Effect of SGLT-2 inhibitors on Non-Alcoholic Fatty Liver Disease among Patients with Type 2 Diabetes mellitus: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials

Kai Wei Lee[1], Navin Kumar Devaraj[1,2], Siew Mooi Ching[1,2], Sajesh K Veettil[3], Fan Kee Hoo[4], Inas Deuraseh[1] and Man Jun Soo[1]

[1]Department of Family Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia.

[2]Malaysian Research Institute on Ageing (MyAgeing), Universiti Putra Malaysia

[3]School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia.

[4]Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia.

Accepted: 8 June 2020

Received: 6 September 2020

**Corresponding author: knavin@upm.edu.my*

DOI 10.5001/omj.2021.62

ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) is a common problem occurring in association with obesity and Type 2 Diabetes mellitus (T2DM). There has been anecdotal report of the efficacy of Sodium glucose cotransporter 2 inhibitors (SGLT2Is) in improving liver function parameters in those with concomitant T2DM and NAFLD/NASH. The aim of this study was to systematically evaluate the evidence of SGLT2Is in improving liver function parameters in T2DM patients with NAFLD taking into consideration the risks of random error based on trial sequential analysis (TSA). We also perform meta-analysis based on random-effects model.

Methods: A systematic literature search was performed through 3 databases, which are Medline, Cochrane and Embase from inception to 20 October 2018. Primary outcome for meta-analyses was the changes of hepatic enzymes levels (alanine transaminase, aspartate transaminase and gamma-glutamyl transpeptidase). We also performed meta-analysis on changes in insulin resistance, glycaemic and lipid parameters with the use of SGLT2Is as a secondary objective.

Results: At last, 8 eligible randomised controlled studies were eligible for analysis. Meta-analysis showed the efficacy of two SLT2Is, dapagliflozin and canagliflozin in reducing these enzymes level. Trial sequential analysis showed that Canagliflozin significantly reduced the GGT level by weighted mean difference =-5.474 (95% CI=-6.289, -4.659) compared to others comparators and the evidence is conclusive. Dapagliflozin also had a statistically significant reduction in HbA1c which is a parameter of glycaemic control and insulin sensitivity-HOMA-IR which is a parameter of insulin sensitivity by a weight mean difference = -0.732 (95% CI=-01.087, -0.378) and -0.804 (95% CI=-1.336, 0.272, respectively.

Conclusion: This study indicated that Canagliflozin is effective in improving liver function parameters among patients with diabetes, while dapagliflozin is more effective in improving glycaemic indices and insulin sensitivity.

Keywords: Sodium glucose cotransporter 2 inhibitors; dapagliflozin; canagliflozin; liver function; Non-alcoholic fatty liver disease;

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a new public health problem and is one of the complication that is associated with diabetes and metabolic syndrome [1]. The defining feature of NAFLD is excess in fat deposition on liver cells (hepatocytes), which may be accompanied by evidence of cell injury with or without the presence of fibrosis and inflammation (NASH) or rarely remains as an isolated event (non-alcoholic fatty liver, NAFL) [2,3]. The importance of recognising this liver condition lies in the fact that it will overtake Hepatitis C infection in the near future as the leading cause of liver failure and the need for transplantation in many developed countries as well as the absence of FDA-approved therapies for this disease, thereby making the early detection or better still its' prevention as an urgent healthcare agenda [4-6].

As the pathogenesis of T2DM or insulin resistance is closely associated with the presence of NASH/NAFLD, the use of various antidiabetic drugs such as pioglitazone, metformin, dipeptidyl peptidase-4 inhibiter (DPP4I) and glucagon-like peptidase-1 agonists, have been postulated to be able to reduce hepatic inflammation in these liver conditions [7-10]. Despite the presence of many studies, there is lack of effective treatment for NAFLD/NASH [11]. Sodium glucose cotransporter 2 inhibitors (SGLT2Is) has revolutionised the treatment of T2DM with a unique mechanism of action and efficacy in reducing the HbA1c levels. It acts by helping in renal excretion of glucose and therefore will cause a reduction of body weight (on average 2.5 to 3.0kg) and prevalence of obesity that may improve the liver histology of those with NAFLD/NASH [12]. Drugs in this class includes canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin and tofogliflozin. It is able to reduce the HbA1c by up to 0.8% and has gain foothold as one of the first line anti-diabetic drugs. Modest blood pressure reduction has also been documented together with lower risk of hypoglycaemia with the use of these drugs [13]. Furthermore, it is also effective in preventing weight gain [14].

A systematic review by Raj et al., published in 2019 summarised its finding based on eights studies [15-22] which showed a significant decrease in ALT and reduction in AST and GGT levels with the use of SGLT2Is [23]. Several randomized clinical trials (RCTs) have been recently published which explored its benefits in improving liver functions [7,24-32], however there is a lack in systematic review that is coupled with meta-analysis and trial sequential analysis that have been conducted to estimate the effect of SGLT2Is on hepatic enzymes among patients with diabetes. Meta-analysis can provide the information on the threshold of statistical significant for weight mean differences. Trial sequential analysis meanwhile will confirm the result from meta-analysis with cumulative sample size of all included studies, thus reducing the chance for type 1 error due to systematic error or small sample size effect that could occur in a meta-analysis.

The aim of this systematic review and meta-analysis is to look at the efficacy of SGLT2 as compared to other anti-diabetic drugs in improving the liver function parameters in T2DM patients with NAFLD. As a secondary objective, we will also perform meta-analysis on changes in insulin resistance, glycaemic and lipid parameters with the use of SGLT2Is in these groups of patients.

2. MATERIAL AND METHODS

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[33]. The protocol was registered in the PROSPERO (Record ID: 126327).

Search strategy

A systematic literature search was performed through 3 databases, which are Medline, Cochrane and Embase from inception to 20 October 2018. Searches were conducted using Medical Subject Headings (MeSH) terms and corresponding keywords as shown in Appendix 1.

Inclusion and exclusion criteria
There were no language or method restrictions and the eligibility criteria extends to all studies done globally (Figure 1). Inclusion criteria are randomized controlled trials (RCTs) conducted on T2DM patients with non-alcoholic fatty liver disease on treatment with anti-diabetic drugs, namely SGLT2 inhibitors along with its effects on NAFLD/NASH. Exclusion criteria will be any other study design such as review articles, prevalence studies or animal and cells models.

Intervention and placebo group definitions
The treatment or intervention group will be patients who are on SGLT-2 inhibitor treatment. The comparator or control group will be placebo / patients who are not on treatment with SGLT-2 inhibitor. Therefore, the context being studied will be patients with T2DM with underlying non-alcoholic fatty liver disease who are randomized to be receiving SGLT-2 inhibitor treatment or other oral anti-diabetic drugs.

Primary outcomes for meta-analysis
Primary outcome for these meta-analyses was the changes in hepatic enzymes levels, namely alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transpeptidase (GGT). In addition, we also assessed the effect of SGLT2Is on insulin resistance, glycaemic and lipid parameters such as triglyceride and cholesterol components.

Data extraction (selection and coding)
Articles screening and data extraction was done through a multi-step process. Articles were preliminarily screened by three independent authors by their titles and abstracts, followed by full-text reading by KWL, MJS and NKD. This was followed by data extraction on the following aspects: primary author, year of publication, study country, sample size of the two groups and levels of liver enzymes level for ALT, AST and GGT that was available for each of the selected articles. A standardized data extraction form was created and the extracted data was inserted into this form. Any disagreement will be brought up in a discussion together with the following authors: ID, FKH, SMC and SKV.

We used mean ± standard deviation (SD) to express our outcomes. If the mean difference and SD were not provided, the mean was calculated by subtracting the mean of baseline measurement from the corresponding mean of post intervention measurement; while the SD was imputed from the end point measurement. If the mean difference was provided, but the SD was not, the latter was imputed either from the end point measurement or calculated using the confidence intervals with the following formula in Excel - "SQRT(sample size)*(upper confidence interval-lower confidence interval)/(T.INV.2T(0.05, D2-1)*2)" as proposed by [34].

Strategy for data synthesis
Data for this study was extracted from the RCT studies and Meta-analysis (random-effects model) was performed to estimate the pooled risk ratio at 95% confidence interval based on the determination of heterogeneity among these studies by I^2 statistics. Trial sequential analyses was performed to assess the effect of SGLT-2 on non-alcoholic fatty liver disease as compared to the control group [35]. The comparative effectiveness of SGLT-2 was also studied using the GRADE approach that was not done in previous systematic reviews. This was done in order to rate the quality of the evidence as either high, moderate, low or very low.

Risk of bias (quality) assessment
Included trials were independently assessed using the Revised Cochrane Risk of Bias Tool (RoB 2.0). Two authors independently assess all trials identified for study inclusion after full-text reading (KWL and NKD). Any discrepancies were discussed with the following authors once again (MJS, ID, FKH,

SMC and SKV). Assessment was done across the five domains of bias (bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result) [36]. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessments were performed to appraise the quality of the evidence [37] which assessed the studies inconsistency, indirectness, imprecision and publication bias [38,39].

3. RESULTS

Description of included studies
Through our initial search, we identified 218 eligible manuscripts as shown in Figure 1. After further removal of duplicates through de-duplication (n=14), 204 studies were then selected for the next screening step. Through review of the abstract, title and keywords, 8 studies were finally included, and its characteristics extracted as described in Table 1 and Appendix 2a-c. These data were described based on the author's name, anti-diabetic drug used, and improvement in liver function as measured by the liver enzyme levels.

Characteristics of included studies
Table 1 shows the key characteristics of the included studies and Appendix 2a-c indicate changes of hepatic functions among T2DM patients. In the final analysis, a total sample of 5984 patients with T2DM was included in which patients had used SGLT2Is in the treatment of their T2DM. The overall quality of included studies appeared to be good.

Effect of SLGT2 against other anti-diabetic drugs
Effect on ALT
Analysis of the effect of Dapagliflozin on ALT reduction using meta-analysis and trial sequential analysis are provided in Figure 2 and Appendix 3a. The meta-analysis showed that Dapagliflozin did not significantly reduced the ALT level by weighted mean difference= -0.151 (95% CI=-0.313, 0.012) as compared to other comparators. Moreover, the cumulative Z-curve (blue curve) did not cross the conventional boundary (Z-statistic above 1.96) and demonstrated that Dapagliflozin did not significantly reduced ALT by using the trial sequential analysis. However, the number of patients included in trial sequential analysis did not exceed the required information size (that is 602 patients), indicating that the cumulative evidence for dapagliflozin that it does not reduce ALT remains inconclusive based on only 266 patients.

Analysis of the effect of Canagliflozin on ALT reduction using meta-analysis and trial sequential analysis are provided in Figure 3 and Appendix 3b. The meta-analysis showed that Canagliflozin significantly reduced the ALT level by weighted mean difference =-5.944 (95% CI=-8.361, -3.527) as compared to other comparators. The cumulative Z-curve (blue curve) crossed the conventional boundary (Z-statistic above 1.96) and demonstrated that Canagliflozin significantly reduced ALT using trial sequential analysis. However, the number of patients included in trial sequential analysis did not exceed the required information size (that is 5364 patients), indicating that the cumulative evidence is also still inconclusive.

Effect on AST
Analysis of the effect of Dapagliflozin on AST reduction using meta-analysis and trial sequential analysis are provided in Figure 4 and Appendix 3c. The meta-analysis showed that Dapagliflozin did not significantly reduced the AST level by weighted mean difference =-0.078 (95% CI=-0.184, 0.029) as compared to comparators. The cumulative Z-curve (blue curve) did not cross the conventional boundary (Z-statistic above 1.96) and demonstrated that Dapagliflozin did not significantly reduced AST using trial sequential analysis. However, the number of patients included in trial sequential

analysis did not exceed the required information size (that is 3178 patients), indicating that the cumulative evidence remains inconclusive based on the 266 patients.

Analysis of effect of Canagliflozin on AST reduction using meta-analysis and trial sequential analysis are provided in Figure 5 and Appendix 3d. The meta-analysis showed that Canagliflozin significantly reduced the AST level by weighted mean difference =-4.069 (95% CI=-6.832, -1.306) as compared to other comparators. Moreover, the cumulative Z-curve (blue curve) crossed the conventional boundary (Z-statistic above 1.96) and demonstrated that Canagliflozin significantly reduced AST using trial sequential analysis. However, the number of patients included did not exceed the required information size (that is 7015 patients), indicating that the cumulative evidence remains inconclusive based on 5287 patients.

Effect on GGT

Analysis of effect of Dapagliflozin on GGT reduction using meta-analysis and trial sequential analysis are provided in Figure 6 and Appendix 3e. The meta-analysis showed that Dapagliflozin did not significantly reduced the GGT level by weighted mean difference =-0.161 (95% CI=-0.476, 0.153) as compared to comparator. The cumulative Z-curve (blue curve) did not cross the conventional boundary (Z-statistic above 1.96) and demonstrated that Dapagliflozin did not significantly reduced GGT using the trial sequential analysis. However, the number of patients included in our meta-analysis did not exceed the required information size (that is 3923 patients), indicating that the cumulative evidence remains inconclusive based on the 723 patients.

Analysis of effect of Canagliflozin on GGT reduction using meta-analysis and trial sequential analysis are provided in Figure 7 and Appendix 3f. The meta-analysis showed that Canagliflozin significantly reduced the GGT level by weighted mean difference =-5.474 (95% CI=-6.289, -4.659) when compared to other comparators. The cumulative Z-curve (blue curve) crossed the conventional boundary (Z-statistic above 1.96) and demonstrated that Canagliflozin significantly reduced GGT using trial sequential analysis. In addition, the number of patients included in trial sequential analysis exceeded the required information size (that is 1627 patients), indicating that the cumulative evidence is conclusive.

Effect on insulin resistance, glycaemic and lipid parameters

Table 2 summarized the results from meta-analysis for subcutaneous adipose tissue, visceral adipose tissue, HbA1c, insulin sensitivity- HOMA-IR, serum triglyceride, total cholesterol, low density lipoprotein, high-density lipoprotein, and adiponectin between dapagliflozin versus comparators. Based on the analysis, dapagliflozin statistical significantly reduced HbA1c and insulin sensitivity-HOMA-IR by weight mean difference = -0.732 (95% CI=-01.087, -0.378) and -0.804 (95% CI=-1.336, 0.272), respectively as compared to comparators. On the other hand, dapagliflozin had no statistical significant changes to subcutaneous adipose tissue, visceral adipose tissue, serum triglyceride, total cholesterol, low-density lipoprotein, high-density lipoprotein and adiponectin.

Adverse effect

Based on the data of included studies, Eriksson et al., reported that 33.3% of participant receiving dapagliflozin monotherapy experienced adverse events as compared to placebo (28.6%), omega-3 monotherapy (40%), and dapaglilflozin and omega-3 (68.2%)[18]; however Eriksson et al., did not mention specifically on what kind of adverse events that were experienced by participants.

Seko et al., 2017 reported as much as 28.7% of participant in the high ALT and 33.4% of those with low ALT subgroups experienced adverse effects due to canagliflozin [7]. There were no differences in the overall incidence of serious adverse events related to the canagliflozin between the high (1.0%) and low ALT (0.3%) subgroups. In addition, they also observed high and low ALT subgroup had similar incidence of adverse events associated with symptomatic hypoglycemia, asymptomatic hypoglycaemia, female genital infection and osmotic diuresis, which of these events were less than 5%. There was only one concern raised by Seko et al., which was ketone bodies were significantly increased in both high and low ALT subgroups as compared to placebo.

Guja et al., 2018; Hayashi et al., 2017; Kurinami et al., 2018, Leitor et al., 2016; Polidori et al., 2017; meanwhile, did not report any adverse events from their studies [25,26,30,31,40].

Quality assessment
Revised Cochrane Risk of Bias Tool assessment findings are presented in Appendix 4-5. The assessment indicated that two studies has low risk of bias for all items [20,30], four studies had at least one item with unclear risk of bias [25,26,31,32], and three studies showed high risk of bias [24,40]. The high risk of bias was noticed in the randomization process and deviation from the intended intervention in the study by Kurinami et al., 2018 [40] as well as bias due to missing outcome data in the study by Eriksson et al., 2018 [24].

GRADE assessment of the overall certainty of the evidence for the association between SGLT and hepatic enzymes levels reduction is presented in Appendix 6. Overall the grade of evidence is low for the association between dapagliflozin and the reduction in hepatic enzymes levels, as well as the association between Canagliflozin and reduction of ALT and AST which was also graded as low except for association between Canagliflozin and GGT reduction which showed high certainty. These studies had to be downgraded for their inconsistency and imprecision.

4. DISCUSSION

The present systematic review and meta-analysis of 8 randomized controlled trials involved 5984 patients with T2DM. The analysis showed that Canagliflozin reduced the hepatic enzyme levels but not dapagliflozin. Based on the trial sequential analysis, we observed that association between canagliflozin and the reduction in GGT is statistically significance and this conclusive statement is drawn based on the total number of participants in those trials had reached the required sample size.

Our results support the use of canagliflozin but not dapagliflozin in the management of NASH/NAFLD as it has been shown to significantly reduced ALT, AST and GGT as shown in our meta-analysis. This is based on findings from Figures 3-14. This indicate the another possible untap use of canagliflozin in the treatment of NASH/NAFLD. This is agreement with study by Leiter et al., which showed similar reduction in the ALT and AST levels with the use of canagliflozin [30].The study by Leiter et al included 4 pools of patients i.e. on canagliflozin alone, add on to metformin, as an add on to metformin and sulphonylurea and also as an add on to metformin plus pioglitazone, i.e. without insulin [30].This indicates the wide range of the benefit of SGLT2 inhibitors that extends beyond any other anti-diabetic drug that is used. The study by Leiter et al had also shown the effectiveness of canagliflozin in reducing the GGT levels [30].

As mentioned earlier, insulin resistance appears to the main link between T2DM and NAFLD/NASH with additional contribution from obesity and other metabolic risk factors such as raised triglycerides and reduced HDL-C [41]. There is increase transportation of free fatty acids to the liver due to insulin resistance which diminishes the natural process of lipolysis by the now defunctioning insulin [2]. As a secondary effect, this extra supply of fatty acid will drive the synthesis of triglycerides that is further stimulated by the recurring phenomenon of impaired hepatic fatty acid oxidation secondary to insulin resistance and the excess secretion of very low density lipoprotein (VLDL) that will further worsens the fatty liver [3].

The result in this study differs from the finding in a systematic review by Raj et al. [23]. The possible explanation for the difference could be due to the fact that the study by Raj et al., summarised the finding based on four RCT [15-18] and four observational studies [19-22] compared to eight RCTs in this study. Secondly, Raj et al. finding was made based on small sample size and that study did not pool the sample size from each studies examining effect of SGLT, compared to this study that was making its conclusion based on a pooled sample size of 5984 patients. Furthermore, Raj et al., did not

perform any meta-analysis and trial sequential analysis. Thus, the beneficial effect of SGLT as reported in Raj et al. study may therefore not be the true effect.

In addition, there may also be a strong molecular basis for the occurrence of NAFLD/NASH. This is based on the theory that Carbon monoxide releasing molecule-A1 (CORM-A1) reduces damages to the liver tissue with steatosis via a dual action of improved mitochondrial function and Nuclear factor-erythroid 2 related factor 2 (Nrf2) activation [5]. This may indicate that CORM-A1 has a huge potential of being an anti-NASH and anti-NAFLD agent [5]. However, more research needs to be done in this exciting prospect before it is actually marketed as a treatment for NAFLD/NASH per se.

There also some literature which had paradoxically noted that the inflammatory changes in NAFLD/NASH may in turn contribute to the development of T2DM that was thought to be mainly autoimmune in origin [6,42]. Therefore, the relationship between this both conditions that are also associated with metabolic syndrome may be a two-way relationship. This actually opens up the hypothesis that curing NAFLD/NASH may improve the hyperglycaemia or even revert it totally to normoglycemia, thereby ending the decades of long search for a cure for T2DM. Curing T2DM will go a low way in improving the health profile of many people worldwide and that in turn which churn out more productivity to spur the world's economy.

In addition when looking at the effect of SGLT-2 inhibitors on insulin resistance, glycaemic and lipid parameters, it was noted that, dapagliflozin significantly reduced HbA1c which is a parameter of glycaemic control and insulin sensitivity-HOMA-IR which is a parameter of insulin sensitivity by weight mean difference = -0.732 (95% CI=-01.087, -0.378) and -0.804 (95% CI=-1.336, 0.272), respectively as compared to comparators. This is expected as the primary action of SGLT2 inhibitors is in reducing renal tubular glucose reabsorption, which enables a HbA1c reduction of between 0.6-0.8% [43]. SGLT-2 inhibitor also can improve insulin sensitivity via several molecular pathways including beta function improvement, reduction of oxidative stress and inflammation as well as causing disposition of calories and weight loss [44]. However, there was no significant effect on lipid parameters such as the triglycerides and cholesterol components.

In a study in Japan, treatment of T2DM patients along with biopsy-proven NASH with dapagliflozin resulted in significant reductions in HbA1c, fasting glucose levels and reduced visceral fat mass as early as 4 weeks of treatment [45]. Another Japanese study using serial liver biopsies in five patients receiving 24 weeks of canagliflozin showed remarkable NASH histology improvement [46]. However, the number of subjects involved was relatively small and therefore more studies are needed to show a definite significant effect of hepatic fat reduction with SGLT2-inhibitors.

Future studies are recommended in view of the findings of this study to instil confidence in doctors in prescribing SGLT2 inhibitors in patients with NASH/NAFLD in view of potential beneficial added effect in reduction in ALT, AST and GGT. This is to ensure that this drug is safe, effective and accessible by patients with T2DM and manages to gain a foothold in many clinical practice guidelines on T2DM worldwide to encourage physicians to confidently prescribe it as a management option in patients with NASH/NAFLD and in the process preventing its unrelentless complication.

The potential adverse events with SGLT2Is could be adverse cardiovascular events. Studies reported that dapagliflozin could lead to major adverse cardiovascular events [47]; canagliflozin could cause genital tract infections and osmotic diuresis-related adverse events [48]. Overall, there were no new or unexpected adverse events compared with previous studies with these treatments (dapagliflozin and canagliflozin).

Strengths and Limitations

This is the first study on effect of SGLT2Is had on hepatic enzymes performed using meta-analysis with trial sequential analysis to estimate the effect of SGLT2Is had on hepatic enzymes. Trial sequential analysis provides the information on the power of sample size of cumulative meta-analysis

and whether it surpasses the conventional and alpha spending boundaries which indicates whether the evidence of our meta-analysis is statistically significant and conclusive or not. However, the current study has several limitations. Firstly, majority of trial sequential analysis indicated that the pooled sample size did not meet the required sample size for drawing conclusive effect of SGLT2Is. Secondly, there are also serious inconsistencies in the pooled weighted mean difference for ALT, AST and GGT using Dapagliflozin and very serious inconsistency in pooled weighted mean difference ALT and AST using Canagliflozin. Thirdly, there is serious imprecision in pooled weighted mean difference for ALT, AST and GGT using Dapagliflozin, this could be due to low certainty. Thirdly, majority of studies did not report data on changes in liver attenuation, liver-to-spleen attenuation ratio, liver magnetic resonance imaging proton density fat fraction and liver fat volume, therefore we could not assessed the effect of SGLT2Is on hepatic fibrosis and hepatic fat content. Notwithstanding these limitations, this study suggests that more higher quality randomized trials testing the effect of Dapagliflozin and Canagliflozin on hepatic enzyme levels reduction are needed to address these uncertainties and to better understand the differences between SGLT2Is effectiveness. There is also a need for large randomized trials that assess more patients so that a conclusive statement can be made.

Trial sequential analysis also shows that the evidence is still inconclusive for the use of these SGLT2Is to improve liver function parameters. Therefore, more studies are needed before any recommendations are made in regard to using SGLT2s as a treatment of NAFLD/NASH. However, with the results obtained from this study, promise holds that SGLT2 inhibitors may be the answer to the yet non-curative NAFLD/NASH.

5. CONCLUSION

This study indicated that Canagliflozin but not Dapagliflozin is effective to improve ALT, AST and GTT among patients with diabetes suggesting them may be useful in the management of diabetes with fatty liver.

Abbreviations
ALT = alanine transaminase
AST = aspartate transaminase
GGT = gamma-glutamyl transpeptidase
GRADE = Grading of Recommendations, Assessment, Development and Evaluation
NAFLD = Non-alcoholic fatty liver disease disease
NASH = non-alcoholic steatohepatitis
RCT = Randomized controlled trials
RoB = Risk of bias
SGLT2Is = Sodium glucose cotransporter 2 inhibitors
T2DM = Type 2 diabetes mellitus
TSA = Trial sequential analysis

ACKNOWLEDGMENT

Funding
This research received no external funding.

Conflicts of Interest
The authors declare that they have no competing interests.

Author statements
NKD was the principal coordinating investigator. He conceived the study, reviewed the scientific literature together with ID and MJS. NKV, SMC and SKV were responsible for study design and data interpretation, writing and reviewing of the report together with FKH. KWL is the first author and takes overall responsibility for the data analysis and report writing. He affirms that the manuscript is

an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained. SMC, SKV, FKH, ID and MJS were study investigators and contributed to study design, data collection and interpretation and reviewed the report. All authors approved the final version of the report.

Data Statement section

Data are available on reasonable request. The datasets analysed for the results presented in this article are available from the corresponding author.

REFERENCES

1. Saponaro C, Gaggini M, Gastaldelli A (2015) Nonalcoholic fatty liver disease and type 2 diabetes: common pathophysiologic mechanisms. Current diabetes reports 15: 34.
2. Wong VW-S, Wong GL-H, Choi PC-L, Chan AW-H, Li MK-P, et al. (2010) Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut 59: 969-974.
3. Gramlich T, Kleiner DE, McCullough AJ, Matteoni CA, Boparai N, et al. (2004) Pathologic features associated with fibrosis in nonalcoholic fatty liver disease. Human pathology 35: 196-199.
4. Oseini AM, Sanyal AJ (2017) Therapies in non-alcoholic steatohepatitis (NASH). Liver International 37: 97-103.
5. Bondini S, Younossi Z (2006) Non-alcoholic fatty liver disease and hepatitis C infection. Minerva gastroenterologica e dietologica 52: 135-143.
6. Sanyal A (2005) non-alcoholic fatty liver disease and hepatitis C–risk factors and clinical implications. Alimentary pharmacology & therapeutics 22: 48-51.
7. Seko Y, Sumida Y, Tanaka S, Mori K, Taketani H, et al. (2017) Effect of sodium glucose cotransporter 2 inhibitor on liver function tests in Japanese patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus. Hepatology Research 47: 1072-1078.
8. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, et al. (2004) A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 39: 188-196.
9. Loomba R, Lutchman G, Kleiner D, Ricks M, Feld J, et al. (2009) Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis. Alimentary pharmacology & therapeutics 29: 172-182.
10. Iwasaki T, Yoneda M, Inamori M, Shirakawa J, Higurashi T, et al. (2011) Sitagliptin as a novel treatment agent for non-alcoholic Fatty liver disease patients with type 2 diabetes mellitus. Hepato-gastroenterology 58: 2103-2105.
11. Hookman P, Barkin JS (2003) Current biochemical studies of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) suggest a new therapeutic approach. The American journal of gastroenterology 98: 495.
12. Brunton S (2015) The potential role of sodium glucose co-transporter 2 inhibitors in the early treatment of type 2 diabetes mellitus. International journal of clinical practice 69: 1071-1087.
13. Malaysia MoH (2015) Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus. CPG Secretariat, Health Technology Assessment Section, Medical Development ….
14. Fonseca VA (2014) New developments in diabetes management: medications of the 21st century. Clinical therapeutics 36: 477-484.
15. Kuchay MS, Krishan S, Mishra SK, Farooqui KJ, Singh MK, et al. (2018) Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT Trial). Diabetes care 41: 1801-1808.
16. Ito D, Shimizu S, Inoue K, Saito D, Yanagisawa M, et al. (2017) Comparison of ipragliflozin and pioglitazone effects on nonalcoholic fatty liver disease in patients with type 2 diabetes: a randomized, 24-week, open-label, active-controlled trial. Diabetes care 40: 1364-1372.

17. Shibuya T, Fushimi N, Kawai M, Yoshida Y, Hachiya H, et al. (2018) Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: a prospective randomized controlled pilot study. Diabetes, Obesity and Metabolism 20: 438-442.
18. Eriksson JW, Lundkvist P, Jansson P-A, Johansson L, Kvarnström M, et al. (2018) Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetologia 61: 1923-1934.
19. Ohki T, Isogawa A, Toda N, Tagawa K (2016) Effectiveness of ipragliflozin, a sodium-glucose co-transporter 2 inhibitor, as a second-line treatment for non-alcoholic fatty liver disease patients with type 2 diabetes mellitus who do not respond to incretin-based therapies including glucagon-like peptide-1 analogs and dipeptidyl peptidase-4 inhibitors. Clinical drug investigation 36: 313-319.
20. Seko Y, Sumida Y, Tanaka S, Mori K, Taketani H, et al. (2017) Effect of sodium glucose cotransporter 2 inhibitor on liver function tests in Japanese patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus. Hepatology Research 47: 1072-1078.
21. Gautam A, Agrawal PK, Doneria J, Nigam A (2018) Effects of Canagliflozin on Abnormal Liver Function Tests in Patients of Type 2 Diabetes with Non-Alcoholic Fatty Liver Disease. Journal of The Association of Physicians of India 66: 62-65.
22. Sumida Y, Murotani K, Saito M, Tamasawa A, Osonoi Y, et al. (2019) Effect of luseogliflozin on hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease: A prospective, single-arm trial (LEAD trial). Hepatology Research 49: 64-71.
23. Raj H, Durgia H, Palui R, Kamalanathan S, Selvarajan S, et al. (2019) SGLT-2 inhibitors in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: A systematic review. World journal of diabetes 10: 114.
24. Eriksson JW, Lundkvist P, Jansson PA, Johansson L, Kvarnstrom M, et al. (2018) Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetologia 61: 1923-1934.
25. Guja C, Repetto E, Han J, Hardy E, Jabbour SA (2018) Effect of the exenatide plus dapagliflozin combination on fatty liver index and insulin resistance in type 2 diabetes patients: The DURATION-8 trial. Diabetologia 61 (Supplement 1): S350.
26. Hayashi T, Fukui T, Nakanishi N, Yamamoto S, Tomoyasu M, et al. (2017) Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: Comparison with sitagliptin. Cardiovascular Diabetology 16 (1) (no pagination).
27. Hayashi T, Yamamoto S, Tomoyasu M, Hara N, Ohara M, et al. (2016) Dapagliflozin increases large, buoyant Ldl but reduces small, dense LDL in patients with type 2 diabetes: Comparison with Sitagliptin. Diabetes 65 (Supplement 1): A161.
28. Kusunoki M, Natsume Y, Miyata T, Tsutsumi K, Oshida Y (2018) Effects of Concomitant Administration of a Dipeptidyl Peptidase-4 Inhibitor in Japanese Patients with Type 2 Diabetes Showing Relatively Good Glycemic Control Under Treatment with a Sodium Glucose Co-Transporter 2 Inhibitor. Drug Research 02.
29. Leiter LA, Forst T, Polidori D, Balis D, Xie J, et al. (2015) Changes in liver function tests (LFTS) with canagliflozin (CANA) vs. Sitagliptin (SITA) in patients with type 2 diabetes mellitus (T2DM) are related to changes in A1c and body weight (BW). Diabetes 1): A328.
30. Leiter LA, Forst T, Polidori D, Balis DA, Xie J, et al. (2016) Effect of canagliflozin on liver function tests in patients with type 2 diabetes. Diabetes and Metabolism 42: 25-32.
31. Polidori D, Meininger G (2017) Effect of canagliflozin (CANA) on liver function tests (LFTs) in patients with type 2 diabetes mellitus (T2DM) and presumed liver fibrosis suggestive of nonalcoholic steatohepatitis (NASH). Diabetes 66 (Supplement 1): A348.

32. Shimizu M, Suzuki K, Kato K, Jojima T, Iijima T, et al. (2018) Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. Diabetes, Obesity and Metabolism.
33. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews 4: 1.
34. Jenkins WL (1955) A quick method for estimating standard deviation. Psychological Reports 1: 77-78.
35. TSA software. 0.9 beta ed. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark2011.
36. Higgin J, Green S (2011) Cochrane Handbook for Systematic reviews of Interventional version 5.10 In: Collaboration TC, editor.
37. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, et al. (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj 336: 924-926.
38. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, et al. (2011) GRADE guidelines: 2. Framing the question and deciding on important outcomes. Journal of clinical epidemiology 64: 395-400.
39. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, et al. (2011) GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology 64: 401-406.
40. Kurinami N, Sugiyama S, Yoshida A, Hieshima K, Miyamoto F, et al. (2018) Dapagliflozin significantly reduced liver fat accumulation associated with a decrease in abdominal subcutaneous fat in patients with inadequately controlled type 2 diabetes mellitus. Diabetes Research and Clinical Practice 142: 254-263.
41. Neuschwander-Tetri BA (2017) Non-alcoholic fatty liver disease. BMC medicine 15: 45.
42. Farrell GC, Wong VW-S, Chitturi S (2013) NAFLD in Asia—as common and important as in the West. Nature reviews Gastroenterology & hepatology 10: 307.
43. Hsia DS, Grove O, Cefalu WT (2017) An update on SGLT2 inhibitors for the treatment of diabetes mellitus. Current opinion in endocrinology, diabetes, and obesity 24: 73.
44. Yaribeygi H, Sathyapalan T, Maleki M, Jamialahmadi T, Sahebkar A (2020) Molecular mechanisms by which SGLT2 inhibitors can induce insulin sensitivity in diabetic milieu: A mechanistic review. Life sciences 240: 117090.
45. Tobita H, Sato S, Miyake T, Ishihara S, Kinoshita Y (2017) Effects of dapagliflozin on body composition and liver tests in patients with nonalcoholic steatohepatitis associated with type 2 diabetes mellitus: a prospective, open-label, uncontrolled study. Current Therapeutic Research 87: 13-19.
46. Akuta N, Watanabe C, Kawamura Y, Arase Y, Saitoh S, et al. (2017) Effects of a sodium-glucose cotransporter 2 inhibitor in nonalcoholic fatty liver disease complicated by diabetes mellitus: Preliminary prospective study based on serial liver biopsies. Hepatology communications 1: 46-52.
47. Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I (2016) Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. Cardiovascular diabetology 15: 37.
48. Yang X-P, Lai D, Zhong X-Y, Shen H-P, Huang Y-L (2014) Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. European journal of clinical pharmacology 70: 1149-1158.