World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2019 February 15; 10(2): 114-132

DOI: 10.4239/wjd.v10.i2.114

ISSN 1948-9358 (online)

SYSTEMATIC REVIEWS

SGLT-2 inhibitors in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: A systematic review

Henith Raj, Harsh Durgia, Rajan Palui, Sadishkumar Kamalanathan, Sandhiya Selvarajan, Sitanshu Sekhar Kar, Jayaprakash Sahoo

ORCID number: Henith Raj (0000-0002-1499-4021); Harsh Durgia (0000-0002-8404-5729); Rajan Palui (0000-0002-2429-3595); Sadishkumar Kamalanathan (0000-0002-2371-0625); Sandhiya Selvarajan (0000-0002-7948-7821); Sitanshu Sekhar Kar (0000-0001-7122-523X); Jayaprakash Sahoo (0000-0002-8805-143X).

Author contributions: Raj H, Durgia H, and Palui R designed the work; Kamalanathan SK, Selvarajan S, Kar SS, and Sahoo JP interpreted the data; Raj H, Durgia H, and Palui R revised it critically for important intellectual content; Kamalanathan SK, Selvarajan S, Kar SS, and Sahoo JP drafted the work; all authors approved the final version of the manuscript.

Conflict-of-interest statement: All authors have no conflicts of interest to report.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Henith Raj, Harsh Durgia, Rajan Palui, Sadishkumar Kamalanathan, Jayaprakash Sahoo, Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India

Sandhiya Selvarajan, Department of Clinical Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India

Sitanshu Sekhar Kar, Department of Preventive and Social Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India

Corresponding author: Jayaprakash Sahoo, MD, DM, Associate Professor, Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Room No. 5444, the 4th Floor, Superspeciality block, Puducherry 605006, India. jayaprakash.s@jipmer.edu.in

Telephone: +91-9629158368

Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a common comorbidity with type 2 diabetes. The existing therapeutic options for NAFLD are not adequate. Hypocaloric diet and exercise is the cornerstone of therapy in NAFLD. Pioglitazone is the only drug recommended in diabetes patients with biopsy proven non-alcoholic steatohepatitis. The frequent coexistence of NAFLD and type 2 diabetes with their combined adverse health consequences and inadequate therapeutic options makes it necessary to search for newer alternatives.

AIM

To assess the effect of sodium glucose cotransporter-2 (SGLT-2) inhibitors on liver enzymes in type 2 diabetes patients with NAFLD.

METHODS

We searched PubMed/MEDLINE, Cochrane library, Google scholar, and Clinicaltrials.gov for the relevant articles to be included in this systematic review. Human studies done in type 2 diabetes patients with NAFLD treated with SGLT-2 inhibitors for at least 12 wk were included. Data from eight studies (four randomised controlled trials and four observational studies) were extracted and a narrative synthesis was done. A total of 214 patients were treated with SGLT-2 inhibitors in these studies (94 in randomised controlled trials and 120 in observational studies).

Manuscript source: Invited manuscript

Received: October 5, 2018
Peer-review started: October 6, 2018
First decision: November 15, 2018
Revised: December 14, 2018
Accepted: December 29, 2018
Article in press: December 30, 2018
Published online: February 15, 2019

RESULTS

The primary outcome measure was change in serum alanine aminotransferase level. Out of eight studies, seven studies showed a significant decrease in serum alanine aminotransferase level. Most of the studies revealed reduction in serum level of other liver enzymes like aspartate aminotransferase and gamma glutamyl transferase. Five studies that reported a change in hepatic fat exhibited a significant reduction in hepatic fat content in those treated with SGLT-2 inhibitors. Likewise, among the three studies that evaluated a change in indices of hepatic fibrosis, two studies revealed a significant improvement in liver fibrosis. Moreover, there was an improvement in obesity, insulin resistance, glycaemia, and lipid parameters in those subjects taking SGLT-2 inhibitors. The studies disclosed that about 17% (30/176) of the subjects taking SGLT-2 inhibitors developed adverse events and more than 40% (10/23) of them had genitourinary tract infections.

CONCLUSION

Based on low to moderate quality of evidence, SGLT-2 inhibitors improve the serum level of liver enzymes, decrease liver fat, and fibrosis with additional beneficial effects on various metabolic parameters in type 2 diabetes patients with NAFLD.

Key words: Alanine aminotransferase; Hepatic fat; Hepatic fibrosis; Non-alcoholic fatty liver disease; Sodium-glucose cotransporter-2 inhibitor; Type 2 diabetes mellitus

Core tip: The frequent coexistence of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes, their adverse health consequences, and lack of adequate therapeutic options makes it necessary to search for newer alternatives. Currently, pioglitazone and vitamin E are recommended in addition to lifestyle modifications for the management of NAFLD. Animal studies have shown that sodium glucose cotransporter-2 inhibitors might be beneficial in NAFLD present in diabetes patients. The current systematic review shows that sodium glucose cotransporter-2 inhibitors improve the serum level of liver enzymes, liver fat, and liver fibrosis with additional beneficial effects on various metabolic parameters in type 2 diabetes patients with NAFLD.

Citation: Raj H, Durgia H, Palui R, Kamalanathan S, Selvarajan S, Kar SS, Sahoo J. SGLT-2 inhibitors in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: A systematic review. *World J Diabetes* 2019; 10(2): 114-132
URL: https://www.wjgnet.com/1948-9358/full/v10/i2/114.htm
DOI: https://dx.doi.org/10.4239/wjd.v10.i2.114

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an emerging public health issue worldwide. The prevalence of NAFLD in type 2 diabetes mellitus patients is three times greater as compared to the general population. Its prevalence in diabetic subjects ranges from 69%-87% depending upon the imaging modality used[1]. The spectrum of NAFLD includes simple steatosis, steatohepatitis, and cirrhosis[2]. Besides NAFLD is a risk factor for extrahepatic complications like cardiovascular disease, chronic kidney disease, and type 2 diabetes. In addition, the prevalence of both microvascular and macrovascular complications is increased in patients with NAFLD and type 2 diabetes[3].

The existing therapeutic options for NAFLD are not adequate. Hypocaloric diet and exercise is the cornerstone of therapy in NAFLD. Pioglitazone and vitamin E are recommended only in biopsy-proven non-alcoholic steatohepatitis (NASH), but vitamin E is not recommended in diabetic patients due to inadequate evidence[4]. The frequent coexistence of NAFLD and type 2 diabetes with their combined adverse health consequences and inadequate therapeutic options makes it necessary to search for newer alternatives. Based on the information from animal studies, sodium glucose

cotransporter-2 (SGLT-2) inhibitors appear promising in the management of NAFLD[5-7]. This systematic review is an effort to review the available literature on the effect of SGLT-2 inhibitors on NAFLD in type 2 diabetes patients.

MATERIALS AND METHODS

Protocol and registration

This systematic review was performed according to the predefined protocol registered in PROSPERO (Registration ID: CRD42018104572). The protocol can be accessed at the website address https://www.crd.york.ac.uk/prospero. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2009 guidelines for reporting this systematic review[8]. Ethics committee approval was not required for this systematic review because it was done using published data found in the public domain.

Eligibility criteria

All observational and randomised controlled trials (RCTs) done using SGLT-2 inhibitors among type 2 diabetes patients with NAFLD having both baseline and post-treatment serum alanine aminotransferase (ALT) level data with a minimum follow-up duration of 12 wk were included in this systematic review. The studies with concomitant pharmacological therapy like pioglitazone or α-tocopherol (vitamin E) for treating NAFLD were excluded to avoid the confounding effects of these drugs on liver function tests. Only those studies that were done in humans and published in English were considered for inclusion. We excluded abstract-only articles, case reports, conference presentations, editorials, reviews, expert opinions, and studies with five participants and less.

Primary and secondary outcomes

The primary outcome was the change in serum ALT levels in type 2 diabetes patients with NAFLD treated with SGLT-2 inhibitors. The secondary outcomes were change in serum aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) levels, hepatic fat, hepatic fibrosis, metabolic profile, anthropometric parameters, and the adverse effects of SGLT-2 inhibitors.

Information sources

PubMed/MEDLINE, Cochrane library, Google scholar, and Clinicaltrials.gov were searched from their date of inception until 31st August, 2018.

Literature search and study selection

The search terms/MeSH terms used were "NAFLD", "Nonalcoholic fatty liver disease", "Non-alcoholic fatty liver disease", "Non alcoholic fatty liver disease", "NASH", "Non-alcoholic steatohepatitis", "Nonalcoholic steatohepatitis", "Non alcoholic steatohepatitis", "Fatty liver", "Type 2 diabetes mellitus", "Type 2 diabetes", "Diabetes mellitus type 2", "Diabetes type 2", "SGLT-2 inhibitors", "Sodium glucose cotransporter-2 inhibitors", "SGLT-2", "SGLT2", "SGLT 2", "Canagliflozin", "Dapagliflozin", "Empagliflozin", "Ipragliflozin", "Luseogliflozin", "Tofogliflozin", "Sotagliflozin", "Remogliflozin", "Ertugliflozin", and "Sergliflozin"(Table 1). The references of the search articles were scrutinised for relevant articles.

Data collection process

The titles and/or abstracts of studies were retrieved using the search strategy and those from additional sources were scrutinised independently by two review authors (HR and JPS) to identify studies that potentially met the inclusion criteria as outlined above. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by three review team members (HD, SS, and RP). Any disagreements between the reviewers over the eligibility of particular studies were resolved through discussion with a fourth senior reviewer (SKK). A standardised, pre-formatted excel form was used to extract data from the included studies for the assessment of study quality.

Data items and synthesis of results

The extracted data included the author of the study with year, the study methodology, the recruitment and study completion rates, the types of population, the exposure/intervention (dose of SGLT-2 inhibitor, duration), the results (outcome measures like change in serum ALT, AST, GGT, hepatic fat, markers of liver fibrosis, fasting plasma glucose (FPG), glycosylated haemoglobin (HbA1c), lipid profile, homeostasis model assessment-estimated insulin resistance (HOMA-IR), body mass

Table 1 Literature search strategy

S. No	Search terms
1	NAFLD
2	Nonalcoholic fatty liver disease
3	Non-alcoholic fatty liver disease
4	Non alcoholic fatty liver disease
5	NASH
6	Non-alcoholic steatohepatitis
7	Nonalcoholic steatohepatitis
8	Non alcoholic steatohepatitis
9	Fatty liver
10	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
11	Type 2 diabetes mellitus
12	Type 2 diabetes
13	Diabetes mellitus type 2
14	Diabetes type 2
15	11 OR 12 OR 13 OR 14
16	SGLT-2 inhibitors
17	Sodium glucose cotransporter-2 inhibitors
18	SGLT-2
19	SGLT2
20	SGLT 2
21	Canagliflozin
22	Dapagliflozin
23	Empagliflozin
24	Ipragliflozin
25	Luseogliflozin
26	Tofogliflozin
27	Sotagliflozin
28	Remogliflozin
29	Ertugliflozin
30	Sergliflozin
31	16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30
32	10 AND 15 AND 31

NAFLD: Non-alcoholic fatty liver disease; NASH: Non alcoholic steatohepatitis; SGLT-2: Sodium glucose cotransporter-2.

index (BMI), any adverse effects, information for the assessment of the risk of bias, and sources of funding/support.

The statistical review of the study was performed by a biomedical statistician (SSK). A narrative synthesis of the results of individual studies was done. The change in the difference in means and difference in proportions and the respective *P* values as mentioned in the original manuscripts were tabulated and explained in our study.

Risk of study bias

The risk of bias of the RCTs was done using Cochrane risk of bias tool[9]. The studies were graded as "good quality" or "fair quality" or "poor quality" according to the level of risk. Methodological Index for Non-Randomized Studies (MINORS) scale was used to assess the risk of bias of observational studies[10]. A study was considered to be an ideal study if the score was 16 for single arm and 24 for comparative studies.

RESULTS

Study selection

Our literature search from all the aforementioned databases yielded 73 articles (including references of the relevant articles). After eliminating duplicate articles, 55

articles were screened. Eight articles met all of the inclusion criteria (total 214 patients were on SGLT-2 inhibitors) (Figure 1).

Study characteristics

The summary of all studies included in this systematic review is given in Tables 2 and 3. Out of the eight studies, four are RCTs[11-14] and four are observational[15-18]. Five studies were conducted amongst the Japanese population. Ipragliflozin was used in three studies whereas canagliflozin and luseogliflozin were used in two studies each, but dapagliflozin and empagliflozin were used in one study each. All studies used one type of SGLT-2 inhibitor except the one authored by Seko *et al*[16], where both canagliflozin and ipragliflozin were used. The change in serum ALT was a secondary outcome while the effect of SGLT- 2 inhibitors on liver fat was the primary outcome in all RCTs.

Risk of bias within studies

The risk of bias of RCTs was assessed using the Cochrane risk of bias tool. Among the four RCTs, the studies done by Kuchay *et al*[11] and Eriksson *et al*[14] were of good quality however those done by Ito *et al*[12] and Shibuya *et al*[13] were of fair quality (Table 4). The risk of bias of observational studies was assessed using the MINORS scale. All the observational studies were of less than ideal quality (Table 5).

Primary outcome

Change in serum ALT levels: In all of the studies, there was a decrease in serum ALT levels from the baseline in those treated with SGLT-2 inhibitors (Table 6) but in the study done by Shibuya *et al*[13] it did not reach statistical significance.

Kuchay *et al*[11] found a significant decrease in serum ALT levels in the empagliflozin arm compared to the control arm at the end of the study (difference between the two arms was -10.9 IU/L, $P = 0.005$). In the study done by Ito *et al*[12] ALT levels decreased equally in both the groups [Change from baseline in ipragliflozin group: -17.5 (4) and pioglitazone group: -20 (3.4), $P = 0.642$]. Similar results were found in the study by Shibuya *et al*[13] [ΔALT in luseogliflozin arm was 9 (-20, 1) and in metformin arm was 4.5 (-5, 9), $P = 0.064$]. Eriksson *et al*[14] found that the ALT reduction in the dapagliflozin arm was more compared to placebo [ΔALT in dapagliflozin arm was -8.24 (8.24) and in the placebo arm was -0.18 (8.82), $P < 0.05$]. Seko *et al*[16] demonstrated that the serum ALT levels in SGLT-2 inhibitor arm was lower compared to the sitagliptin arm at the end of the study [48.8 (5.5) *vs* 71.1 (10), $P = 0.039$]

Secondary outcomes

Change in serum AST levels: Seven of the included studies had data regarding change in serum AST levels (Table 7). The study done by Shibuya *et al*[13] did not have data on AST levels. All the studies showed a significant reduction in serum AST levels in those treated with SGLT-2 inhibitors. The decrease in AST with empagliflozin and ipragliflozin was similar compared to placebo and pioglitazone respectively whereas dapagliflozin was better than placebo.

Change in serum GGT levels: Seven studies had data regarding GGT levels. Six studies reported a significant decrease in serum GGT levels in those treated with SGLT-2 inhibitors (Table 8). In the study done by Seko *et al*[16], there was an insignificant decrease in both the SGLT-2 inhibitor and DPP-4 inhibitor groups. The decrease in GGT with empagliflozin and ipragliflozin was similar compared to placebo and pioglitazone correspondingly while dapagliflozin was better than placebo.

Change in hepatic fat: Kuchay *et al*[11] and Eriksson *et al*[14] evaluated hepatic fat using magnetic resonance imaging- derived proton density fat fraction (Table 9). It was found that there was a significant reduction in hepatic fat in the empagliflozin arm compared to the control arm in the study done by Kuchay *et al*[11]. In the study done by Eriksson *et al*[14], dapagliflozin or omega-3 carboxylic acid when administered alone or in combination reduced hepatic fat fraction significantly. When compared with placebo, only the combination of both drugs reduced hepatic fat fraction significantly. Sumida *et al*[18] showed that luseogliflozin significantly reduced hepatic fat fraction using magnetic resonance imaging-hepatic fat fraction. Ito *et al*[12] and Shibuya *et al*[13] used liver/spleen attenuation ratio for measuring hepatic fat. They found that ipragliflozin was equivalent to pioglitazone in improving liver/spleen attenuation ratio while luseogliflozin was found to be superior to metformin in the same aspect.

Effect on liver fibrosis indices

Ito *et al*[12] and Ohki *et al*[15] evaluated liver fibrosis using the FIB-4 index (Table 10).

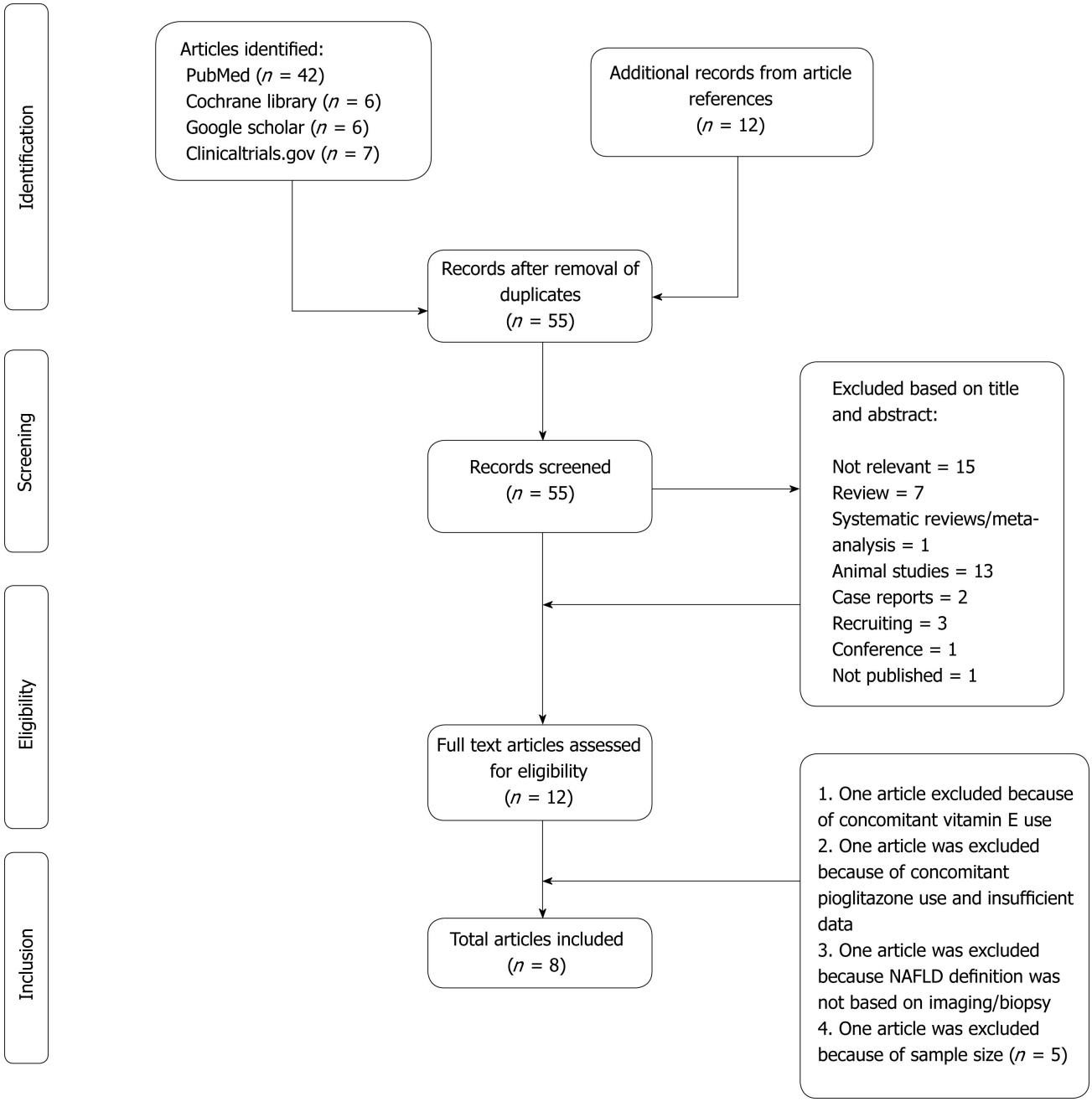

Figure 1 Literature search and study selection.

There was a significant decrease in the FIB-4 index in the ipragliflozin arms compared to baseline. Ipragliflozin was similar to pioglitazone in decreasing the FIB-4 index. Sumida *et al*[18] used both the FIB-4 index and NAFLD fibrosis score. There was no significant change in either indices.

Change in metabolic and anthropometric parameters

Seven studies reported changes in FPG and HbA1c (Tables 11 and 12). The majority of the studies showed a decrease in FPG and HbA1c.

In the study done by Ito *et al*[12] there was no difference in the change in HOMA-IR in those treated with either ipragliflozin or pioglitazone (P = 0.401) (Table 13). There was a significant decrease in HOMA-IR in those treated with dapagliflozin compared to placebo in the study done by Eriksson *et al*[14]. Surprisingly there was an insignificant increase in HOMA-IR in those treated with either a SGLT-2 inhibitor or a gliptin in the study done by Seko *et al*[16].

Six studies included data on the changes in lipid profile (Tables 14, 15, and 16). There was a significant decrease in serum triglycerides in two studies (Kuchay *et al*[11] and Ito *et al*[12]). Three studies exhibited an increase in high-density lipoprotein cholesterol levels (Ito *et al*[12], Ohki *et al*[15], and Seko *et al*[16]). Most of the studies (Ito *et*

Table 2 Randomised controlled trials

S. No	Ref.	Inclusion criteria	Age (yr)	Male gender	Intervention arm	Control arm	Follow-up duration	Primary outcome
1	Kuchay *et al*[11], 2018	Age > 20 yr, hepatic steatosis (MRI-PDFF > 6%), HbA1c > 7.0% to < 10.0%	Intervention arm: 50.7 (12.8) Control arm: 49.1 (10.3)	Intervention arm: 16 (64%) Control arm: 17 (68%)	Standard treatment + Empagliflozin 10 mg daily (*n* = 25)	Standard treatment (*n* = 25)	20 wk	Change in liver fat content by MRI-PDFF
2	Ito *et al*[12], 2017	Age 20-75 yr, HbA1c 7.0–11.0%, BMI < 45 kg/m^2, On diet and exercise therapy alone or with oral hypoglycaemic agents other than SGLT-2 inhibitors and thiazolidinediones and/or insulin, NAFLD, findings suggesting hepatic steatosis and hepatic dysfunction on clinical laboratory tests or on imaging studies (*e.g.*, computed tomography or ultrasound)	Pioglitazone arm: 59.1 (9.8) Ipragliflozin arm: 57.3 (12.1)	Pioglitazone arm: 18 (53%) Ipragliflozin arm: 14 (44%)	Ipragliflozin 50 mg daily (*n* = 32)	Pioglitazone 15-30 mg daily (*n* = 34)	24 wk	Change in L/S attenuation ratio
3	Shibuya *et al*[13], 2018	Fatty liver diagnosed on the basis of computed tomography or abdominal sonography, HbA1c 6.0%–10.0%, age 20–70 yr	Luseogliflozin arm: 51 (47-62) Metformin arm: 60 (53-66)	Luseogliflozin arm: 10 (62.5%) Metformin arm: 8 (50%)	Luseogliflozin 2.5 mg daily (*n* = 16)	Metformin 1.5 g daily (*n* = 16)	24 wk	Change in L/S attenuation ratio
4	Eriksson *et al*[14], 2018	Age 40–75 yr, treated with a stable dose of metformin or sulfonylurea alone or in combination for at least 3 mo, MRI-PDFF > 5.5%, BMI 25–40 kg/m^2	Dapagliflozin arm: 65 (6.5) Omega 3-carboxylic acid arm: 66.2 (5.9) O + D arm: 65(5.4) Placebo arm: 65.6 (6.1)	Dapagliflozin arm: 16 (76.2%) Omega 3-carboxylic acid arm: 11 (55%) O + D arm: 15 (68.2%) Placebo arm: 17 (81%)	Dapagliflozin 10 mg daily (*n* = 21) or Omega 3-carboxylic acid 4 g daily (*n* = 20) or Combination (*n* = 22)	Placebo (*n* = 21)	12 wk	Change in liver fat content by MRI-PDFF

MRI-PDFF: Magnetic resonance imaging-derived proton density fat fraction; L/S: Liver/spleen; O + D: Omega 3-carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2; NAFLD: Non-alcoholic fatty liver disease.

al[12], Eriksson *et al*[14], Ohki *et al*[15], Seko *et al*[16], and Sumida *et al*[18]) showed no change in serum LDL levels.

Five studies included BMI change (Table 17). There was a reduction in BMI in the SGLT-2 inhibitor arms in all the studies. Empagliflozin was similar to placebo in reducing BMI whereas luseogliflozin was superior to metformin in reducing BMI.

Adverse effects of SGLT-2 inhibitors

Out of the eight studies, six studies reported the adverse effects of SGLT-2 inhibitors. There were a total of 30 reported adverse events in 176 patients taking SGLT-2

Table 3 Observational studies

S. No	Ref.	Design	Inclusion criteria	Age (yr)	Male gender	Sample size	SGLT-2 inhibitor	Follow-up duration
1	Ohki *et al*[15], 2016	Prospective study	Type 2 diabetes with NAFLD treated with GLP-1 analogues or DPP-4 inhibitors and failed to normalise serum ALT levels	54.2 (49.3-60.1)	19 (79.2%)	24	Ipragliflozin 25-50 mg daily	320 d (302-329)
2	Seko *et al*[16], 2016	Retrospective cohort study	Type 2 diabetes with NAFLD	SGLT-2 inhibitor arm: 60.3 (1.8) Sitagliptin arm: 59.4 (3.7)	SGLT-2 inhibitor arm: 9 (37.5%) Sitagliptin arm: 8 (38.1%)	24 (SGLT-2 inhibitor); 21 (Sitagliptin)	Canagliflozin 100 mg (n = 18) or Ipragliflozin 50 mg daily (n = 6)	24 wk
3	Gautam *et al*[17], 2018	Prospective study	Type 2 diabetes with NAFLD	-	-	32	Canagliflozin 100 mg daily	24 wk
4	Sumida *et al*[18], 2018	Prospective study	Age > 20 yr, HbA1c > 6.5% to < 8.5%, NAFLD	55.4 (13.6)	28 (70%)	40	Luseogliflozin 2.5 mg daily	24 wk

NAFLD: Non-alcoholic fatty liver disease; SGLT-2: Sodium glucose cotransporter-2; GLP-1: Glucagon like peptide-1; DPP-4: Dipeptidyl peptidase-4.

inhibitors (Table 18). The most common adverse event was genitourinary tract infection (10 events).

DISCUSSION

Type 2 diabetes is commonly associated with NAFLD. Serum ALT levels are commonly above the upper limit of normal with AST levels lesser than ALT levels[19]. Animal studies have shown that SGLT-2 inhibitors decrease liver enzymes (ALT, AST), liver weight, and hepatic steatosis[20-23]. There are several mechanisms for improvement in serum liver enzymes in the patients taking SGLT-2 inhibitors. These drugs cause hyperglucagonemia by increasing glucagon secretion from the pancreatic α cells. Glucagon stimulates gluconeogenesis and β-oxidation of fatty acids in the liver via stimulation of peroxisome proliferator-activated receptor alpha and carnitine palmitoyl transferase-1[13]. Thus SGLT-2 inhibitors help to reduce hepatic fat. They reduce collagen deposition and inflammatory cytokine expression in liver[5,22]. They decrease liver enzymes by additionally improving glycaemic parameters and insulin resistance. Out of eight studies, seven showed a decrease in serum ALT and AST levels in our systematic review. Shibuya *et al*[13] observed a decrease in ALT that almost reached statistical significance, however data regarding AST was unavailable[13]. Out of seven studies, six illustrated a significant decrease in GGT levels while in the study by Seko *et al*[16] the change in serum GGT level almost reached statistical significance.

Liver enzymes are surrogate markers of liver histological response, but an improvement in liver histology is not always associated with a decrease in serum liver enzymes[11]. The five studies that evaluated changes in hepatic fat showed a decrease in hepatic fat. There was no correlation of a change in ALT with a change in hepatic fat in the study by Shibuya *et al*[13], however there was a correlation between these two parameters in the study by Sumida *et al*[18]. The decrease in hepatic fat in the SGLT-2 inhibitor arm was comparable to pioglitazone, which is an approved drug for treatment of NAFLD irrespective of the presence of diabetes. Eriksson *et al*[14] observed that although the hepatic fat content decreased in the dapagliflozin arm it did not reach statistical significance compared to placebo. The lesser duration of this study (12 wk) compared to other studies may have contributed to this difference.

The progression of NAFLD to cirrhosis is determined to a large extent by the liver histology. Studies with up to 20 years follow-up have shown that the risk of progression to cirrhosis for simple steatosis, NASH, and NASH with fibrosis are 0%-4%, 25%, and 38%, respectively[24]. The FIB-4 index is a non-invasive tool to assess liver

Table 4 Assessment of study quality of randomised controlled trials

Study	Criteria	Risk of bias	Study quality
Kuchay *et al*[11]	Random sequence generation	Low risk	Good quality
	Allocation concealment	Low risk	
	Selective reporting	Low risk	
	Other bias	Low risk	
	Blinding of participants and personnel	Low risk	
	Blinding of outcome assessment	Low risk	
	Incomplete outcome data	Low risk	
Ito *et al*[12]	Random sequence generation	Low risk	Fair quality
	Allocation concealment	Unclear risk	
	Selective reporting	Low risk	
	Other bias	Low risk	
	Blinding of participants and personnel	Low risk	
	Blinding of outcome assessment	Low risk	
	Incomplete outcome data	Low risk	
Shibuya *et al*[13]	Random sequence generation	Unclear risk	Fair quality
	Allocation concealment	Unclear risk	
	Selective reporting	Low risk	
	Other bias	Low risk	
	Blinding of participants and personnel	Low risk	
	Blinding of outcome assessment	Low risk	
	Incomplete outcome data	Low risk	
Eriksson *et al*[14]	Random sequence generation	Low risk	Good quality
	Allocation concealment	Low risk	
	Selective reporting	Low risk	
	Other bias	Low risk	
	Blinding of participants and personnel	Low risk	
	Blinding of outcome assessment	Low risk	
	Incomplete outcome data	Low risk	

fibrosis[25]. It is calculated from the patient's age, platelet count, ALT levels, and AST levels. The FIB-4 index was decreased with SGLT-2 inhibitor therapy in two out of three studies. Sumida *et al*[18] used the NAFLD fibrosis score in addition to the FIB-4 index to assess liver fibrosis. The NAFLD fibrosis score is a composite score of six variables (age, BMI, hyperglycaemia, platelet count, albumin, and AST/ALT ratio)[26]. There was no significant change in either indices in this study.

It has been shown that NAFLD is more common in those with poor glycaemic control than those with good glycaemic control[27]. SGLT-2 inhibitors promote glycosuria by inhibiting SGLT-2 in the proximal convoluted tubule. Therefore their action is dependent on blood glucose levels but insulin independent[28]. They cause a significant reduction in FPG[29]. A meta-analysis of RCTs has concluded that the average HbA1c reduction at 52 wk of SGLT-2 inhibitor therapy to be 0.6%[30]. Another meta-analysis has shown that SGLT-2 inhibitor monotherapy is equivalent to metformin monotherapy in reducing HbA1c levels[31]. However, the decrease in HbA1c was more in the luseogliflozin arm compared to the metformin arm in the study by Shibuya *et al*[13]. Four out of seven studies and six out of seven studies showed a decrease in FPG and HbA1c, respectively, in the SGLT-2 inhibitor arm. Thus, the improved glycaemic status is one of the mechanisms by which SGLT-2 inhibitors ameliorate NAFLD.

SGLT-2 inhibitors ameliorate insulin resistance in numerous ways. SGLT-2 inhibitors improve obesity associated insulin resistance by regulating macrophage

Table 5 Assessment of study quality of observational studies

S. No	Criteria	Ohki *et al*[15]	Seko *et al*[16]	Gautam *et al*[17]	Sumida *et al*[18]
1	A clearly stated aim	2	2	2	2
2	Inclusion of consecutive patients	0	2	2	1
3	Prospective collection of data	2	0	2	2
4	Endpoints appropriate to the aim of the study	2	2	2	2
5	Unbiased assessment of the study endpoint	0	0	0	0
6	Follow-up period appropriate to the aim of the study	2	2	2	2
7	Loss to follow up less than 5%	2	2	2	2
8	Prospective calculation of the study size	0	0	0	0
9	An adequate control group	NA	0	NA	NA
10	Contemporary groups	NA	2	NA	NA
11	Baseline equivalence of groups	NA	2	NA	NA
12	Adequate statistical analyses	NA	2	NA	NA
13	Total score	10/16	16/24	12/16	11/16

recruitment and altering the proportion of pro-inflammatory and anti-inflammatory macrophages. They enhance fat utilization by promoting β-oxidation of fatty acids and browning of white adipose tissue by inducing the expression of thermogenin leading to an improvement in the lipid profile. Similar to other antidiabetic drugs, SGLT-2 inhibitors reduce insulin resistance by decreasing glucotoxicity. Dapagliflozin has been shown to improve insulin sensitivity by increasing adiponectin and zinc-A2-glycoprotein levels[32]. Only dapagliflozin was shown to decrease insulin resistance in the study by Eriksson *et al*[14].

SGLT-2 inhibitors cause weight reduction. The major mechanism that causes weight reduction is the decrease in fat mass. The decrease in fat mass is due to the shift in substrate utilization to lipids instead of carbohydrates[33,34]. Ito *et al*[12] and Shibuya *et al*[13] demonstrated that SGLT-2 inhibitors caused a significant reduction in abdominal visceral and subcutaneous fat area as measured by computed tomography scan. Similarly, Eriksson *et al*[14] showed that dapagliflozin significantly reduced abdominal visceral and subcutaneous adipose tissue volume as assessed by magnetic resonance imaging. The other mechanisms of weight loss are the urinary glucose loss which amounts to approximately 200 Kcal/d and osmotic diuresis[33,35]. Unlike the other weight-reducing effects of SGLT-2 inhibitors, which are potentially beneficial, osmotic diuresis is clearly an adverse effect. Seko *et al*[16] showed that ipragliflozin and canagliflozin significantly reduced total body water in addition to body fat mass as measured by bioelectrical impedance analysis. Five studies showed a significant decrease in BMI in patients on SGLT-2 inhibitor therapy. Thus, the major beneficial effects of SGLT-2 inhibitors on NAFLD are exerted via reduction in hepatic fat and fibrosis, improved glycaemic control, decrease in insulin resistance, and weight loss.

The most common adverse effects of SGLT-2 inhibitors are genitourinary tract infections. In addition, they may cause diabetic ketoacidosis, dizziness, acute kidney injury, lower limb amputations, and bone fractures[36,37]. A meta-analysis concluded that there was no difference between placebo and SGLT-2 inhibitors for serious adverse events[38]. Among the 30 adverse events reported in all the studies, the most common was genitourinary tract infections (10 out of 23 characterised events).

The major strength of this systematic review was that the effect of five SGLT-2 inhibitors on NAFLD in patients with type 2 diabetes was evaluated in both RCTs and observational studies. Moreover, liver fat, liver fibrosis, metabolic, and anthropometric parameters in addition to liver enzymes were assessed as outcome variables following SGLT-2 inhibitor therapy. Yet this systematic review has a few limitations. First, most of the studies were done amongst the Japanese population. As a result, the study findings may not be applicable to patients from other ethnicities. Second, the sample size was considerably small and the duration of follow-up was of limited period in most of the studies. Third, the confounding effect of concomitant anti-diabetes drugs like metformin, DPP- 4 inhibitors, and glucagon like peptide-1 analogues on NAFLD cannot be ruled out, particularly in observational studies. Fourth, two studies (Eriksson *et al*[14] and Sumida *et al*[18]) were funded by pharmaceutical companies, which is a source of potential conflicts of interest.

Summary and conclusion

In conclusion based on the available evidence, SGLT-2 inhibitors were found to

Table 6 Change in serum alanine aminotransferase levels in individual studies

Study	Serum ALT level (IU/L)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	64.3 (20.2)	49.7 (25.8)	0.001	0.005
	Control	65.3 (40.3)	61.6 (38.4)	0.422	
Ito *et al*[12]	Ipragliflozin	57.4 (27.3)	38.2 (20.5)	< 0.05	0.642
	Pioglitazone	53.1 (26.6)	36.8 (15.1)	< 0.05	
Shibuya *et al*[13]	Luseogliflozin	49.5 (31.0, 70.0)	31 (26.0, 55.0)	0.057	0.064
	Metformin	39 (23.0, 56.0)	39 (27.0, 51.0)	0.518	
Eriksson *et al*[14]	Placebo	33.53 (12.4)	-0.2 (8.8)[1]	-	-
	Omega-3 CA	37.65 (14.7)	+5.9 (16.5)[1]	-	Non-significant[2]
	Dapagliflozin	39.41 (14.7)	-8.2 (8.2)[1]	-	< 0.05[2]
	O + D	35.88 (17.1)	+0.1 (12.9)[1]	-	Non-significant[2]
Ohki *et al*[15]	Ipragliflozin	62 (43.0-75.0)	38.0 (31.0-65.0)	0.01	-
Seko *et al*[16]	SGLT-2 inhibitor	70.8 (8.1)	48.8 (5.5)	0.002	0.039
	Sitagliptin	92.4 (11.2)	71.1 (10.0)	0.012	
Gautam *et al*[17]	Canagliflozin	96 (18.7)	60.0 (17.6)	< 0.00001	-
Sumida *et al*[18]	Luseogliflozin	54.7 (28.2)	42.4 (26.5)	< 0.001	-

[1]Change from baseline.
[2]Compared to placebo.
ALT: Alanine aminotransferase; CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

improve serum levels of liver enzymes, liver fibrosis indices, and liver fat without significant side effects in type 2 diabetes patients with NAFLD. They showed additional beneficial effects on obesity, glycaemic parameters, insulin resistance, and dyslipidaemia in these subjects. However, the quality of evidence was low to moderate. Prospective studies, preferably RCTs, comparing different SGLT-2 inhibitors with standard treatments of NAFLD in multi-ethnic populations with a longer follow-up period are needed in the future.

Table 7 Change in serum aspartate aminotransferase levels in individual studies

Study	Serum AST levels (IU/L)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	44.6 (23.5)	36.2 (9.0)	0.04	0.212
	Control	45.3 (24.3)	44.6 (23.8)	0.931	
Ito *et al*[12]	Ipragliflozin	39.7 (16.7)	27.3 (8.9)	< 0.05	0.802
	Pioglitazone	43.3 (20.5)	32.4 (15.4)	< 0.05	
Eriksson *et al*[14]	Placebo	29.4 (13.2)	-1.2 (7.2)[1]	-	-
	Omega-3 CA	30.6 (10.2)	+4.8 (9.0)[1]	-	Non-significant[2]
	Dapagliflozin	31.2 (11.4)	-4.2 (5.4)[1]	-	< 0.05[2]
	O + D	30 (10.2)	+1.2 (5.4)[1]	-	Non-significant[2]
Ohki *et al*[15]	Ipragliflozin	37 (29.0-52.0)	28 (23.0-31.0)	0.03	-
Seko *et al*[16]	SGLT-2 inhibitor	54.4 (5.6)	38 (3.1)	0.001	-
	Sitagliptin	67 (7.7)	52.5 (7.7)	0.016	
Gautam *et al*[17]	Canagliflozin	72 (16.7)	53 (10.3)	< 0.00001	-
Sumida *et al*[18]	Luseogliflozin	40.7 (22.2)	31.9 (18.2)	< 0.001	-

[1]Change from baseline.
[2]Compared to placebo.
AST: Aspartate aminotransferase; CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 8 Change in serum gamma-glutamyl transferase levels in individual studies

Study	Serum GGT (IU/L)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	65.8 (36.1)	50.9 (24.6)	0.002	0.057
	Control	63.9 (45.3)	60.0 (39.0)	0.421	
Ito *et al*[12]	Ipragliflozin	62.8 (58.3)	44.0 (38.3)	< 0.05	0.642
	Pioglitazone	71.6 (54.1)	48.8 (61.2)	< 0.05	
Eriksson *et al*[14]	Placebo	32.4 (17.4)	+2.4 (9.6)[1]	-	-
	Omega-3 CA	54.0 (57.6)	+2.4 (12.0)[1]	-	Non-significant[2]
	Dapagliflozin	58.2 (43.2)	-4.8 (13.8)[1]	-	< 0.05[2]
	O + D	40.2 (14.4)	-0.6 (13.8)[1]	-	Non-significant[2]
Ohki *et al*[15]	Ipragliflozin	75.0 (47.0-105.0)	60.0 (40.0-101.0)	0.03	-
Seko *et al*[16]	SGLT-2 inhibitor	61.7 (9.1)	58.7 (11.5)	0.051	-
	Sitagliptin	89.2 (11.8)	82.4 (11.9)	0.36	
Gautam *et al*[17]	Canagliflozin	75.1 (31.8)	69.2 (26.2)	0.003	-
Sumida *et al*[18]	Luseogliflozin	62.4 (77.1)	48.2 (56.3)	0.003	-

[1]Change from baseline.
[2]Compared to placebo.
CA: Carboxylic acid; GGT: Gamma-glutamyl transferase; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 9 Change in hepatic fat in individual studies

Study	Parameter	Group	Baseline	Study completion	*P* value	*P* value between groups
Kuchay *et al*[11]	MRI-PDFF	Empagliflozin	16.2 (7)	11.3 (5.3)	< 0.0001	< 0.0001
		Control	16.4 (7.3)	15.5 (6.7)	0.054	
Ito *et al*[12]	L/S ratio	Ipragliflozin	0.8 (0.2)	1.0 (0.2)	< 0.05	0.90
		Pioglitazone	0.8 (0.3)	1.0 (0.2)	< 0.05	
Shibuya *et al*[13]	L/S ratio	Luseogliflozin	0.9 (0.6-1.0)	1.0 (0.8-1.2)	0.0008	0.00002
		Metformin	1.0 (0.8-1.1)	0.9 (0.7-1.0)	0.017	
Eriksson *et al*[14]	MRI-PDFF	Placebo	15.1 (6.5)	-0.6 (1.9)[1]	-	-

		Omega-3 CA	22.2 (11.0)	-3.2 (2.9)[1]	-	Non-significant[2]
		Dapagliflozin	17.3 (9.1)	-2.2 (3.3)[1]	-	Non-significant[2]
		O + D	17.8 (9.2)	-3.2 (3.5)[1]	-	< 0.05[2]
Sumida *et al*[18]	MRI-HFF	Luseogliflozin	21.5 (7.2)	15.7 (6.8)	< 0.001	-

[1]Change from baseline.
[2] Compared to placebo.
MRI-PDFF: Magnetic resonance imaging-derived proton density fat fraction; L/S ratio: Liver/spleen attenuation ratio; MRI-HFF: Magnetic resonance imaging-hepatic fat fraction; CA: Carboxylic acid; O + D: Omega-3 CA + Dapagliflozin.

Table 10 Assessment of liver fibrosis in individual studies

Study	Parameter	Group	Baseline	Study completion	*P* value	*P* value between groups
Ito *et al*[12]	FIB-4 index	Ipragliflozin	1.44 (0.64)	1.22 (0.55)	< 0.05	0.596
		Pioglitazone	1.84 (1.13)	1.71 (1.19)	Non-significant	
Ohki *et al*[15]	FIB-4 index	Ipragliflozin	1.75 (0.82-1.93)	1.39 (0.77-1.99)	0.04	-
Sumida *et al*[18]	FIB-4 index	Luseogliflozin	1.63 (1.19)	1.52 (0.92)	0.17	-
	NAFLD fibrosis score	Luseogliflozin	1.61 (0.71)	1.62 (0.88)	0.86	-

FIB: Fibrosis 4; NAFLD: Non-alcoholic fatty liver disease.

Table 11 Change in fasting plasma glucose in individual studies

Study	Fasting plasma glucose (mg/dL)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	173.0 (44.0)	124.0 (17.0)	< 0.001	0.85
	Control	176.0 (57.0)	120.0 (19.0)	< 0.0001	
Ito *et al*[12]	Ipragliflozin	160.1 (38.7)	136.5 (26.7)	< 0.05	0.785
	Pioglitazone	169.4 (50.9)	139.0 (26.6)	< 0.05	
Shibuya *et al*[13]	Luseogliflozin	127.0 (116.0, 136.0)	125.0 (113.0, 138.0)	0.87	0.583
	Metformin	147.0 (126.0, 161.0)	134.0 (122.0, 145.0)	0.32	
Eriksson *et al*[14]	Placebo	169.2 (29.7)	+6.7 (14.8)[1]	-	-
	Omega-3 CA	162.4 (26.6)	+3.8 (19.3)[1]	-	Non-significant[2]
	Dapagliflozin	161.8 (33.3)	-17.6 (26.8)[1]	-	< 0.05[2]
	O + D	168.8 (35.5)	-16.4 (36.0)[1]	-	< 0.05[2]
Ohki *et al*[15]	Ipragliflozin	162.0 (135.0-189.0)	135.0 (120.0-166.0)	0.3	-
Seko *et al*[16]	SGLT-2 inhibitor	125.0 (6.0)	116.6 (4.2)	0.07	Non-significant
	Sitagliptin	114.6 (7.0)	134.0 (10.5)	0.067	
Sumida *et al*[18]	Luseogliflozin	142.0 (30.3)	135.4 (25.6)	0.04	-

[1]Change from baseline.
[2]Compared to placebo.
CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 12 Change in glycosylated haemoglobin in individual studies

Study	Glycosylated haemoglobin (%)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	9.0 (1.0)	7.2 (0.6)	< 0.001	0.88
	Control	9.1 (1.4)	7.1 (0.9)	< 0.0001	
Ito *et al*[12]	Ipragliflozin	8.5 (1.5)	7.6 (1.0)	< 0.05	0.522
	Pioglitazone	8.3 (1.4)	7.1 (0.9)	< 0.05	
Shibuya *et al*[13]	Luseogliflozin	7.8 (7.2, 7.9)	6.5 (6.4, 7.0)	0.002	0.023
	Metformin	7.4 (6.9, 7.7)	7.3 (6.7, 7.6)	0.362	

Eriksson *et al*[14]	Placebo	7.4 (0.8)	-0.1 (0.4)[1]	-	-
	Omega-3 CA	7.4 (0.7)	+0.1 (0.4)[1]	-	Non-significant[2]
	Dapagliflozin	7.4 (0.6)	-0.6 (0.7)[1]	-	< 0.05[2]
	O + D	7.5 (0.8)	-0.5 (0.5)[1]	-	Non-significant[2]
Ohki *et al*[15]	Ipragliflozin	8.4 (7.8-8.9)	7.6 (6.9-8.2)	< 0.01	-
Seko *et al*[16]	SGLT-2 inhibitor	6.7 (0.1)	6.5 (0.1)	0.055	Non-significant
	Sitagliptin	7.0 (0.3)	6.9 (0.3)	0.331	
Sumida *et al*[18]	Luseogliflozin	7.3 (0.7)	7.0 (0.7)	0.002	-

[1]Change from baseline.
[2]Compared to placebo.
CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 13 Change in homeostasis model assessment-estimated insulin resistance in individual studies

Study	HOMA-IR			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Ito *et al*[12]	Ipragliflozin	5.2 (2.5)	4.8 (5.5)	Non-significant	0.401
	Pioglitazone	5.7 (3.4)	4.5 (2.7)	< 0.05	
Eriksson *et al*[14]	Placebo	4.2 (2.4)	-0.2 (1.4)[1]	-	-
	Omega 3-CA	5.4 (2.9)	+0.3 (2.4)[1]	-	Non-significant[2]
	Dapagliflozin	4.3 (1.9)	-1.1 (1.4)[1]	-	< 0.05[2]
	O + D	4.4 (1.7)	-0.9 (1.6)[1]	-	< 0.05[2]
Seko *et al*[16]	SGLT-2 inhibitor	4.5 (0.5)	7.9 (2.3)	0.955	-
	Sitagliptin	4.4 (0.5)	6.5 (0.8)	0.163	

[1]Change from baseline.
[2] Compared to placebo.
HOMA-IR: Homeostasis model assessment-estimated insulin resistance; CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 14 Change in serum triglycerides in individual studies

Study	Serum triglycerides (mg/dL)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	201.0 (124.0)	155.0 (52.0)	0.01	0.678
	Control	212.0 (115.0)	175.0 (43.0)	0.019	
Ito *et al*[12]	Ipragliflozin	166.9 (76.4)	143.4 (81.4)	< 0.05	0.938
	Pioglitazone	188.4 (148.8)	169.3 (131.3)	Non-significant	
Eriksson *et al*[14]	Placebo	169.2 (84.1)	-11.5 (45.6)[1]	-	-
	Omega-3 CA	186.9 (81.5)	-15.9 (47.4)[1]	-	Non-significant[2]
	Dapagliflozin	178.0 (103.6)	+14.2 (40.5)[1]	-	Non-significant[2]
	O + D	168.3 (72.6)	-25.7 (57.1)[1]	-	Non-significant[2]
Ohki *et al*[15]	Ipragliflozin	148.0 (107.0, 222.)	145.0 (114.0, 172.0)	0.75	-
Seko *et al*[16]	SGLT-2 inhibitor	153.8 (15.9)	137.8 (10.5)	0.236	-
	Sitagliptin	193.4 (25.2)	191.1 (23.8)	0.986	
Sumida *et al*[18]	Luseogliflozin	158.1 (110.5)	129.4 (59.5)	0.062	-

[1]Change from baseline.
[2]Compared to placebo.
CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 15 Change in serum low-density lipoprotein cholesterol in individual studies

Study	Serum low-density lipoprotein cholesterol (mg/dL)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	112.0 (35.0)	95.0 (22.0)	0.018	0.512
	Control	114.0 (30.0)	96.0 (17.0)	0.001	
Ito *et al*[12]	Ipragliflozin	108.3 (36.2)	110.7 (40.1)	Non-significant	0.057
	Pioglitazone	104.0 (27.9)	114.6 (29.5)	< 0.05	
Eriksson *et al*[14]	Placebo	98.2 (34.4)	+1.6 (15.5)[1]	-	-
	Omega-3 CA	111.8 (34.4)	+2.3 (17.4)[1]	-	Non-significant[2]
	Dapagliflozin	109.4 (34.8)	+7.7 (20.5)[1]	-	Non-significant[2]
	O + D	88.9 (23.2)	+5.8 (21.7)[1]	-	Non-significant[2]
Ohki *et al*[15]	Ipragliflozin	113.0 (89.0-142.0)	103.0 (92.0-122.0)	0.08	-
Seko *et al*[16]	SGLT-2 inhibitor	119.2 (5.8)	119.8 (5.7)	0.943	-
	Sitagliptin	112.9 (4.9)	127.1 (8.8)	0.063	
Sumida *et al*[18]	Luseogliflozin	101.0 (22.4)	105.0 (24.4)	0.11	-

[1]Change from baseline.
[2]Compared to placebo.
CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 16 Change in serum high-density lipoprotein cholesterol in individual studies

Study	Serum high-density lipoprotein cholesterol (mg/dL)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	42.0 (12.0)	45.0 (12.0)	0.087	0.752
	Control	45.0 (15.0)	47.0 (12.0)	0.097	
Ito *et al*[12]	Ipragliflozin	48.9 (9.3)	54.7 (10.4)	< 0.05	0.82
	Pioglitazone	47.4 (11.6)	52.7 (13.5)	< 0.05	
Eriksson *et al*[14]	Placebo	51.4 (14.9)	-0.4 (5.0)[1]	-	-
	Omega-3 CA	49.9 (14.1)	+0.4 (3.2)[1]	-	Non-significant[2]
	Dapagliflozin	49.9 (9.5)	+0.4 (4.8)[1]	-	Non-significant[2]
	O + D	51.4 (10.2)	+1.6 (5.0)[1]	-	Non-significant[2]
Ohki *et al*[15]	Ipragliflozin	42.0 (40.0-50.0)	44.0 (42.0-59.0)	0.01	-
Seko *et al*[16]	SGLT-2 inhibitor	53.9 (2.5)	55.4 (2.6)	0.043	-
	Sitagliptin	54.8 (3.3)	55.6 (2.3)	0.531	
Sumida *et al*[18]	Luseogliflozin	55.6 (11.7)	57.5 (13.4)	0.062	-

[1]Change from baseline.
[2]Compared to placebo.
CA: Carboxylic acid; O + D: Omega-3 carboxylic acid + Dapagliflozin; SGLT-2: Sodium glucose cotransporter-2.

Table 17 Change in body mass index in individual studies

Study	Body mass index (kg/m^2)			*P* value	*P* value between groups
	Group	Baseline	Study completion		
Kuchay *et al*[11]	Empagliflozin	30.0 (3.8)	28.7 (3.5)	0.001	0.124
	Control	29.4 (3.1)	28.8 (2.8)	0.019	
Shibuya *et al*[13]	Luseogliflozin	27.9 (26.2, 28.7)	27.0 (25.6, 28.3)	0.002	0.031
	Metformin	27.2 (24.8, 32.1)	27.3 (24.3, 31.6)	0.646	
Ohki *et al*[15]	Ipragliflozin	30.1 (26.1-31.4)	27.6 (25.3-30.2)	< 0.01	-
Seko *et al*[16]	SGLT-2 inhibitor	29.6 (0.7)	28.3 (0.7)	< 0.001	-
	Sitagliptin	29.2 (1.5)	28.9 (1.4)	0.295	

Sumida *et al*[18]	Luseogliflozin	27.8 (3.6)	27.2 (1.0)	< 0.001	-

SGLT-2: Sodium glucose cotransporter-2.

Table 18 Adverse effects of sodium glucose cotransporter-2 inhibitors in individual studies

Study	No. of adverse events	No. of patients	Types of adverse events
Kuchay *et al*[11]	3	25	Nonspecific fatigue: 1
			Arthralgia: 1
			Balanoposthitis: 1
Ito *et al*[12]	9	32	UTI: 3
			Increased appetite: 2
			Nausea: 1
			Headache: 1
			Diarrhoea: 1
			Vaginal candidiasis: 1
Eriksson *et al*[14]	7	21	-
Seko *et al*[16]	2	26	UTI: 2
Gautam *et al*[17]	1	32	Recurrent UTI with genital candidiasis: 1
Sumida *et al*[18]	8	40	Low blood pressure: 3
			Vaginal itching: 2
			Constipation: 1
			Vertigo: 1
			Dehydration: 1
Total	30	176	Most common adverse event: Genitourinary tract infections-10

UTI: Urinary tract infection.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) is a common comorbidity with type 2 diabetes. The existing therapeutic options for NAFLD are not adequate. Hypocaloric diet and exercise is the cornerstone of therapy in NAFLD. Pioglitazone is the only drug recommended in diabetes patients with biopsy proven non-alcoholic steatohepatitis. The frequent coexistence of NAFLD and type 2 diabetes along with their combined adverse health consequences and inadequate therapeutic options makes it necessary to search for newer alternatives. This systematic review is an effort to review the available literature on the effect of sodium glucose cotransporter-2 (SGLT-2) inhibitors on NAFLD in type 2 diabetes patients.

Research motivation

Because the existing therapeutic options are not adequate for NAFLD patients, there is a need for finding newer alternatives. SGLT-2 inhibitors have shown promise in the management of NAFLD in animals. Hence, we reviewed the available literature on the effect of SGLT-2 inhibitors in NAFLD in type 2 diabetes patients. This will promote further high quality research on the effect of SGLT-2 inhibitors in NAFLD.

Research objectives

The primary outcome was the change in serum alanine aminotransferase levels in type 2 diabetes patients with NAFLD treated with SGLT-2 inhibitors. The secondary outcomes were change in serum aspartate aminotransferase and gamma-glutamyl transferase levels, hepatic fat, hepatic fibrosis, metabolic profile, anthropometric parameters, and the adverse effects of SGLT-2 inhibitors.

Research methods

This systematic review was registered in PROSPERO and performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. We searched PubMed/MEDLINE, Cochrane library, Google scholar, and Clinicaltrials.gov for the relevant articles to be included in this systematic review. A narrative synthesis of the results of individual studies was done. The change in the difference in means and difference in proportions and the respective *P* values as mentioned in the original manuscripts were tabulated and explained. The quality of the randomised controlled trials and observational studies was analysed using the

Cochrane risk of bias tool and MINORS scale, respectively.

Research results
Eight articles (four randomised controlled trials and four observational studies) were included in this systematic review. A total of 214 patients were treated with SGLT-2 inhibitors. SGLT-2 inhibitors caused a significant improvement in liver enzymes, hepatic fat, hepatic fibrosis, glycaemia, insulin resistance, obesity, and lipid parameters with minimal adverse effects. However, the quality of evidence is low to moderate.

Research conclusions
We found that SGLT-2 inhibitors improved the serum levels of liver enzymes, liver fat, and liver fibrosis with additional beneficial effects on various metabolic and anthropometric parameters in type 2 diabetes patients with NAFLD. However, the number of patients treated with SGLT-2 inhibitors was small. The findings of this systematic review will have impact in choosing anti-diabetes medication like SGLT-2 inhibitors to treat NAFLD associated with type 2 diabetes.

Research perspectives
The studies included in this systematic review were heterogeneous with regard to study design and intervention drugs. Most of the studies were done amongst the Japanese population. Prospective studies, preferably randomised controlled trials, comparing different SGLT-2 inhibitors with standard treatments of NAFLD in multi-ethnic populations with a longer follow-up period are needed in the future.

REFERENCES

1 **Saponaro C**, Gaggini M, Gastaldelli A. Nonalcoholic fatty liver disease and type 2 diabetes: common pathophysiologic mechanisms. *Curr Diab Rep* 2015; **15**: 607 [PMID: 25894944 DOI: 10.1007/s11892-015-0607-4]

2 **Burt AD**, Lackner C, Tiniakos DG. Diagnosis and Assessment of NAFLD: Definitions and Histopathological Classification. *Semin Liver Dis* 2015; **35**: 207-220 [PMID: 26378639 DOI: 10.1055/s-0035-1562942]

3 **Williams KH**, Shackel NA, Gorrell MD, McLennan SV, Twigg SM. Diabetes and nonalcoholic Fatty liver disease: a pathogenic duo. *Endocr Rev* 2013; **34**: 84-129 [PMID: 23238855 DOI: 10.1210/er.2012-1009]

4 **Chalasani N**, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; **67**: 328-357 [PMID: 28714183 DOI: 10.1002/hep.29367]

5 **Qiang S**, Nakatsu Y, Seno Y, Fujishiro M, Sakoda H, Kushiyama A, Mori K, Matsunaga Y, Yamamotoya T, Kamata H, Asano T. Treatment with the SGLT2 inhibitor luseogliflozin improves nonalcoholic steatohepatitis in a rodent model with diabetes mellitus. *Diabetol Metab Syndr* 2015; **7**: 104 [PMID: 26594248 DOI: 10.1186/s13098-015-0102-8]

6 **Tahara A**, Kurosaki E, Yokono M, Yamajuku D, Kihara R, Hayashizaki Y, Takasu T, Imamura M, Li Q, Tomiyama H, Kobayashi Y, Noda A, Sasamata M, Shibasaki M. Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. *Eur J Pharmacol* 2013; **715**: 246-255 [PMID: 23707905 DOI: 10.1016/j.ejphar.2013.05.014]

7 **Yokono M**, Takasu T, Hayashizaki Y, Mitsuoka K, Kihara R, Muramatsu Y, Miyoshi S, Tahara A, Kurosaki E, Li Q, Tomiyama H, Sasamata M, Shibasaki M, Uchiyama Y. SGLT2 selective inhibitor ipragliflozin reduces body fat mass by increasing fatty acid oxidation in high-fat diet-induced obese rats. *Eur J Pharmacol* 2014; **727**: 66-74 [PMID: 24486393 DOI: 10.1016/j.ejphar.2014.01.040]

8 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

9 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]

10 **Slim K**, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* 2003; **73**: 712-716 [PMID: 12956787 DOI: 10.1046/j.1445-2197.2003.02748.x]

11 **Kuchay MS**, Krishan S, Mishra SK, Farooqui KJ, Singh MK, Wasir JS, Bansal B, Kaur P, Jevalikar G, Gill HK, Choudhary NS, Mithal A. 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* 2018; **41**: 1801-1808 [PMID: 29895557 DOI: 10.2337/dc18-0165]

12 **Ito D**, Shimizu S, Inoue K, Saito D, Yanagisawa M, Inukai K, Akiyama Y, Morimoto Y, Noda M, Shimada A. 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* 2017; **40**: 1364-1372 [PMID: 28751548 DOI: 10.2337/dc17-0518]

13 **Shibuya T**, Fushimi N, Kawai M, Yoshida Y, Hachiya H, Ito S, Kawai H, Ohashi N, Mori A. 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 Obes Metab* 2018; **20**: 438-442 [PMID: 28719078 DOI: 10.1111/dom.13061]

14 **Eriksson JW**, Lundkvist P, Jansson PA, Johansson L, Kvarnström M, Moris L, Miliotis T, Forsberg GB, Risérus U, Lind L, Oscarsson J. 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* 2018; **61**: 1923-1934 [PMID: 29971527 DOI: 10.1007/s00125-018-4675-2]

15 **Ohki T**, Isogawa A, Toda N, Tagawa K. 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. *Clin Drug Investig* 2016; **36**: 313-319 [PMID: 26914659 DOI: 10.1007/s40261-016-0383-1]

16 **Seko Y**, Sumida Y, Tanaka S, Mori K, Taketani H, Ishiba H, Hara T, Okajima A, Umemura A, Nishikawa T, Yamaguchi K, Moriguchi M, Kanemasa K, Yasui K, Imai S, Shimada K, Itoh Y. 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. *Hepatol Res* 2017; **47**: 1072-1078 [PMID: 27925353 DOI: 10.1111/hepr.12834]

17 **Gautam A**, Agrawal PK, Doneria J, Nigam A. Effects of Canagliflozin on Abnormal Liver Function Tests in Patients of Type 2 Diabetes with Non-Alcoholic Fatty Liver Disease. *JAPI* 2018; **66**: 62-66

18 **Sumida Y**, Murotani K, Saito M, Tamasawa A, Osonoi Y, Yoneda M, Osonoi T. 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). *Hepatol Res* 2019; **49**: 64-71 [PMID: 30051943 DOI: 10.1111/hepr.13236]

19 **Sattar N**, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. *Diabetologia* 2018; **61**: 2155-2163 [PMID: 30066148 DOI: 10.1007/s00125-018-4702-3]

20 **Nakano S**, Katsuno K, Isaji M, Nagasawa T, Buehrer B, Walker S, Wilkison WO, Cheatham B. Remogliflozin Etabonate Improves Fatty Liver Disease in Diet-Induced Obese Male Mice. *J Clin Exp Hepatol* 2015; **5**: 190-198 [PMID: 26628836 DOI: 10.1016/j.jceh.2015.02.005]

21 **Komiya C**, Tsuchiya K, Shiba K, Miyachi Y, Furuke S, Shimazu N, Yamaguchi S, Kanno K, Ogawa Y. Ipragliflozin Improves Hepatic Steatosis in Obese Mice and Liver Dysfunction in Type 2 Diabetic Patients Irrespective of Body Weight Reduction. *PLoS One* 2016; **11**: e0151511 [PMID: 26977813 DOI: 10.1371/journal.pone.0151511]

22 **Jojima T**, Tomotsune T, Iijima T, Akimoto K, Suzuki K, Aso Y. Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. *Diabetol Metab Syndr* 2016; **8**: 45 [PMID: 27462372 DOI: 10.1186/s13098-016-0169-x]

23 **Wang D**, Luo Y, Wang X, Orlicky DJ, Myakala K, Yang P, Levi M. The Sodium-Glucose Cotransporter 2 Inhibitor Dapagliflozin Prevents Renal and Liver Disease in Western Diet Induced Obesity Mice. *Int J Mol Sci* 2018; **19** [PMID: 29301371 DOI: 10.3390/ijms19010137]

24 **Calzadilla Bertot L**, Adams LA. The Natural Course of Non-Alcoholic Fatty Liver Disease. *Int J Mol Sci* 2016; **17** [PMID: 27213358 DOI: 10.3390/ijms17050774]

25 **Shah AG**, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1104-1112 [PMID: 19523535 DOI: 10.1016/j.cgh.2009.05.033]

26 **Angulo P**, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, Enders F, Saksena S, Burt AD, Bida JP, Lindor K, Sanderson SO, Lenzi M, Adams LA, Kench J, Therneau TM, Day CP. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 2007; **45**: 846-854 [PMID: 17393509 DOI: 10.1002/hep.21496]

27 **Afolabi BI**, Ibitoye BO, Ikem RT, Omisore AD, Idowu BM, Soyoye DO. The Relationship Between Glycaemic Control and Non-Alcoholic Fatty Liver Disease in Nigerian Type 2 Diabetic Patients. *J Natl Med Assoc* 2018; **110**: 256-264 [PMID: 29778128 DOI: 10.1016/j.jnma.2017.06.001]

28 **Kalra S**. Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors: A Review of Their Basic and Clinical Pharmacology. *Diabetes Ther* 2014; **5**: 355-366 [PMID: 25424969 DOI: 10.1007/s13300-014-0089-4]

29 **Abdul-Ghani MA**, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev* 2011; **32**: 515-531 [PMID: 21606218 DOI: 10.1210/er.2010-0029]

30 **Monami M**, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2014; **16**: 457-466 [PMID: 24320621 DOI: 10.1111/dom.12244]

31 **Palmer SC**, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, Maggo J, Gray V, De Berardis G, Ruospo M, Natale P, Saglimbene V, Badve SV, Cho Y, Nadeau-Fredette AC, Burke M, Faruque L, Lloyd A, Ahmad N, Liu Y, Tiv S, Wiebe N, Strippoli GF. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA* 2016; **316**: 313-324 [PMID: 27434443 DOI: 10.1001/jama.2016.9400]

32 **Mohammad SH**, Fadhil NN, Mahmood MD. Effects of metformin and dapagliflozin on glycemic indices and HOMA-IR in type 2 diabetes mellitus patients. *Int J Pharm Biol Sci* 2018; **8**: 66-73

33 **Trujillo JM**, Nuffer WA. Impact of Sodium-Glucose Cotransporter 2 Inhibitors on Nonglycemic Outcomes in Patients with Type 2 Diabetes. *Pharmacotherapy* 2017; **37**: 481-491 [PMID: 28102030 DOI: 10.1002/phar.1903]

34 **Ferrannini E**, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, Mari A, Pieber TR, Muscelli E. Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes. *Diabetes* 2016; **65**: 1190-1195 [PMID: 26861783 DOI: 10.2337/db15-1356]

35 **Ferrannini G**, Hach T, Crowe S, Sanghvi A, Hall KD, Ferrannini E. Energy Balance After Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care* 2015; **38**: 1730-1735 [PMID: 26180105 DOI: 10.2337/dc15-0355]

36 **Esteban-Jiménez O**, Navarro-Pemán C, Urieta-González L. Seguridad de los iSGLT-2. Revisión de las reacciones adversas notificadas a nivel nacional. *Med Fam SEMERGEN* 2018; **44**: 23–29 [DOI: 10.1016/j.semerg.2017.10.003]

37 **Blau JE**, Taylor SI. Adverse effects of SGLT2 inhibitors on bone health. *Nat Rev Nephrol* 2018; **14**: 473–474 [DOI: 10.1038/s41581-018-0028-0]

38 **Storgaard H**, Gluud LL, Bennett C, Grøndahl MF, Christensen MB, Knop FK, Vilsbøll T. Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0166125 [PMID: 27835680 DOI: 10.1371/journal.pone.0166125]

P- Reviewer: Joseph PM, Serhiyenko VA, Tzamaloukas AHH
S- Editor: Ma YJ **L- Editor:** Filipodia **E- Editor:** Song H

Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk:https://www.f6publishing.com/helpdesk
https://www.wjgnet.com