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Editorial

Effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors on non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Ex quo et quo vadimus?

1. Introduction

In this issue of *Metabolism*, Omori et al [1] report that dapagliflozin, a sodium-glucose co-transporter-2 inhibitor (SGLT2i), prevents hepatic steatosis (assessed by triglyceride liver content) after 8 weeks of administration in db/db mice, a mouse model of obesity and diabetes.

SGLT2i represent the latest antidiabetic drug category; members of this class exert their glucose-lowering effect via inhibiting glucose reabsorption in the kidneys and thus causing glucosuria and osmotic diuresis [2]. Furthermore, these drugs have been reported to improve several cardiovascular (CV) risk factors, including fasting and postprandial plasma glucose, body weight, blood pressure, mixed dyslipidemia, and serum uric acid, as well as endothelial dysfunction, arterial stiffness and inflammation [3–7]. Apart from diuresis and the subsequent reduction in preload, SGLT2i also favour the production of ketone bodies (acting as a "superfuel" for the heart and the kidneys), block the renin-angiotensin-aldosterone-system (causing positive intropic effects and vasodilation) and the sympathetic nervous system, and downregulate the activity of the Na + –H+ exchanger in myocytes (restoring mitochondrial calcium in cardiomyocytes) [8,9]. These mechanisms contribute to the cardiorenal benefits of SGLT2i, resulting in a reduction of CV and total mortality [10], as well as a decrease of renal causes of death and end-stage kidney disease in type 2 diabetes mellitus (T2DM) patients [11]. In contrast, the benefits of treatment with SGLT2i in terms of liver function and of possible reduction of hepatic steatosis, inflammation or fibrosis are under investigation. In the USA and Europe, there are currently 3 SGLT2i available in the market (i.e. canagliflozin, dapagliflozin and empagliflozin) [12], whereas ertugliflozin has also been approved for T2DM treatment (but it is not available in the market yet [13]). Furthermore, ipragliflozin, luseogliflozin and tofogliflozin are available only in Japan [14]. The main side effect of these drugs is genital infections which are mostly mild and transient. However, canagliflozin has also been linked to an increased risk of bone fractures and amputations of the lower extremities [12,15].

Obesity and insulin resistance are related to adipose tissue inflammation, impaired adipokine secretion, elevated fatty acid concentrations and fatty acid oxidation and are considered major factors in the development and progression of non-alcoholic fatty liver disease (NAFLD), [16–24]. NAFLD and its advanced form, i.e. non-alcoholic steatohepatitis (NASH), have been associated with increased CV risk [25–29] and the majority of these patients will die from CV (and not liver) causes [30]. Furthermore, NAFLD predisposes to the development of albuminuria and chronic kidney disease (CKD) [31,32] which is improved in response to SGLT2i [11]. Currently, there are several medications being evaluated in the context of clinical trials (Table 1) but there is no medication approved for NAFLD/NASH patients. Lifestyle interventions remain the cornerstone of NAFLD/NASH therapy since weight loss can significantly improve biochemical, radiological and histological features of the disease [33,34].

Based on the above and also taking into consideration the growing prevalence of NAFLD/NASH worldwide, especially in patients with T2DM, it is of interest to study in depth and then translate into the creation of a new treatment, acting alone or in combination with other agents, any beneficial effects of SGLT2i on NAFLD.

2. Canagliflozin and NAFLD/NASH: preclinical and clinical data

Canagliflozin has been reported to reduce liver weight in obese animal models [35] as well as to protect against the development of NASH (via reversal of hepatic lipid accumulation and liver weight gain) in type-2 diabetic rats [36]. In addition, canagliflozin attenuated the onset of hepatocellular carcinoma in a mouse model of NASH [37].

Similar beneficial effects of canagliflozin on NAFLD/NASH have also been reported in human studies assessing NAFLD/NASH related outcomes although specific large and long term randomized controlled trials (RCTs) on hard NAFLD/NASH outcomes have not yet been performed. In a retrospective analysis of 17 patients with NAFLD and T2DM treated with canagliflozin (100 mg/day, $n = 7$) or dapagliflozin (5 mg/day, $n = 10$), hepatic fat mass (measured by proton magnetic resonance spectroscopy) was significantly reduced (from 19 to 9%) and liver tests were improved [i.e. alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transpeptidase (γ-GT)], [38]. Similarly, in another retrospective study of 24 T2DM patients with biopsy-proven NAFLD, treatment with SGLT2i (canagliflozin $n = 18$, 100 mg/day; or ipragliflozin 50 mg/day for 24 weeks) reduced ALT and AST levels by ~30% [39]. In a prospective open-label uncontrolled study involving 9 T2DM patients with NAFLD (assessed by liver biopsy), 24 weeks of canagliflozin (100 mg/day) treatment led to histological improvements according to NAFLD activity score (NAS) in all subjects, mainly due to improvement of steatosis (7/9) and secondarily of lobular inflammation (3/9) or fibrosis (3/9) [40].

Itani et al. reported [41] in a prospective open label study that serum levels of ALT, AST and γ-GT were significantly decreased after 3 and 6 months (up to 45%) of canagliflozin (100 mg/day) treatment in 35 T2DM patients with NAFLD (diagnosed by abdominal ultrasonography). Fibrosis-4 (FIB-4) index was also reduced slightly at 3 months, whereas the decrease reached significance at 6 months [41]. Of note, canagliflozin (300 mg/day) decreased (by 4.6%) intrahepatic triglyceride (IHTG) accumulation (assessed by proton magnetic resonance

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Table 1
Clinical trials Phase II-IV for the medical treatment of NAFLD in "recruiting" or "active status" with primary or secondary hepatic outcomes.

Medication	Class/mechanism of action	Hepatic outcomes	Status	Sponsor	Primary completion date
Antidiabetic drugs					
Dulaglutide	GLP-1 receptor agonist	Histologic improvement	Phase 4	Central Hospital Nancy, France Eli Lilly and Company	09/2023
Tofogliflozin vs Glimepiride	SGLT2 inhibitor Sulfonylurea	Histologic improvement	Phase 4	Kowa Company Ltd. Kanazawa University	09/2020
Dapagliflozin	SGLT2-inhibitor	Histologic improvement	Phase 3	Nanfang Hospital of Southern Medical University	11/2021
Semaglutide	GLP-1 receptor agonist	Histologic Improvement	Phase 2	NIDDK, NCI, CC	01/2023
Semaglutide	GLP-1 receptor agonist	Liver stiffness by MRE Hepatic fat content (MRI-PDFF)	Phase 2	Novo Nordisk A/S	03/2020
Semaglutide	GLP-1 receptor agonist	Histologic improvement	Phase 2	Novo Nordisk A/S	11/2019
LIK066	Dual SGLT1/2 Inhibitor	ALT and AST	Phase 2	Novartis Pharmaceuticals	09/2019
Oral Insulin	Insulin	Hepatic fat content (MRI-PDFF), Fibroscan, Fibrosis score	Phase 2	Oramed, Ltd. Hadassah Medical Organization	12/2019
PPAR agonists					
Elafibranor	PPARα/δ agonist	Histologic improvement	Phase 3	Genfit	12/2021
Saroglitazar	PPARα and γ agonist	Hepatic fat content (MRI-PDFF)	Phase 2	Zydus Discovery DMCC	10/2019
Saroglitazar	PPARα and γ agonist	Histologic improvement	Phase 2	Zydus Discovery DMCC	02/2020
Pemafibrate	PPARα agonist	Hepatic fat content (MRI-PDFF)	Phase 2	Kowa Company Ltd	02/2020
Lanifibranor	PPARα, γ, δ agonist	Intrahepatic triglycerides by ^{1}H-MRS	Phase 2	University of Florida, Inventiva Pharma	12/2020
IVA337	Pan-PPAR agonist	Histologic improvement SAF score	Phase 2	Inventiva Pharma	12/2019
Combination antidiabetics and PPAR agonists					
Evogliptin Pioglitazone	DPP4 inhibitor PPARγ agonist	Intrahepatic fat content (method not reported)	Phase 4	Dong-A ST Co., Ltd.	09/2020
Empagliflozin vs/and Pioglitazone	SGLT2 inhibitor PPARγ agonist	Hepatic fat content (MRI-PDFF) Liver fibrosis by MRE	Phase 4	Yonsei University	09/2020
Nesinaact (Alogliptin, Pioglitazone)	DPP4-Inhibitor PPARγ agonist	Histologic improvement	Phase 4	Yonsei University	06/2020
FXR agonists					
Obeticholic acid	Bioavailable FXR agonist	Histologic improvement	Phase 3	Intercept Pharmaceuticals	10/2022
Obeticholic acid	Bioavailable FXR agonist	Histologic improvement in cirrhosis	Phase 3	Intercept Pharmaceuticals	07/2020
Tropifexor	FXR agonist	Transaminases, Hepatic fat content (MRI)	Phase 2	Novartis Pharmaceuticals	07/2019
Tropifexor Cenicriviroc	FXR agonist Inhibitor of CCR2 and CCR5	Histologic improvement in fibrosis or NASH	Phase 2	Novartis Pharmaceuticals Allergan	07/2020
EDP-305	FXR agonist	ALT	Phase 2	Enanta Pharmaceuticals ICON Clinical Rsearch Triangle Biostatistics	06/2019
EYP001a	Non-bile acid FXR agonist	Hepatic fat content (MRI)	Phase 2	Enyo Pharma	12/2019
Selonsertib Firsocostat Cilofexor	ASK1 inhbitor ACC inbhitor FXR agonist	Histologic improvement in fibrosis	Phase 2	Gilead Sciences	10/2019
FGFs					
Pegbelfermin	PEGylated FGF21 analog	Histologic improvement	Phase 2	Bristol-Myers Squibb	01/2020
AKR-001	FGF21 analogue	Hepatic fat content (MRI-PDFF)	Phase 2	Akero Therapeutics, Inc	03/2020
NGM282	FGF19 analogue	Hepatic fat content (MRI)	Phase 2	NGM Biopharmaceuticals, Inc	09/2019
NGM282	FGF19 analogue	Histologic improvement	Phase 2	NGM Biopharmaceuticals, Inc	09/2020
Other					
Cenicriviroc	Inhibitor of CCR2 and CCR5	Histologic improvement	Phase 3	Tobira Therapeutics, Inc.	10/2021
MGL-3196	Thyroid Hormone Receptor agonist	Histologic improvement	Phase 3	Madrigal Pharmaceuticals, Inc.	06/2021

Table 1 (*continued*)

Medication	Class/mechanism of action	Hepatic outcomes	Status	Sponsor	Primary completion date
PF-05221304 PF-06865571	ACC inhibitor DGAT2 inhibitor	Hepatic fat content (MRI-PDFF)	Phase 2	Pfizer	04/2020
PXL770	Selective AMPK activator	Hepatic fat content (MRI-PDFF)	Phase 2	Poxel SA	02/2020
TVB 2640	FASN Inhibitor	Hepatic fat content (MRI-PDFF)	Phase 2	3 V Biosciences, Inc.	05/2020
PF-06835919	Ketohexokinase Inhibitor	Whole liver fat (MRI-PDFF)	Phase 2	Pfizer	10/2021
MSDC-0602K	Modulator of mitochondrial pyruvate carrier	Histologic improvement	Phase 2	Cirius Therapeutics, Inc. Chiltern International Inc.	06/2019
HTD1801	Lipid modulator	Hepatic fat content (MRI)	Phase 2	HighTide Biopharma Pty Ltd	09/2019
CORT118335	Dual selective glucocorticoid receptor modulator and mineralocorticoid receptor antagonist	Hepatic fat content (MRI-PDFF)	Phase 2	Corcept Therapeutics	03/2020
AZD4076	*N*-acetylgalactosamine (GalNAc)-conjugated anti-miR-103/107 oligonucleotide	Hepatic fat content (MRI)	Phase 1 Phase 2	AstraZeneca	12/2020
Spironolactone	Mineralcorticoid receptor blockade	Histologic improvement in young women with NASH	Phase 1/2	University of California, San Francisco	07/2023
Tesamorelin	Growth hormone releasing hormone analog	Hepatic fat content by ^{1}H-MRS	Phase 2	Mass General Hospital	08/2019
SGM-1019	Small molecule modulator of inflammasome activity	Hepatic fat content (MRI)	Phase 2	Second Genome	11/2019
SNP-610	Targeting cytochrome P450 2E1	ALT, Hepatic fat content (MRI)	Phase 2	Sinew Pharma Inc.	06/2019
Nitazoxanide	Anti-parasite	Liver stiffness with Fibroscan	Phase 2	Pinnacle Clinical Research, PLLC	12/2019
Emricasan	Caspase Inhibitor	MELD score, Child-Pugh score in cirrhosis	Phase 2	Conatus Pharmaceuticals	08/2019
Metreleptin	Recombinant leptin in subjects with NAFLD and FPL	Histologic improvement	Phase 2	University of Michigan	02/2025
Rosuvastatin vs/and Ezetimibe	Antihyperlipidemics	Hepatic fat content (MRI-PDFF)	Phase 4	Yonsei University	01/2020
CF102	A3 adenosine receptor agonist	Serum ALT, Hepatic fat content (MRI)	Phase 2	Can-Fite BioPharma	12/2019
Berberine	Quaternary ammonium salt extracted by plants	Histologic improvement	Phase 4	Multicentric (Six centers in China)	12/2020

Abbreviations: ACC, Acetyl CoA-Carboxylase; ALT, alanine aminotransferase; AMPK, AMP-activated protein kinase; ASK1, Apoptosis Signal-Regulated Kinase 1; AST, aspartate aminotransferase; CAP, Controlled Attenuation Parameter; DGAT, diacylglycerol O-acyltransferase 2; DPP4, Dipeptidyl peptidase-4 inhibitor; LSM, liver stiffness measurements; CC, National Institutes of Health Clinical Center; FASN, fatty acid synthase; FGF21, Fibroblast growth factor 21; FPL, Familial Partial Lipodystrophy; FXR, Farnesoid X receptor; MRE, Magnetic resonance elastography; MRI-PDFF, MRI-proton density fat fraction; MRS, magnetic resonance spectroscopy; NCI, National Cancer Institute; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; PPAR, peroxisome proliferator-activated receptor; SAF, Steatosis, activity and fibrosis; SGLT2, Sodium glucose cotransporter-2; GLP-1: glucagon like peptide 1.

spectroscopy) in 56 T2DM patients after 24 weeks, but this reduction was more evident (6.9%) and reached significance only in those with NAFLD ($n = 37$) i.e. those with IHTG ≥5.56% [42].

Canagliflozin-related liver benefits were observed when the drug was administered for a longer period of time i.e. up to 12 months. Briefly, in 20 T2DM patients with NAFLD (diagnosed by ultrasonography), canagliflozin (100 mg/day) significantly improved serum liver enzymes (i.e. AST, ALT and γ-GT), as well as hepatic fat fraction (measured by magnetic resonance imaging) at both 6 and 12 months [43]. Even in T2DM patients ($n = 10$) with biopsy-proven NASH (liver fibrosis stage 1–3), canagliflozin (100 mg/day) was shown to significantly reduce ALT, AST and γ-GT activities, as well as FIB-4 and FM-fibro index at 12 weeks [44].

In a large diabetes registry (including 1325 T2DM patients on canagliflozin, 661 on sitagliptin, 521 on liraglutide and 430 controls; mean follow-up 4.8 months), canagliflozin treatment was associated with significantly lower ALT levels (weight- and HbA1c-indepedently) compared with sitagliptin, liraglutide and control groups [45]. Similar results were reported in a pooled analysis of data from four 26-week placebo-controlled trials ($n = 2313$ T2DM patients on canagliflozin 100 or 300 mg/day) and two 52-week active-controlled trials ($n = 1488$ T2DM patients on canagliflozin 300 mg/day or sitagliptin 100 mg/day) [46]. Briefly, liver tests (ALT, AST, γ-GT and alkaline phosphatase) were significantly decreased by canagliflozin compared with either placebo or sitagliptin [46]. This decrease though was fully explained by the reduction in HbA1c and body weight. Finally, a recent meta-analysis (11 randomized, double-blind, placebo- or active-controlled trials; $n = 6745$ T2DM patients) showed significant reductions in ALT, AST and γ-GT (weighted mean differences: −11.68, −7.50 and − 15.17%, respectively) following 26 or 52 weeks of canagliflozin therapy [47]. Of note, Seko et al. [48] performed a *post-hoc* analysis of 3 studies (12- and 24-week placebo-controlled trials and one 52-week monotherapy/combination therapy study), involving a total of 916 T2DM patients. Canagliflozin significantly decreased ALT and AST levels only in patients with baseline ALT >30 U/L (and not in those with baseline ALT ≤30 U/L) [48].

3. Dapagliflozin and NAFLD/NASH: preclinical and clinical data

As mentioned previously, Omori et al. [1] reported that dapagliflozin prevented liver steatosis in db/db mice. Similarly, dapagliflozin was shown to ameliorate ALT elevation, liver lipid accumulation, inflammation, oxidative stress and fibrosis in db/db mice [49].

In a retrospective observational study involving 115 Chinese participants (69 treated with dapagliflozin and 46 with empagliflozin), serum ALT was significantly decreased following a 6-month therapy with dapagliflozin (5 mg/day) [50]. In a prospective study involving 55

Japanese T2DM patients, treatment with dapagliflozin (5 mg/day) vs no SGLT2i for six months led to a reduction in hepatic fat accumulation measured by the liver-to-spleen attenuation with CT, as a well as to a decrease in ALT, AST and γ-GT levels at 6 months [51].

In T2DM patients with NAFLD ($n = 57$), diagnosed according to biochemical and ultrasonographical features, serum ALT, AST and γ-GT were significantly improved after dapagliflozin (5 mg/day) treatment for 24 weeks [52]. In another study, 102 T2DM patients with NAFLD (confirmed by abdominal ultrasonography) were divided into 2 groups: 50 treated with dapagliflozin (10 mg/day) plus metformin and 52 on dipeptidyl peptidase-4 inhibitors (DDP4i) (33 sitagliptin 100 mg/day and 19 linagliptin 5 mg/day) plus metformin [53]; ALT decline at 3 months was greater in the dapagliflozin than the DPP4i group (−21.1 vs. −9.5 U/L, respectively; $p = 0.008$), as was the percentage of patients achieving ALT normalization (80.0 vs. 61.5%, respectively; $p = 0.041$) and these effects remained significant after adjustment for body weight loss.

Apart from liver tests, dapagliflozin was shown to reduce liver lipid content in T2DM patients with NAFLD. Briefly, Arase et al. [38] reported that dapagliflozin (5 mg/day), when given for 24 weeks in 10 T2DM patients with NAFLD (diagnosed by imaging techniques or liver biopsy), led to significant decreases in liver fat mass (measured by proton magnetic resonance spectroscopy) and liver enzymes (ALT, AST, γ-GT). In another study ($n = 57$ T2DM patients with NAFLD confirmed by ultrasonography and elevated liver tests), 24-week therapy with dapagliflozin (5 mg/day) improved liver steatosis (assessed by transient elastography); hepatic fibrosis was significantly attenuated only in those patients with advanced liver fibrosis (defined by liver stiffness measurement ≥8.0 kPa [54]. Finally, Eriksson et al. [55] randomly assigned 84 T2DM patients with NAFLD (diagnosed by magnetic resonance imaging) in a 1:1:1:1 ratio to dapagliflozin (10 mg/day), omega-3 carboxylic acids, combination of both or placebo for a 12-week treatment in the EFFECT-II trial. All active treatments significantly decreased liver fat content (assessed by proton density fat fraction [PDFF]) from baseline, but only the combination group significantly lowered it compared with placebo [55]. Furthermore, ALT, AST and γ-GT significantly declined only in the dapagliflozin monotherapy group.

Regarding T2DM patients with biopsy-proven NASH, Tobita et al. [56] in their study ($n = 16$) reported that dapagliflozin (5 mg/day) administration for 24 weeks led to significant improvements in serum levels of ALT and AST.

4. Empagliflozin and NAFLD/NASH: preclinical and clinical data

Empagliflozin has been reported to reduce hepatic steatosis in rats [57] and histological NASH activity score in a mouse model of NASH with diabetes [58].

In a previous study involving 46 T2DM patients, empagliflozin significantly decreased serum ALT levels after 6 months [50]. Similarly, in a pooled analysis of four 24-week placebo-controlled trials ($n = 2477$), a 104-week empagliflozin vs glimepiride study ($n = 1545$) and the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) ($n = 7020$), empagliflozin therapy was linked to significant declines in ALT and AST levels, with ALT reduction being greater than AST [59]. Importantly, the reduction in ALT was largely independent of weight or HbA1c changes.

In the first RCT evaluating the efficacy of SGLT2i in patients with T2DM and NAFLD [Effect of Empagliflozin on Liver Fat trial (*E*-LIFT)], empagliflozin (10 mg/day) as add-on to standard T2DM treatment for 20 weeks was shown to lower hepatic fat by 4% (assessed by PDFF) compared to placebo, as well as to reduce serum ALT levels in 50 T2DM patients with NAFLD (diagnosed by magnetic resonance imaging) [60]. In T2DM patients with biopsy-proven NASH ($n = 9$), empagliflozin (25 mg/day), administered for 24 weeks, also led to significantly greater improvements in steatosis (67 vs. 26%; $p = 0.025$), ballooning (78 vs. 34%; $p = 0.024$) and fibrosis (44 vs. 6%; $p = 0.008$) compared with placebo [61].

5. Other SGLT2i and NAFLD/NASH: preclinical and clinical data

Ipragliflozin, currently available in Japan, was also shown to reduce or even prevent hepatic steatosis and fibrosis in mice and rats [62–65].

In T2DM patients ($n = 21$), 16-week therapy with ipragliflozin (50 mg/day) led to a significant reduction in fatty liver index (FLI) [66]. In another study involving 24 T2DM patients with abnormal serum ALT levels and ultrasonographically-proven NAFLD, that were already treated with DPP4i or glucagon like peptide-1 receptor agonists (GLP-1 RAs), the addition of ipragliflozin (25 or 50 mg/day) significantly lowered ALT and FIB-4 index after a median follow-up of 320 days [67]. Ito et al. [68] also showed that ipragliflozin (50 mg/day) exerted similar improvements in ALT, AST and liver-to-spleen attenuation (L/S) ratio with pioglitazone (15–30 mg/day) after 24 weeks in 66 T2DM patients.

Furthermore, subgroup analyses of the STELLA-LONG TERM study, an ongoing 3-year post-marketing surveillance trial, evaluated the effects of ipragliflozin on liver function in T2DM patients at 3 and 12 months [69,70]. At 3 months, FLI was significantly decreased in all patients ($n = 5809$), whereas ALT, AST and γ-GT levels were significantly reduced only in those with abnormal ALT at baseline ($n = 3239$), leading to ALT normalization in 20.5% of this patient population [69]. Similar were the results at 12 months with AST levels also being significantly lowered after this period of time [70].

Regarding NASH, 24 weeks of ipragliflozin (50 mg/day) treatment was reported to significantly improve ALT, AST, γ-GT and hepatic steatosis (assessed by transient elastography) in 12 T2DM patients with biopsy-proven NASH [71]. In the same study, there were also 31 T2DM patients with NAFLD (diagnosed by ultrasonography) in whom ipragliflozin significantly decreased only AST and ALT.

Luseogliflozin, available in Japan, was reported to improve NASH in rodents [72]. In 32 T2DM patients with NAFLD (diagnosed by ultrasonography or computed tomography) luseogliflozin (2.5 mg/day) led to significantly greater reductions in liver fat deposition (defined by the L/S ratio) compared with metformin at 6 months [73]. In another 24-week prospective study ($n = 40$ T2DM patients with ultrasonographically proven NAFLD), treatment with luseogliflozin (2.5 mg/day) significantly lowered transaminase activities (ALT AST and γ-GT) and hepatic fat content (assessed by magnetic resonance imaging-hepatic fat fraction) [74].

Tofogliflozin, currently available in Japan, was shown to decrease liver weight and triglyceride content in mice [75] as well as prevent hepatic fat accumulation and delay liver fibrosis progression in a medaka model of NASH [76]. Data in humans are missing.

Ertugliflozin is another SGLT2i that has been approved in the USA and Europe, although not available in the market yet [13]. No data exist for its effects on NAFLD/NASH.

Sotagliflozin is the first dual SGLT2/SGLT1 inhibitor that has been developed for the treatment of both T2DM and type 1 diabetes mellitus (T1DM) [77]. Currently, sotagliflozin has been approved for use in T1DM in Europe as an adjunct to insulin therapy [78]. There are no data on its effects on NAFLD/NASH. Of note, dapagliflozin is also approved for the treatment of T1DM in Europe [79] as is ipragliflozin in Japan [80]. Thus, these SGLT2i are approved for use in both T1DM and T2DM.

Apart from SGLT2i, there are also other drug categories that are being investigated as promising therapeutic options in NAFLD/NASH in Phase II-IV clinical trials, including GLP-1 RAs, peroxisome proliferator-activated receptor (PPAR) agonists, Farnesoid X receptor (FXR) agonists and Fibroblast growth factors (FGFs) (Table 1).

6. SGLT2i, antidiabetic and cardiorenal effects and NAFLD/NASH improvement

SGLT2i have shown cardiorenal benefits in randomized clinical trials with T2DM patients. In particular, empagliflozin significantly reduced major adverse cardiovascular events (MACE; i.e. myocardial infarction, stroke or CV death), as well as, hospitalization for heart failure (HF), CV and total mortality in T2DM patients with established CV disease in the EMPA-REG OUTCOME [10]. Canagliflozin significantly decreased MACE and HF hospitalization (but not CV or all-cause death) in T2DM patients with (65.6%) or without CV disease at baseline in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program [81]. Dapagliflozin significantly lowered only HF hospitalization in T2DM patients with (40%) or without established CV disease in the DECLARE TIMI 58 trial [82]. All 3 SGLT2i (empagliflozin, canagliflozin and dapagliflozin) also improved renal outcomes in RCTs with T2DM patients [81,83,84]. In this context, canagliflozin was recently reported to significantly lower the composite of end-stage kidney disease (defined as sustained estimated GFR <15 ml/min/1.73 m^2, dialysis or transplantation), a doubling of the serum creatinine level, or death from CV or renal causes in T2DM patients with albuminuric CKD in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [11]. In secondary analyses, canagliflozin also significantly reduced HF hospitalization and MACE [11]. Of note, the rates of fracture or amputation were similar between canagliflozin and placebo.

There are no head-to-head comparisons of SGLT2i in terms of cardiorenal effects and thus large-scale trials with matching inclusion/exclusion criteria and outcomes are needed [85]. However, based on these results, the US Food and Drug Administration (FDA) approved a new indication (apart from the treatment of T2DM) for empagliflozin (to reduce CV death [86]) in adults with T2DM and established CV disease.

As mentioned above, NAFLD has been linked to an increased CV and CKD risk. Since SGLT2i exert cardiorenal benefits, their use in T2DM patients with NAFLD/NASH appears even more clinically important. Ongoing trials with empagliflozin and dapagliflozin in patients with HF or CKD (but without T2DM), i.e. the EMPA-Kidney study [87], the Dapa-CKD study [88], the Dapa-HF study [89], the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) [90] and the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) [91] will show if these drugs can reduce cardiorenal risk also in non-diabetic individuals. Similarly, potential efficacy for NAFLD/NASH in nondiabetic individuals would be of extreme importance.

In conclusion, there is growing evidence for a beneficial role of SGLT2i (including canagliflozin, dapagliflozin and empagliflozin) on NAFLD/NASH development and/or progression. Further research is needed to elucidate their clinical use and compare relative efficacy vs. side effects in such patients when used alone or in combination with other effective agents. In this context, Phase II RTCs with specific NASH outcomes involving biopsy improvement in large numbers of humans should be performed to obtain a formal proof of concept before proceeding with well-designed Phase III RTCs. Additionally, taking into consideration the high prevalence but slow progression of NAFLD, these studies should aim to define which patients are most likely to benefit in terms of liver function improvements by SGLT2i, how early a treatment with SGLT2i in NAFLD should be initiated, whether it should be prioritized compared to other alternatives and for how long it should be prescribed to maximize efficacy. In the meantime, lifestyle modification should be intensively implemented in NAFLD/NASH patients (with or without T2DM).

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Niki Katsiki
Nikolaos Perakakis
Christos Mantzoros*
Beth-Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States of America
*Corresponding author at: 330 Brookline Avenue, Boston, MA 02215 United States of America.330 Brookline Avenue Boston MA 02215, United States of America
E-mail address: nikikatsiki@hotmail.com.

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