

# Role of Insulin Resistance in the Development of Nonalcoholic Fatty Liver Disease in People With Type 2 Diabetes: From Bench to Patient Care

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Insulin resistance is implicated in both the pathogenesis of nonalcoholic fatty liver disease (NAFLD) and its progression from steatosis to steatohepatitis, cirrhosis, and even hepatocellular carcinoma, which is known to be more common in people with type 2 diabetes. This article reviews the role of insulin resistance in the metabolic dysfunction observed in obesity, type 2 diabetes, atherogenic dyslipidemia, and hypertension and how it is a driver of the natural history of NAFLD by promoting glucotoxicity and lipotoxicity. The authors also review the genetic and environmental factors that stimulate steatohepatitis and fibrosis progression and their relationship with cardiovascular disease and summarize guidelines supporting the treatment of NAFLD with diabetes medications that reduce insulin resistance, such as pioglitazone or glucagon-like peptide 1 receptor agonists.

People with type 2 diabetes have the highest risk of developing nonalcoholic fatty liver disease (NAFLD) (1,2). However, the high prevalence and clinical implications of this disease are just now becoming better recognized. Not only is NAFLD more common in people with type 2 diabetes, but the coexistence of NAFLD and type 2 diabetes is associated with more rapid progression to cirrhosis (3). The prevalence of NAFLD in people with type 2 diabetes has been reported to be between 60 and 86% globally (4). Recent clinical practice guidelines for NAFLD (5–9) recommend systematic screening of all people with type 2 diabetes using the Fibrosis-4 (FIB-4) index. Studies using transient elastography or MRI-based techniques have reported the prevalence of NAFLD to exceed 70% (10). Even more concerning, about half of all patients with coexisting type 2 diabetes and NAFLD have steatohepatitis (11), and about one in six have moderate to advanced fibrosis (10,12,13).

NAFLD is a multisystem disease with extrahepatic disease implications that include type 2 diabetes and cardiovascular disease (CVD) (14). Patients with NAFLD have a twofold higher risk of developing type 2 diabetes than those without NAFLD, with more severe liver disease perhaps increasing this risk (15,16). The presence of NAFLD in people with type 2 diabetes is often associated with a worse cardiometabolic profile, as well as a higher risk of more severe hypertension, atherogenic dyslipidemia, cardiac arrhythmias, and cardiovascular events (17).

Why are people with type 2 diabetes at such high risk of steatohepatitis and the eventual development cirrhosis? The answer is not straightforward, but multiple factors appear to be at play. As will be reviewed below, these include genetic factors that may modulate insulin action or hepatocyte lipid metabolism and a web of acquired factors driven by insulin resistance such as glucotoxicity and lipotoxicity linked to dysfunctional adipose tissue and ectopic fat accumulation in the liver in people with obesity and diabetes (1,2,18). Central among factors is insulin resistance, which promotes multiple alterations of glucose and lipid metabolism, intracellular inflammatory pathways, mitochondrial dysfunction, and endothelial reticulum stress (19). Among multiple mechanisms, a common finding is more severe hyperinsulinemia, atherogenic dyslipidemia, and adipose tissue, hepatic, and muscle insulin resistance (20,21).

Because of the clinical implications of insulin resistance in people with type 2 diabetes and NAFLD, this article focuses on its role in the development of the disease and how reversing insulin resistance with either weight loss (via lifestyle modification or glucagon-like peptide 1 [GLP-1] receptor agonist therapy) or use of the insulin sensitizer pioglitazone can reverse steatohepatitis and may even heal fibrosis (22). Our hope is that a better understanding of the pathophysiology of NAFLD may assist clinicians in the management of this complex condition.

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<https://doi.org/10.2337/dsi23-0013>

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## Practical Aspects of the Pathophysiology and Natural History of NAFLD

### *Genetic Factors Play a Role*

The severity of NAFLD in a given individual is influenced by an interplay of environmental and genetic factors. Several genetic variants of clinical relevance have been identified by genome-wide association studies and candidate gene approaches. Among those associated with a greater risk of cirrhosis from steatohepatitis are patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), transmembrane 6, superfamily member 2 (*TM6SF2*), glucokinase regulatory protein (*GCKR*), and membrane bound *O*-acyltransferase domain-containing 7 (*MBOAT7*), among others, while hydroxysteroid 17- $\beta$  dehydrogenase 13 (*HSD17B13*) is associated with lower risk (23).

The practical value of genetic polymorphisms is that they could, in the near future, help to better estimate the future risk of developing cirrhosis and guide more aggressive treatments toward patients with higher risk. These genetic polymorphisms may explain as much as half of the interindividual variations in the risk of NAFLD and future cirrhosis. Thus, the sum of risk-increasing alleles may become a powerful clinical instrument for people with NAFLD (24). For example, genetic risk scores calculated from *PNPLA3*, *TM6SF2*, *MBOAT7*, and other variants are associated with worse liver outcomes (25,26).

One of the best genetic variants studied is the triacylglycerol lipase *PNPLA3*, which regulates intracellular lipid droplet metabolism. Of note, patients with the *PNPLA3* variant are as insulin resistant as those without the mutation (1) but usually have worse steatohepatitis and higher risks not only of cirrhosis, but also of hepatocellular cancer (HCC) (27), which is amplified in the presence of obesity or diabetes (28). The *PNPLA3* variant rs738409 C>G, which encodes I148M, promotes intracellular lipid accumulation by reducing the lipidation of very-low-density lipoprotein (VLDL) cholesterol (21). A mutation in *TM6SF2*, most commonly in *E167K*, causes steatosis by intracellular retention of VLDL cholesterol within the hepatocyte (23). On the other hand, both genetic variants of *PNPLA3* and *TM6SF2* are associated with lower plasma triglyceride levels and an apparent lower risk of CVD despite higher hepatic triglycerides (29).

Defects in *MBOAT7*, of which the most common splice variant is rs72613567, also affects lipid droplet function with decreased secretion of triglycerides, mitochondrial dysfunction, increased susceptibility to steatohepatitis and fibrosis in NAFLD, alcohol-associated liver disease, and viral hepatitis (30,31). The *GCKR* rs1260326 gene variant is associated with greater rates of glycolysis and increases hepatic de novo lipogenesis (DNL) in patients with obesity and NAFLD

(32). Inversely, *HSD17B13* rs72613567-A variants play a protector role against liver disease progression, and a loss of function of the *HSD17B13* allele increases the risk of steatohepatitis (24). The genetic variants discussed above are being exploited to identify individuals at higher risk of future cirrhosis and also to develop NASH pharmacological agents targeting these pathways.

### *Insulin Resistance Produces Steatosis*

The prevalence of hepatic steatosis is very high in individuals with type 2 diabetes, especially those with overweight or obesity, affecting at least two in three individuals studies using transient elastography or MRI-based techniques (10). The mechanisms remain unclear, but clinicians may better understand the impact of insulin resistance by considering how insulin interacts with regulation of hepatic glucose and lipid metabolism during feeding and fasting (18,31,33).

In the fasting state, the insulin concentration is low, and muscles fundamentally relies on fatty acids from adipose tissue as their source of energy. The low insulin level promotes adipose tissue-stored triglyceride lipolysis and its release as free fatty acid (FFA) into the plasma. In addition, low insulin, together with an increase in glucagon secretion, stimulate liver glycogen breakdown and gluconeogenesis to maintain hepatic glucose production and normal fasting plasma glucose (34). With a meal, the increment of plasma insulin concentration inhibits adipose tissue lipolysis (thereby lowering plasma FFA levels) and promotes muscle and liver glucose uptake and utilization, with a metabolic switch from fat to glucose as their main source of energy. This transition from the fasting to the fed state, with the consequent shift from FFA to glucose as an energy substrate, is known as metabolic flexibility (18,35).

A key feature of insulin-resistant states such as obesity, NAFLD, and type 2 diabetes is their metabolic inflexibility—disruption of this important glucose-lipid (FFA) energy switch caused by insulin resistant, dysfunctional adipose tissue (sometimes call “sick fat”). This disruption promotes a relentless, chronic excess offer of fat (FFA) as the main source of daily energy for the liver and muscle, at the expense of glucose utilization. This chronic FFA excess energy supply, which is typical of insulin-resistant states, is known as lipotoxicity (18,36). Impaired cellular glucose uptake to insulin, plus an excess influx of energy as FFA from increased lipolysis of white adipose tissue, compounded by increased rates of hepatic DNL, leads to steatosis (37). The liver disposes of FFA through mitochondrial  $\beta$ -oxidation, re-esterification into triglycerides, and storage in lipid droplets or its release as VLDL cholesterol into the systemic circulation. Over-secretion of

VLDL cholesterol in insulin-resistant individuals with type 2 diabetes or NAFLD causes atherogenic dyslipidemia (i.e., an increased number of apolipoprotein B particles, hypertriglyceridemia, and low HDL cholesterol) and is often proportional to the degree of hepatic triglyceride excess (32).

The accumulation of intrahepatic triglycerides may be viewed as a defense mechanism to avoid the formation of more toxic lipid intermediates (e.g., diacylglycerols and ceramides), endoplasmic reticulum stress, and formation of reactive oxygen species (ROS). These worsen in the transition from simple steatosis to steatohepatitis (20). Of note, relatively small increases of liver triglycerides, even within the normal range, are associated with the development of insulin resistance, atherogenic dyslipidemia, lower plasma adiponectin, and an unfavorable metabolic profile (38,39). However, the severity of steatohepatitis (i.e., necroinflammation or fibrosis) does not appear to be directly proportional to worse steatosis (38), although this finding remains controversial.

*Metabolic Dysregulation From Insulin Resistance Contributes to Steatohepatitis*

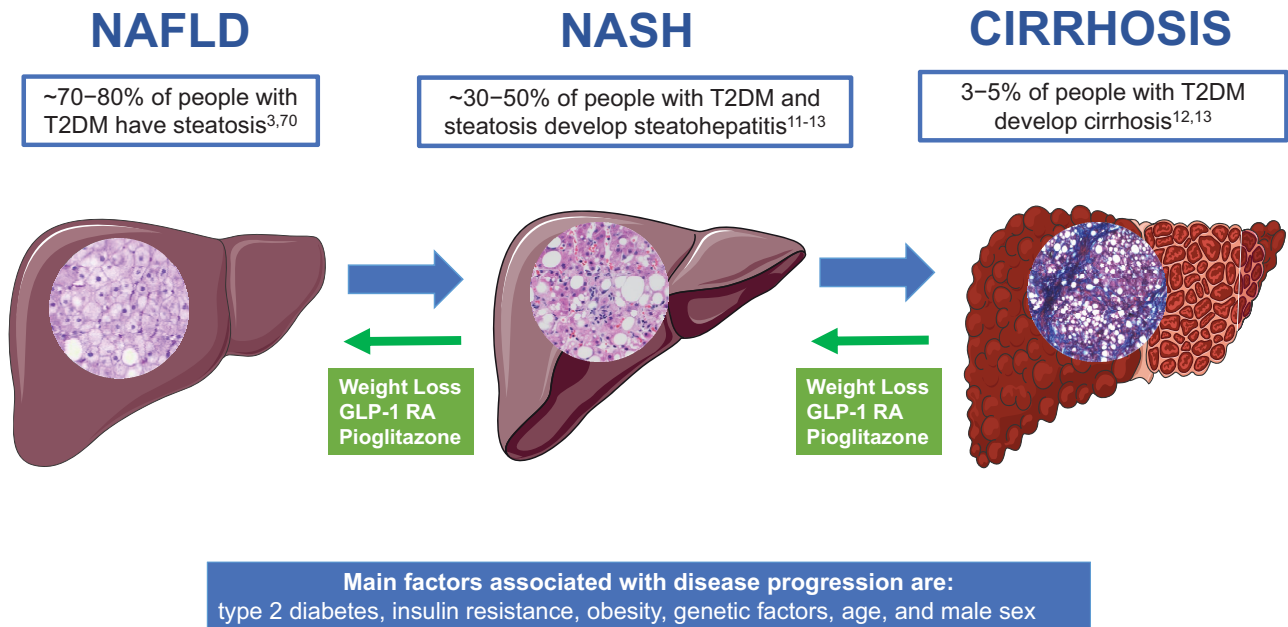
Nonalcoholic steatohepatitis (NASH) is a histological diagnosis defined as having, in addition to steatosis, active hepatocyte injury (ballooning) and lobular inflammation, often with liver fibrosis (5). As illustrated in Figure 1, steatosis

promotes fibrosis by many different pathways, but the molecular mechanisms remain elusive, as reviewed elsewhere (40–43). However, the metabolic dysregulation that results from insulin resistance, as observed often in obesity and type 2 diabetes, is almost universal among those with steatohepatitis and central to disease progression (1,18,44). Because insulin resistance is a clinically identifiable target with potential for intervention compared with more poorly defined molecular pathways (many of which are also affected by insulin resistance), it is important for clinicians to understand its role. This understanding is the basis for identifying and treating insulin resistance by promoting weight loss and prescribing medications that reverse it.

As previously mentioned, people with overweight or obesity have abnormal adipose tissue metabolism and peripheral insulin resistance, with a state of lipotoxicity (1,2,18,44), often with hyperglycemia and chronic glucotoxicity, if prediabetes or type 2 diabetes are present (45,46). Glucotoxicity and lipotoxicity associated with steatosis in obesity, type 2 diabetes, and NAFLD lead to the accumulation of toxic intracellular lipid intermediates such as diacylglycerols and ceramides, that are related to whole-body and hepatic insulin resistance, hepatocyte necroinflammation, and cellular apoptosis (41,47–50).

Within this context, mitochondria have been implicated in the pathogenesis of NAFLD because of their role in fatty

FIGURE 1



**FIGURE 1** Disease progression in NAFLD. NAFLD encompasses a spectrum of liver disease, ranging from steatosis to steatohepatitis, with bouts of progression and regression from early to advanced fibrosis and cirrhosis. The more advanced the disease, the more limited the potential for regression is, until decompensated cirrhosis develops. At least 70% of people with type 2 diabetes are estimated to have NAFLD, and among them about half may have NASH. Fibrosis is believed to be present in 12–20% of all people with type 2 diabetes (3,11–13,65,68,89,90). RA, receptor agonist. T2DM, type 2 diabetes mellitus.

acid oxidation, lipogenesis, and gluconeogenesis (36,41). In metabolic diseases associated with insulin resistance, to prevent steatosis, hepatic mitochondria adapt and increase FFA oxidation to dispose of the larger supply. However, in individuals with insulin resistance (i.e., obesity or type 2 diabetes) who develop steatohepatitis, this mitochondrial adaptation appears to be transient and to diminish over time as it promotes oxidative stress, gradually exhausting cellular antioxidative capacity and leading to mitochondrial abnormalities (49,51; S. Kalavalapalli, D. Barb, K.C., unpublished observations). In the end, chronic insulin resistance with diminishing mitochondrial oxidative capacity creates the conditions for rapid progression from steatosis to steatohepatitis to cirrhosis (36,52,53).

Although patients with type 2 diabetes have a higher prevalence of steatosis (10), the prevalence of the associated steatohepatitis (i.e., necroinflammation) in patients in the general population has been more difficult to establish because liver biopsy is an invasive procedure and cannot be ethically justified as a tool for population-based studies.

Retrospective studies based on liver histopathology are limited by small size, spectrum bias, varying case definitions, and unclear indications for liver biopsy. However, a recent study using iron-corrected (cT1) MRI in randomly selected patients from outpatient clinics reported that the overall prevalence of steatohepatitis was 14% (11). More worrisome was that people with type 2 diabetes had a much higher prevalence (35%) compared with those without diabetes (10%) and that, in those with diabetes, obesity, and hypertension, the prevalence of NASH was almost 50%. In another recent prospective study, researchers performed liver biopsies in all people with type 2 diabetes who also had steatosis and/or elevated plasma aminotransferase (12). In this selected population, almost two-thirds had steatohepatitis and one-third had advanced fibrosis or cirrhosis. Of note, as had been reported in previous studies (20,54–57), most individuals with NASH and advanced fibrosis had normal or near-normal plasma aminotransferase levels. This finding has been the main reason for recent clinical practice guidelines recommending FIB-4 screening of all people with type 2 diabetes or metabolic syndrome (5–9), because the traditional paradigm that elevated ALT or AST should be the main criterion for additional liver testing is deeply flawed. This concept is discussed in depth elsewhere (58).

Finally, although the disease progression rate is relatively slow in most people, clinicians may be aware that progression may be faster in some individuals with risk factors, including people with insulin resistance (whether

lean or with obesity), obesity, or type 2 diabetes and those with some gene variants (e.g., the *PNPLA3* variant).

### *Insulin Resistance, Obesity, and Type 2 Diabetes Predispose to Advanced Liver Fibrosis*

Fibrosis progression is influenced by many factors, including the genomic profile and comorbidities such as obesity and type 2 diabetes (Figure 1). The underlying mechanisms are poorly understood, but they are diverse and often worsened by insulin resistance (41,59). Weight gain, obesity, and type 2 diabetes are the typical risk factors for fibrosis progression (8). Activation of inflammatory pathways in the setting of insulin resistance and metabolic dysfunction in NASH triggers M1 macrophages to secrete proinflammatory cytokines and accelerate fibrosis by promoting extracellular matrix deposition and tissue remodeling (60). This is followed by reparative phases with liver macrophages undergoing alternative activation to M2-type macrophages that promote extracellular matrix degradation (i.e., fibrolysis) (42,43). The net effect over time of fibrogenesis versus fibrolysis determines disease progression to cirrhosis.

Hepatic fibrosis, rather than inflammation, especially in insulin-resistant individuals, appears to be the key histological feature of NASH that defines the progression of the disease. This feature can be traced to the loss of mitochondrial adaptation and oxidative capacity discussed earlier for steatohepatitis. Fibrosis in individuals with NASH who have any degree of hepatic fibrosis, is associated with lower mitochondrial respiration rates than in those showing no signs of fibrosis (49,51,61; S. Kalavalapalli, D. Barb, K.C., unpublished observations). The impact of mitochondrial maladaptation points to its key role in metabolic liver injury and the development of the conditions that lead to progression to cirrhosis. In type 2 diabetes, hyperglycemia might contribute to mitochondrial respiration, increased ROS, glycosylation of proteins, and increased formation of advanced glycation end products (45,46).

From a clinical perspective, advanced liver fibrosis is common in patients with type 2 diabetes (3,20). An early study reported a 17.7% prevalence of advanced fibrosis in a cohort of 1,918 individuals with type 2 diabetes from Hong Kong who were screened by transient elastography (62). More recent studies, also with transient elastography or MRI-based techniques, have reported significant fibrosis (stage  $\geq$ F2) prevalence to range between 12 and 20% (10). A recent prospective study of 501 U.S. adults with type 2 diabetes who were tested by the gold-standard MRI and elastography (MRE) technique reported a prevalence of steatosis of 65% and of advanced fibrosis of 14%, with 6%

having cirrhosis. Having diabetes increases the risk of major complications of cirrhosis, such as ascites, hepatic encephalopathy, bacterial infections, and chronic kidney disease, and is associated with higher mortality rates (63).

Retrospective studies often highlight type 2 diabetes as the most significant clinical factor for advanced fibrosis and cirrhosis (42). For example, a large retrospective study in 619 individuals with biopsy-confirmed NASH who were followed for a mean of 12.6 years reported that age (hazard ratio [HR] 1.07), type 2 diabetes (HR 1.62), and smoking (HR 2.62) were the most relevant factors for disease stage severity (64). Among the few prospective studies, a recent observational study reported a significantly higher prevalence of type 2 diabetes among individuals with cirrhosis (65). Individuals with type 2 diabetes who have overweight or obesity increase their risk of advanced fibrosis in proportion to their excess weight (66), making obesity prevention and screening imperative in this population. In support of the deleterious role of obesity, several studies have demonstrated that clinically significant liver fibrosis was strongly associated with adipose tissue insulin resistance (67).

The severity of liver fibrosis at baseline is another major factor (68). In a recent meta-analysis to quantify the prognostic value of the fibrosis stage at diagnosis, the investigators collected data from 4,428 individuals with NAFLD, 2,875 of whom had NASH, and found that worse fibrosis increased all-cause mortality by 3.4-fold and liver-related mortality by 11-fold (69). Finally, in a prospective study involving individuals with biopsy-proven NASH, all-cause mortality increased with increasing fibrosis stages (65). As expected, a more advanced fibrosis stage was associated with more liver-related complications, such as variceal hemorrhage, ascites, encephalopathy, and HCC. Of note, the prevalence of type 2 diabetes was about twofold higher among those with cirrhosis. Taking these findings together, it is clear that having type 2 diabetes significantly increases the risk of liver disease, cirrhosis, and HCC.

### Clinical Implications of Insulin Resistance in NAFLD

Knowing the role of insulin resistance in the metabolic dysfunction associated with NAFLD in diabetes allows health care providers to establish targeted strategies to address it. Having steatosis is often an indication of insulin resistance once secondary causes have been ruled out (e.g., alcohol abuse and certain medications) (8,9). Of note, not only people with type 2 diabetes can be affected, but also those with type 1 diabetes, particularly if they have obesity (8,9).

Clinical practice guidelines recommend risk-stratifying all people with steatosis or elevated liver plasma aminotransferase levels, obesity with cardiometabolic risk factors, prediabetes, or type 2 diabetes for the presence of significant hepatic fibrosis. Initial fibrosis risk-stratification can be done in a cost-effective way by calculating the FIB-4 score derived from age, AST, ALT, and platelet count. A FIB-4 calculator is available online (<https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis>). Clinicians are often unaware that a FIB-4 calculator is also readily available in many existing electronic medical record (EMR) systems or that one can be easily built into a system and incorporated as a template into routine EMR notes.

Clinicians should also be aware that diagnosis of clinically significant fibrosis (i.e., moderate to advanced fibrosis or stage  $\geq$ F2 on histology) and monitoring of disease progression (i.e., worsening of liver fibrosis) can be performed reasonably well in clinical practice without the need for a liver biopsy. This has been clearly shown in a recent individual-participant data meta-analysis of the prognostic performance of liver histology compared with noninvasive tests (70). In this study, 2,518 patients with biopsy-proven NAFLD were followed for a median of 57 months. Both liver fibrosis assessments, liver stiffness measurement (LSM) by transient elastography (area under the receiver operating characteristic [AUROC] curve 0.76 [95% CI 0.70–0.83]) and the FIB-4 index (AUROC curve 0.74 [95% CI 0.64–0.82]) performed well after adjustment for confounders to predict all-cause mortality, HCC, liver transplantation, and cirrhosis complications (70). Moreover, magnetic resonance (MR) techniques, either MR elastography (MRE) alone (71,72), or as multiparametric MRI (cT1) (73), or MR combined with plasma aminotransferase measurement (74) can assist in the assessment of treatment response to weight loss and pharmacotherapy. However, given factors such as limited MRI availability and high costs, the use of these options is best individualized by liver specialists working within a multidisciplinary team (5,9). This issue is discussed in further detail elsewhere in this article collection (58) in the context of clinical practice guidelines that emphasize the importance of a healthy lifestyle in the management of obesity and type 2 diabetes in people with NAFLD (5,8,9).

Table 1 summarizes the negative impacts of weight gain in humans and their reversal by two different and complementary approaches. As discussed earlier, chronic overnutrition causes a loss of normal metabolic flexibility. This loss is not only associated with the development of adipose tissue dysfunction, insulin resistance, and NASH, but also it promotes the development of type 2 diabetes and CVD. Weight gain is also associated with many symptoms that impair quality of life (e.g., fatigue, depression, and impaired mobility).

T1

**TABLE 1** Effect of Weight Loss or Pioglitazone for People With Type 2 Diabetes and NAFLD

Risk Factor	Weight Gain (i.e., Overweight or Obesity)	Weight Loss (via Lifestyle Change, Bariatric Surgery, or GLP-1 Receptor Agonist Therapy)	Insulin Sensitizer (i.e., (PPAR-γ Agonist Pioglitazone)
Insulin resistance <ul style="list-style-type: none"> <li>• Liver fat content</li> <li>• Visceral fat mass</li> <li>• Adipocyte function (insulin sensitivity, FFA, adiponectin secretion)</li> </ul>	Worse	Improved	Improved
Type 2 diabetes <ul style="list-style-type: none"> <li>• Glycemia</li> <li>• Atherogenic dyslipidemia</li> </ul>	Worse	Improved	Improved
Cardiometabolic risk <ul style="list-style-type: none"> <li>• CVD</li> <li>• Endothelial function</li> <li>• Subclinical inflammation</li> </ul>	Worse	Improved	Improved

Thus, a comprehensive medical approach is needed that includes behavioral modification and the appropriate selection of individuals as candidates for pharmacotherapy or bariatric surgery (75). Weight loss in patients with NAFLD requires a long-term multidisciplinary approach with the goal of improving quality of life and helping individuals adopt a healthy eating pattern and increase their physical activity, ideally to achieve a weight loss of  $\geq 10\%$ . Many studies have shown that this goal is best obtained with frequent communication and trust between the health care team and patients that involves setting realistic and flexible weight loss goals and considering the use of pharmacotherapy when needed.

Although there are no approved drug therapies specifically to treat NASH, an ever-increasing number of RCTs have shown that weight loss by any means, including bariatric surgery, reverses steatohepatitis and halts fibrosis progression and the development of cirrhosis. Among weight loss medications, GLP-1 receptor agonists have emerged as a revolutionary approach that takes advantage of human physiology to promote weight loss. The best studied of these agents in RCTs with paired biopsies in people with NASH are liraglutide and semaglutide (76). An in-depth review of current pharmacological interventions in NAFLD is included elsewhere in this article collection (77). Lifestyle changes combined with GLP-1 receptor agonist therapy is more successful than dietary approaches alone in reducing weight by  $\geq 10\%$ , a weight loss threshold that has been associated with significant histological improvement of NASH (9). The beneficial effect of GLP-1 receptor agonists on the liver is closely related to the magnitude of weight loss (18,75,76). As summarized in Table 1, treatment with a GLP-1 receptor agonist is also associated with improved glycemic control, amelioration of atherogenic dyslipidemia, and other cardiometabolic benefits, which, combined, reduce cardiovascular risk.

The role of glycemic control has been controversial in the absence of RCTs designed to establish the role of improving hyperglycemia per se, independent of effects on weight or insulin resistance (1,18). Observational studies have yielded conflicting results, with some studies reporting a modest association between higher A1C and worse fibrosis (78), while others have not found an association (3,20,38,66). For example, a recent study reported that higher A1Cs were observed in people with type 2 diabetes who had NAFLD compared with those without NAFLD (6.9 vs. 6.5%), or in those with versus without NASH (7.7 vs. 7.4%). However, although both differences were statistically significant, the differences in A1C between groups was overall small, and hyperglycemia was not associated to advanced fibrosis (12). When combined, available evidence suggests that hyperglycemia in type 2 diabetes has an overall modest effect on NASH.

Pioglitazone (together with GLP-1 receptor agonists) has been incorporated into the ADA's 2023 NAFLD clinical recommendations as an option to treat NASH (9) and has also been added to other clinical practice guidelines (5–8). Several paired-biopsy RCTs document its efficacy and safety to reverse NASH in people with obesity, prediabetes, or type 2 diabetes (79–83). Recent meta-analyses have confirmed its benefit on steatohepatitis and, to a lesser degree, fibrosis (84,85). Table 1 highlights the metabolic benefits of pioglitazone, which include improvement in insulin sensitivity, glucose and lipid metabolism, and a broad spectrum of cardiometabolic factors (e.g., endothelial function, systemic inflammation, lipids, and adiponectin) (10,18,86).

The ADA's 2023 guidelines also suggest the use of pioglitazone to lower the risk of cerebrovascular events and myocardial infarction in patients with a history of stroke who also have prediabetes and insulin resistance (9). Pioglitazone

significantly decreases cardiovascular risk in patients with (87) or without (88) type 2 diabetes, as well as the progression of atherosclerosis, as reviewed elsewhere (18,86).

## Conclusion

NAFLD does not happen in isolation, but rather is part of a broader metabolic dysfunction emerging from chronic insulin resistance in the context of a broad spectrum of genetic and acquired factors. The prevalence of steatosis is increasing, especially in people with type 2 diabetes (4,68). This increase is not surprising, because steatosis predisposes people to the development of type 2 diabetes (1,2) Both share a common soil of metabolic dysfunction and risk factors linked to insulin resistance. On the other hand, having type 2 diabetes greatly increases the chances of developing steatohepatitis and advanced fibrosis, as well as CVD, which is the main cause of mortality in people with NAFLD.

The best strategy for these complex patients involves early identification, proper fibrosis risk-stratification, referral to a specialist when indicated, and management by a multidisciplinary health care team that can help patients take a proactive approach to reverse the metabolic dysfunction associated with insulin resistance and its comorbidities (Table 1). All clinicians must proactively act now, as we have the tools today to halt disease progression and improve quality of life for millions of people. To do nothing and let people slowly drift toward cirrhosis is the unbearable alternative.

## DUALITY OF INTEREST

K.C. has received research support toward the University of Florida as a principal investigator from Echosens, Inventiva, LabCorp, and Nordic Bioscience, he is also a consultant for Aligos, Arrowhead, AstraZeneca, BMS, Boehringer Ingelheim, Covance, GSK, Eli Lilly, Madrigal, Novo Nordisk, Prosciento, Sagimet, and Siemens. No other potential conflicts of interest relevant to this article were reported.

## AUTHOR CONTRIBUTIONS

Both authors contributed to writing, reviewing, and editing the manuscript. K.C. is the guarantor of this work and, as such, had full access to all materials and takes responsibility for the accuracy and integrity of the content.

## REFERENCES

1. Bril F, Sanyal A, Cusi K. Metabolic syndrome and its association with nonalcoholic steatohepatitis. *Clin Liver Dis* 2023;27:187–210
2. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. *Gastroenterology* 2012;142:711–725.e6
3. Lomonaco R, Godinez Leiva E, Bril F, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening. *Diabetes Care* 2021;44:399–406
4. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology* 2023;77:1335–1347
5. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797–1835
6. Kanwal F, Shubrook JH, Younossi Z, et al. Preparing for the NASH epidemic: a call to action. *Diabetes Care* 2021;44:2162–2172
7. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification and management of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2021;161:1657–1669
8. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022;28:528–562
9. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: *Standards of Care in Diabetes—2023*. *Diabetes Care* 2023;46(Suppl. 1):S49–S67
10. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol* 2022;10:284–296
11. Harrison SA, Gawrieh S, Roberts K, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. *J Hepatol* 2021;75:284–291
12. Castera L, Laouenan C, Vallet-Pichard A, et al.; QUID-NASH investigators. High prevalence of NASH and advanced fibrosis in type 2 diabetes: a prospective study of 330 outpatients undergoing liver biopsies for elevated ALT, using a low threshold. *Diabetes Care* 2023;46:1354–1362
13. Ajmera V, Cepin S, Tesfai K, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. *J Hepatol* 2023;78:471–478
14. Ren Z, Simons PIHG, Wesseliuss A, Stehouwer CDA, Brouwers MCGJ. Relationship between NAFLD and coronary artery disease: a Mendelian randomization study. *Hepatology* 2023;77:230–238
15. Jarvis H, Craig D, Barker R, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of population-based observational studies. *PLoS Med* 2020;17:e1003100
16. Mantovani A, Petracca G, Beatrice G, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and risk of incident diabetes mellitus: an updated meta-analysis of 501 022 adult individuals. *Gut* 2021;70:962–969
17. Cusi K, Godinez Leiva E. Cardiovascular risk in patients with nonalcoholic fatty liver disease: looking at the liver to shield the heart. *Curr Opin Lipidol* 2020;31:364–366
18. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. *JHEP Rep* 2019;1:312–328
19. Scorletti E, Carr RM. A new perspective on NAFLD: focusing on lipid droplets. *J Hepatol* 2022;76:934–945
20. Lomonaco R, Bril F, Portillo-Sanchez P, et al. Metabolic impact of nonalcoholic steatohepatitis in obese patients with type 2 diabetes. *Diabetes Care* 2016;39:632–638

## FROM RESEARCH TO PRACTICE NAFLD in Diabetes: A Call to Action

21. Byrne CD, Targher G. Non-alcoholic fatty liver disease-related risk of cardiovascular disease and other cardiac complications. *Diabetes Obes Metab* 2022;24(Suppl. 2):28–43
22. Budd J, Cusi K. Role of agents for the treatment of diabetes in the management of nonalcoholic fatty liver disease. *Curr Diab Rep* 2020;20:59
23. Longo M, Meroni M, Paolini E, et al. TM6SF2/PNPLA3/MBOAT7 loss-of-function genetic variants impact on NAFLD development and progression both in patients and in in vitro models. *Cell Mol Gastroenterol Hepatol* 2022;13:759–788
24. Jonas W, Schürmann A. Genetic and epigenetic factors determining NAFLD risk. *Mol Metab* 2021;50:101111
25. Dongiovanni P, Stender S, Pietrelli A, et al. Causal relationship of hepatic fat with liver damage and insulin resistance in nonalcoholic fatty liver. *J Intern Med* 2018;283:356–370
26. Luukkonen PK, Qadri S, Ahlholm N, et al. Distinct contributions of metabolic dysfunction and genetic risk factors in the pathogenesis of non-alcoholic fatty liver disease. *J Hepatol* 2022;76:526–535
27. Gellert-Kristensen H, Richardson TG, Davey Smith G, Nordestgaard BG, Tybjaerg-Hansen A, Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. *Hepatology* 2020;72:845–856
28. Stender S, Kozlitina J, Nordestgaard BG, Tybjaerg-Hansen A, Hobbs HH, Cohen JC. Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci. *Nat Genet* 2017;49:842–847
29. Liu DJ, Peloso GM, Yu H, et al.; Charge Diabetes Working Group; EPIC-InterAct Consortium; EPIC-CVD Consortium; GOLD Consortium; VA Million Veteran Program. Exome-wide association study of plasma lipids in >300,000 individuals. *Nat Genet* 2017;49:1758–1766
30. Varadharajan V, Massey WJ, Brown JM. Membrane-bound O-acyltransferase 7 (MBOAT7)-driven phosphatidylinositol remodeling in advanced liver disease. *J Lipid Res* 2022;63:100234
31. Teo K, Abeysekera KWM, Adams L, et al.; EU-PNAFLD Investigators; GOLD Consortium. rs641738C>T near MBOAT7 is associated with liver fat, ALT and fibrosis in NAFLD: a meta-analysis. *J Hepatol* 2021;74:20–30
32. Santos-Baez LS, Ginsberg HN. Nonalcohol fatty liver disease: balancing supply and utilization of triglycerides. *Curr Opin Lipidol* 2021;32:200–206
33. Yki-Järvinen H, Luukkonen PK, Hodson L, Moore JB. Dietary carbohydrates and fats in nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol* 2021;18:770–786
34. Packard CJ, Boren J, Taskinen MR. Causes and consequences of hypertriglyceridemia. *Front Endocrinol (Lausanne)* 2020;11:252
35. Smith RL, Soeters MR, Wüst RCI, Houtkooper RH. Metabolic flexibility as an adaptation to energy resources and requirements in health and disease. *Endocr Rev* 2018;39:489–517
36. Fromenty B, Roden M. Mitochondrial alterations in fatty liver diseases. *J Hepatol* 2023;78:415–429
37. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest* 2005;115:1343–1351
38. Bril F, Barb D, Portillo-Sanchez P, et al. Metabolic and histological implications of intrahepatic triglyceride content in nonalcoholic fatty liver disease. *Hepatology* 2017;65:1132–1144
39. Gastaldelli A, Sabatini S, Carli F, et al. PPAR- $\gamma$ -induced changes in visceral fat and adiponectin levels are associated with improvement of steatohepatitis in patients with NASH. *Liver Int* 2021;41:2659–2670
40. Tacke F, Puengel T, Loomba R, Friedman SL. An integrated view of anti-inflammatory and antifibrotic targets for the treatment of NASH. *J Hepatol* 2023;79:552–566
41. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. *Cell* 2021;184:2537–2564
42. Schuppan D, Surabattula R, Wang XY. Determinants of fibrosis progression and regression in NASH. *J Hepatol* 2018;68:238–250
43. Lee YA, Friedman SL. Inflammatory and fibrotic mechanisms in NAFLD-Implications for new treatment strategies. *J Intern Med* 2022;291:11–31
44. Lee E, Korf H, Vidal-Puig A. An adipocentric perspective on the development and progression of non-alcoholic fatty liver disease. *J Hepatol* 2023;78:1048–1062
45. Portillo PYS, Bril F, Cusi K. Role of insulin resistance and diabetes in the pathogenesis and treatment of NAFLD. *Curr Hepatol Rep* 2014;13:159–170
46. Mota M, Banini BA, Cazanave SC, Sanyal AJ. Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease. *Metabolism* 2016;65:1049–1061
47. Dewidar B, Kahl S, Pafili K, Roden M. Metabolic liver disease in diabetes: from mechanisms to clinical trials. *Metabolism* 2020;111S:154299
48. Koliaki C, Roden M. Hepatic energy metabolism in human diabetes mellitus, obesity and non-alcoholic fatty liver disease. *Mol Cell Endocrinol* 2013;379:35–42
49. Moore MP, Cunningham RP, Meers GM, et al. Compromised hepatic mitochondrial fatty acid oxidation and reduced markers of mitochondrial turnover in human NAFLD. *Hepatology* 2022;76:1452–1465
50. Apostolopoulou M, Gordillo R, Koliaki C, et al. Specific hepatic sphingolipids relate to insulin resistance, oxidative stress, and inflammation in nonalcoholic steatohepatitis. *Diabetes Care* 2018;41:1235–1243
51. Koliaki C, Szendroedi J, Kaul K, et al. Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. *Cell Metab* 2015;21:739–746
52. Sunny NE, Kalavalapalli S, Bril F, et al. Cross-talk between branched-chain amino acids and hepatic mitochondria is compromised in nonalcoholic fatty liver disease. *Am J Physiol Endocrinol Metab* 2015;309:E311–E319
53. Longo M, Meroni M, Paolini E, Macchi C, Dongiovanni P. Mitochondrial dynamics and nonalcoholic fatty liver disease (NAFLD): new perspectives for a fairy-tale ending? *Metabolism* 2021;117:154708
54. Ortiz-Lopez C, Lomonaco R, Orsak B, et al. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). *Diabetes Care* 2012;35:873–878
55. Portillo-Sanchez P, Bril F, Maximos M, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. *J Clin Endocrinol Metab* 2015;100:2231–2238
56. Maximos M, Bril F, Portillo Sanchez P, et al. The role of liver fat and insulin resistance as determinants of plasma aminotransferase elevation in nonalcoholic fatty liver disease. *Hepatology* 2015;61:153–160
57. Kalavalapalli S, Leiva EG, Lomonaco R, et al. Adipose tissue insulin resistance predicts the severity of liver fibrosis in



- patients with type 2 diabetes and NAFLD. *J Clin Endocrinol Metab* 2023;108:1192–1201
58. Cusi K, Budd J, Johnson E, Shubrook J. Making sense of NAFLD clinical practice guidelines: what clinicians need to know. *Diabetes Spectr* 2024;37:XXX–XXX
  59. Schuppan D, Myneni S, Surabattula R. Liquid biomarkers for fibrotic NASH: progress in a complex field. *J Hepatol* 2022;76:5–7
  60. Friedman SL, Pinzani M. Hepatic fibrosis 2022: unmet needs and a blueprint for the future. *Hepatology* 2022;75:473–488
  61. Gancheva S, Kahl S, Pesta D, et al. Impaired hepatic mitochondrial capacity in nonalcoholic steatohepatitis associated with type 2 diabetes. *Diabetes Care* 2022;45:928–937
  62. Kwok R, Choi KC, Wong GL, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. *Gut* 2016;65:1359–1368
  63. Elkrief L, Rautou PE, Sarin S, Valla D, Paradis V, Moreau R. Diabetes mellitus in patients with cirrhosis: clinical implications and management. *Liver Int* 2016;36:936–948
  64. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015;149:389–97.e10
  65. Sanyal AJ, Van Natta ML, Clark J, et al.; NASH Clinical Research Network (CRN). Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med* 2021;385:1559–1569
  66. Barb D, Repetto EM, Stokes ME, Shankar SS, Cusi K. Type 2 diabetes mellitus increases the risk of hepatic fibrosis in individuals with obesity and nonalcoholic fatty liver disease. *Obesity (Silver Spring)* 2021;29:1950–1960
  67. Lomonaco R, Ortiz-Lopez C, Orsak B, et al. Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with nonalcoholic fatty liver disease. *Hepatology* 2012;55:1389–1397
  68. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019;71:793–801
  69. Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology* 2020;158:1611–1625.e1612
  70. Mózes FE, Lee JA, Vali Y, et al.; LITMUS investigators. Performance of non-invasive tests and histology for the prediction of clinical outcomes in patients with non-alcoholic fatty liver disease: an individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8:704–713
  71. Selvaraj EA, Mózes FE, Jayaswal ANA, et al.; LITMUS Investigators. Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: a systematic review and meta-analysis. *J Hepatol* 2021;75:770–785
  72. Gidener T, Dierkhising RA, Mara KC, et al. Change in serial liver stiffness measurement by magnetic resonance elastography and outcomes in NAFLD. *Hepatology* 2023;77:268–274
  73. Jayaswal ANA, Levick C, Selvaraj EA, et al. Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease. *Liver Int* 2020;40:3071–3082
  74. Truong E, Gornbein JA, Yang JD, et al. MRI-AST (MAST) score accurately predicts major adverse liver outcome, hepatocellular carcinoma, liver transplant, and liver-related death. *Clin Gastroenterol Hepatol* 2023;21:2570–2577.e1
  75. Blüher M, Aras M, Aronne LJ, et al. New insights into the treatment of obesity. *Diabetes Obes Metab* 2023;25:2058–2072
  76. Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide-1 receptor agonists for the management of NAFLD. *J Clin Endocrinol Metab* 2022;107:29–38
  77. Genua I, Cusi K. Pharmacological approaches to nonalcoholic fatty liver disease: current and future therapies. *Diabetes Spectr* 2024;37:XXX–XXX
  78. Alexopoulos AS, Crowley MJ, Wang Y, et al. Glycemic control predicts severity of hepatocyte ballooning and hepatic fibrosis in nonalcoholic fatty liver disease. *Hepatology* 2021;74:1220–1233
  79. Bril F, Biernacki DM, Kalavalapalli S, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2019;42:1481–1488
  80. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355:2297–2307
  81. Sanyal AJ, Chalasani N, Kowdley KV, et al.; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362:1675–1685
  82. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165:305–315
  83. Huang JF, Dai CY, Huang CF, et al. First-in-Asian double-blind randomized trial to assess the efficacy and safety of insulin sensitizer in nonalcoholic steatohepatitis patients. *Hepatol Int* 2021;15:1136–1147
  84. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med* 2017;177:633–640
  85. Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. *Lancet Gastroenterol Hepatol* 2022;7:367–378
  86. DeFronzo RA, Inzucchi S, Abdul-Ghani M, Nissen SE. Pioglitazone: the forgotten, cost-effective cardioprotective drug for type 2 diabetes. *Diab Vasc Dis Res* 2019;16:133–143
  87. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279–1289
  88. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016;374:1321–1331
  89. Huang DQ, Wilson LA, Behling C, et al.; NASH Clinical Research Network. Fibrosis progression rate in biopsy-proven nonalcoholic fatty liver disease among people with diabetes versus people without diabetes: a multicenter study. *Gastroenterology* 2023;165:463–472.e5
  90. Julián MT, Ballesta S, Pera G, et al. Abdominal obesity and dysglycemia are risk factors for liver fibrosis progression in NAFLD subjects: a population-based study. *Front Endocrinol (Lausanne)* 2023;13:1051958

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