Gut and Gastroenterology

REVIEW ARTICLE

Non-Alcoholic Fatty Liver: Current Management and Future Trends

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease and is becoming recognized as a global health problem. It is a spectrum of liver disease with progression from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. Progression of the disease is mediated through different inflammatory pathways with subsequent fibrosis resulting in cirrhosis and its related complications. The condition seems to be more associated with patients with type II diabetes mellitus (70%) and morbid obesity (90%). NAFLD is now considered as a hepatic component of the metabolic syndrome because of its close association with obesity, insulin resistance (IR), and type II diabetes. Cardiovascular related deaths are common among patients with NAFLD and with the onset of NASH and cirrhosis they have increased liver-related mortality

Despite intense research, therapy for NAFLD always remains unmet medical attention. Interventions aim at different aspects of presumed risks for hepatic steatosis (obesity, insulin resistance, and hypertension). Lifestyle modifications are proven to be useful not only in the prevention and control of the disease but also in the reduction of associated comorbidities, with promising results. Long-term adherence and sustained improvement are not, however, documented in most subjects. Targeting therapies aiming at mitigating specific pathways of NAFLD along with cellular and molecular events at various stages of the pathogenesis are attempted with varying degree of success. Many longitudinal studies have shown that the presence and severity (stage) of fibrosis on liver histology correlates with increased risk of all-cause as well as liver-related mortality in patients with NAFLD. Specific treatments aimed at this aspect are also evaluated. This review summarizes the current treatment options in the management of NASH and therapies which are being actively evaluated (including phase II/III clinical trials) with promising data.

Keywords: NASH, NAFLD, Fibrosis, Apoptosis, Insulin resistance, Fatty liver

Abbreviations: ALT: Alanine Aminotransferase; ASK 1: Apoptosis Signal-Regulating Kinase 1; BMI: Body Mass Index; FA: Fatty Acids; FFA: Free Fatty Acids; FXR: Farnesoid X Receptor; GLP -1: Glucagon-Like Peptide 1; HDL: High Density Lipoprotein; HOMA-IR: homeostatic model assessment; IR: insulin resistance; LDL: Low Density Lipoprotein; LOXL-2: Lysyl Oxidase-Like 2; MRI-PDFF: MRI Proton Density Fat Fraction; NAFLD: Non-Alcoholic Fatty Liver Disease; NAS: Non-Alcoholic Fatty Liver Disease Activity Score; NASH: Non-Alcoholic Steatohepatitis; OCA: Obeticholic Acid; PPAR: peroxisome proliferator-activated receptor; PTX: Pentoxifylline; PUFA: Polyunsaturated Fatty Acid; RCT: Randomized Controlled Trial; SGLT-2: Sodium-Glucose Co-Transporter-2; TG: Triglycerides; TNF-α: Tumor Necrosis Factor- α; TZD: Thiazolidinedione; UDCA: Ursodeoxycholic Acid; VAP-1: Vascular Adhesion Protein-1

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease ranging from simple steatosis to the formation of inflammation and fibrosis, with progression to cirrhosis [1]. Hepatic steatosis occurs in the presence of metabolic risks such as obesity, hypertension, hyperlipidemia, and insulin resistance (in the absence of other causes of steatosis such as excessive alcohol). Some of these patients develop non-alcoholic steatohepatitis (NASH) with progressive inflammation [2]. With the increasing prevalence of obesity, insulin resistance, and hypertension, the diagnosis of NAFLD is frequently seen and has become the most common (>30%) chronic liver disease in the United States [3, 4]. It is more prevalent amongst patients with type II diabetes mellitus (70%) and among morbidly obese patients (90%) [5].

Non-alcoholic steatohepatitis (NASH), is a progressive form of NAFLD. In addition to the presence of hepatic steatosis, liver cell injury is associated with inflammatory cells/ballooning cells with subsequent progression to fibrosis [6]. This form of NAFLD can progress to cirrhosis in 20% of patients, with its associated complications and mortality in 8% [5]. NAFLD is not unique

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to western countries and is increasingly recognized worldwide, affecting 20-30% of the general population. It is also recognized in subjects who may not have usual features such as obesity [7]. NASH is predicted to become the leading indication for liver transplantation in the next 10 years [8]. NASH patients have an increased presence of metabolic risk factors, which is associated with cardiovascular disease and its related mortality [2]. They also have increased mortality due to liver-related causes [7].

Disorders of lipid metabolism are an important component of the development of NAFLD. Dysfunctional lipid metabolism, including triglycerides (TG) and free fatty acids (FFA), as well as insulin resistance, has been correlated with hepatic steatosis [9]. Increased TG reflects an imbalance in the input/output of hepatic FFA metabolism. Dysfunctional adipose tissue, altered calorie, and dietary intake, and gut microbiota all play a role in hepatic TG accumulation resulting in NAFLD [9].

The occurrence of hepatic steatosis due to triglyceride accumulation without associated inflammation (NAFLD without NASH) has less risk for significant long-term complications [2, 6]. However, abnormal metabolic pathways related to lipids, including lipotoxicity, results in inflammation. This has been related to stress on the mitochondria, endoplasmic reticulum, and peroxisomes with excess FFA and in its metabolism resulting in liver injury by releasing reactive oxygen species and recruitment of immune cells and other mediators of cell injury [10, 11]. With the onset of hepatocyte injury, further mediators of inflammation are recruited, including programmed cell death, autophagy, and fibrotic remodeling by activated stellate cells [9].

Current therapies for patients with non-alcoholic fatty liver disease involve a reduction of the metabolic risk factors that are associated with the disease, with the goal of reducing the progression of steatosis and inflammatory changes in the development of NASH and cirrhosis [2]. Lifestyle modifications, including dietary habits, calorie-restricted diet, and exercise, have proven to be effective for preventing and controlling the disease. The lifestyle modifications have also been found to reduce associated comorbidities, with promising results [2, 12, 13]. Unfortunately, while lifestyle modifications are beneficial in NAFLD, long-term adherence and sustained improvement are not documented in most subjects [13]. Because inflammatory cells (including ballooning degeneration) are key in progression to NASH, therapies targeting these cells are being studied. These include an intervention to mitigate specific pathways involved in inflammation, apoptosis, fibrosis formation, and progression (Figure).

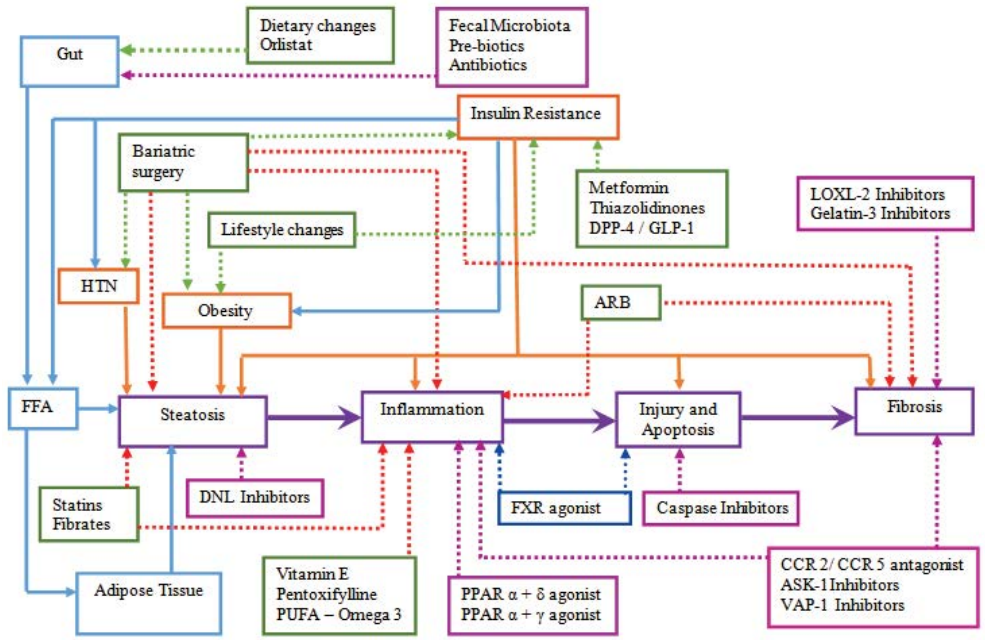
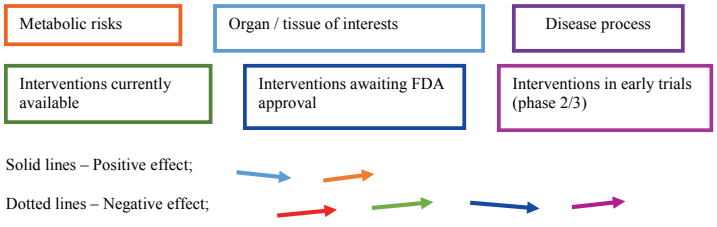


Figure: Pathophysiology of NASH and mechanistic action of different therapeutic agents.

ARB: Angiotensin Receptor Blockers; ASK 1: Apoptosis Signal-Regulating Kinase 1; CCR2: Chemokine Receptor-2; CCR5: Chemokine Receptor-5; DDP-4: Dipeptidyl Peptidase -1; DNL: Denovo Lipogensis; FFA: Free Fatty Acids; FXR : Farnesoid X Receptor; GLP -1: Glucagon-Like Peptide 1; HTN: Hypertension; LOXL-2: Lysyl Oxidase-Like 2; PPAR: Peroxisome Proliferator-Activated Receptor; PUFA: Polyunsaturated Fatty Acid; VAP-1: Vascular Adhesion Protein-1



Since NAFLD has become the most common chronic liver disease with significant morbidity and mortality, there has been a keen interest in the development of specific therapies to help these patients, in addition to lifestyle modification [2]. Studies are currently undergoing to develop treatment modalities to target cellular and molecular events at different stages of NASH pathogenesis to reduce the risk of progression of the disease [2]. A few studies involving the impact of differences in genetics and epigenetics are also being considered. Furthermore, a reliable noninvasive method of diagnosis is also being evaluated as this will aid in treatment guidance and follow up, as well as reduce the need for liver biopsies, which is the current gold standard for diagnosis of NASH [14].

Current interventions (Table 1 & 2).

Treatment of Risk Factors

Lifestyle modifications

Lifestyle changes with restricted calorie intake and physical activity have shown to improve both hepatic and peripheral insulin sensitivity, along with improvement in lipid profile. In randomized control trials (RCT) with liver biopsies, weight loss of 3-5% has shown to reduce the hepatic triglyceride content by 90%. In addition, 7-9% weight loss led to a decrease in necroinflammation and NAFLD activity score (NAS), as well as regression of fibrosis in those with more than 10% weight loss [15].

Table 1: Lifestyle modifications in NASH

Study	(n)	Methodology/Outcome Measurement/Intervention	Duration	BMI	TG/ Lipids	ALT/ AST	Glucose/ IR/ HOMA-IR	Steatosis grade	Inflammation	NAS Score	Fibrosis Stage
DIET											
Huang MA et al. 2005 [19]	23	OL, Pilot study Liver biopsy diet vs None	1 year	↔	↔	↓	↓	↔	↔	↔	↔
Viljanen AP et al. 2009 [20]	34	OL, H-MRS, very low calorie diet vs None	6 weeks	↓			↓	↓			
Yamamoto M et al. 2007 [21]	27	Observational study, restriction of energy, fat and iron	6 months			↓		↓			
Ryan MC et al. 2013 [23]	12	Cross-over study, editerranean Diet vs low fat-high carbohydrate diet (LF/HCD)	6 weeks				↓	↓			
Properzi C et al. 2018 [24]	48	Mediterranean vs low fat [LF]	12 weeks		↓	↓		↓			
EXERCISE											
Johnson NA et al. 2009 [27]	19	RCT, 1H-MRS, AEx (Progressing 50-70% VO2max 30 - 45 minutes 3 days /week) vs none	4 weeks	↔		↔	↓	↓			
Kirwan JP et al. 2009 [29]	14	Observational study, two-stage hyperinsulinemic euglycemic clamp, 30 min cycling and 30 min treadmill walking	7 days	↔			↓				
Kistler KD et al. 2011 [31]	813	Retrospective analysis, liver biopsies,> 75 min/wk (> 6 METs) vs 150 min/wk (3-5 METs)									↓
DIET AND EXERCISE											
Promrat K et al 2010 [15]	31	RCT, liver biopsy, diet and exercise vs education alone	48 weeks	↓				↓	↓	↓	↔
Shah K et al. 2009 [17]	18	RCT, H-MRS, AEx (70-85% MHR) +PRT (1-2 sets, 8-12 reps at 65% 1RM progressing to 2-3 sets, 6-8 reps at 80% 1 RM 90 min 3 days/ week) vs control	26 weeks	↔		↔		↔			
Larson-Meyer DE et al. 2008 [18]	23	RCT, H-MRS, AEx (5 days/week) +Diet vs Diet	6 weeks	↔		↔		↔			
Ueno T et al. 1997 [28]	25	NRCT, liver biopsies, diet and exercise no intervention	3 months	↓	↓	↓	↓	↓	↔	↔	↔
Oh S et al. 2015 [30]	169	Dietary restrictions plus aerobic exercise. 40 performed MVPA for <150 min/wk, 42 MVPA for 150-250 min/wk, and 87 MVPA for >250 in/wk	12 weeks					↓			

1H-MRS: Proton Magnetic Resonance Spectroscopy; AEx: Aerobic Exercise Therapy; ALT: Alanine Aminotransferases; AST: Aspartate Aminotransferases; BMI: Body Mass Index; Ex: Exercise; HOMA-IR: Homeostatic Model Assessment – Insulin Resistance; IR: Insulin Resistance; MET: Metabolic Equivalent; MHR: Maximum Heart Rate; MVPA: Moderate To Vigorous Intensity Physical Activity; NAS: Non-Alcoholic Fatty Liver Disease (NAFLD) Activity Score; NASH: Non-Alcoholic Steato-Hepatitis; NRCT: Non-Randomized; OL: Open Label; PRT: Progressive Resistance Exercise Therapy; RCT: Randomized, Controlled Trial; TG: Triglycerides; ↑ Indicates Increase; ↓ Indicates Decrease; ↔ Indicates No Change

Table 2: Interventions currently available for NASH

Study	(n)	Methodology/outcome measurement/Intervention	Duration	BMI	TG/ Lipids	ALT/ AST	Glucose/ IR/ HOMA-IR	Steatosis Grade	Inflammation	NAS Score	Fibrosis Stage
THIAZOLIDINEDIONE'S											
Boettcher E et al. 2012 [39]		Meta-analysis, 4 RPCTs, TZDs, Pioglitazone vs Placebo		↑				↓	↓		↔
Sanyal A et al. 2010 [40]	247	RCT, Liver biopsy, Pioglitazone 30 mg vs Vit E 800 IU vs Placebo	96 weeks	↑		↓		↓	↓	↓	↔
Harrison SA et al. 2020 [45]	392	RCT, oral placebo or 1 of 3 MSDC-0602K doses	52 weeks			↓	↓			↓	
METFORMIN											
Marchesini G et al. 2001 [46]	20	OL, SA, US Metformin 1.5 g/day vs none	4 months			↓		↓		↓	
Lavine JE et al. 2011 [47]	173	RCT, liver biopsy, Metformin 1000 mg vs Vit E 800 IU/day vs placebo in pediatric patients	96 weeks						↔	↔	
Shyangdan D et al. 2011 [48]		Systemic review, 15 RCTs, Metformin		↓		↓		↔			
GLP-1											
Armstrong MJ et al. 2016 [52]	26	Double blinded RCT, Phase II, Liraglutide 1·8 mg/day vs placebo	48 weeks					↓	↓		↔
Carbone LJ et al 2016 [53]	136	Systemic review and Meta-analysis, 4 studies				↓		↓	↓		↓
Newsome P et al. 2019. [54]		Post hoc analysis of Semaglutide from two RCTs				↓					
DPP-4 INHIBITORS											
Cui et al. 2016 [55]	50	Double blinded RCT, Sitagliptin orally 100 mg/day vs placebo, MRI-PDFF	24 weeks		↔	↔	↔				
SGLT-2 INHIBITORS											
Honda et al. 2016 [57]		Murine model study, AMLN diet for 12 weeks and an AMLN diet with 40 mg Ipragliflozin/kg for 8 weeks.	20 weeks		↓		↓	↓	↓		↓
Takase T et al. 2017 [58]	21	Observational study, Ipragliflozin at 50 mg/day	16 weeks	↓			↓	↓			
Sumida Y et al. 2019 [59]	40	Prospective, single-arm study, Efficacy of luseogliflozin	24 weeks			↓		↓			↔
ORLISTAT											
Harrison SA et al. 2009 [33]	50	RCT, 1,400 Kcal/day diet plus vitamin E 800 IU/day with or without Orlistat 120 mg three times a day, BMI ≥ 27	36 weeks.	↓			↓	↓	↓	↓	
LIPID LOWERING THERAPY											
Tzefos M et al 2011 [60]		Systemic review			↓	↓					
Kargiotis K et al. 2015 [61]	20	Biopsy proven NASH, Rosuvastatin 10 mg/day	12 months	↔	↓	↓	↓				
Foster DW et al. 2011 [62]	1005	RCT, Atorvastatin 20 mg, vitamin C 1 g, and vitamin E 1,000 IU vs. placebo	3.6 years					↓			
Musso G et al. 2012 [63]		Systemic review, 78 RCTs, Lifestyle intervention, Thiazolidinediones, Statins, Metformin and Anti-oxidants			↓			↓			
Dongiovanni P et al. 2015 [64]	107	Systemic review, Statin use in NASH						↓	↓		↓

Stein E et al. 2016 [65]	66	RCT, Gemcabene 300 or 900 mg plus statin	8 weeks		↓						
VITAMIN E											
Lavine JE et al. 2011 [47]	173	Double blinded RCT, pediatric biopsy-confirmed NAFLD, 800 IU of Vitamin E, 1000 mg of Metformin, or placebo	96 weeks			↔		↔	↔		↔
Sanyal A et al. 2010 [40]	247	RCT, liver biopsy, Pioglitazone 30 mg vs Vit E 800 IU vs Placebo	96 weeks			↓		↓	↓	↓	↔
PENTOXIFYLLINE											
Zein CO et al. 2011 [71]	55	RCT, biopsy proven NASH, PTX 400 mg 3/day vs placebo	1 year					↓	↓	↓	↔
Li W et al. 2011 [72]		Systemic review, PTX with placebo or UDCA-controlled groups				↓					↔
OMEGA-3/PUFA											
Dasarathy S et al. 2015 [73]	37	Double blinded RCT, NASH, DM, eicosapentaenoic acid 2160 mg and docosahexaenoic acid 1440 mg/day or an isocaloric, identical placebo	48 weeks	↔		↔	↑	↓		↓	
URSODIAL											
Lindor KD et al. 2004 [74]	166	RCT, biopsy–proven, UDCA 13 and 15 mg/kg/day vs placebo	2 years					↔	↔		↔
Musso G et al. 2012 [63]		Systemic review, 78 RCTs, lifestyle intervention, Thiazolidinediones, Statins, Metformin and Antioxidants			↓			↓			
ANGIOTENSIN RECPTOR BLOCKERS											
Goh GB et al. 2015 [75]	290	Cross sectional study, HTN, biopsy proven NAFLD, RAS blocker							↓		↓
BARIATRIC SURGERY											
Furuya CK et al 2007 [36]	18	NRCT, liver biopsy, RYGB	24 months	↓		↓	↓	↓	↓	↓	↓
Mummadi RR et al. 2008 [35]		Meta-analysis, 15 studies		↓				↓			↓

ALT: Alanine Aminotransferases; AMLN: amylin Liver NASH Model; ARB: Angiotensin Receptor Blocker; AST: Aspartate Aminotransferases; BMI: Body Mass Index; DM: Diabetes Mellitus; DPP-4: Dipeptidyl Peptidase-4 Inhibitor; Ex: Exercise; GLP-1: Glucagon-Like Peptide-1; HOMA-IR: Homeostatic Model Assessment – Insulin Resistance; HTN: Hypertension; IR: Insulin Resistance; MET: Metabolic Equivalent; MRI-PDFF: MRI-Derived Proton Density Fat Fraction; NAFLD: Non-Alcoholic Fatty Liver Disease; NAS: NAFLD Activity Score; NASH: Non-Alcoholic Steato-Hepatitis; NRCT: Non-Randomized; OL: Open Label; PRT: Progressive Resistance Exercise Therapy; RAS: Renin Angiotensin System; RCT: Randomized, Controlled Trial; RYGB: Roux-En-Y Gastric Bypass; RPCT: Randomized Placebo-Controlled Trial; SGLT-2: Sodium/Glucose Co-Transporter 2; TG: Triglycerides; TZD: Thiazolidinedione; UDCA: Ursodeoxycholic Acid ↑ Indicates Increase; ↓ Indicates Decrease; ↔ Indicates No Change

Diet

A high-calorie diet with high-fat or high fructose was significantly associated with increased intrahepatic triglyceride levels [16]. Calorie restriction has been attempted with beneficial effects [17, 18]. Improvement in NAFLD was seen histologically in nearly 60% of patients following one year of intensive nutritional therapy [19]. Reduction in liver triglyceride and improvement in insulin sensitivity was found with aggressive nutritional therapy [20]. Reduced consumption of specific macronutrient components of a diet such as a carbohydrate, fructose and fat, along with calorie reduction, led to an improvement in the histology of NAFLD and hepatic insulin sensitivity. There was also an improvement in aminotransferases in these subjects [21]. However, the inability of subjects to continue with a dietary plan for a prolonged course with the associated continued weight loss rendered most of these interventions limited [2, 13].

A higher dietary saturated fatty acids compared to unsaturated fat intake increases intrahepatic triglyceride content (55% vs 15% increase, $p<0.05$) [22]. Mediterranean diet, which is based on a relative intake of olive oil, nuts, vegetables, fruits, legumes, whole grains, and fish, provides a high monounsaturated fatty acid in the diet. In a randomized cross over study of biopsy-proven NAFLD subjects' intake of Mediterranean diet reduced hepatic steatosis when compared to a low-fat high-calorie diet (39% vs 7%, $P<0.012$) [23]. In another randomized control trial, the Mediterranean diet decreased total cholesterol, serum TG, and glycated hemoglobin (HbA1c) compared to a low-fat diet ($p<0.05$), but without a significant difference in hepatic steatosis [24]. Based on these studies, current European guidelines recommends the Mediterranean diet for the management of NAFLD [25].

Exercise with or without diet modifications

Aerobic, resistance/strength training, and high-intensity interval training are among the different types of exercises studied in NAFLD subjects. These exercises result in a 20-30% relative reduction in hepatic steatosis with no significant differences in specific exercise methods [26]. Regular aerobic exercise improves insulin sensitivity and increases oxidation of body fat [27]. Exercise intervention, along with a calorie-restricted diet, has been found to improve serum aminotransferases, cholesterol, and blood glucose levels, reduce hepatic steatosis, and inflammation on liver histology, along with a weight loss [28, 29]. Although exercise alone can be effective in the reduction of many risk factors of NAFLD, the combination of exercise and dietary changes has a greater benefit in liver histology [15]. Studies evaluating the intensity of an exercise program have found moderate to high-intensity exercise (>250 min/week and VO_2 max 30-60 minutes) leads to favorable changes in hepatic fat content [30, 31].

Obesity

Orlistat

Orlistat, a gut lipase inhibitor taken with meals, it reduces approximately 30% of dietary triglyceride absorption and a weight loss. A RCT of orlistat compared to placebo improved histological scores of NASH, reduction of steatosis besides an additional weight loss. This beneficial effect was seen when orlistat was used alone or in combination with vitamin E [32, 33].

Endoscopic interventions

Endoscopic placement of intragastric devices has been studied with success in the reduction of weight. These devices occupy gastric space and reduce functional gastric volume, causing early satiety, and reduced food intake. The common intragastric devices used are different balloons (Orebera balloon, ReShape dual balloon, Obalon Balloon) filled with gas or saline after endoscopic placement. They can be removed easily. Studies suggest up to 25% of excess weight loss was found with the use of some of these devices. Reduction in intra-gastric volume also has been endoscopically achieved by an overstitch device. This procedure creates a sleeve gastroplasty, similar to a surgical approach. A new percutaneous endoscopic gastrostomy-like device, Aspire Assist, allows aspiration of 25-30% of calories ingested. A study found a 31% excess weight loss with 52 weeks of use of this device [34].

Bariatric surgery

Currently, there are several different surgical interventions for weight reduction. They are restrictive (laparoscopic adjustable gastric banding), malabsorptive (Roux-en-Y gastric bypass) or a combination of them (biliopancreatic diversion). They are usually performed for patients with a BMI ≥40 or with ≥35 kg/m^2 along with two or more comorbidities. Bariatric surgery improves many components of metabolic risks, with a marked reduction of obesity, diabetes, hypertension, and hyperlipidemia. In a meta-analysis of NASH patients undergoing bariatric surgery, a sustained improvement in NASH histological features with a resolution of steatosis, steatohepatitis, and no progression of fibrosis was found [35, 36].

Diabetes

Insulin resistance is an important factor in both the development of hepatic steatosis and its progression to NASH. Patients with insulin resistance have reduced glucose metabolism, increased de-novo lipogenesis, and increased lipolysis in adipose tissue. There is also an excessive influx of FFAs in the circulation and increased FFA uptake in the liver. These changes in metabolic pathways increase the risk of hepatic steatosis [37, 38].

Thiazolidinedione

Thiazolidinedione's (TZD) act through nuclear receptor peroxisome proliferator-activator receptors (PPAR) and regulates lipid metabolism and insulin sensitivity. Among the many TZDs (Troglitazone, Rosiglitazone, and Pioglitazone) Pioglitazone, a PPAR γ agonist, has been studied and approved for the treatment of type II diabetes mellitus. It has been shown to improve hepatic inflammation and fibrosis for both diabetic and non-diabetic patients with NASH in a pre-clinical study [39]. In a large trial (PIVENS) of 247 non-diabetic biopsy proven NASH patients comparing pioglitazone, vitamin E, and placebo, pioglitazone reduced aminotransferases, hepatic steatosis, lobular inflammation, and fibrosis. This drug, however, is not commonly used for NASH, owing to marked weight gain compared to vitamin E and placebo, which is a significant comorbidity in these subjects [40]. There are also concerns of increased cardiovascular risk but without increased mortality, as well as an increased risk of bladder carcinoma raising the concern for long term safety of pioglitazone [41, 42]. PPAR γ activation increases bone resorption while decreasing bone formation, increasing osteoporosis risk, which is another drawback for pioglitazone use in the elderly population [43]. Hence TZDs are not commonly used, especially with the removal of rosiglitazone by FDA from the market.

MSDC-0602K is a newer thiazolidinedione agent acting on mitochondrial target of TZD without PPARγ activity [44]. In a phase II, EMMINENCE trial comparing different doses (62.5 mg, 125 mg & 250 mg) with placebo demonstrated a significant liver histological improvement at 12 months without worsening fibrosis. Significant reduction in liver aminotransferases (AST & ALT) was also noticed at higher doses, 125 mg, and 250 mg groups [45].

Metformin

An open-labeled study on metformin suggested improvement in both insulin resistance and aminotransferases when compared to diet alone [46]. However, in a study of 173 pediatric NAFLD patients (TONIC Study) who were followed for 96 weeks, metformin did not show improvement in aminotransferases (p=0.4) or liver histology (including NAS (p=0.25)) compared to vitamin E [47]. A further systemic review of 8 randomized control trials also did not show any histological benefits of

metformin in NAFLD patients [48]. Metformin, however, has been found to improve glycemic index and reduces the risk of all diabetes-related endpoints, including microvascular disease, myocardial infarction, large vessel disease, and cardiovascular mortality, in addition to aiding weight loss [49]. Hence, it is frequently used even in NASH subjects without diabetes. There is also new epidemiological evidence to suggest that metformin is associated with a reduction in the incidence of both liver and non-liver related malignancies, including hepatocellular carcinoma, in those with NASH cirrhosis by 7% [50].

Glucagon like peptide - 1

Glucagon like peptide 1 (GLP-1) is an incretin hormone secreted by the L cells in distal ileum and colon. It stimulates pancreatic beta cells and increases insulin biosynthesis and reduces insulin resistance. GLP-1 inhibits glucose-dependent pancreatic glucagon secretion, decreases gluconeogenesis and glycogenolysis, and decreases liver fat besides delay gastric emptying, regulating appetite and facilitating weight loss [51]. These hormones are rapidly deactivated by dipeptidyl peptidase (DPP)-4. Exenatide and liraglutide are GLP 1 analogues used for the treatment of type II diabetes mellitus. Liraglutide (LEAN study) administered over 48 weeks at an higher dose (1.8 mg daily) resulted in improved resolution of NASH (39% vs 9%; p=0.019) without worsening of fibrosis compared to placebo [52]. In a meta-analysis, the use of GLP-1 analogues has shown improvements in ALT, hepatic fat content, and fibrosis in NASH patients with metabolic syndrome [52, 53]. GLP-1 agents also have the beneficial effect of weight loss in these patients. Semaglutide is another GLP-1 analogue had a dose-dependent reduction of liver aminotransferases (ALT) and markers of inflammation, high sensitive C reactive protein (hsCRP) in patients with obesity [54].

Dipeptidyl peptidase -1 inhibitors

DPP-4 is an enzyme that is known to degrade GLP-1 rapidly. DPP-4 inhibitors such as sitagliptin and vidagliptin can expect to have similar benefits as GLP-1 analogues. However, no convincing beneficial outcome in NASH patients has been found so far [55].

Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors block the SGLT2 protein (involved in 90% of glucose reabsorption) in the proximal renal tubule, resulting in increased renal glucose excretion and lower blood glucose levels and are used in the management of type II diabetes mellitus. These agents (dapagliflozin, canagliflozin, and empagliflozin) increase insulin sensitivity, decrease gluconeogenesis, and improves insulin release from pancreatic beta cells [56]. Newer agents (ipragliflozin) have been found to improve steatosis, inflammation, and fibrosis in a murine NASH model [57]. Although histological improvement was not assessed, the use of ipragliflozin for 16 weeks reduced fatty liver index (70.1 ± 19.4 to 60.3 ± 25.5; p = 0.0009), fasting plasma glucose (p = 0.03) and HbA1c (p = 0.047) [58]. This group of drugs is promising, although there are concerns for increased urinary tract infection following its use. Luseogliflozin, a second-generation, SGLT-2 inhibitor improved HbA1c, liver aminotransferases, and hepatic fat content without a change in fibrosis after 24 weeks of treatment in a single-arm trial (LEAD trial) [59].

Lipid-lowering drugs

There has been a concern with the use of statins in patients with liver disease, as an increased aminotransferase is frequently seen. However, it has the potential benefits in NAFLD patients in improving their lipid profile and reducing the inflammatory process. A systematic review found a transient, asymptomatic elevation of serum aminotransferases in the first 12 weeks of statin use. Hence, the use of statin is considered safe in the management of dyslipidemia in NAFLD patients, even in those who have a mild elevation of aminotransferases [60].

Statin therapy

Rosuvastatin at 10 mg per day for 12 months reduced serum liver aminotransferases along with resolution of steatosis by ultrasound imaging and resolution of NASH on liver biopsy in 19 of the 20 NASH patients studied [61]. In large RCT of NAFLD patients, atorvastatin at 20 mg per day, in combination with anti-oxidants (vitamin E 1,000 IU per day + vitamin C 1,000 mg per day) improved steatosis (as assessed by imaging) compared with placebo [62]. Similarly, with use of ezetimibe, an improvement in histological features of NASH, including steatosis, ballooning and fibrosis was found [63]. In a meta-analysis of RCTs, the use of statins improved aminotransferases, improved radiological evidence of steatosis but without histological improvement in patients with NAFLD [63]. Hence, lipid-lowering agents can be used alone, or probably in combination with other agents, to improve the metabolic syndrome in NASH. This beneficial effect of statins on steatohepatitis was stronger (p=0.02) in subjects without I148M variant of patatin-like phospholipase-3, a genetic variant associated with NAFLD [64].

Gemcabene

Gemcabene, a novel lipid-lowering drug by enhancing the clearance of very low-density lipoprotein (VLDL). In phase II clinical trial on hypercholesterolemic patients, the addition of gemcabene (at different doses 300 mg and 900 mg) to statins reduced low-density lipoprotein (LDL) cholesterol by more than 20% in a dose-dependent manner. It also reduced C- reactive protein (CRP) by >40% compared to placebo [65]. Currently, this drug is being evaluated in children with NAFLD and adults with familial partial lipodystrophy [66].

Reduction of inflammation/progression of NASH

Vitamin E

α-tocopherol, the most common form of natural vitamin E is a fat-soluble anti-oxidant. It is preferentially incorporated into polyunsaturated fatty acid (PUFA) rich domains and optimizes membrane protection from deleterious oxidation and functional destruction. Vitamin E can limit membrane

injury induced by reactive oxygen species, a key component in inflammatory processes in NASH [67].

Vitamin E (1000 IU/day) was found to improve hepatic steatosis by 71% when used in combination with vitamin C (1000 mg/day) and atorvastatin (40 mg/day). In a RCT (TONIC) comparing metformin (1000 mg/day) and vitamin E (800 IU/day) for 96 weeks in 57 children, histological improvement with reduction in hepatocellular ballooning and NAS was observed with vitamin E compared to placebo (58 vs 28%; p=0.006). However, no changes in aminotransferases were noted [47]. Similarly, in a 96 week RCT study in non-diabetic, biopsy-proven NASH patients (PIVENS study), a histological improvement was seen (43% vs 19%; P=0.001) along with decreased steatosis and inflammation (P=0.005) with vitamin E (800 IU/day). Again, there was no improvement in fibrosis (P=0.24) [40]. Vitamin E was also found to improve histological parameters of NASH in pooled data analysis from PIVENS trial and placebo arm of FLINT trial. There have been concerns with the usage of vitamin E following a finding of increased all-cause mortality (39 per 10,000 persons) observed in a meta-analysis of 19 studies [68]. An increased risk of hemorrhagic stroke attributed to its platelet effect at high doses [69] and an increased risk of prostate cancer (odds ratio=1.6) in SELECT trial among elderly patients receiving vitamin E for cancer prevention [70].

Pentoxifylline

Tumor necrosis factor (TNF)-α is a pro-inflammatory cytokine, it promotes necroinflammation, apoptosis, and fibrogenesis, along with hepatic insulin resistance. Pentoxifylline (PTX) is a competitive phosphodiesterase inhibitor with antagonistic action for adenosine-2 receptor and inhibits TNF-α. In a RCT of 55 patients with biopsy-proven NASH, the addition of 400 mg of PTX three times a day compared to placebo reduced steatosis (P<0.001), lobular inflammation (P=0.02), and/or hepatocellular ballooning (P=0.04), along with a decrease of NAS ≥2 points (p=0.01) [71]. In a systemic review, the use of PTX has shown improvement in aspartate and alanine aminotransferases levels with no significant effect on cytokine markers such as TNF-α and IL-6 [72]. Given its safety profile, PTX can be considered: however, there is uncertainty on the effects of liver fibrosis with the use of this drug; hence it is not frequently used in NASH patients.

Omega-3 / polyunsaturated fatty acids

N-6-polyunsaturated fatty acids (PUFA) such as arachidonic acid can oxidize and causes inflammation. These agents also lead to lipid peroxidation and alter the phospholipid composition of cellular membranes. Omega-3-PUFA, have anti-inflammatory properties and inhibit lymphocyte proliferation, antibody and cytokine production, adhesion molecule expression, and natural killer cell activity [51]. In a small RCT, omega - 3 PUFA was found to improve hepatic steatosis and aminotransferase levels in NASH patients. In addition, the use of Omega 3 PUFA has also shown to reduce serum TG and TNF-α concentration while improving insulin sensitivity and high-density lipoprotein (HDL) cholesterol. Compared to placebo, it failed to show improvement in NAS scores, inflammation, or hepatic steatosis [73]. Larger multi-center trials using PUFA is underway to elucidate the role of PUFA in NASH.

Ursodeoxycholic acid

Several early studies found improvement in aminotransferases and steatosis in patients with NAFLD following the addition of ursodeoxycholic acid (UDCA). However, a multi-center RCT did not find any histological improvement over placebo in NASH patients [74]. A similar finding of no significant improvement in histological features of NASH was seen in a meta-analysis of all RCTs [63]. Hence, the use of UDCA it is not recommended for use in NASH patients [2].

Angiotensin receptor blockers

Angiotensin receptor blockers (ARB) modulate insulin sensitivity, systemic inflammation, hepatic lipogenesis, and fibrogenesis. They also help in managing hypertension, which commonly occurs in patients with NAFLD. The use of renin-angiotensin blockers has been found to have a negative association (odds ratio=0.37) for advanced fibrosis in NAFLD in a cross-sectional study [75]. Telmisartan was found to benefit hypertensive NASH patients with improved insulin resistance, TG, along with histologic improvement in steatosis, necro-inflammation, and fibrosis in a RCT. Similarly, losartan, along with simvastatin, showed improvement in hepatic steatosis, inflammatory markers, and homeostatic model assessment (HOMA) in comparison to amlodipine and simvastatin combination [63].

Newer therapies: (Table 3)

Therapies with benefit in NASH by large studies but not approved by FDA

Bile acids

Bile acids are synthesized in the liver from cholesterol; they act as a signaling molecule via nuclear receptor farnesoid X receptor (FXR) and the G-protein-coupled receptor (TGR5) [76] and affect lipid metabolism, inflammation, and fibrosis of the liver. FXR is located primarily in the liver, intestine, and kidneys. Activation of this receptor causes a decrease in bile acid synthesis, hepatic gluconeogenesis, and lipogenesis.

Obeticholic acid (OCA), is a synthetic variant of bile acid and a selective agonist of FXR. OCA has been approved for the treatment of primary biliary cholangitis and has shown to have hepato-protective and anti-cholestatic activity [77, 78]. In a phase II multi-center double-blinded RCT of 64 type II diabetes mellitus patients with NAFLD (by imaging), treatment with OCA improved insulin sensitivity (24.5% vs - 5.5%; p=0.011) compared to placebo. There was an improvement of enhanced liver fibrosis score in OCA group (p=0.04) and a reduction in ALT levels (p=0.03) [79]. A larger phase IIb multi-center double-blinded RCT on biopsy-proven NASH patients (FLINT trial), compared 25 mg of OCA with

Table 3: Newer therapies under investigation for NASH

Study	(n)	Methodology/Outcome Measurement/Intervention	Duration	BMI	TG/ Lipids	ALT/ AST	Glucose/ IR/ HOMA-IR	Steatosis Grade	Inflammation	NAS Score	Fibrosis Stage
BILE ACIDS											
Mudaliar S et al. 2013 [79]	64	Double-blind RCT, 25 or 50 mg OCA vs placebo	6 weeks	↓	↑LDL	↓	↓			↓	
Neuschwander-Tetri BA et al. 2015 [80]	283	Double-blind RCT, non-cirrhotic, NASH, OCA 25 mg/day vs placebo	72 weeks	↓	↑LDL	↓		↓	↓		↓
Younossi Z et al. 2019 [82]	2400	RCT, Liver biopsy, OCA 10 or 25 mg vs placebo	72 weeks		↑LDL	↓			↓	↓	↓
Patel K et al. 2018 [83]	140	Double blinded RCT, placebo, cilofexor 30 mg or 100 mg once daily	24 weeks					↓			
Harrison SA et al. 2019 [86]	43	Double blinded RCT, placebo, subcutaneous NGM282 (FGF 19) 1 mg or 3 mg once daily	12 weeks			↓			↓	↓	↓
Sanyal A et al. 2018 [87]	75	Double blinded RCT, SC placebo once a day, 10 mg pegbelfermin once a day, or 20 mg pegbelfermin once a week	16 weeks		↓TG ↑HDL			↓			
GUT MICROBIOME											
Mizrahi et al. 2012 [88]	10	Pilot Study, OL trial, biopsy-proven NASH and IR, Imm124-E	30 days			↓	↓				
REDUCTION OF HEPATIC STEATOSIS											
Safadi R et al. 2014 [93]	60	RCT, biopsy proven NASH, Aramchol 300 mg	3 months			↔		↓			
Loomba R et al. 2018 [96]	126	RCT, 2:2:1 Firsocostat (GS-0976) 5 mg, 20 mg, or placebo daily	12 weeks		↑TG	↓		↓			
Stiede K et al. 2017 [95]	30	Double blinded RCT, two-period, two-treatment crossover, NDI-010976 20, 50, or 200 mg	2 Time points		↓DNL						
Siebers N et al. 2018 [100]	8	Phase 1, OL, Volixibat 50 mg	6 days					↓	↓		↓
Harrison SA et al. 2019 [99]	348	Double blinded RCT, 2:1 Resmetirom (MGL-3196) 80 mg or placebo, orally once a day	36 weeks		↓			↓			
INFLAMMATION & APOPTOSIS											
Schwimmer JB et al. 2016 [101]	169	RCT, Phase II, biopsy proven NAFLD children, CBDR 300, 375 and 450 mg vs placebo twice daily	1 year			↓			↓		
Friedman SL et al. 2017 [102]	289	Double blinded RCT, phase II, biopsy proven NASH, NAS>4, Fibrosis stage 1-3, CVC 150 mg vs placebo	1 year							↔	↓
Loomba R et al. 2017 [103]	72	RCT, Selonsertib 6 or 18 mg/ day with or without once-weekly injections of 125 mg of Simtuzumab, or Simtuzumab alone.	24 weeks						↓		↓
Oral EA et al. 2017 [107]	42	Double blinded RCT, Amlexanox	12 weeks				↓ HBA1C	↔			
Shiffman ML et al. 2010 [108]	204	Double blinded RCT, chronic hepatitis C, PF-03491390 5, 25 or 50 mg	12 weeks			↓				NAS Score	
FIBROSIS											
Harrison SA et al 2018 [115]	219	Double blinded RCT, phase II, cirrhosis due to NASH, DM in NASH, safety and efficacy of Simtuzumab, 200 & 700 mg	96 weeks								↔

ALT: Alanine Aminotransferases; AST: Aspartate Aminotransferases; BMI: Body Mass Index; CBDR: Cysteamine Bitartrate Delayed Release; DM: Diabetes Mellitus; DNL: De Novo Lipogenesis; HOMA-IR: Homeostatic Model Assessment – Insulin Resistance; IR: Insulin Resistance; LDL: Low Density Lipoprotein; NAS: Non-Alcoholic Fatty Liver Disease; (NAFLD) Activity Score; NASH: Nonalcoholic Steato-Hepatitis; OCA: Obeticholic Acid; OL: Open Label; RCT: Randomized, Controlled Trial; TG: Triglycerides; ↑ Indicates Increase; ↓ Indicates Decrease; ↔ Indicates No Change

placebo on 283 patients over 72 week's period [80]. Subjects receiving OCA showed great improvement in steatosis (p=0.01) hepatic ballooning (p=0.03), lobular inflammation (p=0.006) and fibrosis (p=0.04). Significant weight loss and a decrease in systolic blood pressure were also seen in patients treated with OCA compared to placebo (p=0.05). The study was terminated early after an interim analysis showing significant improvement of liver histology in OCA group compared to placebo (p=0.02). Interestingly, study patients had increased total serum cholesterol, LDL cholesterol with a reduction in HDL cholesterol levels. Elevated LDL cholesterol was managed adequately by co administration of atorvastatin (CONTROL trial) [81]. Study subjects had a higher occurrence of pruritus (23% vs 6%; p<0.0001) compared to placebo. However, overall adverse effects were equal in both groups [80]. A phase III trial, (REGENERATE) with OCA among NASH subjects with stage 2 & 3 fibrosis found improvement in fibrosis compared to placebo (23.1% with OCA, 25 mg; 17.6% with OCA, 10 mg; and 11.9% in placebo) at 18 months interim analysis [82].

Cilofexor (GS-9674), a non-bile acid and nonsteroidal FXR agonist are being evaluated as it is considered safe and well tolerable without worsening of lipid profile. Cilofexor decreased liver fat on MRI-PDFF by14% and 39% at 30 mg and 100 mg doses, respectively in comparison to the placebo of 12.5%. Pruritus was observed at a higher dosage of 100 mg [83].

FGF 19, a downstream target for FXR, secreted in intestine inhibits gluconeogenesis and increases glycogen synthesis. It regulates bile acid synthesis via CYP7A1 [84]. NGM282, an engineered non-tumorigenic molecule activates FGF 19 with inhibition of de novo lipogenesis (DNL), improvement in insulin sensitivity, and a decrease in liver aminotransferases in a murine model [85]. A 12-week phase II study in humans have shown a reduction in liver chemistries at both 1 mg and 3 mg doses along with histological improvement (74% vs 33%), inflammation (42% vs 32%), ballooning (53% vs 30%), and fibrosis (42% vs 21%) [86].

FXR activation also leads to the expression and secretion of FGF 21 that has shown effects on the bile acid pool by reducing CYP7A1 expression. Pegbelfermin is a pegylated formulation of FGF 21 that was evaluated on biopsy-proven NASH subjects with a statistically significant reduction in the liver fat fraction on MDR-PDFF, at 10-mg daily (6.8%) and 20-mg weekly (5.2%) doses compared placebo (1.3%) [87]. An increase in HDL and a decrease in TG levels were also observed in both groups.

Gut microbiome

The gut-liver axis is involved in the pathogenesis of NAFLD by the production of metabolic products like lipopolysaccharides from gut-derived micro bacteria. Drugs targeting the gut bacterial flora, modulating their metabolic production, or inhibiting the translocation of bacterial products to liver could be of beneficial effect [88].

Dysbacteriosis of intestinal bacteria in the development of NAFLD is of growing interest now. Manipulating the bacterial content of gut by the use of probiotics was tested in patients with NAFLD, with an improvement of insulin resistance, lipid profile, and tumor necrosis factor, but their effect on hepatic histology is unknown [89, 90].

Therapies being evaluated for NASH based on preliminary trials

Reduction of hepatic steatosis

De novo lipogenesis

Fatty acid (FA) accumulation is the primary event in NAFLD. Increased de novo lipogenesis has been a significant contributing factor in this disease process. Interventions reducing de novo lipogenesis (DNL) are being considered.

Aramchol - a stearoyl coenzyme A desaturase inhibitor

Monounsaturated fatty acids, such as palmitoleic acid and oleic acid the two most abundant monounsaturated FA, regulate adipose tissue inflammation. They alter adipocyte signaling pathways and the secretion of pro-inflammatory cytokines. Stearoyl-CoA desaturase, is the rate-limiting enzyme in the synthesis of these FA and has an important role in adipose tissue inflammation [91]. Inhibition of stearoyl-CoA desaturase -1 has shown to decrease hepatic steatosis and improvement of insulin sensitivity [92].

Aramchol, a stearoyl CoA desaturase inhibitor, reduces DNL. In a small study of 60 patients with biopsy-proven NASH aramchol showed a reduction of hepatic fat content by 12.6% by MR spectroscopy [93]. A phase III/IV RCT (ARMOR) on NASH subjects with obesity and diabetes receiving 300 mg aramchol twice daily is under investigation with a primary endpoint of resolution in NASH and improvement in fibrosis [66].

Acetyl coenzyme A carboxylase inhibitor

Malonyl coenzyme A controls the balance between de novo lipogenesis and fatty acid oxidation. Acetyl coenzyme A carboxylase (ACC) is the primary enzyme involved in the generation of malonyl coenzyme A. Inhibition of acetyl coenzyme A carboxylase results in a decrease in lipogenesis, improve insulin sensitivity and a reduction of hepatic fat content [94]. Phase 1 RCT involving NDI-010976, an allosteric inhibitor of acetyl coenzyme A carboxylase inhibitor, has shown marked reduction (>90%) in DNL following a single dose [95]. Another acetyl coenzyme A carboxylase inhibitor, firsocostat (GS-0976), in a phase II trial for 12 weeks duration showed a reduction in the liver fat fraction on MRI-PDFF from baseline by 30% in 20 mg vs 23% in 5 mg doses compared to 15% in placebo. A decrease in markers of fibrosis and liver chemistries was also observed in this study. As a potential side effect in the study arm recceing 20 mg, there was an elevation in triglyceride level in a week and returned to baseline by the end of the study [96]. PF-05221304 (PF'1304), a liver-targeted ACC inhibitor and MK-4074 is a liver-specific inhibitor of ACC1 and ACC2, enzymes are currently under investigation

in phase IIa and phase 1 respectively, for changes in liver fat from baseline in adult NAFLD patients [66].

Thyroid hormone receptor β agonist

Thyroid hormone receptor β (THR β) activation causes accelerated hepatic fatty acid oxidation, by increased hepatic mitochondrial respiration rates, changes in hepatic gene expression, and increased plasma acyl-carnitine levels. It's activation results in increased clearance of liver lipids. Four weeks of therapy with thyroid hormone receptor β agonist (MB07811) improved steatosis and decreased cholesterol, while nine weeks of intervention improved aminotransferases and decreased liver triacyl glycerol in animal studies [97, 98].

Resmetiron (MGL-3196), a THR β agnosit in phase II multi-centered double-blinded RCT evaluated in biopsy-proven NASH patients for reduction of hepatic steatosis has shown a significant reduction in the liver fat fraction on MRI-PDFF (37.3% vs 8.9%) compared to placebo. Resolution in NASH without worsening in fibrosis was observed in 27% of subjects' vs 6% in the placebo group at 36 weeks. Improvement in biomarkers of fibrosis and lipid profile was also noticed [99]. Currently, this drug is being planned for a phase III trial.

Reduction of intrahepatic bile acid absorption

Disruption of enterohepatic circulation of bile acids has a favorable outcome with the reduction of serum lipids. Sevelamer, a phosphate binding medication with bile salt binding capacity, was found to have benefit in NASH with an improvement of hepatic steatosis, inflammation, and fibrosis. However, colesevelam, another intestinal bile salt sequestrant did not show benefit [78]. Inhibitors for apical sodium-dependent bile acid transporter, reduce bile acid reabsorption in the ileum. Volixibat, an oral apical sodium-dependent bile acid transporter inhibitor, has proven to be safe and tolerable in subjects. Its use can have beneficial metabolic, anti-inflammatory, anti-steatotic, and anti-fibrotic effects in NASH [100].

Inflammation and apoptosis

Cysteamine

Cysteamine, an aminothiol, is a free radical scavenger and reduces oxidative stress in NAFLD patients. This drug was studied in a phase II RCT in 169 biopsy-proven NAFLD children for 1 year. The study compared weight-based cysteamine therapy with the placebo. A reduction of alanine aminotransferase levels (p=0.002) and lobular inflammation was seen without any histological benefit [101].

C-C chemokine receptor types 2 and 5 antagonists

Kupffer cell activation, resident macrophages of the liver, causes recruitment of inflammatory cells in the liver via C-C chemokine receptor types 2 and 5 (CCR2/CCL5) and propagation of fibrosis. Cenicriviroc, an antagonist of C-C chemokine receptor types 2/5, was studied in HIV-infected patients without any liver disease and showed improvement in serum markers of fibrosis [78]. A high level of expression of these chemokines is seen in NASH patients. In a randomized placebo-controlled, CENTAUR study on 81 biopsy-proven NASH patients, improvement in fibrosis score was noticed (20% vs 10%; p=0.02), while no significant differences in steatohepatitis score were found compared to placebo [102]. A phase III, (AURORA) trial with cenicriviroc for 12 months duration is currently ongoing.

Apoptosis signal-regulating kinase 1 inhibitors

Apoptosis signal-regulating kinase 1 (ASK 1), a mitogen-activated protein kinase, is activated under oxidative stress and by tumor necrosis factor-α. Its activation causes downstream phosphorylation of the p38 MAPK/JNK pathway resulting in hepatic apoptosis and fibrosis. In a murine model, inhibition of ASK 1 showed a reduction in hepatic steatosis and fibrosis [78]. In a phase II trial on 72 NASH patients with selonsertib (ASK -1 inhibitor), 43% of subjects showed ≥1 stage reduction in fibrosis following 24 weeks of 18 mg therapy. Improvement in fibrosis was also found to correlate with a decrease in liver stiffness on MR elastography, collagen content, and lobular inflammation on liver biopsy, as well as improvements in serum biomarkers of apoptosis and necrosis [103]. Recent phase III trials (STELLAR-3 & 4) with selonsertib, however, did not achieve its primary endpoint of ≥ 1 stage reduction in fibrosis on liver histology [104].

Vascular adhesion protein-1 inhibitors

Vascular adhesion protein-1 (VAP-1), also known as semicarbazide-sensitive amine oxidase, acts as an adhesion receptor and is expressed in the hepatic endothelium and non-hepatic endothelium of smooth muscles cells. It helps in the transmigration of lymphocytes under physiological stress. It has insulin-like effects and generates reactive oxygen species causing hepatic injury and subsequent fibrosis [105]. In a mouse model, PXS-4728 (VAP1 inhibitor) showed histological improvement of NASH with decreased hepatic inflammation, injury, and fibrosis and has completed phase I trials in healthy volunteers [78].

IKKε / TANK-binding kinase 1 inhibitors

Kupffer cell activation, resident macrophages of the liver, causes recruitment of inflammatory cells in the IκB kinases IKK-ε and TANK-binding kinase 1. IκB kinases IKK-ε and TANK-binding kinase 1 are upregulated in the liver and adipose tissue upon high-fat diet feeding and are associated with obesity, hepatic steatosis, and insulin resistance [78]. Amlexanox, an approved small-molecule therapeutic presently used in the clinic to treat aphthous ulcers and asthma, is an inhibitor of these kinases [106]. Amlexanox reduced insulin resistance and hepatic steatosis in animal models. In a recent phase II RCT study in type II obese diabetic patients with NAFD, amlexanox at 25 mg improved HbA1C values (p=0.05) but without significant change in hepatic steatosis compared to the placebo group (p=0.38) [107].

Caspase Inhibitors

Apoptosis is the physiological death of the cell and is required for cellular maintenance of homeostasis. Caspases play a

major role in this process. Several studies have explored the possibility of using caspase inhibitors to prevent the disorders occurring when the levels of caspases are excessive. Emricasan, an irreversible pan-caspase inhibitor studied in a phase II placebo-controlled clinical trial at different doses (5, 25, 50 mg) resulted in the improvement of liver biomarkers within a week. These effects were maintained until the drug was discontinued [108]. In recent two double-blind RCT, emricasan did not show improvement in fibrosis among non-cirrhotic 318 NASH subjects or improvement in portal pressures among 263 patients with NASH cirrhosis [109, 110].

Fibrosis

Liver related mortality among patients with NASH has been found to correlate with stage of fibrosis [111, 112]. Hence, either reduction/resolution of fibrosis, or delaying progression of fibrosis is an important management goal in these patients. A few anti-fibrotic managements are currently being considered to improve outcome in NASH subjects.

Lysyl oxidase-like 2 inhibitors

Lysyl oxidase-like 2 (LOXL-2), a matrix enzyme, is secreted by fibrogenic cells. It causes fibroblast and TGF-β activation causing cross-linking of collagen chains and hepatic fibrosis [78, 113]. Serum LOXL2 levels have been shown to correlate with stages of fibrosis, the strongest predictor of mortality in NASH patients [114]. Hence, Simtuzumab, a monoclonal antibody, and a LOXL-2 inhibitor were evaluated for its benefit in cirrhotic and non-cirrhotic NASH patients [103, 115]. The drug was found to be ineffective in reducing fibrosis and hepatic venous pressure gradient following 96 weeks of therapy [103].

Gelatin-3 protein inhibitors

Galectin-3 protein, expressed by immune cells, binds to terminal galactose residues in glycoproteins. It is expressed in the liver, kidneys, and lungs and plays a critical role in the pathogenesis of parenchymal fibrogenesis, including fibrosis in NASH [116]. GR-MD-02 inhibits galectin-3 protein and acts as an antifibrotic agent. It was found to reduce hepatic fibrosis and disease activity in NASH animal models [78]. There are ongoing studies evaluating its ability to reduce hepatic fibrosis and hepatic venous pressure gradient.

Other agents being evaluated

Peroxisome proliferator-activator receptors

Peroxisome proliferator-activator receptors (PPARs) are a family of nuclear receptors. They regulate the metabolic process relating to fatty acids. There are three PPARs α, β/δ, and γ, they differ in ligand selectivity and tissue distribution but share the same target DNA sequence.

Pemafibrate (K-877) selective PPARα modulator

Pemofibrate has been approved in Japan in the management of dyslipidemia. It has promising results with a decrease in liver aminotransferases, improving atherogenicity by lowering serum TG levels, and increasing HDL cholesterol compared to fenofibrate and placebo [117, 118].

Elafibranor a dual PPAR α/δ agonist

Elafibranor (GFT505) has shown improvement in steatosis, inflammation, and fibrosis in a mouse model of NASH [119]. A phase IIb RCT trial on 276 NASH patients showed a non-significant reduction in NASH histological scores at different doses compared to placebo. Additionally, it has shown a favorable cardiometabolic profile in study subjects [120]. Currently, a phase III RESOLVE-IT trial is underway with a primary outcome of histological improvement and liver-related outcomes in NASH subjects with fibrosis.

Newer FXR agonists

Obeticholic acid, which has been found to be effective in NASH as mentioned earlier, has long term safety and tolerability concerns. Hence newer synthetic agents (Nidufexor, EDP305 and GS-9674 / INT 767) with reduced enter hepatic circulation and a predictable pharmacokinetics are being evaluated in NASH [121, 122].

Nor ursodeoxycholic acid

Nor UCDA, a side-chained shortened derivative of UCDA, has demonstrated improvement in liver injury in animal models with cholestatic liver and bile duct injury [123]. In pre-clinical animal studies, mice treated with Nor UDCA showed a significant reduction in serum liver aminotransferases and alkaline phosphatase levels and faster blood glucose clearance. There was also a reduction in inflammatory markers and reduced hepatic injury suggesting an improvement in many components and pathways of NASH disease progression, including insulin sensitivity, steatosis, and inflammation favoring its use in NAFLD [124].

Newer PPAR agonist

Lanifibranor (IVA337) is a novel pan-PPAR (α, β, γ and δ) agonist that has potent antifibrotic properties in skin and lung fibrosis is being evaluated in phase IIb multi-center NATIVE trial with a primary endpoint of decrease in hepatic steatosis, activity, and fibrosis from baseline [66].

Conclusion

In conclusion, NAFLD has become the commonest chronic liver disease. The progressive form of this disease has significant morbidity and mortality. There are many agents available for the management of NAFLD. Besides lifestyle modifications, which are crucial for management, newer therapies and interventions are being actively considered for the reduction of different aspects of the disease. Many studies are underway in evaluating specific pathways involved in the disease process, and interventions of these pathways are being evaluated in mitigating the disease process and in the reduction of long-term complications from this disease.

Conflicts of Interest

No potential conflict of interest relevant to this article is reported from any authors

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