Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Exploring Promising Therapies for Non-Alcoholic Fatty Liver Disease: A ClinicalTrials.gov Analysis

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Background: Non-alcoholic fatty liver disease (NAFLD) is a common disease and has been increasing in recent years. To date, no FDA-approved drug specifically targets NAFLD.

Methods: The terms "Non-alcoholic Fatty Liver Disease" and "NAFLD" were used in a search of ClinicalTrials.gov on August 24, 2023. Two evaluators independently examined the trials using predetermined eligibility criteria. Studies had to be interventional, NAFLD focused, in Phase IV, and completed to be eligible for this review.

Results: The ClinicalTrials.gov database was searched for trials examining pharmacotherapeutics in NAFLD. The search revealed 1364 trials, with 31 meeting the inclusion criteria. Out of these, 19 were finalized for evaluation. The dominant intervention model was Parallel. The most prevalent studies were in Korea (26.3%) and China (21.1%). The most common intervention was metformin (12.1%), with others like Exenatide and Pioglitazone accounting for 9.1%.

Conclusion: Therapeutics used to manage NAFLD are limited. However, various medications offer potential benefits. Further investigations are definitely warranted.

Keywords: NAFLD, hepatology, clinical trials, therapeutics, metabolic disorder

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common disease today, reflecting the increasing rates of obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM).[1,2] The pathophysiology of NAFLD includes multifaceted interactions between insulin resistance, abnormal lipid homeostasis, oxidative stress, and inflammation.[3,4] While non-pharmacological interventions, especially dietary and weight loss strategies, are the foundational management techniques for NAFLD, the persistence and adherence to such measures remain a challenge.[5]

Several promising therapeutic agents such as Peroxisome proliferator-activated receptor agonists, Farnesoid X receptor agonists, Glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter 2 (SGLT2) inhibitors are undergoing further analysis for their potential efficacy to counteract NAFLD progression. They work by modulating insulin sensitivity, rectifying lipid metabolism, abating hepatic inflammation, and reducing the risk of fibrosis and cirrhosis.[6–8] Current management emphasizes lifestyle modification including weight management. For instance, the

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Mediterranean diet, abundant in whole foods and beneficial fats, has shown promise in ameliorating hepatic lipid content and insulin dynamics in NAFLD individuals.[9,10]

Clinical trial databases, with ClinicalTrials.gov leading the cohort, serve as indispensable repositories for gauging the efficacy and safety of innovative interventions.[11] As of today, ClinicalTrials.gov alone encompasses a large range of clinical trials. Despite the growing amount of literature highlighting the potential of pharmacological interventions for NAFLD, the methodical assessment of clinical trials assessing these remedies is conspicuously lacking. Although ClinicalTrials.gov serves as an invaluable corpus of such trials, a dedicated review encapsulating the role of pharmacotherapeutics within the NAFLD therapeutic landscape is still awaited.

Methodological Framework and Research Design

Search Strategy and Inclusion Criteria

On August 24, 2023, a thorough search of ClinicalTrials.gov was conducted using the keywords "Non-alcoholic Fatty Liver Disease" and "NAFLD". Two evaluators reviewed the trials using established eligibility standards to ensure objectivity. To qualify, studies needed to focus predominantly on NAFLD and be interventional, in addition to being in Phase IV and being concluded.

Results

The preliminary search of the ClinicalTrials.gov database yielded 1364 trials. These were subsequently screened and filtered. Exclusion criteria were applied, eliminating trials that were incomplete (n = 762), non-interventional (n = 98), or outside of phase IV (n = 473). Initially, 31 studies met the inclusion parameters for our review. Upon further examination, 12 trials were excluded due to their inadequate focus on NAFLD. Thus, a total of 19 clinical trials were finalized for evaluation. The stepwise selection methodology is graphically represented in Figure 1, detailing the approach used to discern the pertinent clinical trials for this study.

Characteristics of Included Studies

Table 1 shows the description of the clinical trials studied. Most studies (89.5%) were randomized, while 10.5% were non-applicable regarding allocation. The primary intervention model used was Parallel (84.2%), followed by Single Group (10.5%) and Crossover (5.3%).

In terms of masking, nearly half (47.4%) had no masking, and the remaining studies employed Single (10.5%), Double (5.3%), Triple (15.8%), or Quadruple (21.1%) masking techniques. Geographically, Korea was the most common location for these studies, hosting just over one quarter (26.3%). China followed with 21.1%, and other countries, including Egypt and Germany, ranged from 5.3% to 10.5% of the studies.

Various interventions were used, with metformin being the most prevalent (12.1%). Other interventions such as Exenatide and Pioglitazone were used in 9.1% of the trials, and a diversity of other treatments appeared in 3.0% to 6.1% of the studies. Further details can be found in Table 2.

Pharmacological Treatment and Management Strategies

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, is used mainly for hyperuricemia and gout. Other indications include cardiovascular and kidney diseases.[12,13] Allopurinol exerts its therapeutic effect by inhibiting xanthine oxidase, a critical enzyme in the metabolic pathway that transforms hypoxanthine into xanthine and subsequently into uric acid.[13] Through this inhibition, allopurinol not only effectively lowers serum uric acid concentrations but also diminishes the production of reactive oxygen species.[14,15]

Elevated serum uric acid levels correlate independently with a heightened severity of hepatic steatosis and fibrosis.[16–18] The underlying pathophysiological mechanisms that might bridge hyperuricemia with NAFLD include insulin resistance and oxidative stress.[19] Notably, one specific trial incorporated allopurinol to evaluate the impact of xanthine oxidase inhibitors on MAFLD by regulating uric acid concentrations.

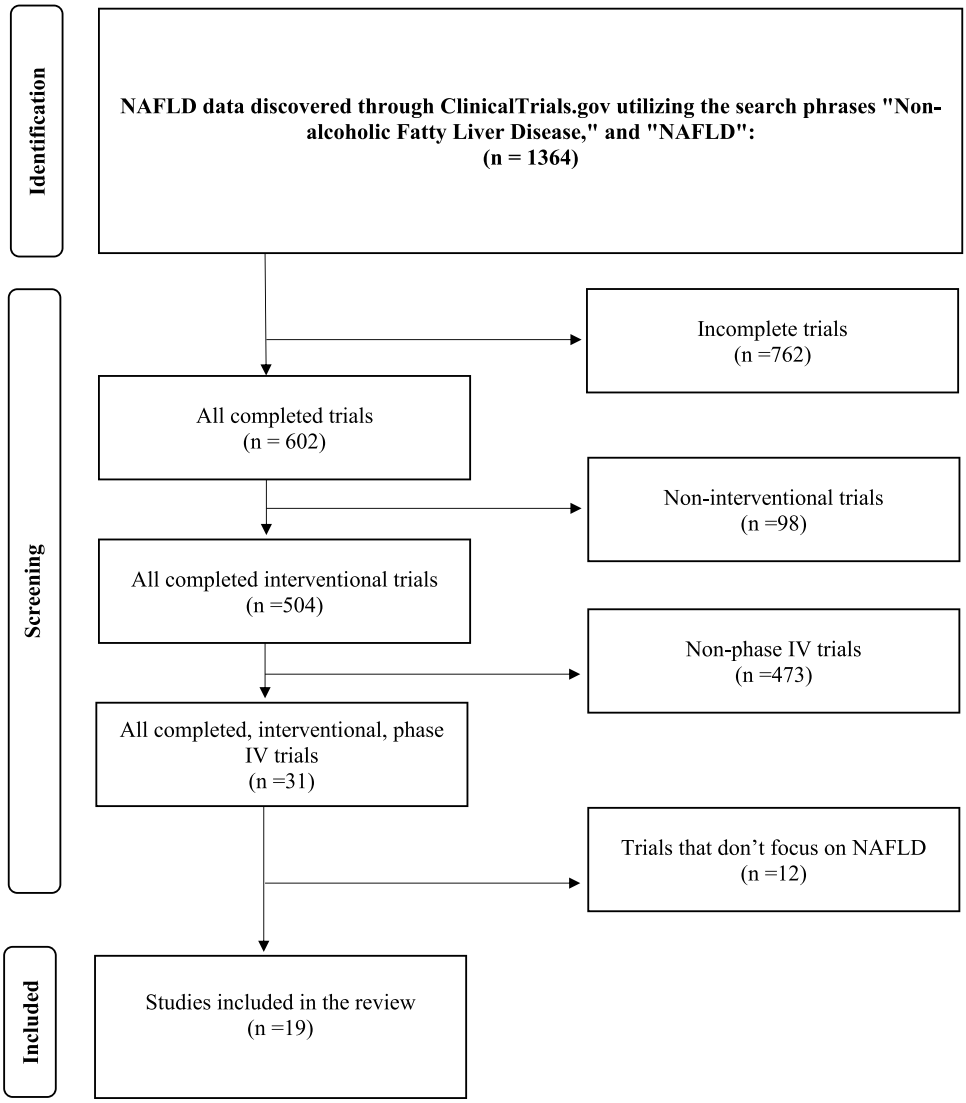

Figure 1 Flow diagram of trial selection process.

Empagliflozin

Empagliflozin, an SGLT2 inhibitor, is predominantly used to manage type 2 diabetes. Its mechanism of action involves inhibiting the SGLT2 protein within the proximal tubules of the kidneys, which in turn facilitates the excretion of glucose via the urine. This results in a notable reduction of blood glucose concentrations.[20] Empagliflozin is used also for weight reduction, decreased blood pressure, and enhancements in cardiovascular health outcomes.[21]

The intricate relationship between T2DM and NAFLD has been conclusively identified. NAFLD is currently acknowledged as the hepatic representation of the metabolic syndrome.[22] Given the proven efficacy of SGLT2 inhibitors in managing T2DM, there is' growing interest in their potential applicability in NAFLD therapy.[23,24] Empirical evidence from studies on empagliflozin indicates that its administration is linked to a substantial reduction in hepatic fat accumulation and improved liver enzyme in people with T2DM.[25] Moreover, Empagliflozin's potential to exert anti-inflammatory and antifibrotic effects is a subject of ongoing research. Preliminary findings are pointing toward encouraging results.[26] Notably, two clinical trials incorporated empagliflozin to report its influence on liver lipid content, energy metabolism, and overall body composition in recently diagnosed T2DM patients.

Table 1 Trial Characteristics

Characteristics	N (%)
Allocation	
N/A	2 (10.5)
Randomized	17 (89.5)
Intervention model	
Single group	2 (10.5)
Parallel	16 (84.2)
Crossover	1 (5.3)
Masking	
None	9 (47.4)
Single	2 (10.5)
Double	1 (5.3)
Triple	3 (15.8)
Quadruple	4 (21.1)
Locations	
N/A	1 (5.3)
China	4 (21.1)
Egypt	2 (10.5)
Finland	1 (5.3)
Germany	2 (10.5)
Japan	1 (5.3)
Korea	5 (26.3)
Malaysia	1 (5.3)
United Kingdom	1 (5.3)
United States	1 (5.3)
Intervention	
Allopurinol	1 (3.0)
Empagliflozin	2 (6.1)
Evogliptin	1 (3.0)
Exenatide	3 (9.1)
Febuxostat	1 (3.0)
Gliclazide	1 (3.0)
Glimepiride	1 (3.0)
Insulin glargine	2 (6.1)
Ipragliflozin	1 (3.0)
Liraglutide	2 (6.1)
Lobeglitazone	1 (3.0)
Metformin	4 (12.1)
Omega-3 acid ethyl esters	1 (3.0)
Pentoxifylline	1 (3.0)
Pioglitazone	3 (9.1)
Rifampicin	1 (3.0)
Salsalate	1 (3.0)
Sitagliptin	1 (3.0)
Tofogliflozin	1 (3.0)
Ursodeoxycholic acid	1 (3.0)
Vitamin D	2 (6.1)
Vitamin E	1 (3.0)

Evogliptin

Evogliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is predominantly used for managing T2DM by augmenting insulin secretion and reducing glucagon secretion.[27] Research has suggested that DPP-4 inhibitors could have therapeutic

Table 2 Overview of the Clinical Trials

NCT Number	Study Title	Objectives	Interventions	Primary Outcome Measures	Secondary Outcome Measures	Allocation	Intervention Model	Masking	Enrollment	Duration	Locations
NCT04910178	Follow-up of NAFLD Patients With MRI-PDFF	Investigate the liver's role in T2DM development and its association with NAFLD pathogenesis.	Empagliflozin 25 MG, Ursodeoxycholic acid, Pentoxifylline 400 MG.	Liver fat percentage via MRI-PDFF at six months; Fatty liver stage (0-III) via ultrasound at six months.	Evaluate 6-month changes in γ-GT, HbA1c, glucose levels, lipid profile, liver enzymes, bilirubin, and protein levels.	Randomized	Parallel	Single	80	364 days	Egypt
NCT01006889	Adding Exenatide to Insulin Therapy for Patients with Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease	Determine the effects of replacing premeal insulin with exenatide on hepatic steatosis, treatment efficacy, insulin secretion, weight impact, hypoglycemia rates, and biomarkers in T2DM and NAFLD patients.	Exenatide.	Hepatic Steatosis assessment via MRS at six months.	Assess 6-month A1c in T2DM patients on bedtime insulin with or without eventide, change in weight, hypoglycemic events, C-peptide levels, glucose infusion, and lipid profiles.	N/A	Single group	None	24	762 days	United States
NCT02649465	SGLT2 Inhibitor Versus Sulfonylurea on Type 2 Diabetes With NAFLD	Assess the efficacy of tofogliflozin vs glimepiride on liver histology and metabolic markers in NAFLD patients with T2DM over 48 weeks.	Tofogliflozin, Glimepiride.	Histologic improvement in NAFLD at 48 weeks.	Examine 48-week baseline changes in liver enzymes, body composition, glucose metabolism, insulin sensitivity, lipid profile, renal function, oxidative stress, cytokine, hepatokine levels, and more.	Randomized	Parallel	None	40	2052 days	Japan
NCT00760513	Treatment of Non-Alcoholic Fatty Liver Disease With n-3 Fatty Acids	Evaluate whether long-chain n-3 fatty acid supplementation influences NAFLD biomarkers and CVD/T2DM risk factors over 18 months.	OMACOR.	Change in Liver Fat Percentage via MR spectroscopy at 18 months; Liver Fibrosis Score at 18 months; NAFLD Fibrosis Score at 18 months.		Randomized	Parallel	Single	103	3293 days	United Kingdom

(*Continued*)

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Table 2 (Continued).

NCT Number	Study Title	Objectives	Interventions	Primary Outcome Measures	Secondary Outcome Measures	Allocation	Intervention Model	Masking	Enrollment	Duration	Locations
NCT02875821	Effects of Ipragliflozin on Excessive Fat in Type 2 Diabetes Patients with Non-alcoholic Fatty Liver Disease Treated with Metformin and Pioglitazone	Investigate ipragliflozin's impact on visceral fat and fatty liver degree in T2DM subjects under metformin and pioglitazone therapy.	Ipragliflozin, metformin with pioglitazone.	Change in visceral fat area via DEXA at six months.	Assess changes in subcutaneous fat area and liver fat after 6-month treatment using DEXA, CT, and fibroscan.	Randomized	Parallel	None	44	408 days	Korea
NCT03068065	Antidiabetic Effects on Intrahepatic Fat	Compare the effects of gliclazide, liraglutide, and metformin on diabetes with NAFLD over 24 weeks.	Liraglutide, Metformin, Gliclazide.	Intrahepatic fat change via quantitative ultrasound from baseline to 168±3 days.	Monitor liver function, lipid levels, glucose, insulin during meal tests, glucose control, HbA1c, body composition, weight, and waist circumference over various days.	Randomized	Parallel	None	87	519 days	China
NCT02285205	A 24 Week, Multicenter, Prospective, Open-labeled, Single-arm, Exploratory Phase 4 Clinical Trial to Evaluate the Safety and Efficacy of Lobeglitazone in Decreasing Intrahepatic Fat Contents in Type 2 Diabetes With NAFLD	Evaluate the efficacy and safety of Lobeglitazone on intrahepatic fat in T2DM with NAFLD patients over 24 weeks.	Oral administration of Lobeglitazone.	CAP change via transient elastography post-Lobeglitazone treatment at 24 weeks.	N/A	N/A	Single group	None	38	365 days	Korea
NCT01208649	Effects of Exenatide (Byetta®) on Liver Function in Patients with Non-alcoholic Steatohepatitis (NASH)	Test if 24-week exenatide treatment improves NASH histological activity compared to dietary guidance alone.	Exenatide.	Histological NASH activity (steatosis, necroinflammation, ballooning) at 24 weeks.	Determine liver fibrosis using the fibrosis score at 24 weeks.	Randomized	Parallel	Triple	13	793 days	Germany
NCT02147925	Efficacy Study of Liraglutide vs.Sitagliptin vs Glargine on Liver Fat in T2DM Subjects	Examine the effectiveness of liraglutide with metformin versus sitagliptin and insulin glargine in NAFLD patients with T2DM.	Liraglutide combined with metformin, Insulin glargine combined with metformin, and sitagliptin combined with metformin.	Change in Intrahepatic lipids (IHL) after 26-week treatment.	Compare 26-week abdominal SAT, VAT, and HbA1c changes in type 2 diabetic patients.	Randomized	Parallel	None	75	974 days	China

NCT03222206	The Comparison of Effect Between Salsalate and Placebo in Osteoarthritis with Non-alcoholic Fatty Liver Disease	Assess changes in NAFLD factors after salsalate injection in osteoarthritis patients with NAFLD.	Salsalate.	Change in CAP, hepatokine (Fetuin-A), pulse wave velocity, and adipokine (Adiponectin) from baseline to 8 weeks.	Estimate changes over weeks in parameters such as controlled attenuation, hepatokine, pulse wave velocity, adipokine, fatty liver index, saccharometabolic and lipid metabolic factors, inflammatory markers, liver fibrosis indicators, osteoarthritis symptoms, and treatment-related side effects in salsalate and placebo groups.	Randomized	Parallel	Double	34	471 days	Korea
NCT02329405	The Effects of PXR Activation on Hepatic Fat Content	Investigate PXR activation's effects on hepatic fat content in volunteers using rifampicin vs placebo.	Rifampicin.	Hepatic fat fraction on Day 8.	N/A	Randomized	Crossover	None	16	762 days	Finland
NCT05474560	Febuxostat Versus Allopurinol on Hepatic Steatosis in MAFLD Patients	Assess the impact of xanthine oxidase inhibitors on MAFLD by controlling uric acid levels.	Allopurinol (100 mg/day) with lifestyle intervention, Febuxostat 40 mg with lifestyle intervention.	Change in hepatic steatosis via FibroScan CAP score at three months.	Change in serum uric acid levels in hyperuricemia patients over three months.	Randomized	Parallel	None	90	393 days	Egypt
NCT02303730	Exenatide Compared with Insulin Glargine to Change Liver Fat Content in Type 2 Diabetes	Determine if exenatide outperforms insulin glargine in reducing liver fat in newly diagnosed T2DM and NAFLD patients after 24 weeks.	Exenatide, insulin glargine.	Change in liver fat content (%) via MRS from baseline to 24 weeks.	MRI-assessed changes in intra-abdominal and subcutaneous fat content and ratios, glucose metabolism, blood lipid profiles, and body dimensions at 24 weeks.	Randomized	Parallel	None	76	976 days	China
NCT04038853	Vitamin D in Fatty Liver Disease	Evaluate vitamin D's (Plivit D3) influence on NAFLD components compared to a placebo.	1,25-Dihydroxyvitamin D.	Change in elastographic parameters (CAP & LSM) at 6 and 12 months.	Changes in AST, ALT, GGT levels, HOMA-IR score, and serum lipid levels at 6 and 12 months.	Randomized	Parallel	Quadruple	360	1216 days	N/a
NCT03910361	Efficacy and Safety of Evoglitin in Patients with Type 2 Diabetes and Non-alcoholic Fatty Liver Diseases	Assess the efficacy and safety of evogliptin in T2DM patients with NAFLD.	Evogliptin, Pioglitazone.	Change from baseline intrahepatic fat (%) post-treatment at 24 weeks.	N/A	Randomized	Parallel	Quadruple	51	446 days	Korea

(*Continued*)

Table 2 (Continued).

NCT Number	Study Title	Objectives	Interventions	Primary Outcome Measures	Secondary Outcome Measures	Allocation	Intervention Model	Masking	Enrollment	Duration	Locations
NCT03796975	Efficacy of Pioglitazone Hydrochloride and Metformin Hydrochloride Tablets on the Patients with Newly Diagnosed T2DM Combined with Non-alcoholic Fatty Liver Disease	Evaluate the efficacy of pioglitazone hydrochloride and metformin hydrochloride tablets on newly diagnosed T2DM patients with NAFLD.	Combination of Pioglitazone and Metformin Tablets, Metformin Hydrochloride Tablets.	Change in liver fat content, B-cell function, and liver enzyme after 24-week treatment.	Changes in HbA1c, fasting blood glucose, weight, and waistline after 24 weeks of treatment.	Randomized	Parallel	Quadruple	120	510 days	China
NCT02637973	Effects of Empagliflozin on Liver Fat Content, Energy Metabolism, and Body Composition in Patients with Type 2 Diabetes	Investigate empagliflozin's effects on liver lipid content, energy metabolism, and body composition in new T2DM patients.	Empagliflozin.	Liver fat content change via MR spectroscopy from baseline to 24 weeks.	N/A	Randomized	Parallel	Quadruple	84	973 days	Germany
NCT05905185	Interventional Strategy in Tackling Emerging Non-alcoholic Fatty Liver Disease in Childhood Obesity	Examine tocotrienol-rich fraction of vitamin E's impact on liver enzymes and DNA damage in overweight children with NAFLD over six months.	Tocotrienol-rich fraction vitamin E (TRF).	Differences in fibrosis, inflammation, and steatosis scores; fasting blood glucose, AST & ALT, cholesterol, triglycerides, apo-A1 levels; liver steatosis and stiffness changes at six months.	Determination of DNA damage, cytokine levels, and age-based weight measurements at the end of a 6-month trial.	Randomized	Parallel	Triple	29	752 days	Malaysia
NCT01854463	The Effect of Vitamin D Supplementation on Type 2 Diabetes	Investigate high dose 25-hydroxy vitamin D's effect on glycemic controls, NAFLD, arterial stiffness, and bone markers in T2DM.	Vitamin D3.	Glycemic control status evaluation via HbA1c at 0, 12, and 24 weeks.	Assess arterial stiffness and blood pressure metrics at 0 and 24-week intervals.	Randomized	Parallel	Triple	158	427 days	Korea

implications in NAFLD due to their influence on hepatic lipid metabolism and their inherent anti-inflammatory attributes.[28] In preclinical models, Evogliptin has demonstrated notable benefits by mitigating hepatic steatosis, inflammation, and fibrosis.[29] One trial incorporated Evogliptin to evaluate its efficacy and safety for T2DM patients concurrently diagnosed with NAFLD.

Exenatide

Exenatide, a GLP-1 receptor agonist, is commonly prescribed for managing T2DM. Its mechanism of action involves enhancing insulin release, curbing glucagon secretion, and decelerating gastric emptying.[30,31] Within the realm of NAFLD, Exenatide, alongside other GLP-1 agonists, has attracted attention due to its potential benefits: promoting weight reduction, heightening insulin sensitivity, and exhibiting hepatoprotective properties.[32,33] Notably, the weight reduction achieved via exenatide might indirectly confer advantages to NAFLD patients, considering the pronounced link between obesity and the onset of NAFLD.[33]

Three trials integrated exenatide into their experimental designs with varied objectives. One aimed to assess the outcomes of substituting premeal insulin with exenatide in terms of hepatic steatosis, therapeutic efficacy, insulin secretion, weight modulation, rates of hypoglycemia, and pertinent biomarkers in patients with T2DM and NAFLD. Another sought to evaluate whether a 24-week Exenatide regimen ameliorates histological activity in NASH compared to dietary guidance alone. The last delved into the comparative efficacy of exenatide and insulin glargine in diminishing liver fat in patients newly diagnosed with T2DM and NAFLD over 24 weeks.

Febuxostat

Febuxostat, a non-purine selective xanthine oxidase inhibitor, is mainly prescribed for managing hyperuricemia in patients with gout.[34] Numerous studies have underscored the potential influence of uric acid on the pathogenesis of NAFLD, pinpointing oxidative stress as a pivotal mechanism.[14,15] Emerging evidence indicates that Febuxostat has the potential to counteract oxidative stress, reduce lipid accumulation in the liver, and alleviate inflammation; factors that are fundamental to the onset and progression of NAFLD.[35] One trial incorporated Febuxostat in its design, aiming to evaluate the effects of xanthine oxidase inhibitors on MAFLD through the modulation of uric acid levels.

Gliclazide

Gliclazide is an oral sulfonylurea antidiabetic agent that stimulates insulin secretion from the pancreatic beta cells by binding to specific receptors on these cells, causing ATP-sensitive potassium channels to close.[36,37]

Intriguingly, research has shed light on gliclazide's potential for mitigating liver steatosis and inflammation, especially as evidenced in rodent models.[38] Key mechanisms that have been posited include enhancing insulin sensitivity, promoting antioxidant actions, and modulating the release of proinflammatory cytokines.[39–41] In a singular trial, gliclazide was incorporated to compare its effects with those of liraglutide and metformin, specifically addressing diabetes concomitant with NAFLD over 24 weeks.

Glimepiride

Glimepiride is an oral medication often used for treating T2DM. It operates similarly to gliclazide, enhancing insulin release from the pancreas by specifically interacting with the sulfonylurea receptor. This interaction leads to the shutting down of ATP-sensitive potassium channels.[42] Notably, glimepiride exhibits a range of additional effects, including significant anti-inflammatory and antioxidative properties. Emerging research suggests that glimepiride may also protect the liver. This potential benefit is primarily due to its ability to reduce oxidative stress and inflammation, key factors in the development of NAFLD.[43] Moreover, glimepiride's role in improving blood sugar control and increasing insulin sensitivity could indirectly help in alleviating NAFLD.[44] In one study, the effectiveness of glimepiride was compared to that of tofogliflozin, focusing on their effects on liver health and metabolic indicators in NAFLD patients with T2DM over a period of 48 weeks.

Insulin Glargine

Insulin glargine, a long-acting insulin, is used for DM. Its relevance in NAFLD is notable, as it may counteract fat buildup in the liver by improving blood sugar control.[45–47] While there is' a theory that exogenous insulin administration

might intensify hepatic steatosis,[48] insulin glargine, through its potential to enhance glycemic control and reduce glycemic variability, might counteract these adverse effects.[49,50] This aspect was investigated in two studies: one compared the efficacy of liraglutide with metformin against that of sitagliptin and insulin glargine, for treating T2DM patients with NAFLD. The other study evaluated whether exenatide is more effective than insulin glargine in reducing liver fat in newly diagnosed T2DM and NAFLD patients over 24 weeks.

Ipragliflozin

Ipragliflozin, part of the SGLT2 inhibitor medication class, is noted for its promising effects on liver steatosis and fibrosis.[51,52] Extensive studies indicate that Ipragliflozin can reduce liver fat, improve liver enzyme levels, and potentially reduce signs of liver fibrosis.[52–54] These positive effects are thought to stem from several mechanisms, such as weight reduction, increased insulin sensitivity, and direct anti-inflammatory effects on the liver.[53,55] One trial incorporated Ipragliflozin to investigate its impact on visceral fat and the extent of fatty liver in T2DM patients undergoing metformin and pioglitazone treatment.

Liraglutide

Liraglutide, a GLP-1 receptor agonist similar to Exenatide, has garnered attention in the study of NAFLD. The LEAN trial highlighted its effectiveness, demonstrating liraglutide's ability to resolve non-alcoholic steatohepatitis more effectively than a placebo, without worsening fibrosis.[56] The positive effects of liraglutide in patients with NAFLD/NASH may be attributed to various factors including weight loss promotion, reduction in liver fat accumulation, anti-inflammatory properties, and possible direct antifibrotic effects.[57–61] Two trials incorporated liraglutide into their study design with distinct objectives. One trial sought to compare the effects of gliclazide, liraglutide, and metformin on diabetes patients afflicted by NAFLD over 24 weeks. Another aimed to compare the efficacy of combining liraglutide with metformin with the effectiveness of sitagliptin and insulin glargine, specifically targeting NAFLD patients diagnosed with T2DM.

Lobeglitazone

Lobeglitazone is a member of the thiazolidinedione family, known for enhancing insulin sensitivity.[62] These medications work by activating the peroxisome proliferator-activated receptor gamma, leading to improved insulin response in peripheral tissues.[63] Research indicates that Lobeglitazone may reduce liver fat, improve the histological characteristics of NASH, and potentially have antifibrotic effects.[64,65] One study was conducted to evaluate the effectiveness and safety of Lobeglitazone in reducing intrahepatic fat in patients with T2DM patients and NAFLD over 24 weeks.

Metformin

Metformin, a biguanide antihyperglycemic agent, is widely used to treat T2DM, mainly by reducing liver glucose production and increasing muscle insulin sensitivity.[66] Its potential effectiveness in managing NAFLD has become a subject of interest. However, research outcomes have been inconsistent; while some studies suggest benefits like reduced liver enzymes and liver fat, others find its effects comparable to those of lifestyle changes in terms of improving liver health.[67,68] Recent clinical trials have further explored its efficacy, including its use in combination with other treatments like ipragliflozin, pioglitazone, liraglutide, gliclazide, sitagliptin, and insulin glargine, in patients with coexisting T2DM and NAFLD.

Omega-3 Acid Ethyl Esters (OMACOR)

In the field of molecular biochemistry, Omega-3 acid ethyl esters, which are derived from longer-chain omega-3 fatty acids like eicosapentaenoic acid and docosahexaenoic acid, have been recognized for their heart-protective properties.[69,70] Recently, there has' been growing interest in these fatty acids within the scope of NAFLD, largely due to their reported anti-inflammatory, antioxidative, and lipid-modulating effects.[5,71] In a trial, Omega-3 acid ethyl esters were incorporated to discern the influence of long-chain n-3 fatty acid supplementation on NAFLD biomarkers and the risk factors associated with cardiovascular disease and T2DM over an 18-month span.

Pentoxifylline

Pentoxifylline, a drug derived from methylxanthine, is primarily used to treat intermittent claudication resulting from peripheral artery disease.[72] Its possible role in treating NAFLD arises from its significant anti-inflammatory and antifibrotic properties. A key mechanism of pentoxifylline involves inhibiting tumor necrosis factor-alpha (TNF-α), a critical cytokine involved in inflammation and the progression of NAFLD. Various clinical studies have assessed its effectiveness in patients with NAFLD/NASH, with initial results highlighting its potential benefits, particularly in reducing liver enzymes and indicators of liver damage. Additionally.[73] One trial incorporated pentoxifylline to examine the liver's contribution to the onset of T2DM and its correlation with the pathogenesis of NAFLD.

Pioglitazone

Pioglitazone, a key drug in the thiazolidinedione class, primarily acts as an insulin sensitizer by targeting the peroxisome proliferator-activated receptor gamma.[74] The drug helps reduce liver steatosis and inflammation, possibly due to improved insulin sensitivity, reduced inflammation in fat tissue, and altered lipid metabolism.[75] Recent studies also highlight its potential in managing NAFLD by reducing liver fat and inflammation, attributed to enhanced insulin sensitivity and adjustments in lipid metabolism.[76] Despite its efficacy in improving NAFLD, particularly in diabetic patients, caution is necessary due to side effects like weight gain and the risks of bone fractures and bladder cancer, underscoring the need for a balanced risk-to-benefit assessment.[8,77] Three clinical trials involving pioglitazone were conducted with distinct goals: assessing ipragliflozin's impact on visceral fat in T2DM patients on metformin and pioglitazone; evaluating the efficacy and safety of evogliptin in T2DM patients with NAFLD, and examining the effectiveness of pioglitazone hydrochloride and metformin hydrochloride combination therapy in newly diagnosed T2DM patients with NAFLD symptoms.

Rifampicin

Rifampicin is primarily recognized as a potent antibiotic targeting Mycobacterium tuberculosis. Intriguingly, it also is a robust inducer of the liver's cytochrome P450 system.[78] Its connection to NAFLD is primarily underscored by its influence on bile acid metabolism and its potential therapeutic role in alleviating pruritus, a symptom often associated with liver diseases, including primary biliary cholangitis.[79] While direct evidence advocating for rifampicin's application in NAFLD remains scarce, its ability to regulate bile acid transport and synthesis might indirectly affect the disease's progression. However, the use of rifampicin for NAFLD must be judiciously considered due to its potent antibiotic nature and the possible hepatotoxic repercussions, particularly with extended usage.[80] One trial incorporated rifampicin to discern the effects of PXR activation on hepatic fat content by comparing rifampicin with a placebo in volunteers.

Salsalate

Salsalate, a derivative of salicylate that does not contain acetyl groups, is primarily known for its anti-inflammatory properties.[81] Recently, it has attracted attention for its potential use in treating metabolic disorders, especially due to its ability to reduce inflammation, a key aspect in conditions like T2DM and NAFLD.[82,83] NAFLD is characterized by chronic, low-level inflammation, and targeting this aspect of the disease could offer significant therapeutic benefits. Studies have shown that salsalate can improve insulin sensitivity and glucose control in people with T2DM. Its effects on NAFLD are believed to stem from its ability to inhibit the nuclear factor-kappa B pathways, leading to a decrease in the release of proinflammatory cytokines from the liver.[84] In one trial, salsalate was included in a treatment plan for patients with osteoarthritis who also had NAFLD, to observe changes in NAFLD indicators following its administration.

Sitagliptin

Sitagliptin, a type of DPP-4 inhibitor, plays a crucial role in treating T2DM.[85] Its primary mechanism involves prolonging the action of incretin hormones, which leads to increased insulin production and decreased glucagon release, thereby achieving a balanced metabolic effect.[86] Recently, the use of DPP-4 inhibitors like sitagliptin has shown promise in treating NAFLD, especially in patients with both T2DM and NAFLD. Studies indicate that sitagliptin can significantly improve liver function and reduce liver fat, as evidenced by advanced imaging methods such as magnetic resonance spectroscopy.[87] The drug works by reducing cell death in liver cells, decreasing fat production in the liver, and managing oxidative stress and related

inflammation.[88] In one clinical trial, researchers explored the effectiveness of combining sitagliptin with insulin glargine for treating NAFLD in T2DM patients, comparing it to the combination of liraglutide and metformin.

Tofogliflozin

Tofogliflozin, a key SGLT2 inhibitor, is mainly used to treat T2DM.[89] It works by blocking SGLT2 in the kidney's proximal tubules. This action significantly lowers glucose reabsorption in the kidneys, leading to increased glucose excretion in urine and improved blood sugar control.[90] Recent studies also highlight the potential benefits of SGLT2 inhibitors for treating NAFLD.[23] These benefits are thought to arise from reduced visceral fat, lower hepatic glucose production, increased fat oxidation, and decreased fat synthesis in the liver.[91–93] Specific research on tofogliflozin has shown its ability to reduce liver fat and improve indicators of liver damage in patients with both NAFLD and T2DM.[94] One trial compared tofogliflozin with glimepiride, focusing on their effects on liver histology and metabolic markers in NAFLD patients with T2DM over a 48-week period.

Ursodeoxycholic Acid (UDCA)

Ursodeoxycholic acid (UDCA) is a naturally occurring bile acid that is traditionally used to treat primary biliary cholangitis.[94] Due to its cytoprotective, immunomodulatory, and anti-apoptotic properties, there is growing interest in exploring its use in treating other liver diseases, such NAFLD.[95,96] Preliminary studies have posited that UDCA may improve liver function and reduce liver cell damage in NAFLD by stabilizing cell membranes, reducing harmful bile acids, and protecting against oxidative stress.[97] One trial incorporated UDCA to understand the hepatic role in the onset of T2DM and its interrelation with NAFLD pathogenesis.

Vitamin E

Vitamin E, recognized for its robust fat-soluble antioxidant qualities, is of interest to researchers due to its possible role in addressing NAFLD and its more advanced form, NASH.[98] The antioxidant effects of Vitamin E show promise in potentially decelerating or reversing the progression of these conditions. However, it is' important to approach its use with caution. Certain studies have highlighted possible adverse effects associated with prolonged consumption, such as an increased risk of overall mortality, hemorrhagic stroke, and a greater likelihood of prostate cancer in men, particularly when used in therapeutic doses.[98,99] One trial studied the impact of a tocotrienol-rich fraction of vitamin E on liver enzymes and DNA damage in overweight children with NAFLD over a span of 6 months.

Vitamin D

Vitamin D impacts cellular growth, immune function, and inflammation reduction, suggesting its involvement in the development and progression of NAFLD.[100–102] Epidemiological data reveal an inverse correlation between vitamin D levels and NAFLD prevalence, with deficiencies more prevalent in NAFLD patients.[103,104] This vitamin has shown the potential to inhibit NAFLD progression through anti-inflammatory antifibrotic effects and to improve insulin sensitivity.[105] Rodent studies further support these findings, indicating that vitamin D supplementation reduces liver steatosis and inflammation.[106–108] Two trials explored Vitamin D's influence on NAFLD and its related metabolic parameters in T2DM patients.

Discussion

An exploration of the therapeutic potential of various agents in managing NAFLD indicates the multifaceted nature of the disease and its intricate interconnections with other metabolic disorders, especially T2DM. This complexity is aptly mirrored in the multitude of therapeutic agents being considered.

Thiazolidinediones like Lobeglitazone and Pioglitazone have traditionally been harnessed for their insulin-sensitizing capacities.[61,73] Their potential utility in NAFLD hinges on enhancing insulin sensitivity in peripheral tissues, consequently diminishing liver fat accumulation and ameliorating histological indicators of the disease.[62,75] Nevertheless, caution is imperative with pioglitazone, given the associated risks of bone fractures, weight gain, and potential long-term safety concerns.[76]

Metformin is a cornerstone for T2DM management in the same metabolic milieu, and its implications for NAFLD management cannot be sidelined.[65] However, its efficacy is contested, with some studies highlighting its potential

advantages in liver aminotransferase reduction and hepatic steatosis mitigation, and others debating its superiority over lifestyle modifications.[67]

A noteworthy entry into this therapeutic spectrum is the Omega-3 acid ethyl esters or OMACOR. These derivatives, notably eicosapentaenoic acid and docosahexaenoic acid, bring cardioprotective capabilities.[69] Their burgeoning role in NAFLD is rooted in their anti-inflammatory, lipid-regulating, and antioxidative attributes, elucidating their potential as a therapeutic adjunct.[7,70]

Agents like Pentoxifylline and Salsalate, despite their primary roles in managing peripheral artery disease and inflammation, respectively, have demonstrated potential benefits in NAFLD due to their anti-inflammatory properties. Their therapeutic impact, especially that of pentoxifylline, can be attributed to their potential to suppress vital inflammatory cytokines, such as TNF-α, which are pivotal in NAFLD progression.[71,83]

While rifampicin's primary role as a potent antibiotic is widely acknowledged, its implications for NAFLD hinge on its influence on bile acid metabolism and potential therapeutic role in alleviating pruritus, a symptom often associated with liver diseases.[78] However, it must be prescribed with caution due to possible hepatotoxic repercussions.[79]

DPP-4 inhibitors like Sitagliptin and SGLT2 inhibitors such as Tofogliflozin showcase the intertwined pathophysiology of NAFLD and T2DM, underscoring the potential benefits these antidiabetic agents might confer on hepatic steatosis and inflammation.[84,88]

Moreover, traditional agents like UDCA and vitamins like Vitamin E and Vitamin D underscore the multifactorial therapeutic approach to NAFLD. While UDCA's hepatoprotective and anti-apoptotic properties offer therapeutic possibilities, Vitamin E's antioxidant prowess suggests potential therapeutic benefits. Still, the latter must be approached cautiously, given the potential risks associated with high doses.[96,97] Vitamin D, on the other hand, bridges the realm of bone health with cellular growth, immune function, and inflammation, suggesting an intricate role in NAFLD's development and progression.[101]

Future Directions

As NAFLD research and therapy advance, it is' evident that a multifaceted approach is crucial. Personalized treatments rooted in genomic and metabolic profiling appear to be the way forward, while long-term studies remain vital to establish the safety and efficacy of new agents. Understanding NAFLD's molecular foundations can lead to novel therapeutic targets, potentially offering more effective treatments. Given the disease's multifactorial nature, there is' potential for combining various therapeutic agents and merging them with lifestyle modifications.

Conclusion

Since NAFLD has become a major health concern, more clinical trials and different pharmacological approaches are required to counteract the potential side effects associated with the disease. Agents like Thiazolidinediones, Metformin, Omega-3 acid ethyl esters, and DPP-4 inhibitors, among others, highlight the diverse approaches toward NAFLD management. At the same time, each agent presents potential therapeutic benefits but has associated risks and limitations. Further investigations are definitely warranted.

Data Sharing Statement

All data are contained within the article.

Disclosure

The authors declare no conflicts of interest.

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