Acta Diabetologica (2019) 56:385–396
https://doi.org/10.1007/s00592-018-1266-0

REVIEW ARTICLE

A round trip from nonalcoholic fatty liver disease to diabetes: molecular targets to the rescue?

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Received: 17 October 2018 / Accepted: 27 November 2018 / Published online: 5 December 2018

Abstract

Evidence suggests a close relationship between nonalcoholic fatty liver disease (NAFLD) and type two diabetes (T2D). On the grounds of prevalence of disease, both conditions account for a significant financial cost for health care systems and individuals. Aim of this review article is to explore the epidemiological basis and the putative molecular mechanisms underlying the association of NAFLD with T2D. Epidemiological studies have shown that NAFLD is associated to the development of incident T2D and either reversal or improvement of NAFLD will result into decreased risk of developing incident T2D. On the other side of the coin data have shown that T2D will worsen the course of NAFLD doubling the risk of disease progression (i.e. evolution from simple steatosis to advanced fibrosis, cirrhosis, hepatocellular carcinoma, liver transplant and death). Conversely, NAFLD will contribute to metabolic decompensation of T2D. The pathogenesis of T2D in NAFLD patients may be mediated by several hepatokines impairing metabolic control. Among these, Fetuin-B, which causes glucose intolerance and is increased in patients with T2D and NAFLD with fibrosis is one of the most promising. T2D may affect the progression of NAFLD by acting at different levels of the pathogenic cascade involving gut microbiota and expanded, inflamed, dysfunctional adipose tissue. In conclusion, T2D and NAFLD are mutually, closely and bi-directionally associated. An improved understanding of molecular pathogenesis underlying this bi-directional association may allow us to be able to prevent the development of T2D by halting the progression of NAFLD.

Keywords HCC · Insulin resistance · Natural history · NASH · Type 2 diabetes

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CI	Confidence interval
DAG	Diacylglycerol
HCC	Hepatocellular carcinoma
HDL	High density lipoproteins
HOMA-IR	Homeostasis model assessment of insulin resistance
HR	Hazard ratio
IKKβ/NfκB pathway	IκB-kinase/nuclear factor κB pathway
IR	Insulin resistance
IL	Interleukin
LOXL2	Lysil oxidase 2
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NFS	NAFLD fibrosis score
PDGFA	Platelet-derived growth factor A
PK	Protein kinase
RPG	Random plasma glucose
TNF	Tumor necrosis factor
T2D	Type 2 diabetes
WC	Waist circumference

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Background

Nonalcoholic fatty liver disease (NAFLD) which defines simple steatosis, nonalcoholic steatohepatitis (NASH), NAFLD-cirrhosis and NAFLD-HCC has a global diffusion accounting for a heavy financial burden [1, 2]. By definition, diagnosis and staging of NAFLD remain based on liver biopsy [3]. However, an invasive approach is not invariably necessary and, in most patients as well for epidemiological studies, non-invasive diagnostic techniques, such as ultrasonography, are available to this end [1, 3]. To non-invasively predict presence or absence of advanced fibrosis a scoring system with 6 routinely available demographic, clinical, and laboratory variables: age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio is available [4].

Compared to NAFLD, the diagnosis of type 2 diabetes (T2D) is much more straightforward [5]. However, similar to NAFLD, diabetes represents an expanding worldwide pandemic: 415 million adults globally have diabetes and 642 million adults are projected to be affected by 2040; up to 95% with T2D [6, 7]. Diabetes is a major cause of end-stage renal failure, adult-onset blindness, and non-traumatic amputations and significantly contributes to cardiovascular morbidity and mortality [7]. Although a narrow glycemic control will minimize microvascular complications, macrovascular complications and cardiovascular mortality remain difficult to prevent despite intensive glucose control [8, 9]. Given its prevalence and burden of complications, T2D [7], similar to NAFLD, poses a significant financial cost both for individuals and health care systems.

On this background, the present review article aims to explore the epidemiological basis and the putative molecular mechanisms underlying the association of NAFLD with T2D. The method we followed was to interrogate the PubMed database, between October 2013 and October 2018, using pertinent key-words and relative combinations: TD2, NAFLD, NASH, NAFLD-cirrhosis, NAFLD HCC. Given the restricted number of references based on Journal's editorial policy, we selected the most relevant, recent original articles, reviews and the appropriate cross-references, limited to those published in peer-reviewed journals. Of all the retrieved material, only those references which were unanimously held relevant were retained. We excluded articles published in languages other than English.

From NAFLD to diabetes

The classical view (i.e. "hepatogenous diabetes") maintained that diabetes was a complication of advanced liver disease, i.e. liver cirrhosis chiefly of viral etiology. However, the advent of NAFLD as a leading cause of chronic liver disease in many areas of the world has revolutionized this paradigm by showing that non-cirrhotic, pre-fibrotic NAFLD may predispose to the development of incident T2D suggesting that the dysmetabolic milieu in which NAFLD thrives may be, per se, associated with incident diabetes before the development of an advanced stage of liver fibrosis. Bringing this notion further, a meta-analytic study identified NAFLD as a factor which almost doubles the risk of incident T2D over a 5-year follow-up and that this occurs irrespective of the technique used to diagnose NAFLD, namely either otherwise unexplained raised liver enzymes or the more direct ultrasonographic evidence [10].

Indices of overall and visceral adiposity such as body mass index (BMI) and waist circumference (WC) are among the most important drivers of the development of T2D [11, 12]. However, two studies have shown, NAFLD may supersede BMI and WC in predicting incident T2D both in non-obese and in obese individuals. Kim et al. retrospectively selected 2920 participants who attended a health check-up center in 2000 and followed them through to December 2010. Interestingly, in the regression tree model predicting incident T2D, NAFLD was placed upstream to WC suggesting that, in non-obese individuals, visceral obesity is probably a less important diabetogenic risk factor than NAFLD [13]. Sung et al. reached the same conclusions though using a completely different paradigm. These Authors, by evaluating 29,836 obese [Asian-specific BMI threshold $\geq$ 25 kg/m2] non-diabetic subjects participating in a Korean health screening program found that, compared to the reference groups, those individuals who were free of fatty liver (together with other components of the Mets) were protected from developing incident T2D [14]. Collectively, the findings from these two studies [13, 14] are reminiscent of two different examples of virus-associated fatty liver disease, i.e. the infections with HCV and HIV, both of which are identified as diabetogenic risk factors and support the notion that, irrespective of their etiology, fatty liver will often associate with the risk of incident T2D over time [15].

The independent predictors of incident T2D in the general population include for both sexes: age, BMI, HDL cholesterol and parental history of diabetes; for women: serum uric acid, inactivity during leisure time; for men: systolic pressure, smoking and alcohol intake [16]. Are there any strong specifically liver-related predictors of

incident T2D in NAFLD? A cross-sectional study from our group identified HOMA-IR as being strongly associated with ballooning, the histological hallmark of NASH [17] such as to suggest that NASH might predict T2D. However, this was a cross-sectional study and the outcome was HOMA-IR rather than T2D. Two subsequent studies overcame these methodological limitations and confirmed that NASH predicts incident T2D. Mantovani et al., by conducting a meta-analysis on 4 Asian studies were able to show that the most severe forms of NAFLD (presumably NASH) assessed with either ultrasonography or the NAFLD fibrosis score (NFS) were associated with an increased risk of incident T2D [18]. Enooku et al. submitted to liver biopsy 146 patients with NAFLD and followed them for a median follow-up of 2.33 years. In their series, at multivariate analysis, ballooning was the only significant risk factor for incident T2D [19].

The paradigm associating NAFLD/NASH with the development of incident T2D postulates that either reversal or improvement of NAFLD/NASH will translate into either a protection or a decreased risk of developing incident T2D. This postulate has indeed been confirmed by four epidemiological studies shown in Table 1 [20–23]. Interestingly, one of such studies found that even a transient remission of NAFLD will reduce the risk of incident diabetes [22]. This finding is of major clinical significance owing to the difficulties in obtaining a definite remission of NAFLD.

From diabetes to NAFLD

The coexistence of T2D and NAFLD in the same individuals exerts profound effects on several features of epidemiology and course of NAFLD. For example, NAFLD is a sexually dimorphic disease and male sex is more prone than fertile women to developing NAFLD [24]. However, T2D rescinds the higher prevalence of men in NAFLD [25]. A recent meta-analytic study conducted in 24 studies involving 35,599 patients with T2D (20,264 of whom had NAFLD) found that the pooled prevalence of NAFLD among individuals with T2D was 60.11% (95% CI 53.63–66.41) in men and 59.35% (95% CI 53.28–65.28) in women [26]. These data highlight the importance of the impact of T2D on the physiopathology of NAFLD suggesting that impaired glucose disposal overcomes the sexual dimorphism of NAFLD.

Individuals in whom NAFLD and T2D concur are exposed to the worrisome complications of this dangerous combination. Indeed, data have shown that T2D will worsen the course of NAFLD and that, conversely, NAFLD will contribute to metabolic decompensation of T2D.

Regarding the impact of T2D on NAFLD, Simeone et al., by evaluating the large NAFLD cohort ($N = 18,754$) of Geisinger Health System, in the USA, showed that, compared to those individuals with NAFLD who though were non-diabetics, T2D was associated with approximately twice the risk of disease progression, defined as the evolution from simple steatosis to advanced fibrosis, cirrhosis, HCC, liver transplant and death [27]. A large epidemiological survey conducted in China in half million people confirmed this worrying outcome. These Authors demonstrated that compared to those without diabetes, individuals with diabetes had an increased risk of developing HCC [adjusted HRs 1.49 (95% CI 1.30–1.70); NAFLD [1.76 (CI 1.47–2.16)] and cirrhosis [1.81 (CI 1.57–2.09)] [28]. However, the risk of progressive liver disease was not restricted to those with known T2D. Indeed, among those 8000 individuals forming the cohort of those without previously diagnosed diabetes in whom data were available, random plasma glucose (RPG) values were positively associated with liver diseases [adjusted HRs per 1 mmol/L higher RPG of 1.04 (CI 1.03–1.06) for HCC; 1.07 (CI 1.05–1.10) for NAFLD and 1.07 (CI 1.05–1.09) for cirrhosis] [28] suggesting a dose–response relationship between deranged gluco-regulation, NAFLD and its complications.

The development of hepatic fibrosis is the key link in the chain of events leading from uncomplicated steatosis to liver-related complications and mortality [1; 3]. In this regard, there is ample evidence for a strong association between diabetes and liver fibrosis. Table 2 identifies three European epidemiological studies and one Italian cohort

Table 1 NAFLD reversal/improvement decreases the risk of incident T2D

Author [Ref.]	Method	Findings
Sung [20]	13,218 T2D-free people at baseline were examined at baseline and after 5 years	Change in fatty liver status over time strongly affects risks of incident diabetes
Yamazaki [21]	NAFLD group ($n = 728$) and a non-NAFLD group ($n = 2346$) followed up for 10 years	NAFLD improvement is associated with T2D incidence reduction
Fukuda [22]	Population-based health check-up study	Transient remission of NAFLD significantly decreased the risk of incident T2D
Bae [23]	7849 subjects T2D-free at baseline followed annually for 5 years	The persistence of fatty liver status is associated with incident diabetes

NAFLD nonalcoholic fatty liver disease, *T2D* type 2 diabetes

Table 2 Evidence for an increased risk of liver fibrosis in those with T2D

Author [Ref.]	Method	Findings
Roulot [29]	Population study; 1358 participants	Factors associated with LSM > 8 kPa: age, BMI, waist; DM; hypertension; GGT and ALT
Koehler [30]	Population study; 3041 participants	LSM ≥ 8.0 kPa, suggestive of relevant fibrosis, was strongly associated with steatosis and DM
Pelusi [31]	Cohort study of 118 Italian biopsied patients evaluated according to Kleiner	Fibrosis progression and faster fibrosis progression rate were associated with absence of RAS inhibitors, and baseline T2D
Caballería [32]	Population study; 3076 participants	Factors independently associated with increased LSM were male sex, abdominal obesity, T2D, serum glucose, HDL, and TG levels

ALT alanine transaminase, *DM* diabetes mellitus, *GGT* gammaglutamyl transpeptidase, *HDL* high density lipoproteins, *kPa* kilopascals, *LSM* liver stiffness measurement, *RAS* renin-angiotensin system, *TG* triglycerides, *T2D* type 2 diabetes

survey which consistently report T2D as a strong risk factor for hepatic fibrosis both in the general population and in cohorts followed at academic tertiary referral centers [29–32].

Although HCC may also develop in NAFLD patients on the background of non-cirrhotic livers, advanced fibrosis is a risk factor for hepatocarcinogenesis. Analysis from another perspective provides consistent results by showing that diabetics are at risk of HCC. A survey conducted in Scotland demonstrated that, if a diabetic patient had ever been discharged with a hospital diagnosis of NAFLD, his/her HR for either incident or recurrent HCC was 19.33 (CI 11.8–31.4) and the HR for mortality due to HCC was 6.16 (CI 8.02–12.6) [33]. A seminal study conducted in the general population in northern Italy, had already raised an alert regarding the increased risk of mortality owing to liver disease in those with T2D compared to those free of diabetes; standardized mortality ratio (2.86; CI 2.65–3.08) was specifically increased for those with "non-viral nonalcoholic liver disease", i.e. NAFLD [34].

From the diabetological point of view, NAFLD and T2D is a dangerous combination owing to increased requirement of insulin and worse metabolic control (Table 3) [35–37].

Putative biological mechanisms underlying the association of NAFLD with T2D and the progression of liver disease in those with T2D

From NAFLD to T2D

Although a consistent line of research has highlighted the key role played by the liver in the development of T2D, in addressing this topic one should never neglect that what we are dealing about is a complex, systemic picture of integrated organ pathology. This involves not only the liver, but also the immune system, brown and white adipose tissue, skeletal and cardiac muscle, vascular system, gut, pancreas and brain [38]. Ertung and Hotamisligil have recently pointed out that an integrated set of responses is available to cells to cope with those fluctuations in the availability of nutrients which occur during scarcity and abundance of food as well as during the alternation of fasting and post-prandial states [38]. However, whenever metabolic stress becomes chronic, such as occurs in obesity, these adaptive mechanisms are overwhelmed, lipid influx exceeds the capacity of adipose tissue to store them and harmful lipid species accumulate

Table 3 NAFLD increases the requirements of insulin in diabetics

Author [Ref.]	Method	Findings
Ryysy [35]	20 stable T2D patients on combination therapy (insulin + metformin). LFC assessed with proton spectroscopy	LFC is associated with insulin requirements during insulin therapy in T2D patients
Cusi & Sanyal [36]	204 T1D 197 T2D Insulin-naive 188 T2D previously IT LFC assessed with MRI	T1D and T2D patients with NAFLD require more intense diabetes treatment to achieve similar glycemic control
Patel [37]	230 patients, submitted to liver stiffness measurements and simultaneous CAP	Patients with higher CAP scores were more likely to have HBA1c ≥ 7 and requirement for insulin

CAP controlled attenuation parameter, *HBA1c* glycated haemoglobin, *IT* insulin treated, *LFC* liver fat content, *MRI* magnetic resonance imaging, *T1D* type 1 diabetes, *T2D* type 2 diabetes

at ectopic sites, i.e. organs, such as the liver and the muscle which are not suited to exert such function [38]. Given that metabolic and immune responses are highly integrated, this storage of harmful lipids can trigger a vicious cycle of immune-metabolic dysregulation. This dysregulation is systemic in nature and its central features are probably incompletely understood as shown, for example, by the finding that insulin resistance (IR) in the central nervous system is closely connected with altered eating habits [38] which, via hyperphagia and ensuing obesity, may undoubtedly participate in the pathogenesis of at least a fraction of cases of both T2D and NAFLD. Keeping in mind that IR and lipotoxicity are systemic disorders, studies have recently emphasized the key role of the liver which is at the crossroad of gut dysbiosis with an expanded and dysfunctional adipose tissue which are deemed to be the root causes of NAFLD. Once it is developed, NAFLD will promote hepatic IR which, whenever coupled with functional/anatomical damage of pancreatic β-cells will eventually conduce to the development of overt T2D [39]. No doubts that the normal liver, which is virtually devoid of fatty changes, is a key requirement for effective transmission of insulin signaling and that, conversely, fatty liver will hamper such insulin signaling thus promoting IR [40]. Studies have highlighted the molecular mechanism underlying hepatic IR occurring in NAFLD by identifying diacylglycerol (DAG) of the hepatocyte membrane as the lipidomic signature associated with hepatic IR. Indeed DAG interacting with Protein Kinase epsilon (PKε) will activate this kinase and promote the phosphorylation of a residue of threonine at position 1160 of insulin receptor which will, in its turn, result in a decreased functional activity of this receptor and, finally, into an impaired intracellular transmission of insulin signalling [41]. Based on this notion, what we expect is that, by inhibiting Acetyl-CoA Carboxylase, a key enzyme in the synthesis of fatty acids we might obtain a reversal of macro- and microscopic steatosis, a reduction in the content of hepatocyte membrane DAG, a reduction in Pkε and an improved insulin sensitivity as assessed with clamp technique. Goedeke et al. showed that all these predictions are indeed fully confirmed in a rat model [42]. However, DAG is not the unique class of lipids which are implicated in the development of IR and also ceramides play a role [43]. Recently, Abderrahmani et al. using DNA methylome and transcriptome analyses of livers from obese individuals, found that both hypomethylation at a CpG site in platelet-derived growth factor A gene (*PDGFA*), (encoding platelet derived growth factor alpha) and *PDGFA* overexpression were associated with increased T2D risk [44]. These findings suggest that, in the liver of obese patients with T2D, the increased PDGF-A signaling contributes to IR, and open new therapeutic avenues against T2D and possibly NAFLD [44]. Interestingly, a large set of liver secreted soluble mediators (hepatokines) such as Adropin, ANGPTL4, Fetuin A, Fetuin B, FGF21, Hepassocin, LECT2, RBP4, Selenoprotein P link steatosis with impaired metabolic control [45]. Among these, Fetuin-B, which causes glucose intolerance and is increased in patients with T2DM and NAFLD with fibrosis is one of the most promising [45].

Finally, long noncoding RNAs (lncRNAs) are a large number in human genome and dysregulated expression of lncRNA has been specifically implicated in the pathogenesis of beta-cell dysfunction, hepatic glucose and lipid metabolism, and thus their characterization promises to shed light on the pathogenesis of T2D [46].

Impact of T2D on the pathogenesis of NASH and its liver-related complications

T2D may affect the development of NASH and progressive liver disease by acting at different levels of the pathogenic cascade involving gut microbiota and expanded, inflamed, dysfunctional adipose tissue [1]. For example, changes in the composition of intestinal microbiome are deemed to play a role of pathophysiological significance in T2D [47]. Consistently, the gut microbiome has been regarded as a potential target for preventing and treating hyperglycemia in T2D [48].

Epidemiological evidence supports the notion that subclinical inflammation is strongly associated with IR and predicts incident T2D. Obesity activates inflammation via the IKKβ/NFκB pathway and, consistently, the inhibition of this pathway via either genetic or pharmacological manipulation will result into an improvement of obesity-induced IR [49] and the glycemic control of T2D patients, along with concomitant inhibition of NFκB activity in their peripheral blood mononuclear cells (PBMCs) [50]. Collectively, these studies strongly support the notion that obesity-induced inflammation in the adipose tissue plays an important role in the development of IR and T2D [51, 52].

As a result of these physiopathological derangements, the "diabetic liver" will undergo a double attack via both portal and systemic route and will react to such an aggression by activating *de novo* lipogenesis, Toll-like receptors and M1-polarized macrophages (i.e. the proinflammatory macrophage phenotype) which secrete pro-inflammatory cytokines such as TNF-α, IL-6, IL-12. Steatosis will ensue, with an inherent trend to developing into steatohepatitis owing to the concurrent activation of the pro-inflammatory-profibrogenic cascade associated with oxidative stress [1]. A recent study contributed to highlighting the role of key molecules, such as Lysil Oxidase 2 (LOXL2) in the fibrogenic process of NAFLD in those with T2D [53]. LOXL2 is one of a family of enzymes which play a key role in the cross-linking of collagen in the extracellular matrix such as shown by the finding that by blocking LOXL2 with monoclonal

antibodies prevented liver fibrosis deposition, a therapeutic approach which has been under clinical investigation in chronic liver diseases [54, 55].

Although NAFLD-HCC may develop also on the background of non-cirrhotic livers, fibrosis is a definite risk factor for the development of HCC. Studies have shown that each HCC has about four to six driver mutations, i.e. functional mutations which target the key signalling pathway which are along the hepatic carcinogenetic cascade such as telomere maintenance, p53 and cell cycle gene, oxidative stress pathway, Wnt/β catenin pathway, Map kinase and mTor pathway [56]. Some of these pathways are specifically involved in NAFLD-HCC.

Principles of treatment

Treating NAFLD to prevent T2D: How can IR be pharmacologically contrasted in NAFLD?

Other than lifestyle changes, there is no universally accepted drug treatment to contrast IR in those with NAFLD aimed at preventing T2D. Although T2D is characterized by systemic IR, hepatic IR recapitulates many aspects of T2D such as enhanced production of endogenous glucose [57]. Based on the molecular targets previously described in the present review, several molecular targets may be aimed at to pursue this end. They include DAG and ceramides, hepatokines, protein kinases and platelet-derived growth factor A (PDGFA).

DAG—further to physical exercise, DAG was inhibited by Metformin in rats with high-fat diet induced IR [58, 59]. Smith et al. reported that Met (500 mg/kg), with treadmill exercise, or with both exercise and Met interventions for 8 weeks were equally effective in significantly blunting hyperglycemia in rats fed a high fat diet with (48 kcal %fat) [60]. These Authors concluded that the reduction of skeletal muscle FAT/CD36 and content of ceramide and DAG may be important mechanisms by which exercise training attenuates the progression of diet-induced IR in skeletal muscle [60]. Zabielski et al. reported that Metformin improved systemic IR and augmented the hepatic insulin signaling cascade. It reduced both the concentration and fractional synthesis rate of signaling lipids of Ceramide, DAG, and increased acylcarnitine content and the expression of mitochondrial markers [61]. This study postulates, that in the liver, the insulin sensitizing effect of metformin depends on augmentation of mitochondrial β-oxidation, which protects from hepatic accumulation of both the Ceramide and DAG and, in high-fat diet fed rats, preserves insulin sensitivity.

Hepatokines—multiple hepatokines have been associated with the development of hepatic IR [45]. Therefore, it is fully conceivable that blockade of one of such liver-secreted signaling proteins may increase insulin sensitivity so contributing to halt the progression from NAFLD to T2D. A pioneering study targeting a hepatokine to reduce hepatic IR was published by Meex et al. [58]. These Authors showed that the secreted factors from steatotic hepatocytes induce pro-inflammatory signaling and IR in vitro. Targeted analysis showed that fetuin B was increased in humans with liver steatosis and T2D patients. Fetuin B impaired caused glucose intolerance in mice via hepatic IR and, consistently obese mice submitted to silencing of fetuin B exhibited an improved glucose tolerance. Therefore, they concluded that preventing NAFLD may limit the development of T2D [58]. Clearly, Fetuin-B is not the only hepatokine responsible for hepatic IR. For example, Tao et al. recently reported that Knockdown of hepatic Follistatin in the LDKO mouse liver restored glucose tolerance, insulin sensitivity in white adipose tissue and the normal suppression, by insulin, of hepatic glucose production; however, the expression of Follistatin in the liver of healthy LTKO mice had the opposite effect. Knockdown of Follistatin also improved glucose tolerance in high-fat-fed obese mice, and the reduction of serum Follistatin concentration occurred in parallel with the reduction of glycated hemoglobin in obese patients with T2D submitted to gastric bypass bariatric surgery. Although these Authors conclude that Follistatin might be targeted for diabetes therapy in those with hepatic IR [57], it is tempting to speculate that an earlier administration, might in principle, abrogate hepatic IR and thus prevent T2D in NAFLD.

Protein kinases (PK)—activation of PKC-theta is associated with lipid-induced IR and PKC-theta knockout mice are protected from this lipid-induced IR [59]. Haasch et al. demonstrated that PKC-theta has a key role in the development of IR in the muscle and in the liver, and may thus contribute to the development of systemic IR and T2D [59]. Incidentally, inhibition of the PKC pathway using calphostin C and GF109203X suppressed TNFα-induced ICAM-1 expression in human aortic endothelial cells suggesting that this strategy may beneficially influence the atherogenic process inherent in a state of IR [62].

A recent study, which specifically evaluated the role of lncRNA suppressor of hepatic gluconeogenesis and lipogenesis (lncSHGL), concluded that activating the lncSHGL/heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) hnRNPA1 axis represents a potential strategy for the treatment of both T2D and NAFLD [46].

Platelet-derived growth factor A (PDGFA)—the potential role of inhibition of PDGFA to contrast IR in NAFLD is totally unexplored. Interestingly, Gonzalo et al. [63] used specific delivery of a PDGF kinase inhibitor (PAP19-M6PHSA) to hepatic stellate cells and found that this approach was a promising technology. This study opens the way for a largely unexplored research area and pinpoints the

Table 4 Effects of various antidiabetic medications on NAFLD

Drug [Ref.]	Sites of action	Effect on body weight	Molecular mechanism of action	Effects on liver histology	Effects on cardio-metabolic outcomes	Overall assessment
Biguanides (Metformin) [24, 66, 67, 69, 70]	Liver, skeletal muscle, intestine	Neutral to body weight-reduced body weight	Insulin sensitizer; blocks hepatic glucose production; affects energy homeostasis by Inducing the activation of the cell energy-sensor AMPK; alleviates hepatic steatosis through SIRT1-mediated effects on autophagy	Limited and controversial information regarding a possible benefit on steatosis and lobular inflammation. No significant improvement in liver fibrosis Reduces HCC risk in a dose–response manner	Cardiovascular beneficial effect	First-line monotherapy drug option for newly diagnosed IGT/T2D in individuals with overweight/PCOS; also recommended in combined treatment when monotherapy is no longer effective. Potential relevance to CVD and cancer. Histological efficacy on NAFLD unproven. Does not cause hypoglycemia. Lack of weight gain and usually good tolerance (aside from occasional GI side-effects and increased risk of lactic acidosis in patients with severe CKD, particularly when iodinated contrast is administered)
PPAR—agonists (pioglitazone, elafibranor, fibrates and sarogl-itazar) [24, 66, 67, 69, 70]	Liver, adipose tissue, muscle	Increase peripheral fat stores resulting in significant weight gain	TZDs are PPAR-γ ligands, a nuclear transcription receptor activated by FAs Which modulates glucolipidic metabolism, inflammation and atherogenesis Elafibranor (GFT505) is an unlicensed dual agonist of the PPAR α and δ receptors	Pioglitazone improves steatosis, inflammation and ballooning without any significant change in liver fibrosis (potential positive role of long-term therapy in one study) Elafibranor clears NASH without worsening fibrosis A phase III trial is now evaluating the ability of elafibranor in clearing without worsening fibrosis (NCT02704403)	For pioglitazone meta-analytic evidence of cardiovascular benefit is available. It reduces mortality and CVE from 5.7 to 4.4% in T2D patients with after a 1 year course	Pioglitazone has shown significant histological benefit in a number of trials. EASL and AASLD guidelines currently recommend pioglitazone for NASH, albeit with careful consideration of the potential long-term risks especially weight gain, risk of cardiac decompensation and bladder cancer and, in women, bone fractures

Table 4 (continued)

Drug [Ref.]	Sites of action	Effect on body weight	Molecular mechanism of action	Effects on liver histology	Effects on cardio-metabolic outcomes	Overall assessment
GLP-1RA (exenatide, liraglutide, exenatide extended-release, albiglutide, lixisenatide) [66, 67, 69, 70]	GLP-1r is expressed in various organs, including the liver	Weight loss	GLP-1 is a naturally occurring incretin secreted by the enteroendocrine L-cells. It stimulates insulin secretion; inhibits glucagon secretion, promotes satiety via delayed gastric emptying GLP-1RA reproduce all the above listed biological effects through direct agonism of GLP-1 receptors	The LEAN trial (Liraglutide sc 1.8 mg/day vs placebo) showed a significant improvement in steatosis and ballooning and controversial data on fibrosis	Compared to placebo, liraglutide reduces the mortality rate owing to CV causes, nonfatal myocardial infarction, or nonfatal stroke among T2D patients	It remains uncertain whether liraglutade is effective irrespective of weight loss (in LEAN trial histological responders lost on average 2.1 kg more than nonresponders) Risk of retinopathy. Gastrointestinal side effects are common, and are the primary reason for discontinuing treatment. Further study with longer follow-up and larger study groups is awaited
DPP-4 inhibitors sitagliptin, saxagliptin linagliptin, alogliptin [66, 67, 69, 70]	Intestine, pancreas, liver	Modest weight loss	DPP-4 is an enzyme which inactivates GLP-1. Therefore, inhibition of DDP-4 will eventually result in a more prolonged GLP-1 activity and namely the same biological effects described above for GLP-1 agonism	Sitagliptin, an orally administered DPP-4 inhibit, did not show histological benefit in a controlled trial of NASH. However, limited data do not allow a firm conclusion	DPP4 inhibitors do not reduce CV deaths, non-fatal MI and non-fatal stroke	Pancreatic toxicity (pancreatitis and cancer) and a number of skin- and immune-related adverse effect have alerted regarding the safety of DPP-4 inhibitors. Moreover, there is no definite evidence supporting the use of DPP-4 inhibitors in treating NASH
SGLT2 inhibitors (Dapagliflozin, canagliflozin, empagliflozin) [66, 67, 69]	Renal proximal tubules	Weight loss	SGLT2 reabsorbs 90% of glucose filtered at the renal glomeruli; its inhibition will thus result in glycosuria	Lack of data regarding liver histology in human NAFLD (improvement of steatosis and fibrosis in animal models) Empagliflozin reduces liver fat assessed using MRI-PDFF	A meta-analysis has shown that the use of empagliflozin (but not all SGLT2 inhibitors) improved all-cause and CV mortality	There are no studies proving efficacy on histological outcome in human NASH Safety concerns regard the presence of urinary glucose being associated with increased risk of mild genital mycotic infections and potentially serious UTIs for all SGLT2 inhibitors Canagliflozin use has been associated with increased incidence of bone fractures

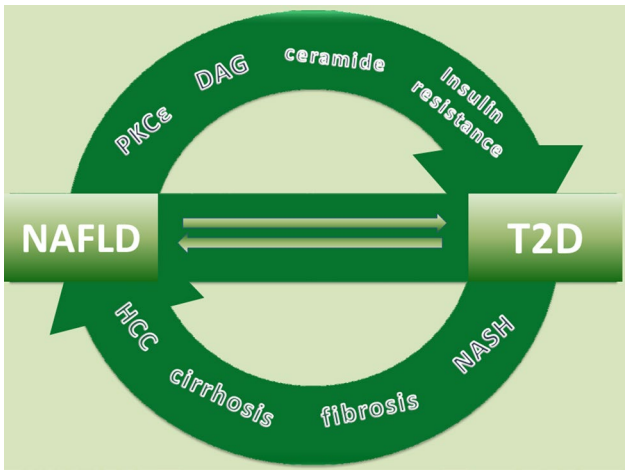

Fig. 1 Implications of the association of NAFLD with type 2 diabetes. This graphical abstract schematically illustrates the "round trip" leading from NAFLD to T2D via increased IR. T2D and NAFLD form a dangerous combination owing to the risk of progression to fibro- cirrhotic liver disease and primary liver cancer. In addition, individuals with NAFLD have a worse metabolic control of their T2D

commonalities between the pathogenic mechanisms of IR and fibrogenesis.

Drug treatment of NASH associated with diabetes

The benefits of significant weight loss for both NAFLD and T2D cannot be overemphasized given that this would potentially result in improved hepatic fibrosis and diabetes reversal. Lifestyle intervention (diet associated with physical activity/exercise) is the first-line approach to be universally implemented in all those individuals featuring concurrent T2D and NAFLD unless specifically contra-indicated by other conditions. To this end, low-carbohydrate low-fat hypocaloric regimens should be advised, ideally based on the Mediterranean paradigm: intake of certain nutrients (i.e, saturated and trans fatty acids, carbohydrates, and animal-derived proteins) should thus be curtailed whereas other nutrients (e.g., polyunsaturated fatty acids, monounsaturated fatty acids, vegetal proteins, antioxidants) should be more liberally consumed [64]. In humans, exercising 10 min for at least 5 times a week is associated with a significant improvement in NAFLD [65] and, in parallel, reduced sedentariety and improved cardiorespiratory fitness contribute to the primary prevention of cardiovascular events in T2D patients.

Lifestyle changes and substantial weight loss maintained over time, however, cannot be easily accomplished in most cases, supporting the use of drugs to treat diabetes in patients with NAFLD.

The ideal antidiabetic drug should be cheap, free of side effects, to able to reduce body weight, normalize HbA1c and atherogenic dyslipidemia so decreasing major cardiovascular

Table 4 (continued)

AMPK AMP-activated protein kinase, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *CVE* cardiovascular events, *DPP-4* dipeptidyl peptidase-4, *GLP-1RA* glucagon like peptide-1 receptor agonists, *HCC* hepatocellular carcinoma, *IGT* impaired glucose tolerance, *MI* myocardial infarction, *MRI-PDFF* Magnetic Resonance Imaging-derived proton density fat fraction, *NASH* nonalcoholic steatohepatitis, *PCOS* Polycystic ovary syndrome, *PPAR-γ* Peroxisome proliferator-activated receptors-γ, *Sc* subcutaneous, *SGLT2* sodium glucose co-transporter 2, *SIRT-1* sirtuin-1, *T2D* type 2 diabetes, *TZD* thiazolidinediones, *UTIs* urinary tract infections

events and improving life expectancy. Moreover, it should also prevent/slow/arrest the progression toward chronic/end-stage kidney failure and, specifically, improve hepatic histology thus preventing/slowing/arresting the progression of fibrosing NAFLD toward cirrhosis, end-stage liver failure, HCC and liver transplantation. None of the currently available anti-diabetic drugs conforms to this ideal profile.

Antidiabetic drugs exert their glucose-lowering effect by targeting all the organs which are physiologically involved in all the steps of glucose metabolism from (intestinal) absorption to (muscular and hepatic) utilization to (pancreatic and renal) disposal [66].

Table 4 summarizes the principal biological and clinical features for each class of anti-diabetic medications [24, 66–69]. It is widely accepted that any treatment of decompensated T2D may potentially benefit those patients with NASH [67]. However, analysis of findings reported in Table 1 interestingly reveals that not all classes of antidiabetic agents have proven effective in improving liver histology in NASH. Moreover, certain antidiabetic agents, such as insulin or insulin secretagogues increase body weight, steatosis and the risk of HCC. Collectively, data suggest that individuals with concurrent T2D and NASH are a population exposed at a very high cardio-metabolic and hepatic risk. In this specific population, antidiabetic agents per se are not invariably effective or may even turn deleterious supporting the notion that, despite insulin resistance is an early trigger of NASH, treating insulin resistance will not necessarily inhibit NASH progression [68]. Consistently, other classes of drugs (e.g. obeticolic acid, statins, Vitamin E, antioxidants, probiotics, etc.) may potentially prove more useful in diabetic NASH despite that they do not directly target glucose disposal.

Conclusions

Some take-home messages should be highlighted (Fig. 1). First, T2D and NAFLD are mutually, closely and bi-directionally associated. Second, regression of NAFLD will result in a reduced risk of incident T2D. Third the NAFLD-T2D association increases the risk of progression of NAFLD (fibrosis, NAFLD-cirrhosis and NAFLD-HCC); and worsens metabolic compensation of T2D. Finally, an improved understanding of molecular pathogenesis underlying the bi-directional association promises to attain the prevention of T2D by halting the progression of NAFLD.

Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to disclose.

Human and animal rights statement This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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