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RECENT APPROACHES FOR SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS IN THE MANAGEMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

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NAFLD is an umbrella term for a variety of illnesses of ranging severity starts with simple steatosis, develops to non-alcoholic steatohepatitis (NASH), then cirrhosis, and if not controlled, eventually can develop to fibrosis and even hepatocellular carcinoma (HCC). The disease is linked to obesity, insulin resistance, and type 2 diabetes mellitus (T2DM), thus addressing these interconnected disorders could be an effective approach for its management.

This review gives an overview the most recent relevant research studies and the on-going therapeutic options for NAFLD focusing on the recently discovered sodium glucose cotransporter 2 inhibitors (SGLT2i), the new antihyperglycemic class of drugs which recently gained adequate popularity, as well as their efficacy and applications in experimental and clinical work.

Keywords: *Non-alcoholic fatty liver disease; Sodium glucose co-transporter 2 inhibitors, Insulin resistance, oxidative stress*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has emerged as a serious public health issue in recent decades as its global prevalence has increased[1&2]. The term NAFLD refers to a group of pathophysiological conditions that begin with hepatic fat deposition "steatosis" and progress to non-alcoholic steatohepatitis "NASH," NASH-cirrhosis, and finally hepatocellular carcinoma HCC[3&4] . As a result, the disease has evolved into a major global health problem, and developing effective treatment/management tools to control and/or delay progression has become a global focus[5] .

Lifestyle changes, such as healthy diet, weight loss, and physical exercise, continue to be the cornerstone for NAFLD management [6], despite the fact that various drugs are currently being investigated for their efficacy; the anti-diabetic effect of such drugs were supporting their choice because insulin resistance is the initial factor for the development of NAFLD[7] , Figure (1), role of insulin resistance in the incidence and development of NAFLD.

Insulin resistance occurs when tissues do not respond adequately to circulating insulin[8] . As a result, insulin's normal ability to suppress lipolysis in adipose tissues is impaired, resulting in an excess release of free fatty acids, which are then taken up by the liver in addition to fat obtained from the diet[9&10] . The tissues' inability to respond appropriately to insulin causes aberrant hyperglycaemia, which leads to insulin overproduction and release, leading in hyperinsulinemia[8] . Unfortunately, hyperglycaemia and hyperlipidaemia both induce *de novo* lipogenesis (DNL), leading to an increase in hepatic lipid accumulation[11&12].

Patients with NAFLD are more likely to develop type 2 diabetic mellitus (T2DM)[13] , chronic kidney disease (CKD)[14] , and cardiovascular disease (CVD)[15], as illustrated in Figure 1.

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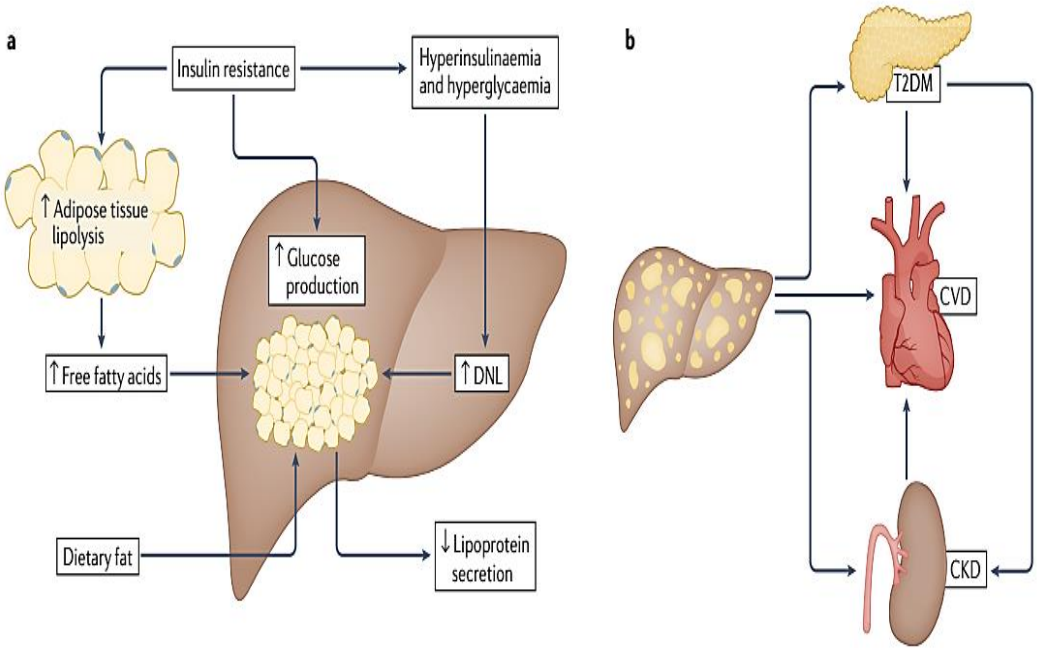

Fig. 1: Role of insulin resistance in the incidence and development of NAFLD.

a. Insulin resistance is characterised by inadequate tissue responsiveness to insulin. This impairment can lead to increase of adipose tissue lipolysis, resulting in excessive fatty acid production that is taken by the liver, generating additional fatty loads. **b.** NAFLD is associated with several extrahepatic comorbidities, including an increased risk of developing type 2 diabetic mellitus (T2DM), cardiovascular disease (CVD), and chronic renal disease (CKD)[7].

Sodium-glucose co-transporter type-2 inhibitors (SGLT2i) are a new class of oral antihyperglycemic drugs that are gaining popularity due to their ability to block glucose reabsorption and facilitate urine excretion[16]. SGLT2i also promote weight loss, lower blood uric acid levels, and have significant antioxidant and anti-inflammatory actions, therefore they are regarded as eligible pharmacological candidates with the potential to benefit NAFLD therapy[16] .

Fortunately, recent scientific reports revealed the effects of SGLT2i on hepatic fat accumulation, as evidenced by improved biochemical markers and histopathological investigations of isolated liver specimens in NAFLD animal models[17-20], while a few clinical trials revealed that canagliflozin and empagliflozin improved liver steatosis and had a protective effect on fatty liver in T2DM patients[21-24] .

In this overview, we provide the latest approaches for the use of SGLT2i for controlling the development of NAFLD, focusing on their mechanisms of action on endoplasmic reticulum (ER) stress, oxidative stress, minor inflammation, autophagy and apoptosis which all are existing throughout the SGLT2i processes, those revealed to mediate the beneficial effects of SGLT2i on NAFLD. Moreover, the various research data obtained from *in vitro and in vivo "*animal and human" studies on the influence of SGLT2i on NAFLD incidence and progression is discussed.

NAFLD pathogenesis

Regarding the theories of NAFLD pathophysiology, we found that they changed over time due to the advances in exploring and understanding its nature as a multi-factorial disease[16] . The "two-hit" theory was the prevailing one long time ago, it classified NAFLD pathophysiology into first "hit" which represented by just simple steatosis alone (NAFL), this hit is characterizes by lipid accumulation in liver cells and hepatic insulin resistance[25] . The second "hit" is represented by disease development caused by various factors such as oxidative stress, ER stress and

other injuries leading to progression of hepatic inflammation (NASH) and fibrosis[16,18-22, 24,26-28].

The more recent "multiple parallel-hit" concept was proposed for a better understanding of the complicated pathophysiology of NAFLD[29] . The theory reported different amalgamations of several genetic and environmental factors, simulating the "hits" which are dynamically interplayed leading to the incidence and development of the disease[30] . These factors encompass specific genetic polymorphisms and epigenetic modifications[31], high caloric diet, reduced physical exercise, increased body weight and body mass index, dysregulation of adipokines and insulin resistance, lipotoxicity[32&33], unbalancing of the intestinal microbiota[32], irregularity in autophagy and functions of the mitochondria[34&35], ER stress[36], homeostasis[37], as well as inflammatory and fibrotic consequences [38&39].

The intrahepatic lipid accumulations are controlled through the equilibrium between lipid synthesis, uptake, and lysis[40], so the disequilibrium between lipogenesis and lipolysis can result in free fatty acid (FFA) accumulation inside the hepatic cells, subsequently hepatocellular dysfunction, insulin resistance, altered liver functions, hepatic steatosis, and development to NASH, cirrhosis, and finally hepatocellular carcinoma HCC[40].

Notably, the majority of NAFLD patients exhibit dysregulated adipokines as leptin and adiponectin; the inflammation caused by metabolic factors causes impairment of insulin signalling in adipocytes[41], and this dysregulation contributes deceased FA uptake and enhances lipolysis in subcutaneous adipose tissue, leading to excessive hepatic FA delivery[42]. Furthermore, when liver cells are overloaded with lipids, the minor β-oxidation pathways in the peroxisomes and ER are enhanced causing an elevation of hepatocytes' production of reactive oxygen species (ROS)[40] and creation of highly reactive aldehyde by-products[43] with consequent damage in nuclear and mitochondrial DNA, rupture of the cell membrane rupture and eventually cell death.

Mitochondrial dysfunction and impaired β-oxidation drive alternative FA esterification, the esterified FA are then accumulated as tiny fat drops in the ER[44], produces toxic metabolites as diacylglycerols[45], ceramides[46], and lysophosphatidyl choline species[47], leading to hepatocyte dysfunction "lipotoxicity"[48].

Furthermore, the intestinal microbiota appears to participate in NAFLD pathogenesis; the intestine derived pathogens and the damage-associated molecular patterns activate an intrahepatic inflammatory response through Toll-like receptor signalling and the activation of NLR family pyrin domain containing-3 (NLRP3) inflammasome[23, 49]. Consequently, activation of the hepatic innate immune cells as Kupffer cells, dendritic cells, and hepatic stellate cells (HSCs) occurred, in addition, recruited neutrophils, monocytes, T-lymphocytes, and macrophages infiltrate the hepatic parenchyma[50], aligned with the effects of cytokines and growth factors which exacerbate the inflammatory process and contribute to fibrosis as an inefficient effort at tissue regeneration[39].

In recent years, the process of autophagy was emerged as a crucial topic in the context of liver disorders, the process of autophagy constitutes a catabolic cell mechanism which participate with an essential role in different organs' homeostasis, immune response, and energy balance[51]. The modulation of autophagy to be a participant in anti-steatogenic and anti-inflammatory activities, in addition to, the protective properties of mitophagy, which is a selective form of autophagy for the isolation of dysfunctional mitochondria, on hepatocytes can provide distinct targets for the control of NAFLD, while, insulin resistance, oxidative stress, hyperglycaemia, and lipotoxicity cause significant decline in autophagy contributing in the pathophysiology of NAFLD[51&52].

In conclusion, NAFLD is a multifactorial disease which pathogenesis has complex pathogenetic mechanism characterized by various implicated pathways.

Antihyperglycemic agents for the management of NAFLD

The link between NAFLD and insulin resistance and hyperglycaemia is extensively documented and is widely accepted as a bidirectional interaction[53], so the scope of scientific activity addressing the control of NAFLD through the use of antihyperglycemic agents is expanding.

Previous research found a link between the incidence of NAFLD and the risk of T2DM; numerous prospective observational studies found that the disease independently enhanced the occurrence of T2DM [54&55], while only one study contradicts this finding which reported that the incidence of NAFLD is independently related to poor glucose metabolism[56]. T2DM has also been linked to worsening NAFLD, NASH, and hepatocellular carcinoma (HCC)[57].

The aetiologies of NAFLD and T2DM appear to be related to the liver's crucial function in the regulation of glucose and lipid metabolism which happened with fat-associated chronic low-grade inflammation thought to be the initial event for NAFLD incidence[58]. There is strong evidence that NAFLD and T2DM share several shared pathogenesis events[59] explains why the antihyperglycemic agents have been widely recommended as an important drug for the control of NAFLD.

Metformin

Metformin, the biguanide insulin sensitizer, is the most used drug in the control of hyperglycaemia; it inhibits hepatic glucose production while increasing skeletal muscle glucose uptake. A previous study on its usage in NASH has been undertaken, it reported that the drug delays the onset of NAFLD and changes in intestinal microbiota and small intestinal barrier[60]. On the other hand, metformin had no effect on steatosis, inflammation, hepatocyte ballooning, serum ALT activity, fibrosis, or body weight in NASH patients[61].

Thiazolidinediones

Thiazolidinediones, the PPAR- agonists that boost insulin sensitivity[62]. A study comparing pioglitazone which is a PPAR-agonist, to placebo revealed a significant reduction in serum ALT activity, improved histopathological manifestations of NAFLD as steatosis, inflammation, and liver cells ballooning, however, the drug failed in attenuating the development of fibrosis[63].

Incretin-based therapy

Incretin based agents "GLP-1 agonists" are used to manage T2DM through promoting glucose-dependent insulin secretion[64]. A research study comparing the effect of liraglutide, the GLP-1 agonist, and placebo in NASH patients revealed that the drug improved steatosis[65], and attenuated the development of NASH[65].

Sitagliptin, the dipeptidyl-peptidase 4 (DPP-4) inhibitor reduced the degradation of incretins and thus stimulate insulin secretion in T2DM patients; moreover, the drug exhibited protective effect for the liver cells against high caloric diet-induced steatosis and consequently NAFLD through some extra-pancreatic pathways[66]. In addition to the effects of sitagliptin in attenuating the development of NAFLD, it exerts an effect in disease treatment through controlling the elevated liver enzymes' activities serum ALT, AST and GGT[67]. DPP-4 inhibitor drugs were recommended as effective mono-therapies for NAFLD[68], but no randomised controlled trials were performed to confirm their therapeutic efficacy in NAFLD.

SGLT2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have revolutionised the treatment of T2DM due to their unique insulin-independent mechanism, they inhibit glucose absorption from the proximal renal tubules causing glycosuria. SGLT2i also reduce body weight and improve liver functions in NAFLD/NASH patients[19].

SGLT2i drug category includes canagliflozin, dapagliflozin, ipragliflozin, empagliflozin, luseogliflozin, remogliflozin, tofogliflozin and ertugliflozin[69]. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are the four drugs approved by U.S. Food and Drug Administration "FDA" and the European Medicines Agency "EMA" for the treatment of T2DM, they are currently available in many countries in commercial pharmaceutical products[68].

Phlorizin, the first natural SGLT inhibitor discovered, it characterized by its high-affinity, selectivity, and competitive inhibitory activity for both SGLT1 and SGLT2[70] , the drug was used for the treatment of fever, malaria, and infectious diseases for many years until it was discovered that it causes glycosuria.

Phlorizin analogues with varying potencies and selectivity against SGLT were created; in 2008, Dapa was developed with a

about 1200-fold higher efficacy for SGLT2 than SGLT1[71] , The second drug developed was Cana, which has 400-fold higher inhibitory activity for SGLT2 than for SGLT1 [72], the third was Empa, which has the highest selectivity for SGLT2 over SGLT1 (approximately 2700-fold) among commercially available SGLT2i[73], and the fourth was Ertu, which has 2200-fold higher selectivity for SGLT2 than for SGLT1[74].

SGLT2i in NAFLD

SGLT2i medications have emerged as a viable strategy for NAFLD/NASH therapy via alleviating hyperglycaemia [75] and body weight by inducing urinary glucose excretion and osmotic diuresis[76] and, presumably, by reducing oxidative stress and inflammation[73, 77-79], as shown in Figure (2).

Research investigations on the effects of SGLT2i on dyslipidaemia associated with T2DM revealed that SGLT2i administration is associated with slight elevation in LDL-C and HDL-C levels, whereas triglycerides and small dense LDL levels tend to decrease modestly[21, 79-81].

Cardiovascular events are considered the most serious side effects of SGLT2i. Research studies revealed that dapagliflozin can cause serious cardiovascular events [82]. Urinary tract and genital infections, euglycemic diabetic ketoacidosis are other common side effects, while special concerns about links between SGLT2i and lower limb amputations, Fournier gangrene, bone fracture risk, female breast cancer, male bladder cancer, orthostatic hypotension, and acute kidney injury are elevated[83].

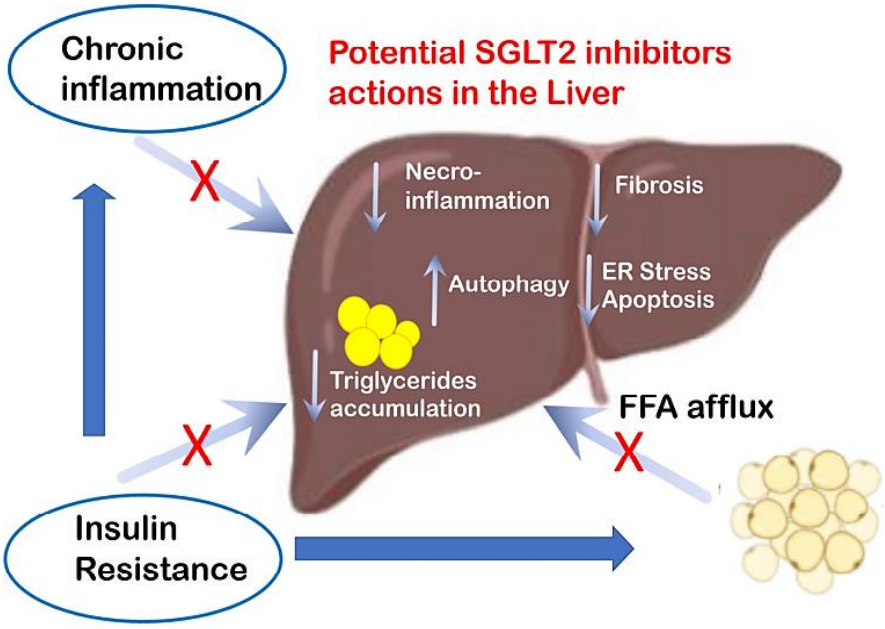

Fig. 2: **Potential actions of SGLT2-i on several functions related to NAFLD.**

Sodium-glucose co-transporter type-2 inhibitors (SGLT-2i) reduce serum glucose levels and have been shown to reduce fatty liver accumulation by alleviating insulin resistance and inhibiting fatty acid afflux, decreasing necro-inflammation, and increasing autophagy, with a consequent decrease in endoplasmic reticulum stress (ER stress), fibrosis, and apoptosis[18].

Canagliflozin

Canagliflozin was reported to improve NAFLD through regulating lipid metabolism and reducing hepatic inflammation *via* autophagy activation[26, 84].

When canagliflozin was given to animals fed on a high-fat diet, it lowered serum ALT activity and averted cirrhosis development, as revealed through reduced steatosis proved through histopathological investigation [85]. The drug also outperformed sitagliptin, which is a

DPP4 inhibitor, in the control of NAFLD in Japanese patients[86], it lowered fasting blood glucose, body weight, HbA_{1c}, and serum ALT activity[86], however this study was a retrospective cohort research, so the gained results could not be directly related to canagliflozin[86].

Another trial revealed that the administration of canagliflozin for 24 weeks to NAFLD patients aged 20 to 64 complicated by T2DM caused significant loss in body weight and BMI, fasting blood glucose, ferritin levels and GGT activity[87]. All trial participants exhibited reduced NAFLD score[87], however, because the trail was a single-centre, single-arm study with just five patients, generalization of the gained results was inconvenient [87].

An overview of four studies comparing canagliflozin to placebo or sitagliptin for 26 / 52 weeks revealed lowering effect of HbA_{1c}, reduced body weight as well as decreased serum ALT, AST, AP, and GGT levels. The best improvements were attributed to reductions in HbA_{1c} and total body weight [88].

Canagliflozin exhibited significant improvements in elevated blood glucose, insulin, and liver enzymes levels as manifested by biochemical tests as early as 8 weeks from initiation of the treatment, as well as significant improvement in hepatic fibrosis after 20 weeks, and a significant decrease in the liver tumours' number after one year [89].

Recently, a human study revealed significant decrease in steatosis, liver cells' ballooning, fibrosis, and inflammation after 24 weeks of treatment in NAFLD patients complicated with T2DM [90]. Another study on prospective cohort basis exhibited significant lowering in serum ALT, AST, GGT, triglycerides, HbA_{1c} levels, in addition to reductions body weights[91&92].

Dapagliflozin

Previous research investigating the hepatoprotective effect of dapagliflozin which is a selective competitive SGLT2i, in hereditary animal models of obesity and T2DM revealed that the drug improved liver damage markers as MPO and ROS [93]. The drug reduced serum ALT, AST, hepatocytes' lipid accumulation, and fibrosis in mice fed on western diet in comparison to low-fat diet group; the treatment caused reduction in the elevations in BMI, blood glucose, triglycerides levels, as well as renal fibrosis caused by western diet-induced obesity[94].

An overview and meta-analysis of randomised controlled trials (RCTs) concerning the use of dapagliflozin for the treatment of NAFLD was undertaken to assess its beneficiary and safety in adults with NAFLD. The overview explored that, dapagliflozin caused highly significant reductions in serum HbA_{1c}, and fasting plasma glucose, ALT, AST, GGT, triglycerides levels, in addition to lowering effect on total body weight and body mass index when compared to the control conditions. However, there were almost no difference in cholesterol, LDL-C, HDL-C, fibrosis 4 index, type IV collagen 7S, homeostatic model assessment of insulin resistance, or adverse events between dapagliflozin and control group[95].

These findings imply that dapagliflozin has potential as an effective therapeutic agent for controlling NAFLD, due to its capability of alleviating and/or reversing steatosis associated with NAFLD in both in vivo and in vitro studied on HepG2 cells, the mechanism was suggested as restoring autophagy *via* AMPK-mTOR pathway. The drug raised ACC1 phosphorylation and activated acyl-CoA oxidase-1 (ACOX1), the lipid-oxidation enzyme[96], which can be linked to the decline in serum ALT activity in NAFLD/T2DM patients, this alteration was not related to HbA_{1c} and fasting glucose levels [97&98].

Ipragliflozin

The effect of ipragliflozin on NAFLD in streptozotocin nicotinamide induced T2DM was investigated on animal models. The results gained after 4 weeks of therapy revealed that the drug improved glucose tolerance, blood glucose, insulin, and lipid levels, ALT and AST activities, steatosis, and oxidative stress biomarker levels[**99&100**].

Similarly, the administration of ipragliflozin for 8 weeks improved insulin resistance, AST and ALT activities, and hepatocyte fat content in choline-deficient l-amino acid-defined diet fed animal models that developed liver triglyceride increase, liver fibrosis, and mild inflammation [**101**]. These alterations were achieved within 5 weeks of treatment showing that ipragliflozin may

participate in the prevention of hepatic fibrosis[102].

Ipragliflozin reduced AST and ALT activities and improved glycaemic control in NAFLD/T2DM patients. The amount of tiny lipid drops in liver and body cells were reduced in NASH patients without a reduction in muscle mass[103].

Ipragliflozin administration for sixteen weeks in T2DM patients caused significant reduction in fatty liver index, fasting blood glucose, HbA_{1c}, BMI, adipose cells in viscera and subcutaneous tissues, as well as total body fat mass[104&105].

The therapeutic effects of ipragliflozin on NAFLD/T2DM patients were compared to pioglitazone, the PPAR agonist, the gained results exhibited that both drugs exhibited similar effects in terms of fasting blood glucose, HbA_{1c}, the ratio between liver to spleen, serum AST and ALT activities, while ipragliflozin showed significant reduction in total body weight and body fat area with[72].

In contrast, the co-administration of ipragliflozin with incretin-based drugs "GLP-1 agonists or DPP-4 inhibitors" produced significant reductions in HbA_{1c}, BMI, serum ALT activity, and fibrosis-4 index[106&107]. In this trail, the most striking finding was that incretin-based drugs could not decrease ALT activity unless they are combined with ipragliflozin demonstrating the synergistic effect of incretin-based drugs and SGLT2i[106& 107].

A multi-centre prospective trial was done to investigate the effect administration by NAFLD/T2DM patients for 24 weeks with significant lowering in HbA_{1c}, serum AST and ALT activities, BMI and steatosis[103].

Consequently, the collective findings highlights ipragliflozin as a promising novel drug for the treatment of T2DM patients complicated with NAFLD[108].

Empagliflozin

Empagliflozin, a well-established therapy T2DM which improved steatosis and fibrosis in both animals and humans with T2DM complicated with NAFLD, and NASH[109].

Empagliflozin was reported to diminish serum glucose levels, white adipocyte size, hepatocytes' lipid accumulation, and triglycerides, as well as the drug caused attenuating effect in the development of hepatic cholesterol esters and steatosis[8, 109], the proposed mechanism is through enhancing glycosuria and improving hyperglycaemia and producing an effective shift in fatty acid accumulation and metabolism, resulting in a protective effect against steatosis[18].

Recently, an overview and meta-analysis of the efficacy and safety of empagliflozin in NAFLD patients revealed that the drug reduced BMI, liver stiffness measurement, AST activity, and homeostasis model assessment of insulin resistance (HOMA-IR) when compared to the control group in four articles involving 244 NAFLD patients, indicating that the drug can improve body composition, insulin resistance, liver fibrosis and decrease the hepatic enzymes, so empagliflozin was recommended as a new option for controlling NAFLD[110].

A clinical trial "E-LIFT" trial was conducted, it included patients with T2DM/NAFLD, the gained results revealed that empagliflozin, in addition to its ordinary antihyperglycemic properties, it reduced hepatic fat content and ALT activity while having no effect on GGT or AST activities [73]. Moreover, a subgroup analysis from the EMPA-REG trial exhibited a substantial reduction in ALT activity independent of HbA_{1c} or body weight alterations[111].

Empagliflozin monotherapy reduced NASH severity in NASH mouse models within 21 days, while the co-administration of empagliflozin and linagliptin reduced both body weight and fibrosis indicating a possible synergistic effect [112].

Luseogliflozin

Studies on the hepatoprotective effect of luseogliflozin on streptozotocin and nicotinamide mouse models demonstrated that the drug lowered ALT activity as well as the rise in collagen deposition[113].

A single-centre, prospective, randomised, open-label, controlled study was conducted for assessing the luseogliflozin treatment (2.5 mg daily) for 6 months when compared to metformin. The gained results revealed that the drug reduced liver fat deposition in 32 T2DM/NAFLD compared to metformin, and demonstrated significant reductions in the ratio

between liver and spleen, visceral fat, HbA_{1c}, and BMI after 6 months of use[114].

Another prospective, single-arm trial found that luseogliflozin (2.5 mg daily) treatment for 24 weeks caused significant reductions in ALT, AST, BMI, and GGT levels, as well as reduced hepatic fat content as measured by MRI in T2DM/NAFLD patients but had no effect on hepatic fibrosis markers[74].

A recent trial on the short-term (12 weeks) add-on dose of luseogliflozin demonstrated that the drug lowered plasma glucose in T2DM/NAFLD and reported that there was significant suppression in fatty liver markers, most likely through improved insulin sensitivity[114].

Remogliflozin

Experimental investigations for assessing the potential of remogliflozin on high fat fed mice for 11 weeks, then administration of remogliflozin or placebo for 4 weeks revealed that the drug reduced both serum ALT and ALT activities, liver weight, and triglycerides. Comparing the outcomes of the drug to canagliflozin and dapagliflozin, remogliflozin had a significantly higher potential regarding oxygen radial absorbance capacity. Eventually, the study demonstrated that remogliflozin had clear significant effects on mice with NAFLD and NASH [115].

In a randomised, double-blind, placebo-controlled, parallel arm study, 336 T2DM patients were randomly assigned to one of five doses of remogliflozin etabonate (Islet Sciences at dose levels of 50, 100, 250, 500 or 1000 mg twice a day, pioglitazone 30 mg once a day, or matching placebo. The efficacy and safety of remogliflozin etabonate were assessed at baseline, 4, 8, and 12 weeks where the patients used remogliflozin etabonate exhibited improved insulin sensitivity (6-33 percent) and β-cell functions (23-43 percent) by the end of week 12, while all doses resulted in distinct weight reduction when compared to placebo or pioglitazone, which both caused gaining weight.

Even though the research was not powered for ALT, post-hoc analysis demonstrated a substantial reduction in ALT activity across all remogliflozin dose levels ranging from 32-42 percent. The author hypnotised that the reduction in ALT activity could be related to remogliflozin's intrinsic antioxidant activity when compared to other SGLT2i based on a preclinical model that revealed a reduction in oxidative stress and a decrease in ALT/AST **[115]**.

Tofogliflozin

The research studies concerning the hepatoprotective potential of tofogliflozin in mice models demonstrated that it reduced mRNA expression levels of the hepatic inflammation macrophage marker F4/80 and a considerable reduction in serum glucose and FFA levels[96].

Another study exhibited that tofogliflozin improved NASH-like liver phenotypes in WD-fed Mc4r-KO mice and prevented the development of NASH-originated tumours in WD-fed Mc4r-KO mice given diethyl nitrosamine (DEN), expressed as the count of tumours of 2 mm diameter which was fewer in tofogliflozin-treated group[116].

Recently, a research study for assessing the effect of tofogliflozin on the progression of NASH-originated hepatic tumorigenesis in C57BL/KsJ-+Leprdb/+Leprdb obese diabetic mice revealed that the drug significantly suppressed the progression of liver pre-neoplastic lesions, reduced steatosis, ballooning, hepatocyte damage, and inflammation.

The assessment was conducted using non-alcoholic fatty liver disease activity score (NAS) compared to the control mice [117].

Recent evidence suggested that the co-administration of pemafibrate, the selective PPAR modulator, and tofogliflozin showed greater therapeutic potential in alleviation of NASH-related HCC development. The results revealed that the drugs combination improved the rates of HCC related survivals in STAM mice and reduced the frequency of hepatic tumours when compared to NASH control group, concluding that liver injury can be averted through inhibiting the IRE1-XBP1-PHLD3A pathway[118].

The first study investigated the efficacy of tofogliflozin in NAFLD/T2DM patients showed that the treatment for 24 weeks caused significant improvement in steatosis when compared to pioglitazone at low dose levels, while pioglitazone improved MR elastography liver stiffness measurement (MRE-LSM),

however, tofogliflozin did not reduce MRE-LSM[119].

Another retrospective study concerning the effects of SGLT2i drugs, including tofogliflozin, on T2DM/NAFLD patients revealed that the drug caused improvement in glycaemic control and reduced liver fatty infiltration and fibrosis on the basis of ultrasound and/or liver biopsy[120].

Ertugliflozin

A post-hoc analysis of seven randomised, double-blind phase 3 VERTIS trials was performed to evaluate the effect of ertugliflozin on hepatic enzymes in T2DM patients compared to non-ertugliflozin (placebo, glimepiride, or sitagliptin), the results revealed that the drug reduced serum ALT and AST activities after 52 weeks when compared to non-ertugliflozin treatment group. These results were similar to the results obtained with other SGLT2i[91], the reduction was highest in individuals with higher baseline ALT and AST levels, while the Fibrosis-4 Index data revealed minimal differences between therapy groups [121, 122]. The reductions in serum ALT and AST activities were not large, but were statistically significant when associated with changes in HbA_{1c} and body weight in all treatment groups, implying that these changes in hepatic transaminases are partially explained by body weight and HbA_{1c}[122].

Conclusion

In recent years, a large amount of data has been amassed that has shown unique cellular and molecular mechanisms involved in the incidence of NAFLD and its development to NASH, fibrosis, and finally HCC. These data have disclosed novel linkages and management possibilities. Meanwhile, various issues have arisen regarding the mechanisms that contribute to the development of NAFLD or NASH and, ultimately, HCC. These factors include genetic and environmental modifiers such as nutrition, drugs, and/or lifestyle.

The data presented in this review article constructs a theoretical framework that will assist investigators in further evaluating the safety and efficacy of SGLT2i for the management of NAFLD with the goal of improving therapeutic outcomes. More mechanistic studies are needed to gain clear insights into the molecular pathways that connect gliflozins' actions with the mechanisms involved in the incidence of NAFLD, NASH, cirrhotic ascites, and eventually HCC.

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الأساليب الحديثة لمثبطات النواقل المشتركة للصوديوم والجلوكوز من النوع الثاني فى السيطرة على مرض الكبد الدهنى غير الكحولى

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يتزايد انتشار مرض الكبد الدهني غير الكحولي (NAFLD) في جميع أنحاء العالم بشكل كبير .وحتى الآن تعد تعديلات نمط الحياة المؤدية إلى فقدان الوزن بمثابة حجر الزاوية في العلاج حيث أن الخيارات الدوائية ذات الفعالية المثبتة محدودة ، مما يجعل التحكم في المرض من أصعب التحديات. و تتباين حدة مرض الكبد الدهني غير الكحولي حيث تتصاعد من التنكس الدهني البسيط ، والتهاب الكبد الدهني غير الكحولي (NASH) ، وتليف الكبد وقد تتطور في نهاية المطاف الي سرطان بالخلايا الكبدية ، ويرتبط المرض ارتباطًا وثيقًا بالسمنة ومقاومة الأنسولين و مرض السكري من النوع الثاني وبالتالي ، فإن استهداف هذه الحالات المترابطة يمكن إثبات أنه يمثل نهجًا مفيدًا للتحكم في المرض. و سوف تستكشف هذه المراجعة أحدث الدراسات البحثية ذات الصلة وتناقش الخيارات العلاجية الجاري العمل عليها للتحكم في المرض مع التركيز على مثبطات الناقل المساعد ل صوديوم/ جلوكوز ٢ (SGLT2) المضادة لفرط سكر الدم ، وفعاليتها وكذلك تطبيقاتها في العمل التجريبي والسريري.