Journal of Mind and Medical Sciences

https://scholar.valpo.edu/jmms/
https://proscholar.org/jmms/
ISSN: 2392-7674

The effects of SGLT2 inhibitors in patients with metabolic dysfunction-associated fatty liver disease; a narrative review

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ABSTRACT

Worldwide, metabolic dysfunction-associated fatty liver disease (MAFLD) is a significant public health concern, especially since more than fifty percent of people with type 2 diabetes are affected by it. This pathological condition includes all states of fatty liver disease, from non-alcoholic fatty liver disease (NAFLD) to steatohepatitis (NASH). Prolonged evolutions can lead to cirrhosis and cancer, so treatment must be started early. Hepatic steatosis may be improved by sodium glucose co-transporter 2 inhibitors (SGLT2 inhibitors), which prevent glucose reabsorption in the proximal renal tubule and increase urinary excretion, thus lowering plasma glucose levels. Experimental studies in animal models have suggested that SGLT2 inhibitors may have beneficial modulatory effects on NAFLD and NASH, while numerous clinical trials have demonstrated their favorable effects on the liver enzymes, body mass index, blood lipids, blood glucose, and insulin resistance in NAFLD patients. This review highlights the state of knowledge regarding the epidemiology, diagnosis and pathogenetic pathways of MAFLD, focusing primarily on the effectiveness of SGLT2 inhibitors as a promising drug class in the treatment of NAFLD.

Category: Review

Received: October 11, 2023

Accepted: January 14, 2024

Published: April 25, 2024

Keywords:

NAFLD, SGLT2 inhibitors, fatty liver, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, inflammation

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Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a metabolic disorder characterized by the presence of excessive fat accumulation in the liver. In addition to fat accumulation, at least one of the following criteria should be present: overweight/obesity, type 2 diabetes mellitus, or other metabolic disorder [1]. MAFLD includes two distinct physiopathological conditions: non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The primary histological feature of NAFLD is the accumulation of at least 5% lipids in hepatocytes, but without the presence of hepatocellular injury and unrelated to alcohol, drug use, or other diseases that could lead to hepatic steatosis [2]. In contrast, NASH is defined by at least 5% lipid in the liver cells, along with inflammatory symptoms and hepatocellular damage (regardless of whether there is fibrosis or not) and having the potential to lead to liver failure, cirrhosis, or the emergence of hepatocellular carcinoma (HCC) [3].

NAFLD is considered to have the highest global rate of increase among chronic liver diseases due to the recent expansion of obesity and the metabolic syndrome (MetS), with an estimated global incidence of 25% in the adult population [4]. The regions which highest rates of prevalence are South America (31%), the Middle East (32%), the United States (24%), and Europe (23%), while Africa (14%) has the lowest rates [5]. NAFLD is the most common liver disease in the Western world, where it affects 30%–40% of men and 15%–20% of women. It exceeds 70% prevalence in patients with type 2 diabetes mellitus (T2DM) [6,7]. The frequency and severity of secondary NAFLD related liver fibrosis are also likely to increase. The incidence of these conditions increases considerably with

To cite this article: Popoviciu MS, Păduraru L, Rahman MM, Supti FA, Stoica RA, Reurean-Pintilei D, Bica CI, Cavalu S. The effects of SGLT2 inhibitors in patients with metabolic dysfunction-associated fatty liver disease; a narrative review. *J Mind Med Sci*. 2024;11(1):62-77. doi:10.22543/2392-7674.1439

age, as a result of the prolonged evolution of the disease that favors exposure to factors that cause liver damage [8].

T2DM and NAFLD are frequently associated in medical practice (MAFLD), acting synergistically and leading to undesirable outcomes [9]. One in five T2DM patients with normal liver function had biopsy-proven NASH [10]. The risk of cardiovascular disease, liver cirrhosis, liver cancer, and death are significantly increased when T2DM and NAFLD (MAFLD) are associated [11-14].

NASH occurrence is a difficult and poorly understood process. Numerous animal studies have recently been performed to better understand the pathophysiology of NAFLD and NASH [15,16]. There is evidence that the development of NASH usually consists of two stages. Accumulation of fat in the liver is the initial stage of this process, leading to worsening insulin resistance. Modifications in both cells and molecules that result from oxidative stress and the oxidation of fatty acids in the liver (as a result of numerous factors: cytokine damage, hyperinsulinemia, hepatic iron and/or lipid peroxidation, extracellular matrix variation, energy homeostasis, and altered immune system function) represent the second stage of this process [17]. The development insulin resistance is generally a complex process. In metabolic syndrome, as is the case in most patients with MAFLD, increased fat mass and adipocyte differentiation play a pivotal role in the development of insulin resistance.

MAFLD can be divided into two distinct types. The first type is NAFLD, where insulin resistance is now considered to be the main pathophysiological cause. The second type is NASH, being linked to infectious pathologies and the use of liver toxic substances (including drugs), which can lead to the appearance of hepatic steatosis [18].

For T2DM patients with NAFLD, it has been shown that lifestyle changes related to diet and exercise continue to be the cornerstone of contemporary therapy [18]. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are anti-diabetic medications that proved to have multiple positive effects on patients' weight and liver enzymes (in addition to their hypoglycemic activity), which may ameliorate or even stop the progression of NAFLD [19,20].

The aim of the review is to describe the current knowledge about the pathogenetic pathways of MAFLD, and the mechanisms by which SGLT2 inhibitors act on NAFLD and NASH. Thus, we systematically reviewed several studies to highlight the therapeutic benefits of the class of SGLT2 inhibitors, especially in patients with NAFLD.

Methodology. The medical literature search was conducted in several databases (PubMed, Springer Link, ScienceDirect and Scopus), to identify relevant publications related to this topic. The search terms and keywords, alone or in combination, were: NAFLD, Non-alcoholic fatty liver disease, NASH, Non-alcoholic steatohepatitis, Fatty liver, Type 2 diabetes, Diabetes mellitus type 2, SGLT-2 inhibitors, Sodium glucose-cotransporter-2 inhibitors, Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin, Tofogliflozin, Sotagliflozin, Ertugliflozin, Remogliflozin, and Sergliflozin. The relevant articles were selected using predefined algorithms according to the PRISMA criteria, the obtained data being carefully examined by two independent researchers. The selection procedure, evaluation and final inclusion criteria are presented in Figure 1.

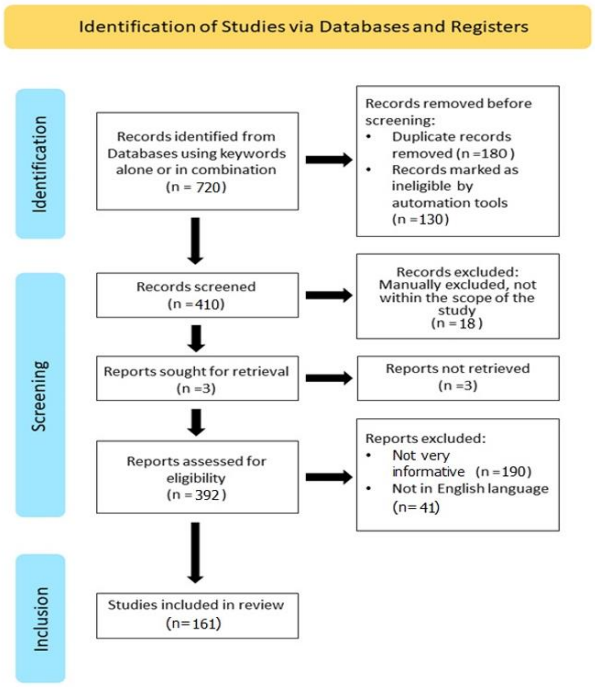

Figure 1. Flow chart presenting the literature selection, inclusion and exclusion criteria

Discussions

SGLT2 inhibitors- general features

SGLT2 inhibitors seem to be among the most promising medications used to treat T2DM and show clear advantages in individuals with NAFLD. The limit of glucose filtration in the kidneys is equivalent to 180 g/day under normo-glycemic settings and with intact renal function; when plasma glucose levels above this threshold, they are removed in the urine with salt. There are two different kinds of cotransporters: SGLT1, which is found in the intestine and the area of the proximal convoluted tubule below the Bowman's capsule, and SGLT2, which is only found in the renal tubule. SGLT2 reabsorbs 97% of the glucose upstream of the proximal tubule, while SGLT1 reabsorbs the remaining 3%. To limit renal glucose loss in hyperglycemic situations, the kidneys raise their renal resorption capacity to a maximum of 600 g/day [2]. Therefore, inhibiting this transporter would not only improve glycemic control but also salt homeostasis and water retention. This activity, which is mediated by the SGLT cotransporter, increases the reabsorption of salt and liquids in addition to glucose.

A novel family of oral active medications called SGLT2 inhibitors is used to treat T2DM. Phlorizin, a glucoside isolated from apple tree bark, was subsequently shown to have the potential to produce glycosuria, its effectiveness to lower blood sugar levels to restore insulin sensitivity being demonstrated in diabetic rats. However, its application as a medicinal agent was limited due to low oral availability, intestinal adverse effects and a short half-life time. Following, dapagliflozin, other (empagliflozin, canagliflozin, and ertugliflozin) SGLT2 inhibitors were authorized for the treatment of T2DM (starting with 2012 in Europe). Today, SGLT2 inhibitors, also known as gliflozin, include additional medications like ipragliflozin, luseogliflozin, and tofogliflozin (launched in Japan in 2014), sotagliflozin (approved in Europe for specific patients with type 1 diabetes who could not achieve adequate glycemic control, but withdrawn at the request of marketing authorization holder), and finally remogliflozin (launched in India in April 2019). Phlorizin and remogliflozin are examples of O-glucoside analogs, in which the sugar group is linked to another group via a glycoside bond. C-glucoside analogs, such as dapagliflozin and numerous others, have higher pharmacokinetic stability and SGLT2 selectivity (Figure 2) [21]. Given their distinct mode of action, SGLT2 inhibitors may be used in combination with other glucose-lowering treatments as an adjuvant therapy for greater glucose reduction.

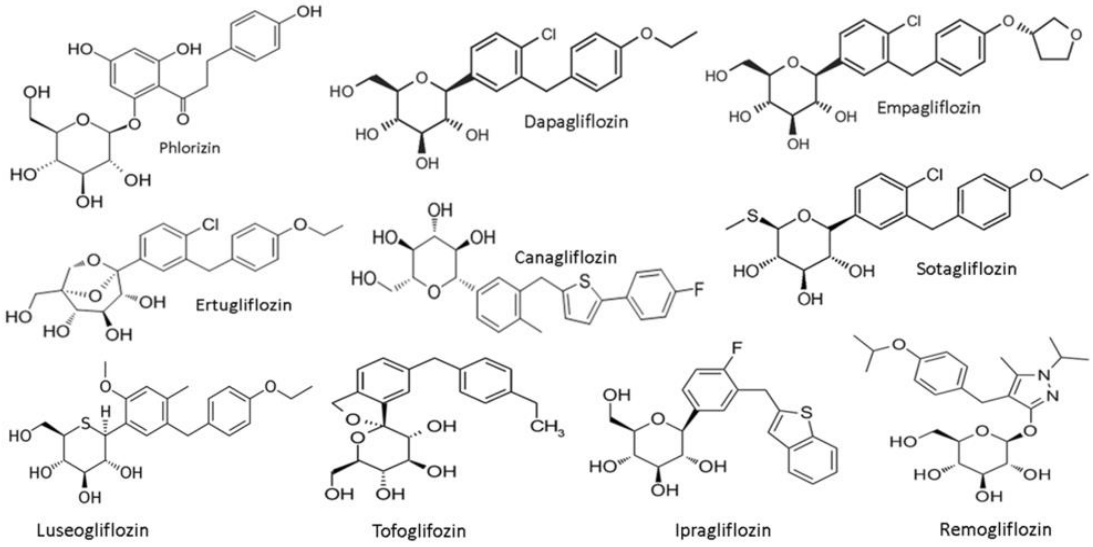

Figure 2. The SGLT2 inhibitors class

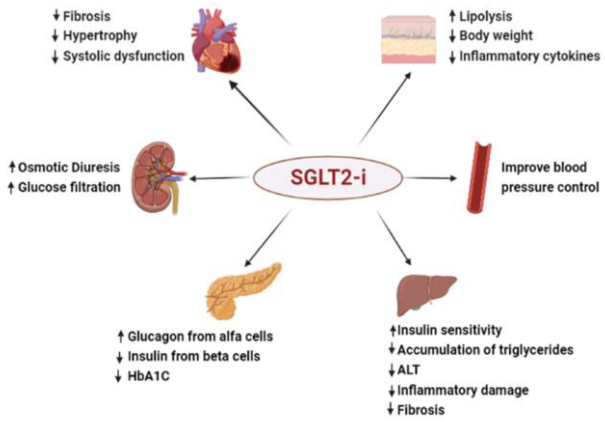

Figure 3. Multisystemic effects of SGLT2i

SGLT2 inhibitors were conceived to treat T2DM by preventing the kidneys from reabsorption of glucose and lowering blood sugar levels [22]. In addition, they can enhance liver function in MAFLD patients, according to clinical investigations (Figure 3). They also advocated for the treatment of T2DM and cirrhosis-related ascites, due to a consistent influence on natriuresis and diuresis [3].

The role of SGLT-2 inhibitors in the current treatment of type 2 diabetes

T2DM is a complex metabolic disease characterized by chronic hyperglycemia due to defective insulin secretion, insulin resistance, and increased endogenous glucose or glucagon production [23-26]. Cardiovascular disease is two to three times more probable to develop in T2DM, and the risk is enhanced in the context of chronic kidney disease [25].

Type 2 diabetes treatment alternatives have expanded with the introduction of SGLT2 inhibitors. These drugs improve glycemic control but also have other cardiovascular and metabolic benefits. This class reduces HbA1c by approximately 0.6–1.0% [25,27]. Additionally, SGLT2 inhibitors enhance β-cell performance by enhancing glucotoxicity and decreasing -cell burden rather than by increasing insulin release [27,28]. By increasing endogenous suppression of glucose synthesis after delivery and improving beta-cell function and insulin sensitivity, SGLT2 inhibitor-induced glycosuria reduced fasting and postprandial glycemia. It also decreased tissue glucose excretion [29]. Also, studies have shown that the secretion

of low glucagon and hepatic gluconeogenesis was improved [30]. The end-of-treatment liver fat content (MRI-PDFF) for the empagliflozin group significantly decreased compared to baseline, whereas the control group had no significant change. The main outcomes highlighted by the clinical trials using empagliflozin or dapagliflozin versus placebo in patients with T2DM associated with NAFLD or CVD, are summarized in Table 1.

Table 1. Evaluation of the effects of SGLT2 inhibitors against placebo on liver enzymes and measurements of hepatic fat content in people with T2DM included in randomized controlled trials

Patients	Duration (weeks)	Treatment	N	ALT	AST	GGT	MRI-PDFF (% liver fat)	Ref.
NAFLD+ T2DM (1RCT)	20	Empagliflozin 10 mg	22	64.3→ 49.7 P=0.001	44.6 → 36.2 P=0.040	65.8 → 50.9 P=0.002	16.2 → 11.3 P<0.0001	[31]
		Placebo	20	65.3→ 61.6 P= NA	45.3 → 44.6 P= NA	63.9 → 60.0 P= NA	16.4 → 15.5 P=0.054	
T2DM (RCT)	24	Empagliflozin 10 or 25mg	1,652	28.2→ 23.6 P<0.0001	23.0 → 21.0 P<0.0001	NA	NA	[32]
		Placebo	825	28.4→ 27.0 P= NA	23.1 → 22.5 P= NA	NA	NA	
T2DM+CVD (EMPAREG OUTCOME® trial)	164	Empagliflozin 10 or 25 mg	4,611	25.5→ 22.5 P=0.004	22.5 → 21.3 P=0.107	NA	NA	[33]
		Placebo	2,313	26.2→ 24.4 P= NA	22.9 → 22.4 P= NA	NA	NA	
NAFLD +T2DM (RTCs parallel group study)	12	Dapagliflozin 10 mg	19	67 → 53 P<0.05	52 → 45 P<0.05	97 → 89 P<0.05	17.3 → 15.1 P<0.05	[34]
		Placebo	19	57 → 54 P= NA	49 → 47 P= NA	54 → 50 P= NA	15.1 → 14.5 NS	

Legend: MRI-PDFF = magnetic resonance imaging-proton density fat fraction; NA = not available; NS = not significant; NAFLD = non-alcoholic fatty liver disease; RCTs = randomized controlled trials; ALT =alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase

Current recommendations for the use of SGLT 2 inhibitors in type 2 diabetes therapy

The American Diabetes Association and the European Association for the Study of Diabetes are the two recognized societies that meet annually to update previous consensus statements on the management of hyperglycemia in adult type 2 diabetes mellitus. In 2022, following the systematic examination of previous publications, new recommendations were established. Among them are the indications related to therapy with SGLT2 inhibitors. Cardiorenal outcomes studies have shown their effectiveness in lowering the risk of major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, heart failure hospitalization (HF) and all-cause mortality and improving renal outcomes. The type 2 diabetic's unique profile, including the presence of comorbidities, adverse reactions risk, preferences and circumstances, should be taken into consideration while choosing a hypoglycemic medication [35,36]. Certain medications, particularly SGLT2 inhibitors, have been demonstrated to protect organs (heart, kidney) in part independently of their blood glucose-lowering effect. Such organ protection is also seen in people who do not have T2DM. Based on these criteria, all individuals with diabetes and established or subclinical CVD should be prescribed a drug with a demonstrated cardiovascular benefit from the glucagon-like peptide-1 receptor agonist (GLP-1 RA) or the SGLT2 inhibitor class, independent of HbA1c level or the presence of additional glucose-lowering medications [37]. Also, all people with diabetes and CKD (eGFR 60 mL/min per 1.73 m^2 or Urinary Albumin Creatinine Ration >3.0 mg/mmol/ >30 mg/g) should be given a medication from the SGLT2 inhibitor class that has a documented renal benefit.

Those who have heart failure - HF (HF with reduced ejection fraction or HF with preserved ejection fraction) should also take a medication from the class of SGLT2 inhibitors with proven benefits for this population. The choice to utilize a GLP-1 RA or an SGLT2 inhibitor with demonstrated effectiveness in persons with HF, CKD, CVD, or multiple risk factors for CVD should be made independently of baseline HbA1c. It is recommended to prioritize the use of organ protective drugs (GLP-1RA, SGLT2i) in those with cardiorenal disease or NASH or at increased risk of developing them [38].

Effects of SGLT-2 inhibitors on insulin resistance

Chronic hyperglycemia causes a condition known as glucose toxicity, which impairs insulin sensitivity by reducing -cell activity and endogenous insulin secretion. This "glucose poisoning" is a factor in how hyperglycemia worsens over time [39] and to maintain glycemic control as the condition worsens, most T2DM patients need greater doses of insulin [40]. However, increasing the daily dose of insulin can cause

more insulin resistance, which would raise the risk of hypoglycemia and lead to an increase in body weight.

Glycemic lowering effect

The mechanism underlying the blood glucose-lowering effect is represented by SGLT2 blockade, which will result in a decrease in the renal threshold for glucose (RTG) [41]. Thus, in diabetes patients, SGLT2 inhibitors lower glucose absorption by 30–50% [42,43].

Patients who took SGLT2 inhibitors in conjunction to insulin therapy had lower levels of HbA1c than control patients, according to a 2017 meta-analysis of nine randomized controlled studies with a total of 3,069 individuals (n = 1,000, MD-1.35%, 95% confidence interval/ CI -2.36 to -0.34; p = 0.009). In addition, a marginally significant drop in fasting blood sugar was seen (n = 905, MD-1.01 mmol/L, 95% CI-1.98 to 0.04; p = 0.04) [44]. The Canagliflozin Cardiovascular Assessment Study found that canagliflozin doses of 100 and 300 mg combined with insulin therapy decreased HbA1c by 0.62% compared to placebo (95% CI 0.54 –0.69; p < 0.001) vs. −0.73% (95% CI 0.65–0.81; p < 0.001) after 18 weeks and 0.58% (95% CI 0.48 to −0.68; p < 0.001) vs. 0.73% (95% CI 0.63-0.83; p <0.83) after 52 weeks. In addition, a significant decrease in fasting glucose was observed after 18 weeks, as well as after 52 weeks [45]. Other SGLT2 inhibitors, like dapagliflozin and empagliflozin, were also shown to lower HbA1c and fasting blood glucose levels in clinical trials [46-50].

Reduction of the daily dose of insulin

The potential mechanisms by which SGLT2 inhibitors improve β-cell function and reduce insulin resistance in T2D patients have been examined in recent research [51].

- Insulin resistance and inflammation are reduced by SGLT2 inhibitors through polarizing M2 macrophages. Obesity, insulin resistance, and T2DM are all linked to chronic inflammation [52,53]. In addition to increasing immune cell recruitment and innate immune responses, obesity and heterotopic fat deposition also alter the phenotype of macrophages and enhance the infiltration of proinflammatory immune cells into metabolic organs, which leads to the development of insulin resistance [54,55]. Macrophage recruitment and polarization in particular, are key to obesity-induced inflammation and insulin resistance. Inhibition of M1 macrophage polarization and activation of the alternative M2 macrophage could prevent worsening of inflammation and insulin resistance [53,55,56]. Empagliflozin has been shown to decrease macrophage accumulation and promote the M2-dominant phenotypic differentiation of liver and white adipose tissue macrophages, hence reducing inflammation caused by obesity [57]. Empagliflozin may also attenuate inflammation and insulin resistance in obesity by decreasing M1 macrophage and T-cell accumulation and increasing the number of M2 macrophages [58].
- SGLT2 inhibitors impact the hormones produced by adipocytes. Serum leptin levels in T2DM patients [59] and FGF-21 [60] is increased while the level of serum adiponectin is decreased [61]; these alterations are thought to be closely connected to the start and progression of insulin resistance [62,63]. According to Tahara et al., mice and people with T2D have different levels of these adipocyte-derived hormones, but these alterations can be undone if the diabetic condition is stabilized. These results suggest that SGLT2 inhibitors decrease insulin resistance in T2DM [64]. The Matsuda-DeFronzo index and mood index, which are recognized markers of insulin secretion and insulin resistance, respectively, improved after administration of long-acting SGLT2 inhibitors, demonstrating that SGLT2 inhibitors reduce insulin resistance and secretion to insulin [65]. Long-acting SGLT2 inhibitors may lower daily blood glucose excursion, safeguard pancreatic function, and enhance glucose tolerance and insulin resistance as compared to intermediate-acting SGLT2 inhibitors [65].
- The development of numerous β-cell-related factors is encouraged by SGLT2 inhibitors. A larger mass of pancreatic beta cells was seen in mice receiving luseogliflozin treatment because of increased cell proliferation and decreased apoptosis. The levels of β-cell-related elements, including as insulin, MafA, PDX1, the GLP-1 receptor, and the glucose transporter Glut2, were elevated in mice receiving empagliflozin treatment. After empagliflozin treatment for one week, β-cell growth was encouraged and its protective effects against pancreatic β-cells were noticed [66].

Nine randomized controlled studies comparing SGLT2 inhibitors plus insulin therapy to placebo plus insulin therapy were examined in a 2017 meta-analysis. Studies that used an insulin pump or numerous daily basal treatment injections of bolus insulin were also included. According to research, SGLT2 inhibitors may reduce the overall daily dose of insulin, (n = 813, MD 4.85 U/24 h, 95% CI 2.29–7.42, p = 0.002) compared with placebo-controlled studies [44].

A decrease in the total daily insulin dose was found in several randomized controlled clinical trials (ie, basal plus bolus insulin dose or total daily insulin pump dose) after one group received SGLT2 inhibitors plus insulin compared to the placebo plus insulin group [44-50]. Harris et al. found that SGLT2 inhibitors may result in a more pronounced reduction in insulin dose for participants on an increased insulin regimen (100 IU/day). At 3 and 6 months, canagliflozin caused an insulin dose reduction of 17 IU for patients taking 101–200 IU of insulin daily. Additionally, between 20 and 70 IU/day less insulin was administered to people taking more than 200 IU daily at three and six months following canagliflozin and dapagliflozin administration [66]. Another cross-sectional study indicates that SGLT2

inhibitors may block glucagon-induced insulin secretion in β-cells and decrease insulin resistance, evidenced by a significant 21% reduction in HOMA2-IR (homeostatic model assessment of insulin resistance) [67].

Body weight reduction

Body weight loss is caused by a variety of reasons, in addition to the caloric deficit caused by glycosuria and energy imbalance [68,69]. First, SGLT2 inhibitors change the energy metabolism to rely more on sugar and fat.

According to studies, the usage of fat as fuel was shifted as a result of the increased oxygen use and carbon dioxide expiration brought on by SGLT2 inhibitors. By triggering the adenosine monophosphate-activated protein kinase (AMPK) pathway and modulating the production of adiponectin and leptin, SGLT2 inhibitors promote fatty acid β-oxidation. Additionally, SGLT2 inhibitors boost the expression of adiponectin and leptin in white adipose tissue and boost fatty acid oxidation. The regulation of food intake and energy homeostasis depends on the adipokines leptin and adiponectin, which are known as adipose tissue-specific adipokines [70]. Empagliflozin decreases leptin expression and up-regulates adiponectin mRNA expression. Adiponectin increases fatty acid β-oxidation and decreases serum triglyceride and free fatty acid levels. As a result, increased adiponectin expression and decreased leptin expression promote energy expenditure and lipolysis, which reduce body weight [71]. Weight gain is frequently a side effect of insulin therapy [72,73]. Combining other antidiabetic drugs such as sulfonylureas and thiazolidinediones with insulin also leads to significant weight increase [74-76].

The use of SGLT2 inhibitors in conjunction with insulin as a T2D therapy regimen was found to avoid this weight gain and result in a considerable reduction in body weight, according to meta-analysis [44] and additional clinical investigations [45–50]. SGLT2 inhibitors can dramatically speed up weight loss compared to other diabetes medications like pioglitazone and DPP-4 inhibitors with weight reductions of up to 3.5 kg recorded at 52 weeks after canagliflozin [76-78].

Studies on animals have also shown that using SGLT2 inhibitors causes weight reduction. Rats' development of hepatic steatosis and weight gain brought on by a high-fat diet (HFD) were prevented after 8 weeks of tofogliflozin use [68]. Body weight was greatly lowered and lipid breakdown was enhanced after taking dapagliflozin for 35 days [79].

Effects of SGLT-2 inhibitors on plasma lipid values

Current research suggests that these medications may offer extra advantages beyond their glycemic-lowering effects by restoring normal lipid metabolism and so protecting against diseases caused by dyslipidemia and those related to it. At least five cellular pathways—lipid biogenesis (lipogenesis and lipolysis), lipid peroxidation, lipid transport, cholesterol biosynthesis, and fatty acid -oxidation—are influenced by SGLT2 inhibitors when it comes to regulating lipid metabolism [80]. Other supplements or antioxidants for NAFLD improvement have been studied [81,82].

Lipid biogenesis

Two crucial factors that govern lipid homeostasis and total body fat are lipogenesis and lipolysis, both of which are tightly regulated metabolic processes [83,84]. However, this balance is disturbed and dyslipidemia occurs in a pathological setting like diabetes [85]. Lipolysis and lipogenesis are significantly impacted by SGLT2 inhibitors [65].

In diabetic mice, de novo lipogenesis was lowered by empagliflozin, according to Jojima et al. [86]. Through the down regulation of FAS (fatty acid synthesis) and ACC (Acetyl-CoA carboxylase) and a reduction in lipogenesis in the hepatocytes of diabetic mice, researchers discovered that empagliflozin medication for three weeks prevented the onset of fatty liver [87]. In hospitalized T2DM patients, Lauritsen et al. discovered that 4 weeks of empagliflozin medication increased circulating free fatty acids and caused lipolysis [87]. They hypothesized that the reason empagliflozin had this effect was probably because it reduced CIDEC (Cell Death Inducing DFFA like Effector C - a regulator of adipocyte lipid metabolism) and PDE3B (Phosphodiesterase 3B - a key regulator of lipolysis and energy homeostasis) [88].

Furthermore, according to Osataphan et al., canagliflozin's SGLT2 inhibition improved non-diabetic mice lipogenesis by lowering the expression levels of genes implicated in de novo lipogenesis [88]. They showed that canagliflozin caused white adipose tissue to undergo lipolysis, most likely through FGF21 (fibroblast growth factor 21)-dependent pathways and transcriptional reprogramming of lipolysis [89]. ATP-citrate synthase, Acetyl-CoA carboxylase, SREBP-1c (sterol response element binding protein 1c - a major regulator of FFA metabolism), and sterol response were all decreased by canagliflozin, according to Day et al [89]. Another study discovered that canagliflozin inhibited the mitochondrial respiratory chain complex I, which in turn phosphorylated and activated ACC and reduced lipogenesis in mouse liver tissue. This activation of AMPK (adenosine monophosphate-activated protein kinase) was then mediated by the inhibition of MRC complex I [90]. Together, SGLT2 inhibitors can decrease lipogenesis and promote lipolysis via a variety of physiological routes.

Cholesterol homeostasis

A crucial lipid molecule, cholesterol plays multiple roles in the creation of hormones and steroids as well as in the composition of cell membranes [91]. Its circulating amount is linked to a major risk of atheroma plaque development and atherosclerotic cardiovascular disorders [92]. As a result, it

is crucial to maintain its normal homeostasis and normalize its level in order to slow down atherogenesis [93]. There are a variety of publications on how SGLT2 inhibitor medication affects cholesterol metabolism, and while some have claimed positive results [94], others have documented negative effects [95] or no effects at all [96]. There is proof that using canagliflozin or dapagliflozin as an SGLT2 inhibitor may lower cholesterol levels [97].

For instance, Osataphan et al. showed that canagliflozin decreased circulating levels of cholesterol in mice by inhibiting PCSK9 (Hmgcr, Lss, and Hmgcs1) genes, which are implicated in cholesterol uptake and synthesis [88]. Six months of dapagliflozin medication, according to Gürkanet al., reduced serum levels of TG and LDL-cholesterol in T2DM patients [96]. In a different clinical trial, T2DM patients who received SGLT2i treatment for 6 months had a rise in HDL cholesterol and a decrease in LDL cholesterol [96]. The levels of LDL-cholesterol and total cholesterol may, however, rise as a result of SGLT2 inhibition, according to some data [94].

For instance, Basu et al. showed that canagliflozin elevated TG, LDL-cholesterol, and total cholesterol in diabetic mice. This was probably because LPL (lipoprotein lipase) activity was increased, postprandial lipemia was decreased, and VLDL was cleared from the bloodstream more quickly [94]. They came to the conclusion that increased substrate for cholesterol production and lipolysis (LPL activity) were both associated with SGLT2 inhibition [94]. In individuals with T2DM, SGLT2 inhibitors increased total cholesterol, LDL cholesterol, and HDL cholesterol levels while decreasing TG levels [97]. Another clinical trial showed that canagliflozin medication enhanced HDL-cholesterol levels after 12 weeks, resulting in cardiovascular benefits for T2D patients [98]. High-dose treatment produced this advantage [99]. Higher doses of canagliflozin and dapagliflozin, raised HDL cholesterol and lowered TG levels in diabetic individuals, according to Shi et al. [99]. Moreover, Cha et al. found that SGLT2 inhibitors therapy for 24 weeks was associated with a significant increase in HDL-C and LDL-C in patients with T2DM [100].

However, some data suggested that SGLT2 inhibitors treatment did not significantly enhance the lipid profile [95]. In clinical research involving T2D patients, Fadini et al. showed that dapagliflozin medication for 12 weeks had no appreciable impact on HDL cholesterol [95]. In a clinical trial with T2DM patients, Bosch et al. discovered that empagliflozin had no appreciable impact on levels of total cholesterol, HDL cholesterol, or LDL cholesterol [101]. Although it appears that SGLT2 inhibitors have a variety of impacts on cholesterol metabolism and may increase, decrease, or have no effect on cholesterol levels, the mechanisms by which any of these actions is carried out are not yet fully understood.

Absorption/Transport of lipids

Body fat mass and the risk of hyperlipidemia are affected by the amount of dietary lipids that are absorbed and/or transported [102]. The main determinant of hepatic lipid production and blood levels of HDL, LDL, and VLDL is plasma lipid concentration [103-105]. Lower levels of dietary lipid absorption are linked to decreased levels of circulating TG and LDL cholesterol, as well as lower risks for the development of atherosclerotic plaque, the expansion of adipose tissue, and dyslipidemia. The possibility that SGLT2 inhibitors might change lipid transport is not supported by a lot of data [87]. SGLT2 inhibition with empagliflozin for 4 weeks boosted lipid mobilization and decreased lipid buildup in abdominal adipose tissue, according to a recent study by Lauritsen et al. [87]. Similar to this, Wallenius et al. showed that 4 weeks of dapagliflozin-induced SGLT2 inhibition increased free fatty acid mobilization and transport from adipose tissue in obese rats [106]. This subject needs more research because there is currently no data to support the impact that these medications play in lipid absorption.

The effects of SGLT-2 inhibitors on inflammation

SGLT2 inhibitors have pleiotropic effects that go beyond glycemic control [107]. They increase distal tubule sodium elimination by blocking SGLT2-dependent glucose and sodium reabsorption and decrease intraglomerular pressure. The shift in metabolism to gluconeogenesis and ketosis is thought to protect the kidneys and heart [108]. By reducing inflammation and mitochondrial dysfunction, SGLT2 inhibitors can lower renal tubular cells' glucotoxicity. They can also lower renal hypoxia by lowering the demand for energy and oxygen in the tubules [108]. SGLT2 inhibitors can change IL-6, adiponectin, and serum leptin levels and enhance adipose tissue function, which will increase insulin sensitivity and reduce the risk of cardiovascular disease [109,110]. SGLT2 inhibitors can significantly lower systolic blood pressure (SBP) and induce weight loss (Figure 4) [111].

The benefits of using an SGLT2 inhibitor on atherosclerosis may be attributable to a number of different factors, including decreased inflammatory molecule secretion, decreased macrophage infiltration, improved autophagy impairment, and reduced endothelial dysfunction [112] brought on by the hypoglycemic effects [113]. Recent research has demonstrated that SGLT2 inhibitors, regardless of glycemic management, enhance the inflammatory and oxidative state in T2DM patients [114]. These findings back up the theory that SGLT2 inhibitors have anti-inflammatory and cardioprotective effects.

A meta-analysis including 30 animal studies examined the effect of SGLT2 inhibitors on inflammatory markers (interleukin-6/IL-6, C-reactive protein/CRP, tumor

necrosis factor-α/TNF-α and chemoattractant monocyte protein-1/MCP-1). Differences in inflammatory marker levels between treatment groups were assessed as the primary outcome. The results suggested that treatment with an SGLT2 inhibitor resulted in decreases in IL-6 (SMD: -1.56, 95% CI -2.06 to -1.05), CRP (SMD: - 2.17, 95% CI -2.80 to -1.53), TNF-α (SMD: -1.75, 95% CI -2.14 to -1.37) and MCP-1 (SMD: -2.04, 95% CI -2.91 to -1.17). The effect on CRP and TNF-α was of lesser magnitude in cases of empagliflozin use [115].

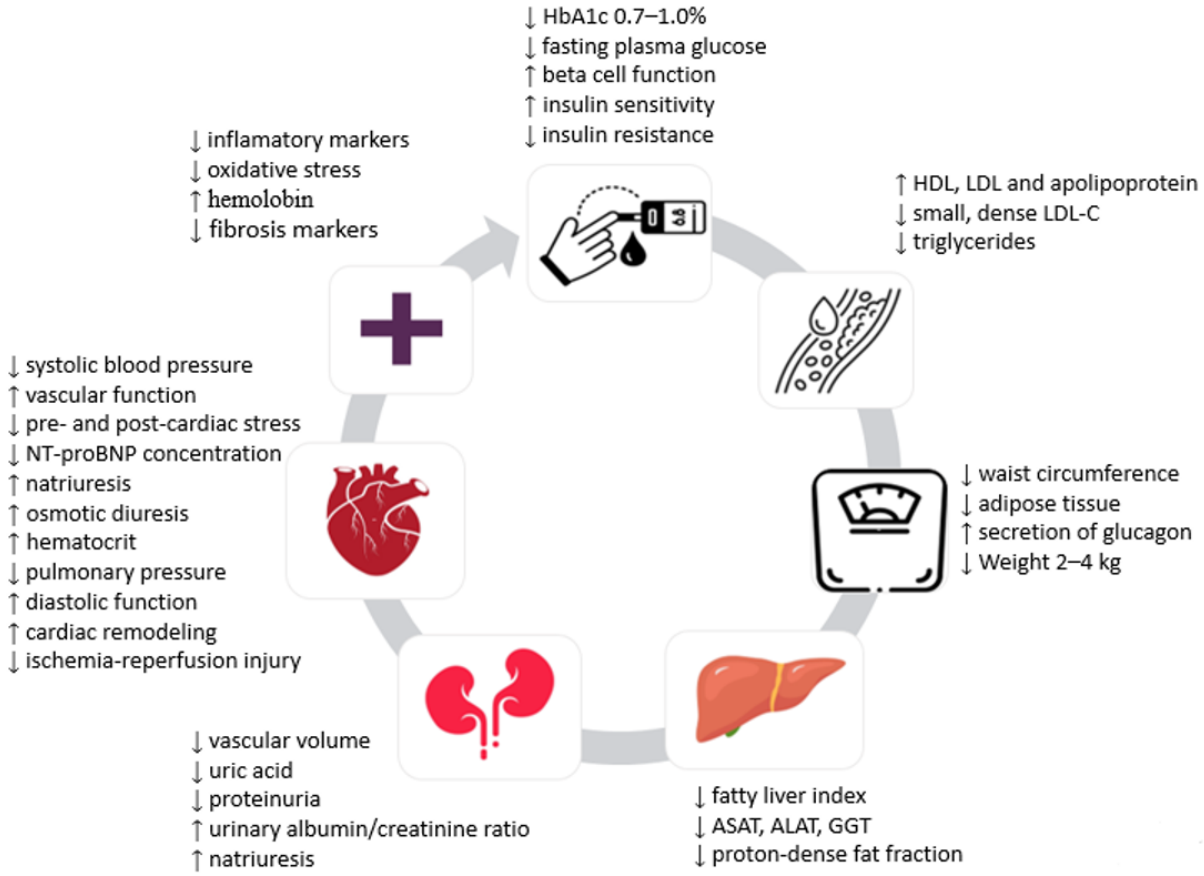

Figure 4. Pleiotropic effects of SGLT2 inhibitors

Clinical studies were also performed to monitor the changes in the main biomarkers of inflammatory and oxidative stress, in order to evaluate the potential role of SGLT2 inhibitors in protecting against atherosclerosis. CRP, IL-6, and TNF-α are the inflammatory biomarkers considered to be implicated in the progression of atherosclerosis. In a non-blinded randomized study, 51 diabetes individuals received empagliflozin (10 mg/day for 12 months), which significantly reduced plasma concentrations of hs-CRP when compared to baseline and placebo (-74.4% compared to placebo and -55.6% compared to the starting value) [116].

Similarly, the CANOSSA study showed that the administration of canagliflozin (100 mg/day for 12 months) caused a significant decrease in hs-CRP after 3, 6, and 12 months compared to baseline (3 months: p = 0.002, 6 months: p = 0.001, and 12 months: p = 0.007). This study enrolled 35 patients with diabetes and chronically stable hearts [117]. A comparative clinical trials study comparing canagliflozin and empagliflozin was conducted in 32 diabetic patients to evaluate the effect on inflammatory cytokines. The results showed that canagliflozin was more successful at lowering HbA1c, while empagliflozin was more successful at lowering inflammatory cytokines IL-6 (p = 0.002 vs. p = 0.27) and TNF-alpha (p = 0.002 vs. p = 0 29).

SGLT2 inhibitors are therefore novel therapeutics with pleiotropic effects on metabolic regulation and the decrease of inflammation related to cardiovascular problems.

Effects of SGLT-2 inhibitors in patients with MAFLD (NAFLD or NASH)

Among all the medications used to treat T2DM, SGLT2 inhibitors seem to be promising in individuals with NAFLD and show definite advantages same as GLP1 RA or thiazolidinediones in adults [118]. The use of SGLT2 inhibitors has been demonstrated to be effective in lowering plasma levels of ALT, body weight [119], blood pressure and glycated hemoglobin (HbA1c) improvement [120], as well as lowering cardiovascular and renal risks, all of which are elements that prevent the development of NASH [121]. Moreover, SGLT2 inhibitors slow down the growth of NASH by reducing fat accumulation and preventing adipocytes from

releasing pro-inflammatory cytokines, which is one of the key factors contributing to the development of NASH [109].

Several theories have been proposed to explain the pathophysiology of NAFLD improvement following SGLT2 therapy. When patients with diabetes are treated with SGLT2 inhibitors, their blood sugar and insulin levels fall, which further reduces the production of new hepatic lipids [122]. Furthermore, because SGLT2 is expressed in glucagon-secreting alpha pancreatic cells, the treatment of SGLT2 inhibitors enhances glucagon secretion [123,124].

The switch from carbohydrate to fatty acid metabolism causes a drop in triglyceride content, which then causes hepatic steatosis [123,125,126]. The ensuing rise in plasma glucagon levels also stimulates oxidation, which then causes the aforementioned fall in triglyceride content. It is likely that the primary strategies for preventing and slowing the course of NAFLD, including calorie reduction, activity, the use of metformin, GLP1 RA, and SGLT2 inhibitors, act on crucial autophagy targets (Figure 5) [125-127]. Despite not having received approval to treat NAFLD, ezetimibe similarly seems to engage the same mechanisms for autophagy activation [127].

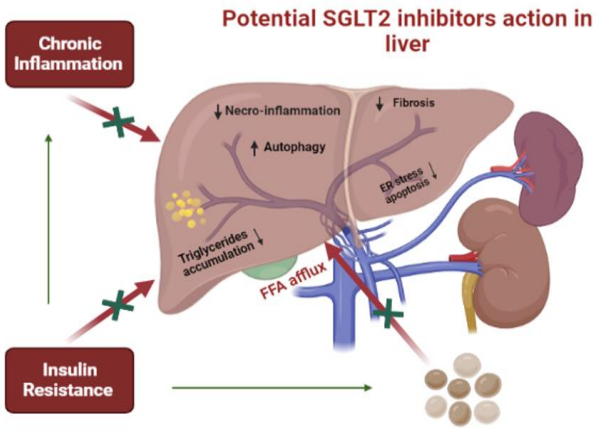

Figure 5. Potential actions of SGLT2-i on several functions related to NAFLD

The antioxidant properties of SGLT2 inhibitors are a mediator for another putative pathway. In addition to lowering the production of free radicals, suppressing pro-oxidants, and regulating antioxidant systems, they can also lessen the oxidative stress brought on by glucose [128-133]. The effectiveness of SGLT2 inhibitors in the management of NAFLD has been examined in a number of trials to date [134]. According to a 2018 randomized controlled clinical trial (the E-LIFT trial) conducted in India on 50 patients with T2DM and NAFLD, liver fat as measured by proton density MRI decreased significantly (16.2% vs. 11.3%) and serum ALT levels improved when empagliflozin 10 mg was added to standard T2DM therapy for 20 weeks [135]. A notable reduction in liver fat levels (LFC) was seen in individuals with T2DM, 80% of whom had NAFLD. They compared a daily dose of 25 mg of empagliflozin to placebo [136]. Additionally, individuals with T2DM and NAFLD were enrolled in a 24-week open-label controlled clinical trial in which they were randomly assigned to either the dapagliflozin (5 mg/day; n=33) group or the control group (n = 24). Transient elastography was used to measure the CAP (controlled attenuation parameter) and the liver stiffness, respectively, in order to evaluate fatty liver and liver fibrosis. According to this study's findings, dapagliflozin significantly decreased both liver stiffness and CAP in the dapagliflozin group [137]. In a prospective study, the liver histology of nine patients with NAFLD and T2DM was evaluated at baseline and 24 weeks after therapy started. The patients received daily canagliflozin doses of 100 mg for 24 weeks. The primary result was histological improvement, which was defined as a decrease of at least one point in the NAFLD activity score without a worsening fibrosis stage. The histology outcomes for each of the nine patients were improved. A reduction in insulin resistance was seen in six individuals, and an improvement in insulin secretion was seen in three more patients [138].

Inoue et al. studied the effects of 100 mg canagliflozin given once/day for a year on plasma biomarkers, body weight as measured by bioimpedance analysis, and liver fat as determined by MRI in T2DM patients with NAFLD. At 6 and 12 months, a considerable decrease in body mass and fat was seen, but there was no comparable decline in muscle mass. While blood liver enzymes and type IV collagen concentrations increased, hepatic fat fraction decreased from a baseline value of 17.6% 7.5% to 12.0% 4.6% after 6 months and 12.1% 6.1% after 12 months. Canagliflozin significantly decreased HbA1c from 8.7% 1.4% to 7.3% 0.6% and 7.7% 0.7%, respectively, after 6 and 12 months (p= 0.0005 and p= 0.01) [139]. The effectiveness of canagliflozin at a dose of 100 mg every day in a group of 10 patients with T2DM and NAFLD was examined in a separate trial in addition to the patients' current medication. Three imaging techniques were used to determine the degree of steatosis: MRI, computed tomography and transient elastography. The parameters of lipid, hepatic, and glucose metabolism were analyzed. The trial demonstrated that canagliflozin is beneficial in decreasing inflammation, hepatic steatosis, and insulin resistance [140].

Additionally, 100 mg/day of canagliflozin was found to be effective for lowering body weight, HbA1c and enhancing liver function tests by Gautam et al. [141]. In their trials, Sumida et al. (LEAD trial) and Miyake et al. showed that luseogliflozin 2, 5 mg/day was effective in improving a number of metabolic markers related to liver function and fat loss in individuals with T2DM and NAFLD [142,143]. An evaluation of the effectiveness of SGLT2 inhibitors in a group of patients with NAFLD and T2D treated for 24 weeks was published by several authors. SGLT2 inhibitors (canagliflozin 100 mg/day or ipragliflozin 50 mg/day) were

compared with a DPP4 inhibitor (sitagliptin 100 mg/day) in a retrospective study which showed a substantial decrease in weight and glycosylated hemoglobin in patients with T2DM and NAFLD. Across the two groups, transaminase activity was similarly decreased [144]. There is only one small study in non-DM patients that looked at 12 people taking dapagliflozin and 10 people taking the DPP4 inhibitor teneligliptin for a total of 12 weeks. It found that plasma transaminases were lower in both groups, while in the dapagliflozin group, overall body water and fat decreased, resulting in a reduction in total body weight [144].

The use of SGLT2 inhibitors is therefore associated with decreased liver enzymes and liver fat in T2D individuals with NAFLD, according to the existing data. The evidence of improved liver function based on liver biopsies from SGLT2 inhibitor clinical studies is still scant. The use of SGLT2 inhibitors for T2DM patients with NAFLD is potentially a reasonable choice given the impact on weight reduction and decreased risk of cardiovascular and renal events, as studies have indicated [145,146]. The main results summarizing the impact of SGLT2 treatment in people with NAFLD are highlighted in Table 2.

Table 2. Summary of the main features and results of clinical trials and observational studies highlighting the SGLT2 inhibitor effects in NAFLD patients

Drug	Duration	Posology	Outcomes	Ref.
Ipragliflozin vs. Pioglitazone	RCT, OL, single center, 24 weeks, (n= 66)	Ipragliflozin 50 mg daily (n= 32), vs. Pioglitazone 15–30 mg daily (n= 34)	Change from baseline in L/S ratio on CT	[147]
Ipragliflozin	Observational (retrospective) 45 weeks, median (n= 24)	Ipragliflozin 50 mg + DPP-4I (n= 13) vs. Ipragliflozin 50 mg + GLP-1 RA (n=11)	Changes ALT levels and body weight at the end of the follow-up	[148]
DPP4-I vs. SGLT2-I	Observational (retrospective) 24 weeks (n= 45)	Sitagliptin 100 mg daily (n= 21) vs. Canagliflozin 100 mg daily or ipragliflozin 50 mg daily (n= 24)	Correlation between changes in amino-transferase, body weight, glycemic control, and HbA1c	[149]
Dapagliflozin vs. ST T2DM	RCT, OL, single center, 24 weeks (n= 57)	Dapagliflozin 5 mg daily (n= 33) vs. ST T2DM (n= 24)	HS and fibrosis were assessed using transient elastography to measure CAP and liver stiffness, respectively	[150]
Luseogliflozin vs. Metformin	RCT, OL, single center, rospective 24 weeks (n= 32)	Luseogliflozin 2.5 mg daily (n= 16) vs. Metformin 1500 mg daily (n= 16)	Change in L/S ratio obtained by CT	[151]
Canagliflozin	Prospective, OL, single center, 24 weeks (n= 9)	Canagliflozin 100 mg daily	Histological improvement, defined as a decrease in NAFLD activity score without worsening in fibrosis stage	[152]
Empagliflozin vs. Placebo	RCT, prospective, multi center, 24 weeks (n= 84)	Empagliflozin 25 mg daily (n= 42) vs. Placebo (n= 42)	Change in liver fat content measured with MRI	[153]
Canagliflozin + ST T2DM	Prospective, single center 24 weeks (n= 9)	Canagliflozin 100 mg daily + ST T2DM	Change in HS assessed using the hepatic MRI-PDFF	[154]

Legend. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAP: controlled attenuated pressure; CT: computed tomography; DPP4-I: dipeptidyl peptidase-4 inhibitor; FIB-4: Fibrosis-4 score; GGT: gamma-glutamyl transferase; GLP1-RA: glucagon-like peptide 1 receptor agonist; HS: hepatic steatosis; LFT: liver function test; L/S ratio: liver-to-spleen attenuation ratio; MRI-PDFF: magnetic resonance imaging estimated proton density fat fraction; NAFLD: non-alcoholic fatty liver disease; OL: open label; RCT: randomized controlled trial; SGLT2-I: sodium glucose cotransporter-2 inhibitors; ST: standard treatment; T2DM: type 2 diabetes mellitus.

Conclusions

SGLT2 inhibitors can directly reduce body weight and blood glucose levels by reversing the effects of insulin resistance in T2DM, causing a reduction in liver enzymes and liver fat, while improving liver histology in patients with T2D and MAFLD. Moreover, SGLT2 inhibitors are able to attenuate abnormal oxidative and inflammatory responses by their protective roles in inhibiting hepatocyte death. This review highlights the main features of SGLT2 inhibitors by acting as a beneficial modulator for NAFLD/NASH based on numerous clinical trials which demonstrated their

favorable effects on the liver enzymes, blood lipids, blood glucose, BMI and insulin resistance in NAFLD patients. Overall, the presented data offer the perspective that SGLT2 use could lead to stopping the progression of liver damage.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

References

1. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol*. 2020;73(1):202-209. doi: 10.1016/j.jhep.2020.03.039
2. Francque SM, Marchesini G, Kautz A, et al. Non-alcoholic fatty liver disease: A patient guideline. *JHEP Rep*. 2021;3(5):100322. Published 2021 Sep 17. doi:10.1016/j.jhepr.2021.100322
3. Associazione Italiana per lo Studio del Fegato (AISF), Società Italiana di Diabetologia (SID) and Società Italiana dell'Obesità (SIO). Non-alcoholic fatty liver disease in adults 2021: A clinical practice guideline of the Italian Association for the Study of the Liver (AISF), the Italian Society of Diabetology (SID) and the Italian Society of Obesity (SIO). *Eat Weight Disord*. 2022;27(5):1603-1619. doi: 10.1007/s40519-021-01287-1
4. Cotter TG, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. *Gastroenterology*. 2020;158(7):1851-1864. doi:10.1053/j.gastro.2020.01.052
5. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73-84. doi:10.1002/hep.28431
6. Bica C, Sandu C, Suceveanu AI, et al. Non-alcoholic fatty liver disease: A major challenge in type 2 diabetes mellitus (Review). *Exp Ther Med*. 2020;20(3):2387-2391. doi:10.3892/etm.2020.8882
7. Mazzotti A, Caletti MT, Sasdelli AS, Brodosi L, Marchesini G. Pathophysiology of Nonalcoholic Fatty Liver Disease: Lifestyle-Gut-Gene Interaction. *Dig Dis*. 2016;34 Suppl 1:3-10. doi: 10.1159/000447275
8. Lonardo A, Nascimbeni F, Maurantonio M, et al. Nonalcoholic fatty liver disease: Evolving paradigms. World *J Gastroenterol*. 2017;23(36):6571-6592. doi:10.3748/wjg.v23.i36.6571
9. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. *Metabolism*. 2016;65(8):1096-1108. doi:10.1016/j.metabol.2016.01.001
10. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793-801. doi: 10.1016/j.jhep.2019.06.021
11. Portillo-Sanchez P, Bril F, Maximos M, et al. High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. *J Clin Endocrinol Metab*. 2015;100(6):2231-2238. doi:10.1210/jc.2015-1966
12. Loomba R, Wong R, Fraysse J, Shready S, Li S, et al. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. *Aliment Pharmacol Ther*. 2020;51(11):1149-1159. doi:10.1111/apt.15679
13. Fiorentino TV, Succurro E, Sciacqua A, Andreozzi F, Perticone F, Sesti G. Non-alcoholic fatty liver disease is associated with cardiovascular disease in subjects with different glucose tolerance. *Diabetes Metab Res Rev*. 2020;36(8):e3333. doi:10.1002/dmrr.3333
14. Wang C, Wang X, Gong G, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Int J Cancer*. 2012;130(7):1639-1648. doi:10.1002/ijc.26165
15. Erbas O, Erdogan MA, Khalilnezhad A, et al. Neurobehavioral effects of long-term maternal fructose intake in rat offspring. *Int J Dev Neurosci*. 2018;69:68-79. doi:10.1016/j.ijdevneu.2018.07.001
16. Lau JK, Zhang X, Yu J. Animal models of non-alcoholic fatty liver disease: current perspectives and recent advances. *J Pathol*. 2017; 241(1):36-44. doi:10.1002/path.4829
17. Edmison J, McCullough AJ. Pathogenesis of non-alcoholic steatohepatitis: human data. *Clin Liver Dis*. 2007;11(1):75-ix. doi: 10.1016/j.cld.2007.02.011
18. Chitturi S, Farrell GC. Etiopathogenesis of nonalcoholic steatohepatitis. *Semin Liver Dis*. 2001;21(1):27-41. doi:10.1055/s-2001-12927
19. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol*. 2015;62(1 Suppl):S47-S64. doi:10.1016/j.jhep.2014.12.012
20. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol*. 2013;10(6):330-344. doi:10.1038/nrgastro.2013.41
21. Giugliano D, Esposito K. Class effect for SGLT-2 inhibitors: a tale of 9 drugs. Cardiovasc *Diabetol*. 2019;18(1):94. Published 2019 Jul 23. doi:10.1186/s12933-019-0899-9
22. Saffo S, Taddei T. SGLT2 inhibitors and cirrhosis: A unique perspective on the comanagement of diabetes mellitus and ascites. *Clin Liver Dis (Hoboken)*. 2018;11(6):141-144. Published 2018 Jul 26. doi:10.1002/cld.714
23. Taylor SI, Yazdi ZS, Beitelshees AL. Pharmacological treatment of hyperglycemia in type 2 diabetes. *J Clin Invest*. 2021;131(2):e142243. doi:10.1172/JCI142243
24. Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet*. 2006;368(9548):1681-1688. doi: 10.1016/S0140-6736(06)69703-1
25. Marx N, Davies MJ, Grant PJ, et al. Guideline recommendations and the positioning of newer drugs in type 2 diabetes care. *Lancet Diabetes Endocrinol*. 2021;9(1):46-52. doi:10.1016/S2213-8587(20)30343-0
26. Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. *Nat Med*. 2015;21(5):512-517. doi: 10.1038/nm.3828
27. Moses RG, Colagiuri S, Pollock C. SGLT2 inhibitors: New medicines for addressing unmet needs in type 2 diabetes. *Australas Med J*. 2014;7(10):405-415. doi:10.4066/AMJ.2014.2181
28. Saisho Y. SGLT2 Inhibitors: the Star in the Treatment of Type 2 Diabetes?. *Diseases*. 2020;8(2):14. doi:10.3390/diseases8020014

29. Chen LH, Leung PS. Inhibition of the sodium glucose co-transporter-2: its beneficial action and potential combination therapy for type 2 diabetes mellitus. *Diabetes Obes Metab*. 2013;15(5):392-402. doi: 10.1111/dom.12064
30. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest*. 2014;124(2):499-508. doi:10.1172/JCI72227
31. Kuchay MS, Krishan S, Mishra SK, et al. 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(8):1801-1808. doi:10.2337/dc18-0165
32. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015; 373(22):2117-2128. doi:10.1056/NEJMoa1504720
33. 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(10):2155-2163. doi:10.1007/s00125-018-4702-3
34. Eriksson JW, Lundkvist P, Jansson PA, et al. 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(9):1923-1934. doi:10.1007/s00125-018-4675-2
35. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S144-S174. doi:10.2337/dc22-S010
36. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 Inhibitors With Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes: A Meta-analysis. *JAMA Cardiol*. 2021;6(2): 148-158. doi:10.1001/jamacardio.2020.4511
37. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2018;61(12):2461-2498. doi:10.1007/s00125-018-4729-5
38. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2020;63(2):221-228. doi:10.1007/s00125-019-05039-w
39. Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. *J Clin Invest*. 2006;116(7):1802-1812. doi:10.1172/JCI29103
40. Zangeneh F, Arora PS, Dyck PJ, et al. Effects of duration of type 2 diabetes mellitus on insulin secretion. *Endocr Pract*. 2006;12(4):388-393. doi:10.4158/EP.12.4.388
41. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. *Drug Des Devel Ther*. 2014;8:1335-1380. Published 2014 Sep 11. doi:10.2147/DDDT.S50773
42. Lu Y, Griffen SC, Boulton DW, Leil TA. Use of systems pharmacology modeling to elucidate the operating characteristics of SGLT1 and SGLT2 in renal glucose reabsorption in humans. *Front Pharmacol*. 2014;5:274. doi:10.3389/fphar.2014.00274
43. Liu JJ, Lee T, DeFronzo RA. Why Do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans?. *Diabetes*. 2012;61(9):2199-2204. doi:10.2337/db12-0052
44. Yang Y, Chen S, Pan H, et al. Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes: Systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2017;96(21):e6944. doi:10.1097/MD.0000000000006944
45. Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes Care*. 2015;38(3):403-411. doi:10.2337/dc14-1237
46. Rosenstock J, Jelaska A, Zeller C, et al. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2015;17(10):936-948. doi:10.1111/dom.12503
47. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care*. 2014;37(7):1815-1823. doi:10.2337/dc13-3055
48. Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S; Dapagliflozin 006 Study Group. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diabetes Obes Metab*. 2014;16(2):124-136. doi:10.1111/dom.12187
49. Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Ann Intern Med*. 2012; 156(6):405-415. doi:10.7326/0003-4819-156-6-201203200-00003
50. Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. *Diabetes Care*. 2009;32(9):1656-1662. doi:10.2337/dc09-0517
51. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest*. 2014;124(2):509-514. doi:10.1172/JCI70704
52. Sell H, Habich C, Eckel J. Adaptive immunity in obesity and insulin resistance. *Nat Rev Endocrinol*. 2012;8(12):709-716. doi: 10.1038/nrendo.2012.114
53. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444(7121):860-867. doi:10.1038/nature05485
54. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest*. 2007; 117(1):175-184. doi:10.1172/JCI29881
55. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112(12):1796-1808.
56. Wan J, Benkdane M, Teixeira-Clerc F, et al. M2 Kupffer cells promote M1 Kupffer cell apoptosis: a protective mechanism against alcoholic and nonalcoholic fatty liver disease. *Hepatology*. 2014;59(1):130-142. doi:10.1002/hep.26607
57. Patsouris D, Li PP, Thapar D, Chapman J, Olefsky JM, Neels JG. Ablation of CD11c-positive cells normalizes insulin sensitivity in obese insulin resistant animals. *Cell Metab*. 2008;8(4):301-309. doi:10.1016/j.cmet.2008.08.015
58. Xu L, Nagata N, Nagashimada M, et al. SGLT2 Inhibition by Empagliflozin Promotes Fat Utilization and Browning and Attenuates Inflammation and Insulin Resistance by Polarizing M2 Macrophages in Diet-induced Obese Mice. *EBioMedicine*. 2017;20:137-149. doi:10.1016/j.ebiom.2017.05.028
59. Zuo H, Shi Z, Yuan B, Dai Y, Wu G, Hussain A. Association between serum leptin concentrations and insulin resistance: a population-based study from China. *PLoS One*. 2013;8(1):e54615. doi: 10.1371/journal.pone.0054615

60. Chavez AO, Molina-Carrion M, Abdul-Ghani MA, Folli F, Defronzo RA, Tripathy D. Circulating fibroblast growth factor-21 is elevated in impaired glucose tolerance and type 2 diabetes and correlates with muscle and hepatic insulin resistance. *Diabetes Care*. 2009;32(8): 1542-1546. doi:10.2337/dc09-0684
61. Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol*. 2000;20(6):1595-1599. doi: 10.1161/01.atv.20.6.1595
62. Camporez JP, Jornayvaz FR, Petersen MC, et al. Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. *Endocrinology*. 2013;154(9):3099-3109. doi:10.1210/en.2013-1191
63. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta*. 2013;417:80-84. doi:10.1016/j.cca.2012.12.007
64. Tahara A, Takasu T, Yokono M, Imamura M, Kurosaki E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors: Part 2. Antidiabetic effects in type 2 diabetic mice. *J Pharmacol Sci*. 2016;131(3):198-208. doi:10.1016/j.jphs.2016.06.004
65. Shimo N, Matsuoka TA, Miyatsuka T, et al. Short-term selective alleviation of glucotoxicity and lipotoxicity ameliorates the suppressed expression of key β-cell factors under diabetic conditions. *Biochem Biophys Res Commun*. 2015;467(4):948-954. doi: 10.1016/j.bbrc.2015.10.038
66. Harris SB, Mequanint S, Miller K, Reichert SM, Spaic T. When Insulin Therapy Fails: The Impact of SGLT2 Inhibitors in Patients With Type 2 Diabetes. *Diabetes Care*. 2017;40(10):e141-e142. doi:10.2337/dc17-0744
67. Suceveanu AI, Stoian AP, Parepa I, et al. Gut microbiota patterns in obese and type 2 diabetes (T2D) patients from romanian black sea coast region. *Revista de Chimie (Rev Chim).* 2018;69(8):2260-2267. doi:10.37358/RC.18.8.6512
68. Obata A, Kubota N, Kubota T, et al. Tofogliflozin Improves Insulin Resistance in Skeletal Muscle and Accelerates Lipolysis in Adipose Tissue in Male Mice. *Endocrinology*. 2016;157(3):1029-1042. doi:10.1210/en.2015-1588
69. Xu L, Ota T. Emerging roles of SGLT2 inhibitors in obesity and insulin resistance: Focus on fat browning and macrophage polarization. *Adipocyte*. 2018;7(2):121-128. doi:10.1080/21623945.2017.1413516
70. Nishimura S, Manabe I, Nagasaki M, et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med*. 2009;15(8):914-920. doi:10.1038/nm.1964
71. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care*. 2014;37(8):2108-2113. doi:10.2337/dc13-3010
72. Pontiroli AE, Miele L, Morabito A. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. *Diabetes Obes Metab*. 2011; 13(11):1008-1019. doi:10.1111/j.1463-1326.2011.01433.x
73. de Boer H, Jansen M, Koerts J, Verschoor L. Prevention of weight gain in type 2 diabetes requiring insulin treatment. *Diabetes Obes Metab*. 2004;6(2):114-119. doi:10.1111/j.1463-1326.2004.00322.x
74. Scheen AJ. Combined thiazolidinedione-insulin therapy: should we be concerned about safety?. *Drug Saf*. 2004;27(12):841-856. doi: 10.2165/00002018-200427120-00002
75. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR; U.K. Prospective Diabetes Study Group. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care*. 2002;25(2):330-336. doi:10.2337/diacare.25.2.330
76. Min SH, Yoon JH, Hahn S, Cho YM. Comparison between SGLT2 inhibitors and DPP4 inhibitors added to insulin therapy in type 2 diabetes: a systematic review with indirect comparison meta-analysis. *Diabetes Metab Res Rev*. 2017;33(1):10.1002/dmrr.2818. doi: 10.1002/dmrr.2818
77. Cho YK, Kim YJ, Kang YM, et al. Comparison between sodium-glucose cotransporter 2 inhibitors and pioglitazone as additions to insulin therapy in type 2 diabetes patients: A systematic review with an indirect comparison meta-analysis. *J Diabetes Investig*. 2018; 9(4):882-892. doi:10.1111/jdi.12787
78. Singh AK, Singh R. Dipeptidyl peptidase-4 inhibitors or sodium glucose co-transporter-2 inhibitors as an add-on to insulin therapy: A comparative review. *Indian J Endocrinol Metab*. 2016;20(1):32-42. doi:10.4103/2230-8210.172278
79. Devenny JJ, Godonis HE, Harvey SJ, Rooney S, Cullen MJ, Pelleymounter MA. Weight loss induced by chronic dapagliflozin treatment is attenuated by compensatory hyperphagia in diet-induced obese (DIO) rats. *Obesity (Silver Spring).* 2012;20(8):1645-1652. doi:10.1038/oby.2012.59
80. Patti AM, Rizvi AA, Giglio RV, Stoian AP, Ligi D, Mannello F. Impact of Glucose-Lowering Medications on Cardiovascular and Metabolic Risk in Type 2 Diabetes. *J Clin Med*. 2020;9(4):912. Published 2020 Mar 26. doi:10.3390/jcm9040912
81. Patti AM, Carruba G, Cicero AFG, et al. Daily Use of Extra Virgin Olive Oil with High Oleocanthal Concentration Reduced Body Weight, Waist Circumference, Alanine Transaminase, Inflammatory Cytokines and Hepatic Steatosis in Subjects with the Metabolic Syndrome: A 2-Month Intervention Study. *Metabolites*. 2020; 10(10):392. doi:10.3390/metabo10100392
82. Gheorghe G, Stoian AP, Gaman MA, Socea B, Neagu TP, Stanescu AMA, et al. The Benefits and Risks of Antioxidant Treatment in Liver Diseases. *Revista de Chimie. (Rev. Chim.)* 2019;70(2):651–5. doi:10.37358/RC.19.2.6977
83. Zhao X, Feng D, Wang Q, et al. Regulation of lipogenesis by cyclin-dependent kinase 8-mediated control of SREBP-1. *J Clin Invest*. 2012;122(7):2417-2427. doi:10.1172/JCI61462
84. Ducheix S, Lobaccaro JM, Martin PG, Guillou H. Liver X Receptor: an oxyster ol sensor and a major player in the control of lipogenesis. *Chem Phys Lipids*. 2011;164(6):500-514. doi: 10.1016/j.chemphyslip.2011.06.004
85. Athyros VG, Doumas M, Imprialos KP, et al. Diabetes and lipid metabolism. *Hormones (Athens).* 2018;17(1):61-67. doi: 10.1007/s42000-018-0014-8
86. 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. Published 2016 Jul 26. doi:10.1186/s13098-016-0169-x
87. Lauritsen KM, Voigt JH, Pedersen SB, et al. Effects of SGLT2 inhibition on lipid transport in adipose tissue in type 2 diabetes. *Endocr Connect*. 2022;11(4):e210558. Published 2022 Apr 15. doi:10.1530/EC-21-0558
88. Osataphan S, Macchi C, Singhal G, et al. SGLT2 inhibition reprograms systemic metabolism via FGF21-dependent and -

independent mechanisms. *JCI Insight*. 2019;4(5):e123130. Published 2019 Mar 7. doi:10.1172/jci.insight.123130

89. Day EA, Ford RJ, Lu JH, Lu R, Lundenberg L, et al. The SGLT2 inhibitor canagliflozin suppresses lipid synthesis and interleukin-1 beta in ApoE deficient mice. *Biochem J*. 2020;477(12):2347-2361. doi:10.1042/BCJ20200278
90. Hawley SA, Ford RJ, Smith BK, et al. The Na+/Glucose Cotransporter Inhibitor Canagliflozin Activates AMPK by Inhibiting Mitochondrial Function and Increasing Cellular AMP Levels. *Diabetes*. 2016;65(9):2784-2794. doi:10.2337/db16-0058
91. Zhang J, Liu Q. Cholesterol metabolism and homeostasis in the brain. *Protein Cell*. 2015;6(4):254-264. doi:10.1007/s13238-014-0131-3
92. Groenen AG, Halmos B, Tall AR, Westerterp M. Cholesterol efflux pathways, inflammation, and atherosclerosis. *Crit Rev Biochem Mol Biol*. 2021;56(4):426-439. doi:10.1080/10409238.2021.1925217
93. Aguilar-Ballester M, Herrero-Cervera A, Vinué Á, Martínez-Hervás S, González-Navarro H. Impact of Cholesterol Metabolism in Immune Cell Function and Atherosclerosis. *Nutrients*. 2020;12(7):2021. Published 2020 Jul 7. doi:10.3390/nu12072021
94. Basu D, Huggins LA, Scerbo D, et al. Mechanism of Increased LDL (Low-Density Lipoprotein) and Decreased Triglycerides With SGLT2 (Sodium-Glucose Cotransporter 2) Inhibition. *Arterioscler Thromb Vasc Biol*. 2018;38(9):2207-2216. doi:10.1161/ATVBAHA.118.311339
95. Fadini GP, Bonora BM, Zatti G, et al. Effects of the SGLT2 inhibitor dapagliflozin on HDL cholesterol, particle size, and cholesterol efflux capacity in patients with type 2 diabetes: a randomized placebo-controlled trial. *Cardiovasc Diabetol*. 2017;16(1):42. Published 2017 Apr 4. doi:10.1186/s12933-017-0529-3
96. Gürkan E. Effects of dapagliflozin on serum low-density lipoprotein cholesterol and triglyceride levels. *Eur J Ther*. 2020;26(1):76–80. doi:10.5152/eurjther.2020.19005
97. Sánchez-García A, Simental-Mendía M, Millán-Alanís JM, Simental-Mendía LE. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: A systematic review and meta-analysis of 48 randomized controlled trials. *Pharmacol Res*. 2020;160:105068. doi: 10.1016/j.phrs.2020.105068
98. Kamijo Y, Ishii H, Yamamoto T, et al. Potential Impact on Lipoprotein Subfractions in Type 2 Diabetes. Clin Med Insights *Endocrinol Diabetes*. 2019;12:1179551419866811. Published 2019 Aug 14. doi:10.1177/1179551419866811
99. Shi FH, Li H, Shen L, et al. High-dose sodium-glucose co-transporter-2 inhibitors are superior in type 2 diabetes: A meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2021;23(9):2125-2136. doi:10.1111/dom.14452
100. Cha SA, Park YM, Yun JS, et al. A comparison of effects of DPP-4 inhibitor and SGLT2 inhibitor on lipid profile in patients with type 2 diabetes. *Lipids Health Dis*. 2017;16(1):58. Published 2017 Apr 13. doi:10.1186/s12944-017-0443-4
101. Bosch A, Ott C, Jung S, et al. How does empagliflozin improve arterial stiffness in patients with type 2 diabetes mellitus? Sub analysis of a clinical trial. *Cardiovasc Diabetol*. 2019;18(1):44. Published 2019 Mar 29. doi:10.1186/s12933-019-0839-8
102. Ejiri K, Miyoshi T, Kihara H, et al. Effects of luseogliflozin and voglibose on high-risk lipid profiles and inflammatory markers in diabetes patients with heart failure. *Sci Rep*. 2022;12(1):15449. Published 2022 Sep 14. doi:10.1038/s41598-022-19371-6
103. Spratt CJ, MacKenzie Myles LA, Merlo EM. Eating Disorders in Men: A Comprehensive Summary. *J Mind Med Sci*. 2022;9(2):249-254. doi: 10.22543/2392-7674.1362
104. Socea B, Silaghi A, Rebegea LF, Balan DG, Balalau C, Tenea-Cojan TS, Mihai DA, Paunica I. Diabetes mellitus: interdisciplinary medical, surgical and psychological therapeutic approach. *J Mind Med Sci*. 2023;10(2):217-236. doi:10.22543/2392-7674.1445
105. Arvind A, Osganian SA, Cohen DE, Corey KE. Lipid and Lipoprotein Metabolism in Liver Disease. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; July 21, 2019.
106. Wallenius K, Kroon T, Hagstedt T, et al. The SGLT2 inhibitor dapagliflozin promotes systemic FFA mobilization, enhances hepatic β-oxidation, and induces ketosis. *J Lipid Res*. 2022;63(3):100176. doi:10.1016/j.jlr.2022.100176
107. Youssef ME, Yahya G, Popoviciu MS, Cavalu S, Abd-Eldayem MA, Saber S. Unlocking the Full Potential of SGLT2 Inhibitors: Expanding Applications beyond Glycemic Control. *Int J Mol Sci*. 2023; 24(7):6039. Published 2023 Mar 23. doi:10.3390/ijms24076039
108. Fonseca-Correa JI, Correa-Rotter R. Sodium-Glucose Cotransporter 2 Inhibitors Mechanisms of Action: A Review. *Front Med (Lausanne)*. 2021;8:777861. doi:10.3389/fmed.2021.777861
109. Garvey WT, Van Gaal L, Leiter LA, et al. Effects of canagliflozin versus glimepiride on adipokines and inflammatory biomarkers in type 2 diabetes. *Metabolism*. 2018;85:32-37. doi:10.1016/j.metabol.2018.02.002
110. Mudaliar S, Henry RR, Boden G, et al. Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. *Diabetes Technol Ther*. 2014;16(3):137-144. doi: 10.1089/dia.2013.0167
111. Xu B, Li S, Kang B, Zhou J. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. *Cardiovasc Diabetol*. 2022;21(1):83. Published 2022 May 25. doi:10.1186/s12933-022-01512-w
112. Salvatore T, Galiero R, Caturano A, et al. An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors. *Int J Mol Sci*. 2022;23(7):3651. doi:10.3390/ijms23073651
113. Tsai KF, Chen YL, Chiou TT, et al. Emergence of SGLT2 Inhibitors as Powerful Antioxidants in Human Diseases. *Antioxidants (Basel)*. 2021;10(8):1166. doi:10.3390/antiox10081166
114. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. *Int J Physiol Pathophysiol Pharmacol*. 2019;11(3):45-63. Published 2019 Jun 15.
115. Theofilis P, Sagris M, Oikonomou E, et al. The impact of SGLT2 inhibitors on inflammation: A systematic review and meta-analysis of studies in rodents. *Int Immunopharmacol*. 2022;111:109080. doi:10.1016/j.intimp.2022.109080
116. Hattori S. Anti-inflammatory effects of empagliflozin in patients with type 2 diabetes and insulin resistance. *Diabetol Metab Syndr*. 2018;10:93. Published 2018 Dec 18. doi:10.1186/s13098-018-0395-5
117. Real J, Vlacho B, Ortega E, et al. Cardiovascular and mortality benefits of sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes mellitus: CVD-Real Catalonia. *Cardiovasc Diabetol*. 2021;20(1):139. doi:10.1186/s12933-021-01323-5
118. Popoviciu MS, Păduraru L, Yahya G, Metwally K, Cavalu S. Emerging Role of GLP-1 Agonists in Obesity: A Comprehensive Review of Randomised Controlled Trials. *Int J Mol Sci*. 2023;24(13): 10449. doi:10.3390/ijms241310449
119. Alshnbari A, Idris I. Can sodium-glucose co-transporter-2 (SGLT-2) inhibitor reduce the risk of adverse complications due to COVID-19? - Targeting hyperinflammation. *Curr Med Res Opin*. 2022;38(3):357-364. doi:10.1080/03007995.2022.2027141

120. Vilar-Gomez E, Yasells-Garcia A, Martinez-Perez Y, et al. Development and validation of a noninvasive prediction model for nonalcoholic steatohepatitis resolution after lifestyle intervention. *Hepatology*. 2016;63(6):1875-1887. doi:10.1002/hep.28484
121. Hamaguchi E, Takamura T, Sakurai M, et al. Histological course of nonalcoholic fatty liver disease in Japanese patients: tight glycemic control, rather than weight reduction, ameliorates liver fibrosis. *Diabetes Care*. 2010;33(2):284-286. doi:10.2337/dc09-0148
122. Yabiku K. Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors in Patients With Concurrent Type 2 Diabetes Mellitus and Non-Alcoholic Steatohepatitis: A Review of the Evidence. *Front Endocrinol (Lausanne).* 2021;12:768850. Published 2021 Dec 7. doi:10.3389/fendo.2021.768850
123. Daniele G, Xiong J, Solis-Herrera C, et al. Dapagliflozin Enhances Fat Oxidation and Ketone Production in Patients With Type 2 Diabetes. *Diabetes Care*. 2016;39(11):2036-2041. doi:10.2337/dc15-2688
124. Wang D, Luo Y, Wang X, et al. The Sodium-Glucose Cotransporter 2 Inhibitor Dapagliflozin Prevents Renal and Liver Disease in Western Diet Induced Obesity Mice. *Int J Mol Sci*. 2018;19(1):137. Published 2018 Jan 3. doi:10.3390/ijms19010137
125. Ferrannini E, Baldi S, Frascerra S, et al. 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(5):1190-1195. doi:10.2337/db15-1356
126. Yokono M, Takasu T, Hayashizaki Y, et al. 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. doi:10.1016/j.ejphar.2014.01.040
127. Morel E, Mehrpour M, Botti J, Dupont N, Hamaï A, Nascimbeni AC, Codogno P. Autophagy: A Druggable Process. *Annu Rev Pharmacol Toxicol*. 2017 Jan 6;57:375-398. doi: 10.1146/annurev-pharmtox-010716-104936
128. Steven S, Oelze M, Hanf A, et al. The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats. *Redox Biol*. 2017;13:370-385. doi:10.1016/j.redox.2017.06.009
129. Terami N, Ogawa D, Tachibana H, et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. *PLoS One*. 2014;9(6):e100777. doi:10.1371/journal.pone.0100777
130. Tahara A, Kurosaki E, Yokono M, et al. Effects of sodium-glucose cotransporter 2 selective inhibitor ipragliflozin on hyperglycaemia, oxidative stress, inflammation and liver injury in streptozotocin-induced type 1 diabetic rats. *J Pharm Pharmacol*. 2014;66(7):975-987. doi:10.1111/jphp.12223
131. Yaribeygi H, Atkin SL, Butler AE, Sahebkar A. Sodium-glucose cotransporter inhibitors and oxidative stress: An update. *J Cell Physiol*. 2019;234(4):3231-3237. doi:10.1002/jcp.26760
132. Oshima H, Miki T, Kuno A, et al. Empagliflozin, an SGLT2 Inhibitor, Reduced the Mortality Rate after Acute Myocardial Infarction with Modification of Cardiac Metabolomes and Antioxidants in Diabetic Rats. *J Pharmacol Exp Ther*. 2019;368(3):524-534. doi: 10.1124/jpet.118.253666
133. Osorio H, Coronel I, Arellano A, et al. Sodium-glucose cotransporter inhibition prevents oxidative stress in the kidney of diabetic rats. *Oxid Med Cell Longev*. 2012;2012:542042. doi:10.1155/2012/542042
134. Dougherty JA, Guirguis E, Thornby KA. A Systematic Review of Newer Antidiabetic Agents in the Treatment of Nonalcoholic Fatty Liver Disease. *Ann Pharmacother*. 2021;55(1):65-79. doi: 10.1177/1060028020935105
135. Kannan S, Nelliyanil M, Mendagudli R, et al. Evaluation of risk factors for non-alcoholic fatty liver disease in India: A systematic review and meta-analysis. *J Educ Health Promot*. 2024;12:435. Published 2024 Jan 22. doi:10.4103/jehp.jehp_208_23
136. Karaağaç Y. Sarcopenic obesity, pathogenesis, and treatment with a focus on exercise and protein intake. *J Mind Med Sci*. 2023;10(2):237-246. doi:10.22543/2392-7674.1419
137. Hu C, Qu T, Li L, Huang Y, Liu H, Rao C. Therapeutic outcome of dapagliflozin in patients with type 2 diabetes and non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Afr Health Sci.* 2023;23(2):416-421. doi:10.4314/ahs.v23i2.48
138. Jensterle M, Herman R, Janež A, et al. The Relationship between COVID-19 and Hypothalamic-Pituitary-Adrenal Axis: A Large Spectrum from Glucocorticoid Insufficiency to Excess-The CAPISCO International Expert Panel. *Int J Mol Sci*. 2022;23(13):7326. Published 2022 Jun 30. doi:10.3390/ijms23137326
139. Inoue M, Hayashi A, Taguchi T, et al. Effects of canagliflozin on body composition and hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease. *J Diabetes Investig*. 2019;10(4): 1004-1011. doi:10.1111/jdi.12980
140. Borisov AN, Kutz A, Christ ER, Heim MH, Ebrahimi F. Canagliflozin and Metabolic Associated Fatty Liver Disease in Patients With Diabetes Mellitus: New Insights From CANVAS. *J Clin Endocrinol Metab.* 2023;108(11):2940-2949. doi:10.1210/clinem/dgad249
141. 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. *J Assoc Physicians India*. 2018; 66(8):62-66.
142. Sumida Y, Murotani K, Saito M, et al. 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(1):64-71. doi:10.1111/hepr.13236
143. Miyake T, Yoshida O, Matsuura B, et al. Additional Effect of Luseogliflozin on Semaglutide in Nonalcoholic Steatohepatitis Complicated by Type 2 Diabetes Mellitus: An Open-Label, Randomized, Parallel-Group Study. *Diabetes Ther*. 2022;13(5):1083-1096. doi:10.1007/s13300-022-01239-7
144. Mantovani A, Petracca G, Csermely A, Beatrice G, Targher G. Sodium-Glucose Cotransporter-2 Inhibitors for Treatment of Nonalcoholic Fatty Liver Disease: A Meta-Analysis of Randomized Controlled Trials. *Metabolites*. 2020;11(1):22. Published 2020 Dec 30. doi:10.3390/metabo11010022
145. Stefan N, Häring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. *Lancet Diabetes Endocrinol*. 2019;7(4):313-324. doi:10.1016/S2213-8587(18)30154-2
146. Katsiki N, Perakakis N, Mantzoros C. Effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors on non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: Ex quo et quo vadimus?. *Metabolism.* 2019;98:iii-ix. doi:10.1016/j.metabol.2019.07.009
147. Ito D, Shimizu S, Inoue K, et al. 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(10):1364-1372. doi: 10.2337/dc17-0518
148. 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(4):313-319. doi: 10.1007/s40261-016-0383-1

149. Seko Y, Sumida Y, Tanaka S, et al. 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(10):1072-1078. doi:10.1111/hepr.12834
150. Shimizu M, Suzuki K, Kato K, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. *Diabetes Obes Metab*. 2019;21(2):285-292. doi:10.1111/dom.13520
151. Shibuya T, Fushimi N, Kawai M, et al. 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(2):438-442. doi: 10.1111/dom.13061
152. Akuta N, Kawamura Y, Watanabe C, et al. Impact of sodium glucose cotransporter 2 inhibitor on histological features and glucose metabolism of non-alcoholic fatty liver disease complicated by diabetes mellitus. *Hepatol Res*. 2019;49(5):531-539. doi:10.1111/hepr.13304
153. Kahl S, Gancheva S, Straßburger K, et al. Empagliflozin Effectively Lowers Liver Fat Content in Well-Controlled Type 2 Diabetes: A Randomized, Double-Blind, Phase 4, Placebo-Controlled Trial. *Diabetes Care*. 2020;43(2):298-305. doi:10.2337/dc19-0641
154. Nishimiya N, Tajima K, Imajo K, et al. Effects of Canagliflozin on Hepatic Steatosis, Visceral Fat and Skeletal Muscle among Patients with Type 2 Diabetes and Non-alcoholic Fatty Liver Disease. *Intern Med*. 2021;60(21):3391-3399. doi:10.2169/internalmedicine.7134-21