Metabolism Clinical and Experimental 101 (2019) 154001

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Reviews

Effects of newer antidiabetic drugs on nonalcoholic fatty liver and steatohepatitis: Think out of the box!

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ARTICLE INFO

Article history:
Received 29 July 2019
Accepted 15 October 2019

Keywords:
Nonalcoholic fatty liver disease
Nonalcoholic steatohepatitis
Dipeptidyl peptidase 4 inhibitors
Sodium glucose cotransporter 2 inhibitors
Glucagon-like peptide-1 receptor agonists
Type 2 diabetes mellitus

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western societies and a major cause of hepatic disease worldwide. Its more severe type, namely nonalcoholic steatohepatitis (NASH), may result in the development of cirrhosis and hepatocellular carcinoma. NAFLD, and especially NASH, are also associated with increased cardiovascular morbidity and mortality. Type 2 diabetes mellitus (T2DM) predisposes to NAFLD development and progression via insulin resistance and hyperglycemia. It has also been reported that the majority of T2DM patients have NAFLD/NASH, thus potentially further increasing their cardiometabolic risk. Current guidelines recommend to screen for NAFLD in all T2DM patients and vice-versa. Lifestyle remains the first-line therapeutic option for NAFLD/NASH. Among antidiabetic drugs, pioglitazone was shown to improve histological features of NASH. More recently, there is an increasing interest regarding the effects of newer antidiabetic drugs, such as dipeptidyl peptidase 4 inhibitors (DPP-4i), sodium glucose cotransporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on NAFLD/NASH. The present narrative review considers the up-to-date data on the impact of DPP-4i, SGLT2i, and GLP-1 RAs on biochemical and/or histological markers of NAFLD/NASH. The potential clinical implications of these findings in daily practice are also discussed. Taking into consideration the global increasing prevalence of NAFLD/NASH, therapeutic options that can prevent or treat this disease will exert considerable benefits on human health.

Contents

1. Introduction . . . 1
2. Literature search methodology . . . 2
3. DPP-4i . . . 2
4. GLP-1 RAs . . . 3
5. SGLT2i . . . 5
6. Future perspectives . . . 8
7. Conclusions . . . 10
Declaration of competing interest . . . 10
References . . . 10

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most frequent chronic liver disease in Western countries and a major cause of hepatic disease worldwide, affecting approximately 25% of the world's adult population [1]. In this context, the prevalence of NAFLD in 2013 in Europe was nearly 30–40% in men and 15–20% in women, reaching 70% in patients with T2DM [2]. It is also estimated that NAFLD will be the main reason for liver transplantation by 2030 [3].

NAFLD is characterized by accumulation of micro/macrovesicular fat in overall >5% of the hepatocytes (steatosis) in the absence of viral hepatitis, alcohol abuse or other secondary causes of liver disease

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https://doi.org/10.1016/j.metabol.2019.154001
0026-0495/

[4–6]. Its more severe form, nonalcoholic steatohepatitis (NASH), is characterized by the development of liver inflammation, fibrosis and necrosis, potentially leading to cirrhosis, hepatocellular carcinoma (HCC) and end-stage liver disease [7]. NASH prevalence is anticipated to reach 18 million by 2027 in the US, Japan, and 5 European countries (i.e. England, France, Germany, Italy and Spain) [8,9].

The clinical burden of NAFLD is not limited to liver-related morbidity and mortality, but also involves extra-hepatic organs. In this context, NAFLD is associated with an increased risk of T2DM, chronic kidney disease (CKD), and cardiovascular disease (CVD) morbidity and mortality [3,10–13]. It should be noted that the leading cause of death in NAFLD/NASH patients is CVD [1]. Interestingly, NAFLD has also been related to excessive fat deposition in other organs such as the heart, kidneys, pancreas, muscles and blood vessels, highlighting the increased cardiometabolic burden in these patients [14–16].

Regarding the link between T2DM and NAFLD, these two cardiometabolic diseases share common pathophysiological pathways including insulin resistance, hyperinsulinemia, hyperglycemia, lipotoxicity, inflammation, and oxidative stress [17]. Therefore, in terms of pathophysiology, treating T2DM could prevent NAFLD/NASH development and/or progression and vice versa. It is believed that NAFLD predicts the development and progression of NAFLD through metabolic syndrome components; on the other hand, NAFLD initiates the future development of metabolic syndrome components. Consequently, current evidence suggests a bi-directional relationship and reciprocal causality between T2DM and metabolic syndrome [18].

There are potential effects of pro-inflammatory and hemostatic mediators that could increase oxidative stress levels and the synthesis of prothrombotic markers in NAFLD and chronic vascular complications of T2DM [14]. The pathogenesis of T2DM in NAFLD patients may be associated with the adverse effect of fetuin-B on glucose tolerance and the increase in its levels in patients with T2DM and NAFLD [19]. It is suggested that T2DM may affect the development of NASH through the activity of diverse pathogenic cascades such as gut microbiota, dysfunctional adipose tissue and inflammation [20]. Inflammation through the IKKβ/NFκB (Inhibitory Kappa B Kinases/Nuclear factor kappa-light-chain-enhancer of activated B cell) signaling pathway could be activated under diabetic conditions; therefore inflammation-related insulin resistance is expected in these patients [21]. According to these physiopathological imbalances in T2DM and NAFLD, toll-like receptors and M1-polarized macrophages are expected to activate de novo lipogenesis through secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-12 (Tumour necrosis factor alpha, Interleukin-6, Interleukin-12) [21].

Moreover, the role of lysyl oxidase like 2 (LOXL2) in the histological fibrosis progression process of NAFLD in those with T2DM has been reported; LOXL2 may be a new therapeutic target in chronic liver diseases [22].

Furthermore, the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO), in their joint clinical practice guidelines for the management of NAFLD recommend to screen for NAFLD in T2DM patients and vice versa (EASL-EASD-EASO Clinical Practice Guidelines for the management of nonalcoholic fatty liver disease, 2016).

Currently, lifestyle interventions, such as dietary caloric restriction and exercise, represent the first-line therapeutic approach for NAFLD, with weight loss being the key element to improve both biochemical and histological features of the disease [23]. Regarding drug therapy, current guidelines support the use of pioglitazone in NAFLD patients (with or without T2DM) [23]. Of note, apart from antidiabetic drugs, statins can also improve NAFLD/NASH biochemical and histological features as reported by an expert panel statement [23]. Research on the role of newer antidiabetic drugs, such as dipeptidyl peptidase 4 inhibitors (DPP-4i), sodium glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on NAFLD/NASH treatment is growing [23–26]. The increasing prevalence of NAFLD, especially in T2DM patients, as well as the difficulties in relation to the achievement and maintenance of weight loss by lifestyle changes, highlight the need for drug therapy to overcome this global health problem.

The present narrative review considers the up-to-date literature on the effects of newer drugs used to treat diabetes (i.e. DPP-4i, SGLT2i and GLP-1 RAs) on biochemical and/or histological markers of NAFLD/NASH. The potential clinical implications of these data in daily practice are also discussed.

2. Literature search methodology

The search was conducted in the PubMed, Scopus and Science Direct databases and bibliographies and reference lists of relevant articles were manually scanned. The search was carried out by two independent researchers and studies published in English with the following key words were retrieved: Non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; dipeptidyl peptidase 4 inhibitors; sodium glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists; type 2 diabetes mellitus. The titles and abstracts of the most relevant articles were scanned and duplicate publications were then removed. The reference lists of the relevant articles were also reviewed to ensure study identification. Finally, all the relevant human studies in full-text were obtained and read. Editorials, case reports, letters to the editor and animal studies were excluded.

3. DPP-4i

These drugs exert their glucose-lowering effects primarily by blocking the enzyme DPP-4 that is involved in the degradation of incretins i.e. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [27]. Serum DPP-4 levels were reported to be elevated in NASH patients, as well as to correlate with hepatic steatosis and histopathological grade of NASH [28]. Similarly, circulating DPP-4 concentrations were positively associated with liver fibrosis and hepatocytes apoptosis [29]. Such findings supported the notion that DPP-4i may improve the histological features of NAFLD/NASH. In this context, animal studies showed that DPP-4i could suppress oxidative stress and inflammation, leading to improvements in hepatic steatosis [29].

Among DPP-4i, sitagliptin has been most widely studied ($n = 12$ human studies) in relation to its effects on NAFLD/NASH. Iwasaki and colleagues reported that sitagliptin 50 mg/day for 4 months among T2DM patients ($n = 30$) who were diagnosed with NAFLD by ultrasound, improved the plasma glucose and serum HbA1c (hemoglobin A1c), AST (aspartate transaminase), ALT (alanine transaminase) and γ-GT (gamma-glutamyltransferase) levels [30]. According to an observational pilot study on 15 T2DM patients with biopsy-proven NASH, treatment for 1 year with daily sitagliptin 100 mg ameliorated body mass index, AST, ALT, hepatocyte ballooning, and NASH scores [31]. In contrast, a case-control study involving 20 NAFLD patients with T2DM treated with sitagliptin 50 mg/day and 20 NAFLD patients with T2DM on diet and exercise, followed-up for 48 weeks, found that sitagliptin decreased HbA1c and fasting plasma glucose levels but ALT and AST levels did not change significantly in any group [32]. Of note, in this study, NAFLD was diagnosed by ultrasonography and/or computed tomography. Similarly, Fukuhara and colleagues evaluated the effects of sitagliptin (50 mg/day) for 12 months among 44 T2DM patients with biopsy-proven NAFLD. They showed that sitagliptin reduced HbA1c by 0.7%, but liver transaminases remained unchanged during treatment [33]. Furthermore, in a retrospective study, 122 T2DM patients with chronic liver injury (62 patients had NAFLD) received sitagliptin 50 mg/day for an average of 13.7 months; HbA1c levels improved but ALT, AST and γ-GT were not altered [34]. The same results were reported by another randomized clinical trial ($n = 72$ Chinese T2DM patients with NAFLD diagnosed by ultrasonography, computed tomography or both), with sitagliptin (50–100 mg/day) exerting no significant effects on ALT and AST during the 52-weeks follow-up [35].

Of note, it has been reported that liver fat content was greater in Japanese citizens compared with non-Hispanic whites and Japanese living in the USA [36], supporting the existence of an ethnic predisposition to NAFLD.

In another pilot study involving 7 Japanese T2DM patients with NAFLD determined by ultrasonography, sitagliptin (50 or 100 mg/day) significantly decreased HbA1c levels, but had no effects on intramyocellular and intrahepatic lipid content assessed by H magnetic resonance spectroscopy [37]. In contrast, Kato et al., compared the effects of sitagliptin (25 mg titrated up to 50 mg) with glimepiride (0.5 mg titrated up to 1 mg) on intrahepatic lipid content and body fat in 20 overweight Japanese patients with T2DM, reported that only sitagliptin significantly reduced intrahepatic lipid content and total body fat mass after 24 weeks [38]. On the other hand, a randomized clinical trial carried out on 50 NAFLD patients with prediabetes or early DM, found that sitagliptin (100 mg/day) administered for 24 weeks did not affect liver fat count [measured by magnetic resonance imaging (MRI)-derived proton density-fat fraction], ALT, AST, low-density lipoprotein (LDL), homeostatic model assessment insulin resistance, and magnetic resonance elastography (MRE) [39]. Similarly, a randomized clinical trial of 20 weeks with sitagliptin (100 mg/day) in T2DM patients showed no significant effects on hepatic fat content and fibrosis (assessed by proton magnetic resonance spectroscopy) [40].

The effects of sitagliptin on histological features of NASH were evaluated in 12 patients with biopsy-proven NASH [41]. Sitagliptin at 100 mg/day did not reduce liver fibrosis score, NAFLD activity score, lobular inflammation, steatosis, and hepatocellular ballooning after 24 weeks of therapy. In contrast, according to a 1-year randomized control trial in 40 patients with biopsy-proven NASH, sitagliptin (100 mg/day) significantly improved NAS (NAFLD Activity Score) and hepatocellular ballooning [42] Similarly, as mentioned above, 1 year of sitagliptin (100 mg/day) therapy ameliorated hepatocyte ballooning and NASH scores, apart from liver tests, in 15 T2DM patients with biopsy-proven NASH [31]. Therefore, longer duration of sitagliptin therapy (e.g. 1 year) may be needed to provide significant benefits in terms of NASH histology.

Vildagliptin, a DPP-4i class drug, was reported to exert beneficial effects on NAFLD in 2 human studies. Briefly, Hussain et al. conducted a randomized placebo-controlled trial with 58 NAFLD patients who were treated with either vildagliptin 50 mg twice daily or placebo for 12 weeks. Liver tests and steatosis grading (assessed by ultrasound) were significantly improved in vildagliptin-treated patients [43]. Similar results were observed in a study with vildagliptin (50 mg twice daily for 6 months) in 44 T2DM patients; vildagliptin significantly decreased ALT activity and intrahepatic triglyceride content (assessed by magnetic resonance imaging) [44].

Regarding alogliptin, there is only 1 (single arm, non-randomized, multi-center) study in humans; T2DM patients with NAFLD ($n = 39$) were diagnosed by ultrasound and treated with 25 mg of alogliptin daily for 12 months [45]. According to NAFIC scores (NASH, ferritin, insulin and type IV collagen 7S), 16 patients had NASH. Alogliptin significantly reduced NAFIC scores in 6 patients, indicating NASH resolution. Similarly, there is only 1 human study carried out in saxagliptin on 95 T2DM patients with NAFLD (assessed by ultrasound), showing significant reduction in liver tests and steatosis after treatment for 24 weeks [46]. Moreover, linagliptin has been shown to improve liver steatosis in animal studies [47]; however, there is no available data on human subjects. Overall, DPP-4i may beneficially affect NAFLD/NASH. However, the majority of available data (mainly studies with a small n) refer to the effects of sitagliptin on liver tests and steatosis rather than fibrosis. The duration of treatment may be relevant (Table 1).

4. GLP-1 RAs

Apart from glucose-lowering effects, GLP-1 RAs promote weight loss [48], thus emphasizing their potential role in NAFLD/NASH treatment. It is important to note that GLP-1 RAs have been shown to improve insulin sensitivity [49]. They also seem to cause a direct effect on hepatocytes through metabolism of lipids, therefore reducing hepatic steatosis [50]. Moreover, GLP-1 agonists exert protective effects on hepatocytes through inhibition of dysfunctional endoplasmic reticulum stress response in relation to fatty acid-related death [50].

Liraglutide has been approved for obesity management at the dose of 3 mg daily, exerting cardiometabolic benefits [51]. Liraglutide (3 mg/day) for 26 weeks was also shown to significantly reduce liver tests (ALT and AST) in a pilot study with 12 obese patients with NAFLD [52]. However, conflicting data exists in relation to the presence of GLP-1 receptors on human hepatocytes [53]. These receptors could reduce hepatic steatosis through modulating components of the insulin signaling pathway [49]. Besides, they appear to have a direct effect on lipid metabolism of hepatocytes through suppression of lipogenesis [54].

Among GLP-1 RAs, the effects of exenatide on NAFLD have been evaluated in 7 human studies. In this context, Fan and colleagues showed that exenatide (5–10 μg/day) significantly improved weight, body mass index (BMI), waist-to-hip ratio, HbA1c, fasting plasma glucose, 2-h postprandial glucose, ALT, AST, γ-GT, hsCRP (high-sensitivity C-reactive protein) and adiponectin compared with metformin in 170 T2DM patients with NAFLD (diagnosed by ultrasonography) after 12 weeks of treatment [55]. In another randomized study, exenatide (10 μg/day) co-administered with insulin glargine led to significant reductions in weight, waist circumference, ALT, AST, and γ-GT compared with the intensive insulin group after 12 weeks of therapy in 60 T2DM patients with NAFLD determined by ultrasonography [56]. Moreover, according to a comparative trial, HbA1c, weight, waist circumference, serum triglycerides and fatty liver index (FLI) were significantly decreased after 6 months of exenatide (10 μg/day) therapy compared with metformin or/and sulphonylurea treatment [57]. In another observational pilot study ($n = 58$ T2DM patients with NAFLD), more patients on exenatide (80%) showed qualitative ultrasonographic improvements in NAFLD features compared with gliclazide, pioglitazone, sitagliptin and liraglutide (33.3, 37.5, 45.5 and 33%, respectively); however, these differences were not significant [58]. Dutour and colleagues showed that exenatide (10 μg twice a day) for 26 weeks led to a significant reduction in HbA1c, weight, epicardial adipose tissue and hepatic triglyceride content in 44 obese T2DM patients [59]. Similarly, exenatide significantly decreased intrahepatic fat by 68% in T2DM patients ($n = 33$), as did insulin (by 58%) and pioglitazone (by 49%) after 6 months of treatment [60]. Importantly, exenatide also reduced visceral and subcutaneous fat (by 36 and 13%, respectively), whereas insulin did not affect them and pioglitazone only decreased visceral fat (by 30%). In another study, GLP-1 RAs (exenatide in 19 patients and liraglutide in 6 patients) significantly decreased intrahepatic lipid content (assessed by proton magnetic resonance spectroscopy) by 42% when given for 6 months in 25 obese T2DM patients with NAFLD on top of metformin and DPP-4i/sulphonylurea treatment [61]. Exenatide 5 μg was administered twice daily during the first few weeks and titrated to 10 μg twice daily after one month; liraglutide was initiated at 0.6 mg once daily and titrated to 1.2 mg once daily.

Regarding lixisenatide, there are studies in obese or overweight T2DM patients evaluating its impact on liver tests; a meta-analysis of these studies reported that lixisenatide increased the proportion of patients achieving normalization of ALT [62]. However, no data exists on the effects of lixisenatide on hepatic steatosis or fibrosis.

Liraglutide has been shown to improve both biochemical and histological features of NAFLD/NASH in human studies [63]. A retrospective cohort study showed that liraglutide (0.3–0.6 mg/day) after 6 months significantly reduced weight, BMI, ALT, AST, fasting plasma glucose, HbA1c and AST to platelet ratio in 26 patients with T2DM and NAFLD assessed by ultrasonography and liver tests [64]. In another study, liraglutide (0.6–1.2 mg/day) significantly decreased fasting plasma glucose, 2 h postprandial glucose, HbA1c, AST/ALT and adiponectin after 12 weeks in 52 T2DM patients with NAFLD diagnosed by

Table 1
Summary of the studies evaluating the effects of DPP-4i on NAFLD/NASH.

Pathological condition	Drug name	Drug mechanism of action	Dose	Type of study	Assessment of NAFLD	Treatment duration	Participants (number)	Reference
NASH	Sitagliptin	Improvement in hyperglycemia. Blockage of fatty acid synthase leads to improvement in liver fat.	100 mg/day	Open-label randomized controlled trial	Liver biopsy	1 year	$n = 48$ Treatment = 24 Control = 24	[42]
T2DM with NAFLD	Sitagliptin	Blocking GLP-1 and GIP breakdown. Insulin secretion increases and suppresses glucagon levels.	50 mg/day	Case-control study	Liver biopsy	48 weeks	$n = 40$ Treatment = 20 Control = 20	[32]
T2DM complicate by liver injury	Sitagliptin	Attenuation of hepatic fibrosis by suppressing activated hepatic stellate cells. Modulation of insulin components in insulin signaling pathway.	50 mg/day	Retrospective observational study	Abdominal ultrasonography and/or computed tomography (CT)	3.7 ± 10.1 months	$n = 122$	[34]
NAFLD with prediabetes or early diabetes	Sitagliptin + placebo	Sitagliptin inactivates GLP-1 and GIP is released in response to meals. Downregulation of sterol regulatory element binding protein-1c (SREBP-1c).	100 mg/day	Randomized, double-blind, allocation-concealed, placebo-controlled trial	MRI-derived proton density-fat fraction (MRI-PDFF)	24 weeks	=47 Treatment = 25 Placebo = 22	[39]
T2DM + NAFLD	Sitagliptin	Blocking GLP-1 and GIP breakdown, sitagliptin increases insulin secretion and suppresses glucagon release, which lowers blood glucose levels.	100 mg/day	A randomized controlled trail	Laboratory measurements-changes from baseline (ALT, AST, HbA1c)	52 weeks	n = 72 Treatment = 36 Control = 36	[35]
NAFLD with T2DM	Sitagliptin	Downregulation of SREBP-1c	50 mg/day	Randomized controlled trial phase-2	Biopsy	12 months	$n = 44$	[33]
NAFLD with T2DM	Sitagliptin	Enhances fatty acid oxidation. Suppresses fatty acid synthesis. Block accumulation of triglyceride in liver. Increases insulin secretion.	50 mg/day	Prospective, Uncontrolled study	Ultrasonography	4 months	n = 30	[30]
	Sitagliptin + glimepiride	Insulin secretion. Glucagon release suppression. Less blood glucose levels.	Sitagliptin (25 mg titrated up to 50 mg) or glimepiride (0.5 mg titrated up to 1 mg: G)	A prospective, single-center, open-label comparative study	H-magnetic resonance spectroscopy (1H-MRS) and DEXA	24 weeks	$n = 20$ Sitagliptin = 10 Glimepiride = 10	[38]
T2DM with fatty liver	Sitagliptin	Decreased EGP level at fasting and postprandial states, which is accompanied by decreased glucagon and increased insulin levels.	50–100 mg/day	Open-label, non-randomized, single-arm pilot study	H magnetic resonance spectroscopy	12 weeks	n = 7	[37]
T2DM with nonalcoholic steatohepatitis	Sitagliptin	Preservation of pancreatic beta cell function in patients with T2DM.	100 mg/day	Open-label, single-arm observational pilot stud	Biopsy	1 year	n = 15	[31]
NAFLD + dyslipidemia	Vildagliptin + placebo	Increase in insulin levels, decreases glucagon level, decreases appetite and delays gastric emptying.	50 mg/day twice a day	Randomized placebo controlled trial	Ultrasound	12 weeks	n = 58 Treatment = 29 Placebo = 29	[43]
T2DM with hepatic steatosis	Vildagliptin + placebo	Metabolic effects, low appearance of palmitate (i.e. lipolysis) and lipid oxidation. Less de novo lipogenesis with less extent of fat accumulation.	50 mg twice a day	Randomized placebo controlled trail phase-2	Imaging (CT or ultrasound)	6 months	n = 44 Treatment = 22 Placebo-22	[44]
NAFLD with T2DM	Alogliptin	Reduction in oxidative stress, suppression in the liver injury induced by inflammatory cytokines.	25 mg/day	Single arm, multi-center, non-randomized study	Ultrasonography	12 months	n = 39 NAFlC score 0–1 ($n = 23$) NAFlC score 2–4 ($n = 16$)	[45]

ALT: alanine aminotransferase, AST: aspartate aminotransferase, EGP: endogenous glucose production; FG: fasting glucose, γ-GT: gamma-glutamyltransferase; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; HbA1c: hemoglobin A1c; IHL: intrahepatic lipid; NAFIC: NAS: nonalcoholic fatty liver disease activity score; NASH, ferritin, insulin and type IV collagen 7S; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; T2DM: type 2 diabetes mellitus; TGF-β1: transforming growth factor beta 1.

ultrasonography [65]. Similarly, 6–12 months of liraglutide therapy (1.2 mg/day) led to significant improvements in blood glucose and lipid levels (except for high-density lipoprotein cholesterol; HDL-C), as well as decreases in AST, ALT, and γ-GT in 424 patients with T2DM complicated by NAFLD [66].

Liraglutide (1.8 mg/day for 12 weeks) reduced hepatic steatosis (assessed by proton magnetic resonance spectroscopy) by 10% in 17 T2DM patients but this effect did not differ significantly compared with placebo [40]. Furthermore, in the Lira-NAFLD study, liraglutide (1.2 mg/day) significantly decreased body weight, HbA1c and liver fat content (measured by proton magnetic resonance spectroscopy) in 68 patients with inadequately controlled T2DM after 6 months [67]. In another randomized controlled trial, liraglutide led to significant improvements in liver attenuation index and visceral fat area (assessed by abdominal computed tomography), as well as urinary albumin-to-creatinine ratio, CRP levels and quality of life in 17 T2DM patients following 24 weeks of treatment [68]. Liraglutide was initially administered at a dose of 0.3 mg/day, gradually increasing the dose to 0.6 mg/day after one week and to 0.9 mg/day after another week [68]. Another randomized clinical trial in 31 T2DM patients with ultrasonography-proven NAFLD found that liraglutide therapy for 24 weeks significantly reduced not only weight and HbA1c levels, but also liver tests and intrahepatic fat content (assessed by ultrasound) [69]. Of note, liraglutide dose was 0.6 mg/day initially for the first week, being progressively increased to 1.2 mg/day in the second week and 1.8 g/day from the third week and after [69]. Similarly, liraglutide (1.8 mg/day for 26 weeks) significantly decreased body weight, HbA1c and intrahepatic lipid content (measured by magnetic resonance imaging-estimated proton density fat fraction), as well as subcutaneous and visceral fat [70]. However, in another randomized clinical trial with 35 T2DM patients, liraglutide (1.8 mg/day) therapy for 12 weeks did not significantly affect liver proton density fat fraction, liver volume and total liver fat index assessed by magnetic resonance imaging [71]. It seems that the longer the duration of liraglutide treatment, the greater the improvements in liver fat.

Interestingly, in a pilot study, liraglutide therapy (0.9 mg/day for 24 weeks) significantly improved BMI, visceral fat accumulation, liver tests and glycemic control in 19 T2DM patients with biopsy-proven NAFLD/NASH [72]. Ten of the 19 patients underwent a repeated liver biopsy at 96 weeks while still on liraglutide therapy; 7/10 showed improved histological inflammation, 6/10 reduced liver fibrosis and 8/10 improved NAS scores. Furthermore, in the Liraglutide safety and efficacy in patients with nonalcoholic steatohepatitis (LEAN) study, a randomized, double-blind, placebo-controlled phase 2 study, liraglutide (1.8 mg/day) was reported to resolve biopsy-proven NASH in 9 out of 23 patients, whereas this was observed in only 2 out of 22 patients in the placebo group ($p = 0.019$) at 48 weeks [73]. Another randomized trial [$n = 30$ obese patients with NAFLD defined as liver fat fraction (LFF) >5% on MRI] showed that liraglutide (3 mg/day) significantly reduced weight and improved hepatocellular apoptosis and hepatic steatosis at 26 weeks, similar to lifestyle modification (including a supervised program of diet and moderate-intensity exercise) [74]. However, after liraglutide discontinuation, weight and LFF increased, whereas the benefits were sustained in the diet + exercise group. Interestingly, the maintenance of LFF reduction was found to be exercise dependent [74].

Semaglutide (once weekly) significantly decreased plasma ALT activity, in a dose-dependent pattern, both in obese patients ($n = 957$) (data derived from a 52-week phase 2 randomized controlled trial) [75] and in T2DM patients ($n = 3268$) (data derived from the 104-week Trial to Evaluate Cardiovascular and Other Long-term Outcomes with 0.5 or 1.0 mg/weekly semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6)) [75,76]. Semaglutide treatment also showed a significant dose-dependent reduction in hsCRP levels, which could be associated with the extent of weight loss in these obese and/or T2DM patients [76]. According to a Japanese retrospective case series study, dulaglutide (0.75 mg once weekly) also significantly improved serum aspartate transaminase, ALT activities and liver stiffness (measured by transient elastography) after 12 weeks of therapy in T2DM patients with biopsy-proven NASH [77]. There was also a significant improvement in body fat mass without changes in skeletal muscle mass or total body water after measuring skeletal muscle mass index, followed by reduction in body weight and HbA1c levels in these NAFLD patients with T2DM [77] Furthermore, in a total of 1499 T2DM patients from 4 randomized clinical trials [i.e. Assessment of Weekly Administration of LY2189265 (dulaglutide) in Diabetes (AWARD)-1, AWARD-5, AWARD-8 and AWARD-9], dulaglutide (1.5 mg once weekly) significantly lowered plasma ALT, AST, γ-GT activity and liver fat compared with placebo after 6 months [78]. The reductions were more prominent in a subgroup of patients with NAFLD (diagnosed by ALT ≥30 IU/l for men and ≥19 UI/l for women). It is suggested that the reduction in liver fat could be associated with lower ALT and γ-GT levels after dulaglutide treatment compared with placebo. However, this study demonstrated a weak association of ALT with decreases in weight and HbA1c levels [78].

No data exist on the effects of albiglutide (another once weekly administered GLP-1 RA) on NAFLD/NASH features. However, there is an oral form of semaglutide [79] but there are still no data regarding the effects of oral semaglutide on NAFLD/NASH. Oral semaglutide was shown to be superior in decreasing weight compared with subcutaneously administered liraglutide (and placebo) at week 26 [80], thus supporting its potential beneficial effects on NAFLD. Surprisingly this paper does not mention liver tests. Both albiglutide and oral semaglutide are currently unavailable in the market.

Overall, liraglutide seems to be the most promising GLP-1 RA for NAFLD/NASH prevention and/or treatment. Further large randomized controlled trials should be conducted to establish whether GLP-1 RAs represent the first-line drug choice in NAFLD/NASH patients with or without T2DM. Also, there is need to show if improved NAFLD/NASH is associated with a significant decrease in vascular events (Table 2).

5. SGLT2i

SGLT2i inhibit glucose reabsorption in the proximal tubule, thus leading to glycosuria and plasma glucose lowering [81]. Apart from glucose reduction, SGLT2i exert several cardiorenal and metabolic benefits [82–84] including weight reduction due to glycosuria-induced caloric loss [85]. Therefore, SGLT2i appear as promising therapeutic agents in NAFLD/NASH patients.

Regarding canagliflozin, a recent meta-analysis (11 trials with a total of 6745 T2DM patients) reported that canagliflozin significantly decreased AST, ALT and γ-GT levels [86]. A prospective cohort study in 35 patients with NAFLD (diagnosed by ultrasonography) showed that canagliflozin (100 mg/day) significantly decreased weight, AST, ALT, γ-GT, triglycerides, HbA1c, fasting plasma glucose, ferritin, uric acid and fibrosis-4 (FIB-4) index after 6 months of treatment [87]. Another randomized clinical trial in 56 inadequately controlled T2DM patients found that canagliflozin (300 mg/day) significantly reduced HbA1c, body weight and improved hepatic insulin sensitivity after 24 weeks [88]. Intrahepatic triglyceride content (measured by proton-magnetic resonance spectroscopy) was also decreased by canagliflozin but this change was significant only in NAFLD patients ($n = 37$) [88]. Similarly, a prospective non-randomized, open-label, single-arm study in 20 T2DM patients with NAFLD reported that canagliflozin (100 mg/day) significantly reduced HbA1c, weight and body fat mass (assessed by bioimpedance analysis), as well as liver enzymes and hepatic fat fraction (measured by magnetic resonance imaging) at 6 and 12 months [89]. With regard to NASH, canagliflozin (100 mg/day) led to significant decreases in HbA1c, body weight, ALT, AST, FIB-4 and FM-fibro index, observed in 10 T2DM patients with biopsy-proven NASH after 12 weeks of treatment [90]. Furthermore, a prospective study in 9 T2DM patients with biopsy-proven NAFLD/NASH showed that

Table 2
Summary of the studies evaluating the effects of GLP-1 RAs on NAFLD/NASH.

Pathological condition	Drug name	Drug mechanism of action	Dose	Type of study	Assessment of NAFLD	Treatment duration	Participants (number)	Reference
T2DM with NASH	Liraglutide	Expression of GLP-1 receptor is reduced in NASH patients. Loss of appetite.	1.8 mg/day	Randomized-placebo controlled trial	Biopsy	48 weeks	Placebo-26 Treatment-26	[73]
T2DM with insulin treatment	Liraglutide Insulin	Reduction in visceral fat, due to changes in albuminuria, hepatic steatosis, and systemic micro-inflammation.	First day 0.3 mg/day, increased to 0.6 mg after one week and 0.9 mg after a further week.	Randomized, open-label, comparative study	Abdominal computed tomography	24 weeks	n = 17 Liraglutide + insulin, n = 8 Insulin alone, n = 9	[68]
NASH and NAFLD with glucose intolerance	Liraglutide	Improved glucose abnormalities. Decreased histological inflammation.	0.9 mg/body/day	A pilot study (LEAN-J)	Biopsy	24 weeks	n = 26	[72]
T2DM with NAFLD	Liraglutide Gliclazide Metformin	Fewer hypoglycemic events and less weight gain. Greater reductions in total body, trunk, limb.	Liraglutide dose was 0.6 mg/day at first week, 1.2 mg/day, second week 1.8 g/day from the third week onwards. −120 mg/day gliclazide	A single-center, open-label, prospective, randomized trial	Ultrasonography	24 weeks	*n* = 85 Gliclazide, *n* = 27 Liraglutide, *n* = 29 or metformin n = 29	[69]
Obese patients with NAFLD	Liraglutide	Insulin mimetic effect. Extra-pancreatic effects on satiety and increase in insulin sensitivity.	3 mg/day	A pilot randomized trial	Magnetic resonance imaging	26 weeks	n = 24 Liraglutide *n* = 24 Diet restrictions plus moderate exercise (200 min/walk/week) *n* = 12	[52]
Obese adults with NAFLD	Liraglutide	Effective in hepatocellular apoptosis in NAFLD. Decrease in hepatic lipogenesis.	3 mg/daily	Randomized clinical trial	Magnetic resonance imaging (MRI)	26 weeks	*n* = 30 Liraglutide *n* = 15 Moderate-intensity exercise group *n* = 15	[74]
NAFLD with T2DM	Liraglutide Sitagliptin, Pioglitazone	Regulation of hepatic lipid metabolism by activating AMP-activated protein kinase Reduction of body weight.	Injection liraglutide 0.3–0.6 mg/day Oral-sitagliptin 50 mg/day Oral-pioglitazone 15 mg/day	Retrospective-active treatment study	Ultrasonography	6 months	Liraglutide-*n* = 26 Sitagliptin, *n* = 36 Pioglitazone-*n* = 20	[64]
T2DM	Liraglutide	Reduction in liver lipogenesis and body weight and less liver de novo lipogenesis.	1.2 mg/day	A prospective, single-center study	Proton magnetic resonance spectroscopy and MRI	6 months	*n* = 68	[67]
T2DM	Liraglutide Sitagliptin	Positive effects on glycemic control, body weight, insulin resistance, lipid metabolism and inflammation.	Liraglutide 1.8 mg/day Sitagliptin 100 mg/day	A randomized placebo controlled trail	Proton magnetic resonance spectroscopy (H-MRS)	12 weeks	Liraglutide *n* = 17, sitagliptin *n* = 100 mg or matching placebos, *n* = 17	[40]
T2DM with NAFLD	Liraglutide Metformin	Regulation of hepatic lipid metabolism by activating. AMP-activated protein kinase-promoting fatty acid oxidation.	Liraglutide injection: 0.6–1.2 mg/day Metformin: 1000–1500 mg/day	A randomized clinical trail	B-mode ultrasonic scanning	12 weeks	*n* = 127 Liraglutide *n* = 52 Metformin *n* = 75	[65]
NAFLD with T2DM	Liraglutide Sitagliptin Insulin glargine	Liraglutide induced browning of white fat through activating killer T cells. Induced fibroblast growth factor. Sitagliptin preserved pancreatic beta cell function.	Liraglutide at 0.6 mg/day (day1) increased by weekly-1.8 mg/day, maximum dose (at least 1.2 mg/day). Insulin glargine was started at 0.2 IU/kg/day, titrated by 2 to 6 units each day	Open-label, active-controlled, parallel-group, multicenter trial	Magnetic resonance imaging (MRI)-estimated proton density fat fraction (MRI-PDFF)	26 weeks	n = 75 Liraglutide *n* = 24 Sitagliptin *n* = 27 Insulin glargine n = 24	[70]
T2DM with NAFLD	Liraglutide Metformin	Regulatory effect on pancreatic β cells. Reduction of hepatocyte triglycerides by activation of elements of insulin receptor substrate.	Liraglutide 1.2 mg/day administered by injection -Metformin 500 mg, 3 times per day	Retrospective study	Automatic biochemical analyzer	6 months and 1 year	*n* = 835 Liraglutide group *n* = 424 Metformin group *n* = 411	[66]

Table 2 (*continued*)

Pathological condition	Drug name	Drug mechanism of action	Dose	Type of study	Assessment of NAFLD	Treatment duration	Participants (number)	Reference
T2DM	Exenatide Insulin Pioglitazone	Glycemic control Increase in plasma adiponectin levels Enhanced mitochondrial fat oxidation.	Exenatide 10 μg twice daily Pioglitazone 15 mg/day	Randomized non-controlled clinical trail	Proton nuclear magnetic resonance spectroscopy	6 months	n = 33	[60]
Obese patients with T2DM	Exenatide Liraglutide	Down-regulation of transcription factors in hepatic lipogenesis. Up-regulation of carnitine palmitoyltransferase-1 (CPT1).	Exenatide 5 μg twice daily, 10 μg twice daily after one month; liraglutide 0.6 mg once daily, titrated to 1.2 mg once daily	Prospective cohort study	Proton magnetic resonance imaging and MRI	6 months	$n = 25$ Exenatide $n = 19$ Liraglutide n = 6	[61]
Obese patients with T2DM	Exenatide	A significant effect on gastric slowing. Suppression of postprandial increase in triglycerides.	10 μg/day	Prospective uncontrolled randomized clinical trial	MRI and spectroscopy	26 weeks	n = 44	[59]
NAFLD with T2DM not controlled on metformin alone	Metformin in combination with gliclazide, pioglitazone, sitagliptin, exenatide, or liraglutide	GLP-1 receptor in human hepatocyte caused reduction of hepatocyte triglycerides by activation of insulin receptor substrate 2 in hepatocytes.	Metformin (850 mg/8–12 h) Gliclazide 30 mg/day–60 mg/day after 3 months Pioglitazone 15 mg/day-30 mg/day after 3 months Sitagliptin 50 mg twice a day Exenatide 5 μg twice a day, after 3 months Exenatide 10 μg twice a day after 1 month Liraglutide 0.6 mg/day, increased to 1.2 mg/day after the first week	Observational pilot study	Ultrasonography	6 months	$n = 58$ Gliclazide ($n = 15$), pioglitazone ($n = 13$), sitagliptin (n = 15), exenatide ($n = 7$), liraglutide ($n = 8$)	[58]
T2DM with NAFLD	Exenatide Metformin	Improved oxidative stress. Induced fatty acid deposition and inflammation in the liver.	Exenatide was administrated from week 1 to week 4 at 5 μg/day and from week 5 to week 12 at 10 μg/day Metformin group: Metformin was initially administered at 0.5 g/day. -Maximum of 2 g/day	Randomized controlled trail	Ultrasonography	12 weeks	$n = 117$ Exenatide $n = 49$ Metformin $n = 68$	[55]
NAFLD with T2DM	Exenatide Insulin	Improved levels of fatty liver. Insulin resistance. Body weight loss.	Exenatide 10 μg with insulin glargine	Randomized-parallel clinical trail	Ultrasonography	12 weeks	$n = 60$ Exenatide $n = 30$ Intensive insulin therapy ($n = 30$)	[56]
T2DM with NAFLD/NASH	Dulaglutide	Reduction in body weight and liver mass. Improved hepatic insulin sensitivity. Reduction in hepatic triglycerides by activating GLP-1 receptors on hepatocytes.	Once weekly 1.5 mg vs. placebo	Clinical trials-AWARD program 1, 5, 8, and 9	Laboratory liver tests with thresholds of ALT levels ≥30 IU/l in men and ≥19 IU/l in women	6 months	$n = 1499$ Dulaglutide $n = 971$ Placebo $n = 528$	[78]
NAFLD with T2DM	Dulaglutide	Reduction in hepatic inflammation by GLP-1RA. Decreased in the liver stiffness measurements	Once weekly 0.75 mg	Retrospective case-series study	Transient elastography Biopsy	12 weeks	n = 15	[77]

(*continued on next page*)

Table 2 (*continued*)

Pathological condition	Drug name	Drug mechanism of action	Dose	Type of study	Assessment of NAFLD	Treatment duration	Participants (number)	Reference
T2DM and/or obese	Semaglutide	Dose-dependent effect of semaglutide on ALT reduction levels Weight loss by GLP-1 receptor agonists may cause pleiotropic effects.	Semaglutide 0.5 or 1.0 mg/week (T2DM) Semaglutide 0.05–0.4 mg/day (obesity)	Post hoc from two clinical randomized, double-blind, multinational, placebo-controlled trail	NAFLD fibrosis score and fibrosis index 4 were calculated	104 weeks (cardiovascular outcomes in T2DM) 52-weeks for (weight management trial)	n = 957 (weight management trial) $n = 3268$ (cardiovascular outcomes in T2DM trial)	[76]

ALT: alanine aminotransferase, AST: aspartate aminotransferase, γ-GT: gamma-glutamyltransferase, FG: fasting glucose, GLP-1: glucagon-like peptide-1; HbA1c: hemoglobin A1c; IHL: intrahepatic lipid; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis T2DM: type 2 diabetes mellitus, hsCRP: high-sensitivity C-reactive protein.

canagliflozin (100 mg/day for 24 weeks) improved histological features of NASH, including steatosis, lobular inflammation, ballooning and fibrosis stage [90].

Dapagliflozin (10 mg/day) was also shown to significantly reduce ALT levels to a greater extent than DPP-4i in 102 T2DM patients with NAFLD (determined by ultrasonography) after 3 months of therapy [91]. ALT normalization was achieved at a higher proportion of patients taking dapagliflozin compared with DPP-4i (80 vs 61.5%; $p = 0.041$) [91]. In another retrospective, observational study, dapagliflozin significantly decreased HbA1c, fasting glucose, body weight, systolic blood pressure and ALT levels at 6 months in 69 T2DM patients [92]. Furthermore, 24 weeks of treatment with dapagliflozin (5 mg/day) in 57 T2DM patients with NAFLD (defined by biochemical and ultrasonographic criteria) led to improvements in liver tests, steatosis and fibrosis (measured by transient elastography, FibroScan), potentially due to the dapagliflozin-induced decrease in visceral adipose tissue and body weight [93]. Similarly, dapagliflozin (10 mg/day) combined with omega-3 carboxylic acids were reported to significantly reduce liver fat content (measured by magnetic resonance imaging-proton density fat fraction) in 84 T2DM patients with NAFLD after 12 weeks [94]. Another clinical study showed that dapagliflozin (5 mg/day) significantly improved liver and subcutaneous fat in 55 T2DM patients at 6 months [95]. Of note, in a prospective, non-randomized, open-label study in 11 T2DM patients with biopsy-proven NASH, dapagliflozin therapy for 24 weeks led to significant reductions in BMI, waist circumference, waist-to-hip ratio, body fat mass, HbA1c, fasting plasma glucose, insulin and liver tests [96].

The Effect of Empagliflozin on Liver Fat trial (E-LIFT), a prospective, open-label, randomized clinical study involving 50 T2DM patients with NAFLD (diagnosed by magnetic resonance imaging-derived proton density fat fraction), showed that empagliflozin (10 mg/day) for 20 weeks significantly reduced ALT and liver fat [97]. Another single-center, retrospective, observational study found that empagliflozin (5 mg/day) significantly improved HbA1c, body weight, systolic blood pressure and fasting glucose, as well as ALT levels in 46 T2DM patients after 6 months of treatment [92]. Of note, reductions in ALT levels were associated with decreases in HbA1c and fasting glucose. Furthermore, empagliflozin led to decreases in AST and ALT compared with placebo [in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial ($n = 7020$) at week 28 and in 4 other 24-week placebo-controlled trials ($n = 2477$)] as well as compared with glimepiride in week 104 ($n = 1545$) in T2DM patients [98]. These empagliflozin-induced reductions were greater with higher baseline ALT and AST levels.

Ipragliflozin was shown to significantly improve ALT in a 24-week, randomized, open-label, active-controlled trial with T2DM patients with NAFLD ($n = 66$; 32 on 50 mg/daily ipragliflozin) [99]. When added on DPP-4i or GLP-1 RAs, ipragliflozin significantly decreased ALT and the Fibrosis-4 score in 130 T2DM patients with NAFLD [100].

Overall, SGLT2i can be used in T2DM patients with NAFLD, especially in combination with GLP-1 RAs. Further research is needed with well-designed randomized controlled trials to elucidate whether SGLT2i should be used as the first-line drug choice in NAFLD/NASH patients with or without T2DM (Table 3).

6. Future perspectives

As discussed above, certain antidiabetic drugs may improve the biochemical and/or histological features of NAFLD/NASH. Some of these drugs, especially SGLT2i and GLP-1 RAs, have also been reported to exert cardiorenal benefits in randomized, placebo-controlled, clinical trials including the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) [101], the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) [102] the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program [103] the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial [104], the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) [75], the Harmony Outcomes trial (with albiglutide) [105] and, very recently, the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial [106]. Of note, the Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trial with oral semaglutide was neutral compared with placebo in terms of the primary endpoint of CVD morbidity and mortality; however, oral semaglutide significantly decreased total and CVD death in exploratory analyses [107]. It is of interest to investigate whether the beneficial effects that these drugs exert on NAFLD/NASH may have also contributed to any cardiorenal benefits observed in the abovementioned randomized clinical trials.

Apart from NAFLD, excessive fat depositions in other organs (e.g. heart, muscle, pancreas, kidney and vasculature) may also be linked to cardiometabolic disorders [108,109]. There is a growing interest on the effects of DPP-4i, GLP-1 RAs and SGLT2i on these fat depots, and especially on epicardial thickness [59,110–113]. Further research is needed in this field to elucidate whether any of these drugs can reduce abnormal peri- and intra-organ fat (APIFat) and whether such beneficial effects decrease cardiorenal risk.

It should be noted that apart from antidiabetic drugs, statins and some antihypertensive drugs, especially renin-angiotensin-aldosterone system blockers, may also beneficially affect NAFLD/NASH [114–119]. Therefore, combinations of such drugs, along with aggressive lifestyle interventions, may further improve liver and CVD outcomes [115].

A previous study has reported that statins can be safely prescribed in patients with NASH and T2DM [120] although several meta-analyses have reported the risk of new onset diabetes after treatment with intensive doses of statins. However, this side effect of statins is remedied by its cardiovascular and kidney protective effects. Therefore, prescription of statin should not be discouraged in patients with NAFLD who are risk of high CVR and TD2M [121].

Finally, postprandial lipemia (PPL) has also been linked to NAFLD [122] as well as increased CV risk [123,124]. It should be noted that there are limited data on the effects of the newer antidiabetic drugs

Table 3
Summary of the studies evaluating the effects of SGLT2i on NAFLD/NASH.

Pathological condition	Drug name	Drug mechanism of action	Dose	Type of study	Assessment of NAFLD	Treatment duration	Participants (number)	Reference
T2DM with NAFLD	Dapagliflozin OM3CA	Improved mitochondrial function. Reduced endoplasmic reticulum stress in liver.	Dapagliflozin 10 mg/day OM3CA 4 g/day	Double-blind randomized placebo-controlled study	MRI	12 weeks	Dapagliflozin n = 21 OM3CA n = 20 A combination of both *n* = 22 or placebo *n* = 21	[94]
Inadequately controlled T2DM	Dapagliflozin and non-SGLT2i	Significant changes in liver-to-spleen ratio. Alleviation of hyperglycemia-improvement in insulin resistance.	Dapagliflozin 5 mg/day	Prospective cohort study	CT scan	6 months	*n* = 55	[95]
T2DM	Dapagliflozin or empagliflozin	Improvement in glycemia due to the amelioration of hepatic dysfunction. Changes in both HbA1c and FG levels.	Dapagliflozin 5 mg/day Empagliflozin 5 mg/day	Single center, retrospective, observational study	ALT and AST measured at baseline and after 26 weeks	6 months	*n* = 115 Dapagliflozin *n* = 69 Empagliflozin *n* = 46	[92]
T2DM with NAFLD	Dapagliflozin	Significant increase in adiponectin, which may be related to the reduction in visceral fat mass in these patients.	Dapagliflozin 5 mg/day	Randomized, active-controlled, open-label trial	Transient elastography	24 weeks	*n* = 57 Dapagliflozin (*n* = 33) Control (n = 24)	[93]
NASH with T2DM	Dapagliflozin	Reduction in median values of waist circumference and waist-to-hip-ratio visceral fat. Improvement in body composition	Dapagliflozin 5 mg/day	Prospective, open-label, uncontrolled study	Percutaneous liver biopsy	24 weeks	n = 11	[96]
NAFLD with T2DM	Canagliflozin	Decrease in exosome miR-122 ratios. Increase in extracellular miR-122 ratios.	Canagliflozin 100 mg/day	Prospective cohort study	Extracellular and exome microRNA-122 test	24 weeks	n = 9	[91]
Inadequately controlled type-T2DM	Canagliflozin	Changes in body weight and glucose metabolism. Less accumulation of intrahepatic triglyceride.	Canagliflozin 300 mg/day or placebo	Double-blind, parallel-group, placebo-controlled study	Proton-magnetic resonance spectroscopy	24 weeks	Treatment = 56 Control = 37	[88]
T2DM with NAFLD	Canagliflozin	Beneficial effects on body composition, hepatic fat storage, liver enzymes, and glycemic control. Fatty acids consumption instead of glucose without changing the whole-body energy consumption.	Canagliflozin 100 mg/day	Pilot, prospective, non-randomized, open-label, single-arm study	Magnetic resonance imaging	12 months	n = 19	[89]
NAFLD	Canagliflozin	Excretion of glucose and decrease in body fluid volume via osmotic diuretics. Decrease in oxidative stress and increase in insulin resistance.	Canagliflozin 100 mg/day	Prospective cohort study	FIB-4 score system by using AST & ALT levels	3 and 6 months	*n* = 35	[87]
T2DM with NASH	Canagliflozin	A negative energy balance, followed by decrease in body weight.	Canagliflozin 100 mg/day	Single-arm, exploratory study	Hepatic fibrosis stage 1–3 Liver biopsy	12 weeks	n = 10	[90]
T2DM + NAFLD	Empagliflozin	Urinary glucose excretion and decrease in blood glucose levels. Improvement in hyperglycemia downregulates carbohydrates binding protein (ChREBP)	10 mg/day	Randomized controlled trial (E-LIFT Trial)	MRI/PDFF	20 weeks	Treatment = 22 Control = 20	[97]
T2DM	Dapagliflozin Empagliflozin	Improvement in glycemia due to the amelioration of hepatic dysfunction. Changes in both HbA1c and FG levels.	Dapagliflozin 5 mg/day Empagliflozin 10 mg/day	Single center, retrospective, observational	Liver tests for ALT and AST measured at baseline and after 26 weeks	6 months	n = 115 Dapagliflozin (*n* = 69) Empagliflozin (*n* = 46)	[92]
T2DM	Metformin Empagliflozin	Changes in weight or HbA1c. Reduction in fat mass, may lead to inhibition of inflammatory cytokines released from adipocytes.	Empagliflozin 10 mg/day	Randomized trial-including the EMPA-REG OUTCOME® trial	Changes from baseline ALT and AST levels	A trial of empagliflozin vs glimepiride over 104 weeks	n = 7020 pooled data Empagliflozin *n* = 4687 Placebo *n* = 2333	[98]
NAFLD + T2DM	Ipragliflozin Pioglitazone	Prevent the reabsorption of glucose in the proximal renal tubule Increase urinary glucose excretion. Lowering effects on blood glucose and body weight.	Ipragliflozin 50 mg/day Pioglitazone 15–30 mg/day	Open-label active controlled trial	CT scan	24 weeks	n = 66 Ipragliflozin treatment = 32 Pioglitazone treatment-34	[99]
T2DM	Empagliflozin	Changes in glycosylated hemoglobin levels.	10 mg/day	Retrospective study	Laboratory measurements-	320 days	*n* = 130	[100]

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Table 3 (*continued*)

Pathological condition	Drug name	Drug mechanism of action	Dose	Type of study	Assessment of NAFLD	Treatment duration	Participants (number)	Reference
		Hyperinsulinemia results in the downregulation of sterol regulatory element binding protein-1c (SREBP-1c).			changes from baseline (ALT) and body weight			

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BS: blood sugar; CT: computed tomography; DPP-4i: dipeptidyl peptidase 4 inhibitors; FG: fasting glucose, FGF21: fibroblast growth factor 21; FIB-4: fibrosis-4; FM-fibro: γ-GT: gamma-glutamyltransferase; GLP-1: glucagon-like peptide-1; HbA1c: hemoglobin A1c; MRI: magnetic resonance imaging; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; OM3CA: omega-3 carboxylic acids; PDFF: proton density fat fraction; SFA: subcutaneous fat area; SGLT2i: sodium glucose cotransporter 2 inhibitors; T2DM: type 2 diabetes mellitus; TG: triglycerides; UA: uric acid.

mentioned above on PPL. Among them, vildagliptin, alogliptin, exenatide and liraglutide were reported to improve PPL [125–129]. Further research in this field is required.

7. Conclusions

NAFLD represents a very common cause of chronic liver disease which together with NASH, are associated with increased liver- and CVD-morbidity and mortality. Lifestyle measures are the cornerstone of NAFLD/NASH treatment. There are data supporting beneficial effects of DPP-4i, GLP-1 RAs and SGLT2i on biochemical and/or histological features of NAFLD/NASH. Further well-designed randomized controlled trials should be conducted to establish the role of these antidiabetic drugs on NAFLD/NASH prevention and treatment.

Declaration of competing interest

DPM has given talks and attended conferences sponsored by Amgen, Libytec and AstraZeneca. Other authors have no competing interests to disclose.

References

[1] Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. J Hepatol 2016;64:73–84.
[2] Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013;58:593–608.
[3] Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62:S47–64.
[4] Takahashi Y, Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014;20:15539–48.
[5] Benedict M, Zhang X. Nonalcoholic fatty liver disease: an expanded review. World J Hepatol 2017;9:715–32.
[6] Katsiki N, Mikhailidis DP. Abnormal peri-organ or intra-organ fat deposition and vascular risk. Angiology 2018;69:841–2.
[7] Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterol 2017;152:1090–9.
[8] Nakamura J, Kamiya H, Haneda M, et al. Causes of death in Japanese patients with diabetes based on the results of a survey of 45,708 cases during 2001–2010: report of the committee on causes of death in diabetes mellitus. J Diabetes Invest 2017;8:397–410.
[9] Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol 2018;53:362–7.
[10] Katsiki N, Mikhailidis DP. Epicardial fat: a novel marker of subclinical atherosclerosis in clinical practice? Anatol J Cardiol 2017;17:64–5.
[11] Katsiki N, Mikhailidis DP, Mantzoros CS. Nonalcoholic fatty liver disease and dyslipidemia: an update. Metabolism 2016;65:1109–23.
[12] Athyros VG, Katsiki N, Karagiannis A. Nonalcoholic fatty liver disease and severity of cardiovascular disease manifestations. Angiology 2013;64:572–5.
[13] Athyros VG, Tziomalos K, Katsiki N, Doumas M, Karagiannis A, Mikhailidis DP. Cardiovascular risk across the histological spectrum and the clinical manifestations of nonalcoholic fatty liver disease: an update. World J Gastroenterol 2015;21:6820–34.
[14] Katsiki N, Imprialos K, Vlachopoulos C. Editorial: arterial stiffness, central haemodynamics and nonalcoholic fatty liver disease: links with cardiovascular risk and effects of drug treatment. Curr Vasc Pharmacol 2018;16:401–4.
[15] Katsiki N, Mikhailidis DP, Theodorakis MJ. Sodium-glucose cotransporter 2 inhibitors (SGLT2i): their role in cardiometabolic risk management. Curr Pharm Des 2017;23:1522–32.
[16] Katsiki N, Athyros VG, Mikhailidis DP. Abnormal peri-organ or intra-organ fat (APIFat) deposition: an underestimated predictor of vascular risk? Curr Vasc Pharmacol 2016;14:432–41.
[17] Hu M, Phan F, Bourron O, Ferré P, Foufelle F. Steatosis and NASH in type 2 diabetes. Biochimie 2017;143:37–41.
[18] Lonardo A, Nascimbeni F, Mantovani A, Targher G. Hypertension, diabetes, atherosclerosis and NASH: cause or consequence? J Hepatol 2018;68:335–52.
[19] Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. Nat Rev Endocrinol 2017;14:99–114.
[20] Italian Association for the Study of the Liver (AISF). AISF position paper on nonalcoholic fatty liver disease (NAFLD): updates and future directions. Dig Liver Dis 2017;49:471–83.
[21] Lonardo A, Lugari S, Ballestri S, Nascimbeni F, Baldelli E, Maurantonio M. A round trip from nonalcoholic fatty liver disease to diabetes: molecular targets to the rescue? Acta Diabetol 2019;56:385–96.
[22] Dongiovanni P, Meroni M, Baselli GA, et al. Insulin resistance promotes lysyl oxidase like 2 induction and fibrosis accumulation in non-alcoholic fatty liver disease. Clin Sci (Lond) 2017;131:1301–15.
[23] Leoni S, Tovoli F, Napoli L, Serio I, Ferri S, Bolondi L. Current guidelines for the management of nonalcoholic fatty liver disease: a systematic review with comparative analysis. World J Gastroenterol 2018;24:3361–73.
[24] Athyros VG, Alexandrides TK, Bilianou H, Cholongitas E, Doumas M, Ganotakis ES, et al. The use of statins alone, or in combination with pioglitazone and other drugs, for the treatment of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis and related cardiovascular risk. An expert panel statement. Metabolism 2017;71:17–32.
Katsiki N, Purrello F, Tsioufis C, Mikhailidis DP. Cardiovascular disease prevention strategies for type2 diabetes mellitus. Expert Opin Pharmacother 2017;18:1243–60.
[25] Tacelli M, Celsa C, Magro B, Giannetti A, Pennisi G, Spatola F, et al. Antidiabetic drugs in NAFLD: the accomplishment of two goals at once? Pharmaceuticals (Basel) 2018;11:4–14.
[26] Raschi E, Mazzotti A, Poluzzi E, De Ponti F, Marchesini G. Pharmacotherapy of type 2 diabetes in patients with chronic liver disease: focus on nonalcoholic fatty liver disease. Expert Opin Pharmacother 2018;19:1903–14.
[27] Weston CJ, Shepherd EL, Claridge LC, et al. Vascular adhesion protein-1 promotes liver inflammation and drives hepatic fibrosis. J Clin Invest 2015;125:501–20.
[28] Balaban YH, Korkusuz P, Simsek H, Gokcan H, Gedikoglu G, Pinar A, et al. Dipeptidyl peptidase IV (DDP IV) in NASH patients. Ann Hepatol 2007;6:242–50.
[29] Wang X, Hausding M, Weng SY, Kim YO, Steven S, Klein T, et al. Gliptins suppress inflammatory macrophage activation to mitigate inflammation, fibrosis, oxidative stress, and vascular dysfunction in models of nonalcoholic steatohepatitis and liver fibrosis. Antioid Redox Signal 2018;28:87–109.
[30] Iwasaki T, Yoneda M, Inamori M, Shirakawa J, Higurashi T, Maeda S, et al. Sitagliptin as a novel treatment agent for nonalcoholic fatty liver disease patients with type 2 diabetes mellitus. Hepatogastroenterology 2011;58:2103–5.
[31] Yilmaz Y, Yonal O, Deyneli O, Celikel CA, Kalayci C, Duman DG. Effects of sitagliptin in diabetic patients with nonalcoholic steatohepatitis. Acta Gastroenterol Belg 2012;75:240–4.
[32] Arase Y, Kawamura Y, Seko Y, Kobayashi M, Suzuki F, Suzuki Y, et al. Efficacy and safety in sitagliptin therapy for diabetes complicated by nonalcoholic fatty liver disease. Hepatol Res 2013;43:1163–8.
[33] Fukuhara T, Hyogo H, Ochi H, Fujino H, Kan H, Naeshiro N, et al. Efficacy and safety of sitagliptin for the treatment of nonalcoholic fatty liver disease with type 2 diabetes mellitus. Hepatogastroenterology 2014;61:323–8.
[34] Asakawa M, Mitsui H, Akihisa M, Sekine T, Niitsu Y, Kobayashi A, et al. Efficacy and safety of sitagliptin for the treatment of diabetes mellitus complicated by chronic liver injury. Springerplus 2015;4:346.
[35] Deng XL, Ma R, Zhu HX, Zhu J. Short article: a randomized-controlled study of sitagliptin for treating diabetes mellitus complicated by nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2017;29:297–301.
[36] Azuma K, Curb JD, Kadowaki T, Edmundowicz D, Kadowaki S, Masaki KH, et al. Ethnic difference in liver fat content: a cross-sectional observation among Japanese American in Hawaii, Japanese in Japan, and non-Hispanic whites in United States. Obes Res Clin Pract 2013;7:e198–205.

[37] Watanabe T, Tamura Y, Kakehi S, Funayama T, Gastaldelli A, Takeno K, et al. Effects of sitagliptin on ectopic fat contents and glucose metabolism in type 2 diabetic patients with fatty liver: a pilot study. J Diabetes Investig 2015;6:164–72.
[38] Kato H, Nagai Y, Ohta A, Tenjin A, Nakamura Y, Tsukiyama H, et al. Effect of sitagliptin on intrahepatic lipid content and body fat in patients with type 2 diabetes. Diabetes Res Clin Pract 2015;109:199–205.
[39] Cui J, Philo L, Nguyen P, Hofflich H, Hernandez C, Bettencourt R, et al. Sitagliptin vs. placebo for nonalcoholic fatty liver disease: a randomized controlled trial. J Hepatol 2016;65:369–76.
[40] Smits MM, Tonneijck L, Muskiet MH, Kramer MH, Pouwels PJ, Pieters-van den Bos IC, et al. Twelve week liraglutide or sitagliptin does not affect hepatic fat in type 2 diabetes: a randomised placebo-controlled trial. Diabetol 2016;59:2588–93.
[41] Joy TR, McKenzie CA, Tirona RG, Summers K, Chakrabarti S, Malhotra N, et al. Sitagliptin in patients with nonalcoholic steatohepatitis: a randomized, placebo-controlled trial. World J Gastroenterol 2017;23:141–50.
[42] Alam S, Ghosh J, Mustafa K, Ahmad N. Effect of sitagliptin on hepatic histological activity and fibrosis of nonalcoholic steatohepatitis patients: a 1-year randomized control trial. Hepatic medicine: Evidence and Research 2018;10:23–31.
[43] Hussain M, Majeed Babar MZ, Hussain MS, Akhtar L. Vildagliptin ameliorates biochemical, metabolic and fatty changes associated with nonalcoholic fatty liver disease. Pak J Med Sci 2016;32:1396–401.
[44] Macauley M, Hollingsworth KG, Smith FE, Thelwall PE, AlMrabeh A, Schweizer A, et al. Effect of vildagliptin on hepatic steatosis. J Clin Endocrinol Metab 2015;100:1578–85.
[45] Mashitani T, Noguchi R, Okura Y, Namisaki T, Mitoro A, Ishii H, et al. Efficacy of alogliptin in preventing nonalcoholic fatty liver disease progression in patients with type 2 diabetes. Biomed Rep 2016;4:183–7.
[46] Li JJ, Zhang P, Fan B, Guo XL, Zheng ZS. The efficacy of saxagliptin in T2DM patients with non-alcoholic fatty liver disease: preliminary data. Rev Assoc Med Bras (1992) 2019;65:33–7.
[47] Michurina SV, Ishenko IJ, Klimontov VV, Archipov SA, Myakina NE, Cherepanova MA, et al. Linagliptin alleviates fatty liver disease in diabetic db/db mice. World J Diabetes 2016;7:534–46.
[48] Ryan D, Acosta A. GLP-1 receptor agonists: nonglycemic clinical effects in weight loss and beyond. Obesity (Silver Spring) 2015;23:1119–29.
[49] Gupta NA, Mells J, Dunham RM, Grakoui A, Handy J, Saxena NK, et al. Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. Hepatol 2010;51:1584–92.
[50] Kalogirou M, Sinakos E. Treating nonalcoholic steatohepatitis with antidiabetic drugs: will GLP-1 agonists end the struggle? World J Hepatol 2018;10:790–4.
[51] Katsiki N, Christou GA, Kiortsis DN. Liraglutide and cardiometabolic effects: more than just another antiobesity drug? Curr Vasc Pharmacol 2016;14:76–9.
[52] Khoo J, Hsiang J, Taneja R, Law NM, Ang TL. Comparative effects of liraglutide 3 mg vs structured lifestyle modification on body weight, liver fat and liver function in obese patients with nonalcoholic fatty liver disease: a pilot randomized trial. Diabetes Obes Metab 2017;19:1814–7.
[53] Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Nonalcoholic fatty liver disease and diabetes. Metabolism 2016;65:1096–108.
[54] Bernsmeier C, Meyer-Gerspach AC, Blaser LS, Jeker L, Steinert RE, Heim MH, et al. Glucose-induced glucagon-like peptide 1 secretion is deficient in patients with non-alcoholic fatty liver disease. PLoS One 2014;9:e87488.
[55] Fan H, Pan Q, Xu Y, Yang X. Exenatide improves type 2 diabetes concomitant with non-alcoholic fatty liver disease. Arq Bras Endocrinol Metabol 2013;57:702–8.
[56] Shao N, Kuang HY, Hao M, Gao XY, Lin WJ, Zou W. Benefits of exenatide on obesity and nonalcoholic fatty liver disease with elevated liver enzymes in patients with type 2 diabetes. Diabetes Metab Res Rev 2014;30:521–9.
[57] Blaslov K, Zibar K, Bulum T, Duvnjak L. Effect of exenatide therapy on hepatic fat quantity and hepatic biomarkers in type 2 diabetic patients. Clin Res Hepatol Gastroenterol 2014;38:e61–3.
[58] García Díaz E, Guagnozzi D, Gutiérrez V, Mendoza C, Maza C, Larrañaga Y, et al. Effect of incretin therapies compared to pioglitazone and gliclazide in nonalcoholic fatty liver disease in diabetic patients not controlled on metformin alone: an observational, pilot study. Endocrinol Nutr 2016;63:194–201.
[59] Dutour A, Abdesselam I, Ancel P, Kober F, Mrad G, Darmon P, et al. Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy. Diabetes Obes Metab 2016;18:882–91.
[60] Bi Y, Zhang B, Xu W, Yang H, Feng W, Li C, et al. Effects of exenatide, insulin, and pioglitazone on liver fat content and body fat distributions in drug-naive subjects with type 2 diabetes. Acta Diabetol 2014;51:865–73.
[61] Cuthbertson DJ, Irwin A, Gardner CJ, Daousi C, Purewal T, Furlong N, et al. Improved glycaemia correlates with liver fat reduction in obese, type 2 diabetes, patients given glucagon-like peptide-1 (GLP-1) receptor agonists. PLoS One 2012;7:e50117.
[62] Gluud LL, Knop FK, Vilsbøll T. Effects of lixisenatide on elevated liver transaminases: systematic review with individual patient data meta-analysis of randomised controlled trials on patients with type 2 diabetes. BMJ Open 2014;4:e005325.
[63] Armstrong MJ, Houlihan DD, Rowe IA, Clausen WH, Elbrond B, Gough SC, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther 2013;37:234–42.
[64] Ohki T, Isogawa A, Iwamoto M, Ohsugi M, Yoshida H, Toda N, et al. The effectiveness of liraglutide in nonalcoholic fatty liver disease patients with type 2 diabetes mellitus compared to sitagliptin and pioglitazone. Scientific World Journal 2012;2012:496453.
[65] Tian F, Zheng Z, Zhang D, He S, Shen J. Efficacy of liraglutide in treating type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. Biosci Rep 2018;38(6).
[66] Zhang Z, Qi Y, Kong W, Jin Q, Wang X, Dong Y, et al. Efficacy and clinical value of liraglutide for treatment of diabetes mellitus complicated by nonalcoholic fatty liver disease. Med Sci Monit 2018;24:7399–404.
[67] Petit JM, Cercueil JP, Loffroy R, Denimal D, Bouillet B, Fourmont C, et al. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes: the Lira-NAFLD study. J Clin Endocrinol Metab 2017;102:407–15.
[68] Bouchi R, Nakano Y, Fukuda T, Takeuchi T, Murakami M, Minami I, et al. Reduction of visceral fat by liraglutide is associated with ameliorations of hepatic steatosis, albuminuria, and micro-inflammation in type 2 diabetic patients with insulin treatment: a randomized control trial. Endocr J 2017;64:269–81.
[69] Feng WH, Bi Y, Li P, Yin TT, Gao CX, Shen SM, et al. Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: a randomized trial. J Diabetes Investig 2019;10:399–407.
[70] Yan J, Yao B, Kuang H, Yang X, Huang Q, Hong T, et al. Liraglutide, sitagliptin, and insulin glargine added to metformin: the effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. Hepatology 2019;69:2414–26.
[71] Tang A, Rabasa-Lhoret R, Castel H, Wartelle-Bladou C, Gilbert G, Massicotte-Tisluck K, et al. Effects of insulin glargine and liraglutide therapy on liver fat as measured by magnetic resonance in patients with type 2 diabetes: a randomized trial. Diabetes Care 2015;38:1339–46.
[72] Eguchi Y, Kitajima Y, Hyogo H, Takahashi H, Kojima M, Ono M, et al. Pilot study of liraglutide effects in nonalcoholic steatohepatitis and nonalcoholic fatty liver disease with glucose intolerance in Japanese patients (LEAN-J). Hepatol Res 2015;45:269–78.
[73] Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with nonalcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679–90.
[74] Khoo J, Hsiang JC, Taneja R, Koo SH, Soon GH, Kam CJ, et al. Randomized trial comparing effects of weight loss by liraglutide with lifestyle modification in nonalcoholic fatty liver disease. Liver Int 2019;39:941–9.
[75] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.
[76] Newsome P, Francque S, Harrison S, Ratziu V, Van Gaal L, Calanna S, et al. Effect of semaglutide on liver enzymes and markers of inflammation in subjects with type 2 diabetes and/or obesity. Aliment Pharmacol Ther 2019;50:193–203.
[77] Seko Y, Sumida Y, Tanaka S, Mori K, Taketani H, Ishiba H, et al. Effect of 12-week dulaglutide therapy in Japanese patients with biopsy-proven nonalcoholic fatty liver disease and type 2 diabetes mellitus. Hepatol Res 2017;47:1206–11.
[78] Cusi K, Sattar N, García-Pérez LE, Pavo I, Yu M, Robertson KE, et al. Dulaglutide decreases plasma aminotransferases in people with type 2 diabetes in a pattern consistent with liver fat reduction: a post hoc analysis of the AWARD programme. Diabet Med 2018;35:1434–9.
[79] Hedrington MS, Davis SN. Oral semaglutide for the treatment of type 2 diabetes. Expert Opin Pharmacother 2019;20:133–41.
[80] Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet 2019;394:P39–50.
[81] Kalra S, Singh V, Nagrale D. Sodium-glucose cotransporter-2 inhibition and the glomerulus: a review. Adv Ther 2016;33:1502–18.
[82] Yaribeygi H, Butler AE, Atkin SL, Katsiki N, Sahebkar A. Sodium-glucose cotransporter 2 inhibitors and inflammation in chronic kidney disease: possible molecular pathways. J Cell Physiol 2018;234:223–30.
[83] Katsiki N, Athyros VG, Mikhailidis DP. Cardiovascular effects of sodium-glucose cotransporter 2 inhibitors: multiple actions. Curr Med Res Opin 2016;32:1513–4.
[84] Katsiki N, Athyros VG, Mikhailidis DP. Nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: effects of statins and antidiabetic drugs. J Diabetes Complications 2017;31:521–2.
[85] Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD, Ferrannini E. Energy balance after sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015;38:1730–5.
[86] Li B, Wang Y, Ye Z, Yang H, Cui X, Wang Z, Liu L. Effects of canagliflozin on fatty liver indexes in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. J Pharm Pharm Sci.
[87] Itani T, Ishihara T. Efficacy of canagliflozin against nonalcoholic fatty liver disease: a prospective cohort study. Obes Sci Pract 2018;4:477–82.
[88] Cusi K, Bril F, Barb D, Polidori D, Sha S, Ghosh A, et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. Diabetes Obes Metab 2018 Nov 16. https://doi.org/10.1111/dom.13584 [Epub ahead of print].
[89] Inoue M, Hayashi A, Taguchi T, Arai R, Sasaki S, Takano K, et al. Effects of canagliflozin on body composition and hepatic fat content in type 2 diabetes patients with nonalcoholic fatty liver disease. J Diabetes Investig 2019;10:1004–11.
[90] Seko Y, Nishikawa T, Umemura A, Yamaguchi K, Moriguchi M, Yasui K, et al. Efficacy and safety of canagliflozin in type 2 diabetes mellitus patients with biopsy-proven nonalcoholic steatohepatitis classified as stage 1–3 fibrosis. Diabetes Metab Syndr Obes 2018;11:835–43.
[91] Akuta N, Kawamura Y, Watanabe C, Nishimura A, Okubo M, Mori Y, et al. Impact of sodium glucose cotransporter 2 inhibitor on histological features and glucose metabolism of nonalcoholic fatty liver disease complicated by diabetes mellitus. Hepatol Res 2018;49:531–9.

[92] Lee PCH, Gu Y, Yeung MY, Fong CHY, Woo YC, Chow WS, et al. Dapagliflozin and empagliflozin ameliorate hepatic dysfunction among Chinese subjects with diabetes in part through glycemic improvement: a single-center, retrospective, observational study. Diabetes Ther 2018;9:285–95.
[93] Shimizu M, Suzuki K, Kato K, Jojima T, Iijima T, Murohisa T, 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 nonalcoholic fatty liver disease. Diabetes Obes Metab 2019;21:285–92.
[94] Eriksson JW, Lundkvist P, Jansson PA, Johansson L, Kvarnström M, Moris L, et al. Effects of dapagliflozin and n-3 carboxylic acids on nonalcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. Diabetol 2018;61:1923–34.
[95] Kurinami N, Sugiyama S, Yoshida A, Hieshima K, Miyamoto F, Kajiwara K, et al. Dapagliflozin significantly reduced liver fat accumulation associated with a decrease in abdominal subcutaneous fat in patients with inadequately controlled type 2 diabetes mellitus. Diabetes Res Clin Pract 2018;142:254–63.
[96] Tobita H, Sato S, Miyake T, Ishihara S, Kinoshita Y. Effects of dapagliflozin on body composition and liver tests in patients with nonalcoholic steatohepatitis associated with type 2 diabetes mellitus: a prospective, open-label, uncontrolled study. Curr Ther Res Clin Exp 2017;87:13–9.
[97] Kuchay MS, Krishan S, Mishra SM, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT trial). Diabetes Care 2018;41:1801–8.
[98] Sattar N, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. Diabetol 2018;61:2155–63.
[99] Ito D, Shimizu S, Inoue K, et al. Comparison of ipragliflozin and pioglitazone effects on nonalcoholic fatty liver disease in patients with type 2 diabetes: a randomized, 24-week, open-label, active-controlled trial. Diabetes Care 2017;40:1364–72.
[100] Ohki T, Isogawa A, Toda N, Tagawa K. Effectiveness of ipragliflozin, a sodium-glucose co-transporter 2 inhibitor, as a second-line treatment for nonalcoholic fatty liver disease patients with type 2 diabetes mellitus who do not respond to incretin-based therapies including glucagon-like peptide-1 analogs and dipeptidyl peptidase-4 inhibitors. Clin Drug Investig 2016;36:313–9.
[101] Nagahisa T, Saisho Y. Cardiorenal protection: potential of SGLT2 inhibitors and GLP-1 receptor agonists in the treatment of type 2 diabetes. Diabetes Ther 2019;5:1–22.
[102] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375:311–22.
[103] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[104] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.
[105] Hernandez AF, Green JB, Janmohamed S, D'Agostino Sr RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–29.
[106] Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 394, 2019;394: 121–30.
[107] Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 381, 2019;381:841–51.
[108] Katsiki N, Dimitriadis G, Mikhailidis DP. Perirenal adiposity and other excessive intra- and peri-organ fat depots: what is the connection? Angiology 2019;70:581–3.
[109] Ferrara D, Montecucco F, Dallegri F, Carbone F. Impact of different ectopic fat depots on cardiovascular and metabolic diseases. J Cell Physiol 2019;234: 21630–41.
[110] Lima-Martínez MM, Paoli M, Rodney M, Balladares N, Contreras M, D'Marco L, et al. Effect of sitagliptin on epicardial fat thickness in subjects with type 2 diabetes and obesity: a pilot study. Endocrine 2016;51:448–55.
[111] Iacobellis G, Mohseni M, Bianco SD, Banga PK. Liraglutide causes large and rapid epicardial fat reduction. Obesity (Silver Spring) 2017;25:311–6.
[112] Sato T, Aizawa Y, Yuasa S, Kishi S, Fuse K, Fujita S, et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc Diabetol 2018;17:1–9.
[113] Yagi S, Hirata Y, Ise T, Kusunose K, Yamada H, Fukuda D, et al. Canagliflozin reduces epicardial fat in patients with type 2 diabetes mellitus. Diabetol Metab Syndr 2017;9:78.
[114] Athyros VG, Katsiki N, Karagiannis A. Editorial: can glucagon like peptide 1 (GLP1) agonists or sodium-glucose co-transporter 2 (SGLT2) inhibitors ameliorate nonalcoholic steatohepatitis in people with or without diabetes? Curr Vasc Pharmacol 2016;14:494–7.
[115] Athyros VG, Katsiki N, Mikhailidis DP. Editorial: resolution of nonalcoholic-steatohepatitis. More than one drug needed? Curr Vasc Pharmacol 2016;14: 313–5.
[116] Athyros VG, Polyzos SA, Kountouras J, Katsiki N, Anagnostis P, Doumas M, et al. Nonalcoholic fatty liver disease treatment in patients with type 2 diabetes mellitus; new kids on the block. Curr Vasc Pharmacol 2019 Apr 5. https://doi.org/10.2174/1570161117666190405164313 [Epub ahead of print].
[117] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402.
[118] Moreira de Macêdo S, Guimarães TA, Feltenberger JD, Sousa Santos SH. The role of renin-angiotensin system modulation on treatment and prevention of liver diseases. Peptides 2014;62:189–96.
[119] Oikonomou D, Georgiopoulos G, Katsi V, Kourek C, Tsioufis C, Alexopoulou A, et al. Nonalcoholic fatty liver disease and hypertension: coprevalent or correlated? Eur J Gastroenterol Hepatol 2018;30:979–85.
[120] Bril F, Portillo Sanchez P, Lomonaco R, Orsak B, Hecht J, Tio F, et al. Liver safety of statins in prediabetes or T2DM and nonalcoholic steatohepatitis: post hoc analysis of a randomized trial. J Clin Endocrinol Metab 2017;102:2950–61.
[121] Nascimbenia F, Pellegrinia E, Lugarib S, Mondellib A, Bursib S, Onfianib G, et al. Statins and nonalcoholic fatty liver disease in the era of precision medicine: more friends than foes. Atherosclerosis 2019;284:66–74.
[122] Kolovou GD, Watts GF, Mikhailidis DP, Pérez-Martínez P, Mora S, Bilianou H, et al. Postprandial hypertriglyceridaemia revisited in the era of non-fasting lipid profile testing: a 2019 expert panel statement, main text. Curr Vasc Pharmacol 2019;17: 498–514.
[123] Kolovou GD, Mikhailidis DP, Nordestgaard BG, Bilianou H, Panotopoulos G. Definition of postprandial lipaemia. Curr Vasc Pharmacol 2011;9:292–301.
[124] Kolovou GD, Mikhailidis DP, Kovar J, Lairon D, Nordestgaard BG, Ooi TC, et al. Assessment and clinical relevance of non-fasting and postprandial triglycerides: an expert panel statement. Curr Vasc Pharmacol 2011;9:258–70.
[125] Noda Y, Miyoshi T, Oe H, Ohno Y, Nakamura K, Toh N, et al. Alogliptin ameliorates postprandial lipemia and postprandial endothelial dysfunction in non-diabetic subjects: a preliminary report. Cardiovasc Diabetol 2013;12:1–8.
[126] Derosa G, Bonaventura A, Bianchi L, Romano D, Fogari E, D'Angelo A, et al. Vildagliptin compared to glimepiride on post-prandial lipemia and on insulin resistance in type 2 diabetic patients. Metabolism 2014;63:957–67.
[127] Voukali M, Kastrinelli I, Stragalinou S, Tasiopoulou D, Paraskevopoulou P, Katsilambros N, et al. Study of postprandial lipaemia in type 2 diabetes mellitus: exenatide versus liraglutide. J Diabetes Res 2014;2014:304032.
[128] Hermansen K, Bækdal TA, Düring M, Pietraszek A, Mortensen LS, Jørgensen H, et al. Liraglutide suppresses postprandial triglyceride and apolipoprotein B48 elevations after a fat-rich meal in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, cross-over trial. Diabetes Obes Metab 2013;15:1040–8.
[129] Vergès B, Duvillard L, Pais de Barros JP, Bouillet B, Baillot-Rudoni S, Rouland A, et al. Liraglutide reduces postprandial hyperlipidemia by increasing ApoB48 (apolipoprotein B48) catabolism and by reducing ApoB48 production in patients with type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 2018; 38:2198–206.