Review Article

Diabetes and NAFLD: A Synergistic Threat to Metabolic Health

Shilpa Chaudhary[1] , Keerti Manocha[2], Praveen Malik[2], Monica Aggarwal[2], Rekha Rao[3], Minakshi Garg[1]*

[1]School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar Sector 3, New Delhi- 110017, India
[2]ESIC Medical College & Hospital, NH-3, NIT, Faridabad-121001, India
[3]Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, Hisar 125001, India

Abstract

Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2Dm) are increasingly recognized as interrelated metabolic disorders, each contributing to the other's progression. NAFLD, a leading cause of chronic liver disease globally, is often underdiagnosed due to its asymptomatic nature. The startlingly high frequency of NAFLD, especially in those with T2Dm, emphasizes the need of thorough screening in high-risk groups. In the setting of T2Dm, the pathophysiology of NAFLD comprises intricate metabolic pathways that exacerbate the disease's progression. These pathways include insulin resistance, lipotoxicity, and chronic inflammation. Early diagnosis and timely intervention are crucial to prevent the advancement of NAFLD to more severe stages, such as nonalcoholic steatohepatitis (NASH) and cirrhosis. Current guidelines advocate for routine NAFLD screening in patients with T2Dm, emphasizing the importance of early detection. Therapeutic approaches have evolved that are pivotal in managing these intertwined conditions. Each of these treatments offers unique benefits, from improving glycemic control to mitigating liver fat accumulation and reducing cardiovascular risks. This review highlights the pathophysiological linkages, clinical implications, and therapeutic advancements in managing these conditions. By exploring global prevalence, emerging diagnostic tools, and novel therapies, we propose an integrative framework for improved patient outcomes.

Introduction

Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of liver conditions in which excessive fat accumulates in the liver (steatosis) of individuals who consume little or no alcohol. This spectrum includes nonalcoholic steatohepatitis (NASH), marked by inflammation and liver cell damage, and simple fatty liver (NAFL), which shows minimal or no inflammation or damage. NASH increases the risk of liver failure, cirrhosis, and fibrosis.[1,2] The disease can progress from steatosis to cirrhosis, often with periods of stability or regression.

Clinicians diagnose NAFLD by detecting steatosis in more than 5% of hepatocytes on histology or by measuring liver fat content above 5.6% using proton magnetic resonance spectroscopy (^{1}H-MRS).[3] NAFLD has become a leading cause of hepatocellular carcinoma (HCC) and now ranks among the primary indications for liver transplantation in Western countries.[4,5] Rising obesity rates, particularly in rural areas, along with sedentary lifestyles and poor diets linked to urbanization, have driven this trend.[6,7] The prevalence of NAFLD also increases with age, especially among postmenopausal women.[8]

Treatment primarily aims to reduce cardiovascular (CV) and liver-related mortality. Clinicians monitor intermediate outcomes, such as hepatic fibrosis and steatosis, to track disease progression. Although many individuals with hepatic steatosis remain complication-free, some progress to NASH, which can advance to cirrhosis and HCC.[9] Early diagnosis and management of diabetes-associated NAFLD play a crucial role in preventing progression and related complications.[10] In 2023, experts revised the NAFLD nomenclature to "metabolic dysfunction-associated steatotic liver disease (MASLD)" to improve awareness and reduce stigma associated with terms like "fatty liver" and "nonalcoholic."[11] However, this review uses term NAFLD, as the American Diabetes Association (ADA) has not yet formally adopted MASLD.

NAFLD often coexists with type 2 diabetes mellitus (T2DM), metabolic syndrome (MetS), obesity, and dyslipidemia.[1] Among patients with MetS, cardiovascular disease remains the leading cause of death in those with NAFLD.[1] Coexisting T2DM and NAFLD significantly

raise cardiovascular risk, largely due to atherogenic dyslipidemia marked by high triglycerides, low HDL cholesterol, and small, dense LDL particles.[12] NAFLD severity—including advanced fibrosis, cirrhosis, and HCC—strongly correlates with diabetes, even when liver enzymes remain normal.[13,14]

T2DM and NAFLD share a bidirectional, mutually reinforcing relationship: individuals with T2DM have a higher risk of NAFLD, and vice versa. Globally, the incidence of T2DM in individuals with NAFLD reaches 24 cases per 1,000 person-years.[15] Overweight and obese individuals face nearly triple the risk of NAFLD compared to those with normal weight.[16] Common pathophysiological mechanisms, such as obesity, dyslipidemia, and insulin resistance (IR), link these conditions.[12]

Given this close association, clinicians must adopt integrated treatment strategies to manage T2DM and NAFLD together. This review explores the complex interplay between these two metabolic disorders and proposes strategies for their joint prevention and management.

Global prevalence and incidence

According to the National Diabetes Statistics Report released by the Centers for Disease Control and Prevention in 2021, approximately 11.6% of Americans have T2DM, while 38% are affected by prediabetes. The burden of both conditions increases substantially with age: among individuals aged 65 and older, the prevalence of diabetes and prediabetes is reported at 29.2% and 48.8%, respectively. Stratified by ethnicity, the highest prevalence of diagnosed diabetes was observed in American Indian and Alaska Native adults (13.6%), followed by non-Hispanic Black (12.1%), Hispanic (11.7%), non-Hispanic Asian (9.1%), and non-Hispanic White adults (6.9%) (CDC, 2021).[17]

Globally, the prevalence of NAFLD continues to rise, particularly among individuals who are overweight or obese. Current estimates indicate that NAFLD affects nearly 38% of the world's population. A recent meta-analysis reported a global pooled prevalence of 30.05%, with East Asia exhibiting the highest regional prevalence at 32.31%. Notably, NAFLD prevalence has increased by more than 50%, rising from 25.26% during 1990–2006 to 38.20% between 2016–2019. The more advanced and progressive form of the disease, NASH, has a global prevalence ranging from 5% to 7%. However, this figure increases substantially in individuals with T2DM, in whom the prevalence of NASH is estimated at 37%, with approximately 17% affected by advanced liver fibrosis. Additionally, the pooled incidence of NAFLD is estimated at 48.89 cases per 1,000 persons per year, reflecting a 58% increase compared to earlier estimates from 1994–2006. Males tend to exhibit a higher median prevalence of NAFLD than females (40% vs. 26%; $P < 0.0001$).[18]

Association between NAFLD and T2Dm
Cardiovascular risks

Individuals with T2DM who also have NAFLD are at significantly elevated risk for CV complications. Studies indicate that the presence of NAFLD increases the risk of developing CV disease by approximately twofold in individuals with T2DM compared to those without NAFLD.[19] This increased risk is supported by evidence of greater carotid intima-media thickness in patients with NAFLD and T2DM, a surrogate marker of atherosclerosis and predictor of CV events.[20] Moreover, these individuals often exhibit elevated coronary artery calcium (CAC) scores, which are indicative of subclinical coronary artery disease and correlate with higher risk of adverse cardiac outcomes.[21] Additionally, patients often present with early left ventricular diastolic dysfunction, reduced myocardial perfusion, and impaired oxygen delivery to cardiac tissue, all of which contribute to ischemic heart disease.[22] These patients also show diminished myocardial high-energy phosphate metabolism, compromising cardiac contractility and overall function.[23]

Microvascular complications

Beyond macrovascular disease, NAFLD exacerbates diabetic microvascular complications, such as diabetic retinopathy and chronic kidney disease.[24] These pathological changes are driven by a constellation of harmful mediators—pro-inflammatory, procoagulant, and prooxidant molecules—which contribute to systemic IR, atherogenic dyslipidemia, and hepatic secretion of key proteins including retinol-binding protein-4 (RBP-4), fibroblast growth factor-21 (FGF-21), and fetuin-A.[25] Notably, fetuin-A impairs insulin signaling by inhibiting insulin receptor tyrosine kinase activity in the liver and skeletal muscle, thereby worsening IR. This contributes to the accelerated onset of microvascular complications in diabetic patients.[25]

Shared mechanism

Advanced stages of NAFLD—including NASH, liver fibrosis, cirrhosis, and HCC—occur more frequently in T2DM populations.[26] Disease progression from simple steatosis to these advanced forms is driven by worsening metabolic dysfunction.[27] A predictive model by Bazick et al for diagnosing NASH and advanced fibrosis in NAFLD patients with T2DM achieved 90% specificity and 56.8% sensitivity by integrating BMI, waist circumference, HbA1c, insulin resistance, ferritin, albumin, ALT, and AST.[28] Elevated inflammatory markers and hyperinsulinemia further link T2DM to increased HCC risk.[29] These associations highlight the importance of reciprocal screening for NAFLD and T2DM. Non-invasive tools like elastography are increasingly valuable for detecting hepatic fibrosis in these patients.[30] Although strong associations exist between NAFLD and CV disease, chronic kidney disease, and liver outcomes in T2DM,

further research is essential to confirm causality and refine integrated screening and management strategies.

Pathogenesis

NAFLD develops through multiple interacting mechanisms. Excess hepatic lipid accumulates when fatty acid influx from diet, adipose lipolysis, and de novo lipogenesis surpasses disposal via VLDL export and β-oxidation.[31] Although these pathways initially upregulate to compensate, they eventually fail, leading to hepatocyte lipid retention. Hepatic IR, partly driven by diacylglycerol (DAG)-mediated activation of PKCε, disrupts insulin signaling and aggravates systemic IR in skeletal muscle and adipose tissue.[32] Inefficient mitochondrial fat oxidation and toxic lipid intermediates further induce hepatocyte injury, oxidative stress, and cytokine-driven necroinflammation—creating a "lipotoxic" environment that drives progression from simple steatosis to NASH and fibrosis.[33] Figure 1 describes the key risk factors for NAFLD development and progression.

Recent findings expand this mechanistic view to include broader metabolic and cardiometabolic implications. For example, a paediatric meta-analysis reported that structured lifestyle interventions and targeted supplementation reduce ALT, AST, BMI, and insulin resistance in children with NAFLD. However, the review also revealed major evidence gaps and heterogeneity in trial design, highlighting the need for more robust studies.[34]

Clinical presentation and diagnostic approaches

Most patients with NAFLD remain asymptomatic in early stages and report no liver-related symptoms. Hepatomegaly is the most common clinical finding, detected by abdominal palpation. As the disease progresses

to NASH or cirrhosis, complications such as portal hypertension become more evident.[34] Clinicians should suspect NAFLD in patients with MetS components—obesity, hypertension, hyperglycemia, or dyslipidemia—and hepatic steatosis on imaging. Diagnosis relies on exclusion of other causes like alcohol use or hepatotoxic drugs.[28,34]
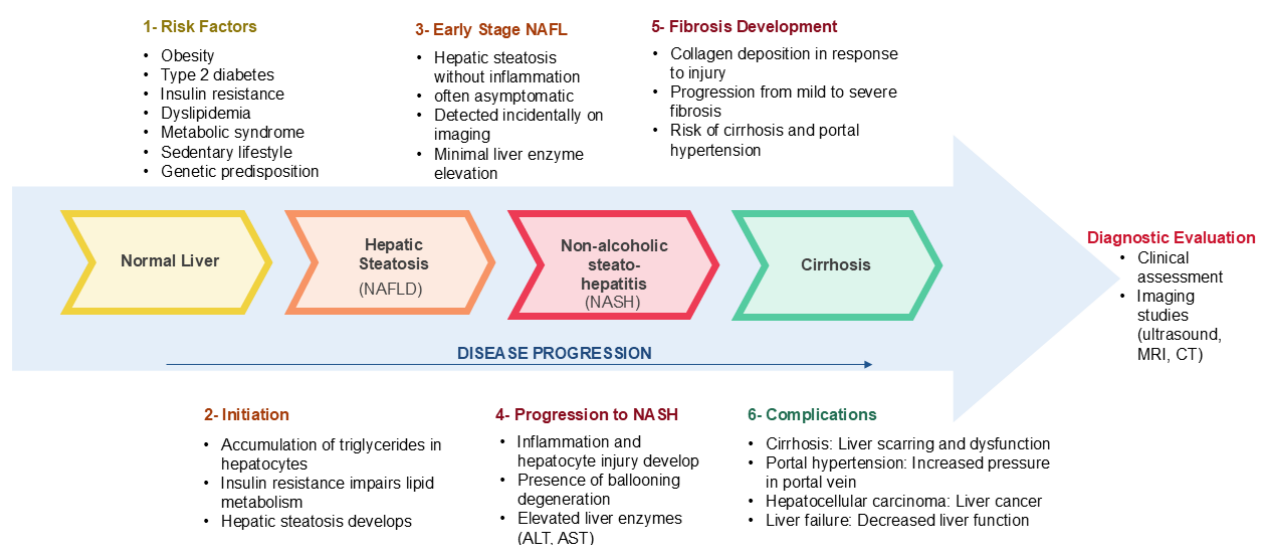
After identifying NAFLD, clinicians must determine progression to NASH or fibrosis because these increase complication risk and worsen outcomes. Liver biopsy remains the gold standard for differentiating NAFL from NASH, staging fibrosis, and excluding other chronic liver diseases.[35] However, its invasiveness, cost, and associated risks—pain, bleeding, and rare complications—limit its routine use.

Non-invasive tools, such as elastography for liver stiffness assessment, now play a key role in fibrosis evaluation.[36,37] Clinicians also use scoring systems like NAFLD Fibrosis Score, FIB-4, and APRI, based on clinical and biochemical data.[38] Table 1 summarizes these serum-based markers.

Despite progress, these methods lack the accuracy of biopsy in some cases.[39] Current guidelines recommend biopsy for patients with high suspicion of NASH or advanced fibrosis, while non-invasive tests guide evaluation and monitoring in low-risk cases.[40-42] Research is advancing novel tools—biomarkers, metabolomics, and genetic testing—to improve diagnostic precision and enable early risk stratification.[43]

Current guidance on screening for NAFLD in High-risk patients

There is increasing recognition of the need for early identification of NAFLD, particularly within primary care settings, given its high prevalence and severity in

1- Risk Factors
- Obesity
- Type 2 diabetes
- Insulin resistance
- Dyslipidemia
- Metabolic syndrome
- Sedentary lifestyle
- Genetic predisposition

3- Early Stage NAFL
- Hepatic steatosis without inflammation
- often asymptomatic
- Detected incidentally on imaging
- Minimal liver enzyme elevation

5- Fibrosis Development
- Collagen deposition in response to injury
- Progression from mild to severe fibrosis
- Risk of cirrhosis and portal hypertension

Normal Liver → Hepatic Steatosis (NAFLD) → Non-alcoholic steato-hepatitis (NASH) → Cirrhosis

DISEASE PROGRESSION

Diagnostic Evaluation
- Clinical assessment
- Imaging studies (ultrasound, MRI, CT)

2- Initiation
- Accumulation of triglycerides in hepatocytes
- Insulin resistance impairs lipid metabolism
- Hepatic steatosis develops

4- Progression to NASH
- Inflammation and hepatocyte injury develop
- Presence of ballooning degeneration
- Elevated liver enzymes (ALT, AST)

6- Complications
- Cirrhosis: Liver scarring and dysfunction
- Portal hypertension: Increased pressure in portal vein
- Hepatocellular carcinoma: Liver cancer
- Liver failure: Decreased liver function

Figure 1. Key risk factors for NAFLD development and progression. This figure highlights the primary risk factors linked to the onset and advancement of NAFLD. Abbreviations: NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MRI, Magnetic resonance imaging; CT, Computed Tomography

Table 1. Non-invasive Serum biomarkers methods for NAFLD screening [44]

Diagnostic panel	Description	Accuracy			Dual cut offs	Detection capacity
		AUROC score	Sensitivity	Specificity		
Blood based tests						
HSI	Parameters involved BMI, sex, AST: ALT ratio and T2D presence	0.81 in detecting NAFLD	93.1% 46%	92.4% 92%	HSI<30- rule out FL HSI>36- rule in FL	Detect Steatosis but inadequate distinction of severity
FLI	Parameters involved BMI, WC, serum GGT, Triglycerides	0.84 in detecting FL	87% 61%	64% 86%	FLI<30 rule out FL, FLI≥60 rule in FL	Detect Steatosis but cannot distinguish between grades
Steato Test	Rare biomarkers not done routinely like GGT, total bilirubin, α2m, ApoA-1, haptoglobin, ALT, BMI, total cholesterol, Triglycerides, and glucose adjusted for age, gender, weight and height	0.80 for steatosis>5%	90% 46%	54% 88%	Steato Test<0.3 can exclude grade 2–4 steatosis; Steato Test≥0.7 is suggestive of grade 2–4 steatosis	High cost and α2m, ApoA1, haptoglobin are not available in routine examination
K-NAFLD score	Parameters involve sex, WC, SBP and Triglycerides	0.93 in detecting NAFLD	PPV 99% and NPV 72.3%		K-NAFLD<−3.285 rule out NAFLD, K-NAFLD>0.884 rule in NAFLD	For reference standard NAFLD liver fat score is used instead of biopsy
NAFL screening score	Parameters involved AST: ALT, BMI, fasting plasma glucose, age, uric acid, triglycerides	0.825 for males 0.861 for females	79.9% 89.4%	66.3% 69%	Cut-off of NAFL screening score Male: 33 Female: 29	For reference standard NAFLD liver fat score is used instead of biopsy
NFL Score	AST: ALT ratio and T2D presence, metabolic syndrome,	0.86	84% 95%	69% 56%	NFL≤0.640 and≥1.413	Limited availability as insulin level is needed
NAFL risk score	BMI, triglycerides multiply by GGT, AST: ALT ratio, LDL-C, HDL-C, uric acid	0.743 for males 0.820 for females	- -	- -	-	No validation study, Suboptimal gold standard based on ultrasonography
LAP score	Parameters involve sex, WC and TG	0.79 0.68	93% 86%	34% 50%	LAP score>30 LAP score>40	No validation study, Suboptimal gold standard based on ultrasonography
ION	Male: waist-to-hip ratio, triglycerides, ALT and HOMA Female: triglycerides, ALT and HOMA	0.77	81% 60%	56% 82%	ION<11 ION≥22	No validation study, Suboptimal gold standard based on ultrasonography

α2M, α2-macroglobulin; ALT, alanine aminotransferase; ApoA-1, Apolipoprotein AI; AST, aspartate aminotransferase; AUROC: Area under the receiver-operating characteristics curve; BMI, body mass index; FL, Fatty liver; FLI, Fatty liver index; FSI, Fasting insulin serum; GGT, gamma-glutamyl transferase, HDL-C, high density lipoprotein cholesterol; HOMA, homeostatic model assessment for insulin resistance; HSI, Hepatic steatosis Index; ION, index of nonalcoholic steatohepatitis; LAP, Lipid accumulation product; LDL-C, low-density lipoprotein cholesterol; NFL, NAFLD Liver fat; NAFLD, non-alcoholic fatty liver disease; NPV: Negative predictive value; PPV: Positive predictive value; SBP: Systolic blood pressure; T2D, Type 2 Diabetes mellitus; WC, waist circumference.

individuals with MetS and T2DM.[45] Due to the often-silent nature of the disease, a significant proportion of individuals with undiagnosed NAFLD and advanced fibrosis remain in the community. Detecting these cases early is critical, as no pharmacological treatments are currently approved for NAFLD or NASH.[46] While routine population-based screening remains controversial—primarily due to concerns about cost-effectiveness, test reliability, biopsy-related risks, and the absence of disease-specific therapies—there is growing consensus that targeted screening of high-risk groups (such as individuals over 50 years of age, and those with T2DM or MetS) is important for prognostic assessment, particularly when advanced fibrosis is suspected.[47,48]

However, existing clinical guidelines offer divergent recommendations regarding NAFLD screening. The American Association for the Study of Liver Diseases (AASLD) currently discourages routine screening in the general population, irrespective of body mass index (BMI), though it emphasizes the importance of increased awareness among individuals with T2DM.[48] Similarly, the National Institute for Health and Care Excellence (NICE) in the United Kingdom has not recommended routine screening in its clinical guidelines.[34] In contrast, the European Association for the Study of the Liver (EASL), along with the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO), advocates for targeted screening in individuals with MetS or obesity, particularly those meeting specific risk criteria.[49] Likewise, regional organizations such as the Asian Pacific Association for the Study of the Liver (APASL) and the Korean Association for the Study of the Liver (KASL) also support risk-based screening strategies.[50,51] Furthermore, screening recommendations vary across professional societies, including those specializing in diabetes, paediatrics, and endocrinology, reflecting ongoing debate and evolving evidence in these subpopulations.[52-54] Figure 2 outlines a proposed protocol for screening and managing NAFLD, incorporating current international recommendations and risk stratification strategies.

Lifestyle and pharmacological approaches in NAFLD management

No anti-diabetic drug currently holds approval for NAFLD treatment. Weight loss and physical activity
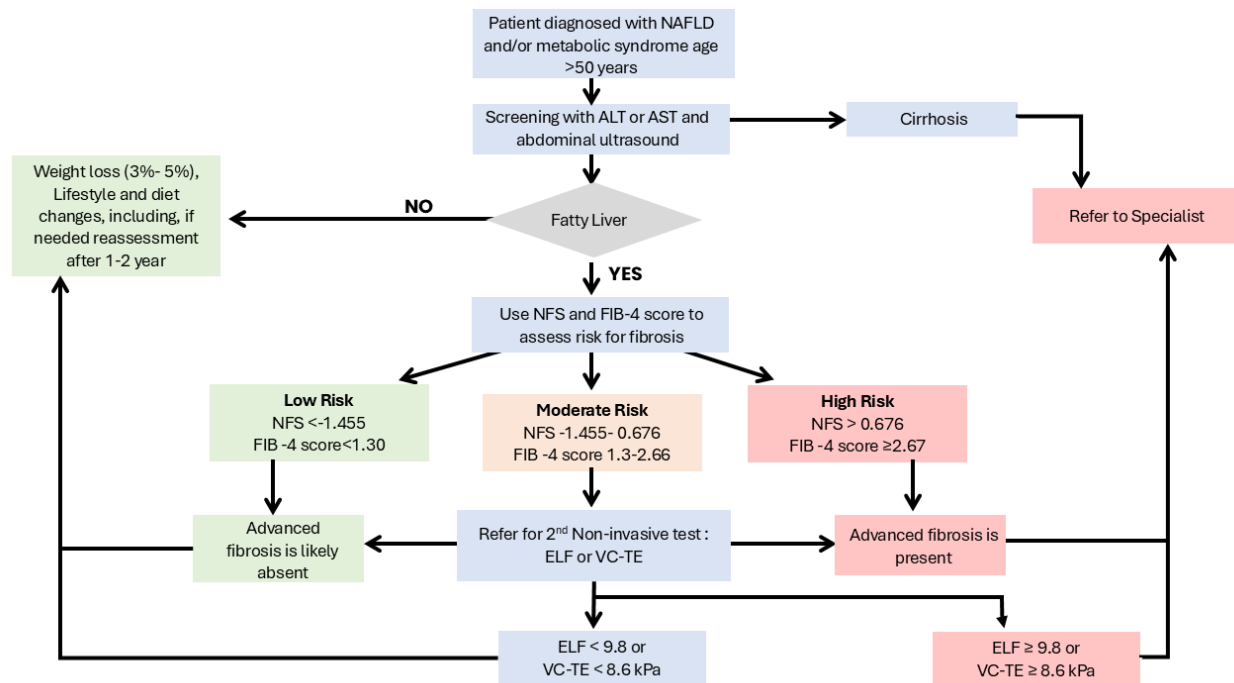
Figure 2. Proposed protocol for NAFLD screening and management. A stepwise approach for the screening and management of non-alcoholic fatty liver disease (NAFLD) is illustrated. The protocol incorporates initial risk stratification followed by non-invasive assessment using either the Enhanced Liver Fibrosis (ELF) test or vibration-controlled transient elastography (VC-TE). Patients are guided through diagnostic and management pathways based on fibrosis risk, aiming for early identification of advanced liver disease and timely intervention

remain the only consistently effective interventions for improving biochemical markers and histological features—steatosis, inflammation, and fibrosis. Evidence shows physical activity benefits liver health even without significant weight loss,[55,56] but sustained weight reduction offers the greatest improvements.[57,58]

RCTs and observational studies confirm that weight loss correlates with better liver biomarkers in NAFLD and NASH.[59] A ≥ 5% weight loss improves steatosis, while 7–9% reduces inflammation and ballooning. Meaningful fibrosis regression usually requires > 10% reduction.[2,60] Despite proven benefits, maintaining such weight loss remains challenging, especially in obese and insulin-resistant patients.

Because NAFLD and T2DM share epidemiological and metabolic pathways, researchers have explored antidiabetic agents—such as insulin sensitizers, GLP-1 receptor agonists, and SGLT2 inhibitors—for NAFLD treatment. Many show promise in reducing steatosis and inflammation, but large-scale, long-term trials are needed before recommending them clinically.[61-63]

Metformin
Metformin, a widely prescribed biguanide for T2DM, reduces hepatic glucose production and improves insulin sensitivity, thereby lowering blood sugar levels without causing weight gain.[64,65] It primarily activates AMP-activated protein kinase (AMPK) in hepatocytes, which suppresses gluconeogenesis and decreases hepatic lipid accumulation.[66] Additionally, metformin inhibits de novo

lipogenesis and promotes fatty acid oxidation, reducing liver fat content.[67] These actions make metformin effective for glycemic control in T2DM and for addressing metabolic dysfunctions linked to NAFLD and MetS.[68,69]

Metformin also modulates gut microbiota by promoting beneficial bacteria and reducing harmful microbes, potentially enhancing gut barrier function and preventing harmful substances from entering the bloodstream—key factors in NAFLD pathogenesis.[68,69] Studies, including those by Mazza et al, indicate that metformin may benefit NAFLD management even in non-diabetic patients, especially when combined with a hypocaloric diet and weight control.[70]

Thiazolidinediones (TZDs)
TZDs primarily manage T2DM by activating peroxisome proliferator-activated receptor-gamma (PPAR-γ) receptors. These nuclear receptors, present in adipose tissue, liver, skeletal muscle, and the gastrointestinal tract, regulate energy balance, lipid storage, and glucose metabolism. By activating PPAR-γ, TZDs promote adipogenesis to lower free fatty acids, improve insulin sensitivity in the liver, adipose tissue, and muscles, enhance glucose uptake in peripheral and splanchnic regions, and reduce hepatic glucose production.[71,72]

Troglitazone, the first TZD, improved liver histology in NASH patients but was later withdrawn due to liver toxicity.[73] Newer TZDs—pioglitazone and rosiglitazone—remain approved and have not shown a similar risk of hepatotoxicity, even with extensive clinical and post-

marketing exposure.[74] Both agents improve histological and biochemical features of NASH, reinforcing the role of insulin resistance in its pathogenesis.[75]

Pioglitazone

Clinicians recommend pioglitazone, a TZD derivative and PPAR-γ agonist, for T2DM.[76] At low doses, it reduces inflammation and fibrosis in NAFLD, increases adiponectin, and enhances insulin sensitivity. Pioglitazone improves glucose and lipid metabolism, lowers triglycerides and small, dense LDL, raises HDL, and normalizes free fatty acids, reversing atherogenic dyslipidemia.[74] Studies show pioglitazone improves liver histology and biochemical markers, while discontinuation worsens NASH.[77] Mahady et al reported improvements in steatosis, inflammation, ballooning, and fibrosis.[78]

Pioglitazone promotes adipogenesis and can cause weight gain, especially with long-term use.[79] Meta-analyses confirm higher weight and BMI in non-diabetic patients vs. placebo, consistent with earlier studies.[78–80] Weight gain in diabetic NAFLD patients was not statistically significant and may result from increased fat and fluid retention.[81]

Pioglitazone slows progression from prediabetes to T2DM[82,83] and reduces CVD risk in both diabetic and non-diabetic individuals.[83,84] It also slows atherosclerosis, improves diastolic function, and reduces epicardial fat.[85,86] In Sanyal's trial of 247 non-diabetic NASH patients, vitamin E—but not pioglitazone—showed significant NASH improvement, although both improved LFTs.[87] Cusi et al observed NASH resolution in 51% of pioglitazone-treated patients vs. 19% placebo ($P < 0.001$).[88]

Use of pioglitazone in non-diabetic patients is debated. Tang and Ferwana linked long-term use to bladder cancer,[89,90] though Korhonen disputed this claim.[91] Meta-analyses indicate risks of heart failure[92] and fractures,[93] while edema is more common when combined with insulin.

European guidelines (EASL, EASD, EASO) recommend pioglitazone for treating NAFLD in patients with T2DM and occasionally off-label for non-diabetics. In contrast, American (AASLD) and UK (NICE) guidelines restrict its use to diabetic patients with NAFLD.[94] Recently, the ADA included pioglitazone in its recommendations for drug classes that improve NASH in diabetic patients.[95]

Rosiglitazone

The FDA approved rosiglitazone for T2DM, but Europe withdrew it in 2010 and the U.S. restricted its use in 2011 due to CV safety concerns, despite favourable NAFLD outcomes.[96] In a single-arm study of 30 NASH patients with impaired glucose tolerance or T2DM, 8 mg/day for 48 weeks resolved NASH in 45% and significantly reduced ALT.[97] A larger trial of 68 patients showed improved glycemic control and liver enzymes after 24 weeks, with a mean weight gain of 2.6 ± 2.4 kg.[98]

The FLIRT trial reported that rosiglitazone improved steatosis in 47% vs. 16% with placebo and normalized transaminases, but prolonged use did not improve fibrosis and caused weight gain.[99,100] A subsequent study of 135 NASH patients found no significant histological benefit from adding metformin or losartan; metformin slightly reduced weight gain, but not significantly.[101] Further FLIRT analysis showed increased hepatic PPARγ and pro-inflammatory gene expression, raising safety concerns.[102] These findings, combined with CV risk and weight gain, limit rosiglitazone's role in NAFLD management.

Lobeglitazone

Lobeglitazone, a newer TZD and dual PPARγ/partial PPARα agonist, is marketed in Korea as Duvie® for diabetes.[103] In a mouse model of diet-induced NAFLD, 4 weeks of lobeglitazone improved glucose regulation, steatosis, and lipid levels by upregulating fatty acid β-oxidation genes and downregulating lipogenesis and gluconeogenesis genes.[104] Human data are limited. In a single-arm trial of 50 T2DM patients with NAFLD (CAP > 250 dB/m), 0.5 mg lobeglitazone for 24 weeks modestly but significantly reduced steatosis, improved glycemic control, and decreased atherogenic dyslipidemia.[105]

Sodium–glucose linked transporter-2 (SGLT2) inhibitors

SGLT2 inhibitors improve NAFLD via multiple mechanisms: better glycemic control, reduced visceral fat, increased adiponectin, lower uric acid, reduced oxidative stress and inflammation, and weight loss. They also provide cardiorenal protection.[106] These agents block renal glucose reabsorption, causing glycosuria, and are effective in heart failure and CKD, even without diabetes.[107] They improve mitochondrial function and increase β-hydroxybutyrate levels but carry risks of genitourinary infections and rare ketoacidosis.[106] Studies show SGLT2 inhibitors lower AST more effectively than pioglitazone, though their advantage over GLP-1 RAs is not significant.[108] GLP-1 RAs remain effective but limited by GI side effects and injection requirements.

Glucagon-like peptide-1 (GLP-1) RAs

GLP-1 RAs reduce major adverse cardiovascular events (MACEs) and slow kidney disease progression in T2DM.[109] These agents improve insulin sensitivity, suppress hepatic glucose production, and reduce hepatic fat via decreased lipogenesis and increased fatty acid oxidation.[110,111] They also promote weight loss and are approved for obesity treatment.[112] FDA-approved agents include exenatide, lixisenatide, liraglutide, semaglutide, dulaglutide, and albiglutide, administered daily or weekly.[113] Long-term use lowers HbA1c by 0.8–1.9%, with long-acting forms offering superior glycemic control.[114,115]

Liraglutide is the most studied GLP-1 RA for NAFLD. It improves insulin sensitivity, reduces liver fat, and

lowers fibrosis risk (3.1% vs. 6.1%) in T2DM patients.[116] A Phase II trial showed daily 1.8 mg liraglutide for 48 weeks improved histology and resolved NASH in 39% vs. 9% with placebo ($P = 0.019$).[117]

Semaglutide demonstrated safety and improved glycemic control in compensated NASH cirrhosis but did not significantly improve fibrosis after 48 weeks. Non-invasive measures and MRI-PDFF showed fat reduction.[118]

Tirzepatide, a dual GIP/GLP-1 agonist, reduced liver fat in the SURPASS-3 substudy across all doses.[119]

α-Glucosidase inhibitors

Agents like acarbose, miglitol, and voglibose slow carbohydrate digestion and modestly lower glucose but have limited NAFLD data.[120] A 24-week mouse study combining ezetimibe and acarbose improved histology.[121] In a human trial of 17 T2DM patients with NASH, miglitol (150 mg/day, 12 months) reduced BMI, ALT, and improved steatosis and inflammation, but not fibrosis or ballooning.[122] Acarbose appears safe in cirrhosis[123,124] and reduces CV events and hypertension in prediabetes,[125] though it can mildly raise ALT and, rarely, cause hepatotoxicity.[126]

Recent evidences and pipeline studies

Recent evidence strengthens the role of IR and metabolic dysfunction in NAFLD and highlights its bidirectional relationship with T2DM. Oh et al reported that NAFLD independently increases the risk of heart failure and CV mortality in T2DM patients.[127] Zhang et al identified triglyceride-glucose (TyG) indices—especially TyG-WWI—as strong predictors of all-cause and CV mortality in MASLD with diabetes or prediabetes.[128] Novel biomarkers, including the TG/APOA1 ratio[129] and TyG-BMI index,[130] show superior diagnostic value for detecting NAFLD in T2DM patients. Nontraditional lipid markers, such as the atherogenic index of plasma (AIP) and residual cholesterol (RC), outperform traditional lipid panels in predicting abnormal glucose metabolism.[131] Wu et al also linked elevated thyroid autoantibodies to a higher risk of NAFLD in T2DM.[132] In paediatric NAFLD, lifestyle changes and nutritional supplements significantly improved liver enzymes and insulin resistance, emphasizing early intervention benefits.[133] Collectively, these findings underscore the metabolic and cardiovascular impact of NAFLD and the need for early detection and integrated care.

In March 2024, the US FDA approved resmetirom as the first drug specifically for NAFLD treatment.[134] Previously, no FDA-approved therapy existed for NAFLD, including antidiabetic agents. Although clinicians frequently used drugs like metformin, thiazolidinediones, SGLT2 inhibitors, and GLP-1 RAs off-label to manage metabolic dysfunction in NAFLD, none held official approval for this indication. Numerous studies remain ongoing, and over 10 active trials are investigating antidiabetic drugs for NAFLD treatment (Supplementary file 1, Table S1).[135]

Several clinical trials aim to identify effective treatments for NAFLD and NASH. A trial measuring hepatic mitochondrial fluxes will compare pioglitazone to placebo, with results expected by March 2027.[136] AIM 2 is testing low-dose pioglitazone in NASH, with completion anticipated in August 2027.[137] Another study is evaluating efinopegdutide versus Semaglutide and placebo in precirrhotic NASH, with results expected in February 2026.[138] The WAYFIND trial is assessing semaglutide combined with cilofexor and firsocostat in cirrhotic NASH patients, reporting in December 2024.[139] Additional trials with dapagliflozin, bempedoic acid, and henagliflozin are underway, with completion dates between December 2024 and November 2026.[140–142] Upcoming trials will also compare empagliflozin with pioglitazone in non-diabetic NASH and examine SGLT2 inhibitors in MASLD, both launching later in 2024.[143] These studies reflect a comprehensive effort to develop targeted therapies for NAFLD and NASH across different disease stages.

Table S2 summarizes key studies on pioglitazone in NAFLD.

Challenges and future directions

Managing NAFLD and T2DM remains challenging despite increasing recognition of their interconnection. Clinicians often miss NAFLD in T2DM patients because it typically remains asymptomatic until advanced stages. The lack of standardized screening protocols further complicates detection and management. Current pharmacological options—metformin, thiazolidinediones, SGLT2 inhibitors, and GLP-1 RAs—show promise but do not fully address NAFLD pathogenesis and exhibit inconsistent efficacy. Researchers must also clarify the long-term safety and potential adverse effects of these drugs across diverse populations.

This review has limitations. Included studies vary widely in design, sample size, and diagnostic criteria, limiting comparability and generalizability. Long-term outcomes, such as fibrosis regression and cardiovascular risk reduction, remain underexplored due to short follow-up durations. Most pharmacological evidence relies on off-label use and preliminary findings rather than robust, large-scale randomized controlled trials. Additionally, publication bias and the exclusion of unpublished or ongoing trial data may have influenced the completeness of this review.

Future research should focus on developing precise diagnostic tools and early-stage biomarkers, especially for T2DM patients. Personalized medicine approaches using genetic, epigenetic, and metabolic profiling could enable tailored therapies. Large-scale, long-term clinical trials are essential to confirm the safety and efficacy of both existing and emerging treatments. Integrating lifestyle interventions such as dietary modifications and

physical activity with pharmacotherapy offers additional benefits. Progress will require close collaboration among endocrinologists, hepatologists, and primary care providers. Ultimately, a multidisciplinary approach and sustained research are critical to reducing the global burden of NAFLD and T2DM.

Conclusion

NAFLD and T2DM are closely linked metabolic disorders that demand a unified, comprehensive management approach. There is an urgent need to raise awareness, promote early detection, and implement evidence-based strategies to alleviate the burden of these comorbidities. A holistic approach that considers the complex relationship between NAFLD and T2DM can help healthcare providers improve patient outcomes and reduce the societal impact of these growing public health challenges. Due to its asymptomatic nature, NAFLD often remains undiagnosed. Early screening and risk stratification are essential to prevent progression to advanced liver disease.

Authors' Contribution
Conceptualization: Shilpa Chaudhary, Minakshi Garg.
Data curation: Praveen Malik.
Formal analysis: Praveen Malik.
Validation: Praveen Malik, Minakshi Garg.
Visualization: Monica Aggarwal.
Supervision: Minakshi Garg.
Writing–original draft: Shilpa Chaudhary, Keerti Manocha.
Writing–review & editing: Shilpa Chaudhary, Keerti Manocha, Praveen Malik, Monica Aggarwal, Rekha Rao Minakshi Garg.

Competing Interests
The authors declare that they have no competing interests.

Ethics Approval
Not applicable.

Supplementary Files
Supplementary file 1 contains Table S1 and Table S2.

References
1. Marchesini G, Day CP, Dufour JF, Canbay A, Nobili V, Ratziu V, et al. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016;64(6):1388-402. doi: 10.1016/j.jhep.2015.11.004
2. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67(1):328-57. doi: 10.1002/hep.29367
3. Bugianesi E. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: disease mongering or call to action? *Diabetologia* 2016;59(6):1145-7. doi: 10.1007/s00125-016-3930-7
4. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol* 2015;62(1 Suppl):S47-64. doi: 10.1016/j.jhep.2014.12.012
5. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. *Clin Gastroenterol Hepatol* 2019;17(4):748-55. e3. doi: 10.1016/j.cgh.2018.05.057
6. Zhang X, Goh GB, Chan WK, Wong GL, Fan JG, Seto WK, et al. Unhealthy lifestyle habits and physical inactivity among Asian patients with non-alcoholic fatty liver disease. *Liver Int* 2020;40(11):2719-31. doi: 10.1111/liv.14638
7. Wong VW, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. *J Hepatol* 2023;79(3):842-52. doi: 10.1016/j.jhep.2023.04.036
8. Wang W, Chen J, Wang Z, Chen J, Cheng W, Zhou Z. An estimation model of urban land accessibility. *Int J Environ Res Public Health* 2021;18(3):1258. doi: 10.3390/ijerph18031258
9. Mehta SR. Advances in the treatment of nonalcoholic fatty liver disease. *Ther Adv Endocrinol Metab* 2010;1(3):101-15. doi: 10.1177/2042018810379587
10. Khandelwal R, Dassanayake AS, Conjeevaram HS, Singh SP. Non-alcoholic fatty liver disease in diabetes: when to refer to the hepatologist? *World J Diabetes* 2021;12(9):1479-93. doi: 10.4239/wjd.v12.i9.1479
11. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;78(6):1966-86. doi: 10.1097/hep.0000000000000520
12. Bril F, Cusi K. Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action. *Diabetes Care* 2017;40(3):419-30. doi: 10.2337/dc16-1787
13. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013;10(6):330-44. doi: 10.1038/nrgastro.2013.41
14. Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). *Medicine (Baltimore)* 2018;97(13):e0214. doi: 10.1097/md.0000000000010214
15. Cao L, An Y, Liu H, Jiang J, Liu W, Zhou Y, et al. Global epidemiology of type 2 diabetes in patients with NAFLD or MAFLD: a systematic review and meta-analysis. *BMC Med* 2024;22(1):101. doi: 10.1186/s12916-024-03315-0
16. Younossi ZM, Henry L. Understanding the burden of nonalcoholic fatty liver disease: time for action. *Diabetes Spectr* 2024;37(1):9-19. doi: 10.2337/dsi23-0010
17. Centers for Disease Control and Prevention (CDC). *National Diabetes Statistics Report*. CDC; 2023. Available from: https://www.cdc.gov/diabetes/data/statistics-report/index.html.
18. 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(4):1335-47. doi: 10.1097/hep.0000000000000004
19. Ruan S, Yuan X, Liu J, Zhang Q, Ye X. Predictors of high cardiovascular risk among nonobese patients with type 2 diabetes and non-alcoholic fatty liver disease in a Chinese population. *Diabetes Metab Syndr Obes* 2024;17:493-506. doi: 10.2147/dmso.S441641
20. Shabbirhussain BV, Singh S, Dixit VK, Verma A, Singh SK. Carotid intima media as predictor of liver fibrosis in type 2 diabetes mellitus with NAFLD. *Diabetes Metab Syndr* 2022;16(7):102560. doi: 10.1016/j.dsx.2022.102560
21. Kwak MS, Yim JY, Kim D, Park MJ, Lim SH, Yang JI, et al. Nonalcoholic fatty liver disease is associated with coronary artery calcium score in diabetes patients with higher HbA1c. *Diabetol Metab Syndr* 2015;7:28. doi: 10.1186/s13098-015-0025-4

22. Wang S, Zhang X, Zhang Q, Zhang B, Zhao L. Is non-alcoholic fatty liver disease a sign of left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus? A systematic review and meta-analysis. *BMJ Open Diabetes Res Care* 2023;11(1):e003198. doi: 10.1136/bmjdrc-2022-003198

23. Rijzewijk LJ, Jonker JT, van der Meer RW, Lubberink M, de Jong HW, Romijn JA, et al. Effects of hepatic triglyceride content on myocardial metabolism in type 2 diabetes. *J Am Coll Cardiol* 2010;56(3):225-33. doi: 10.1016/j.jacc.2010.02.049

24. Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. *Nat Rev Endocrinol* 2018;14(2):99-114. doi: 10.1038/nrendo.2017.173

25. Ix JH, Sharma K. Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: the roles of fetuin-A, adiponectin, and AMPK. *J Am Soc Nephrol* 2010;21(3):406-12. doi: 10.1681/asn.2009080820

26. Anstee QM, McPherson S, Day CP. How big a problem is non-alcoholic fatty liver disease? *BMJ* 2011;343:d3897. doi: 10.1136/bmj.d3897

27. Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. *J Hepatol* 2013;59(3):550-6. doi: 10.1016/j.jhep.2013.04.027

28. Bazick J, Donithan M, Neuschwander-Tetri BA, Kleiner D, Brunt EM, Wilson L, et al. Clinical model for NASH and advanced fibrosis in adult patients with diabetes and NAFLD: guidelines for referral in NAFLD. *Diabetes Care* 2015;38(7):1347-55. doi: 10.2337/dc14-1239

29. Aleksandrova K, Boeing H, Nöthlings U, Jenab M, Fedirko V, Kaaks R, et al. Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology* 2014;60(3):858-71. doi: 10.1002/hep.27016

30. Constantinescu C, Săndulescu L, Săftoiu A. The role of elastography in non-alcoholic fatty liver disease. *Curr Health Sci J* 2020;46(3):255-69. doi: 10.12865/chsj.46.03.07

31. Petersen MC, Shulman GI. Roles of diacylglycerols and ceramides in hepatic insulin resistance. *Trends Pharmacol Sci* 2017;38(7):649-65. doi: 10.1016/j.tips.2017.04.004

32. Zhang CH, Zhou BG, Sheng JQ, Chen Y, Cao YQ, Chen C. Molecular mechanisms of hepatic insulin resistance in nonalcoholic fatty liver disease and potential treatment strategies. *Pharmacol Res* 2020;159:104984. doi: 10.1016/j.phrs.2020.104984

33. du Plessis J, van Pelt J, Korf H, Mathieu C, van der Schueren B, Lannoo M, et al. Association of adipose tissue inflammation with histologic severity of nonalcoholic fatty liver disease. *Gastroenterology* 2015;149(3):635-48.e14. doi: 10.1053/j.gastro.2015.05.044

34. Glen J, Floros L, Day C, Pryke R. Non-alcoholic fatty liver disease (NAFLD): summary of NICE guidance. *BMJ* 2016;354:i4428. doi: 10.1136/bmj.i4428

35. Forlano R, Sigon G, Mullish BH, Yee M, Manousou P. Screening for NAFLD-current knowledge and challenges. *Metabolites* 2023;13(4):536. doi: 10.3390/metabo13040536

36. Neuberger J, Patel J, Caldwell H, Davies S, Hebditch V, Hollywood C, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. *Gut* 2020;69(8):1382-403. doi: 10.1136/gutjnl-2020-321299

37. Rinaldi L, Giorgione C, Mormone A, Esposito F, Rinaldi M, Berretta M, et al. Non-invasive measurement of hepatic fibrosis by transient elastography: a narrative review. *Viruses* 2023;15(8). doi: 10.3390/v15081730

38. Zain SM, Tan HL, Mohamed Z, Chan WK, Mahadeva S, Basu RC, et al. Use of simple scoring systems for a public health

approach in the management of non-alcoholic fatty liver disease patients. *JGH Open* 2020;4(6):1155-61. doi: 10.1002/jgh3.12414

39. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol* 2014;20(2):475-85. doi: 10.3748/wjg.v20.i2.475

40. Spengler EK, Loomba R. Recommendations for diagnosis, referral for liver biopsy, and treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Mayo Clin Proc* 2015;90(9):1233-46. doi: 10.1016/j.mayocp.2015.06.013

41. Neuberger J, Cain O. The need for alternatives to liver biopsies: non-invasive analytics and diagnostics. *Hepat Med* 2021;13:59-69. doi: 10.2147/hmer.S278076

42. Lai JC, Liang LY, Wong GL. Noninvasive tests for liver fibrosis in 2024: are there different scales for different diseases? *Gastroenterol Rep (Oxf)* 2024;12:goae024. doi: 10.1093/gastro/goae024

43. Piazzolla VA, Mangia A. Noninvasive diagnosis of NAFLD and NASH. *Cells* 2020;9(4):1005. doi: 10.3390/cells9041005

44. Ahn SB. Noninvasive serum biomarkers for liver steatosis in nonalcoholic fatty liver disease: current and future developments. *Clin Mol Hepatol* 2023;29(Suppl):S150-6. doi: 10.3350/cmh.2022.0362

45. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *J Hepatol* 2021;75(3):659-89. doi: 10.1016/j.jhep.2021.05.025

46. Vieira Barbosa J, Lai M. Nonalcoholic fatty liver disease screening in type 2 diabetes mellitus patients in the primary care setting. *Hepatol Commun* 2021;5(2):158-67. doi: 10.1002/hep4.1618

47. Byrne CD, Targher G. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease: is universal screening appropriate? *Diabetologia* 2016;59(6):1141-4. doi: 10.1007/s00125-016-3910-y

48. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology* 2012;142(7):1592-609. doi: 10.1053/j.gastro.2012.04.001

49. Neuschwander-Tetri BA. Pharmacologic management of nonalcoholic steatohepatitis. *Gastroenterol Hepatol (N Y)* 2018;14(10):582-9.

50. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hepatol Int* 2020;14(6):889-919. doi: 10.1007/s12072-020-10094-2

51. Kang SH, Lee HW, Yoo JJ, Cho Y, Kim SU, Lee TH, et al. KASL Clinical Practice Guidelines: management of nonalcoholic fatty liver disease. *Clin Mol Hepatol* 2021;27(3):363-401. doi: 10.3350/cmh.2021.0178

52. Estrada E, Eneli I, Hampl S, Mietus-Snyder M, Mirza N, Rhodes E, et al. Children's Hospital Association consensus statements for comorbidities of childhood obesity. *Child Obes* 2014;10(4):304-17. doi: 10.1089/chi.2013.0120

53. McPherson S, Armstrong MJ, Cobbold JF, Corless L, Anstee QM, Aspinall RJ, et al. Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group. *Lancet Gastroenterol Hepatol* 2022;7(8):755-69. doi: 10.1016/s2468-1253(22)00061-9

54. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr* 2017;64(2):319-34. doi: 10.1097/mpg.0000000000001482

55. Houghton D, Thoma C, Hallsworth K, Cassidy S, Hardy T, Burt AD, et al. Exercise reduces liver lipids and visceral adiposity in patients with nonalcoholic steatohepatitis in a randomized controlled trial. *Clin Gastroenterol Hepatol* 2017;15(1):96-102.e3. doi: 10.1016/j.cgh.2016.07.031

56. Ratziu V. Non-pharmacological interventions in non-alcoholic fatty liver disease patients. *Liver Int* 2017;37 Suppl 1:90-6. doi: 10.1111/liv.13311

57. Glass LM, Dickson RC, Anderson JC, Suriawinata AA, Putra J, Berk BS, et al. Total body weight loss of ≥10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. *Dig Dis Sci* 2015;60(4):1024-30. doi: 10.1007/s10620-014-3380-3

58. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology* 2015;149(2):367-78.e5. doi: 10.1053/j.gastro.2015.04.005

59. Koutoukidis DA, Astbury NM, Tudor KE, Morris E, Henry JA, Noreik M, et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *JAMA Intern Med* 2019;179(9):1262-71. doi: 10.1001/jamainternmed.2019.2248

60. Bischoff SC, Bernal W, Dasarathy S, Merli M, Plank LD, Schütz T, et al. ESPEN practical guideline: clinical nutrition in liver disease. *Clin Nutr* 2020;39(12):3533-62. doi: 10.1016/j.clnu.2020.09.001

61. 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(11):59. doi: 10.1007/s11892-020-01349-1

62. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. *JHEP Rep* 2019;1(4):312-28. doi: 10.1016/j.jhepr.2019.07.002

63. Ong Lopez AM, Pajimna JA. Efficacy of sodium glucose cotransporter 2 inhibitors on hepatic fibrosis and steatosis in non-alcoholic fatty liver disease: an updated systematic review and meta-analysis. *Sci Rep* 2024;14(1):2122. doi: 10.1038/s41598-024-52603-5

64. Flory J, Lipska K. Metformin in 2019. *JAMA* 2019;321(19):1926-7. doi: 10.1001/jama.2019.3805

65. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. *Diabetes Care* 2021;44(Suppl 1):S111-24. doi: 10.2337/dc21-S009

66. Pinyopornpanish K, Leerapun A, Pinyopornpanish K, Chattipakorn N. Effects of metformin on hepatic steatosis in adults with nonalcoholic fatty liver disease and diabetes: insights from the cellular to patient levels. *Gut Liver* 2021;15(6):827-40. doi: 10.5009/gnl20367

67. Lin HV, Accili D. Hormonal regulation of hepatic glucose production in health and disease. *Cell Metab* 2011;14(1):9-19. doi: 10.1016/j.cmet.2011.06.003

68. Brandt A, Hernández-Arriaga A, Kehm R, Sánchez V, Jin CJ, Nier A, et al. Metformin attenuates the onset of non-alcoholic fatty liver disease and affects intestinal microbiota and barrier in small intestine. *Sci Rep* 2019;9(1):6668. doi: 10.1038/s41598-019-43228-0

69. Matafome P, Louro T, Rodrigues L, Crisóstomo J, Nunes E, Amaral C, et al. Metformin and atorvastatin combination further protect the liver in type 2 diabetes with hyperlipidaemia. *Diabetes Metab Res Rev* 2011;27(1):54-62. doi: 10.1002/dmrr.1157

70. Mazza A, Fruci B, Garinis GA, Giuliano S, Malaguarnera R, Belfiore A. The role of metformin in the management of NAFLD. *Exp Diabetes Res* 2012;2012:716404. doi: 10.1155/2012/716404

71. Francque S, Szabo G, Abdelmalek MF, Byrne CD, Cusi K, Dufour JF, et al. Nonalcoholic steatohepatitis: the role of peroxisome proliferator-activated receptors. *Nat Rev Gastroenterol Hepatol* 2021;18(1):24-39. doi: 10.1038/s41575-020-00366-5

72. Raschi E, Mazzotti A, Poluzzi E, De Ponti F, Marchesini G. Pharmacotherapy of type 2 diabetes in patients with chronic liver disease: focus on nonalcoholic fatty liver disease. *Expert Opin Pharmacother* 2018;19(17):1903-14. doi: 10.1080/14656566.2018.1531126

73. Caldwell SH, Hespenheide EE, Redick JA, Iezzoni JC, Battle EH, Sheppard BL. A pilot study of a thiazolidinedione, troglitazone, in nonalcoholic steatohepatitis. *Am J Gastroenterol* 2001;96(2):519-25. doi: 10.1111/j.1572-0241.2001.03553.x

74. Lebovitz HE. Thiazolidinediones: the forgotten diabetes medications. *Curr Diab Rep* 2019;19(12):151. doi: 10.1007/s11892-019-1270-y

75. Boettcher E, Csako G, Pucino F, Wesley R, Loomba R. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2012;35(1):66-75. doi: 10.1111/j.1365-2036.2011.04912.x

76. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022;45(11):2753-86. doi: 10.2337/dci22-0034

77. Lutchman G, Modi A, Kleiner DE, Promrat K, Heller T, Ghany M, et al. The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. *Hepatology* 2007;46(2):424-9. doi: 10.1002/hep.21661

78. Mahady SE, Webster AC, Walker S, Sanyal A, George J. The role of thiazolidinediones in non-alcoholic steatohepatitis - a systematic review and meta-analysis. *J Hepatol* 2011;55(6):1383-90. doi: 10.1016/j.jhep.2011.03.016

79. Boeckmans J, Natale A, Rombaut M, Buyl K, Rogiers V, De Kock J, et al. Anti-NASH drug development hitches a lift on PPAR agonism. *Cells* 2019;9(1):37. doi: 10.3390/cells9010037

80. Wang Z, Du H, Zhao Y, Ren Y, Ma C, Chen H, et al. Response to pioglitazone in non-alcoholic fatty liver disease patients with vs. without type 2 diabetes: a meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)* 2023;14:1111430. doi: 10.3389/fendo.2023.1111430

81. Derosa G. Efficacy and tolerability of pioglitazone in patients with type 2 diabetes mellitus: comparison with other oral antihyperglycaemic agents. *Drugs* 2010;70(15):1945-61. doi: 10.2165/11538100-000000000-00000

82. DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011;364(12):1104-15. doi: 10.1056/NEJMoa1010949

83. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016;374(14):1321-31. doi: 10.1056/NEJMoa1506930

84. Zhou Y, Huang Y, Ji X, Wang X, Shen L, Wang Y. Pioglitazone for the primary and secondary prevention of cardiovascular

and renal outcomes in patients with or at high risk of type 2 diabetes mellitus: a meta-analysis. *J Clin Endocrinol Metab* 2020;105(5):dgz252. doi: 10.1210/clinem/dgz252

85. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008;299(13):1561-73. doi: 10.1001/jama.299.13.1561

86. Moody AJ, Molina-Wilkins M, Clarke GD, Merovci A, Solis-Herrera C, Cersosimo E, et al. Pioglitazone reduces epicardial fat and improves diastolic function in patients with type 2 diabetes. *Diabetes Obes Metab* 2023;25(2):426-34. doi: 10.1111/dom.14885

87. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362(18):1675-85. doi: 10.1056/NEJMoa0907929

88. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, 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(5):305-15. doi: 10.7326/m15-1774

89. Tang H, Shi W, Fu S, Wang T, Zhai S, Song Y, et al. Pioglitazone and bladder cancer risk: a systematic review and meta-analysis. *Cancer Med* 2018;7(4):1070-80. doi: 10.1002/cam4.1354

90. Ferwana M, Firwana B, Hasan R, Al-Mallah MH, Kim S, Montori VM, et al. Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies. *Diabet Med* 2013;30(9):1026-32. doi: 10.1111/dme.12144

91. Korhonen P, Heintjes EM, Williams R, Hoti F, Christopher S, Majak M, et al. Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries. *BMJ* 2016;354:i3903. doi: 10.1136/bmj.i3903

92. Varas-Lorenzo C, Margulis AV, Pladevall M, Riera-Guardia N, Calingaert B, Hazell L, et al. The risk of heart failure associated with the use of noninsulin blood glucose-lowering drugs: systematic review and meta-analysis of published observational studies. *BMC Cardiovasc Disord* 2014;14:129. doi: 10.1186/1471-2261-14-129

93. Zhang YS, Zheng YD, Yuan Y, Chen SC, Xie BC. Effects of anti-diabetic drugs on fracture risk: a systematic review and network meta-analysis. *Front Endocrinol (Lausanne)* 2021;12:735824. doi: 10.3389/fendo.2021.735824

94. Ciardullo S, Vergani M, Perseghin G. Nonalcoholic fatty liver disease in patients with type 2 diabetes: screening, diagnosis, and treatment. *J Clin Med* 2023;12(17):5597. doi: 10.3390/jcm12175597

95. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes-2023. *Diabetes Care* 2023;46(Suppl 1):S49-67. doi: 10.2337/dc23-S004

96. Lu Y, Ma D, Xu W, Shao S, Yu X. Effect and cardiovascular safety of adding rosiglitazone to insulin therapy in type 2 diabetes: a meta-analysis. *J Diabetes Investig* 2015;6(1):78-86. doi: 10.1111/jdi.12246

97. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology* 2003;38(4):1008-17. doi: 10.1053/jhep.2003.50420

98. Wang CH, Leung CH, Liu SC, Chung CH. Safety and effectiveness of rosiglitazone in type 2 diabetes patients with nonalcoholic fatty liver disease. *J Formos Med Assoc* 2006;105(9):743-52. doi: 10.1016/s0929-6646(09)60202-3

99. Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 2008;135(1):100-10. doi: 10.1053/j.gastro.2008.03.078

100. Ratziu V, Charlotte F, Bernhardt C, Giral P, Halbron M, Lenaour G, et al. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. *Hepatology* 2010;51(2):445-53. doi: 10.1002/hep.23270

101. Torres DM, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of nonalcoholic steatohepatitis in humans: a 12-month randomized, prospective, open- label trial. *Hepatology* 2011;54(5):1631-9. doi: 10.1002/hep.24558

102. Lange NF, Graf V, Caussy C, Dufour JF. PPAR-targeted therapies in the treatment of non-alcoholic fatty liver disease in diabetic patients. *Int J Mol Sci* 2022;23(8):4305. doi: 10.3390/ijms23084305

103. Han L, Shen WJ, Bittner S, Kraemer FB, Azhar S. PPARs: regulators of metabolism and as therapeutic targets in cardiovascular disease. Part I: PPAR-α. *Future Cardiol* 2017;13(3):259-78. doi: 10.2217/fca-2016-0059

104. Choung S, Joung KH, You BR, Park SK, Kim HJ, Ku BJ. Treatment with lobeglitazone attenuates hepatic steatosis in diet-induced obese mice. *PPAR Res* 2018;2018:4292509. doi: 10.1155/2018/4292509

105. Lee YH, Kim JH, Kim SR, Jin HY, Rhee EJ, Cho YM, et al. Lobeglitazone, a novel thiazolidinedione, improves non-alcoholic fatty liver disease in type 2 diabetes: its efficacy and predictive factors related to responsiveness. *J Korean Med Sci* 2017;32(1):60-9. doi: 10.3346/jkms.2017.32.1.60

106. Xu B, Li S, Kang B, Zhou J. The current role of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes mellitus management. *Cardiovasc Diabetol* 2022;21(1):83. doi: 10.1186/s12933-022-01512-w

107. Veelen A, Andriessen C, Op den Kamp Y, Erazo-Tapia E, de Ligt M, Mevenkamp J, et al. Effects of the sodium-glucose cotransporter 2 inhibitor dapagliflozin on substrate metabolism in prediabetic insulin resistant individuals: a randomized, double-blind crossover trial. *Metabolism* 2023;140:155396. doi: 10.1016/j.metabol.2022.155396

108. Wei Q, Xu X, Guo L, Li J, Li L. Effect of SGLT2 inhibitors on type 2 diabetes mellitus with non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)* 2021;12:635556. doi: 10.3389/fendo.2021.635556

109. Zhang Y, Jiang L, Wang J, Wang T, Chien C, Huang W, et al. Network meta-analysis on the effects of finerenone versus SGLT2 inhibitors and GLP-1 receptor agonists on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus and chronic kidney disease. *Cardiovasc Diabetol* 2022;21(1):232. doi: 10.1186/s12933-022-01676-5

110. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab* 2018;27(4):740-56. doi: 10.1016/j.cmet.2018.03.001

111. Nevola R, Epifani R, Imbriani S, Tortorella G, Aprea C, Galiero R, et al. GLP-1 receptor agonists in non-alcoholic fatty liver disease: current evidence and future perspectives. *Int J Mol Sci* 2023;24(2):1703. doi: 10.3390/ijms24021703

112. Updike WH, Pane O, Franks R, Saber F, Abdeen F, Balazy DD, et al. Is it time to expand glucagon-like peptide-1 receptor agonist use for weight loss in patients without diabetes? *Drugs* 2021;81(8):881-93. doi: 10.1007/s40265-021-01525-x

113. Kalra S, Bhattacharya S, Kapoor N. Contemporary

classification of glucagon-like peptide 1 receptor agonists (GLP1RAs). *Diabetes Ther* 2021;12(8):2133-47. doi: 10.1007/s13300-021-01113-y

114. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Ther Adv Endocrinol Metab* 2021;12:2042018821997320. doi: 10.1177/2042018821997320

115. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab* 2021;46:101102. doi: 10.1016/j.molmet.2020.101102

116. Tan Y, Zhen Q, Ding X, Shen T, Liu F, Wang Y, et al. Association between use of liraglutide and liver fibrosis in patients with type 2 diabetes. *Front Endocrinol (Lausanne)* 2022;13:935180. doi: 10.3389/fendo.2022.935180

117. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387(10019):679-90. doi: 10.1016/s0140-6736(15)00803-x

118. Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2023;8(6):511-22. doi: 10.1016/s2468-1253(23)00068-7

119. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol* 2022;10(6):393-406. doi: 10.1016/s2213-8587(22)00070-5

120. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. *Diabetes Care* 2017;40(Suppl 1):S64-74. doi: 10.2337/dc17-S011

121. Nozaki Y, Fujita K, Yoneda M, Wada K, Shinohara Y, Takahashi H, et al. Long-term combination therapy of ezetimibe and acarbose for non-alcoholic fatty liver disease. *J Hepatol* 2009;51(3):548-56. doi: 10.1016/j.jhep.2009.05.017

122. Komatsu M, Tanaka N, Kimura T, Fujimori N, Sano K, Horiuchi A, et al. Miglitol attenuates non-alcoholic steatohepatitis in diabetic patients. *Hepatol Res* 2018;48(13):1092-8. doi: 10.1111/hepr.13223

123. Yamagishi S, Nakamura K, Inoue H. Acarbose is a promising therapeutic strategy for the treatment of patients with nonalcoholic steatohepatitis (NASH). *Med Hypotheses* 2005;65(2):377-9. doi: 10.1016/j.mehy.2005.01.032

124. Gentile S, Turco S, Guarino G, Oliviero B, Rustici A, Torella R. [Non-insulin-dependent diabetes mellitus associated with nonalcoholic liver cirrhosis: an evaluation of treatment with the intestinal alpha-glucosidase inhibitor acarbose]. *Ann Ital Med Int* 1999;14(1):7-14.

125. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290(4):486-94. doi: 10.1001/jama.290.4.486

126. Carrascosa M, Pascual F, Aresti S. Acarbose-induced acute severe hepatotoxicity. *Lancet* 1997;349(9053):698-9. doi: 10.1016/s0140-6736(05)60134-1

127. Oh R, Kim G, Lee KN, Cho SH, Kim JY, Kim S, et al. Metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes: risk of heart failure. *Cardiovasc Diabetol* 2024;23(1):391. doi: 10.1186/s12933-024-02489-4

128. Zhang Y, Wu J, Li T, Qu Y, Wang Y. Association of triglyceride-glucose related indices with mortality among individuals with MASLD combined with prediabetes or diabetes. *Cardiovasc Diabetol* 2025;24(1):52. doi: 10.1186/s12933-025-02616-9

129. Wang W, Chen Y, Tu M, Chen HJ. Triglycerides to apolipoprotein A1 ratio: an effective insulin resistance-associated index in identifying metabolic dysfunction-associated fatty liver disease in type 2 diabetes mellitus. *Front Endocrinol (Lausanne)* 2024;15:1384059. doi: 10.3389/fendo.2024.1384059

130. Qian X, Wu W, Chen B, Zhang S, Xiao C, Chen L, et al. Value of triglyceride glucose-body mass index in predicting nonalcoholic fatty liver disease in individuals with type 2 diabetes mellitus. *Front Endocrinol (Lausanne)* 2024;15:1425024. doi: 10.3389/fendo.2024.1425024

131. Liu J, Fu Q, Su R, Liu R, Wu S, Li K, et al. Association between nontraditional lipid parameters and the risk of type 2 diabetes and prediabetes in patients with nonalcoholic fatty liver disease: from the national health and nutrition examination survey 2017-2020. *Front Endocrinol (Lausanne)* 2024;15:1460280. doi: 10.3389/fendo.2024.1460280

132. Wu W, Yang Z, Li O, Gan L, Gao Y, Xiang C, et al. Elevated thyroid autoantibodies as risk factors for metabolic dysfunction-associated fatty liver disease in type 2 diabetes mellitus. *Front Endocrinol (Lausanne)* 2024;15:1478818. doi: 10.3389/fendo.2024.1478818

133. Omaña-Guzmán I, Rosas-Diaz M, Martínez-López YE, Perez-Navarro LM, Diaz-Badillo A, Alanis A, et al. Strategic interventions in clinical randomized trials for metabolic dysfunction-associated steatotic liver disease (MASLD) and obesity in the pediatric population: a systematic review with meta-analysis and bibliometric analysis. *BMC Med* 2024;22(1):548. doi: 10.1186/s12916-024-03744-x

134. Joszt L. *FDA Approves Resmetirom, First Treatment for NASH with Liver Fibrosis*. The American Journal of Managed Care (AJMC); 2024. Available from: https://www.ajmc.com/view/fda-approves-resmetirom-first-treatment-for-nash-with-liver-fibrosis. Accessed August 21, 2024.

135. Clinical Trial. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/search?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:act%20not. Published 2024. Accessed August 21, 2024.

136. The University of Texas Health Science Center at San Antonio. Quantifying Hepatic Mitochondrial Fluxes in Humans. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT05305287?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:rec%20act&rank=1. Published 2024. Accessed August 22, 2024.

137. University of Florida. Low-Dose Pioglitazone in Patients with NASH (AIM 2). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT04501406?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:not%20rec%20act&rank=2. Published 2024. Accessed August 22, 2024.

138. Merck Sharp & Dohme LLC. A Clinical Study of Efinopegdutide in Participants with Precirrhotic Nonalcoholic Steatohepatitis (NASH) (MK-6024-013). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT05877547?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggF-

ilters=status:not%20rec%20act&rank=3. Published 2024. Accessed August 22, 2024.

139. Gilead Sciences. Study of Semaglutide, and Cilofexor/Firsocostat, Alone and in Combination, in Adults with Cirrhosis Due to Nonalcoholic Steatohepatitis (NASH) (WAYFIND). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT04971785?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:not%20rec%20act&rank=4. Published 2024. Accessed August 22, 2024.

140. Medanta. Effect of Bempedoic Acid on Liver Fat in Individuals with Nonalcoholic Fatty Liver Disease and Type 2 Diabetes (B-LIFT). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT06035874?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:not%20rec%20act&rank=7. Published 2024. Accessed August 22, 2024.

141. Werida R. Dapagliflozin in Type 2 Diabetes Mellitus Patients (T2DM) with Nonalcoholic Fatty Liver Disease (NAFLD). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT05459701?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:not%20rec%20act&rank=6. Published 2024. Accessed August 22, 2024.

142. Zhujiang Hospital. Effect of Henagliflozein on Hepatic Fat Content in Patients with T2DM and NAFLD (HHTN). ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT06449833?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:not%20rec%20act&rank=8. Published 2024. Accessed August 22, 2024.

143. Tanta University. Comparative Clinical Study Between Empagliflozin Versus Pioglitazone in Non-Diabetic Patients with Non-Alcoholic Steatohepatitis. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/study/NCT05605158?cond=NAFLD%20-%20Nonalcoholic%20Fatty%20Liver%20Disease&term=NASH%20-%20Nonalcoholic%20Steatohepatitis&intr=Anti-Diabetics&aggFilters=status:not%20rec%20act&rank=5. Published 2024. Accessed August 22, 2024.

144. Yoneda M, Kobayashi T, Honda Y, Ogawa Y, Kessoku T, Imajo K, et al. Combination of tofogliflozin and pioglitazone for NAFLD: extension to the ToPiND randomized controlled trial. Hepatol Commun 2022;6(9):2273-85. doi: 10.1002/hep4.1993

145. Huang JF, Dai CY, Huang CF, Tsai PC, Yeh ML, Hsu PY, 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(5):1136-47. doi: 10.1007/s12072-021-10242-2

146. Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. Diabetes Care 2019;42(8):1481-8. doi: 10.2337/dc19-0167

147. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135(4):1176-84. doi: 10.1053/j.gastro.2008.06.047

148. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355(22):2297-307. doi: 10.1056/NEJMoa060326