Diabetes Epidemiology and Management 11 (2023) 100145

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Review

Comparative effects between old and new antidiabetic agents on metabolic- associated fatty liver disease (MAFLD)

André J. Scheen

Division of Clinical Pharmacology, Centre for Interdisciplinary Research on Medicines (CIRM), Liège University, Liège, Belgium
Division of Diabetes, Nutrition and Metabolic Disorders, CHU Liège, Liège, Belgium

ARTICLE INFO

Article History:
Received 6 April 2023
Revised 17 April 2023
Accepted 1 May 2023
Available online 3 May 2023

Keywords:
Fatty liver
GLP-1 receptor agonist
SGLT2 inhibitor
NAFLD
Type 2 diabetes

ABSTRACT

Type 2 diabetes (T2DM) and liver disease, mainly metabolic-associated fatty liver disease (MAFLD), previously named non-alcoholic fatty liver disease (NAFLD), coexist in many patients. While physicians were reluctant to use glucose-lowering agents other than insulin in patients with T2DM and liver disease for many decades, the scene changed in recent years. While metformin gave controversial results in patients with MAFLD, pioglitazone was the first to demonstrate unequivocal positive effects, but its use in clinical practice is limited by safety concerns. New glucose-lowering agents, both glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors, raised new hope. Indeed, besides a good safety profile, these agents, which are associated with weight loss, pleitotropic effects and cardiorenal protection, have also proven their efficacy in improving MAFLD. The positive effects on liver fat content, hepatic enzymes used as markers of steatosis and indices of tissue inflammation are now well demonstrated, yet available data on fibrosis are more limited. Thus, more dedicated studies, using liver biopsies, are still warranted to demonstrate the efficacy of these two pharmacological classes in preventing the progression from simple steatosis to fibrosis/cirrhosis and further confirm this new opportunity for the management of patients with T2DM and MAFLD.

Introduction

Liver steatosis is a comorbidity frequently encountered in presence of obesity and/or T2DM [1,2]. This metabolic anomaly, initially called NAFLD (« Non-Alcoholic Fatty Liver Disease »), was recently renamed MAFLD (« Metabolic-Associated Fatty Liver Disease »). It comprises a large spectrum that englobes steatosis, steatohepatitis (NASH), fibrosis and cirrhosis, lesions that may progress to hepatocellular carcinoma [3].

The high prevalence of MAFLD in T2DM patients underscores the need for its early assessment to avoid the progression to NASH and possibly fibrosis/cirrhosis, lesions that are associated with increased morbidity and mortality [4]. It also emphasizes the importance of strengthening the management of MAFLD/NASH in T2DM patients. In this context, it appears crucial to analyze the effects of currently available anti-diabetic agents on MAFLD/NASH in patients with T2DM [5,6].

The present comprehensive review briefly discusses the epidemiology of MAFLD in patients with T2DM and gives a more extensive update on the effects on MAFLD of old and new glucose-lowering agents in patients with T2DM (Fig. 1).

Epidemiology of MAFLD in patients with type 2 diabetes

In a first meta-analysis of twenty-four studies involving 35,599 T2DM patients of whom 20,264 were identified with MAFLD, the reported prevalence of MAFLD ranged from 29.6% to 87.1%, with a pooled prevalence of 59.67% (95% confidence interval [CI]: 54.31−64.92%). Of note, a high degree of heterogeneity was observed among the eligible studies [7]. These findings were confirmed and extended in a second meta-analysis of 80 studies from 20 countries, among 49,419 individuals with T2DM. The global prevalence of MAFLD was 55.5% (95% CI 47.3−63.7). In addition, the global prevalence of NASH was 37.3% (95% CI 24.7−50.0%) in 10 studies and the prevalence of advanced fibrosis was estimated to be 17.0% (95% CI 7.2−34.8) in 7 studies [8]. Notably, MAFLD is also commonly observed in patients with type 1 diabetes, yet less frequently than in patients with T2DM : in a meta-analysis of 20 studies, pooled MAFLD prevalence was 22.0% (95% CI, 13.9%−31.2%) in adult patients with type 1 diabetes [9]. Furthermore, epidemiological studies have consistently demonstrated that the coexistence of MAFLD and T2DM is strongly

E-mail address: andre.scheen@chuliege.be

https://doi.org/10.1016/j.deman.2023.100145

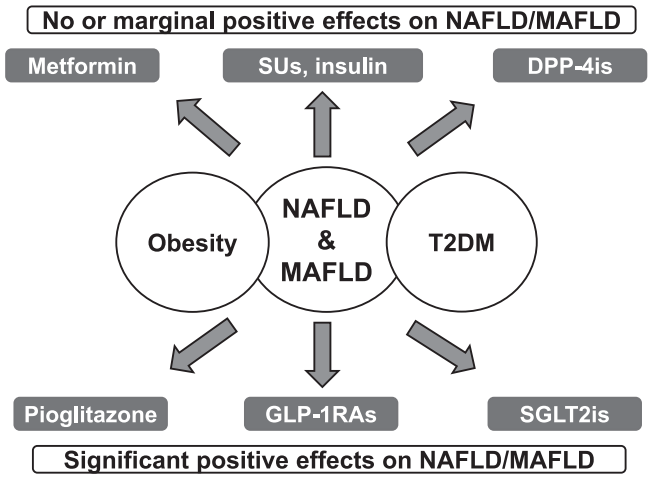

Fig. 1. Effects of antidiabetic medications on MAFLD/NAFLD.
DPP-4is : dipeptidyl peptidase-4 inhibitors. GLP-1RAs : glucagon-like peptide-1 receptor agonists. MAFLD : metabolic-associated fatty liver disease. NAFLD : non-alcoholic fatty liver disease. SGLT2is : sodium-glucose cotransporter 2 inhibitors. SUs : sulphonylureas.

associated with increased mortality and morbidity related to hepatic- and extrahepatic causes [5].

In a nationwide population-based follow-up study (NASHCO) carried out in France, T2DM increased the risk of MAFLD by 6.05 (95% CI 5.68−6.45) and the risk of advanced fibrosis by 3.76-fold (95% CI 2.87−4.91) in subjects with MAFLD [10]. After controlling for confounders, the presence of MAFLD was associated with a significantly increased (by 2 to 3 fold) risk of severe liver-related events, cardiovascular disease and overall mortality. Importantly, the risk of hepatic and extrahepatic complications in diabetic subjects with MAFLD significantly increased with the severity of fibrosis [10]. A US model predicted significant clinical and economic burden due to NASH with T2DM over the next 20 years, which most likely should be reduced through interventions capable of reducing morbidity and mortality in T2DM patients with NASH [11].

Classical glucose-lowering agents and MAFLD

The effects of commonly used anti-hyperglycaemic agents, metformin, sulphonylureas and insulin, on MAFLD were shown rather disappointing, the only exception being thiazolidinediones (TZDs, especially pioglitazone). No specific publications were found regarding the effects of meglitinides (glinides) and alpha-glucosidase inhibitors on MAFLD in dedicated clinical studies. In a recent network meta-analysis, new glucose-lowering agents, both glucagon-like pepide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2is), were superior to other diabetes medications or placebo in reducing liver fat fraction and biomarkers of MAFLD [12].

Metformin

Although evidence exists regarding the benefits of metformin for MAFLD in preclinical studies, reports on the efficacy of metformin in adult patients with T2DM and MAFLD have shown some discrepancies regarding changes in liver biochemistry and hepatic fat content [13]. Overall, available literature does not support any independent favourable effect of metformin on MAFLD in patients with T2DM [14]. In a meta-analysis of nine studies published in 2013, metformin-treated participants showed improvements in liver enzymes (AST : aspartate aminotransferase; ALT : alanine aminotransferase) but not in histological response (steatosis, inflammation, hepatocellular ballooning and fibrosis) [15]. Whether metformin may be related to MAFLD improvement remains controversial in a recent meta-analysis and network pharmacology [16]. However, in a meta-analysis of 19 studies involving 550,882 diabetic subjects, metformin use was associated with a reduction in the ratio of liver cancer by 48% (OR = 0.52; 95% CI, 0.40−0.68) compared with nonusers [17]. Of note, the protective effect of metformin against hepatocellular carcinoma was only reported in NASH-related cirrhosis [18].

Sulphonylureas

The effects of sulphonylureas on MAFLD were poorly reported in the literature. A few studies were unable to demonstrate a significant reduction with sulphonylureas in intrahepatic fat content and liver enzymes [19,20]. A study using multivariate analysis revealed that besides aging and obesity, sulphonylurea usage increased the risk of liver fibrosis in T2DM patients with MAFLD [21].

Insulin

Insulin therapy in T2DM only slightly but significantly reduces liver fat content, while it improves hepatic insulin sensitivity [22]. The effect of insulin has not been extensively studied in MAFLD and there are no studies examining its effect on liver histology [2]. However, insulin-based treatment does not appear to promote or worsen NAFLD [23]. In a large cohort of outpatients in Germany, insulin therapy was significantly associated with lower incidence of MAFLD (HR: 0.72, 95% CI 0.62−0.8), yet to a lower extend than it was with GLP-1RAs and SGLT2is; of note, the precise criteria for the diagnosis of MAFLD were not defined in this report [24].

Thiazolidinediones (pioglitazone)

In a meta-analysis of five RCTs with pioglitazone or rosiglitazone, lobular inflammation decreased in NASH patients who received TZD treatment, without significant improvement in hepatic fibrosis [25]. However, in another meta-analysis of 8 randomized controlled trials (RCTs, 5 evaluating pioglitazone use and 3 evaluating rosiglitazone maleate use) enrolling 516 patients with biopsy-proven NASH for a duration of 6 to 24 months, TZD therapy was associated with significant improvements of advanced fibrosis, fibrosis of any stage, and NASH resolution. Of note, all effects were accounted for by pioglitazone use and not by rosiglitazone use [26]. In a meta-analysis of four studies, pioglitazone compared with placebo significantly improved steatosis grade, inflammation severity and ballooning grade, together with an improvement of liver biological markers, again without significant effects on fibrosis [27]. A recent meta-analysis of seven RCTs confirmed that pioglitazone could alleviate MAFLD, by improving both histopathology and liver enzymes [28]. As a consequence, pioglitazone is recommended by several guidelines for the management of MAFLD because of its positive effects on both liver steatosis and NASH inflammatory activity [29,30].

Novel glucose-lowering agents and MAFLD

Dipeptidyl peptidase-4 inhibitors and MAFLD

Inconclusive results were reported with dipeptidyl peptidase-4 inhibitors (DPP-4is or gliptins) despite in vivo and in vitro evidence suggesting their potential in fatty liver disease. There have been only a few clinical trials demonstrating the efficacy of these agents in patients with MAFLD, yet a greater reduction in liver enzymes was reported [12] but without available histological findings in liver biopsies [31]. In an observational German cohort retrospective study, DPP-4is had no influence on the incidence of MAFLD in patients with T2DM, a finding that contrasted with the reduction reported with

GLP-1RAs, SGLT2is and even insulin therapy [24]. Overall, DPP-4is are not recommended for the treatment of MAFLD [32]. In contrast, both GLP-1RAs and SGLT2is were reported to exert favourable effects on MAFLD in patients with T2DM in numerous clinical studies, an observation that deserves a more detailed analysis [33].

GLP-1 RAs and MAFLD

Table 1 (upper part) summarizes the results of three meta-analyses of trials that investigated the effects of GLP-1RAs on MAFLD. A meta-analysis of five RCTs and three cohort studies found significant improvements following GLP-1RA therapy in hepatic fat content, liver biochemistry, and inflammatory markers, in addition to body composition, insulin sensitivity, glucose control and lipid parameters. Hepatic fat content was significantly decreased with GLP-1RAs compared to metformin and insulin-based therapies, yet the improvement of fibrosis markers did not reach statistical significance [34]. According to another meta-analysis of eleven RCTs, compared to placebo or reference therapies, treatment with GLP-1RAs (mostly liraglutide and semaglutide) was associated with significant reductions in the absolute percentage of liver fat content evaluated with magnetic resonance-based techniques and serum liver enzyme levels, as well as with greater histological resolution of NASH without worsening of liver fibrosis [35]. In a third meta-analysis of 8 RCTs, the administration of GLP-1RAs significantly decreased visceral adipose tissue and the content of intrahepatic fat, changes that were associated with significant reductions in levels of liver enzymes (alanine aminotransferase or ALT and aspartate aminotransferase or AST) in patients with T2DM and MAFLD [36].

A meta-analysis of four RCTs provides positive findings on efficacy of semaglutide weekly subcutaneous injections in improving some liver biological markers and imaging features of interest in MAFLD. However, current conclusions are still limited by the rather small number of patients evaluated. Therefore, an urgent need remains for larger studies with a special focus on histological data derived from liver biopsies to investigate the effect of semaglutide on the progression from steatosis to fibrosis [37]. Reported data with the other once-weekly dulaglutide were less numerous and if anything appeared less impressive on liver enzymes despite a significant reduction in liver fat content in the D-LIFT trial [38]. Recently, the benefit of GLP-1RAs (mainly liraglutide and semaglutide), in NAFLD, suggested from earlier trials, has been confirmed in adults with biopsy-proven NASH, a finding that opens a new paradigm in the use of GLP-1RAs with patients with T2DM and MAFLD and NASH [39].

Dual GIP/GLP-1 receptor agonists and MAFLD

Besides GLP-1, glucose-dependent insulinotropic polypeptide (GIP) is another intestinal incretin hormone. Dual GIP/GLP-1 receptor agonists may represent a new advance for treating T2DM [40]. Tirzepatide, a biased unimolecular GIP-GLP-1 dual agonist, showed potent reductions in glycated hemoglobin and body weight compared to placebo and several active comparators, including semaglutide [41], in the SURPASS phase 3 program [40]. Preliminary results on biological markers of MAFLD with tirzepatide were promising [42,43]. In a subanalysis of SURPASS-3, in patients with T2DM that were studied with a NMR imaging technique, tirzepatide was associated with a significantly more pronounced reduction in visceral adipose tissue and liver fat content when compared with basal insulin degludec [44]. The marked improvement of glucose control and the greater weight reduction, both superior to the corresponding changes seen with pure GLP-1RAs [40,41], should contribute to a better prognosis of patients with MAFLD treated with tirzepatide [45]. Specific studies are planned to demonstrate the positive effect of the dual GIP/GLP-1 receptor agonist in patients with liver disease [46] : "a study of tirzepatide (LY3298176) in participants with nonalcoholic steatohepatitis (NASH) (SYNERGY-NASH)" : ClinicalTrials.gov Identifier: NCT04166773). The hope is that incretin-receptor agonist treatments (dual agonists but also triple agonists in development) could be important not only for decreasing the risk of developing MAFLD, but also for treating MAFLD and MAFLD-related complications, including NASH and the progression to fibrosis and cirrhosis [47,48].

SGLT2 inhibitors and MAFLD

Table 1 (lower part) summarizes the results of three meta-analyses of trials that investigated the effects of SGLT2is on MAFLD. They analyzed the results of, respectively, ten RCTs [49], twelve RCTs [50] and twenty RCTs [51], SGLT2is improved body composition, an effect associated with a reduction of hepatic fat (measured by magnetic resonance-based techniques) and liver enzymes used as biological markers of steatosis. An umbrella review of two systematic reviews indicated that SGLT2is could reduce liver steatosis, as supported by biopsy-proven evidence of improvement from a small clinical trial, but no evidence of liver fibrosis improvement was found [52].

Numerous recent studies compared the effects on MAFLD of SGLT2is with those of other glucose-lowering agents in patients with T2DM as discussed in the next section.

Comparison between different anti-diabetic approaches in MAFLD

Comparison of new medications versus old glucose-lowering agents

In patients with T2DM and MAFLD, no significant change in liver-to-spleen ratio assessed on abdominal computed tomography was recorded with the sulphonylurea glimepiride, whereas significant reductions were noticed with dapagliflozin (and also pioglitazone) [53]. In a small-size RCT, another sulphonylurea, gliclazide, resulted in less improvement in liver function and reduction in intrahepatic fat content in T2DM patients with MAFLD when compared with liraglutide or metformin [20].

In a recent RCT, empagliflozin compared with sitagliptin significantly reduced intrahepatic lipid content measured using proton magnetic resonance spectroscopy in patients with T2DM and MAFLD

Table 1
. Comparative results of three meta-analyses devoted to GLP-1RAs and three meta-analyses devoted to SGLT2is of studies among patients with MAFLD/NAFLD.

References	Studies/patients n/N	Reduction in hepatic fat content (%)	AST IU/L	ALT IU/L	gGT IU/L
GLP-1RAs					
Wong et al. 2021 [34]	8/1454	−1.05 (−1.62 to −0.48)	−1.46 −2.22 to −0.79)	−1.69 (−2.32 to −1.07)	−2.10 (−3.16 to − 1.04)
Mantovani et al. 2021 [35]	11/935	−3.92 (−6.27 to − 1.56)	−7.21 (−13.35 to − 1.07)	−2.92 (−8.15 to + 2.31)	−10.97 (−17.82 to −4.12)
Zhu et al. 2021 [36]	8/468	−3.01 (−4.75 to −1.28)	−2.40 (−4.55 to −0.25)	−3.82 (−7.04 to −0.60)	NA
SGLT2is					
Wei et al. 2021 [49]	10/573	−2.20 (−3.67 to −0.74)	−2.56 (−3.83 to −1.29)	−5.36 (−8.86 to −1.85)	NA
Mantovani et al. 2020 [50]	12/850	−2.05 (−2.61 to −1.48)	−1.87 (−5.88 to 2.14)	−10.00 (−12.2 to − 7.79)	−14.49 (−19.35 to −9.63)
Coelho et al. 2021 [51]	20/1950	−3.39 (−6.01 to −0.77)	−2.83 (−4.71 to −0.95)	−7.43 (−12.14 to −2.71)	−8.21 (−9.52 to −6.91)

AST : aspartate aminotransferase. ALT : alanine aminotransferase. gGT : gamma glutamyl transferase. NA : not available.

assessed by liver biopsy at baseline [54]. Two SGLT2is commercialized in Japan were tested in head-to-head RCTs, tofogliflozin versus glimepiride [19] and luseogliflozin versus metformin [55]. Both SGLT2is were associated with superior beneficial effects on MAFLD compared with old classical glucose-lowering agents.

In a Korean nationwide propensity-score matched cohort study that compared 25,371 patients in each group who received either a DPP-4i or a SGLT2i for an average of about 300 days, SGLT2i therapy showed greater and more significant decrements in all components of fatty liver index when compared to DPP-4i therapy [56]. In a large cohort of outpatients in Germany, prescriptions of SGLT2is and GLP-1RAs were significantly associated with lower incidence of MAFLD, with an effect apparently more marked than that recorded with insulin [24]. In this study, no influence on the incidence of MAFLD could be detected in patients with T2DM treated with DPP-4is. Finally, in a study that assembled two new-user, active comparator cohorts of patients with T2DM using the U.K. Clinical Practice Research Datalink, SGLT2is and possibly GLP-1RAs may be associated with a decreased incidence of MAFLD and hepatic transaminase elevation when compared to patients treated with a DPP-4i [57].

Comparison of new medications versus pioglitazone as a reference

Because pioglitazone demonstrated positive effects on MAFLD and NASH [25-27] and is recommended in some international guidelines [30], it is of major interest to compare the effects of GLP-1RAs and SGLT2is with this reference drug.

A systematic review published in 2020 included 29 RCTs involving a total of 2617 individuals (approximately 45% had T2DM) that have used metformin (n = 6), TZDs (n = 8), GLP-1RAs (n = 6), DPP-4is (n = 4) or SGLT2is (n = 7) to treat MAFLD. Although most anti-hyperglycaemic drugs improved serum liver enzyme levels, only TZDs (especially pioglitazone) and liraglutide showed an improvement of histologic features of MAFLD, with a mild beneficial effect also on liver fibrosis for pioglitazone only [58]. Recently, the same group published another systematic review of a total of 25 active-controlled or placebo-controlled trials with PPAR (peroxisome proliferator-activated receptor) agonists, including TZDs (n = 8), GLP-1RAs (n = 10) and SGLT2is (n = 7). Pioglitazone and GLP-1-RAs (mostly liraglutide and semaglutide) improved individual histological features of NASH (ie, steatosis, ballooning, lobular inflammation) or achieved resolution of NASH without worsening of fibrosis. SGLT2is (mostly empagliflozin and dapagliflozin) reduced liver fat content, as assessed by magnetic resonance-based techniques [59].

In a network meta-analysis of RCTs, GLP-1RAs appear to be as effective as pioglitazone and vitamin E for improvement of liver histology [steatosis, ballooning necrosis, lobular inflammation, fibrosis) among patients with MAFLD [60]. In another recent meta-analysis of five RCTs in patients with MAFLD, the improvement in liver enzymes, steatosis and fibrosis caused by SGLT2is and TZDs was similar [61]. In another network meta-analysis, both PPARgamma agonists and SGLT2is showed a significant reduction in steatosis compared with standard of care; the reduction in steatosis was slightly greater with PPARgamma agonists, but SGLT2is resulted in a statistically significant reduction in fibrosis [62]. In a head-to-head RCT, dapagliflozin and pioglitazone exerted equivalent beneficial effects on MAFLD assessed by the change of the liver-to-spleen ratio on abdominal computed tomography [53]. In an open-label, randomized, active-controlled trial in Japan, the SGLT2i ipragliflozin exerted equally beneficial effects on liver fat content and hepatic enzymes (AST and ALT) compared with the reference drug pioglitazone [63]. Another network meta-analysis provided evidence for the efficacy of pioglitazone, SGLT2is and GLP-1RAs (as well as vitamin E) in treating patients with MAFLD. However, it is necessary to include more head-to-head RCTs to help both patients and clinicians in choosing the best drug and optimizing mutual decisions to tackle MAFLD and NASH in people with T2DM [64]. Because TZDs are exposed to potential adverse events (especially heart failure), SGLT2is and GLP-1RAs [48] appear to offer promising beneficial effects in patients with MAFLD, with the advantage of providing significant weight loss and cardiorenal protection [33,65].

Comparison between GLP-1RAs and SGLT2is

In recent years, numerous positive results on MAFLD were reported with GLP-1RAs [48,66] and SGLT2is [67,68], two antidiabetic agents that also showed cardiorenal protection in patients with T2DM at higher cardiovascular/renal risk [69,70].

Indirect comparison of the meta-analyses reporting the results of either GLP-1RAs or SGLT2is on MAFLD indices summarized in Table 1 suggests quite comparable efficacy between the two pharmacological classes.

In a systematic review, besides a significant reduction in biological markers of steatosis, there was a statistically significant and almost similar reduction in FIB-4 index, a validated marker of fibrosis, with both SGLT2is and GLP-1RAs [71]. A recent GRADE-assessed systematic review and network meta-analysis of RCTs compared the relative efficacy of five SGLT2is and four GLP-1RAs for MAFLD therapy. Indirect comparisons suggested that semaglutide has a therapeutic advantage over the other compounds (presumably in relation with a greater weight reduction), yet head-to-head studies are needed to provide more confidence in clinical decision-making [72].

Discussion

Whereas physicians were for a long time reluctant to prescribe oral antidiabetic agents in patients with liver disease, with a preferential use of insulin, the scene is recently changing following studies that demonstrated a safe use [73] as well as favourable results on MAFLD with newer glucose-lowering agents [2,33,74-76]. Both GLP-1RAs and SGLT2is raised much interest in recent years after the demonstration of their cardiorenal protection [69]. The results summarized in this review suggested that a positive effect on liver disease, especially MAFLD, may also be expected [67]. Regarding SGLT2is, the underlying mechanisms supporting a cardiorenal protection are multiple, combining metabolic, haemodynamic and biochemical effects [77]. Similarly, SGLT2is may be capable of protecting people with MAFLD from severe complications by inhibiting de novo lipogenesis, oxidative responses, inflammation induction, and ultimately hepatocyte death, yet further dedicated clinical trials remain to be carried out to confirm such evidence [68]. Regarding GLP-1RAs, several indirect effects may also contribute to a positive effect on MAFLD : weight loss, improved glucose control, increased insulin sensitivity and reduction in lipotoxicity are generally proposed as the main mechanisms. Yet, the question of a possible direct effect of GLP-1RAs on the improvement of liver fat content is an important one, even if the expression of GLP-1 receptors in hepatocytes is still controversial [66,78]. Several mechanisms have been hypothesized to explain how GLP-1 RAs could reduce hepatocyte storage of triglycerides, regardless of body weight loss. In fact, GLP-1 RAs have been shown to improve hepatic glucose metabolism and promote a reduction in lipogenesis and an increase in fatty acid oxidation [66] Furthermore, GLP-1RAs could reduce oxidative stress and inflammation, which may be associated with resolution of NASH and improvement of liver fibrosis [66,78]. However, the potential of GLP-1RAs in NASH has not been fully explored and long-term trials that aim to evaluate the efficacy of GLP-1RAs in reducing liver fibrosis are not currently available [66]. Because SGLT2is and GLP-1RAs may exert their protection in MAFLD by at least partially different mechanisms, a combination of both pharmacological classes might be of great value for patients with MAFLD/NASH and comorbidities, yet this promise requires validation in dedicated studies using liver biopsies [79].

It is interesting to note that glucose-lowering agents that are associated with a positive impact on MAFLD are also associated with a significant weight reduction, especially GLP-1RAs [80] and SGLT2is [81]. In contrast, anti-hyperglycaemic medications that are weight-neutral (DPP-4is) or favor weight gain (sulphonylureas, insulin) do not exert positive effects on MAFLD. Metformin only induces modest weight reduction and its effect on MAFLD appears limited [14–16]. Among GLP-1RAs, semaglutide that exerts the most impressive weight loss seems also to be the most potent one regarding the improvement of MAFLD [72]. In this respect, further studies regarding the impact of the dual GIP-GLP-1 receptor agonist tirzepatide, which is even more potent than semaglutide regarding weight loss in patients with T2DM [41], or of triple coagonists in current development would be of major interest [47]. The only exception concerns pioglitazone, which positively influences MAFLD while inducing weight gain (also partially due to fluid retention) [28]. However, the use of the TZD pioglitazone is associated with body fat redistribution, with increased subcutaneous adipose tissue but decreased visceral adipose tissue (including liver fat content) [82]. Thus, weight loss and reduction of visceral adipose tissue certainly play a determinant role in the prognosis of MAFLD. This contribution is highlighted by the remarkable improvement of MAFLD reported in obese patients (with or without T2DM) after drastic weight loss following bariatric surgery [83].

Conclusion

MAFLD, which is highly prevalent in patients with abdominal obesity and T2DM, raised huge interest in recent years as it exposes affected individuals to increased morbidity and mortality. A paradigm change is developing between the endocrinologist's which leads to a greater awareness about their critical role to curve the epidemic of MAFLD. Indeed, new clinical care approaches are now available for the management of these complex patients. While only pioglitazone had demonstrated significant improvement in the past, numerous recent reports demonstrated a positive impact of novel antidiabetic medications, both GLP-1RAs and SGLT2is. These pharmacological classes have already shown cardiovascular and renal protection in at risk patients with T2DM, and they now also offer promising effects in patients with MAFLD. However, further mechanistic and clinical studies are still warranted to better understand and validate the use of these agents in patients with MAFLD. More specifically, they have to prove that they are able to protect patients with MAFLD and NASH against the progression to fibrosis/cirrhosis and hepatocellular carcinoma, thus ultimately to improve overall prognosis.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

He has received lecturer/scientific advisor/clinical investigator fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, NovoNordisk and Sanofi. He worked as clinical investigator in PROactive, TECOS, EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58, LEADER and HARMONY Outcomes cardiovascular outcome trials.

Funding details

No sources of funding were used to assist in the preparation of this manuscript.

References

[1] Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. Lancet Diabetes Endocrinol 2022;10(4):284–96.
[2] Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. JHEP Rep 2019;1(4):312–28.
[3] Eslam M, Sanyal AJ, George J, et al. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158(7):1999–2014 e1.
[4] Gaggini M, Morelli M, Buzzigoli E, et al. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013;5(5):1544–60.
[5] Manka PP, Kaya E, Canbay A, et al. A review of the epidemiology, pathophysiology, and efficacy of anti-diabetic drugs used in the treatment of nonalcoholic fatty liver disease. Dig Dis Sci 2021;66(11):3676–88.
[6] Ferguson D, Finck BN. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. Nat Rev Endocrinol 2021;17(8):484–95.
[7] Dai W, Ye L, Liu A, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. Medicine (Baltimore) 2017;96(39):e8179.
[8] Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol 2019;71(4):793–801.
[9] de Vries M, Westerink J, Kaasjager K, et al. Prevalence of nonalcoholic fatty liver disease (NAFLD) in patients with type 1 diabetes mellitus: a systematic review and meta-analysis. J Clin Endocrinol Metab 2020;105(12):3842–53.
[10] Nabi O, Boursier J, Lapidus N, et al. The burden of NAFLD in type 2 diabetic subjects from the general population: a Nationwide population-based follow-up study (NASHCO). Liver Int 2022;42(3):595–606.
[11] Younossi ZM, Tampi RP, Racila A, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the U.S. Diabetes Care 2020;43(2):283–9.
[12] Zou CY, Sun Y, Liang J. Comparative efficacy of diabetes medications on liver enzymes and fat fraction in patients with nonalcoholic fatty liver disease: a network meta-analysis. Clin Res Hepatol Gastroenterol 2023;47(1):102053.
[13] Pinyopornpanish K, Leerapun A, Pinyopornpanish K, et al. Effects of metformin on hepatic steatosis in adults with nonalcoholic fatty liver disease and diabetes: insights from the cellular to patient levels. Gut Liver 2021;15(6):827–40.
[14] Bhat A, Sebastiani G, Bhat M. Systematic review: preventive and therapeutic applications of metformin in liver disease. World J Hepatol 2015;7(12):1652–9.
[15] Li Y, Liu L, Wang B, et al. Metformin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Biomed Rep 2013;1(1):57–64.
[16] Huang Y, Wang X, Yan C, et al. Effect of metformin on nonalcoholic fatty liver based on meta-analysis and network pharmacology. Medicine (Baltimore) 2022;101(43):e31437.
[17] Ma S, Zheng Y, Xiao Y, et al. Meta-analysis of studies using metformin as a reducer for liver cancer risk in diabetic patients. Medicine (Baltimore) 2017;96(19):e6888.
[18] Boursier J, Anty R, Carette C, et al. Management of diabetes mellitus in patients with cirrhosis: an overview and joint statement. Diabetes Metab 2021;47(5):101272.
[19] Takeshita Y, Honda M, Harada K, et al. Comparison of tofogliflozin and glimepiride effects on nonalcoholic fatty liver disease in participants with type 2 diabetes: a randomized, 48-week, open-label, active-controlled trial. Diabetes Care 2022;45(9):2064–75.
[20] Feng W, Gao C, Bi Y, et al. Randomized trial comparing the effects of gliclazide, liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. J Diabetes 2017;9(8):800–9.
[21] Dai CY, Fang TJ, Hung WW, et al. The determinants of liver fibrosis in patients with nonalcoholic fatty liver disease and type 2 diabetes mellitus. Biomedicines 2022;10(7):1487.
[22] Juurinen L, Tiikkainen M, Hakkinen AM, et al. Effects of insulin therapy on liver fat content and hepatic insulin sensitivity in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 2007;292(3):E829–35.
[23] Lingvay I, Roe ED, Duong J, et al. Effect of insulin versus triple oral therapy on the progression of hepatic steatosis in type 2 diabetes. J Investig Med 2012;60(7):1059–63.
[24] Loosen SH, Demir M, Kunstein A, et al. Variables associated with increased incidence of non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes. BMJ Open Diabetes Res Care 2021;9(1):e002243.
[25] He L, Liu X, Wang L, et al. Thiazolidinediones for nonalcoholic steatohepatitis: a meta-analysis of randomized clinical trials. Medicine (Baltimore) 2016;95(42):e4947.
[26] Musso G, Cassader M, Paschetta E, et al. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Int Med 2017;177(5):633–40.
[27] Lian J, Fu J. Pioglitazone for NAFLD patients with prediabetes or type 2 diabetes mellitus: a meta-analysis. Front Endocrinol (Lausanne) 2021;12:615409.
[28] Wang Z, Du H, Zhao Y, et al. Response to pioglitazone in non-alcoholic fatty liver disease patients with vs. without type 2 diabetes: a meta-analysis of randomized controlled trials. Front Endocrinol 2023;14:1111430.
[29] Lange NF, Graf V, Caussy C, et al. PPAR-targeted therapies in the treatment of non-alcoholic fatty liver disease in diabetic patients. Int J Mol Sci 2022;23(8):4305.
[30] Bahirwani R, Griffin C. The diagnosis and management of nonalcoholic fatty liver disease: a patient-friendly summary of the 2018 AASLD guidelines. Clin Liver Dis (Hoboken) 2022;19(6):222–6.

[31] Fu ZD, Cai XL, Yang WJ, et al. Novel glucose-lowering drugs for non-alcoholic fatty liver disease. World J Diabetes 2021;12(1):84–97.
[32] Bae JC. DPP-4 inhibitor in type 2 diabetes mellitus patient with non-alcoholic fatty liver disease: achieving two goals at once? Endocrinol Metab (Seoul) 2022;37 (6):858–60.
[33] Moon JS, Hong JH, Jung YJ, et al. SGLT-2 inhibitors and GLP-1 receptor agonists in metabolic dysfunction-associated fatty liver disease. Trends Endocrinol Metab 2022;33(6):424–42.
[34] Wong C, Lee MH, Yaow CYL, et al. Glucagon-like peptide-1 receptor agonists for non-alcoholic fatty liver disease in type 2 diabetes: a meta-analysis. Front Endocrinol (Lausanne) 2021;12:609110.
[35] Mantovani A, Petracca G, Beatrice G, et al. Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: an updated meta-analysis of randomized controlled trials. Metabolites 2021;11(2):73.
[36] Zhu Y, Xu J, Zhang D, et al. Efficacy and safety of GLP-1 receptor agonists in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2021;12:769069.
[37] Dutta D, Kumar M, Shivaprasad KS, et al. Impact of semaglutide on biochemical and radiologic measures of metabolic-dysfunction associated fatty liver disease across the spectrum of glycaemia: a meta-analysis. Diabetes Metab Syndr 2022;16(6):102539.
[38] Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). Diabetologia 2020;63(11):2434–45.
[39] Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide-1 receptor agonists for the management of NAFLD. J Clin Endocrinol Metab 2022;107(1):29–38.
[40] Scheen AJ. Dual GIP/GLP-1 receptor agonists : new advance for treating type 2 diabetes Ann. Endocrinol 2023;84(2):316–21.
[41] Scheen AJ. Add-on value of tirzepatide versus semaglutide. Lancet Diabetes Endocrinol 2022;10(6):377–8.
[42] Hartman ML, Sanyal AJ, Loomba R, et al. Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of nonalcoholic steatohepatitis in patients with type 2 diabetes. Diabetes Care 2020;43(6):1352–5.
[43] De Block C, Bailey C, Wysham C, et al. Tirzepatide for the treatment of adults with type 2 diabetes: an endocrine perspective. Diabetes Obes Metab 2023;25(1):3–17.
[44] Gastaldelli A, Cusi K, Fernandez Lando L, et al. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. Lancet Diabetes Endocrinol 2022;10(6):393–406.
[45] Ordonez-Vazquez AL, Beltran-Gall SM, Pal SC, et al. Editorial: treatment with dual incretin receptor agonists to maintain normal glucose levels may also maintain normal weight and control metabolic dysfunction-associated fatty liver disease (MAFLD). Med Sci Monit 2022;28:e938365.
[46] Baggio LL, Drucker DJ. Glucagon-like peptide-1 receptor co-agonists for treating metabolic disease. Mol Metab 2021;46:101090.
[47] Targher G, Mantovani A, Byrne CD. Mechanisms and possible hepatoprotective effects of glucagon-like peptide-1 receptor agonists and other incretin receptor agonists in non-alcoholic fatty liver disease. Lancet Gastroenterol Hepatol 2023;8 (2):179–91.
[48] Yabut JM, Drucker DJ. Glucagon-like peptide-1 receptor-based therapeutics for metabolic liver disease. Endocr Rev 2023;44(1):14–32.
[49] Wei Q, Xu X, Guo L, et al. Effect of SGLT2 inhibitors on type 2 diabetes mellitus with non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne) 2021;12:635556.
[50] Mantovani A, Petracca G, Csermely A, et al. Sodium-glucose cotransporter-2 inhibitors for treatment of nonalcoholic fatty liver disease: a meta-analysis of randomized controlled trials. Metabolites 2020;11(1):22.
[51] Coelho FDS, Borges-Canha M, von Hafe M, et al. Effects of sodium-glucose cotransporter 2 inhibitors on liver parameters and steatosis: a meta-analysis of randomized clinical trials. Diabetes Metab Res Rev 2021;37(6):e3413.
[52] Shao SC, Kuo LT, Chien RN, et al. SGLT2 inhibitors in patients with type 2 diabetes with non-alcoholic fatty liver diseases: an umbrella review of systematic reviews. BMJ Open Diabetes Res Care 2020;8(2).
[53] Kinoshita T, Shimoda M, Nakashima K, et al. Comparison of the effects of three kinds of glucose-lowering drugs on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, open-label, three-arm, active control study. J Diabetes Investig 2020;11(6):1612–22.
[54] Hiruma S, Shigiyama F, Kumashiro N. Empagliflozin versus sitagliptin for ameliorating intrahepatic lipid content and tissue-specific insulin sensitivity in patients with early-stage type 2 diabetes with non-alcoholic fatty liver disease: a prospective randomized study. Diabetes Obes Metab 2023;25(6):1576–88.
[55] Shibuya T, Fushimi N, Kawai M, et al. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: a prospective randomized controlled pilot study. Diabetes Obes Metab 2018;20(2):438–42.
[56] Kim J, Han K, Kim B, et al. Sodium-glucose cotransporter 2 inhibitors for non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus: a nationwide propensity-score matched cohort study. Diabetes Res Clin Pract 2022;194:110187.
[57] Pradhan R, Yin H, Yu O, et al. Glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors and risk of nonalcoholic fatty liver disease among patients with type 2 diabetes. Diabetes Care 2022;45(4):819–29.
[58] Mantovani A, Byrne CD, Scorletti E, et al. Efficacy and safety of anti-hyperglycaemic drugs in patients with non-alcoholic fatty liver disease with or without diabetes: an updated systematic review of randomized controlled trials. Diabetes Metab 2020;46(6):427–41.
[59] Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. Lancet Gastroenterol Hepatol 2022;7(4):367–78.
[60] Gu Y, Sun L, He Y, et al. Comparative efficacy of glucagon-like peptide 1 (GLP-1) receptor agonists, pioglitazone and vitamin E for liver histology among patients with nonalcoholic fatty liver disease: systematic review and pilot network meta-analysis of randomized controlled trials. Expert Rev Gastroenterol Hepatol 2023;17(3):273–82.
[61] Hameed I, Hayat J, Marsia S, et al. Comparison of sodium-glucose cotransporter-2 inhibitors and thiazolidinediones for management of non-alcoholic fatty liver disease: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2023:102111.
[62] Ng CH, Lin SY, Chin YH, et al. Antidiabetic medications for type 2 diabetics with nonalcoholic fatty liver disease: evidence from a network meta-analysis of randomized controlled trials. Endocr Pract 2022;28(2):223–30.
[63] Ito D, Shimizu S, Inoue K, et al. Comparison of ipragliflozin and pioglitazone effects on nonalcoholic fatty liver disease in patients with type 2 diabetes: a randomized, 24-week, open-label, active-controlled trial. Diabetes Care 2017;40 (10):1364–72.
[64] Luo Q, Wei R, Cai Y, et al. Efficacy of off-label therapy for non-alcoholic fatty liver disease in improving non-invasive and invasive biomarkers: a systematic review and network meta-analysis of randomized controlled trials. Front Med 2022;9:793203.
[65] Smati S, Canivet CM, Boursier J, et al. Anti-diabetic drugs and NASH: from current options to promising perspectives. Expert Opin Investig Drugs 2021;30(8):813–25.
[66] Nevola R, Epifani R, Imbriani S, et al. GLP-1 receptor agonists in non-alcoholic fatty liver disease: current evidence and future perspectives. Int J Mol Sci 2023;24 (2):1703.
[67] Scheen AJ. Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: a common comorbidity associated with severe complications. Diabetes Metab 2019;45(3):213–23.
[68] Zhang E, Zhao Y, Hu H. Impact of sodium glucose cotransporter 2 inhibitors on nonalcoholic fatty liver disease complicated by diabetes mellitus. Hepatol Commun 2021;5(5):736–48.
[69] Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2022;65(12):1925–66.
[70] Androutsakos T, Nasiri-Ansari N, Bakasis AD, et al. SGLT-2 inhibitors in NAFLD: expanding their role beyond diabetes and cardioprotection. Int J Mol Sci 2022;23 (6):3107.
[71] Zafar Y, Rashid AM, Siddiqi AK, et al. Effect of novel glucose lowering agents on non-alcoholic fatty liver disease: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2022;46(7):101970.
[72] Gu Y, Sun L, Zhang W, et al. Comparative efficacy of 5 sodium-glucose cotransporter protein-2 (SGLT-2) inhibitor and 4 glucagon-like peptide-1 (GLP-1) receptor agonist drugs in non-alcoholic fatty liver disease: a GRADE-assessed systematic review and network meta-analysis of randomized controlled trials. Front Pharmacol 2023;14:1102792.
[73] Scheen AJ. Pharmacokinetic, toxicological and clinical considerations for the treatment of type 2 diabetes in patients with liver disease: a comprehensive update. Expert Opin Drug Metab Toxicol 2023 invited review submitted.
[74] Blazina I, Selph S. Diabetes drugs for nonalcoholic fatty liver disease: a systematic review. Syst Rev 2019;8(1):295.
[75] Petroni ML, Brodosi L, Marchesini G. The treatment of diabetes in advanced liver disease: change of a paradigm. Ann Hepatol 2023;28(1):100772.
[76] Yen FS, Hsu CC, Wei JC, et al. Selection and warning of evidence-based antidiabetic medications for patients with chronic liver disease. Front Med (Lausanne) 2022;9:839456.
[77] Scheen AJ. Sodium-glucose co-transporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. Nature Rev Endocrinol 2020;16(10):556–77.
[78] Petit JM, Verges B. GLP-1 receptor agonists in NAFLD. Diabetes Metab 2017 43 Suppl 1:2S28-2S33.
[79] Patoulias D, Michailidis T. SGLT-2 inhibitor and GLP-1 receptor agonist treatment for patients with nonalcoholic fatty liver disease and type 2 diabetes mellitus: is their combination the optimal treatment option? J Clin Transl Hepatol 2022;10 (4):574–6.
[80] Iqbal J, Wu HX, Hu N, et al. Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. Obes Rev 2022;23(6):e13435.
[81] Cheong AJY, Teo YN, Teo YH, et al. SGLT inhibitors on weight and body mass: a meta-analysis of 116 randomized-controlled trials. Obesity 2022;30(1):117–28.
[82] Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002;87(6):2784–91.
[83] Lee Y, Doumouras AG, Yu J, et al. Complete resolution of nonalcoholic fatty liver disease after bariatric surgery: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17(6) 1040-60 e11.