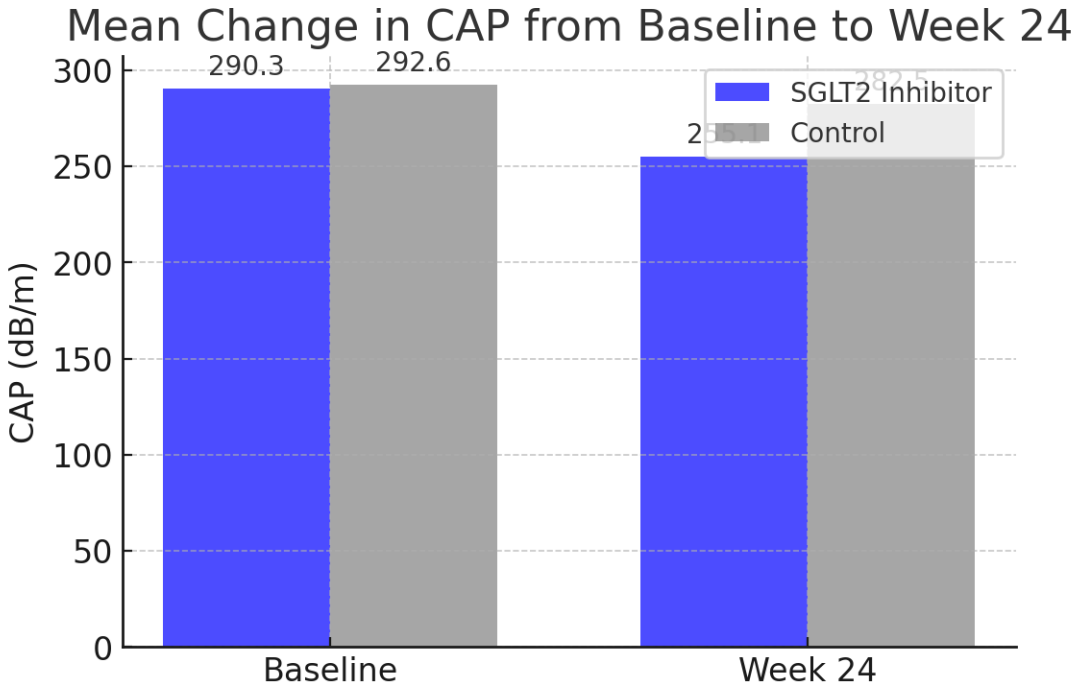

Figure 1.Mean Change in CAP (dB/m) from Baseline to Week 24

(Bar chart illustrating the reduction in CAP in the SGLT2 inhibitor group vs. the control group.)

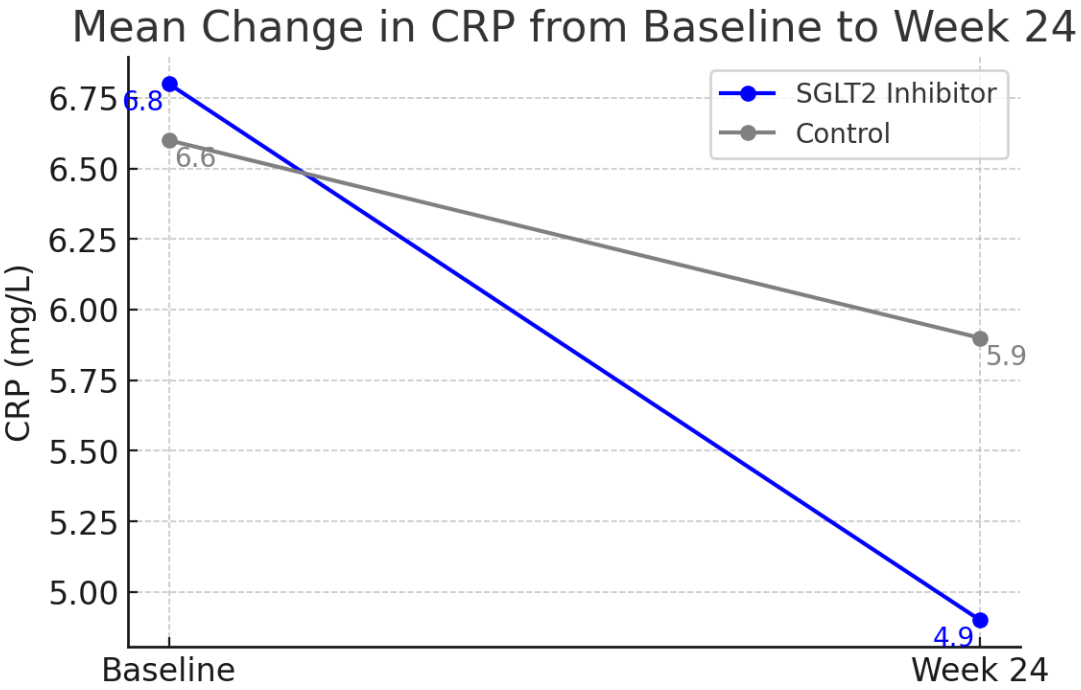

Figure 2.Mean Change in CRP (mg/L) from Baseline to Week 24

(Line graph showing the decline in CRP in both groups, demonstrating a greater reduction in the SGLT2 inhibitor group.)

DISCUSSION

Our results show that SGLT2 inhibitor therapy is associated with substantial decreases in hepatic steatosis and inflammatory markers in patients with T2DM and MAFLD. These findings are consistent with earlier reported favorable effects of SGLT2 inhibitors on metabolic parameters [9,10] and add to the evidence base by demonstrating improvement in both hepatic and systemic inflammation. The pronounced reduction in CAP highlights the potential of SGLT2 inhibitors to reduce hepatic lipid deposition, a central mechanism in MAFLD pathogenesis [11]. A variety of mechanisms could be hypothesized to account for this effect, such as enhanced lipolysis, decreased hepatic gluconeogenesis, and overall enhanced insulin sensitivity [12].

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Besides, decreases in ALT and AST in our study population are in agreement with hepatic tissue health improvements [13]. The reduction of inflammatory markers, especially CRP and IL-6, observed in this study indicates that SGLT2 inhibitors could beneficially modify the proinflammatory environment involved in the transition from simple steatosis to steatohepatitis and severe fibrosis [14]. Though other antidiabetic drug classes, including thiazolidinediones, have similarly demonstrated hepatic advantages, they are hampered by widespread utilization by virtue of safety profiles, necessitating other well-tolerated therapies [15].

Another significant secondary advantage seen was enhanced glycemic control, which could further minimize lipotoxicity and inflammation through lowering adipose tissue insulin resistance. Weight loss and blood pressure optimization, commonly reported with SGLT2 inhibitor treatment, also presumably contribute to the cardiometabolic benefit and secondarily enhance liver function [6]. Together, these metabolic actions can possibly decelerate or even reverse the progress of MAFLD by addressing its multifactorial pathogenesis.

Even with the encouraging findings, our investigation is limited. The comparatively brief trial period of 24 weeks may not reflect the overall magnitude of histopathological gain or the likelihood of long-term effects. An increased sample size and longer trial period could confirm our results and determine if SGLT2 inhibitors affect histological outcomes, including fibrosis severity. Also, although CAP is a safe and non-invasive marker of hepatic steatosis, liver biopsy is still the gold standard for the evaluation of histologic alterations. Non-invasive imaging techniques should be combined in the future with histopathological assessment in order to confirm these findings further [12].

In summary, the current study favors a positive role for SGLT2 inhibitors in enhancing hepatic steatosis and inflammatory markers in T2DM patients with MAFLD. Our findings contribute to the expanding literature favoring the pleiotropic effects of SGLT2 inhibition, highlighting that this class of drugs can effectively treat the interwoven pathophysiology of metabolic derangement and liver disease.

CONCLUSION

In patients with type 2 diabetes and concomitant MAFLD, the addition of SGLT2 inhibitors to conventional treatment resulted in important improvements in hepatic steatosis and decreases in major inflammatory markers. These effects were followed by improved glycemic control, moderate weight loss, and beneficial hemodynamic changes, consistent with the notion of a global metabolic benefit. Although larger and more prolonged studies are needed to confirm these results and assess histological endpoints, our findings indicate that SGLT2 inhibitors play a promising therapeutic role in reducing liver injury and inflammation in this at-risk group.

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