REVIEW

Rise of sodium-glucose cotransporter 2 inhibitors in the management of nonalcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in the Western world. It is more prevalent in male gender, and with increasing age, obesity, and insulin resistance. Besides weight loss, there are limited treatment options. The use of anti-diabetic medications has been studied with mixed results. In this review, we discuss the use of anti-diabetic medications in the management of NAFLD with a specific focus on sodium-glucose cotransporter 2 inhibitors. We shed light on the evidence supporting their use in detail and discuss limitations and future directions.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Sodium-glucose cotransporter 2 inhibitors; Liver cirrhosis; Diabetes

Core tip: Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in the Western world. NAFLD is associated with obesity and insulin resistance. Weight loss is the cornerstone of therapy with no other proven pharmacologic therapy, Sodium-glucose co-transporter 2 (SGLT2) inhibitors may play a role in preventing and treating NAFLD. SGLT2 inhibitors reduce hepatic steatosis, steatohepatitis, and fibrosis in patients with NAFLD.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in Western countries[1] and its prevalence worldwide is increasing substantially. NAFLD constitutes a spectrum of liver disease that extends from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), a more progressive form of the disease that can lead to advanced fibrosis or cirrhosis. The worldwide prevalence is approximately 10%-35%[2]. In the United States, it is estimated that NAFLD affects more than 20% of the population[3,4]. Cardiovascular disease remains the most common cause of death in patients with NAFLD[5].

The underlying pathophysiology of NAFLD is not fully understood, but genetics and insulin resistance seem to play key roles[6]. Certain risk factors have been identified in NAFLD. Gender, age, ethnicity, and the presence of obesity or type 2 diabetes mellitus (T2DM) are differentially associated with NAFLD. Males are affected more often than females with approximately a 2:1 ratio. Most patients are diagnosed in their 40 s and 50 s. Studies demonstrate a higher prevalence in Hispanics, medium prevalence in Caucasians, and relatively low prevalence amongst blacks[7]. Certain genetic polymorphisms (*i.e.*, PNPLA-3 and TM6SF2) have also been implicated in the disease process leading to more progressive form of NAFLD[8].

The multifaceted pathophysiologic nature of NAFLD has challenged the development of targeted therapeutic strategies for this growing disease. Thus far, weight loss is the most effective therapy with 3%-5% weight loss resulting in improvement of liver transaminases and reversal of steatosis[9,10], and 7%-10% weight reduction resulting in reversal of abnormal histologic features[11].

Pharmacologic therapies for NAFLD have not yet gained widespread use, mainly due to the poor quality of evidence supporting their use. Evaluated medications include those with anti-oxidative effects (Vitamin E)[12], anti-inflammatory effects (Ursodeoxycholic acid)[13], lipid-lowering effects (Atorvastatin)[14], anti-diabetic medications, and other nutritional supplements (Omega-3 fatty acids)[15].

In this review, we focus on the use of anti-diabetic agents in the treatment of NAFLD, more specifically on the newly emerging class of Sodium-glucose co-transporter 2 (SGLT2) inhibitors. We shed light on the evidence supporting their use in detail and discuss future directions.

SEARCH CRITERIA

MEDLINE search was conducted using the keywords "SGLT2 inhibitors" and "NAFLD" OR "NASH" and all the studies were included. There were no excluded articles. The studies were mainly focused on the role of SGLT2 inhibitors in NAFLD and were included up to December 2018.

ANTI-DIABETICS IN NAFLD

A cornerstone in the management of NAFLD is treating concomitant diabetes mellitus. The relationship between NAFLD and type-2 diabetes mellitus (T2DM) is well established and is often relayed as a bidirectional relationship. There is an association between the prevalence of NAFLD and T2DM, as multiple prospective observational studies shown NAFLD independently increases the incidence of T2DM[16-21]. In one study, NAFLD was independently associated with impaired glucose metabolism[22]. Previous reports show a high prevalence of NAFLD in patients with T2DM[23,24]. T2DM was also associated with worsening NAFLD and progression to NASH and hepatocellular carcinoma (HCC)[25-27]. The underlying mechanisms between NAFLD and T2DM is complicated, but stems from the critical role the liver plays in regulating glucose and lipid metabolism, where the inciting event is thought to be a fat-associated chronic low-grade inflammatory response[28,29]. As there is

overwhelming evidence that NAFLD and T2DM share a common pathogenesis[30], the treatment of T2DM had been suggested as an important key in the management of NAFLD.

METFORMIN

Metformin is the most commonly used medication in the management of T2DM. It reduces hepatic glucose production and promotes skeletal muscle glucose uptake. Given the pathogenesis of NAFLD and T2DM, multiple investigations have been carried out regarding its use in NASH. However, a meta-analysis published in 2010 demonstrated that metformin failed to improve hepatic steatosis, inflammation, hepatocyte ballooning, Alanine aminotransferase (ALT) levels, liver fibrosis, or body mass index (BMI) in subjects with simple steatosis or biopsy-proven NASH[31]. As a result, metformin is not recommended for use in NAFLD, even in patients with T2DM.

THIAZOLIDINEDIONES

Thiazolidinediones are PPAR-gamma agonists that enhance insulin sensitivity[32]. A study investigating the effect of pioglitazone on patients with NASH but without T2DM showed a significant reduction in ALT levels and improvement in histological features of NAFLD such as steatosis, inflammation, and hepatocyte ballooning when compared to placebo[33], however it did not slow down the progression of hepatic fibrosis[33].

INCRETIN-BASED THERAPY

GLP-1 agonists are incretin-based therapies that are used in the management of T2DM by promoting glucose-dependent insulin secretion[34]. An investigation comparing liraglutide and placebo in patients with NASH showed that liraglutide led to a significant resolution of steatosis as determined by an end-of-treatment liver biopsy[35]. It was also shown to slow down the progression to fibrosis[35].

Dipeptidyl-peptidase 4 (DPP-4) inhibitors, such as sitagliptin, inhibit the degradation of incretins, which in turn stimulate secretion of insulin in patients with T2DM. They have been shown to have extra-pancreatic effects, including protective effects on hepatocytes against diet-induced steatosis and ultimately NAFLD[36]. Not only do they prevent the development of NAFLD, but they seem to exert an effect in treating it by influencing the serum levels of ALT, Aspartate aminotransferase (AST) and gamma-GT[37]. They were also found to be safe in patients with T2DM and NAFLD, and had been suggested as a potential mono-therapeutic agent for NAFLD[38]. However, there are yet to be randomized controlled trials showing their therapeutic effects in NAFLD.

SGLT2 INHIBITORS

SGLT2 inhibitors are a class of drugs that inhibit glucose reabsorption in the kidney *via* inhibition of the SGLT channels which are primarily located in the proximal convoluted tubules epithelial cells, thus promoting glucosuria. Their mechanism of action is independent of insulin secretion making the use of these drugs useful in patients with limited pancreatic beta cell activity. The hypothesized mechanism of SGLT2 inhibitors in NAFLD stems from their glycosuric effect leading to total loss of energy which results in increased pancreatic secretion of glucagon while suppressing insulin secretion. SGLT2 inhibitors also work as alpha-cells secretagogues by directly stimulating glucagon release *via* neuronal stimulation[39]. This mild hyper-glucagonemic state induces hepatic gluconeogenesis, ketogenesis and lipolysis, leading to an overall reduction in the amount of fatty acids. Furthermore, SGLT2 inhibitors exert a direct neurogenic effect that enhances gluconeogenesis and lipolysis in the liver[40]. The sum of such effects leads to reduction in hepatic steatosis and halts the progression of NAFLD (Figure 1). Albeit being of the same group of medications, different SGLT2 inhibitors demonstrated different effects on NAFLD. In the following section, we discuss the evidence that supports the use of different members of this family of drugs in SGLT2.
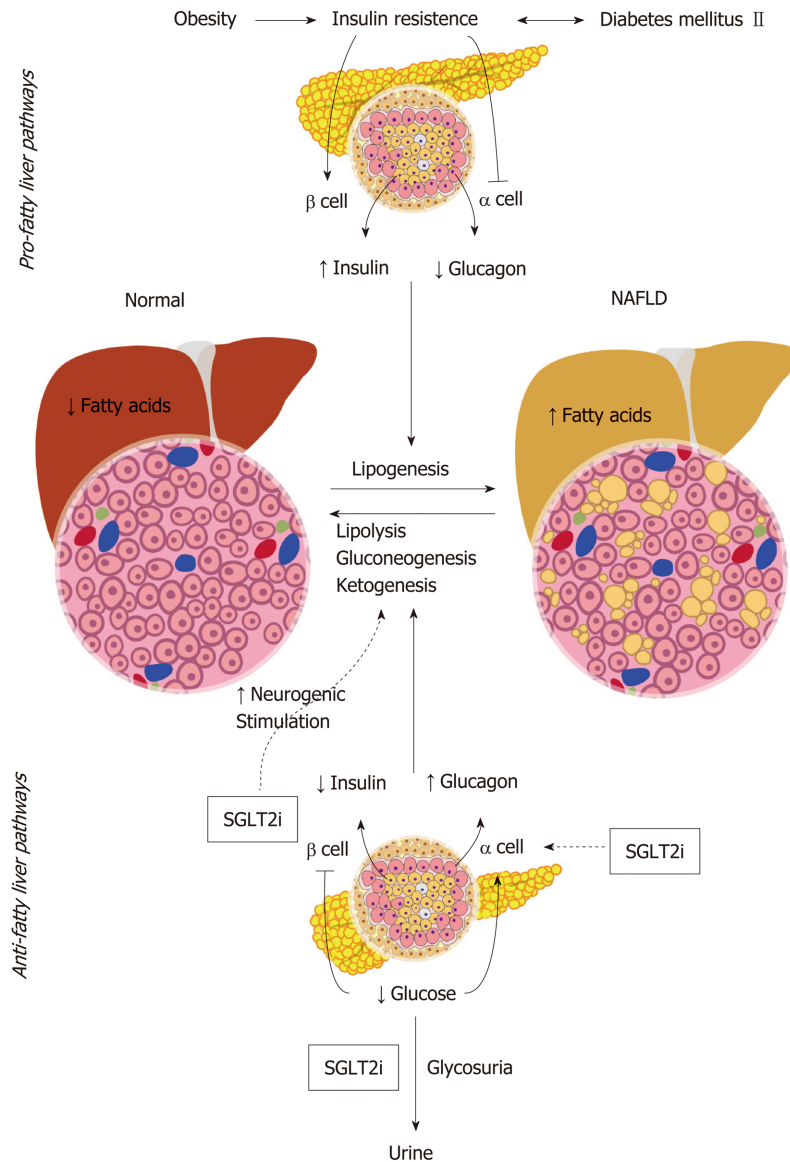
Figure 1 Mechanism of action of Sodium-glucose co-transporter-2 inhibitors in non-alcoholic fatty liver disease. Obesity-induced insulin resistance leading to diabetes are the major risk factors for non-alcoholic fatty liver disease (NAFLD). The increase in insulin secretion and inhibition of glucagon secretion by the islet cells in the pancreas ultimately leads to the stimulation of lipogenesis, ultimately shifting the balance towards hepatic steatosis and NAFLD. Sodium-glucose co-transporter inhibitors primary effect is inducing glycosuria causing lowering of the blood glucose levels. This inhibits the secretion of insulin and stimulates glucagon secretion, causing a higher insulin-to-glucagon ratio, which increases the lipolytic, gluconeogenetic, and ketogenetic pathways. This results in reduction in the hepatic steatosis in NAFLD.

CANAGLIFLOZIN

Canagliflozin is the most commonly prescribed SGLT2 inhibitors for patients with T2DM. In animal models of NAFLD, canagliflozin used in high-fat diet fed mice reduced ALT levels and prevented the development of cirrhosis as evident by reduced steatosis on histologic examination[41]. Canagliflozin also showed favorable outcomes when pitted against sitagliptin, a DPP4-inhibitor, in the management of Japanese patients with biopsy-proven NAFLD[42]. It demonstrated reductions in BMI, fasting blood glucose, body weight, HbA1c, and ALT levels[42]. It is worth noting that the study was a retrospective cohort study and the results could not be directly attributed to canagliflozin[42]. Canagliflozin used for 24 wk in patients aged 20-64 years with biopsy-proven NAFLD complicated with T2DM showed significant reductions in BMI, fasting blood glucose, waist circumference, ferritin level, gamma-glutamyltransferase (GGT) level, and type IV collagen 7S[43]. Furthermore, there was a

decrease in the NAFLD score in all patients included in the study[43]. However, the study was a single center, single arm study and only involved 5 patients. Hence, extrapolation to the general population was difficult[43]. A systemic analysis pooled the results of 4 studies in which canagliflozin was used for 26 or 52 wk *vs* placebo or sitagliptin, and showed significant reductions in HbA1c, body weight, ALT, AST, alkaline phosphatase and gamma-glutamyl transferase. The favorable changes in liver function tests were attributed to reductions in HbA1c and body weight[44]. In western-diet fed murine models, canagliflozin showed significant improvements in hyperglycemia, hyperinsulinemia and liver function tests as early as 8 wk after initiation, and significant improvements in hepatic fibrosis after 20 wk of treatment. There was additionally a significant reduction in the number of liver tumors after 1 year of canagliflozin treatment[45]. More recent evidence emerged on the positive effect of canagliflozin with a human study demonstrating significant reductions in hepatic steatosis, hepatocyte ballooning, fibrosis, and inflammation after 24 wk of treatment in patients with T2DM and NAFLD[46]. Another prospective cohort study also demonstrated significant reductions in ALT, AST, GGT, triglycerides, HbA1c, and body weight[47].

IPRAGLIFLOZIN

Ipragliflozin used in high fat diet fed murine models that had streptozocin nicotanamide-induced T2DM showed improvement in glucose tolerance, blood glucose, insulin, and lipid levels[48]. Moreover, there were reductions in hepatic steatosis and liver levels of oxidative stress biomarkers as well as improvement in aminotransferase levels after 4 wk of treatment[48]. Another murine based study demonstrated similar results by demonstrating improvement in insulin resistance, free fatty acids, AST and ALT levels, and liver fat content with an 8 wk course of ipragliflozin[49]. Murine models fed a choline-deficient l-amino acid-defined diet developed liver triglyceride increase, liver fibrosis, and mild inflammation[50]. These changes were prevented with 5 wk of ipragliflozin therapy which suggests that SGLT2 inhibitors might play a role in the prevention of hepatic fibrosis[50]. In human subjects, ipragliflozin used for 16 wk in patients with T2DM showed significantly reduced fatty liver index, fasting plasma glucose, HbA1c, body weight, visceral adipose tissue, and subcutaneous tissue and fat mass[51]. When ipragliflozin was compared to pioglitazone, a PPAR agonist, in patients with T2DM, similar effects were observed with regards to blood glucose, HbA1c, liver to spleen ratio, AST and ALT levels. There was a significantly reduced body weight and fat area with ipragliflozin[52]. The co-administration of ipragliflozin with incretin-based drugs such as GLP-1 analogs or DPP-4 inhibitors showed significant reductions in HbA1c, body weight, serum ALT levels, and fibrosis-4 index[53]. The most important aspect observed here is that ALT levels were not normalized with incretin-based therapies until combined with iprafliglozin, which suggests a synergistic effect between incretin-based therapies and SGLT2 inhibitors[53]. In a larger multicenter prospective study involving patients with T2DM and NAFLD, ipragliflozin administration for 24 wk showed significant reductions in HbA1c, AST, ALT, body weight, and steatosis[54]. It further suggests that SGLT2 inhibitors can help in the management of patients with T2DM with metabolic syndrome[55].

DAPAGLIFLOZIN

Dapagliflozin is a highly selective competitive inhibitor of SGLT2. In genetic murine models of obesity and diabetes, such as db/db, dapagliflozin was shown to improve markers of liver injury such as MPO and reactive oxygen species[56]. Even in diet-induced obesity, dapagliflozin showed decreased serum ALT, AST, hepatic lipid accumulation, and hepatic fibrosis in mice that were fed western diet compared to low-fat diet. Dapagliflozin also attenuated the western diet-mediated increases in body weight, plasma glucose, plasma triglycerides, and renal fibrosis[57]. This suggests that dapagliflozin can be used for reversal of hepatic steatosis associated with NAFLD, even in humans. Indeed, the use of dapagliflozin and empagliflozin demonstrated a significant reduction in ALT levels in patients with T2DM. This change was independent of HbA1c and fasting glucose levels[58]. Dapagliflozin also showed significant improvement in BMI, AST levels, ALT levels, fasting plasma glucose and HbA1c when used for 24 wk in patients with biopsy-proven NASH and T2DM[59]. More recently, a study investigating the use of dapagliflozin for 24 wk in patients with T2DM and NASH showed a significant reduction in ALT and GGT

levels as well as significant improvement in liver stiffness measurement[60]. Dapagliflozin was also found to significantly reduce hepatic steatosis and attenuate severe liver fibrosis in patients with T2DM and NAFLD[60]. A randomized double-blind placebo-controlled trial involving 84 patients with T2DM and NAFLD demonstrated significant reduction of liver fat content with combination dapagliflozin and n-3 carboxylic acid for 12 wk. Dapagliflozin monotherapy also decreased hepatic injury biomarkers and as mentioned earlier, ALT, AST, GGT and body weight[61].

EMPAGLIFLOZIN

Empagliflozin, *vs* combination empagliflozin and linagliptin, a DPP-IV inhibitor, *vs* placebo demonstrated that empagliflozin monotherapy reduced the severity on NASH at 21 d in NASH mouse-models[62]. Furthermore, the combination of empagliflozin and linagliptin led to reduction in body weight and liver collagen deposition *i.e.*, fibrosis indicating a probable synergistic effect upon coadministration[62]. The E-LIFT trial which involved patients with T2DM and NAFLD, showed that empagliflozin in addition to standard diabetes management causes a significant reduction in liver fat content and ALT and a non-significant difference in GGT and AST levels[63]. A subgroup analysis from the EMPA-REG trial showed significant reduction in ALT independently of changes in HbA1c or body weight[64].

REMOGLIFLOZIN

Mice placed on a high fat diet for 11 wk followed by administration of remogliflozin or placebo for 4 wk resulted in significant reduction of ALT and ALT levels. Both liver weight and hepatic triglyceride content were significantly reduced. Furthermore, when compared to canagliflozin and dapagliflozin, remogliflozin had a significantly higher effect with regards to oxygen radial absorbance capacity. This study demonstrated that remogliflozin had clear significant effects on mice with NAFLD and NASH[65]. Similar studies are yet to occur in humans.

LUSEOGLIFLOZIN

Mice models receiving streptozotocin and nicotinamide to reduce insulin secretion followed by administration of luseogliflozin or placebo exhibited reductions in ALT levels along with reduction in the increase of collagen deposition in the treatment group[66]. A human-based study in which luseogliflozin was compared to metformin in patients with type 2 diabetes and NAFLD demonstrated significantly lower liver-to-spleen ratio, visceral fat, HbA1c, and BMI with luseogliflozin after 6 months of use[67]. Another prospective study showed significant reductions in ALT, AST, BMI, and GGT levels after 24 wk of therapy in patients with T2DM and NAFLD[68].

POTENTIAL ANTITUMORIGENIC EFFECTS OF SGLT2I

One of the dreadful complications of NAFLD is the development of HCC, which appears to be increasing[69], regardless of the presence cirrhosis. One *in vitro* study showed that the effects of canagliflozin on HCC showing effects that include antiproliferation, cellular arrest, and apoptosis of cancer cells[70]. Such effects were also shown to decrease HCC tumor burden in a murine xenograft model of human HCC. Interestingly, those effects were glycemic-state independent[70]. Although the data supporting the antitumorigenic effects of SGLT2 inhibitors is limited, it is potentially a promising medication in preventing HCC in patients with NAFLD. Since normal and cancer colonic tissue express SGLT2, in one case report of colon cancer with liver metastasis, treatment with dapagliflozin in combination with cetuximab showed substantial response to therapy[71]. Although such results remain in need of validation, they show the potential of SGLT2 inhibitors in the carcinogenesis that could not only be HCC-specific.

ADVERSE REACTIONS DUE TO SGLT2 INHIBITORS

There have been a few reported side effects with regards to SGLT2 inhibitors use,

namely vulvovaginal candidiasis and urinary tract infections[72], hypotension[73] through osmotic diuresis causing hypovolemia, acute kidney injury[74] likely secondary to hypoperfusion of the kidneys in the setting of hypovolemia, bone fractures[75], increased risk of amputation[76], and euglycemic diabetic ketoacidosis[77]. Although the mechanisms of SGLT2 inhibitors ketoacidosis is not fully understood, the food and drug administration (FDA) has recognized it as an important side effect to watch for, especially in patient with type-1 diabetes mellitus[78]. Monitoring of kidney function is essential during treatment particularly in those taking concomitant diuretics and other medications that predispose to hypovolemia and acute kidney injury[79]. A major potentially lethal rare consequence of SGLT2 inhibitors use is the development of Fournier's gangrene. However, it has only been reported in 12 cases, but was serious enough the FDA issued an official warning statement for clinicians to be aware of[80]. Further, it is important to acknowledge that SGLT2 inhibitors were only FDA-approved as recently as 2013[81], and as such there is ongoing research for their long-term safety profile[79] (Table 1).

CONCLUSION

Limited pharmacologic options with proven efficacy makes the treatment of NAFLD challenging. Apart from weight-loss, there are few pharmacologic treatment options. However, recent emerging evidence of the use of SGLT2-inhibitors in patients with NAFLD is promising. Those agents have shown to improve levels of serum transaminases, decrease steatosis, prevent cirrhosis and HCC, and reduce body weight. They are also gaining wide popularity due to their anti-diabetic effect and potential cardiovascular benefits. However, prior to establishing the use of those agents clinically, further studies including randomized controlled trials should be conducted.

Table 1 Sodium-glucose co-transporter inhibitors and their use in non-alcoholic fatty liver disease

SGLT2 inhibitor	ALT	AST	GGT	Bilirubin	BMI	Steatosis	Inflam-mation	Fibrosis	HCC	Adverse effects	Study organism	Ref.
Canagli-flozin	↓	↓	↓	↑	↓	↓	↓	↓	↓	Urogenital tract fungal infections, DKA, amputat-ions, bone fractures	Human	[44,46,76]
Ipraglif-lozin	↓	-	-	NR	↓	↓	↓	↓	NR	Urinary tract infections	Human/Mouse	[49,51]
Dapagli-flozin	↓	↓	↓	NR	↓	↓	↓	NR	NR	Urogenital tract infections, bladder cancer, DKA, amputat-ions	Human	[59,61,76,81]
Empagl-iflozin	↓	-	-	-	↓	↓	↓	↓	NR	Genital tract infections, DKA	Human/Mouse	[62-64]
Remogl-iflozin	↓	↓	NR	NR	↓	↓	↓	NR	NR	Urogenital tract fungal infections	Mouse	[65]
Luseogl-iflozin	↓ or -	↓	↓	NR	↓	↓	↓	↓ or -	NR	Vaginal itching, dehydra-tion	Human/Mouse	[66-68]

SGLT2: Sodium-glucose co-transporter 2; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyltransferase; BMI: Body mass index; HCC: Hepatocellular carcinoma; DKA: Diabetic ketoacidosis; NR: Not reported; ↓: Decreases; ↑: Increases; -: No change.

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