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ORIGINAL RESEARCH PAPER

Gastroenterology

THE ROLE OF SGLT2 IN THE TREATMENT OF FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

KEY WORDS: "SGLT2 inhibitors", "NAFLD," "NASH," and "liver function."

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ABSTRACT

Sodium-glucose co-transporter inhibitors (SGLT2) have recently appeared in the field of non-alcoholic fatty liver disease (NAFLD) treatment. They are often associated with treatment for type 2 diabetes and congestive heart failure. This meta-analysis intends to assess the efficacy of SGLT2 inhibitors in NAFLD control, dealing with liver fat content, liver function tests, and histological alterations as the primary outcomes. The review was performed according to the PRISMA statement, which stands for a rigorous and transparent approach. The literature review was performed using the central databases, such as PubMed, Cochrane Library, and Embase, of which five qualified for the meta-analysis were chosen. The meta-analysis used forest plots to display the relative magnitude of SGLT2 inhibitors on liver fat and the accompanying statistics, indicating that the liver fat may be reduced and the liver function improved after treatment with SGLT2 inhibitors. However, the I^2 statistic shows strong consistency in research, which is a crucial aspect to consider when examining the results. This variability may be due to the different study designs, patients' demographic characteristics, treatment period, and SGLT2 inhibitor dose. It might be asserted that SGLT2 inhibitors could be a good remedy in combating NAFLD; however, there is a need to conduct more research to confirm the observed outcomes like randomized, well-designed trials focusing on long-term safety profiles, dose optimization, and possible interactions with other NAFLD treatment modalities.

INTRODUCTION

NAFLD is a global pandemic affecting healthcare systems, associated with metabolic disorders such as obesity, type 2 diabetes, and dyslipidemia [1]. Insulin resistance, a major factor for type 2 diabetes, is the primary reason for NAFLD development. High levels of insulin in the bloodstream enhance lipogenic activity in the liver, facilitating fat synthesis. Concurrently, this elevation in insulin diminishes the rate of hepatic lipid oxidation, effectively reducing the catabolic breakdown of fats within the liver. Such metabolic disorder leads to the accumulation of triacylglycerols in the liver, thus resulting in hepatic steatosis, an early-stage NAFLD [2]. This can culminate in further deterioration of liver cells due to inflammation and oxidative stress that could result in hepatitis and further increase the possibility of fibrosis and cirrhosis. Hence, it is pertinent that we diagnose NAFLD in the early stages to prevent NAFLD from progressing to cirrhosis and Hepatocellular carcinoma.

Conventional management methods for NAFLD mainly emphasize non-pharmacological interventions such as weight reduction, dietary modifications, and increased exercise. This approach, nevertheless, needs constant commitment, and it is not always a reliable treatment option in patients with severe NAFLD [3]. Consequently, scientists and physicians have become intrigued by pharmacological elements that could complement the treatment plan and possibly halt the disease development. SGLT2 inhibitors, developed for diabetes, started gaining recognition because of their unique mechanism of action and metabolic effects beyond diabetes control.

SGLT2 inhibitors block glucose reabsorption in the kidneys, enabling it to be excreted through urine. Lower blood sugar levels indirectly help weight loss by causing the body to burn stored fats by encouraging a more catabolic state. The suggested outcomes imply that SGLT2 inhibition may be a therapeutic option to reduce liver fat content and improve liver function in NAFLD patients [4]. Furthermore, cardiovascular benefits of SGLT2i have been observed, including lowering blood pressure and improving lipid profiles, which are beneficial in managing metabolic syndrome, a common co-morbidity in NAFLD patients.

This novel research reports that SGLT2 inhibitors cause a sharp drop in liver fat levels and enhance liver functionality indexes, indicating their possible use for managing NAFLD. Clinical studies are advancing rapidly, yet the outcomes are still not definitive enough to bridge the divergent perspectives inherent in medical research. The design including the selection of participant groups, are critical factors. Additionally, patient characteristics and health conditions significantly influence the results. Furthermore, the dosage and duration of treatment also play crucial roles in determining the effectiveness of interventions. This meta-analysis aims to synthesize the available data to give a comprehensive picture of how the SGLT2 inhibitors improved the management of NAFLD and thus guide the practices in the future.

The primary objectives of this systematic review and meta-analysis are:

1. To determine whether SGLT2 inhibitors effectively reduce liver fat content among NAFLD patients.

2. The endpoint will be to quantify the effect of the SGLT2 inhibitors on elevated liver enzymes with ALT and AST as markers.

3. To evaluate the SGLT2 inhibitor's safety and tolerance in NAFLD patients.

METHODS

Approach and Selection Criteria

The search strategy was built to identify relevant studies that could investigate the effect of SGLT2 inhibitors on steatosis. The screening was conducted on PubMed, Cochrane Library, and Embase through the use of the words "SGLT2 inhibitors", "NAFLD," "NASH," and "liver function." The search covered studies during the period 2018-2023. The selection criteria focused mainly on the trials that investigated the effects of SGLT2 inhibitors on liver-specific outcomes in NAFLD patients.

Data Collection And Risk Of Bias Assessment

Patients' demographics were pulled to provide an overall sense of the population studied. This included the patient's age, gender, presence of comorbidities, severity of the disease, and medical background. Through this demographic data, the researchers assessed whether the results could be generalized and how different subpopulations would react to specific treatment modalities.

Another important part of the data-gathering process was collecting intervention data. This included information about the type of SGLT2 inhibitors, dose, treatment duration, and other drugs that were taken along with them. This information will be used to discern similarities and comparability of the studies and unveil any modifications of treatment protocols that can affect the results.

The large number of tests in this study were mainly focused on the results of the SGLT2 inhibitor's effectiveness in treating Non-alcoholic fatty liver disease (NAFLD). The outcomes show the impact on the fat content in the liver, AST and ALT blood tests, and the histology of the liver. The initial results were utilized to design the comprehensive investigation of the SGLT2 inhibitor's effect on the progress of non-alcoholic fatty liver disease.

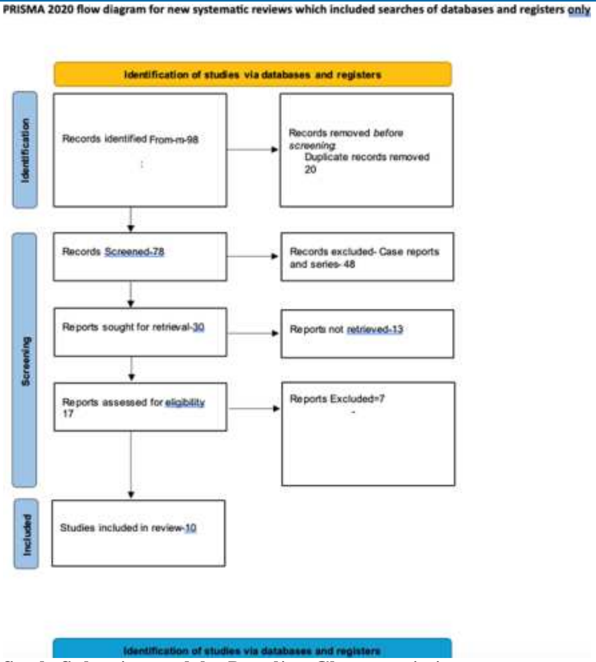
The risk of bias assessment was also undertaken using the Cochrane Risk of Bias assessment scales for randomized controlled trials. It studies behavior in random sequence generation, allocation masking of subjects and personnel, completeness of outcome dates, and reporting selective bias5. The risk rating of each domain helps the researchers identify the domains that are particularly prone to bias, which can thus affect the results of their work.

Outcomes

Meta-analysis results helped determine the effectiveness of SGLT-2. Different studies have adopted different methods to determine the content of fat in the liver, including magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), or ultrasound. They allowed for an ultra-high-resolution evaluation of liver fat content, where different comparison results were observed before and after the treatment with SGLT2 inhibitors. The decrease in liver fat by the tissue content directly shows that the treatment has been successful. Further, SGLT2 inhibitors will be present in the concentrations used in treating people with fatty liver.

The research studies also included liver function tests, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as critical outcomes. High levels of such enzymes usually imply the presence of liver inflammation or damage. Liver function tests decreasing after SGLT2 inhibition therapy suggest less risk of NASH or cirrhosis and a chance for recovery.

The first search showed 98 studies (Figure 1). Applying inclusion and exclusion criteria, ten articles were qualified to be included in the final analysis. These were randomized controlled trials and observational studies. The studies also differed in patient demographics, treatment duration, and doses of SGLT2 inhibitors.



Study Selection and the Baseline Characteristics

Quality assessment results for the study were done as per the Cochrane Risk Bias Tool, shown in Figure 3 below

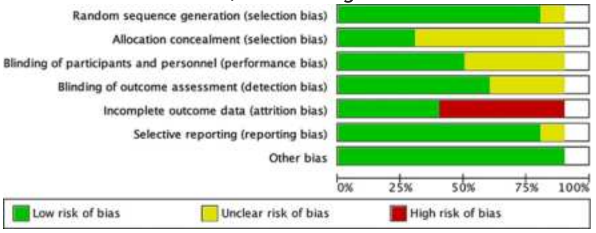


Figure 3: Risk of bias

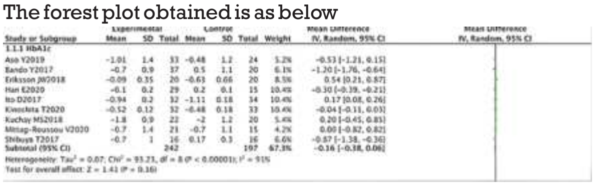
DISCUSSION

The studies are summarized in Figure 1

Source	Sample	Age	Duration	Agent	Comparator
Aso Y[5]	57	55 +/- 8	24 w	Standard treatment-(ST) with Dapagliflozin 5-mg	Standard
Bando Y[6]	62	55.1+/-8.6	12 w	ST with-pragliflozin 50 mga	Standard
Erickson JW[7]	42	65+/-3.6	12 w	Dapagliflozin-10 mg.	
Han E[8]	45	53+/-10.9	24 w	Metformin + pioglitazone. +. bragliflozin 50 mg	Metformin. + pioglitazonen
Ito D[9]	66	58.2+/-10.9	24 w	Ipragliflozin: 50 mg	Piogitazone-15-30 mg/days
Kinoshita T[10]	98	59+/-1	28 w	Ipragliflozin: 50 mg	Piogbtazone 7.5--15 mg/days
Kuchay MS[11]	50	65+/-6.2	20 w	ST + empagliflozin-10-mg	ST

Russou V[12]	39	57.7+/-10.9	26 w	Dapagliflozin 5-10 mg-1 empagliflozin-10-25mga	Exenatide 10-20. pg. iraglutide -0.6.%.1. 8 m
Shibuya T[13]	32	56.5+/-11.7	26 w	Gluflozin 5mga	Metformin 1500 mg

The forest plot obtained is as below



242 SGLT2 inhibitor users and 197 non-users were evaluated for HbA1c levels. Compared with other antihyperglycemic drugs, SGLT2 inhibitors were more likely to reduce HbA1c, but the difference was not statistically significant (Difference - 0.16 [95%CI: -0.38, 0.06], P = 0.16). I2 was 91% with higher heterogeneity, so no heterogeneity analysis was needed because the two groups were not statistically different.

Nine RCTs measured alanine transaminase levels in 268 who used SGLT2 inhibitors and 213 who did not. The meta-analysis showed that SGLT2 inhibitors significantly reduced the ALT levels in patients with NAFLD compared with other drugs (MD -5.36 [95% CI: [male -8.86, -1.85; female -6.56, -0.96], p = 0.003. The results of the studies were significantly heterogeneous (I2 = 90%, p < 0.00001).

Eight RCTs detected aspartate transaminase levels in the SGLT2 inhibitors group, consisting of 252 patients, and the non-users group of 197 people. The meta-analysis showed that SGLT2 inhibitors significantly reduced the AST levels in patients with NAFLD (MD -2.57 [95% CI: (=-3.84, =-1.30), p < 0.0001) Some level of heterogeneity was found between studies as well (p = 0.03 I2 = 54%).

Three RCTs were assessed to determine the SGLT2 inhibitor's influence on FIB-4. Compared with other antihyperglycemic drugs, SGLT2 inhibitors significantly reduced FIB-4 (WMD - 0.06 [95% CI: The estimated effect was statistically significant - coefficient 0.10, 0.02 (p = 0.0010). According to the statistics, no heterogeneity was found among studies (p = 0.88, I2 = 0%) Another crucial element to consider is the safety profile of SGLT2 inhibitors. These inhibitors generally have a good safety profile in diabetes treatment, but the lasting effects and specific concerns of NAFLD patients need to be explored. Common effects, such as urinary tract infections and ketoacidosis, ought to be carefully monitored when such treatments are scaled up in the frame of liver disease.

CONCLUSION

According to this meta-analysis and systematic review, the liver fat content and the indicator liver function tests decreased markedly in the patients using the sodium-glucose transporter 2 (SGLT2) inhibitors. Thus, the latter might be recommended for the NAFLD treatment. It is encouraging to confirm that the therapy of SGLT2 inhibitors could be another option for NASH, particularly in those patients who have other conditions like obesity and diabetes. Although the included studies in the meta-analysis exhibited various degrees of homogeneity, there is still the risk of interpreting the findings carefully. It focuses on the importance of customized treatment, which involves changes in dosages, duration, and demographic characteristics of any patient, for better results.

Since the SGLT2 inhibitors give very diverse results, more research is needed to validate the benefits of these inhibitors. It is imperative to have clinical studies with sound structures that estimate long-term safety and effectiveness in the subgroups of patients taking different SGLT2 inhibitors.

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