Pharmacological Research 181 (2022) 106261

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

The effects of sodium-glucose cotransporter 2 inhibitors on hepatocellular carcinoma: From molecular mechanisms to potential clinical implications

Konstantinos Arvanitakis [a,b], Theocharis Koufakis [c], Kalliopi Kotsa [c], Georgios Germanidis [a,b,*]

[a] First Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, 54636 Thessaloniki, Greece
[b] Basic and Translational Research Unit, Special Unit for Biomedical Research and Education, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, 54636 Thessaloniki, Greece
[c] Division of Endocrinology and Metabolism and Diabetes Centre, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, 54636 Thessaloniki, Greece

ARTICLE INFO

Keywords:
Hepatocellular carcinoma
SGLT2 inhibitors
Nonalcoholic steatohepatitis
Cancer

ABSTRACT

Hepatocellular carcinoma (HCC) occurs in the setting of prolonged liver inflammation, hepatocyte necrosis and regeneration in patients with cirrhosis. Despite the progress made in the medical management of the disorder during the past decades, the available pharmacological options remain limited, leading to poor survival rates and quality of life for patients with HCC. Sodium-glucose cotransporter 2 inhibitors (SGLT2) originally emerged as drugs for the treatment of hyperglycemia; however, they soon demonstrated important extra-glycemic properties, which led to their evaluation as potential treatments for a wide range of non-metabolic disorders. Evidence from animal studies suggests that SGLT2i have the potential to modulate molecular pathways that affect hallmarks of HCC, including inflammatory responses, cell proliferation, and oxidative stress. The impressive benefits of neurohormonal modulation observed with SGLT2i in congestive heart failure set the stage for human trials in cirrhotic ascites. However, future studies need to evaluate several aspects of the benefit to risk ratio of such a therapeutic strategy, including the co-administration with antineoplastic agents and diuretics, infections, use in hospitalized individuals, renal safety and hypovolemia. In this narrative review, we discuss the putative role of SGLT2i in the treatment of patients with HCC, starting with the mechanisms that could justify a possible benefit and ending with potential clinical implications and areas for future research.

1. Introduction

Liver cancer was the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide, while hepatocellular carcinoma (HCC) represents approximately 75–85% of primary liver cancers [1,2]. In the majority of cases, HCC occurs in the setting of prolonged liver inflammation, hepatocyte necrosis and regeneration in patients with cirrhosis [3]. Non-alcoholic steatohepatitis (NASH), which is characterized by hepatic steatosis, lobular inflammation, hepatocellular ballooning and eventually fibrosis, has emerged as a major risk factor for HCC [4]. Despite progress made in the medical management of the disorder during the past decades, available pharmacological options remain limited, leading to poor survival rates and quality of life for patients with HCC [5]. Thus, the development of safe and effective treatments for this type of cancer remains an ongoing challenge.

The kidneys have been recently recognized as important players in the regulation of glucose homeostasis in humans and are known to reabsorb approximately 180 g of filtered glucose daily [6]. More than 90% of the renal glucose uptake is mediated by sodium-glucose cotransporters 2 (SGLT2), which represent high-capacity and low-affinity transporters, located in the early portion of the proximal renal tube. In the context of diabetes, an overexpression of SGLT2 is observed, translated into an amplified renal glucose absorption, which has been demonstrated as one of the numerous contributing mechanisms in the development of hyperglycemia in T2D [7].

SGLT2 inhibitors (SGLT2i) represent a new class of oral, antidiabetic drugs that have radically changed the management of type 2 diabetes (T2D). By inhibiting SGLT2, gliflozins cause glycosuria which subsequently results in lower plasma glucose concentrations and caloric deficit, thus, promoting weight loss. Due to the glucose-dependent

* Correspondence to: Gastroenterology-Hepatology Unit, First Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, St. Kiriakidi 1, 54636, Thessaloniki, Greece.
E-mail address: geogerm@auth.gr (G. Germanidis).

https://doi.org/10.1016/j.phrs.2022.106261
Received 19 March 2022; Received in revised form 11 May 2022; Accepted 12 May 2022
Available online 16 May 2022

mechanism of action, therapy with these agents involves a minimal risk of hypoglycemia. However, the revolutionary impact of the class on the management of diabetes is mainly related to its cardiorenal protective properties. Specifically, in large-scale cardiovascular (CV) outcome trials SGLT2i have demonstrated the potential to reduce the probability of major adverse CV events, CV death, hospitalization for heart failure (HF), and evidence has been provided that they improve outcomes related to chronic kidney disease (CKD), including renal death, decline in glomerular filtration rate, albuminuria, and risk of end-stage renal disease [8]. As a result, recent guidelines advocate the use of SGLT2i in people with diabetes at high CV and renal risk independently of quality of glycemic control or background therapy [9]. The exact mechanisms that facilitate these effects are still under investigation. However, it is postulated that they are related to attenuation in adipose tissue and systemic inflammation, alleviation of oxidative stress and endothelial dysfunction, downregulation of sympathetic activity, favorable changes in heart energetics, natriuresis, and improved erythropoiesis, among others [10]. It should be also noted that as a result of the wide spectrum of the off-target effects of SGLT2i and their ability to mitigate cardiorenal risk regardless of diabetes status, specific agents have recently been approved for the treatment of HF and CKD even in non-diabetic populations.

Nonalcoholic fatty liver disease (NAFLD) has been associated with an increased risk for the development of T2D and, conversely, steatohepatitis, liver fibrosis, and end-stage liver disease are frequent diabetes comorbidities [11]. The above bidirectional relationship is probably suggestive of the implication of common risk factors and pathophysiological pathways in the development of the two entities, including obesity, dyslipidemia, insulin resistance, inflammation and defective immune responses [12,13]. Emerging evidence suggests beneficial effects of SGLT2i on the development and progression of fatty liver disease, as indicated by studies focusing on biological and imaging markers of NAFLD, showing reduced levels of liver enzymes and fatty liver content after the administration of these agents [14]. Potential mechanisms probably extend beyond the glucose and weight-lowering effects of SGLT2i and reflect the impact of gliflozins on low-grade inflammation and oxidative stress [15].

On the other hand, available data on the effects of SGLT2i on HCC remain scarce and are mainly limited to animal studies that attempt to unravel the relevant mechanisms. In this mini-review article, we discuss the putative role of SGLT2i in the treatment of patients with HCC, starting from the molecular pathways that could justify a possible benefit and ending with potential clinical implications and areas for future research.

2. Risk factors and proposed mechanisms of NASH-associated hepatocellular carcinoma

The interplay between hepatic inflammatory changes, one of the histological hallmarks of NASH, and hepatocarcinogenesis has been at the forefront of clinical investigation for the past few decades, while the exact role of tumor-associated neutrophils (TANs) and tumor-associated macrophages (TAMs) in the HCC microenvironment and development is yet to be fully elucidated [16,17]. NAFLD/NASH dramatically increases the prevalence of HCC development; however, the increased risk of HCC development in patients with NAFLD is often misdiagnosed. The degree of fibrosis is considered the strongest predictive factor for correlating the progression of NAFLD with life- threating complications [18]. The progression of NASH-related HCC is a gradual and multifactorial process, encompassing several risk factors such as genomic alterations, obesity, or diabetes, that are associated with alterations in some common signaling pathways, leading to transition of dysplastic hepatocytes into HCC [19,20]. The potential mechanisms of the aforementioned transition, include genetic, metabolic, immunologic, and endocrine pathways, which subsequently activate oncogenic mechanisms. The pathogenesis of NAFLD-associated HCC is a complex landscape composed of mechanisms involved in immune and inflammatory responses, DNA damage, oxidative stress and autophagy [21]. Genetic polymorphism, most commonly of patatin-like phospholipase domain-containing protein (PNPLA3) [22], ectoenzyme nucleotide pyrophosphate phosphodiesterase-1 (ENPP) and insulin receptor substrate [23], may account for the development of HCC in NASH. It has been also demonstrated that dysregulation of gut microbiota, is associated with hepatic inflammation that can progress to NASH and ultimately, NASH-associated HCC [24]. In more detail, NASH patients have increased small intestinal bacterial overgrowth which is associated with enhanced expression of TLR-4 and the release of pro-inflammatory cytokine IL-8 [25]. The activation of TLRs via MAMPs and DAMPs from the gut microbiota and damaged hepatocytes (HMGB1, saturated fatty acids, cholesterol esters and reactive oxygen species (ROS)) has been also demonstrated [26].

However, an important difference in the 'sterile inflammation' of NASH is that the activation of inflammasomes occurs not only in macrophages but also in hepatocytes and other immune cells. Moreover, adaptive immune cells also seem to have a pivotal role in NASH. This is highlighted by experimental data obtained with a mouse model, in which mice are fed a choline-deficient high-fat diet, that recapitulates NASH-induced HCC. Antibody-mediated depletion of CD8 + T cells in established NASH abolishes liver damage, which indicates that metabolically activated intrahepatic CD8 + T cells are the main drivers of liver damage [27]. At the same time, inflammation-induced suppression of the activation of cytotoxic CD8 + T lymphocytes by IgA+ cells has been identified as a tumor-promoting mechanism [28]. NAFLD and especially NASH, reshapes the liver and tumor immune microenvironment and may hamper the efficacy of immune checkpoint blockers. Very recent data, both experimental and human, show that non-viral HCC, and particularly NASH–HCC, might be less responsive to immunotherapy, probably owing to a NASH-related aberrant T cell activation profile in hepatic CD8 + PD1 + T cells causing active tissue damage that leads to an impaired function of anti-tumor immune surveillance [29].

Furthermore, obesity has been linked to a 1.95-fold higher risk of HCC-related mortality, as it has been associated with a chronic inflammatory state attributed to increased levels of leptin, a profibrotic and proangiogenic cytokine that activates the Janus kinase pathway, thereby triggering an intracellular signaling cascade of pro-inflammatory cytokines [30]. Increased lipid accumulation in the liver due to lipolysis within peripheral adipose tissue induces hepatic lipotoxicity, resulting in enhanced production of free fatty acids (FFAs) that undergo β-oxidation leading to the formation of ROS, that have been linked to endoplasmic reticulum (ER) stress, mitochondrial damage and gene transcription, promoting inflammatory cell signaling pathways [31]. Moreover, excessive fat accumulation potentiates hepatic and peripheral insulin resistance leading to compensatory hyperinsulinemia, promoting the development of HCC by the activation of various oncogenic pathways [32]. Both insulin-like growth factor 1 (IGF-1) and insulin receptor substrate stimulate HCC growth by the activation of the mitogen-activate protein kinase (MAPK) pathway and increase the transcription of proto-oncogenes [33]. Activation of the MAPK pathway subsequently activates the Wnt/β-catenin signaling cascade, leading to fibrosis and hepatocarcinogenesis [34]. Finally, it is postulated that androgen and androgen receptors (ARs) might instigate HCC progression, since ARs are activated by androgen hormone and potentiate the transcription of cell cycle-related kinase (CCRK) that enchances β-catenin/T-cell factor signaling, leading to hepatocarcinogenesis [35–37].

There is evidence that the postprandial increase in plasma glucose triggers the production of IL-1β by the macrophages [38]. Following myocardial infarction (MI), a significant upregulation of IL-1β both in the systemic circulation and in the heart tissue has been observed [39]. Moreover, anti-inflammatory therapy targeting the interleukin-1β (IL-1β) innate immunity pathway has been shown to mitigate the risk of recurrent cardiovascular events, independent of an improvement in lipid

levels among high-risk patients with history of MI [40]. In a recent work, Lee et al. demonstrated that empagliflozin attenuated the secretion and mRNA expression of proinflammatory cytokines, such as tumor necrosis factor-a (TNF-α), IL-1β, IL-6, and interferon-γ (IFN-γ), and proinflammatory chemokines, such as C-C Motif chemokine ligand (CCL) CCL3, CCL4, CCL5, and CXCL10 and inhibited prostaglandin E2 (PGE2) release and cyclooxygenase-2 (COX2), inducible nitric oxide synthase (iNOS) gene expression in lipopolysaccharide-stimulated macrophages [41]. Thus, the important anti-inflammatory properties of SGLT2i might explain to some extent their impressive cardioprotective effects. Synchronous dysregulation in the metabolism and immune system could represent a missing link between antidiabetic agents and malignancies. There is data that metabolic remodeling of immune cells contributes to the pathophysiology of several chronic diseases, including infections, obesity and cancers [42]. In this context, it has previously been suggested that metformin exerts anticancer effects through the inhibition of mitochondrial complex I [43]. It could be then postulated that the effects of SGLT2i on HCC might relate to modulating effects on metabolic activity and function of immune cells, a hypothesis deserving further evaluation in future studies.

The ultimate goal of NASH therapy is to inhibit and revert steatohepatitis in order to arrest the progression of hepatocellular injury and fibrosis. Major international societies including the American Association for the Study of Liver Disease, the European Association for the Study of the Liver and the Asian Pacific Association for the Study of the Liver, have recommended enrollment in HCC surveillance programs for adults with cirrhosis and high-risk patients without cirrhosis using ultrasound with or without alpha-fetoprotein (AFP) at six-month intervals [44–46]. The potential favorable effects of SGLT2i in NASH, a disease that when left untreated often progresses to HCC development, have been thoroughly reviewed [47,48]. A meta-analysis of ten randomized controlled trials with 573 study participants provided evidence that SGLT-2i can significantly reduce hepatic enzymes, hepatic fat and improve body composition [49]. An Asian, open-label clinical trial including nine patients with biopsy-proven NASH treated with empagliflozin for six months, reported significant improve of histological outcomes with decrease of steatosis, hepatocyte ballooning and fibrosis, and eventual resolution of NASH in four out of nine patients [50]. Moreover, the administration of SGLT2i ipragliflozin in a patient with NASH and T2D decreased the serum alanine aminotransferase (ALT) and ferritin levels, while it ameliorated type IV collagen and hyaluronic acid, both of which are serum fibrotic markers. Ultrasonography and computed tomography showed decrease of hepatic fat deposition, while liver biopsy showed marked improvement of hepatic steatosis, inflammation, and ballooning [51]. In addition, evidence demonstrated that ipragliflozin improves liver dysfunction irrespective of body weight reduction in patients with T2D, while it improves hepatic steatosis and inhibits lipogenic and macrophage marker gene induction in the liver of obese mice with insulin resistance [52]. Along the same line, evidence from a randomized, open-label trial of 57 patients with T2D and NAFLD, demonstrated that the SGLT2i dapagliflozin, improved liver steatosis and attenuated liver fibrosis, while it decreased ALT and γ-glutamyltranspeptidase levels [53]. Similarly, evidence has been provided that empagliflozin improves liver steatosis, decreases the levels of visceral fat and attenuates liver fibrosis in patients with NAFLD without T2D [54].

2.1. Sodium glucose co-transporter 2 inhibitors' effect on hepatocellular carcinoma

There are several animal studies showing potential favorable effects of SGLT2i on HCC. Luo et al. demonstrated that canagliflozin (CANA) could significantly inhibit hypoxia-induced metastasis, angiogenesis, and metabolic reprogramming in HCC [55]. At the molecular level, this was achieved by inhibiting vascular endothelial growth factor (VEGF) expression, as well as via the reduction of the epithelial-to-mesenchymal transition (EMT)-related proteins and glycolysis-related proteins, while CANA also decreased hypoxia-inducible factor 1-alpha (HIF-1α) protein synthesis without an impact on its proteasomal degradation. Furthermore, they provided evidence that CANA inhibited the AKT/mTOR pathway, which plays a pivotal role in HIF-1 transcription and translation, suggesting that CANA could instigate HIF-1a reduction through the AKT/mTOR pathway via the inhibition of HIF-1a protein synthesis. Evidence regarding the inhibitory effect of CANA on HCC growth was further provided by a study from Hung et al., demonstrating that CANA treatment inhibited the maintenance and growth of HCC cells and HCC stem cells in a dose-dependent manner, decreased the proportions of CD133- and EpCAM-positive HuH7 cells and significantly reduced the glucose uptake of Huh7 cells [56]. Their study also demonstrated in vivo that CANA suppressed HCC growth and prolonged the survival of tumor-bearing mice via the inhibition of PP2A/p-β-catenin, since CANA promoted glucose influx-induced β-catenin signaling activation via its proteasome degradation and enhanced the degradation of β-catenin via the inhibition of its PP2A-mediated dephosphorylation. Similarly, the preventive effects of CANA in a mouse model of human NASH were evaluated by Shiba et al., demonstrating that after one year of CANA treatment, apart from the reduction of liver fibrosis the number of liver tumors was significantly reduced in western diet WD-fed melanocortin-4-receptor-deficient (MC4R-KO) mice with a trend towards a reduction in maximum tumor size [57]. Finally, the effects of CANA on proliferation and metabolic reprograming of HCC cell lines using multi-omics analysis of metabolomics and absolute quantification proteomics (iMPAQT) were investigated by Nakano et al., reaching to a conclusion that CANA hindered the proliferation of HCC cells through alterations in mitochondrial oxidative phosphorylation metabolism, fatty acid metabolism, purine and pyrimidine metabolism [58]. In more detail, they demonstrated that SGLT2 occurred in Hep3B and Huh7 cells and localized on their mitochondria, while CANA upregulated the phosphorylation of 5-adenosine monophosphate-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC), which are sensors of intracellular adenosine triphosphate (ATP) levels and regulators for beta oxidation known to inhibit hepatic de novo lipogenesis and HCC proliferation, while at the same time it downregulated proteins associated with the electron transport system in Hep3B and Huh7 cells.

In addition, an in vivo study by Jojima et al., provided evidence that CANA inhibits hepatic tumorigenesis, since there were significantly fewer hepatic tumors and fewer glutamine synthetase-positive nodules in the continuous CANA group than in the control group, while the expression of AFP mRNA, a marker of HCC, was also downregulated [59]. Flow cytometry further demonstrated that CANA reduced the percentage of HepG2 cells in the G2/M phase due to arrest in the G1 phase alongside downregulated expression of cyclin D and Cdk4 proteins, while it upregulated the percentage of cells in the G0/1 phase. CANA also potentiated the apoptosis of HepG2 cells via the activation of caspase 3, while it exhibited anti-steatotic and anti-inflammatory effects that attenuated the development of NASH and prevented the progression of NASH to HCC, in part due to the induction of cell cycle arrest and apoptosis as well as the inhibition of tumor growth through direct inhibition of SGLT2 in tumor cells. Furthermore, a study by Kaji et al., demonstrated that CANA exhibits anti-proliferative effects on SGLT2-expressing Huh7 and HepG2 cells in a dose-dependent manner, by downregulating glycolytic metabolism including glucose uptake, lactate and intracellular ATP production [60]. CANA also suppressed human HCC cell growth by inducing cell cycle arrest and apoptosis with inhibited phosphorylation of extracellular signal-regulated kinase (ERK), p38, protein kinase B (AKT) and cleavage of caspase3, while its oral administration substantially reduced subcutaneous tumor burden independently of glycemic status, and decreased intratumor vascularization in Huh7- and HepG2-derived xenograft HCC tumors in BALB/c nude mice. CANA also attenuates the proangiogenic activities of human HCC cells, as it inhibited in vitro the increased human umbilical vein endothelial cell (HUVEC) proliferation and tubular formation, which were observed in Huh7 or HepG2 co-cultures. Finally, a recent study by

Khairy et al., shedded some light on the effective combination of CANA and γ-irradiation (γ-IR) in HCC treatment, as evidence demonstrated that CANA enhanced the antitumor potential of γ-IR by inhibiting the clonogenic survival in HepG2 cells via the downregulation of glucose uptake, lactate release, and modulation of ER stress-mediated autophagy, as well as it disabled signaling pathways which partake in metabolic reprogramming and tumor progression induced by γ-IR that confer radioresistance and treatment failure [61]. In more detail, CANA disrupted the crosstalk between PI3K/AKT/GSK-3β/mTOR and Wnt/β-catenin signaling pathways, increased intracellular Ca2 + -mediated apoptosis via caspase-12/caspase-3 activation and down-regulated p53 and BCL-2 expression, alleviating ER stress-mediated cytoprotective autophagy, promoting the crosstalk between autophagy and apoptosis in irradiated HepG2 cells. (Table 1).

Recent evidence has also surfaced, indicating that selective PPARα modulator pemafibrate and SGLT2i tofogliflozin combination treatment has therapeutic potential to prevent NASH-related HCC progression, since results demonstrated that it improves HCC-related survival rates in STAM mice and decreased the number of liver tumors compared to the NASH control group, preventing liver injury by inhibiting the IRE1-XBP1-PHLD3A pathway [62]. Another in vivo study by Yoshioka et al, reached a conclusion that tofogliflozin ameliorates NASH-like liver phenotypes in WD-fed Mc4r-KO mice and that it also prevents the progression of NASH-associated liver tumors utilizing diethylnitrosamine (DEN)-injected WD-fed Mc4r KO mice, since the number of large tumors (≥2 mm in diameter) was significantly less in the tofogliflozin-treated group [63]. Moreover, the role of tofogliflozin on the development of NASH-associated liver tumorigenesis in C57BL/KsJ-+Leprdb/+Leprdb obese and diabetic mice was evaluated by Obara et al., reaching to the conclusion that tofogliflozin significantly suppresses the development of hepatic preneoplastic lesions, reducing hepatic steatosis, ballooning degeneration of hepatocytes and inflammation, as evaluated using the non-alcoholic fatty liver disease activity score (NAS), compared to the control mice [64]. High-dose tofogliflozin-treated mice also showed a significant decrease in mRNA expression levels of macrophage marker F4/80, a marker of liver inflammation, alongside a substantial decrease of serum glucose and FFA levels. In addition, evidence was provided that dapagliflozin alleviated hepatic steatosis both in vivo and in vitro in HepG2 cells, by restoring autophagy via the AMPK-mTOR pathway, while it also promoted the phosphorylation of ACC1 and upregulated lipid β-oxidation enzyme acyl-CoA oxidase-1 (ACOX1) [65]. The effects of combined treatment with CANA and teneligliptin, a dipeptidyl peptidase-4 inhibitor, were analyzed in a study by Ozutsumi et al., demonstrating that their combination inhibited HCC cells and HUVEC proliferation, suppressed VEGF expression and enhanced E-cadherin expression in HUVECs, potentially exhibiting synergistic effects against hepatocarcinogenesis by hindering HCC cell growth and angiogenesis and simultaneously by reducing oxidative stress [66]. (Fig. 1).

2.2. Clinical implications

SGLT2i originally emerged as drugs for the treatment of hyperglycemia; however, they soon demonstrated important extra-glycemic properties, which led to their evaluation as potential treatments for a wide range of non-metabolic disorders, including infections and malignancies. A recent meta-analysis showed that the use of SGLT2i is associated with a lower overall risk of cancer compared to placebo among people with diabetes (Relative Risk 0.35, Confidence Interval 0.33–0.37, $P < 0.001$) [67]. The direct anti-diabetic effects of gliflozins can explain a part of their antineoplastic potential, considering that glucose plays a key role in the metabolism and growth of malignant cells, and serum glucose levels have an inverse relationship with cancer risk [68]. Recent works have highlighted that SGLT2 are expressed in animal and human cancer tissues [69]. Thus, inhibition of these cotransporters in people with malignancies could theoretically block the process of feeding glucose into tumors to support glycolysis, which plays a key role in

Table 1
Summary of studies evaluating the role of SGLT2i in HCC.

Study (year)	Primary Outcome	Secondary outcome
Luo et al. [55]	Canagliflozin hinders metastasis, hypoxia-induced angiogenesis and metabolic reprogramming in HCC by inhibiting HIF-1 protein accumulation, probably by targeting the AKT/mTOR pathway	Canagliflozin inhibits hypoxia-induced glycolysis and the expression of epithelial-to-mesenchymal transition-related proteins
Hung et al. [56]	Canagliflozin inhibits growth of HCC via blocking glucose-influx induced β-catenin activation through promoting its proteasome degradation	Canagliflozin suppresses in vivo HCC growth and prolongs the survival of tumor-bearing mice via inhibiting PP2A/p-β-catenin
Shiba et al. [57]	Canagliflozin attenuates the development of NASH-associated HCC and reduces the number and size of liver tumors in a mouse model of human NASH	Canagliflozin inhibits hepatic steatosis and fibrosis, reduces adipose tissue inflammation and decreases oxidative stress
Nakano et al. [58]	Canagliflozin significantly suppresses the proliferation of Hep3B and Huh7 cells and alters the phosphorylation of AMPK and ACC, which are regulators for beta oxidation and sensors of intracellular ATP levels	Canagliflozin mainly alters the metabolisms of oxidative phosphorylation metabolism, fatty acid metabolism, and purine and pyrimidine metabolism
Jojima et al. [59]	Canagliflozin suppresses the proliferation of HepG2 cells and the expression of α-fetoprotein mRNA, while inducing apoptosis of HepG2 cells via activation of caspase 3	Canagliflozin inhibits hepatic tumorigenesis and the progression of NASH to HCC
Kaji et al. [60]	Canagliflozin attenuates Huh7 and HepG2 cell growth and angiogenic activity by inhibiting glucose uptake and glycolytic metabolism in HCC cells	Canagliflozin inhibits proangiogenic activity in SGLT2-expressing liver cancers
Abdel-Rafei et al. [61]	Canagliflozin enhances the antitumor potential of γ-IR by significantly inhibiting the clonogenic survival in HepG2 cells, disrupting the crosstalk between PI3K/AKT/GSK-3β/mTOR and Wnt/β-catenin signaling pathways	Canagliflozin suppresses SGLT-2 mRNA expression and protein level in irradiated HepG2 cells impairing cancer cell glycolytic metabolism
Murakami et al. [62]	Pemafibrate and tofogliflozin combination improves HCC-related survival and induces lipolysis and fatty acid re-esterification genes expression in STAM mice liver	Pemafibrate and tofogliflozin combination prevents liver injury by inhibiting the IRE1a-XBP1-PHLDA3 Pathway
Yoshioka et al. [63]	Tofogliflozin prevents the progression of NASH-associated HCC in a mouse model of human NASH	Tofogliflozin attenuates the expression of p21 from hepatocytes and inhibits cellular senescence
Obara et al. [64]	Tofogliflozin suppresses the development of hepatic preneoplastic lesions and significantly reduces hepatic steatosis and inflammation	Tofogliflozin reduces the serum levels of glucose and the free fatty acid and mRNA expression levels of pro-inflammatory markers in the liver
Li et al. [65]	Dapagliflozin induces autophagy and regulates fatty acid metabolism in ZDF Rats and PA-stimulated LO2 and HepG2 Cells via the AMPK-mTOR pathway in vitro and in vivo	Dapagliflozin alleviates hepatic lipid accumulation in ZDF Rats and PA-stimulated LO2 and HepG2 Cells
Ozutsumi et al. [66]	Canagliflozin alone or in combination with teneligliptin inhibits human HCC cell lines HepG2 and Huh7 and human umbilical vein endothelial cell	Canagliflozin and teneligliptin combination inhibits HCC cell proliferation, VEGF mediated neovascularization, ROS, and inflammation

(continued on next page)

Table 1 (*continued*)

Study (year)	Primary Outcome	Secondary outcome
	proliferation, increases the expression of E-cadherin and suppresses the expression of VEGF	

HCC: hepatocellular carcinoma; NASH: nonalcoholic steatohepatitis; HIF: hypoxia-inducible factor; AKT: protein kinase B; mTOR: mammalian target of rapamycin; AMPK: AMP-activated protein kinase; ACC: Acetyl-CoA carboxylase; ATP: adenosine triphosphate; mRNA: messenger; γ-IR: γ-irradiation; ZDF: zucker diabetic fatty; PA: palmitic acid; ROS: reactive oxygen species; SGLT: sodium-glucose cotransporter

tumor metabolism and growth [70]. Moreover, insulin resistance, obesity, and hyperinsulinemia have been epidemiologically and pathophysiologically linked to the development and progression of neoplasms, leading to alterations in tumor glucose metabolism and eventually in tumorigenesis [71]. However, evidence from animal studies summarized in this review suggests that the effects of SGLT2i on HCC are not restricted to changes in glucose metabolism and are related to modulation of molecular pathways that affect hallmarks of cancer, including inflammatory responses, cell proliferation, and oxidative stress.

In addition to SGLT2i, alternative agents used for the treatment of cardiometabolic disorders have shown benefit in HCC. Among people with T2D and HCC, metformin therapy has been associated with improved survival rates, an effect that was particularly evident in those in the potentially curative stage of the disease [72]. Although possible mechanisms are still obscure, they could be related to inhibition of liver stellate cell activation, amelioration of hepatic fibrosis, and reduced lipid accumulation in liver cells that result in halting progression to cirrhosis and eventually preventing tumorgenesis [73]. Glucagon-like peptide-1 receptor agonists are a new class of antidiabetic drugs that exert strong glucose-lowering actions and provide cardiorenal protection. Apart from their weight-lowering effect, the improvement seen in liver enzymes and hepatic steatosis after treatment with these agents could be derived from systemic anti-inflammatory actions [74]. In a mouse model of diabetes and NASH, liraglutide was shown to suppress hepatocarcinogenesis by attenuating steatosis, inflammation, and hepatocyte ballooning [75]. Robust data indicate a protective role for statins against several types of malignancies. A recent meta-analysis of observational studies showed that statin use was associated with a 46% lower risk of HCC development [76]. Postulated mechanisms relate to the proapoptotic, antiproliferative, anti-inflammatory, and antifibrotic actions of these drugs, as well as to amelioration of endothelial dysfunction promoted by statins [77]. Recent findings demonstrate that repression of the mevalonate pathway is a crucial component of p53-mediated liver tumor suppression. Pharmacological or RNA inhibition of the mevalonate pathway restricts the development of murine HCC driven by p53 loss. The rate-limiting step of the mevalonate pathway is controlled by 3-hydroxy-3-methyl-glutaryl (HMG)-coenzyme A (CoA) reductase (HMGCR), an enzyme that converts HMG-CoA to mevalonate and is the target of cholesterol-reducing statins. Interestingly, statins have been associated with reduced mortality in multiple cancer types, including prostate, kidney, colorectal, breast, and lung cancer [78]. Given that all of these agents are very commonly co-administered with SGLT2i in people with T2D, a possible synergistic effect on HCC deserves further evaluation by future studies.

Ascites is a common clinical problem in HCC patients, associated with poor prognosis and both tumoral and cirrhosis factors [79]. Loop diuretics and mineralocorticoid receptor agonists (MRAs) are considered the cornerstone of the treatment of cirrhotic ascites; however, both categories have demonstrated little survival benefit and modification of the disease's natural history, primarily providing symptomatic relief [80]. Overactivation of renin-angiotensin-aldosterone-system (RAAS) is a core feature of decompensated liver cirrhosis. Loop diuretics inhibit sodium-potassium-chloride cotransporter 2 in macula densa, resulting in a vicious cycle of exacerbation of renin production and RAAS activation. Spironolactone is co-administered with furosemide to counteract the activation of RAAS. However, in the context of ascites, an increased sodium reabsorption at the proximal convoluted tubule is observed, finally resulting in decreased sodium concentrations in distal nephron segments. Therefore, diuretics that act on this part of the nephron often fail in the management of advanced ascites. In contrast, SGLT2i block

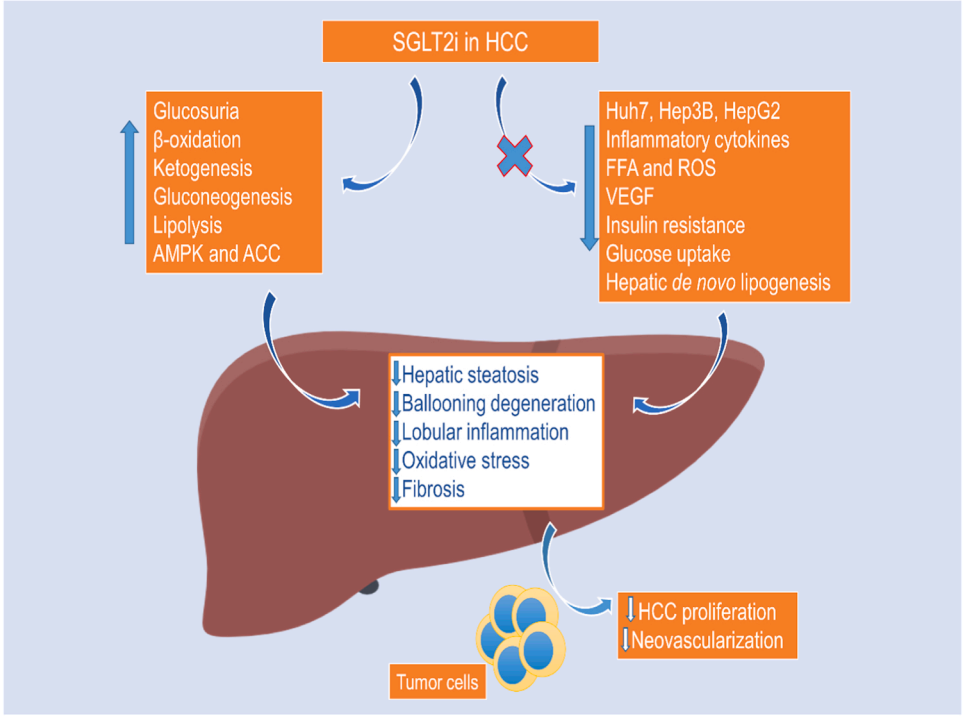

Fig. 1. The inhibitory effect of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in hepatocellular carcinoma. SGLT2i inhibit the release of inflammatory cytokines, attenuate hepatic *de novo* lipogenesis and insulin resistance, decrease free fatty acids (FFAs) and reactive oxygen species formation (ROS), while at the same time increase urinary glucose excretion, ketogenesis, glucagon secretion and potentiate lipolysis. Their overall effect leads to decreased hepatic steatosis and inflammation, attenuating oxidative stress and liver fibrosis.

the reabsorption of glucose and sodium in the proximal tubule without affecting sodium sensing at the macula densa. Therefore, they induce diuresis and natriuresis in absence of RAAS activation [81]. Although still limited, preliminary evidence from isolated case reports indicates an improvement in clinical status, translated into amelioration of ascites and peripheral edema, in patients with cirrhosis and diabetes receiving SGLT2i [82].

Data from studies conducted in HF, a disease model characterized also by overactivation of RAAS, suggest that the co-administration of loop diuretics and SGLT2i has an additive natriuretic effect [83]. Importantly, combined therapy did not increase neurohormonal activation and was safe in terms of electrolyte balance and renal function. On the contrary, Mordi et al. found that empagliflozin used in combination with loop diuretics significantly amplified 24-hour urine volume without a parallel increase in urinary sodium excretion, suggesting that the diuretic effects of SGLT2i are primarily driven by fluid clearance from the interstitial space, rather than the circulating volume [84]. A study by Shirakabe et al. that recruited patients with diabetes and compensated HF showed that co-administration with empagliflozin resulted in a decrease in the dose of loop diuretics, while increasing erythropoietin production, which could protect against the development of renal tubular injury [85]. It should be noted that the use of MRAs in cirrhotic patients with renal impairment is often prohibitive due to the risk of hyperkaliemia. A recent meta-analysis that included data from 24246 individuals with T2D demonstrated a 28% lower risk of hyperkaliemia in those treated with SGLT2i compared to patients receiving placebo [86]. In addition, recent findings suggest that the combined therapy with finerenone, a novel MRA, and SGLT2i promotes greater reductions in albuminuria among patients with diabetic nephropathy compared to finerenone alone [87]. Taken together, these data encourage the evaluation of the synergistic effects of SGLT2i and classical diuretics in patients with cirrhotic ascites in appropriately designed clinical studies.

On the other hand, a number of safety issues should be taken into account when discussing a putative role of gliflozins in the management of HCC. SGLT2i exhibit an extensive hepatic metabolism mainly via glucuronidation to inactive metabolites [88]. However, to date, no safety concerns have emerged regarding the risk of liver dysfunction in large cardiovascular outcome trials conducted with these agents [89]. In contrast, these studies have been suggestive of a protective effect on liver function as indicated by significant reductions in transaminase levels [90]. Of great importance, empagliflozin has been shown to be well tolerated in patients with liver impairment, and no significant alterations in the pharmacokinetics of the drug have been documented in this population [91]. The drop of estimated glomerular filtration rate seen in patients during the first weeks of treatment with SGLT2i, in conjunction with the blood pressure lowering effect of the class, raises concerns over a potential triggering of hepatorenal syndrome. However, this seems to be unlikely without a parallel activation of RAAS [81]. An increased risk of hypovolemia compared to placebo has been shown in patients with T2D and CKD treated with SGLT2i [92]. However, in the long run, gliflozins have been shown to exert renoprotective effects and significantly reduce the odds of renal endpoints. Thus, future studies to evaluate the renal safety of SGLT2i in patients with cirrhosis are needed before reaching definite conclusions.

Patients with liver disease are generally considered immunosuppressed due to the key role that the liver plays in the host immune response [93]. In addition, they experience poor nutritional status, recurrent hospitalizations, and undergo medical procedures that increase the risk of severe infections. Relevant to their mechanism of action that exacerbates glycosuria, the use of SGLT2i has been linked to increased odds of mycotic genital infections, which are usually mild and easy to manage in the daily clinical setting [94]. The magnitude of glucose excretion in the urine after the administration of SGLT2i is dependent on plasma glucose levels;[95] thus, urinary tract infections are not expected to be a major issue when these agents are used in non-diabetic individuals. On the other hand, recent trials have tested the hypothesis that SGLT2i might act as anti-viral drugs, attempting to take advantage from their anti-inflammatory properties [96]. In DARE-19, dapagliflozin was administered to patients with acute COVID-19 and cardiometabolic risk factors [97]. Although the results did not reach statistical significance, numerically fewer individuals in dapagliflozin compared to the placebo group experienced death or organ damage, suggesting a place for SGLT2i in future trials investigating their potential as anti-infective agents.

Patients with HCC and / or cirrhosis are considered to be at high risk for hospital admission [98]. Until recently, physicians were skeptical about using SGLT2i in the inpatient setting, given that there was no enough evidence to support that clinical benefits can outweigh potential risks [99]. Euglycemic diabetic ketoacidosis DKA is a life threatening, still rare, adverse event of therapy with SGLT2i. It is related to a shift in energy metabolism due to an imbalance in insulin / glucagon ratio and changes in renal clearance of ketone bodies caused by these agents [100]. DKA can occur in the context of severe illness in insulinopenic patients; however, it is extremely rare in non-diabetic individuals with adequate endogenous insulin production [101]. In DARE-19, there were only two episodes of DKA among 625 dapagliflozin-treated participants. Both cases were observed in subjects with diabetes, diagnosed timely and rapidly resolved with appropriate treatment, suggesting that the use of these drugs in the inpatient setting is safe, provided that patients are closely monitored [102]. This perspective is further supported by the recently published EMPULSE findings, in which empagliflozin was administered to hospitalized patients with acute HF [103]. The results were encouraging, with significant clinical benefit experienced by more participants in the active treatment compared to the placebo group. At the same time, empagliflozin was well tolerated suggesting “an earlier, better” approach in the use of SGLT2i in people with HF, even before hospital discharge.

Although there aren’t any ongoing clinical trials regarding the use of SGLT2i in patients with HCC, there are some ongoing clinical trials of SGLT2i in NASH, which are expected to shed further light on their potential clinical benefits in patients with NASH and ultimately, in NASH-associated HCC (Table 2). A multicentre phase 3 randomized, placebo-controlled trial, the DEAN study (“Dapagliflozin Efficacy and Action in NASH”; NCT03723252), aims to recruit 100 patients with NASH and T2D in order to study the impact of dapagliflozin on hepatic histology, as determined by liver biopsy after 12 months of treatment, compared to placebo. Secondary outcomes to be investigated are NASH resolution and changes in various metabolic factors and biomarkers. DEAN is expected to be completed on June 2022. Another single-centre randomized open label study (“Efficacy and Safety of Dapagliflozin in Patients With Non-alcoholic Steatohepatitis”; NCT05254626), plans to recruit 160 patients with NASH and T2D to evaluate the efficacy and safety of SGLT2 inhibitors in NASH patients in comparison to pioglitazone. Secondary outcomes to be assessed are NASH resolution and changes in various biomarkers. The study is expected to be completed on August 2025. Moreover, the COMBAT_T2_NASH trial (“Combined Active Treatment in Type 2 Diabetes With NASH”; NCT04639414) is recruiting 192 T2D patients with biopsy-proven NASH and fibrosis stage F1–F3 to receive either empagliflozin and placebo, or empagliflozin in combination with semaglutide, a glucagon-like peptide-1 receptor agonist. The primary aim of the trial is to evaluate the efficacy of combined treatment with semaglutide and empagliflozin and of empagliflozin monotherapy, by means of histological resolution of NASH in T2D patients without progression of fibrosis after 48 weeks’ treatment. Secondary aims include changes in NAFLD activity score, in steatosis-activity-fibrosis score and in fibrosis stage. Finally, another open-label randomized clinical trial, entitled “Comparison of The Effects of Thiazolidinediones, SGLT-2i Alone and Thiazolidinediones/SGLT-2i Combination Therapy on Non-alcoholic Fatty Liver Disease in Type 2 Diabetic Patients With Fatty Liver” (NCT03646292), aims to investigate the comparative effect of empagliflozin monotherapy vs. pioglitazone monotherapy vs. their

Table 2
Ongoing clinical trials on SGLT2i in patients with NASH.

Trial ID	Title	Design	Arms	Patients (n)	Duration	Primary outcome
NCT03723252	Dapagliflozin Efficacy and Action in NASH	Multicentre, randomized, placebo-controlled, phase 3	Dapagliflozin (10 mg) vs. placebo	100	12 months	Improvement of hepatic histology
NCT05254626	Efficacy and Safety of Dapagliflozin in Patients With Non-alcoholic Steatohepatitis	Single-centre, prospective, randomized, 2-arm parallel group, phase 4	Dapagliflozin (10 mg) vs. pioglitazone (30 mg)	160	24 weeks	Improvement of hepatic histology, without worsening of fibrosis
NCT04639414	Combined Active Treatment in Type 2 Diabetes With NASH	Multicentre, prospective, placebo-controlled, double-blind, randomized, 3-arm parallel group, phase 4	Empagliflozin (10 mg) + Semaglutide (1 mg) vs. Empagliflozin (10 mg) vs. placebo	192	48 weeks	Histological resolution of NASH without worsening of fibrosis
NCT03646292	Comparison of The Effects of Thiazolidinediones, (SGLT-2i) Alone and Thiazolidinediones/SGLT-2i Combination Therapy on Non-alcoholic Fatty Liver Disease in Type 2 Diabetic Patients With Fatty Liver	Prospective, open label, randomized, single-centre, phase 4	Empagliflozin (10 mg) vs. Pioglitazone (15 mg) vs. Empagliflozin (10 mg) + Pioglitazone (15 mg)	60	6 months	Changes in hepatic fat deposition measured by MRI-PDFF

MRI-PDFF, magnetic resonance imaging-derived proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SGLT-2i, sodium-glucose co-transporter 2 inhibitors.

combination on hepatic fat, assessed by MRI-PDFF, in patients with T2D and NAFLD. Secondary outcome of this trial is the assessment of liver fibrosis, evaluated by magnetic resonance elastography.

3. Conclusions

A wealth of data has accumulated in the past years that has revealed novel cellular and molecular mechanisms driving NASH and NAFLD-associated HCC. These findings have also opened up novel links and treatment options. At the same time, several questions have emerged. Several factors contribute to the development of NAFLD or NASH and subsequent HCC development; these factors include genetic and environmental modifiers such as diet, medications or lifestyle. The data presented in this review shape a theoretical framework that encourages further evaluation of the safety and efficacy of SGLT2i to improve outcomes related to HCC. Future mechanistic studies are expected to provide deeper insights into the molecular pathways that connect gliflozin actions with the mechanisms involved in the development of NASH, cirrhotic ascites, and eventually HCC. The impressive benefits of neurohormonal modulation observed with SGLT2i in congestive HF set the stage for human trials in cirrhotic ascites. Future research needs to evaluate several aspects of the benefit to risk ratio of such a therapeutic strategy, including the co-administration with antineoplastic agents and diuretics, infections, use in hospitalized individuals, renal safety and hypovolemia.

Funding

No external funds were used in the preparation of this manuscript.

CRediT authorship contribution statement

Konstantinos Arvanitakis: Conceptualization, Investigation, Visualization, Writing – original draft, Editing. **Theocharis Koufakis**: Conceptualization, Investigation, Writing – original draft, Editing. **Kalliopi Kotsa**: Supervision, Writing – review & editing. **Georgios Germanidis**: Supervision, Investigation, Writing – review & editing.

Acknowledgements

None.

Disclosure of potential conflicts of interest

TK has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Pharmaserve Lilly, and Novo Nordisk, for advisory boards from Novo Nordisk, and has participated in sponsored studies by Eli-Lilly and Novo Nordisk. **KK** has received honoraria for lectures/advisory boards and research support from Astra Zeneca, Boehringer Ingelheim, Pharmaserve Lilly, Sanofi-Aventis, ELPEN, MSD, and Novo Nordisk. Other authors report no conflict of interest.

Research involving human participants and/or animals

Not applicable.

Ethics approval and consent to participate

Not applicable.

References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.
[2] C. Global Burden of Disease Liver Cancer, T. Akinyemiju, S. Abera, M. Ahmed, N. Alam, M.A. Alemayohu, C. Allen, R. Al-Raddadi, N. Alvis-Guzman, Y. Amoako, et al., The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015, JAMA Oncol. 3 (2017) 1683–1691, https://doi.org/10.1001/jamaoncol.2017.3055.
[3] G. Fattovich, T. Stroffolini, I. Zagni, F. Donato, Hepatocellular carcinoma in cirrhosis: incidence and risk factors, Gastroenterology 127 (2004) S35–S50, https://doi.org/10.1053/j.gastro.2004.09.014.
[4] O. Massoud, M. Charlton, Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis and hepatocellular carcinoma, Clin. Liver Dis. 22 (2018) 201–211, https://doi.org/10.1016/j.cld.2017.08.014.
[5] S. Ronnebaum, A. Aly, D. Patel, F. Benavente, J.D. Rueda, Systematic literature review of trials assessing recommended systemic treatments in hepatocellular carcinoma, Hepat. Oncol. 9 (2022) HEP41, https://doi.org/10.2217/hep-2021-0003.
[6] E.M. Wright, D.D. Loo, B.A. Hirayama, Biology of human sodium glucose transporters, Physiol. Rev. 91 (2011) 733–794, https://doi.org/10.1152/physrev.00055.2009.
[7] K. Rave, L. Nosek, J. Posner, T. Heise, K. Roggen, E.J. van Hoogdalem, Renal glucose excretion as a function of blood glucose concentration in subjects with type 2 diabetes–results of a hyperglycaemic glucose clamp study, Nephrol. Dial. Transpl. 21 (2006) 2166–2171, https://doi.org/10.1093/ndt/gfl175.
[8] K.B. Lo, F. Gul, P. Ram, A.Y. Kluger, K.M. Tecson, P.A. McCullough, J. Rangaswami, The effects of SGLT2 inhibitors on cardiovascular and renal outcomes in diabetic patients: a systematic review and meta-analysis, Cardiorenal Med. 10 (2020) 1–10, https://doi.org/10.1159/000503919.

[9] C. American Diabetes Association Professional Practice, C. American Diabetes Association Professional Practice, B. Draznin, V.R. Aroda, G. Bakris, G. Benson, F. M. Brown, R. Freeman, J. Green, E. Huang, et al., Cardiovascular disease and risk management: standards of medical care in diabetes-2022, Diabetes Care 45 (2022) S144–S174, https://doi.org/10.2337/dc22-S010.
[10] T. Koufakis, A.N. Pavlidis, S. Metallidis, K. Kotsa, Sodium-glucose co-transporter 2 inhibitors in COVID-19: meeting at the crossroads between heart, diabetes and infectious diseases, Int. J. Clin. Pharm. 43 (2021) 764–767, https://doi.org/10.1007/s11096-021-01256-9.
[11] A. Gastaldelli, K. Cusi, From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options, JHEP Rep. 1 (2019) 312–328, https://doi.org/10.1016/j.jhepr.2019.07.002.
[12] K. Gariani, F.R. Jornayvaz, Pathophysiology of NASH in endocrine diseases, Endocr. Connect 10 (2021) R52–R65, https://doi.org/10.1530/EC-20-0490.
[13] T. Koufakis, G. Dimitriadis, S. Metallidis, P. Zebekakis, K. Kotsa, The role of autoimmunity in the pathophysiology of type 2 diabetes: Looking at the other side of the moon, Obes. Rev. 22 (2021), e13231, https://doi.org/10.1111/obr.13231.
[14] T. Song, S. Chen, H. Zhao, F. Wang, H. Song, D. Tian, Q. Yang, L. Qi, Meta-analysis of the effect of sodium-glucose cotransporter 2 inhibitors on hepatic fibrosis in patients with type 2 diabetes mellitus complicated with non-alcoholic fatty liver disease, Hepatol. Res. 51 (2021) 641–651, https://doi.org/10.1111/hepr.13645.
[15] A.J. Scheen, Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: a common comorbidity associated with severe complications, Diabetes Metab. 45 (2019) 213–223, https://doi.org/10.1016/j.diabet.2019.01.008.
[16] K. Arvanitakis, I. Mitroulis, G. Germanidis, Tumor-associated neutrophils in hepatocellular carcinoma pathogenesis, prognosis, and therapy, Cancers (2021) 13, https://doi.org/10.3390/cancers13122899.
[17] K. Arvanitakis, T. Koletsa, I. Mitroulis, G. Germanidis, Tumor-associated macrophages in hepatocellular carcinoma pathogenesis, prognosis and therapy, Cancers (2022) 14, https://doi.org/10.3390/cancers14010226.
[18] Q.M. Anstee, H.L. Reeves, E. Kotsiliti, O. Govaere, M. Heikenwalder, From NASH to HCC: current concepts and future challenges, Nat. Rev. Gastroenterol. Hepatol. 16 (2019) 411–428, https://doi.org/10.1038/s41575-019-0145-7.
[19] M.S. Ascha, I.A. Hanouneh, R. Lopez, T.A. Tamimi, A.F. Feldstein, N.N. Zein, The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis, Hepatology 51 (2010) 1972–1978, https://doi.org/10.1002/hep.23527.
[20] G. Cholankeril, R. Patel, S. Khurana, S.K. Satapathy, Hepatocellular carcinoma in non-alcoholic steatohepatitis: current knowledge and implications for management, World J. Hepatol. 9 (2017) 533–543, https://doi.org/10.4254/wjh.v9.i11.533.
[21] M. Ringelhan, D. Pfister, T. O'Connor, E. Pikarsky, M. Heikenwalder, The immunology of hepatocellular carcinoma, Nat. Immunol. 19 (2018) 222–232, https://doi.org/10.1038/s41590-018-0044-z.
[22] K. Hotta, M. Yoneda, H. Hyogo, H. Ochi, S. Mizusawa, T. Ueno, K. Chayama, A. Nakajima, K. Nakao, A. Sekine, Association of the rs738409 polymorphism in PNPLA3 with liver damage and the development of nonalcoholic fatty liver disease, BMC Med. Genet. 11 (2010) 172, https://doi.org/10.1186/1471-2350-11-172.
[23] P. Dongiovanni, B. Donati, R. Fares, R. Lombardi, R.M. Mancina, S. Romeo, L. Valenti, PNPLA3 I148M polymorphism and progressive liver disease, World J. Gastroenterol. 19 (2013) 6969–6978, https://doi.org/10.3748/wjg.v19.i41.6969.
[24] D.H. Dapito, A. Mencin, G.Y. Gwak, J.P. Pradere, M.K. Jang, I. Mederacke, J. M. Caviglia, H. Khiabanian, A. Adeyemi, R. Bataller, et al., Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4, Cancer Cell 21 (2012) 504–516, https://doi.org/10.1016/j.ccr.2012.02.007.
[25] A.A. Shanab, P. Scully, O. Crosbie, M. Buckley, L. O'Mahony, F. Shanahan, S. Gazareen, E. Murphy, E.M. Quigley, Small intestinal bacterial overgrowth in nonalcoholic steatohepatitis: association with toll-like receptor 4 expression and plasma levels of interleukin 8, Dig. Dis. Sci. 56 (2011) 1524–1534, https://doi.org/10.1007/s10620-010-1447-3.
[26] G. Szabo, J. Petrasek, Inflammasome activation and function in liver disease, Nat. Rev. Gastroenterol. Hepatol. 12 (2015) 387–400, https://doi.org/10.1038/nrgastro.2015.94.
[27] M.J. Wolf, A. Adili, K. Piotrowitz, Z. Abdullah, Y. Boege, K. Stemmer, M. Ringelhan, N. Simonavicius, M. Egger, D. Wohlleber, et al., Metabolic activation of intrahepatic CD8+ T cells and NKT cells causes nonalcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes, Cancer Cell 26 (2014) 549–564, https://doi.org/10.1016/j.ccell.2014.09.003.
[28] S. Shalapour, X.J. Lin, I.N. Bastian, J. Brain, A.D. Burt, A.A. Aksenov, A. F. Vrbanac, W. Li, A. Perkins, T. Matsutani, et al., Inflammation-induced IgA+ cells dismantle anti-liver cancer immunity, Nature 551 (2017) 340–345, https://doi.org/10.1038/nature24302.
[29] D. Pfister, N.G. Nunez, R. Pinyol, O. Govaere, M. Pinter, M. Szydlowska, R. Gupta, M. Qiu, A. Deczkowska, A. Weiner, et al., NASH limits anti-tumour surveillance in immunotherapy-treated HCC, Nature 592 (2021) 450–456, https://doi.org/10.1038/s41586-021-03362-0.
[30] A. Gupta, A. Das, K. Majumder, N. Arora, H.G. Mayo, P.P. Singh, M.S. Beg, S. Singh, Obesity is independently associated with increased risk of hepatocellular cancer-related mortality: a systematic review and meta-analysis, Am. J. Clin. Oncol. 41 (2018) 874–881, https://doi.org/10.1097/COC.0000000000000388.
[31] D.H. Ipsen, J. Lykkesfeldt, P. Tveden-Nyborg, Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease, Cell Mol. Life Sci. 75 (2018) 3313–3327, https://doi.org/10.1007/s00018-018-2860-6.
[32] S. De Minicis, L. Agostinelli, C. Rychlicki, G.P. Sorice, S. Saccomanno, C. Candelaresi, A. Giaccari, L. Trozzi, I. Pierantonelli, E. Mingarelli, et al., HCC development is associated to peripheral insulin resistance in a mouse model of NASH, PLoS One 9 (2014), e97136, https://doi.org/10.1371/journal.pone.0097136.
[33] L. Longato, S. de la Monte, N. Kuzushita, M. Horimoto, A.B. Rogers, B.L. Slagle, J. R. Wands, Overexpression of insulin receptor substrate-1 and hepatitis Bx genes causes premalignant alterations in the liver, Hepatology 49 (2009) 1935–1943, https://doi.org/10.1002/hep.22856.
[34] W. Wang, R. Smits, H. Hao, C. He, Wnt/beta-catenin signaling in liver, Cancers Cancers (2019) 11, https://doi.org/10.3390/cancers11070926.
[35] T.H. Helms, R.D. Mullins, J.M. Thomas-Ahner, S.K. Kulp, M.J. Campbell, F. Lucas, N. Schmidt, D.M. LeMoine, S. Getaneh, Z. Xie, et al., Inhibition of androgen/AR signaling inhibits diethylnitrosamine (DEN) induced tumour initiation and remodels liver immune cell networks, Sci. Rep. 11 (2021) 3646, https://doi.org/10.1038/s41598-021-82252-x.
[36] P.K. Awuah, S.P. Monga, Cell cycle-related kinase links androgen receptor and beta-catenin signaling in hepatocellular carcinoma: why are men at a loss? Hepatology 55 (2012) 970–973, https://doi.org/10.1002/hep.24774.
[37] H. Feng, A.S. Cheng, D.P. Tsang, M.S. Li, M.Y. Go, Y.S. Cheung, G.J. Zhao, S.S. Ng, M.C. Lin, J. Yu, et al., Cell cycle-related kinase is a direct androgen receptor-regulated gene that drives beta-catenin/T cell factor-dependent hepatocarcinogenesis, J. Clin. Invest. 121 (2011) 3159–3175, https://doi.org/10.1172/JCI45967.
[38] E. Dror, E. Dalmas, D.T. Meier, S. Wueest, J. Thevenet, C. Thienel, K. Timper, T. M. Nordmann, S. Traub, F. Schulze, et al., Postprandial macrophage-derived IL-1beta stimulates insulin, and both synergistically promote glucose disposal and inflammation, Nat. Immunol. 18 (2017) 283–292, https://doi.org/10.1038/ni.3659.
[39] I. Guillen, M. Blanes, M.J. Gomez-Lechon, J.V. Castell, Cytokine signaling during myocardial infarction: sequential appearance of IL-1 beta and IL-6 269 (1995) R229–R235, https://doi.org/10.1152/ajpregu.1995.269.2.R229.
[40] P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease 377 (2017) 1119–1131, https://doi.org/10.1056/NEJMoa1707914.
[41] N. Lee, Y.J. Heo, S.E. Choi, J.Y. Jeon, S.J. Han, D.J. Kim, Y. Kang, K.W. Lee, H. J. Kim, Anti-inflammatory effects of empagliflozin and gemigliptin on LPS-stimulated macrophage via the IKK/NF-kappaB, MKK7/JNK, and JAK2/STAT1 signalling pathways, J. Immunol. Res. 2021 (2021), 9944880, https://doi.org/10.1155/2021/9944880.
[42] A. Jehad, H. Tabinda, S. David, P. Riya, A.-M. Mohamed, M.C. Suzanne, W. M. George, S.P. Clovis, Inflammatory and immunometabolic consequences of gut dysfunction in HIV: parallels with IBD and implications for reservoir persistence and non-AIDS comorbidities, EBioMedicine 46 (2019) 522–531, https://doi.org/10.1016/j.ebiom.2019.07.027.
[43] W.W. Wheaton, S.E. Weinberg, R.B. Hamanaka, S. Soberanes, L.B. Sullivan, E. Anso, A. Glasauer, E. Dufour, G.M. Mutlu, G.S. Budigner, et al., Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis, Elife 3 (2014), e02242, https://doi.org/10.7554/eLife.02242.
[44] J.A. Marrero, L.M. Kulik, C.B. Sirlin, A.X. Zhu, R.S. Finn, M.M. Abecassis, L. R. Roberts, J.K. Heimbach, Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the american association for the study of liver diseases, Hepatology 68 (2018) 723–750, https://doi.org/10.1002/hep.29913.
[45] M. Omata, A.L. Cheng, N. Kokudo, M. Kudo, J.M. Lee, J. Jia, R. Tateishi, K. H. Han, Y.K. Chawla, S. Shiina, et al., Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update, Hepatol. Int. 11 (2017) 317–370, https://doi.org/10.1007/s12072-017-9799-9.
[46] L. European Association for Study of, R. European Organisation for, C. Treatment of, EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma, Eur. J. Cancer 48 (2012) 599–641, https://doi.org/10.1016/j.ejca.2011.12.021.
[47] L. Chrysavgis, A.M. Papatheodoridi, A. Chatzigeorgiou, E. Cholongitas, The impact of sodium glucose co-transporter 2 inhibitors on non-alcoholic fatty liver disease, J. Gastroenterol. Hepatol. 36 (2021) 893–909, https://doi.org/10.1111/jgh.15202.
[48] V.G. Athyros, S.A. Polyzos, J. Kountouras, N. Katsiki, P. Anagnostis, M. Doumas, C.S. Mantzoros, Non-alcoholic fatty liver disease treatment in patients with type 2 diabetes mellitus; new kids on the block, Curr. Vasc. Pharm. 18 (2020) 172–181, https://doi.org/10.2174/1570161117666190405164313.
[49] B. Xing, Y. Zhao, B. Dong, Y. Zhou, W. Lv, W. Zhao, Effects of sodium-glucose cotransporter 2 inhibitors on non-alcoholic fatty liver disease in patients with type 2 diabetes: A meta-analysis of randomized controlled trials, J. Diabetes Invest. 11 (2020) 1238–1247, https://doi.org/10.1111/jdi.13237.
[50] L.L. Lai, S.R. Vethakkan, N.R. Nik Mustapha, S. Mahadeva, W.K. Chan, Empagliflozin for the treatment of nonalcoholic steatohepatitis in patients with type 2 diabetes mellitus, Dig. Dis. Sci. 65 (2020) 623–631, https://doi.org/10.1007/s10620-019-5477-1.
[51] A. Takeda, A. Irahara, A. Nakano, E. Takata, Y. Koketsu, K. Kimata, E. Senda, H. Yamada, K. Ichikawa, T. Fujimori, et al., The improvement of the hepatic histological findings in a patient with non-alcoholic steatohepatitis with type 2 diabetes after the administration of the sodium-glucose cotransporter 2 inhibitor

ipragliflozin, Intern Med. 56 (2017) 2739–2744, https://doi.org/10.2169/internalmedicine.8754-16.
[52] C. Komiya, K. Tsuchiya, K. Shiba, Y. Miyachi, S. Furuke, N. Shimazu, S. Yamaguchi, K. Kanno, Y. Ogawa, Ipragliflozin improves hepatic steatosis in obese mice and liver dysfunction in type 2 diabetic patients irrespective of body weight reduction, PLoS One 11 (2016), e0151511, https://doi.org/10.1371/journal.pone.0151511.
[53] M. Shimizu, K. Suzuki, K. Kato, T. Jojima, T. Iijima, T. Murohisa, M. Iijima, H. Takekawa, I. Usui, H. Hiraishi, 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. 21 (2019) 285–292, https://doi.org/10.1111/dom.13520.
[54] H. Taheri, M. Malek, F. Ismail-Beigi, F. Zamani, M. Sohrabi, M. Reza Babaei, M. E. Khamseh, Effect of empagliflozin on liver steatosis and fibrosis in patients with non-alcoholic fatty liver disease without diabetes: a randomized, double-blind, placebo-controlled trial, Adv. Ther. 37 (2020) 4697–4708, https://doi.org/10.1007/s12325-020-01498-5.
[55] J. Luo, P. Sun, X. Zhang, G. Lin, Q. Xin, Y. Niu, Y. Chen, N. Xu, Y. Zhang, W. Xie, Canagliflozin modulates hypoxia-induced metastasis, angiogenesis and glycolysis by decreasing HIF-1alpha protein synthesis via AKT/mTOR pathway, Int J. Mol. Sci. 22 (2021), https://doi.org/10.3390/ijms222413336.
[56] M.H. Hung, Y.L. Chen, L.J. Chen, P.Y. Chu, F.S. Hsieh, M.H. Tsai, C.T. Shih, T. I. Chao, C.Y. Huang, K.F. Chen, Canagliflozin inhibits growth of hepatocellular carcinoma via blocking glucose-influx-induced beta-catenin activation, Cell Death Dis. 10 (2019) 420, https://doi.org/10.1038/s41419-019-1646-6.
[57] K. Shiba, K. Tsuchiya, C. Komiya, Y. Miyachi, K. Mori, N. Shimazu, S. Yamaguchi, N. Ogasawara, M. Katoh, M. Itoh, et al., Canagliflozin, an SGLT2 inhibitor, attenuates the development of hepatocellular carcinoma in a mouse model of human NASH, Sci. Rep. 8 (2018) 2362, https://doi.org/10.1038/s41598-018-19658-7.
[58] D. Nakano, T. Kawaguchi, H. Iwamoto, M. Hayakawa, H. Koga, T. Torimura, Effects of canagliflozin on growth and metabolic reprograming in hepatocellular carcinoma cells: Multi-omics analysis of metabolomics and absolute quantification proteomics (iMPAQT), PLoS One 15 (2020), e0232283, https://doi.org/10.1371/journal.pone.0232283.
[59] T. Jojima, S. Wakamatsu, M. Kase, T. Iijima, Y. Maejima, K. Shimomura, T. Kogai, T. Tomaru, I. Usui, Y. Aso, The SGLT2 inhibitor canagliflozin prevents carcinogenesis in a mouse model of diabetes and non-alcoholic steatohepatitis-related hepatocarcinogenesis: association with SGLT2 expression in hepatocellular carcinoma, Int J. Mol. Sci. (2019) 20, https://doi.org/10.3390/ijms20205237.
[60] K. Kaji, N. Nishimura, K. Seki, S. Sato, S. Saikawa, K. Nakanishi, M. Furukawa, H. Kawaratani, M. Kitade, K. Moriya, et al., Sodium glucose cotransporter 2 inhibitor canagliflozin attenuates liver cancer cell growth and angiogenic activity by inhibiting glucose uptake, Int. J. Cancer 142 (2018) 1712–1722, https://doi.org/10.1002/ijc.31193.
[61] M.K. Abdel-Rafei, N.M. Thabet, L.A. Rashed, E.M. Moustafa, Canagliflozin, a SGLT-2 inhibitor, relieves ER stress, modulates autophagy and induces apoptosis in irradiated HepG2 cells: Signal transduction between PI3K/AKT/GSK-3beta/mTOR and Wnt/beta-catenin pathways; in vitro, J. Cancer Res Ther. 17 (2021) 1404–1418, https://doi.org/10.4103/jcrt.JCRT_963_19.
[62] K. Murakami, Y. Sasaki, M. Asahiyama, W. Yano, T. Takizawa, W. Kamiya, Y. Matsumura, M. Anai, T. Osawa, J.C. Fruchart, et al., Selective PPARalpha modulator pemafibrate and sodium-glucose cotransporter 2 inhibitor tofogliflozin combination treatment improved histopathology in experimental mice model of non-alcoholic steatohepatitis, Cells (2022) 11, https://doi.org/10.3390/cells11040720.
[63] N. Yoshioka, M. Tanaka, K. Ochi, A. Watanabe, K. Ono, M. Sawada, T. Ogi, M. Itoh, A. Ito, Y. Shiraki, et al., The sodium-glucose cotransporter-2 inhibitor Tofogliflozin prevents the progression of nonalcoholic steatohepatitis-associated liver tumors in a novel murine model, Biomed. Pharm. 140 (2021), 111738, https://doi.org/10.1016/j.biopha.2021.111738.
[64] K. Obara, Y. Shirakami, A. Maruta, T. Ideta, T. Miyazaki, T. Kochi, H. Sakai, T. Tanaka, M. Seishima, M. Shimizu, Preventive effects of the sodium glucose cotransporter 2 inhibitor tofogliflozin on diethylnitrosamine-induced liver tumorigenesis in obese and diabetic mice, Oncotarget 8 (2017) 58353–58363, https://doi.org/10.18632/oncotarget.16874.
[65] L. Li, Q. Li, W. Huang, Y. Han, H. Tan, M. An, Q. Xiang, R. Zhou, L. Yang, Y. Cheng, Dapagliflozin alleviates hepatic steatosis by restoring autophagy via the AMPK-mTOR Pathway, Front Pharm. 12 (2021), 589273, https://doi.org/10.3389/fphar.2021.589273.
[66] T. Ozutsumi, T. Namisaki, N. Shimozato, K. Kaji, Y. Tsuji, D. Kaya, Y. Fujinaga, M. Furukawa, K. Nakanishi, S. Sato, et al., Combined treatment with sodium-glucose cotransporter-2 inhibitor (Canagliflozin) and dipeptidyl peptidase-4 inhibitor (Teneligliptin) alleviates NASH progression in a non-diabetic rat model of steatohepatitis, Int. J. Mol. Sci. (2020) 21, https://doi.org/10.3390/ijms21062164.
[67] R. Benedetti, G. Benincasa, K. Glass, U. Chianese, M.T. Vietri, R. Congi, L. Altucci, C. Napoli, Effects of novel SGLT2 inhibitors on cancer incidence in hyperglycemic patients: a meta-analysis of randomized clinical trials, Pharm. Res. 175 (2022), 106039, https://doi.org/10.1016/j.phrs.2021.106039.
[68] D.J. Crawley, L. Holmberg, J.C. Melvin, M. Loda, S. Chowdhury, S.M. Rudman, M. Van Hemelrijck, Serum glucose and risk of cancer: a meta-analysis, BMC Cancer 14 (2014) 985, https://doi.org/10.1186/1471-2407-14-985.
[69] C. Scafoglio, B.A. Hirayama, V. Kepe, J. Liu, C. Ghezzi, N. Satyamurthy, N. A. Moatamed, J. Huang, H. Koepsell, J.R. Barrio, et al., Functional expression of sodium-glucose transporters in cancer, Proc. Natl. Acad. Sci. USA 112 (2015) E4111–E4119, https://doi.org/10.1073/pnas.1511698112.
[70] E.M. Wright, SGLT2 and cancer, Pflug. Arch. 472 (2020) 1407–1414, https://doi.org/10.1007/s00424-020-02448-4.
[71] Y. Poloz, V. Stambolic, Obesity and cancer, a case for insulin signaling, Cell Death Dis. 6 (2015), e2037, https://doi.org/10.1038/cddis.2015.381.
[72] L. Schulte, B. Scheiner, T. Voigtlander, S. Koch, N. Schweitzer, S. Marhenke, P. Ivanyi, M.P. Manns, T. Rodt, J.B. Hinrichs, et al., Treatment with metformin is associated with a prolonged survival in patients with hepatocellular carcinoma, Liver Int. 39 (2019) 714–726, https://doi.org/10.1111/liv.14048.
[73] R.C. Shankaraiah, E. Callegari, P. Guerriero, A. Rimessi, P. Pinton, L. Gramantieri, E.M. Silini, S. Sabbioni, M. Negrini, Metformin prevents liver tumourigenesis by attenuating fibrosis in a transgenic mouse model of hepatocellular carcinoma, Oncogene 38 (2019) 7035–7045, https://doi.org/10.1038/s41388-019-0942-z.
[74] S.A. Polyzos, D.G. Goulis, O. Giouleme, G.S. Germanidis, A. Goulas, Anti-obesity medications for the management of nonalcoholic fatty liver disease, Curr. Obes. Rep. (2022) (In Press).
[75] M. Kojima, H. Takahashi, T. Kuwashiro, K. Tanaka, H. Mori, I. Ozaki, Y. Kitajima, Y. Matsuda, K. Ashida, Y. Eguchi, et al., Glucagon-like peptide-1 receptor agonist prevented the progression of hepatocellular carcinoma in a mouse model of nonalcoholic steatohepatitis, Int. J. Mol. Sci. (2020) 21, https://doi.org/10.3390/ijms21165722.
[76] M.M. Islam, T.N. Poly, B.A. Walther, H.C. Yang, Y.C. Jack Li, Statin use and the risk of hepatocellular carcinoma: a meta-analysis of observational studies, Cancers (2020) 12, https://doi.org/10.3390/cancers12030671.
[77] G. Kim, E.S. Kang, Prevention of hepatocellular carcinoma by statins: clinical evidence and plausible mechanisms, Semin Liver Dis. 39 (2019) 141–152, https://doi.org/10.1055/s-0039-1679956.
[78] S.H. Moon, C.H. Huang, S.L. Houlihan, K. Regunath, W.A. Freed-Pastor, J. Pt Morris, D.F. Tschaharganeh, E.R. Kastenhuber, A.M. Barsotti, R. Culp-Hill, et al., p53 represses the mevalonate pathway to mediate tumor suppression, Cell 176 (2019) 564–580, https://doi.org/10.1016/j.cell.2018.11.011.
[79] C.Y. Hsu, Y.H. Lee, Y.H. Huang, C.Y. Hsia, C.W. Su, H.C. Lin, R.C. Lee, Y.Y. Chiou, F.Y. Lee, T.I. Huo, et al., Ascites in patients with hepatocellular carcinoma: prevalence, associated factors, prognostic impact, and staging strategy, Hepatol. Int. 7 (2013) 188–198, https://doi.org/10.1007/s12072-011-9338-z.
[80] G.P. Aithal, N. Palaniyappan, L. China, S. Harmala, L. Macken, J.M. Ryan, E. A. Wilkes, K. Moore, J.A. Leithead, P.C. Hayes, et al., Guidelines on the management of ascites in cirrhosis, Gut 70 (2021) 9–29, https://doi.org/10.1136/gutjnl-2020-321790.
[81] Y. Gao, L. Wei, D.D. Zhang, Y. Chen, B. Hou, SGLT2 inhibitors: a new dawn for recurrent/refractory cirrhotic ascites, J. Clin. Transl. Hepatol. 9 (2021) 795–797, https://doi.org/10.14218/JCTH.2021.00418.
[82] G.N. Kalambokis, I. Tsiakas, S. Filippas-Ntekuan, M. Christaki, G. Despotis, H. Milionis, Empagliflozin eliminates refractory ascites and hepatic hydrothorax in a patient with primary biliary cirrhosis, Am. J. Gastroenterol. 116 (2021) 618–619, https://doi.org/10.14309/ajg.0000000000000995.
[83] M. Griffin, V.S. Rao, J. Ivey-Miranda, J. Fleming, D. Mahoney, C. Maulion, N. Suda, K. Siwakoti, T. Ahmad, D. Jacoby, et al., Empagliflozin in heart failure: diuretic and cardiorenal effects, Circulation 142 (2020) 1028–1039, https://doi.org/10.1161/CIRCULATIONAHA.120.045691.
[84] N.A. Mordi, I.R. Mordi, J.S. Singh, R.J. McCrimmon, A.D. Struthers, C.C. Lang, Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the RECEDE-CHF trial, Circulation 142 (2020) 1713–1724, https://doi.org/10.1161/CIRCULATIONAHA.120.048739.
[85] A. Shirakabe, M. Matsushita, K. Kiuchi, H. Okazaki, T. Inami, T. Takayasu, M. Asano, A. Nomura, N. Kobayashi, F. Okajima, et al., Empagliflozin administration can decrease the dose of loop diuretics and prevent the exacerbation of renal tubular injury in patients with compensated heart failure complicated by diabetes, Circ. Rep. 2 (2020) 565–575, https://doi.org/10.1253/circrep.CR-20-0041.
[86] C. Charlwood, J. Chudasama, A. Darling, H. Logan Ellis, M. Whyte, Sodium glucose co-transporter 2 inhibitors do not increase the risk of hyperkaleamia in type 2 diabetes: a systematic review and meta-analysis, Diabetologia 64 (Suppl 1) (2021) S228.
[87] G.L. Bakris, R. Agarwal, S.D. Anker, B. Pitt, L.M. Ruilope, P. Rossing, P. Kolkhof, C. Nowack, P. Schloemer, A. Joseph, et al., Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes, N. Engl. J. Med. 383 (2020) 2219–2229, https://doi.org/10.1056/NEJMoa2025845.
[88] A. Garcia-Ropero, J.J. Badimon, C.G. Santos-Gallego, The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors for type 2 diabetes mellitus: the latest developments, Expert Opin. Drug Metab. Toxicol. 14 (2018) 1287–1302, https://doi.org/10.1080/17425255.2018.1551877.
[89] G.A. Augusto, N. Cassola, P.M. Dualib, H. Saconato, T. Melnik, Sodium-glucose cotransporter-2 inhibitors for type 2 diabetes mellitus in adults: an overview of 46 systematic reviews, Diabetes Obes. Metab. 23 (2021) 2289–2302, https://doi.org/10.1111/dom.14470.
[90] C. Wong, C.Y.L. Yaow, C.H. Ng, Y.H. Chin, Y.F. Low, A.Y.L. Lim, M.D. Muthiah, C. M. Khoo, Sodium-glucose Co-transporter 2 inhibitors for non-alcoholic fatty liver disease in asian patients with type 2 diabetes: a meta-analysis, Front Endocrinol. 11 (2020), 609135, https://doi.org/10.3389/fendo.2020.609135.
[91] S. Macha, P. Rose, M. Mattheus, R. Cinca, S. Pinnetti, U.C. Broedl, H.J. Woerle, Pharmacokinetics, safety and tolerability of empagliflozin, a sodium glucose

cotransporter 2 inhibitor, in patients with hepatic impairment, Diabetes Obes. Metab. 16 (2014) 118–123, https://doi.org/10.1111/dom.12183.
[92] Bhatt, D.L.; Szarek, M.; Pitt, B.; Cannon, C.P.; Leiter, L.A.; McGuire, D.K.; Lewis, J. B.; Riddle, M.C.; Inzucchi, S.E.; Kosiborod, M.N.; et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. 2020, 384, 129–139, doi:10.1056/NEJMoa2030186.
[93] J. Yan, S. Li, S. Li, The role of the liver in sepsis, Int. Rev. Immunol. 33 (2014) 498–510, https://doi.org/10.3109/08830185.2014.889129.
[94] D. Fitchett, A safety update on sodium glucose co-transporter 2 inhibitors, Diabetes Obes. Metab. 21 (Suppl 2) (2019) 34–42, https://doi.org/10.1111/dom.13611.
[95] J.F. List, J.M. Whaley, Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans, Kidney Int. Suppl. (2011) S20–S27, https://doi.org/10.1038/ki.2010.512.
[96] T. Koufakis, S. Metallidis, P. Zebekakis, K. Kotsa, Intestinal SGLT1 as a therapeutic target in COVID-19-related diabetes: a "two-edged sword" hypothesis, Br. J. Clin. Pharm. 87 (2021) 3643–3646, https://doi.org/10.1111/bcp.14800.
[97] M.N. Kosiborod, R. Esterline, R.H.M. Furtado, J. Oscarsson, S.B. Gasparyan, G. G. Koch, F. Martinez, O. Mukhtar, S. Verma, V. Chopra, et al., Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Diabetes Endocrinol. 9 (2021) 586–594, https://doi.org/10.1016/S2213-8587(21)00180-7.
[98] A. Aly, S. Ronnebaum, D. Patel, Y. Doleh, F. Benavente, Epidemiologic, humanistic and economic burden of hepatocellular carcinoma in the USA: a systematic literature review, Hepat. Oncol. 7 (2020) HEP27, https://doi.org/10.2217/hep-2020-0024.
[99] T. Koufakis, O.G. Mustafa, R.A. Ajjan, X. Garcia-Moll, P. Zebekakis, G. Dimitriadis, K. Kotsa, The use of sodium-glucose co-transporter 2 inhibitors in the inpatient setting: Is the risk worth taking? J. Clin. Pharm. Ther. 45 (2020) 883–891, https://doi.org/10.1111/jcpt.13107.
[100] G. Musso, F. Saba, M. Cassader, R. Gambino, Diabetic ketoacidosis with SGLT2 inhibitors, BMJ 371 (2020) m4147, https://doi.org/10.1136/bmj.m4147.
[101] A.K. Papazafiropoulou, A. Melidonis, S. Antonopoulos, Effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on cardiorenal and metabolic outcomes in people without diabetes, Curr. Pharm. Des. 27 (2021) 1035–1042, https://doi.org/10.2174/1381612826666200909142126.
[102] T. Koufakis, G. Maltese, S. Metallidis, P. Zebekakis, K. Kotsa, Looking deeper into the findings of DARE-19: failure or an open door to future success? Pharm. Res 173 (2021), 105872 https://doi.org/10.1016/j.phrs.2021.105872.
[103] A.A. Voors, C.E. Angermann, J.R. Teerlink, S.P. Collins, M. Kosiborod, J. Biegus, J.P. Ferreira, M.E. Nassif, M.A. Psotka, J. Tromp, et al., The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial, Nat. Med. (2022), https://doi.org/10.1038/s41591-021-01659-1.