3rd GLOBAL LIVER HEALTH FORUM

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An overview of recent therapeutic progress of NASH treatment

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Disclosures

- Prof. Lu has no disclosures to declare

Overview

1. How does NASH progress?
2. How are NASH and NAFLD treated?
3. What drugs are in development?
4. What are the challenges in developing drugs for the treatment of NASH and NAFLD?
5. Summary

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

How does NASH progress?

NASH progresses to cirrhosis and HCC

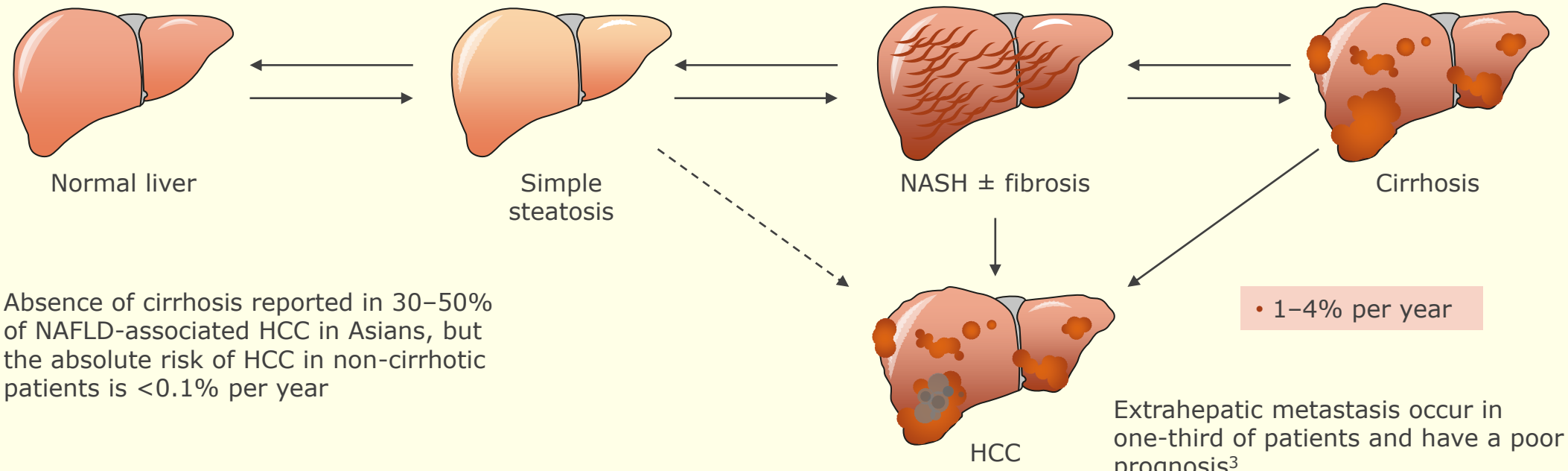
The prevalence of NAFLD in Asia is estimated to be 29.6%[1]

Natural history of NAFLD in Asia:[2]

- Annual incidence of NAFLD 3–4%
- 60% can reverse NAFLD by lifestyle intervention

- 25% of patients progress from simple steatosis to NASH, and have fibrosis progression in 3 years
- Spontaneous reversal of NASH uncommon without intervention

- Fibrosis progression one stage in 7 years in NASH patients; one stage in 14 years in simple steatosis
- No data on reversal of cirrhosis



Absence of cirrhosis reported in 30–50% of NAFLD-associated HCC in Asians, but the absolute risk of HCC in non-cirrhotic patients is <0.1% per year

- 1–4% per year

Extrahepatic metastasis occur in one-third of patients and have a poor prognosis[3]

HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

1. Wong SW, et al. Indian J Gastroenterol 2020;39(1):1–8.; 2. Fan JG, et al. J Hepatol 2017;67:862–73.; 3. Targe et al. Egypt J Radiol Nucl Med 2021;52:228.

How are NASH and NAFLD treated?

How familiar are you with how NASH and NAFLD are treated?

1. I am fully up to date with the latest treatment recommendations for NASH and NAFLD
2. I am aware of most treatment recommendations for NASH and NAFLD
3. I am aware of some treatment recommendations for NASH and NAFLD
4. I am not aware of treatment recommendations for NASH and NAFLD

COVID-19, coronavirus disease 2019; MAFLD, metabolic associated fatty liver disease

Chinese guidelines and consensus recommend lifestyle changes for the treatment of NAFLD

First-line treatment: lifestyle modification[1,2]

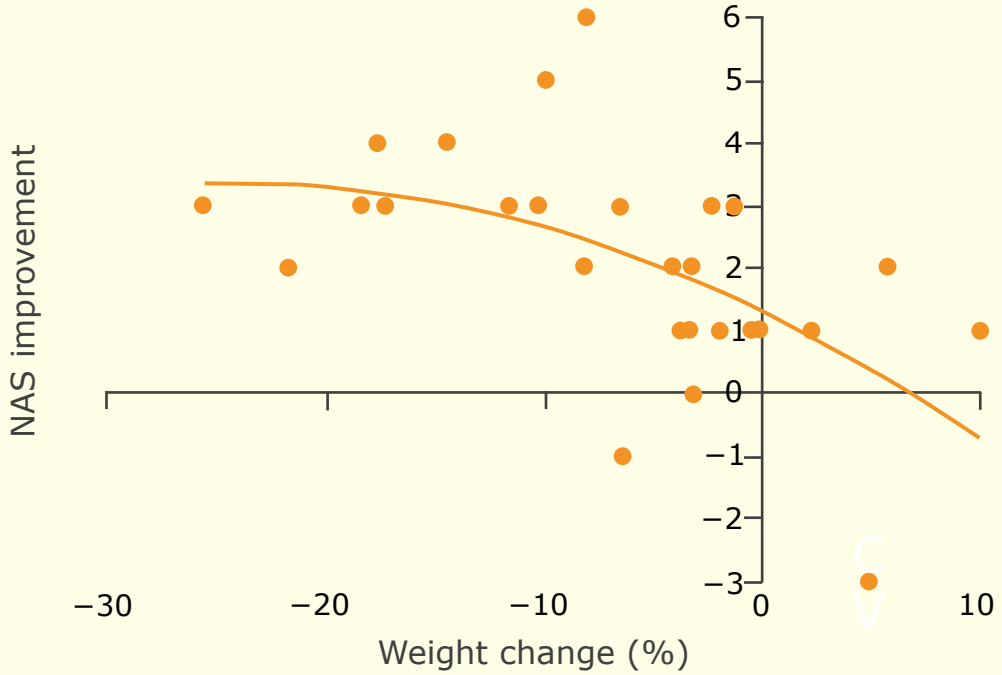
For weight loss, control of metabolic disorders and to improve steatosis/steatohepatitis

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

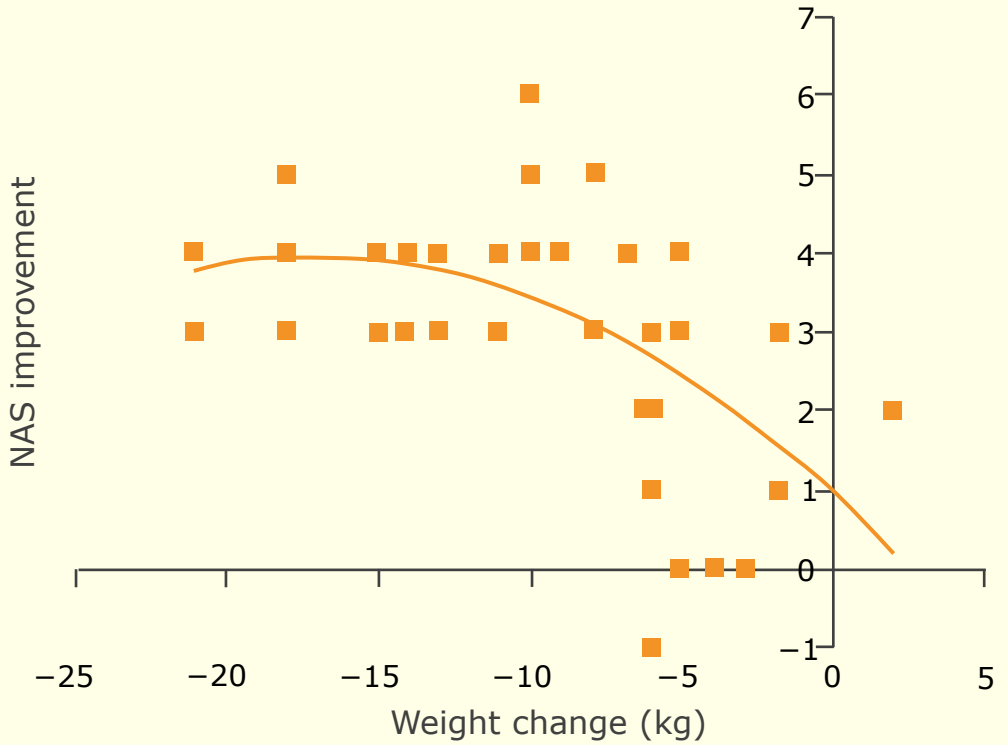
1. Gao X, et al. J Diabetes 2013;5:406–15.; 2. Fan JG, et al. J Dig Dis 2018;1–11

Increased weight loss correlates with improved NAFLD activity scores in patients with NASH and NAFLD

The NAFLD activity score is a widely used measure of grading and includes scores for steatosis (0–3), lobular inflammation (0–2), hepatocellular ballooning (0–2), and fibrosis (0–4)[1]



RCT[2]
n=31



RCT[2]
n=60

NAS, non-alcoholic fatty liver disease activity score; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RCT, randomised controlled trial

1. Kleiner DE, et al. Hepatology 2005;41(6)1312–21.; 2. Musso G, et al. Diabetologia 2012;55:885–904

Chinese guidelines and consensus recommend pharmacological intervention for the treatment of NAFLD/NASH-related metabolic disorders

Pharmacotherapy[1]

	NAFLD	NASH
Metformin	To improve insulin resistance and glucose metabolism (not liver-specific)	
Pioglitazone	To improve glucose metabolism (beneficial for liver with some side effects)	
Statin/Fibrates	To improve lipid metabolism and atherosclerosis/reduction of serum TG (not liver-specific)	
Angiotensin-2 receptor antagonist	To reduce arterial hypertension (not liver-specific)	
Orlistat	If weight reduction of >5% is not achieved with lifestyle modifications	

Hepatoprotectors[1,2]

- The use of 1–2 types of the following **hepatoprotective agents** is optional as adjunct therapy in patients with NAFLD with biopsy-proven **NASH**, abnormal liver enzymes, or signs of **significant fibrosis**:
  - Vitamin E
  - Silymarin
  - **Polyene phosphatidylcholine (EPLs)**
  - Adenosylmethionine
  - Reduced glutathione

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EPLs, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TG, triglyceride

1. Gao X, et al. J Diabetes 2013;5:406–15; 2. Fan JG, et al. J Dig Dis 2018;1–11

There are limited data on the effect of therapies on liver histology

Current medication for the treatment of NASH:[1]

Medication	Mechanism	Effect on liver histology
Pioglitazone	PPAR-γ	Improvement of steatosis, lobular inflammation, and ballooning
Vitamin E	Antioxidant	Improvement of hepatocyte ballooning
Metformin	Amelioration of IR	No beneficial effect
Statin	HMG-CO A reductase inhibition	No beneficial effect
Ezetimibe	Inhibition of cholesterol absorption	Improvement of hepatocyte ballooning
Fibrates	PPAR-α	Improvement of hepatocyte ballooning
Pentoxifylline	Inhibition of TNF-α and anti-oxidants	Improvement of inflammation and ballooning
Losartan	ARB	Improvement of steatosis, lobular inflammation, ballooning and fibrosis
UDCA	Prevention of apoptosis/inflammation	Lacking data
Synbiotic and probiotics	Modulation of gut microbiota	Lacking data

No pharmacological treatments are approved for the treatment of NASH in the US or Europe[2]

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ARB, angiotensin receptor blockers; HMG-CO A, hydroxyl-methyl-glutaryl-coenzyme A reductase; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; PPAR, peroxisome proliferator-activated receptor; TNF-α, tumour necrosis factor alpha; UDCA, ursodeoxycholic acid

1. Eshraghian A. World J Gastroenterol 2017;23:7495–504; 2. Chapman RW, et al. Br Med Bull 2020;133(1):95–104

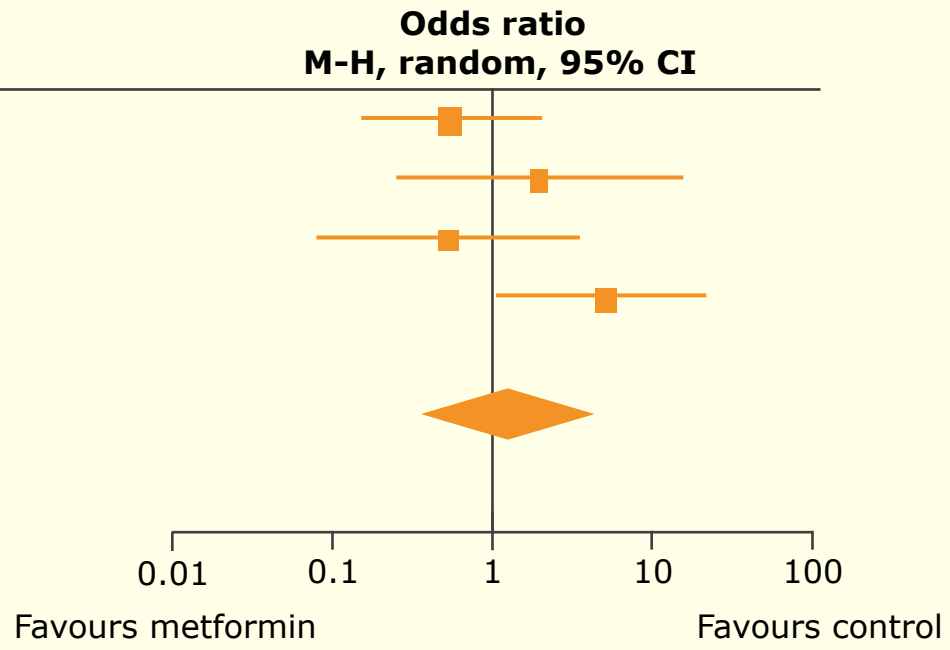
Metformin does not improve steatosis in patients with NAFLD or NASH

Odds ratio of steatosis improvement for treatment with metformin compared with control (placebo or lifestyle changes)[1]

Study or subgroup	Odds ratio M-H, random, 95% CI
Haukeland (2009)[2]	0.56 (0.15–2.05)
Idilman (2008)[3]	2.00 (0.26–15.38)
Shields (2009)[4]	0.54 (0.08–3.53)
Uygun (2004)[5]	5.25 (1.09–25.21)
Total (95% CI)	**1.30 (0.41–4.08)**
Total events	

Heterogeneity: $\tau^2=0.64$; $\chi^2=5.68$, df=3 (p=0.13); $I^2=47\%$

Test for overall effect: Z=0.44 (p=0.66)



The WGO and AASLD do not recommend using metformin to treat NASH in adult patients[6,7]

AASLD, American association for the study of liver diseases; CI, confidence interval; df, degrees of freedom; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; WGO, World Gastroenterology Organisation

1. Li Y, et al. Biomed Rep 2013;1(1):57–64; 2. Haukeland JW, et al. Scand J Gastroenterol 2009;44(7):853–60; 3. Idilman R, et al. Aliment Pharmacol Ther 2008;28(2):200–8; 4. Shields WW, et al. Therap Adv Gastroenterol 2009;2(3):157–63; 5. Uygun A, et al. Aliment Pharmacol Ther 2004;19(5):537–44; 6. LaBrecque DR, et al. J Clin Gastroenterol 2014;48(6):467–73; 7. Chalasani N, et al. Hepatology 2017;67(1):328–57

Effect of EPLs on liver function in patients with T2DM and NASH: study design

Randomised, prospective, single-blind clinical trial investigating the effect of PUPC (EPL)* in patients with T2DM and NASH†

N=215 patients with T2DM of an uncomplicated course which was adequately controlled by diet and treatment with metformin

Primary endpoints: markers of liver function (ALT, AST and γ-GT) and ultrasound results

*Essentiale® forte N, produced by A Nattermann and Cie GmbH, PUPC and EPL are synonymous with one another; †Start date 1998, end date 2012; ‡Basic treatment included a dietary and physical regimen and treatment with metformin 1000 mg/day;
‡This study had a 7-year follow-up not shown here. PUPC refers to phosphatidylcholine molecules carrying essential fatty acids
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipids; γ-GT, γ-glutamyl transferase; NASH, non-alcoholic steatohepatitis; PUPC, polyunsaturated phosphatidylcholine; T2DM, type 2 diabetes mellitus
Sas E, et al. J Hepatol 2013;58:S549

Effect of EPLs on liver function in patients with T2DM and NASH (1/2)

Changes in liver enzyme levels from baseline to 6 months following EPL treatment

- All **liver enzymes** were **significantly reduced** following EPL treatment compared with SOC
- Significant reductions in HbA1c, leading to **improved glycaemic control**, were observed in **86%** of patients receiving EPLs

	Study endpoints	EPL (N=178)
ALT	Baseline 6 months p value	56.5 ± 28.6 IU/L 35.2 ± 18.4 IU/L p=0.02
AST	Baseline 6 months p value	39.0 ± 9.0 IU/L 26.5 ± 7.2 IU/L p=0.04
γ-GT	Baseline 6 months p value	38.2 ± 11.4 IU/L 27.5 ± 8.6 IU/L p=0.03

Data are mean ± SD
ALT, alanine aminotransferase; AST, aspartate aminotransferase; EPL, essential phospholipid; HbA1c, glycated haemoglobin; NASH, non-alcoholic steatohepatitis; SD, standard deviation; SOC, standard of care; T2DM, type 2 diabetes mellitus; γ-GT, gamma glutamyl transferase
Sas E, et al. J Hepatol 2013;58:S549

Effect of EPLs on liver function in patients with T2DM and NASH (2/2)

Changes in hepatic echo-texture and signs of fatty liver following 6 months of EPL treatment

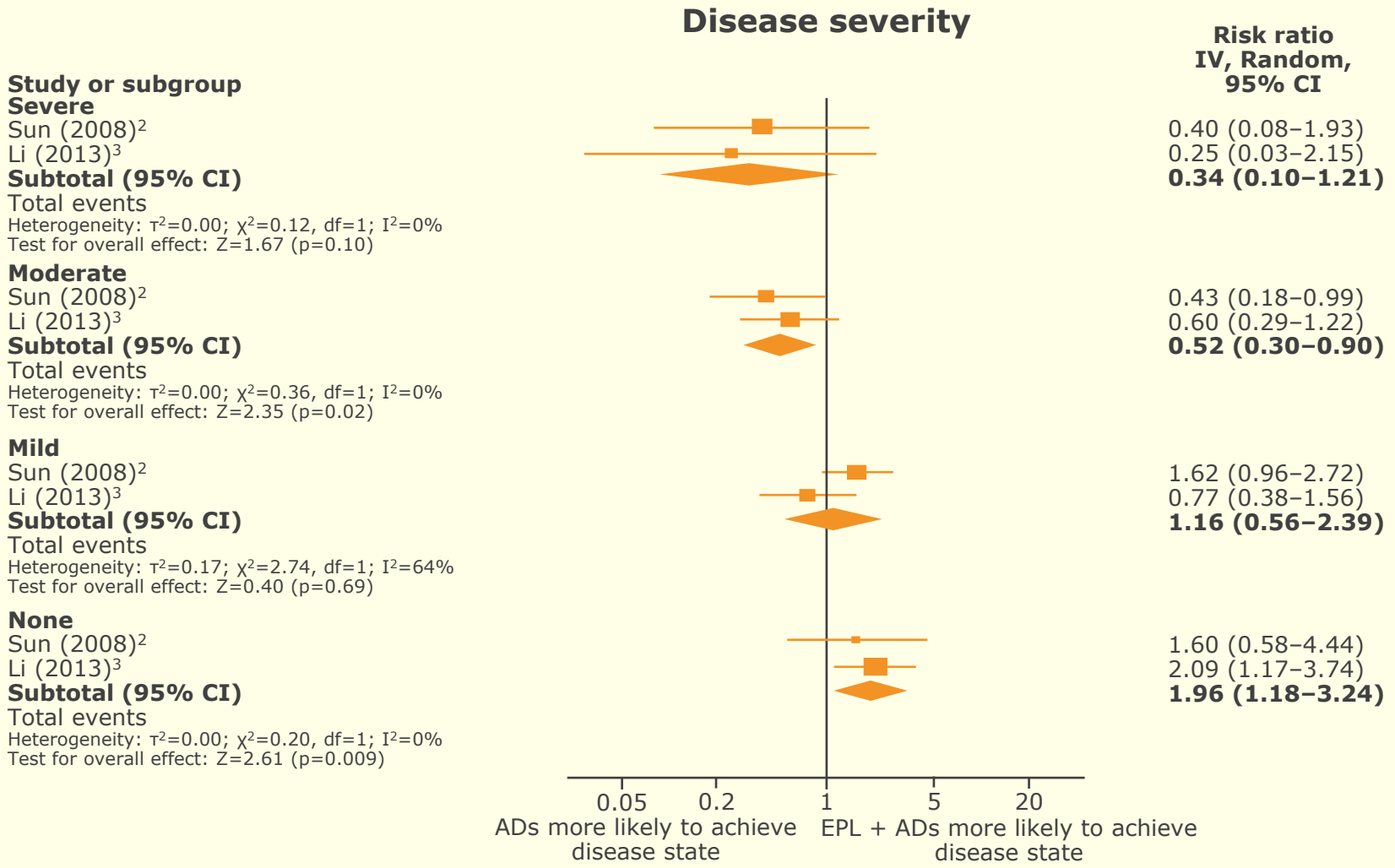
- **Hepatic echo-texture** was significantly improved with EPLs versus SOC
- Ultrasonographic signs of **fatty liver** significantly decreased with EPLs versus SOC
- The development of **hepatic fibrosis** was significantly slowed down with EPLs compared with control (p=0.03)

	Study	EPL (N=178)
Ultrasound studies (hepatic echo-texture)	Improvement	101/152 (66.4%)*
	No change	7/152 (4.6%)
Ultrasonographic signs of fatty liver	Decrease	93/114 (81.6%)**

*p=0.02; **p<0.05. Data shown as n (%)
EPL, essential phospholipid; NASH, non-alcoholic steatohepatitis; SOC, standard of care; T2DM, type 2 diabetes mellitus
Sas E, et al. J Hepatol 2013;58:S549

As previously presented, the results of a network meta-analysis showed a trend in reducing NAFLD disease severity by EPL compared with ADs

In a direct network meta-analysis of RCTs:[1]



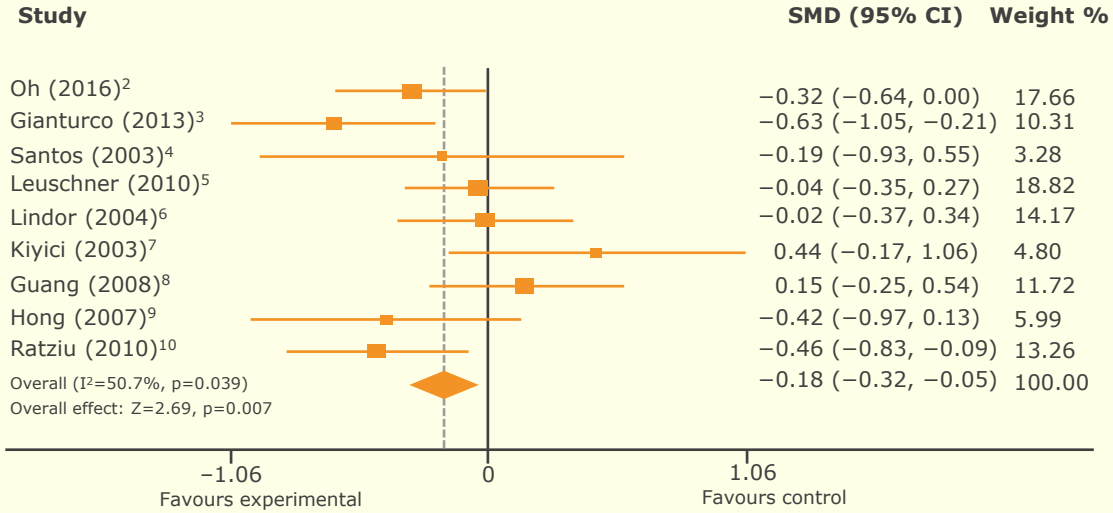
AD, anti-diabetic treatment; CI, confidence interval; df, degrees of freedom; EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease

1. Dajani A, et al. World J Clin Cases 2020;8(21):5235–49; 2. Sun C, et al. Clin Focus 2008;23(17):1272–3; 3. Li Z. Inner Mongol J Tradit Chinese Med 2013;31:10–1

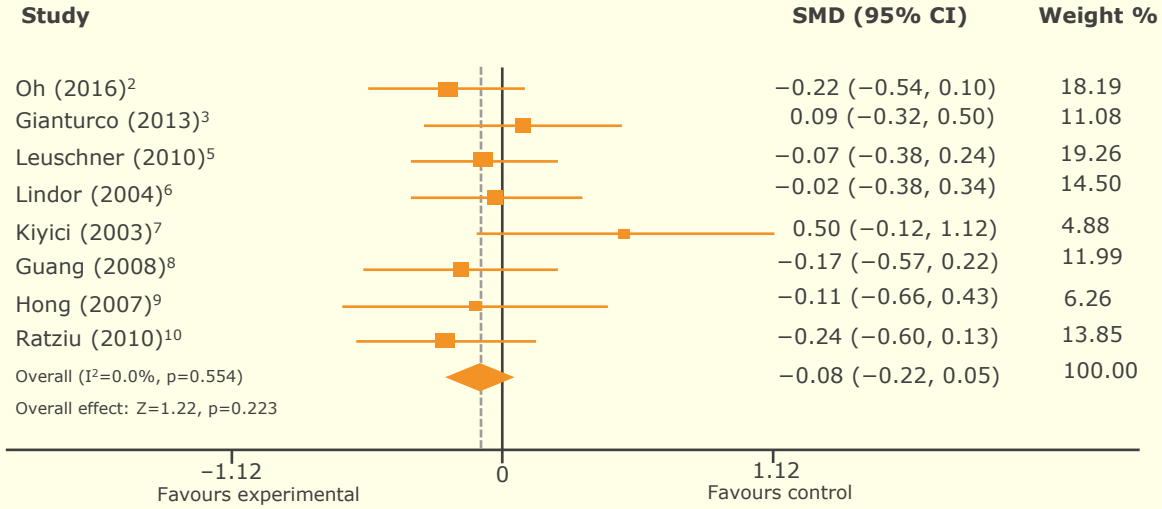
The trends for UDCA in the treatment of NAFLD are less clear

In a meta-analysis, treatment with UDCA reduced ALT compared with control treatment but did not reduce AST:[1]

ALT



AST



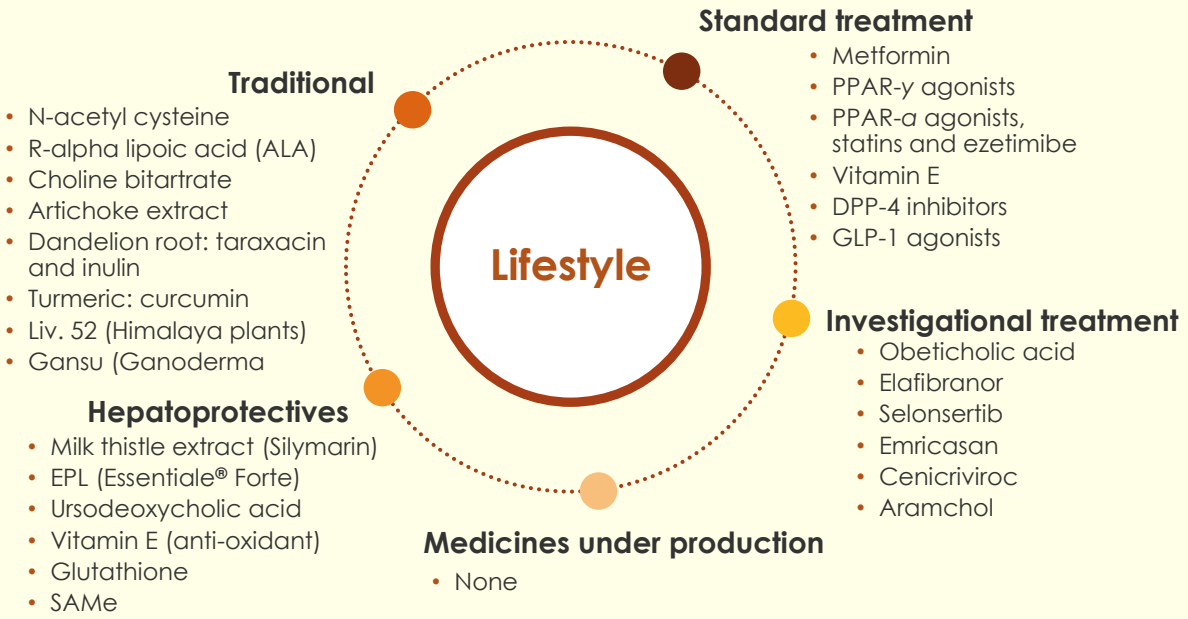
ALT, alanine transaminase; AST, aspartate aminotransferase; NAFLD, non-alcoholic fatty liver disease; SMD, standardised mean difference; UDCA, Ursodeoxycholic acid

1. Zhang W, et al. Asia Pac J Clin Nutr 2020;29(4):696–705; 2. Oh B, et al. Int J Clin Pract 2016;70(4):302–11; 3. Gianturco V, et al. Hepatol Int 2013;7(2):570–6;
4. Santos VN, et al. Braz J Med Biol Res 2003;36(6):723–9; 5. Leuschner UFH, et al. Hepatology 2010;52(2):472–9; 6. Lindor KD, et al. Hepatology 2004;39(3):770–8;
7. Kiyici M, et al. Can J Gastroenterol 2003;17(12):713–8; 8. Guang J, et al. Zhong Xi Yi Jie He Xue Bao 2008;6(2):128–33;
9. Hong Q, et al. Journal of Guandong Medical College 2007;25:528–9; 10. Ratziu V, et al. J Hepatol 2011;54(5):1011–9

Current pharmacological treatments are experimental

- There is an **inconsistent evidence base** for the effect of medications used for the treatment of comorbid conditions associated with NAFLD
  - Traditional SOC agents lack supportive research

The tools



Hepatoprotective agents remain an important, reliable part of the treatment of NAFLD as adjunctive therapies

DPP-4, dipeptidyl peptidase-4; EPL, essential phospholipid; GLP-1, glucagon-like peptide-1; NAFLD, non-alcoholic fatty liver disease; PPAR, peroxisome proliferatory-activated receptor; SAMe, S-adenosylmethionine; SOC, standard of care
Figure adapted from Dajani A, AbuHammour A. Saudi J Gastroenterol 2016;22:91–105 by speaker

What drugs are in development?

Multiple drugs are in late-stage development for NASH and NAFLD

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Ongoing Phase 3 studies investigating **14 therapeutic regimens** in patients with NASH

2 liver-directed therapies: resmetirom[1–3] and aramchol[4]

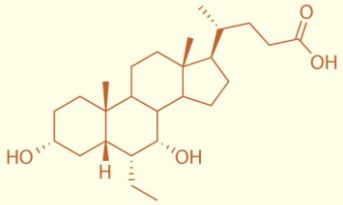
12 non-liver-directed therapies: obeticholic acid[5,6,]; saroglitazar and vitamin E[7]; MSDC-0602K[8]; semaglutide[9,10]; SPP-1[11]; oltipraz[12]; vildagliptin[13]; pentoxifylline[14]; estradiol[15]; dapagliflozin[16]; metadoxine[17]; lanifibranor[18]

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; FXR, farnesoid X receptor

1. https://www.clinicaltrials.gov/ct2/show/NCT04197479; 2. https://www.clinicaltrials.gov/ct2/show/NCT04951219; 3. https://www.clinicaltrials.gov/ct2/show/NCT03900429;
4. https://www.clinicaltrials.gov/ct2/show/NCT04104321; 5. https://www.clinicaltrials.gov/ct2/show/NCT02548351; 6. https://www.clinicaltrials.gov/ct2/show/NCT03439254;
7. https://www.clinicaltrials.gov/ct2/show/NCT04193982; 8. https://www.clinicaltrials.gov/ct2/show/NCT03970031; 9. https://www.clinicaltrials.gov/ct2/show/NCT05067621;
10. https://www.clinicaltrials.gov/ct2/show/NCT04822181; 11. https://www.clinicaltrials.gov/ct2/show/NCT04308980; 12. https://www.clinicaltrials.gov/ct2/show/NCT04142749;
13. https://www.clinicaltrials.gov/ct2/show/NCT03925701; 14. https://www.clinicaltrials.gov/ct2/show/NCT05284448; 15. https://www.clinicaltrials.gov/ct2/show/NCT04833140;
16. https://www.clinicaltrials.gov/ct2/show/NCT03723252; 17. https://www.clinicaltrials.gov/ct2/show/NCT02541045;18. https://www.clinicaltrials.gov/ct2/show/NCT04849728

There are two ongoing Phase 3 trials investigating obeticholic acid in patients with NASH[1]

NCT02548351[1] and NCT03439254[2]



- Obeticholic acid (6-ethtlchenodeoxycholic acid) is:[3]
  - A synthetic variant of the natural bile acid chenodeoxycholic acid
  - A FXR agonist

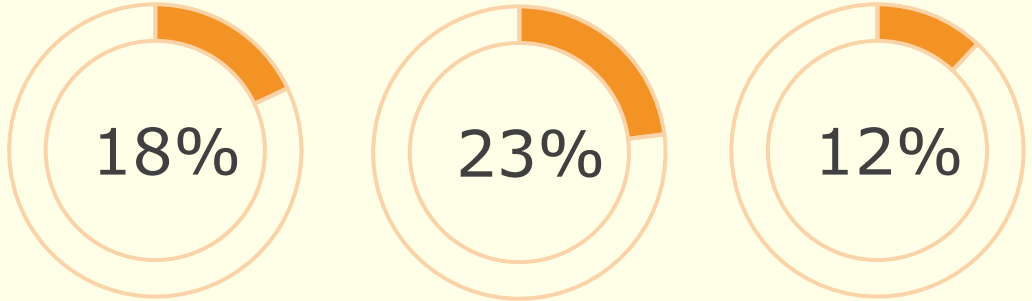
FXR activation has been demonstrated to reduce hepatic glucogenesis, lipogenesis and steatosis[3]

Proportion of patients with **improved liver histology at 72 weeks**, in a Phase 2b trial[4]

Obeticholic acid (n=110)

Placebo (n=109)

Proportion of patients with **fibrosis improvement (≥1 stage)**, in an 18-month interim analysis of a Phase 3 trial[5]



Obeticholic acid, 10 mg (n=312)

Obeticholic acid, 25 mg (n=308)

Placebo (n=311)

FXR, farnesoid X receptor; NASH, non-alcoholic steatohepatitis

1. https://www.clinicaltrials.gov/ct2/show/NCT02548351; 2. https://www.clinicaltrials.gov/ct2/show/NCT03439254; 3. Sumida Y, et al. J Gastroenterol 2018;53(3):362–76; 4. Neuschwander-Tetri BA, et al. Lancet 2015;385(9972):956–65; 5.Younossi ZM, et al. Lancet 2019;394(10215):P2184–96

What are the challenges in developing drugs for NASH and NAFLD?

There are three main challenges within NAFLD drug development

Relevant preclinical models

Most preclinical animal models don’t exhibit the metabolic phenotypes of NAFLD

Target heterogeneity

NAFLD is a complex disease with many potential molecular targets relating to different aspects of the disease

Clinically relevant endpoints

NAFLD is a slow progressing disease and binary endpoints take years to reach. Non-binary endpoints involve liver biopsies which are susceptible to sampling error and inter-investigator variability

NAFLD, non-alcoholic fatty liver disease

Thiagarajan P, et al. J Clin Exp Hepatol 2019;9(4):515–21

Summary

1. Lifestyle changes are the first-line therapy for the treatment of NASH
2. Hepatoprotective agents, such as EPLs, are recommended for the treatment of the metabolic comorbidities of NASH and NAFLD in the Chinese guidelines
3. There are no approved pharmacological treatments for NASH, but as of April 2022 14 therapeutic regimens are in Phase 3 clinical trials
4. Target heterogeneity and the lack of clinically relevant preclinical models and trial endpoints have slowed the progress of drug development for NASH and NAFLD
5. Hepatoprotective therapies, including EPLs and UDCA, are likely to be used alongside new therapies in the future treatment of NASH

EPLs, essential phospholipids; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; UDCA, ursodeoxycholic acid