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The Relationship Between Type 2 Diabetes, NAFLD, and Cardiovascular Risk

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Abstract

Purpose of Review—Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are strongly associated. Both also associate with an increased risk of cardiovascular disease (CVD).

Recent Findings—Several studies have provided evidence that NAFLD could be an independent CVD risk factor. Given the strong association between NAFLD and T2DM, assessing the independent CV effect of these two conditions remains challenging. However, patients with T2DM and NAFLD exhibit higher risk of CVD compared with T2DM without NAFLD suggesting a potential synergistic increase of CV risk in patients with both T2DM and NAFLD supported by several shared pathophysiological pathways. Several anti-diabetic therapies have shown beneficial effect on both NAFLD and CVD.

Summary—Patients with T2DM and NAFLD should be considered at high risk of CVD and could benefit from more intensive CV prevention. Additional long-term follow-up is needed to demonstrate that the treatment of NAFLD effectively reduces the risk of CVD.

Keywords

Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Type 2 diabetes; Fibrosis; Cirrhosis; Cardiovascular disease; Insulin resistance; Metabolic syndrome

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Introduction

Nonalcoholic fatty liver disease (NAFLD) has become a major public health concern, affecting approximately 30% of the adult population worldwide [1]. NAFLD encompasses a large spectrum of condition from simple hepatic steatosis (NAFL) to nonalcoholic steatohepatitis (NASH), which may progress towards liver fibrosis, cirrhosis, and increased risk of liver-related complications including end-stage liver disease, hepatocellular carcinoma, liver transplantation requirement, and liver-related mortality [2••]. Strong evidence indicates that the global burden of NAFLD expands beyond liver-related complications as it increases the risk of developing extra-hepatic complications such as cardio-metabolic diseases including type 2 diabetes mellitus (T2DM), dyslipidemia, metabolic syndrome, and cardiovascular diseases (CVD) [2–5]. Indeed, it is now established that the leading cause of death among patients with NAFLD is CVD [6].

CVDs such as ischemic heart disease and stroke are also major public health burdens as they are the leading causes of death globally. CVDs are responsible for approximately 17.9 million deaths annually, which represent 31% of all global deaths [7]. Hence, CV prevention and early detection and management of established cardiovascular risk factors (CVRF) including dyslipidemia, T2DM, and hypertension are crucial in public health policy.

T2DM has long been recognized as an independent CVRF and is a frequent finding in NAFLD. Approximately 60% of patients with T2DM have NAFLD [8, 9]. Indeed, macrovascular complications constitute the leading cause of death in patients with T2DM [10–12], and intensive glycemic control interventions have been demonstrated to reduce the risk of macrovascular complications compared with a less intensive strategy [13, 14]. Several studies have highlighted the strong interaction between NAFLD and T2DM and describe a complex bidirectional relationship. Indeed, the coexistence of these two conditions pejoratively affect the course and prognoses of both diseases, and T2DM is associated with higher risk of hepatocellular carcinoma [15–18]. Furthermore, patients with T2DM and NAFLD had higher risk of CVD compared with patients with T2DM alone. This suggests a potential synergistic increase of CV risk in patients affected by both conditions [19, 20].

In the current manuscript, we will review the evidence for the association between NAFLD and increased risk of CVD with a specific focus on patients with T2DM. The potential pathophysiological mechanisms linking NAFLD, T2DM, and CVD will be discussed. Finally, we will summarize the current knowledge regarding the effect of glucose-lowering therapies on both NAFLD and risk of CVD.

Increased Risk of CVD in Patients with NAFLD

Several studies have linked NAFLD with an increased risk of either subclinical atherosclerosis or CVD in different populations [21, 22]. A strong association between NAFLD and subclinical atherosclerosis, assessed using four surrogate markers including carotid artery intima-media thickness/plaques, arterial stiffness, coronary artery calcification, and endothelial dysfunction, has been reported by the meta-analysis performed by Zhou et

al. In this systematic review and meta-analysis, which included 26 observational studies with a total of 85,395 participants and 29,493 NAFLD cases, subjects with NAFLD exhibited a significant independent association with subclinical atherosclerosis compared with the non-NAFLD group (odds ratio (OR), 1.60; 95% confidence interval, 1.45–1.78).

The meta-analysis performed by Targher et al., based upon 16 observational studies including 34,043 individuals and a median follow-up of 6.9 years, confirmed the strong association between NAFLD and incidence of CVD events [22]. This meta-analysis showed that the presence of NAFLD, as determined by liver biopsy or imaging, conferred an increased odds of fatal and/or non-fatal CVD events (random effects OR: 1.64, 95% CI 1.26 to 2.13).

Further studies, including patients with biopsy-proven NAFLD, showed that the severity of NAFLD, especially the stage of fibrosis, is associated with the incidence of CVD and CV mortality [23]. Interestingly, in a multinational cohort study of 458 patients with biopsy-confirmed advanced fibrosis (stage F3 and F4), patients with bridging fibrosis (F3) had predominantly non-hepatic cancers and vascular events, whereas patients with compensated cirrhosis had predominantly liver-related events over a mean follow-up of 5.5 years [24]. Likewise, Henson et al. reported in a smaller cohort of 286 patients with biopsy-proven NAFLD that advanced fibrosis on biopsy was a significant and independent predictor of incident CVD, even after considering traditional risk factors and CV risk scores [25]. Further support for a link between NAFLD and CVD comes from a large case-control study that had a longer follow-up of 18.6 years and included 603 biopsy-proven NAFLD patients who were free of CVD at baseline and were age-, sex-, and geographic area-matched with controls from Sweden. In this study, cases with NAFLD had an increased risk of CVD. However, individual histological parameters such as NASH or fibrosis stage were not associated with the risk of CVD in this study [26]. Another recent population-based case-control study, based upon records from European primary care databases, failed to identify a significant association with the incidence of stroke or acute myocardial infarction in cases with NAFLD [27]. However, the findings of this large retrospective study have been called into question due to potential bias including high risk of misclassification as NAFLD remains largely asymptomatic and underdiagnosed in the general population [28]. Hence, additional larger studies with well-characterized subjects with and without NAFLD and long-term follow-up are warranted to determine the precise impact of NAFLD and its histological features on CV risk.

Finally, Paik et al. have recently reported an increase in NAFLD-related deaths in the USA based upon data from the National Vital Statistics System between 2007 and 2016. Interestingly, CVD was the second leading specific cause of death among subjects with NAFLD [29].

Cardiovascular Risk in Patients with T2DM and NAFLD

T2DM patients are considered at higher risk for both the presence of NAFLD and more severe forms of NAFLD independent of other risk factors for advanced fibrosis such as age, hypertension, dyslipidemia, and familial history of NAFLD-related cirrhosis [2, 30]. Given

the strong association between T2DM and both CVD and NAFLD, the question of whether the presence of NAFLD in patients with T2DM confers an additional risk of CVD is of high clinical relevance [31].

Most of the aforementioned studies highlighting the association between NAFLD and CVD included patients with NAFLD with and without T2DM. Statistical adjustment for the presence of T2DM and other CVRF performed in some studies suggests an independent association between NAFLD and CVD [25]. However, to properly and specifically assess the risk of CVD in patients with T2DM and NAFLD compared with those without NAFLD, dedicated studies performed in the T2DM population are needed.

Most studies that assess the association between CVD and NAFLD in T2DM patients implement a cross-sectional design and use imaging modalities such as abdominal ultrasound for the diagnosis of NAFLD [32–38]. These studies report conflicting findings regarding the association between NAFLD and CVD in patients with T2DM. In addition, a few cohort studies that included patients with diabetes have been reported. In a study of 337 subjects with a mean follow-up of 10.9 (± 5.2) years, Adams et al. reported an increased risk of death (hazard ratio 1.7, 95% confidence interval 1.04–2.7) in patients with T2DM and NAFLD. The most common cause of death among T2DM with NAFLD was malignancy followed by liver complications and heart disease as second leading causes of death, which each accounted for 19% of all deaths in patients with diabetes and NAFLD [39]. Another prospective case-control study performed by Targher et al. included 2103 patients with T2DM without CVD at baseline with a 5-year follow-up. In this study, NAFLD associated with a significantly increased risk of CVD after adjustment for other CVR, including age, sex, smoking history, diabetes duration, HbA1c, LDL-cholesterol, liver enzymes, and use of medications [40]. In line with these findings, a retrospective cohort study from a diabetes registry in Scotland, which included a large cohort of 134,368 patients with T2DM, showed that hospital records of patients with NAFLD were independently associated with an increased risk of incident CVD events and mortality over a mean follow-up of nearly 4.5 years [41]. Finally, the association between NAFLD and CVD in patients with diabetes was further confirmed by a meta-analysis of 11 studies that had enrolled a total of 8346 patients with diabetes. Within this pool, 3766 subjects had NAFLD diagnosed primarily by abdominal ultrasound, and 4580 were in the non-NAFLD group. Analysis of the pooled effects estimate showed that patients with diabetes and NAFLD had a doubled risk of CVD compared with patients with diabetes but without NAFLD [19].

All of these studies point toward an additional effect of NAFLD in patients with T2DM in long-term risk of CVD. However, whether advanced stages of NAFLD also associate with an increased risk of CVD in patients with T2DM needs to be determined. A preliminary cross-sectional study has shown that liver stiffness assessed using magnetic resonance elastography associates with surrogate markers of CVD such as coronary artery calcium score in patients with T2DM [42] and correlates with epicardial fat volume [43]. Additional cohort population studies are needed to confirm these findings.

The Potential Pathophysiological Mechanisms Linking NAFLD, T2DM, and CVD

Several shared pathophysiological pathways link NAFLD and T2DM to increased cardiovascular risk including pro-atherogenic lipid alteration, increase in thrombosis factors, insulin resistance, low-grade inflammation, and microbiome alteration (Fig. 1).

Pro-atherogenic Lipid Alteration

Dyslipidemia is a common risk factor for atherosclerosis. Individuals with NAFLD exhibit a specific lipid profile that is often associated with metabolic syndrome, insulin resistance, and T2DM, including elevated triglyceride-rich lipoproteins, low HDL-cholesterol, and increased proportion of circulating small-dense particles of LDL-cholesterol [44•]. Hepatic fat accumulation and insulin resistance lead to an increased production of triglyceride-rich particles such as very low density lipoproteins (VLDL). This increased level of plasma VLDL induces an increase in cholesteryl ester transfer protein (CETP) activity. The CETP is a key enzyme that mediates the reciprocal exchange between triacylglycerols from VLDL particles and cholesteryl esters from LDL and HDL particles in circulation. This will lead to an increase in triacylglycerol content of HDL and LDL particles. These triacylglycerols will be further hydrolyzed by hepatic lipase resulting in small and dense HDL and LDL particles [45]. Small dense LDL particles have been long identified as highly atherogenic [46], whereas epidemiological genetic studies have demonstrated that the level of plasma triacylglycerols causally contributes to the risk of CVD, especially coronary artery disease [47].

Thrombosis Factors

The rupture of unstable atherosclerotic plaques and subsequent thrombosis is responsible for acute ischemic events. The liver is a key organ for production of coagulation and fibrinolytic factors such as plasminogen activator inhibitor type 1 (PAI-1), an inhibitor of the fibrinolytic pathway involved in the resolution of thrombus. Elevated PAI-1 is associated with thrombosis and atherosclerosis [48]. In addition, PAI-1 levels, which are mainly determined by the liver, are increased in the presence of NAFLD and thus may contribute to pro-thrombotic processes involved in CVD [49]. Likewise, T2DM is also a pro-thrombotic condition due to increased platelet reactivity, higher levels of procoagulant agents, and lower concentrations of endogenous anticoagulants. Hence, these alterations may confer additional risk for thrombosis in patient with both T2DM and NAFLD [50].

Insulin Resistance and Hyperglycemia

The accumulation of intrahepatic steatosis is associated with the accumulation of intrahepatic ceramides and diacylglycerols, which have been shown to inhibit insulin signaling and thus favoring hepatic insulin resistance [17]. Due to the increase of hepatic insulin resistance, the presence of NAFLD has a pejorative effect on glycemic control in patients with T2DM. Indeed, patients with T2DM and NAFLD usually require intensive anti-diabetic therapies in order to achieve an optimal glycemic control compared with patients with T2DM without NAFLD [51]. Suboptimal glycemic control could account

for the increased risk of CVD in patients with T2DM and NAFLD. The causal role of hyperglycemia in the development of coronary artery disease in T2DM has been questioned as randomized control trials with significant plasma glucose lowering have reported mixed effects on cardiovascular protection. This could be due to short follow-up periods, lack of statistical power, or heterogeneous populations with T2DM. More recently, data from randomized clinical trials using anti-diabetic agents with longer follow-up or designed specifically to assess CV outcomes have reported CV benefits [13, 14, 52]. Conversely, epidemiological studies using Mendelian randomization have reported that a genetic predisposition to hyperglycemia is associated with an increased risk of coronary artery disease, suggesting a causal effect of [53]. Hyperglycemia may influence coronary artery disease through a direct effect on the structure of the arterial wall via promotion of monocyte/macrophage adhesion to the endothelium, enhancement of vascular smooth muscle cell proliferation, or induction of endothelial dysfunction and inflammatory macrophages [54].

Low-Grade Inflammation

NAFLD and T2DM are both associated with a systemic, low-grade inflammatory state that may promote atherosclerosis by secreting multiple cytokines (e.g., interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), and acute phase proteins (C-reactive protein, fibrinogen, Fetuin-A) [55]. Indeed, hepatic fat accumulation induces endoplasmic reticulum stress, which activates multiple pro-inflammatory pathways such as the nuclear factor-kB (NF-kB) pathway and the mitogen-activated protein kinase (MAPK) pathway. In addition, hepatic steatosis induces mitochondrial dysfunction and subsequently oxidative stress. The precise role of this inflammatory status on the development of CVD is not clearly elucidated. Interestingly, the causal role of IL-1 in the pathogenesis of CVD was recently reported in a clinical trial. Indeed, the inhibition of IL-1β using a monoclonal antibody was associated with a reduction of recurrent CVD events independent of lipid lowering [56].

Microbiome Alteration

Over the last decade, gut dysbiosis has been repeatedly observed in metabolic diseases such as T2DM and NAFLD. Alterations in the gut microbiome have been reported across the whole spectrum of NAFLD [57–61]. Specific gut-microbiome signatures in NAFLD have been demonstrated to accurately detect the presence of advanced fibrosis or cirrhosis [59, 62, 63]. Interestingly, obesity, T2DM, and NAFLD share common gut-microbiome alterations such as a decrease in the abundance of *Lactobacillus*, increased abundance of *Roseburia* and *E. Coli* in both NAFLD and T2DM [60]. Finally, dysbiosis is also associated with CVD. Intestinal barrier dysfunction and gut-microbiome derived mediators could play potential roles in increasing the risk of CVD, as reviewed in reference [64]. Briefly, the potential pathophysiological mechanism involves increased intestinal permeability leading to circulating lipopolysaccharide (LPS). This in turn favors the release of pro-inflammatory cytokines and metabolites such as short chain fatty acids (SCFA) and trimethylamine N-oxide (TMAO) [65, 66]. The increase in TMAO may induce an endoplasmic reticulum stress or pro-inflammatory pathways, but its precise mechanism of action is not fully elucidated. Nevertheless, gut-microbiome derived metabolites including TMAO, SCFA, and LPS are potential important factors associated with CVD NAFLD and T2DM.

Anti-diabetic Drugs, Cardiovascular Benefit, and Potential Effect on NAFLD

Given the strong association between CVD and T2DM, anti-diabetic drugs are required to be at least neutral on CVD events. Hence, over the last decade, many glucose-lowering agents have been tested for their safety and/or efficacy on CV outcomes in T2DM. These CV outcome trials have highlighted the beneficial effect of several medications on CV events beyond glycemic control and led to significant modifications of treatment strategy for patients with T2DM [67]. In addition, T2DM and NAFLD share common pathophysiological mechanisms, including insulin resistance. Thus, the effects of anti-diabetic treatments on insulin resistance have logically been studied in patients with NAFLD with or without T2DM for the treatment of NAFLD. Here, we provide an overview of the main anti-diabetic agents that improve insulin resistance and their effects on CV outcomes in patients with T2DM as well as their potential effects on NAFLD (Table 1).

Metformin

Metformin is considered the first-line drug for the treatment of T2DM, because it effectively reduces HbA1c, is well-tolerated with a modest beneficial effect on body weight, and is highly cost-effective [67].

Effect on NAFLD

Several RCTs have investigated the effect of metformin on NAFLD. Overall, these RTCs failed to demonstrate significant improvement in hepatic steatosis, NASH, or liver fibrosis. Hence, metformin is not recommended for the treatment of patients with NAFLD [2, 3].

Effect on CVD

The beneficial effect of metformin in CV prevention remains debatable. The protective CV effect of metformin has been reported by the UK Prospective Diabetes Study (UKPDS) trial [74]. In this large RCT of 3867 newly diagnosed patients with T2DM, a subgroup of overweight patients with T2DM in the intensive therapy arm with metformin (n = 342) exhibited a 39% reduction in the risk of nonfatal myocardial infarction compared with a subgroup that underwent conventional dietary intervention (n = 411) [74]. The protective CV effect of metformin was further confirmed in the 10-year follow-up study [14]. Another RCT with shorter duration of follow-up (4.3 years) compared CV outcomes in metformin versus placebo in 390 patients with T2DM treated with insulin. Metformin was not associated with improvement of the primary endpoint (a composite endpoint of microvascular, macrovascular outcomes, and mortality) but showed a reduction in the risk of macrovascular events [75]. Although several observational studies have suggested a reduction of CV risk under metformin either in monotherapy or in combination with other oral anti-diabetic drugs, two meta-analyses failed to confirm the protective effect of metformin and raised concerns about an increased risk of CVD when metformin is added to sulfonylurea [77, 78]. The SPREAD-DIMCAD trial, which included 304 patients with T2DM and CAD, confirmed the protective CV effect of metformin. Patients treated with metformin exhibited a 46% risk reduction (p = 0.026) of recurrent cardiovascular events compared with patients treated with the sulfonylurea glipizide [76].

DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) degrades endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). DPP4 inhibitors indirectly promote GLP-1 and GIP action through a longer half-life, thus leading to insulin secretion from beta-cells and decreased secretion of glucagon from alpha-cells.

Effect on NAFLD

Few RCTs have investigated the effect of DPP-4 inhibitors mainly on hepatic steatosis. A study performed by Cui et al. demonstrated that sitagliptin was safe but was not better than placebo in reducing liver fat in patients with pre-diabetes or diabetes and NAFLD [79]. Macauley et al. have reported a significant decrease in hepatic steatosis in patients with T2DM treated with vildagliptin compared with placebo in a 6-month RCT [80]. However, whether DPP-4 inhibitors improve NASH or liver fibrosis is unknown.

Effect on CVD

Four RCTs have assessed CV safety using different DPP-4 inhibitors (saxagliptin [81], sitagliptin [82], alogliptin [83], and linagliptin [85]). All of these studies demonstrated a neutral effect on CV outcomes. Some concerns were raised about the risk of heart failure (HF) with saxagliptin in patients with history of congestive symptoms in the SAVOR-TIMI trial. However, post hoc analysis showed that this effect occurred in patients with pre-existing HF [110]. The neutral effect of DPP-4 inhibitor on CV outcomes was further confirmed by two meta-analyses [86, 87].

Pioglitazone

Pioglitazone is a peroxisome proliferator-activated receptors (PPAR)-gamma agonist. Pioglitazone decreases insulin resistance and lipotoxicity, especially in the liver, and increases lipid storage in subcutaneous adipose tissue.

Effect on NAFLD

Several RCTs have tested pioglitazone versus placebo in patients with biopsy-proven NASH and shown an improvement on both hepatic steatosis and NASH. This beneficial effect on NAFLD and NASH was confirmed in a meta-analysis performed by Musso et al. [68]. However, the effect of pioglitazone on liver fibrosis improvement is less clear, as contradictory results have been reported from RCTs [111]. Recently, a meta-analysis that included 8 RCTs showed that pioglitazone improved advanced liver fibrosis in patients with and without T2DM [88•]. Pioglitazone may be considered for use in patients with pre-diabetes and T2DM and with biopsy-proven NASH, according to American Association for the Study of Liver Diseases (AASLD) [2••] and European Association for the Study of Liver (EASL) [3] guidelines. However, the benefit-risk ratio needs to be considered, as pioglitazone is associated with weight gain, fluid retention, and increased risk of bone fracture.

Effect on CVD

The first CV outcome trial to assess pioglitazone versus placebo was the PROactive trial, which included patients with T2DM at high risk of CVD. Although the trial failed to demonstrate a beneficial effect of pioglitazone on the primary composite endpoint, it showed that the drug has a protective effect on secondary endpoints (all-cause mortality, nonfatal MI, and stroke): HR 0.84; 0.72–0.98, $p = 0.027$ [89]. Several additional RCTs showed a decrease in MI and stroke using pioglitazone, even in patients without diabetes [90]. A comprehensive meta-analysis performed by Zhu et al. also reported that pioglitazone decreased the risk of MACE and MI [87••]. However, several studies, including meta-analyses, also reported that pioglitazone increases the risk of HF [91, 92].

GLP-1 Receptor Agonist

GLP-1 is an incretin hormone secreted by intestinal L-cells at the post-prandial phase. GLP-1 receptor agonists (GLP-1-RA) target GLP-1 receptors expressed in various organs including pancreas, intestine, adipose tissue, and brain. GLP-1 regulates plasma glucose levels by stimulating glucose-dependent insulin secretion and inhibiting glucagon secretion. In addition, GLP-1 induces weight loss by reducing gastric-emptying time while enhancing satiety by activation of GLP-1 receptors in the hypothalamus.

Effect on NAFLD

The efficacy of GLP-1-RA in reducing serum liver enzymes and improving hepatic steatosis using imaging modalities has been reported in several studies [112•]. The LEAN trial further demonstrated a significant histological resolution of NASH without worsening of fibrosis in patients treated with liraglutide 1.8 mg daily versus placebo [93]. Very recently, Newsome and colleagues conducted a large randomized, placebo-controlled trial in patients with biopsy-proven NASH and stage 1–3 fibrosis. They randomized patients to 3 doses of subcutaneous semaglutide versus placebo and treated them for 72 weeks. The highest dose semaglutide group (0.4 mg sq daily) achieved a statistically significant reduction in NASH resolution rate versus placebo (59% versus 17%, p value <0.001). However, despite significant weight loss, no significant improvement in fibrosis was observed in the semaglutide arm versus placebo [94]. Combinatorial therapy approaches are being tried to examine the role of combinations of other drugs with semaglutide in inducing improvement in fibrosis [113].

Effect on CVD

GLP1-RAs are associated with significant reduction of CV risk. Indeed, several trials have demonstrated a beneficial effect on CV outcomes using different GLP1-RAs including liraglutide [95], semaglutide [96], liraglutide [97], and albiglutide [100]. The GLP1-RA class effect on the reduction of CV outcomes was also confirmed by 2 meta-analyses [87, 101]. These strong evidences of CV protection led to a modification in the consensus recommendation for glucose-lowering medications such that GLP1-RA are currently recommended in patients with T2DM and established CVD, regardless of their level of HbA1c [67].

SGLT2 Inhibitors

This class of anti-diabetic agents exert their glucose-lowering effects by inhibition of the sodium/glucose transport protein 2 (SGLT2) that accounts for about 90% of the glucose reabsorbed by the kidney.

Effect on NAFLD

Clinical studies have reported a reduction in plasma ALT levels driven by weight loss and glycemic control [112•]. A few RCT trials including small number of participants have reported a decrease in hepatic fat content using empagliflozin [102], dapagliflozin [103] but not with canagliflozin [104]. The effects on NASH or liver fibrosis remain unknown, as there are no RCTs investigating the effect of SGLT2 inhibitors in patients with biopsy-proven NAFLD.

Effect on CVD

SGLT2 inhibitors have consistently demonstrated a reduction in cardiovascular events in patients with T2DM in large randomized clinical trials using empagliflozin [105], canagliflozin [106], or dapagliflozin [107] versus placebo. Meta-analyses assessing the effect of SGLT2 inhibitors on CV outcomes suggest a class effect on the reduction of MACE and hospitalization for HF in patients with CVD but report no effect on MACE in patients without established atherosclerotic vascular disease [101•] [87••].

Conclusion

The data presented in the current review provide strong evidence of the association between NAFLD and an increased risk of CVD. Given the strong association between CVD, T2DM, and NAFLD, assessments of the individual impacts of T2DM and NAFLD and its advanced stages on the risk of CVD remain challenging. Longitudinal studies specifically designed to address this issue are warranted in the future. However, studies performed in patients with T2DM have shown that the coexistence of both diseases tend to increase the risk of CVD. Several common pathophysiological pathways support the potential synergistic effect of T2DM and NAFLD on CVD. This suggests that patients with both T2DM and NAFLD should be considered at high risk for CVD and could benefit from more intensive CV prevention efforts. Furthermore, several anti-diabetic therapies have shown beneficial effect on either or both NAFLD and CVD. These benefits need to be considered in the individualized management of patients with T2DM. Finally, studies with long-term follow-up are needed to demonstrate that the treatment of NAFLD effectively reduces the risk of CVD.

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Conflict of Interest

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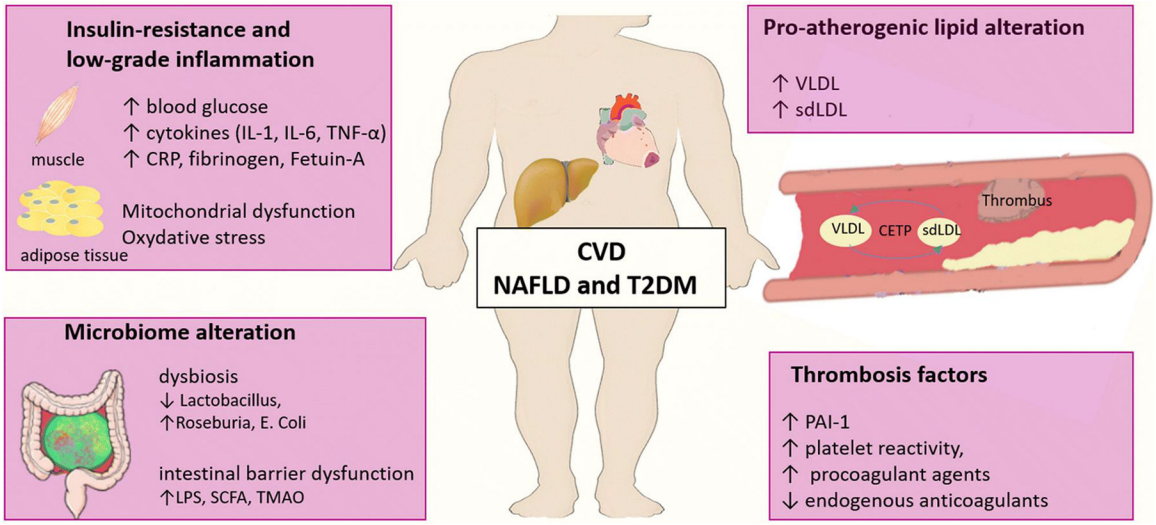

Fig. 1.

Potential pathophysiological mechanisms linking NAFLD, T2DM, and CVD. Several shared pathophysiological pathways link NAFLD and T2DM to an increased cardiovascular risk including pro-atherogenic lipid alteration, increase in thrombosis factors, insulin resistance, low-grade inflammation, and microbiome alteration.

Abbreviations: CRP: C-reactive protein, IL: interleukin, LPS: lipopolysaccharide, PAI-1: plasminogen activator inhibitor type 1, SCFA: short chain fatty acids, sdLDL: small dense low-densitylipoprotein, TMAO: trimethylamine N-oxide, TNF-α: tumor necrosis factor-α, VLDL: very low density lipoprotein

Table 1

Potential effect of anti-diabetic agents on NAFLD and cardiovascular outcomes

Glucose-lowering agent	NAFLD			CV outcomes
	Hepatic steatosis	NASH	Liver fibrosis	
Metformin	Neutral	Neutral	Neutral	Reduction/neutral
	Meta-analysis [68, 69]	Several RCTs [70,71,72,73]	Meta-analyses [68, 69]	-UKPDS [14, 74]: ↓MI *Design: metformin vs conventional dietary measures* *Population: newly diagnosed T2DM and overweight* -HOME TRIAL [75]: ↓ macrovascular events *Design: metformin vs placebo* *Population: T2DM patients with insulin* -SPREAD-DIMCAD [76]: ↓ recurrent CV events *Design: metformin vs glipizide* *Population: T2DM with CAD* -Meta-analysis [77, 78]: neutral * * ↑ CV risk when metformin is combined with sulfonylurea
DPP-4 inhibitors	Neutral/improved	Unknown	Unknown	Neutral
	- Neutral [79]: MRI-PDFF *Design: RCT Sitagliptin* vs *placebo* *Population: Pre-T2DM or T2DM with NAFLD* - Improved [80]: ↓MRI-PDFF *Design: RCT vildaglitin* vs *placebo* *Population: T2DM with NAFLD*			-SAVOR-TIMI 53 [81]: neutral* *Design: RCT saxagliptin vs placebo* *Population: T2DM with high CV risk* * ↑ Hospitalizations for HF in patients with history of HF -TECOS [82]: neutral *Design: RCT sitagliptin vs placebo* *Population: T2DM with CVD* -EXAMINE [83]: neutral* *Design: RCT alogliptin vs placebo* *Population: T2DM with CVD* * ↑ HF incidence in patients already symptomatic at baseline [84] -CARMELINA [85]: neutral *Design: RCT linagliptin vs placebo* *Population: T2DM with high CV risk* -Meta-analyses [86, 87]: neutral
Pioglitazone	Improved	Improved	Neutral/ improved	Reduction/THF
	Several RCTs and meta-analysis [68]	Several RCTs and meta-analysis [88]	-Neutral Several RCTs and Meta-analysis [68] -Improved* in patients with advanced fibrosis (F3F4) Meta-analysis [88]	- PROactive [89]: neutral * *Design: RCT pioglitazone vs placebo* *Population: T2DM with high CV risk* * ↓ all-cause mortality, nonfatal MI, and stroke (secondary endpoint) -IRIS trial 2016 [90]: ↓strokes or MI *Design: RCT pioglitazone vs placebo* *Population: non-diabetic with history of stroke or TIA* - Meta-analyses: ↓MACE [91], ↑ HF incidence ↓ MACE and MI* [87], ↑ HF incidence ↓ All-cause mortality, MI or stroke [92]
GLP-1 receptor agonist	Improved	Improved	Neutral	Reduction
	LEAN trial: ↓hepatic steatosis in liver biopsy [93], *Design: RCT liraglutide* vs *placebo* *Population: overweight patients with NASH with or without T2DM*	- LEAN trial: resolution of definite NASH with no worsening of fibrosis [93] *Design: RCT liraglutide vs placebo* *Population: overweight patients with NASH with or without T2DM* - resolution of definite NASH	Neutral: [94] *Design: semaglutide vs placebo* *Population: patient with NASH and fibrosis F1, F2 or F3 with or without T2DM*	-LEADER [95]: ↓ 3-point MACE *Design: RCT liraglutide vs placebo* *Population: T2DM high CV risk* -SUSTAIN6 [96]: neutral* *Design: RCT semaglutide vs placebo* *Population: T2DM with high CV risk* *↓composite endpoint (CV death , nonfatal MI, stroke) -REWIND [97]: ↓composite endpoint (non fatal MI, non fatal stroke, CV death) *Design: RCT dulaglutide vs placebo* *Population: T2DM at high CV risk* -ELIXA [98]: neutral MACE *Design: RCT lixisenatide versus placebo* Population: T2DM with CVD

Glucose-lowering agent	NAFLD			CV outcomes
	Hepatic steatosis	NASH	Liver fibrosis	
		with no worsening of fibrosis [94] *Design: semaglutide vs placebo* *Population: patient with NASH and fibrosis F1, F2 or F3 with or without T2DM*		-EXSCEL [99]: neutral MACE *Design: RCT exenatide vs placebo* *Population: T2DM with or without CVD* -HARMONY [100]: ↓ 3-point MACE *Design: RCT albiglutide vs placebo* *Population: T2DM and CVD* -Meta-analyses: ↓MACE in secondary CV prevention [101•: ↓ MACE , ↓ HF [87]
SGLT2 inhibitors	Neutral/improved	Unknown	Unknown	Reduction
	-Improved [102]: ↓MRI-PDFF *Design: RCT empaglifozin vs standard of care.* *Population: T2DM with NAFLD* -Improved [103]: ↓ MRI-PDFF Design: RCT *dapagliflozin vs placebo* *Population: T2DM* -Neutral [104]: proton-magnetic resonance spectroscopy *Design: RCT canagliflozin vs placebo* *Population: uncontrolled T2DM*			-EMPA-REG OUTCOME [105] ↓ MACE *empagliflozin vs placebo* T2DM patients at high CV risk -CANVAS [106]: ↓ composite endpoint (CV death, non-fatal MI, non-fatal stroke) *canagliflozin vs placebo* T2DM and high CV risk -DECLARE-TMI 58 [107]: ↓CV death and HF hospitalization *Dapagliflozin vs placebo* T2DM with and without CVD -DAPA HF [108]: ↓composite endpoint (CV death/hospitalization or urgent visit for HF) *dapagliflozin 10 mg/d vs placebo* T2DM and non-diabetic patients, with HFrEF -Meta-analyses [87, 101•, 109] ↓ MACE in patients with CVD ↓ hospitalization for HF

MACE major adverse cardiac events, *CAD* coronary artery disease, *CVD* cardiovascular disease, *HF* heart failure, *HFrEF* heart failure and reduced ejection fraction, *MI* myocardial infarction, *MRI-PDFF* magnetic resonance imaging proton-density fat fraction, *RCT* randomized control trial, *TIA* transient ischemic attack, *T2DM* type 2 diabetes mellitus