From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options

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Summary
The worldwide prevalence of non-alcoholic fatty liver disease (NAFLD) is estimated to have reached 25% or more in adults. NAFLD is prevalent in obese individuals, but may also affect non-obese insulin-resistant individuals. NAFLD is associated with a 2- to 3-fold increased risk of developing type 2 diabetes (T2D), which may be higher in patients with more severe liver disease – fibrosis increases this risk. In NAFLD, not only the close association with obesity, but also the impairment of many metabolic pathways, including decreased hepatic insulin sensitivity and insulin secretion, increase the risk of developing T2D and related comorbidities. Conversely, patients with diabetes have a higher prevalence of steatohepatitis, liver fibrosis and end-stage liver disease. Genetics and mechanisms involving dysfunctional adipose tissue, lipotoxicity and gluco-toxicity appear to play a role. In this review, we discuss the altered pathophysiological mechanisms that underlie the development of T2D in NAFLD and vice versa. Although there is no approved therapy for the treatment of NASH, we discuss pharmacological agents currently available to treat T2D that could potentially be useful for the management of NASH.

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Introduction
The estimated prevalence of non-alcoholic fatty liver disease (NAFLD) has now reached an average of 25%, ranging from 13% in Africa to over 30% in South America.1 It is of no surprise that NAFLD prevalence is very similar to that of obesity, since increased caloric intake (mainly from fat), sedentary lifestyle and consequent development of obesity are major risk factors for the development of NAFLD. Several studies have now shown that individuals with NAFLD/non-alcoholic steatohepatitis (NASH) are at a higher risk of developing type 2 diabetes (T2D).2,3 A recent meta-analysis, including 296,439 individuals (30% with NAFLD) and nearly 16,000 cases of incident diabetes over a median of 5 years from 19 observational studies, has shown that the risk of incident diabetes is more than 2-fold higher in individuals with NAFLD.4

The pathophysiological mechanisms underlying the development of NAFLD are mainly the alterations in glucose and lipid metabolism, insulin resistance (IR) and insulin secretion, explaining the close association between NAFLD and T2D. Moreover, both patients with NAFLD and T2D often share the comorbidities associated with the metabolic syndrome, namely fasting hyperglycaemia, hypertension, hypertriglyceridaemia, low high-density lipoprotein-cholesterol and/or abdominal fat accumulation.5,6

From NAFLD/NASH to diabetes
Increased insulin resistance in NAFLD and risk of diabetes
It is well established that individuals with NAFLD are more insulin resistant than those without NAFLD, even if they are lean and without diabetes.7 Both longitudinal and cross-sectional studies have demonstrated that increased IR is the earliest detectable abnormality in both prediabetes and overt T2D.8–10 The pancreas responds to increased IR by secreting more insulin and the liver decreases insulin clearance in order to increase peripheral insulin concentrations and prevent the development of diabetes (Fig. 1) (i.e., below 126 mg/dl after an overnight fast and below 200 mg/dl 2 hours after a glucose load).8,11

In NAFLD, IR is present in muscle, liver and adipose tissue.3,12,13 As a consequence, hepatic glucose production and adipose tissue lipolysis are only in part suppressed by insulin, resulting in higher fasting glucose and free fatty acid (FFA) concentrations,7,12,13 increasing the risk of T2D in these patients. IR can be assessed directly using the euglycaemic-hyperinsulinaemic clamp, which involves infusing insulin at a constant rate and maintaining glycaemia close to the normal fasting concentrations by infusing glucose intravenously. The rate of glucose infusion gives an estimate of peripheral insulin sensitivity.
i.e., the individual is highly sensitive if the glucose infusion rate is high, or IR if the individual is resistant to the insulin action and thus less glucose is taken up by peripheral tissues (largely muscle). Indirectly IR is estimated using the HOMA-IR (homeostatic model assessment for insulin resistance) index (given by the product of fasting insulin x glucose/22.5) or from oral glucose tolerance test (OGTT) indexes like the Matsuda or oral glucose insulin sensitivity indexes.

In an IR state more insulin is required to obtain the same metabolic effects, namely glucose uptake in the muscle, suppression of lipolysis and of hepatic glucose production. IR also affects glucose tolerance, since post OGGT glucose levels depend on the balance between muscle glucose clearance and hepatic glucose flux. To overcome IR, the pancreas is stimulated to secrete more insulin. Thus, as individuals progress from normal (NGT) to impaired glucose tolerance (IGT) (see Table 1 for criteria of diagnosis) they need more insulin to overcome the postprandial glucose concentrations. In response to changes in glucose concentrations, the pancreas is stimulated to secrete more insulin, which allows more insulin to reach the peripheral circulation. However, in a state of IR the workload of pancreatic beta cells is increased, leading to beta-cell dysfunction and a reduction of beta-cell mass over time, a major risk factor for the development of hyperglycaemia and T2D.

Initial studies on the natural history of T2D indicate that hyperglycaemia results from an imbalance between insulin sensitivity and insulin secretion. There is no doubt that the majority of patients with NAFLD are insulin resistant, even if they are non-obese. However, most of individuals with NAFLD/NASH do not develop hyperglycaemia despite displaying higher insulin concentrations. This is because the liver, as it accumulates triglycerides and toxic lipid-derived metabolites, becomes resistant to the effect of insulin and decreases its capacity to clear insulin, thus increasing peripheral insulin concentrations. In response to changes in glucose concentrations, the pancreas is stimulated to secrete more insulin, which allows more insulin to reach the peripheral circulation. However, in a state of IR the workload of pancreatic beta cells is increased, leading to beta-cell dysfunction and a reduction of beta-cell mass over time, a major risk factor for the development of hyperglycaemia and T2D.

**Fig. 1. Natural history of T2D in the context of NAFLD.** T2D results from an imbalance between insulin sensitivity and insulin secretion. In the progression from normal to impaired glucose tolerance to T2D, insulin secretion increases to overcome insulin resistance. At the same time there is a decrease in insulin clearance (mainly hepatic), especially in individuals with NAFLD, that determines higher peripheral insulin concentrations. However, despite high concentrations, insulin secreted is insufficient (beta-cell dysfunction) and therefore there is an increase in both fasting and postprandial glucose concentrations. Subjects become T2D only when the beta cells are unable to increase insulin secretion (beta-cell failure) and overcome peripheral IR. Redrawn from ref. 8,11,13. IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NGT, normal glucose tolerance; T2D, type 2 diabetes.
concentrations, insulin is initially secreted rapidly in a quantity proportional to the rise in glucose concentration (first phase, early minutes) and then as a dose response to plasma glucose concentration (second phase). Since insulin is secreted in the portal vein, the first phase should have a major effect on decreasing hepatic glucose production, while the second phase acts on the periphery, mainly muscle but also adipose tissue.

In the progression from NGT to IGT, the first phase is already reduced, and the total amount of insulin delivered to the periphery is still insufficient to clear glucose, despite high insulin secretion rates and plasma insulin concentrations; this is referred to as impaired beta-cell function. Together with increased IR the impaired beta-cell function explains the high postprandial glucose concentrations. Both ourselves and others have shown that individuals with IGT have lost almost 80% of their beta-cell capacity and about half of their beta-cell mass compared to those with NGT.

Although an impaired pancreatic beta-cell insulin response to a glucose challenge is already present in normal glucose-tolerant patients with NAFLD, they only develop diabetes when pancreatic beta cells are unable to increase insulin secretion to match their severe peripheral IR (Fig. 1).

### Hepatic insulin resistance and risk of type 2 diabetes

Hepatic steatosis is associated with alterations in both lipid and glucose metabolism. The liver is the main site of glucose production during fasting conditions. Glucose is produced from hepatic glycogenolysis (i.e., from hydrolysis of the glycogen stored after a meal) or gluconeogenesis, i.e., synthesised from amino acids, glycerol or lactate (Fig. 2). Endogenous glucose production is tightly regulated by the pancreatic hormones, insulin and glucagon, which maintain glucose concentrations within the normal range. In patients with hepatic steatosis, fasting glucose production, and in particular gluconeogenesis are elevated, despite high insulin levels, leading to fasting and postprandial hyperglycaemia. Glucagon stimulates gluconeogenesis and glycogenolysis, while insulin suppresses hepatic glucose production mainly by suppressing gluconeogenesis. Both individuals with NAFLD have impaired hepatic glucose metabolism.

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**Table 1. Screening for and diagnosis of prediabetes and type 2 diabetes, according to American Diabetes Association guidelines 2018.**

|                      | Fasting plasma glucose* | Glucose tolerance (2-hour PG)* | Haemoglobin A1c§ |
|----------------------|-------------------------|-------------------------------|------------------|
| Normal (NGT†)        | FPG <100 mg/dl (5.6 mmol/L) | 2-hour PG <140 mg/dl (7.8 mmol/L) during 75 g OGTT | <5.7% (39 mmol/mol) |
| Prediabetes (IFG and/or IGT†) | FPG from 100 mg/dl (5.6 mmol/L) to 125 mg/dl (6.9 mmol/L) (IFG) | 2-hour PG from 140 mg/dl (7.8 mmol/L) to 199 mg/dl (11.0 mmol/L) (IGT†) | 5.7 to 6.4% (39–47 mmol/mol) |
| Type 2 diabetes      | FPG ≥126 mg/dl (7.0 mmol/L) | 2-hour PG ≥200 mg/dl (11.1 mmol/L) during OGTT | ≥6.5% (48 mmol/mol) |

*Fasting is defined as no caloric intake for at least 8 h.

†The OGTT should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/L). In the absence of unequivocal hyperglycaemia, results should be confirmed by repeat testing.

Glucose tolerance measured after OGTT: NGT or IGT.

§The test should be performed in a laboratory using a method that is NGSP certified and standardised to the DCCT assay. DCCT, diabetes control and complications trial; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose; WHO, World Health Organization.
and T2D are insulin resistant at the level of the liver, i.e., insulin is unable to properly suppress glucose production.\textsuperscript{17,27} Moreover, they both tend to have increased glucagon concentrations that exacerbate hepatic IR.\textsuperscript{8,28} Patients with either T2D and/or NAFLD have increased gluconeogenesis\textsuperscript{29,30} that contributes to excessive glucose production and hepatic IR. However, increased gluconeogenesis does not seem to be related to the amount of hepatic triglycerides.\textsuperscript{13} Thus, excess gluconeogenesis is probably a consequence rather than a cause of hepatic IR, since increased gluconeogenesis is closely associated with excess gluconeogenic substrates that overload the liver, rather than with increased hepatic fat accumulation.\textsuperscript{13}

In the postprandial state, hepatic glucose production is suppressed by glucose stimulated insulin secretion and the glucose ingested is in part stored as glycogen, and in part oxidised, used to produce pyruvate, lactate and amino acids like alanine (that are also gluconeogenic substrates), but also re-routed to de novo lipogenesis (DNL) and glycerol synthesis (Fig. 2). Excess gluconeogenic substrates (and glucose itself) can also be used to synthesise glycerol de novo, via glycerol-3-phosphate (Fig. 2). This pathway, previously not considered, is indeed accelerated in individuals with NAFLD.\textsuperscript{32} This is very important because glycerol availability is a limiting step for hepatic triglyceride synthesis.

DNL, i.e., the synthesis of fatty acids from acetyl-CoA subunits derived mainly from carbohydrate catabolism, is much higher after a carbohydrate-rich meal (Fig. 2). Carbohydrate-rich meals together with hyperinsulinemia stimulate the activity of lipogenic enzymes in the liver, the production of newly synthesised fatty acids, and very low-density lipoprotein (VLDL) secretion.\textsuperscript{13–35} DNL is driven mainly by fructose, with very little glucose used for DNL (Fig. 2). However, the western diet is rich in fructose and sucrose (composed of 1 glucose and 1 fructose molecule). For this reason, excess sugar consumption is associated with increased DNL, which is exacerbated by a diet high in saturated fat, but not by a diet rich in unsaturated fat.\textsuperscript{36} DNL is increased more than 3-fold in NAFLD\textsuperscript{17–39} and characterised by an increased production of saturated fatty acids (especially palmitate) and a reduction of unsaturated fatty acid.\textsuperscript{38} Increased saturated fatty acids are known to be lipotoxic, not only in liver cells but also in pancreatic beta cells, endothelial cells, skeletal muscle and cardiomyocytes.\textsuperscript{40,41} Palmitate is also a precursor of ceramides and other lipotoxic lipids.\textsuperscript{42} Excess fructose is only in part used for DNL and can also be metabolised as uric acid through the purine cycle (Fig. 2).

DNL is tightly regulated both by hormone signalling and transcription factors, such as sterol response element binding protein 1c (SREBP1c) and carbohydrate response element binding protein (ChREBP), which regulate the expression of the key lipogenic genes acetyl CoA carboxylase (ACC), fatty acid synthase (FAS) and ATP-citrate lyase (ACL).\textsuperscript{43,44} Insulin also promotes lipogenesis and adiposity. However, ectopic fat accumulates only when fatty acid oxidation is impaired, and subcutaneous adipose tissue becomes insulin resistant and unable to store excess fat and glucose, typically from excess rates of adipose tissue lipolysis.\textsuperscript{7,45–47} This has also been supported by genetic studies.\textsuperscript{48,49} Individuals with NAFLD tend to accumulate ectopic fat not only in the liver and skeletal muscle, but also in the pancreas, likely contributing to beta-cell dysfunction. A recent study showed that the loss of hepatic and pancreatic fat was associated with improved control of hyperglycaemia and of beta-cell function in patients with T2D.\textsuperscript{50}

However, the progression from NAFLD to NASH with liver injury, i.e., fibrosis, cirrhosis and hepatocellular carcinoma, is strongly associated with metabolic changes in both glucose and lipid metabolism. A recent study has shown that decreased glucose tolerance is most closely associated with the presence and severity of liver fibrosis rather than the degree of steatosis or presence of obesity.\textsuperscript{15}

**From diabetes to NAFLD/NASH**

**Role of dysfunctional adipose tissue and lipotoxicity**

Increased adiposity, as often found in NAFLD and T2D, is associated with adipocyte IR and dysfunction.\textsuperscript{7,13,51} This results in excess FFA release into the blood stream and predisposes to lipotoxicity, i.e. when FFA overflow from adipose tissue leads to excess lipid uptake by tissues such as the liver, pancreas or muscle (Fig. 3). FFAs, both from unsuppressed lipolysis and increased DNL in hepatocytes, can either be oxidised through mitochondrial beta oxidation, or re-esterified to triglycerides that are either secreted as VLDL, used to synthesise other toxic lipid metabolites or stored as ectopic fat. Lipotoxicity is associated with increased peripheral IR,\textsuperscript{27,52} hepatic glucose production and gluconeogenesis leading to hyperglycaemia,\textsuperscript{13,27} as well as pancreatic beta-cell dysfunction with impaired insulin secretion.\textsuperscript{23,54}

Overflow of fatty acids to the liver has also been associated with increased cellular levels of toxic lipids such as diacylglycerols, ceramides (Fig. 2), and long-chain fatty acyl-coenzyme A (CoA), which are involved in inflammatory pathways\textsuperscript{17,27,55–59} (Fig. 4). Excess FFAs also promote mitochondrial dysfunction, an increase in oxidative stress and uncouple oxidative phosphorylation. They also activate a fibrogenic response in hepatic stellate cells that can promote the progression to NASH and cirrhosis,\textsuperscript{60–62} and the production of reactive oxygen species\textsuperscript{63} (Figs. 3 and 4). Adipose tissue dysfunction and IR lead to the increased release of pro-
inflammatory cytokines (e.g., MCP-1, TNF-α, TGF-β, PAI-1, IL-6) and reduced release of anti-inflammatory adipokines (e.g., adiponectin) by adipose tissue64 (Fig. 3). These molecules can directly damage the liver, or act indirectly, by increasing oxidative stress, hepatocellular damage, liver fibrosis and tumour development, e.g., through the activation of the oncogenic factor STAT3.61,65 Ceramides, diacylglycerols and saturated fatty acids not only trigger inflammation but also apoptosis.27,31,59 They also alter insulin signalling and action,27,52 decrease muscle ATP synthesis66 and nitric oxide production (as well as endothelial nitric oxide synthase or eNOS),67 impair insulin-stimulated activation of phosphoinositol-3 kinase (PI3K), pyruvate dehydrogenase kinase, isozyme 1, and RAC-alpha

Inflammatory cytokines:
- MCP-1
- TNF-α
- TGF-β
- IL-6
- Leptin

Anti-inflammatory adipokines:
- Adiponectin
- IL-1

Insulin resistance in liver and muscle:
- Activation of pro-inflammatory pathways
- Impaired insulin secretion

Lipotoxicity:
- Lipolysis
- FFA
- Lipid accumulation
- Triglyceride accumulation

Glucotoxicity:
- Hyperlipidaemia
- Hyperglycaemia
- Reactive oxygen species (ROS)
- Mitochondrial dysfunction

Fig. 3. Relationship between adipose tissue insulin resistance and dysfunction and insulin resistance in liver and muscle. Dysfunctional adipose tissue displays resistance to the antilipolytic effect of insulin with increased lipolysis and release of FFAs and glycerol that in turn are responsible for triglyceride accumulation and lipotoxicity in the liver, muscle and pancreas, impairing insulin secretion. Moreover, dysfunctional adipose tissue releases adipokines that activate pro-inflammatory pathways in these organs. FFAs, free fatty acids.

Fig. 4. Relationship between lipotoxicity, glucotoxicity, insulin resistance and beta-cell function. Both lipotoxicity and glucotoxicity contribute to insulin resistance, ectopic fat accumulation and beta-cell dysfunction and vice versa. In NAFLD, lipotoxicity and insulin resistance have been recognised as pathophysiological mechanisms responsible of development and progression to a more severe form of this disease. T2D is a chronic condition of glucotoxicity, although also lipotoxicity is often present and are responsible not only of insulin resistance but also of impaired insulin secretion. DNL, diacylglycerol; DNL, de novo lipogenesis; NAFLD, non-alcoholic fatty liver disease; ROS, reactive oxygen species; T2D, type 2 diabetes.
serine/threonine-protein kinase (also known as proto-oncogene c-Akt).67

Adipose tissue IR can be estimated simply by calculating the Adipo-IR index, as the product of fasting plasma insulin x fasting plasma FFA. Adipo-IR is a reliable marker of dysfunctional adipose tissue and is increased in NAFLD13,17,68–70 and in T2D.13

Role of glucotoxicity in promoting NASH and disease progression

Glucotoxicity is defined as chronically elevated glucose concentrations causing glucose-induced IR, cellular dysfunction and a cycle of progressive metabolic deterioration. T2D is a chronic condition of glucotoxicity, although lipotoxicity is also often present (Fig. 4). Glucotoxicity in T2D often develops from either excess glucose production or an excess consumption of carbohydrates and sugars in the presence of decreased glucose clearance. In particular, fructose and sucrose are considered particularly lipotoxic to hepatocyte function since they have been shown to stimulate DNL and ectopic fat accumulation. However, glucotoxicity might be particularly important in individuals with IGT, where the risk of progression from IGT to diabetes is closely related to the 2-hour plasma glucose test, HbA1c and adipose tissue IR.71

Glucotoxicity and lipotoxicity are closely interrelated and both contribute to worsening IR and impaired insulin secretion72 (Fig. 4). DNL is increased in the presence of hyperglycaemia and/or as a consequence of excess carbohydrate intake, and can favour the synthesis of palmitate.76 Chronically elevated plasma glucose concentrations promote DNL through 2 distinct mechanisms: 1) directly, by increasing TCA cycle activity and synthesis of Acyl CoA that acts as a substrate of both gluconeogenesis and DNL; and 2) indirectly, by activating the expression of ChREBP and liver X receptor α (LXRα) which in turn promote gene transcription of ACL, FAS and SCD-1.73 Glucotoxicity also stimulates the activation of ChREBP in the pancreas, kidney, and skeletal muscle, and exacerbates lipotoxicity, impairing insulin secretion (pancreas) and worsening IR in these tissues. On the other hand, ChREBP expression is decreased in adipocytes, which may exacerbate the state of IR by affecting the release of specific adipokines and lipid species.73 Chronically elevated concentrations of plasma glucose lead to functional and structural damage in beta cells, promoting oxidative stress and production of reactive oxygen species,74 cytoplasmic DNA fragmentation, alteration of mitochondrial morphology and activation of pro-apoptotic pathways.75

Genetics: links to NAFLD in diabetes

Genetic studies also support the hypothesis that IR promotes lipogenesis and adiposity.48,49 Using integrative genomic approaches, these authors have identified a cluster of genes associated with IR, of which the most important is PPARG, which is also associated with the reduced capacity of subcutaneous adipose tissue to expand, resulting in ectopic fat accumulation, NAFLD and a higher visceral-to-subcutaneous adipose tissue ratio.

However, not all individuals with NAFLD are equally resistant to insulin and it is now established that NAFLD has a dual “genetic” and “metabolic” origin. Individuals with mutations in PNPLA3, TM6SF2, MBOAT7, DGAT, or hypo-betalipoproteinaemia, are at an increased risk of NASH and severe liver disease.2 They are usually overweight or obese and IR, but compared to individuals without NAFLD with similar anthropometric characteristics they have similar IR in muscle and/or liver.17,76–78 Moreover, patients with PNPLA3-148MM mutations showed a better response to a 6-day hypocaloric low-carbohydrate diet, with a greater decrease in liver fat content and better improvement in insulin sensitivity.79 Thus, it is still unclear why patients with “genetic NAFLD” accumulate hepatic fat. Different factors appear to act as the primary drivers, although obesity further increases the risk of NASH associated with PNPLA3, TM6SF2 and GCKR genotype.80

Other genes have been associated with an increased risk of developing NAFLD/NASH (reviewed in76). They include genes associated with glucose metabolism and IR, as well as insulin secretion (i.e., ENPP1; IRS1; KLF6; GCKR; SLC2A1; TCF7L2; PPARG), hepatic lipid metabolism (synthesis: DGAT2, SLC25A13; export and oxidation: PNT1A, CD14; TNF; IL6; ADIPOQ, ADIPOR1, ADIPOR2, STAT3). However, only a few of the aforementioned genetic polymorphisms are associated with an increased risk of T2D.81 The most important is probably transcription factor 7-like 2 (TCF7L2), which increases the risk of both T2D82,83 and of NAFLD.84 The risk T allele is associated with beta-cell dysfunction due to both impaired insulin secretion and the incretin response, as well as increased hepatic glucose production.81

Also, genes involved in lipid metabolism are associated with an increased risk of both T2D and NAFLD. Reported polymorphisms include SREBP-2 (involved in cholesterol metabolism), SREBF-2 (regulator of uptake and fatty acid biosynthesis),85 and ADIPOQ that modulates fatty acid oxidation and glucose metabolism.86,87 Genes controlling apolipoprotein B (APOB), apolipoprotein C-III (APOC3), and microsomal triglyceride transfer protein (MTTP) have also been associated with NAFLD.76 APOB and APOC3 are important since they are involved in the mobilisation of hepatic fat through the secretion of VLDL and thus have an impact on fasting plasma concentration of triglycerides. The association between APOC3 and NAFLD
has been shown by some but not confirmed by others, indicating that it is probably not specific for NAFLD but only for increased VLDL secretion. The MTP gene has been implicated in lipoprotein synthesis and secretion by the liver. The polymorphism 493 G/T is associated with liver steatosis and low plasma concentrations of total and low-density lipoprotein-cholesterol (LDL-c), probably because of reduced VLDL secretion.76

TM6SF2 has been linked to the secretion of VLDL, with some polymorphisms resulting in hepatic fat accumulation (but lower circulating atherogenic lipids) and hepatic fibrosis progression.88 Dongiovanni et al.89 confirmed the severity of histological damage associated with the TM6SF2 E167K variant and also showed that TM6SF2 E167K is associated with a lower prevalence of carotid plaques in histologically confirmed NAFLD and reduced cardiovascular events in the SOS study, indicating that mutations in the TM6SF2 gene are a risk factor for NAFLD but at the same time might reduce the risk of cardiovascular disease (CVD). The GCKR (glucokinase regulator) gene regulates the enzyme glucokinase, responsible both for hepatic and pancreatic glucose metabolism. The polymorphism rs780094 is associated with a higher incidence of both NAFLD and diabetes,76,90 while the polymorphism rs1260326-P446L protects against T2D despite high circulating triglyceride levels.76,91 Other genes like KLF6 are also implicated in the regulation of glucokinase as we have shown.92

Pharmacological treatment: Management of NASH with existing T2D medications
Lifestyle is the cornerstone of treatment for patients with obesity, T2D, and NAFLD. Many trials have reported a decrease in the rate of onset of T2D with lifestyle modification in patients with IGT. Patients with obesity, T2D, and/or NAFLD have an increased cardiovascular risk. However, a reduction in CVD in long-term lifestyle intervention trials, where weight loss was overall rather modest (≤5%), has proven difficult to demonstrate in patients with prediabetes.93-95 Cardiovascular risk reduction has been reported in bariatric surgery studies where there is a sustained and significant reduction in body weight (≥20%).96

Glucagon-like peptide-1 receptor agonists for the treatment of NAFLD
After metformin, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become the second-line therapy for patients with T2D (along with SGLT inhibitors) because they help restore normoglycemia as well as ameliorate the risk of CVD or chronic kidney disease.97 Their modified chemical structure, compared to native GLP-1, makes them more resistant to enzymatic degradation by DPP-4, allowing for a prolonged duration of action. Exenatide and lixisenatide are examples of rather short-acting GLP-1RAs, while longer-acting formulations include liraglutide and weekly formulations of exenatide, albiglutide, dulaglutide and semaglutide. They promote satiety and weight loss through direct effects on the central nervous system. They also reverse abnormal insulin and glucagon secretion in T2D. They also have a myriad of other beneficial metabolic effects,98,99 many relevant to the pathophysiology of NAFLD. In vitro and in vivo studies have suggested that GLP-1RAs induce hepatic gene expression of pathways that improve autophagy/endoplasmic reticulum stress, macrophage recruitment, and enhance mitochondrial function and hepatocyte fatty acid oxidation, resulting in a decrease in steatosis and inflammation.100-107 However, their mechanism of action in humans is less clear. GLP-1RAs induce weight loss,108 although there are clear differences in their potency, with minimal weight loss with albiglutide in contrast to the significant weight loss of about 10% observed with semaglutide.109,110

While earlier studies suggested that GLP-1RAs could directly improve hepatic glucose/lipid metabolism and decrease steatosis through GLP-1 signalling,111,112 this has not been confirmed in more recent studies.102,113 It has been postulated that the hepatic effects of GLP-1 and GLP-1RAs are mediated mainly by indirect pathways, such as modulation of insulin and glucagon levels, or amelioration of IR by changes in body weight or other mechanisms. However, this does not fully explain how the infusion of GLP-1 results in a decrease in hepatic glucose production when insulin and glucagon secretion are clamped at basal levels using somatostatin and hormone replacement.114,115 The hepatic effect of a short-acting GLP-1RA, like exenatide, is acute and observable from the first dose.116 Exenatide acutely diminishes hepatic IR by decreasing hepatic glucose production and increasing hepatic glucose uptake during an OGTT, independent of glucagon.116 A recent study in an animal model of NASH reported that exenatide reversed lipotoxicity and mitochondrial dysfunction, but given mild weight loss, it is difficult to establish the relative role of direct vs. indirect hepatic effects.117 Amelioration of hepatic IR after GLP-1RA treatment has been shown not only in individuals with T2D,118 but also in those with NASH119 or with morbid obesity.120 GLP-1RA therapy has also resulted in a reduction in the risk of CVD and chronic kidney disease. However, the mechanisms are still unclear121 and likely complex given that GLP-1 receptors are widely distributed across many tissues.102,113 However, their metabolic and cardiovascular benefit is likely to go beyond that of weight loss alone, as albiglutide (a GLP-1RA that does not induce significant weight loss) has recently been associated with a reduction in CVD.122

A number of pooled analyses from randomised-controlled trials (RCTs) in patients with T2D indicate...
that GLP-1RAs reduce plasma aminotransferases, interpreted as a surrogate endpoint of hepatocyte improvement in NAFLD.108,123–125 Consistent with these findings many small, uncontrolled pilot studies have reported a lowering of plasma aminotransferases126–130 or intrahepatic triglyceride (IHTG)127,128 (BI)130,132 with GLP-1RAs. Adding a GLP-1RA to basal insulin appears to be more effective in lowering plasma alanine aminotransferase (ALT) levels or IHTG than basal-bolus insulin therapy alone.131–134 Liraglutide induces resolution of NASH in patients with biopsy-proven NASH135 and an improvement in hepatic and adipose tissue insulin sensitivity.136 This was only in part mediated by reductions in body weight.135 Still, weight loss may be an important factor, especially for improvement in hepatic steatosis, although this has not been observed in all studies.136,137 It is a challenge to interpret the effect of liraglutide separately from weight loss as it occurs in most studies (10 out of 11 studies).136 Petit et al.135 treated 68 patients with uncontrolled T2D and NAFLD with liraglutide and reported that the reduction in IHTG was highly correlated with baseline liver fat accumulation and the magnitude of weight loss (both p <0.0001), and much less with the change in HbA1c (p = 0.034). Liver fat content was unchanged in those without a significant decrease in body weight.138 Also in a recent study by Matikainen et al.,140 where a dietary-induced weight loss control group was included to match the weight change induced by liraglutide, the decrease in IHTG was numerically greater but not significantly different between both groups, especially when multiple regression analysis and weight change was included as an independent variable. In general, GLP-1RAs are well tolerated and the gastrointestinal side effects minimised with careful titration. Ongoing studies will clarify the role of these agents in the management of NASH. Finally, “dual agonists” combining GLP-1RAs with glucagon141 are also under intense investigation for their potential role in T2D, obesity and NASH.

Dipeptidyl peptidase-IV inhibitors for the treatment of NAFLD

Dipeptidyl peptidase (DPP)-IV inhibitors have been available for the treatment of T2D for about a decade. They are not particularly potent glucose-lowering agents (HbA1c decreases only about 0.5–0.7%) but have become popular among clinicians given their ease of use, oral once daily dosing, potential for combination in the same tablet with metformin, relative low cost and excellent safety record.142 They primarily lower the postprandial glucose level, as they inhibit the plasma degrading enzyme DPP-IV, leading to higher plasma GLP-1 levels.98 There is a good rationale for their use to treat NAFLD as many studies in vitro143 and in animal models of NAFLD/NASH144–154 have reported marked beneficial effects.

Several uncontrolled studies have reported that treatment with DPP-IV inhibitors lowers plasma aminotransferase levels,155–161 In one study, a lower plasma ALT was only observed in those with the most uncontrolled diabetes at baseline.162 Kato et al.163 observed that while sitagliptin reduced IHTG compared to glimepiride, this was also associated with significant weight loss, possibly from concomitant lifestyle changes. Other studies have also reported a modest reduction of hepatic steatosis.164,165 Of note, DPP-IVs per se are believed to be weight neutral.98,142 Liver histological improvement has been reported with sitagliptin in an open-label study in 40 patients with biopsy-proven NASH (also biopsied after treatment), but again results were confounded by a strong correlation between weight loss and histological changes. Others have failed to see any decrease in plasma aminotransferases or IHTG.137,166–168 Of note, in all 3 controlled studies treatment with sitagliptin resulted in negative findings.137,167,168 Taken together, while a number of mechanisms have been proposed for DPP-IV inhibitors in animal models of NASH,96,170 strong clinical evidence for their clinical use in NAFLD/NASH is still lacking.

Metformin and pioglitazone

Among insulin-sensitizers, metformin does not significantly impact resolution of NASH or fibrosis, as reviewed elsewhere171 and is considered neutral by current guidelines.5,172 Pioglitazone has shown beneficial effects in NASH.173–176 It activates peroxisome proliferation-activated receptor gamma (PPAR-γ), a nuclear receptor that adopts a heterodimer configuration with retinoid X receptor (RXRα).177,178 Its activation reverses IR and improves glucose and lipid metabolism, with redistribution of excess triglyceride accumulation from the liver (as well as skeletal muscle and other tissues) to a “metabolically healthier” adipose tissue, explaining the frequent weight gain observed in patients treated with pioglitazone. Other likely mechanisms by which pioglitazone reverses the state of “lipotoxicity” in NASH include an increase in plasma adiponectin (2- to 3-fold) and an amelioration of subclinical inflammation.179 Part of the clinical benefit of pioglitazone in NASH has also been linked to its partial PPAR-α agonism180,181, which enhances hepatocyte fatty acid oxidation and lipoprotein changes leading to a reduction in plasma triglyceride concentrations and an increase in high-density lipoprotein-cholesterol concentrations. This is in contrast to a pure PPAR-γ agonist, such as rosiglitazone, which has limited effect on necroinflammation in NASH, no effect on plasma triglyceride levels and increases LDL-c levels.182 Four RCTs173–176 have provided the evidence supporting the clinical practice guidelines in Europe5 and the United States172 that recognise that pioglitazone may be prescribed for patients
with biopsy-proven NASH. Resolution of NASH ranges from ~47% (or 29% placebo-subtracted) in patients without diabetes treated with pioglitazone 30 mg/day for 2 years,\textsuperscript{175} to ~60% (or 40% placebo-subtracted) in those with T2D treated with pioglitazone 45 mg/day for up to 3 years.\textsuperscript{176} It may reduce fibrosis,\textsuperscript{174,176} but its greatest value may reside in preventing fibrosis progression (rather than regression) by turning off the metabolic drivers of liver fibrosis. These metabolic benefits go beyond the liver and the reduction of hyperglycaemia (i.e., reduction of HbA1c -1.0–1.5%), translating into a decrease in cardiovascular risk in patients with or without T2D.\textsuperscript{186–189}

One would expect pioglitazone to be used more widely in patients with NASH, with or without T2D, given the positive results from RCTs,\textsuperscript{173–176} the guideline recommendations,\textsuperscript{2,172} and the difficulty of treating NAFLD with significant long-term weight loss. However, outside endocrinology, many clinicians are not familiar with the results of recent RCTs, or misunderstand the metabolic significance of pioglitazone-induced weight gain and other potential side effects, leading to its undertuse. It is also not FDA-approved for NASH, only holding an indication for the treatment of T2D. Pioglitazone-induced weight gain ranges from 3% to 5% in patients with NASH, in RCTs lasting 6 months to 3 years\textsuperscript{173–176} or longer in patients with T2D.\textsuperscript{186–189} It tends to occur predominantly in the first 6–12 months of therapy. Clinicians may naturally steer away from a therapy that may be associated with weight gain given the embedded medical training that any weight gain is harmful, or the belief that to improve liver histology weight loss is mandatory. However, by restoring normal adipocyte biology, pioglitazone causes a radical switch from insulin resistant adipose tissue to a metabolically “healthy” obese state (i.e., leading to near-normal or at least significantly improved insulin sensitivity). Indeed, weight gain during pioglitazone treatment often indicates an improvement in insulin action in insulin-sensitive tissues (fat, liver, muscle) that is associated with an increase in plasma adiponectin, reduction in plasma FFA and “lipotoxicity”, amelioration of subclinical inflammation (i.e., high-sensitivity C-reactive protein and other adipokines) and a reduction in visceral fat (most metabolically harmful), as reported in long-term clinical trials in NASH\textsuperscript{175,176} and diabetes.\textsuperscript{186–189} Weight gain may be ameliorated with proper nutritional counselling, but worsened if combined with high-dose insulin regimens, so careful assessment is needed in this setting. An alternative approach that is gaining momentum among hepatologists is to prescribe low-dose pioglitazone (15 mg/day) and titrate over time as needed. Dose-response studies show that lower dose pioglitazone (15 mg/day) retains significant biological activity with minimal weight gain (<1 kg) and rarely oedema.\textsuperscript{190–193} However, the efficacy of low-dose pioglitazone (15 mg/day) in NASH remains to be established.

Significant misunderstanding exists about the effects of pioglitazone on cardiac function. Pioglitazone reduces cardiovascular events in patients with and without T2D.\textsuperscript{186–189} However, because it may cause oedema, and there are reports of congestive heart failure (CHF) associated with pioglitazone use,\textsuperscript{186} many practitioners believe that it causes it. Indeed, pioglitazone improves left ventricular diastolic/systolic function as well as cardiac muscle insulin sensitivity.\textsuperscript{194,195} While lower extremity oedema may develop in a minority of treated patients, more often when associated with high doses of insulin, the thiazolidinedione does not cause CHF per se. The confusion arises because undiagnosed heart failure with preserved ejection fraction (i.e., left ventricular diastolic dysfunction) is common in patients with NAFLD or T2D. In a recent study in 2,813 middle-aged patients with T2D screened by echocardiography, the prevalence of mild/moderate left ventricular diastolic dysfunction was 35% (95% CI 24%–46%),\textsuperscript{196} and even higher in patients with diabetes and NAFLD.\textsuperscript{197} Pioglitazone is contraindicated in patients with clinical evidence of CHF. If fluid retention occurs during pioglitazone therapy in patients who are unaware that they have NAFLD and left ventricular diastolic dysfunction, it would seem to be causing CHF, rather than unmasking it. One way to avoid such a scenario is to obtain a careful history, and if CHF is suspected, perform complementary studies (i.e., plasma brain natriuretic peptide, echocardiogram, other cardiac testing), and if unsure, withhold pioglitazone or start it at the lowest possible dose (15 mg/day).

The effects of pioglitazone on bone metabolism remain poorly understood\textsuperscript{198} but call for close monitoring during long-term treatment, which could be achieved by taking a baseline bone mineral density measurement, followed by repeat tests every 2 years (or sooner in patients with significant bone disease). A recent study in patients with NASH did not observe increased fractures, but the study was relatively small.\textsuperscript{199} An increase in lumbar spine and femoral neck fracture risk, in both males and females, was shown quite conclusively in a large long-term (4 years) RCT.\textsuperscript{200} Finally, mixed results in the literature have been reported about the relationship between thiazolidinediones and bladder cancer, which remains uncertain, although most studies have failed to observe such an association, particularly if low quality studies are excluded.\textsuperscript{201}

In summary, many general practitioners and specialists remain unaware that pioglitazone has
the potential to induce resolution of NASH in~60% of patients, as well as conferring extrahepatic benefits (i.e., reduction of new-onset diabetes or CVD). However, it is likely that its use will continue to increase in patients with NASH to prevent fibrosis progression. Of interest, many novel insulin-sensitizers are being investigated for the treatment of NASH, with the aim of achieving an improved safety and efficacy profile. 170

SGLT2 inhibitors for the treatment of NAFLD

From a broad spectrum of animal models to large multicentre RCTs, SGLT2 inhibitors have been shown to improve glucose homeostasis, as well as conferring cardiorenal protection via multiple mechanisms. 102 This building body of evidence has led to the recent diabetes management guidelines 116 that place SGLT2 inhibitors (along with GLP-1RAs) as second-line agents for the management of T2D. 97 There is also a growing expectation that this class of agents will assist in the treatment of NASH. As recently reviewed, 170 a number of recent in vivo studies report significant benefits, including the reversal of liver steatosis, hepatocyte necrosis, inflammation and/or fibrosis. Most clinical studies have reported a reduction in plasma aminotransferases with the SGLT2 inhibitors empagliflozin, 203,204 dapagliflozin, 205–207 canagliflozin, 207–210 luseogliflozin, 211 and ipragliflozin 212–216 in patients with T2D. Typically, the reduction in plasma ALT concentration is proportional to the magnitude of weight loss, with higher baseline plasma aminotransferases resulting in a more significant reduction with treatment.

While the assumption is that a reduction in plasma aminotransferases reflects a reduction in hepatic steatosis and necroinflammation, there are no controlled trials with liver histology as the primary endpoint. Liver imaging trials have led to more mixed results. Several small, uncontrolled 6-month studies have reported a decrease in IHTG, either using the liver-to-spleen attenuation ratio (a rather qualitative measurement of liver fat) 211,213,216 or proton magnetic resonance spectroscopy (1H-MRS). 215 However, placebo-controlled studies have been negative despite reductions in subcutaneous and visceral fat, as observed in an early study of dapagliflozin where IHTG was measured by 1H-MRS. 217 Recently, a 24-week RCT treated 56 patients with uncontrolled T2D with canagliflozin 300 mg or placebo, where hepatic insulin sensitivity was measured by a 2-step euglycaemic-insulin clamp and IHTG by 1H-MRS. 218 In patients with NAFLD (n = 37), canagliflozin significantly improved hepatic insulin sensitivity. Canagliflozin also improved pancreatic beta-cell function and insulin clearance. However, the relative decrease in IHTG, while numerically greater with canagliflozin than placebo, did not reach statistical significance (−38% vs. −20%, respectively, p = 0.09; Fig. 5, left panel). Also, a weight loss ≥5% associated with ≥30% relative reduction in IHTG, was more common in patients on canagliflozin than placebo (38% vs. 7%, respectively, p < 0.01). The investigators concluded that while canagliflozin improved hepatic insulin sensitivity, reduction in IHTG appeared to fundamentally depend on the magnitude of weight loss (Fig. 5, right panel), which was greater and more frequent with the SGLT2 inhibitor.

In summary, SGLT2 inhibitors decrease plasma ALT concentrations, and often hepatic steatosis, if accompanied by weight loss. The clinical translation of these findings to the treatment of NASH is unknown in the absence of studies with histological outcomes. Only a case report, 219 and an uncontrolled 12-week study in 10 patients with biopsy-confirmed NASH and T2D, 210 have suggested some benefit with canagliflozin on liver fat and fibrosis biomarkers, but both studies were too small to offer any firm conclusions. If improvement of steatohepatitis is only dependent on weight loss, one would anticipate the effect to be rather modest. Usually weight loss with SGLT2 inhibitors is in the range of 3 to 5% while resolution of NASH and of fibrosis calls for a weight loss
of ~7 to 10%.172 Of note, “positive studies” with SGLT2 inhibitors in NAFLD have been open-label, short-term trials (12 to 24-week duration) and not placebo-controlled RCTs. SGLT2 inhibitors are usually well tolerated but physicians should educate patients about their potential side effects, such as osmotic diuresis/volume depletion that may lead to orthostatic hypotension and falls, vulvovaginitis/balanitis and related genital mycotic infections, urinary tract infections, osteoporosis and lower extremity amputations (canagliflozin) and diabetic ketoacidosis (although rare in patients with T2D).220

**Insulin for the treatment of NAFLD**

Insulin remains a valuable agent for many patients with T2D that remain uncontrolled on a combination of oral agents or have comorbidities that preclude a given patient from using them. The effect of insulin has not been extensively studied in NAFLD and there are no studies examining its effect on liver histology. One study reported that 76% of patients with T2D not previously treated with insulin had hepatic steatosis, measured by magnetic resonance imaging, compared to 62% of those treated with insulin, while the median hepatic fat fraction was 13% compared to 10.2%, respectively (both \( p < 0.01 \)).221 Basal exogenous insulin decreases hepatic fat accumulation222,223 likely by suppressing FFA and glucose flux to the liver in patients with T2D and NAFLD.

**Conclusions**

NAFLD in T2D is a disease with unclear mechanisms and an individual genetic susceptibility that promotes the development and progression from fatty liver disease to NASH, cirrhosis and hepatocellular carcinoma. Not only the close association with obesity, but also with IR and lipotoxicity, increases the risk of T2D and related comorbidities in NAFLD. Screening in the primary care setting, diabetes clinics and among hepatologists is more relevant than ever, as effective therapies are available, including lifestyle changes that induce weight loss, bariatric surgery, and medications currently available to treat diabetes and proven to be effective in NASH (i.e., pioglitazone, liraglutide). The American Diabetes Association in 2019 recommended universal screening for advanced fibrosis in all patients with prediabetes or T2D with steatosis or elevated ALT, in an effort to identify and treat those at the highest risk of developing advanced fibrosis.224

Of note, the target of screening and treatment is not steatosis *per se*, but NASH-induced liver fibrosis as it has been associated with increased morbidity and mortality.2,172 Many new compounds are undergoing phase IIb/III RCTs. It is critically important to increase awareness among primary care physicians, specialists and health policy makers about the risks associated with this disease, since early diagnosis and treatment will be the only way to tackle the looming epidemic of NASH.

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**Conflict of interest**

AG is a consultant for Eli Lilly, Inventiva, Genentech, Menarini, Gilead, outside the submitted work. KC has received research support as principal investigator from the National Institutes of Health (NIH), Cirius, Echosens, Inventiva, Novartis, Novo Nordisk, Poxel and Zydius. KC is a consultant for Allergan, Astra-Zeneca, BMS, Boehringer Ingelheim, Coherus, Deuterex, Eli Lilly, Genentech, Gilead, Janssen, Pfizer, Poxel, Novo Nordisk, and Sanofi-Aventis. Please refer to the accompanying ICMJE disclosure forms for further details.

**Authors’ contributions**

Both authors contributed equally to this manuscript.

**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2019.07.002.

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