The importance of fast identification and understanding disease progression – key notes for NAFLD management

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Disclosures

- Consultant to pharmaceutical Companies: KRKA, Vedra International, Alfasigma, Sanofi, Neola Pharma, Sun Wave Pharma, Biessen Pharma, Sun Pharma Terapia

- Member of advisory boards: Sanofi, Neola, Takeda

- Lecturer for many pharmaceutical companies locally and internationally

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Outline

1. Natural history of NAFLD (MAFLD)
2. Identification of patients with NAFLD at risk for NASH
3. The progression of NASH: key factors in disease management
4. The current treatment landscape

MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

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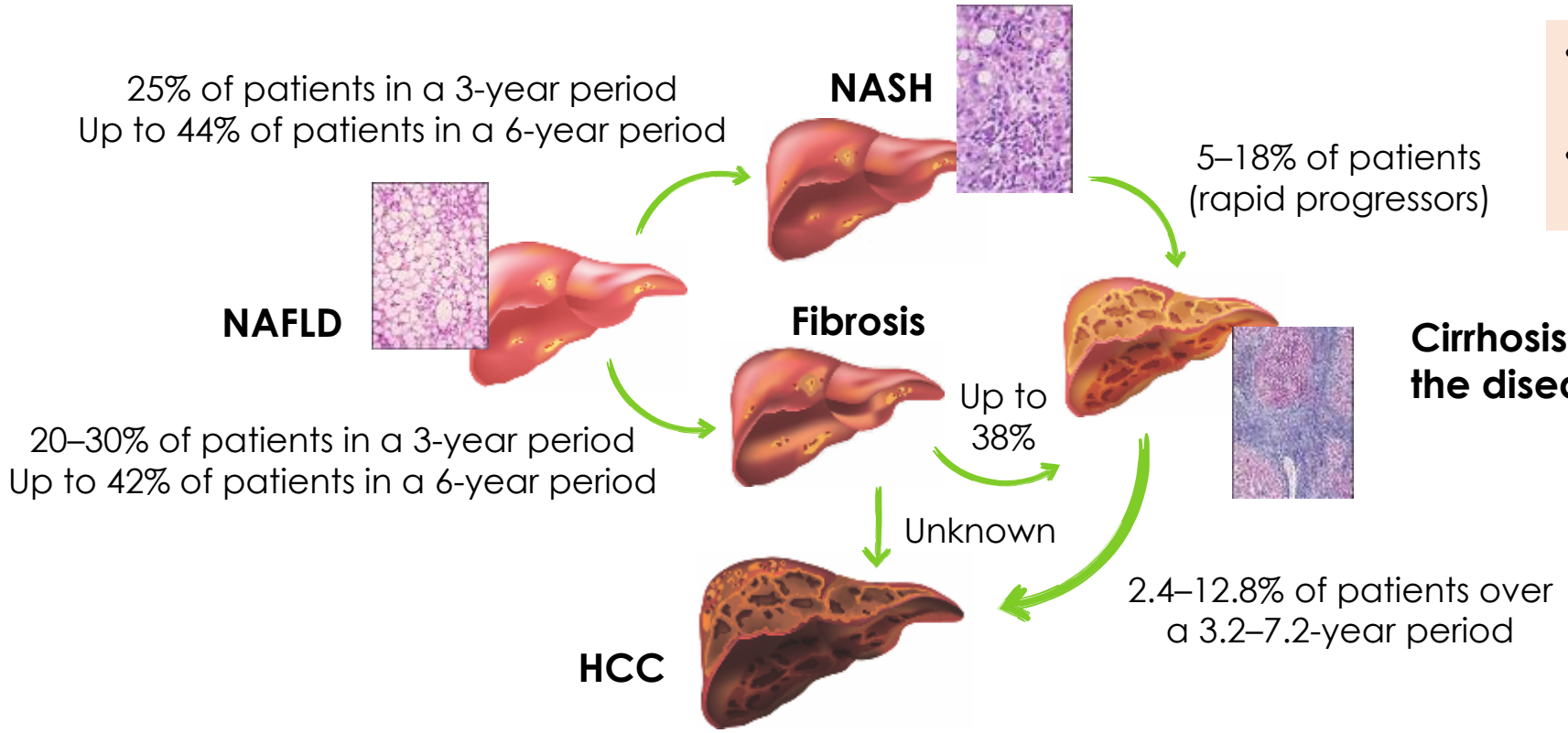
Natural history of NAFLD



- Fibrosis progression rate in NASH: 1 stage per 7 years[1,2]
- 25% of patients progress quickly to cirrhosis in 9 years[1]

Risk of death in NASH:[2]

- 1st CVD
- 2nd Cancer
- 3rd Liver

CVD, cardiovascular disease; HCC, heptacellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
Figure adapted from: 1. Bertot LC and Adams LA. Int J Mol Sci 2016;17(5):774; 2. Pais R and Maurel T. J Clin Med 2021;10(6):1161

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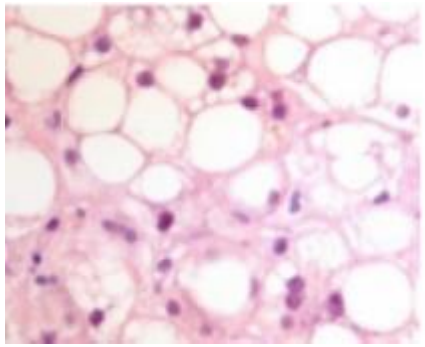
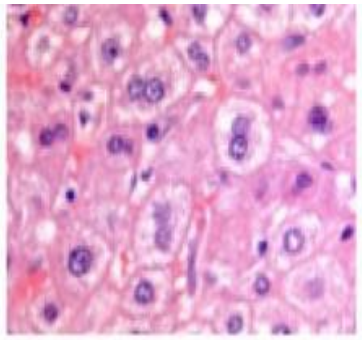
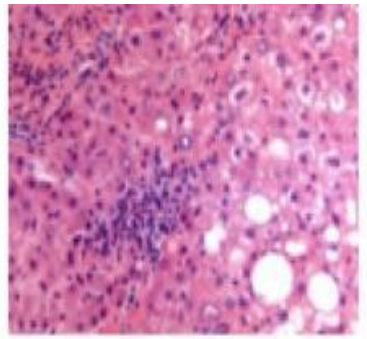
Histological features in NAFLD/NASH



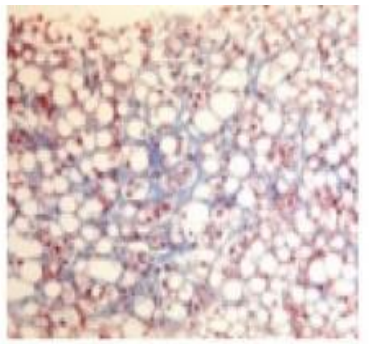
Steatosis



Ballooning hepatocyte



Inflammatory infiltrate



Fibrosis

NAFL

- Steatosis 5% of hepatocytes*
- No liver injury

NASH

- Steatosis >5%
- Hepatocellular ballooning
- Lobular inflammation
- ± Fibrosis

*According to histological analysis NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
World Gastroenterology Organisation, 2012 WGO Global Guidelines NAFLD/NASH (long version). Available at: http://www.worldgastroenterology.org/guidelines/global-guidelines/nafld-nash

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Role of liver biopsy

Not always required, and should be tailored to the patient

- Confirm diagnosis/exclude alternative pathology
- Stage disease
- Stratify progression risk

Liver biopsy to classify such a large population is:

- Impractical
- Expensive
- Invasive
- Prone to sampling and reading variability

World Gastroenterology Organisation, 2012 WGO Global Guidelines NAFLD/NASH (long version).
Available at: http://www.worldgastroenterology.org/guidelines/global-guidelines/nafld-nash

AASLD: Non-invasive quantification of hepatic steatosis in NAFLD

Some studies suggest that the degree of steatosis may predict:

- The severity of histological features (e.g., ballooning and steatohepatitis)
- The incidence and prevalence of diabetes in patients with NAFLD

MR imaging, either by spectroscopy or by proton density fat fraction, is an excellent non-invasive modality for quantifying hepatic steatosis, and is being widely used in NAFLD clinical trials

The use of transient elastography to obtain continuous attenuation parameters (CAP) is a promising tool for quantifying hepatic fat in ambulatory settings

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD, American Association for the Study of Liver Diseases; MR, magnetic resonance; NAFLD, non-alcoholic fatty liver disease
Chalasani N, et al. Hepatology 2018;67(1):328–357

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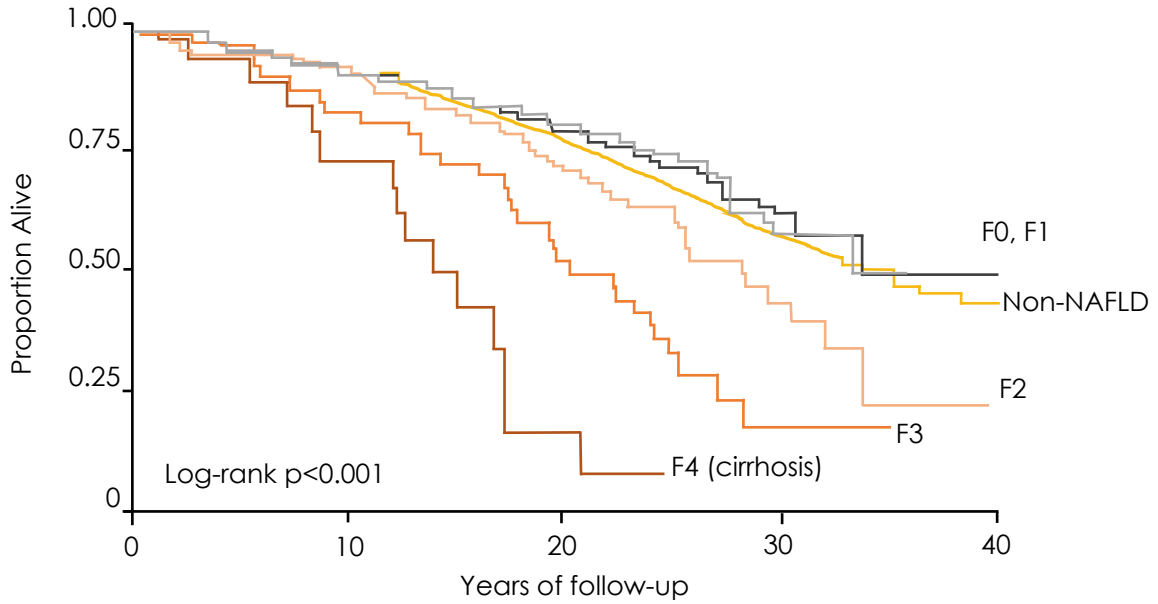
Liver fibrosis is associated with outcomes in patients with NAFLD

Retrospective survival analysis of 646 patients with NAFLD and matched controls



- Liver fibrosis is the most important histological feature associated with liver-related mortality and liver-related complications
- Presence of fibrosis, rather than the histological diagnosis of NASH, is associated with long-term overall mortality, liver transplantation, and liver-related events

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis
Hagström H, et al. J Hepatol 2017;67(6):1265–1273

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Predictors of NAFLD progression to fibrosis

Factors	Details
Sex	Men and post-menopausal women have a higher risk of fibrosis vs pre-menopausal women Estrogen inhibits stellate cell activation and fibrogenesis[1,2]
Age	Increase in age is associated with more severe fibrosis in patients with NASH[1]
T2DM	The emergence of T2DM parallels fibrosis progression[1]
BMI	An increase or decrease in BMI has been associated with progression or resolution of liver fibrosis, respectively, in patients with NAFLD[1]
Inflammation	The degree of inflammation is associated with progression to advanced fibrosis[1]
AST/ALT ratio	Ratio >1 is a risk factor for progression[3]
Hepatic iron deposits, or hemochromatosis	Iron accumulation in hepatocytes is linked to mild NAFLD[3]
Polymorphisms in the PNPLA3 and TM6SF2 genes	These genes code for proteins responsible for the production and breakdown of fats[1]

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; T2DM, type 2 diabetes mellitus; TM6SF2, transmembrane 6 superfamily 2

1. Bertot LC & Adams LA. Int J Mol Sci 2016;17(5):774; 2. Yang JD, et al. Hepatology 2014;59(4):1406–1414; 3. Croke B & Sampson D. Journal for Nurse Practitioners 2012;8(1):45–50

Which of the following statements regarding the progression of NAFLD to fibrosis is FALSE?

1. The degree of inflammation is associated with progression to advanced fibrosis
2. The risk of fibrosis is greater in pre-menopausal women vs men and post-menopausal women
3. A decrease in BMI has been associated with stabilization and/or resolution of liver fibrosis
4. Patients with T2DM have a higher risk of progression to fibrosis

BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

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Scores for identifying advanced fibrosis in NAFLD: NFS and FIB-4

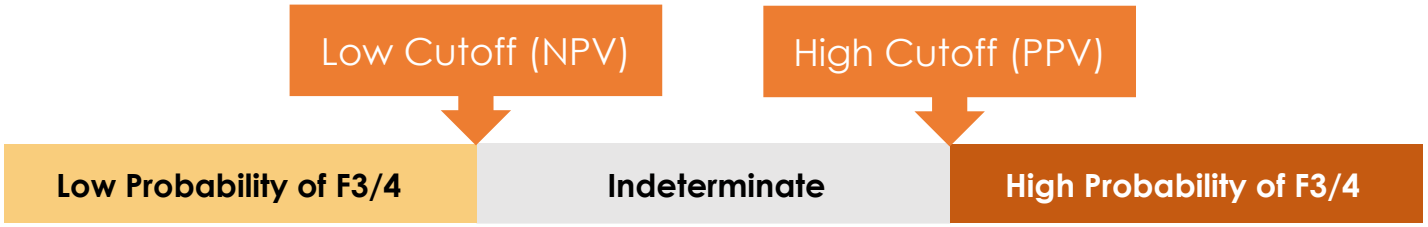
NFS[1]

NFS	Effect	NPV or PPV, %
<–1.455	Rules out fibrosis	88–93
>0.676	Predicts fibrosis	82–90

Parameter
Age
AST
ALT
Platelet count
BMI
Albumin
Impaired fasting glucose/diabetes

FIB-4 Score[2,3]

FIB-4 Score	Effect	NPV or PPV, %
<1.30	Rules out fibrosis	95
>3.25	Predicts fibrosis	75



ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 Index; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD Fibrosis Score; NPV, negative predictive value; PPV, positive predictive value

1. Angulo P, et al. Hepatology 2007;45(4):846–854; 2. Sterling R, et al. Hepatology 2006;43(6):1317–1325; 3. McPherson S, et al. Gut 2010;59(9):1265–1269

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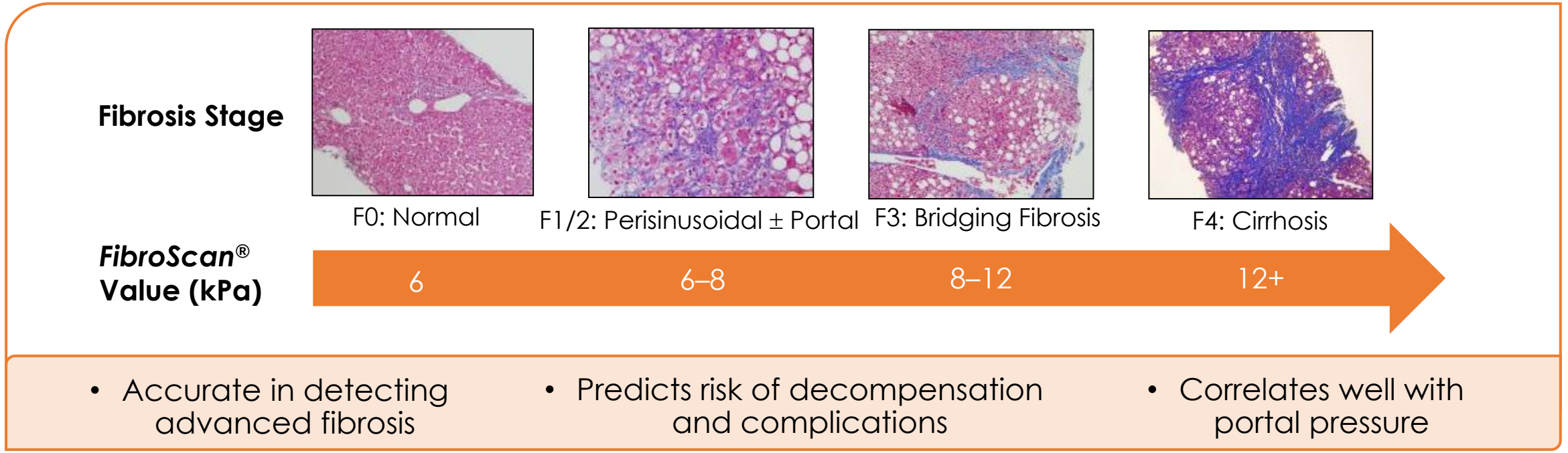
VCTE (*FibroScan*®) for steatosis and NASH fibrosis[1,2]

- CAP: degree of steatosis may predict the severity of histological features (ballooning and steatohepatitis)
- Quantification of hepatic steatosis in routine clinical practice is limited



- Accurate in detecting advanced fibrosis
- Predicts risk of decompensation and complications
- Correlates well with portal pressure

CAP, controlled attenuation parameter; NASH, non-alcoholic steatohepatitis; VCTE, vibration-controlled transient elastography

1. Karlas T, et al. J Hepatol. 2017;66(5):1022–1030; 2. Vuppalanchi R, et al. Hepatology 2018;67(1):134–144

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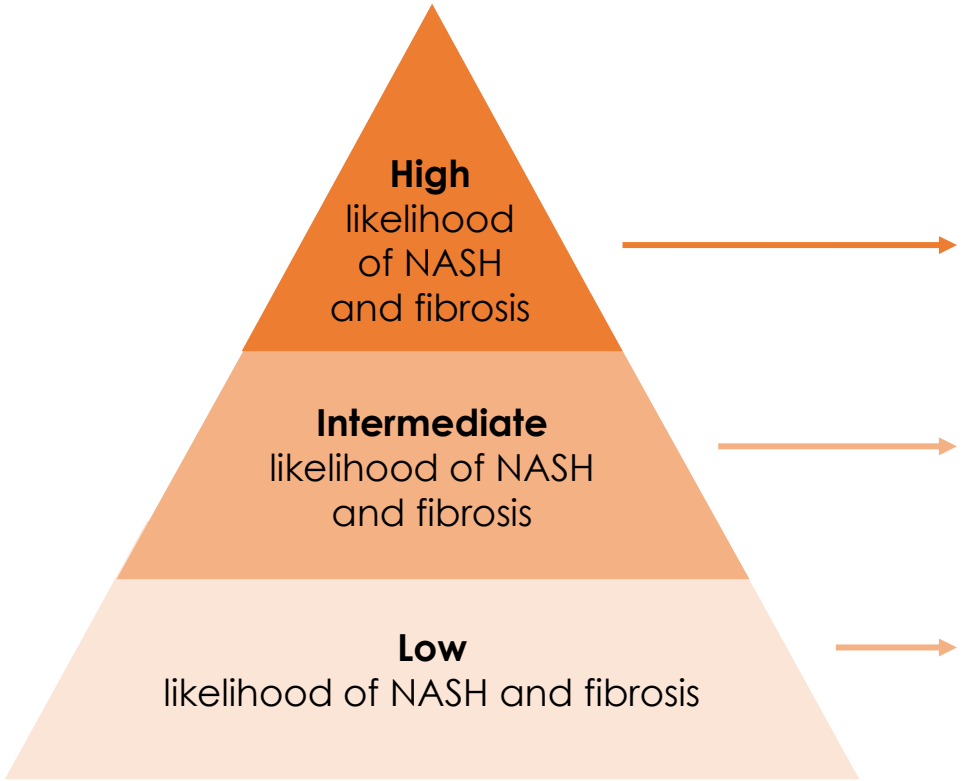
Determining high-risk features for NASH



Age, Years	Comorbidities	VCTE, kPa	AST, IU/L	NFS	FIB-4	Other
>50	DM, obesity, HTN	>8.5	>40	>0.676	>2.67	AST:ALT ratio ≥1
>40	Well-controlled DM, obesity, HTN	>7.0	>20	–	–	–
<40	No DM, no obesity	<7.0	<20	<–1.455	<1.30	–

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus (type not specified); FIB-4, Fibrosis-4 Index; HTN, hypertension; NASH, non-alcoholic steatohepatitis; NFS, NAFLD Fibrosis Score; VCTE, vibration-controlled transient elastography

Konerman M, et al. J Hepatol 2018;68(2):362–375

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Management approaches for NASH (1/2)

Calorie intake reduction

≥ 30%; 750–1000 kcal/day improved **insulin resistance** and **hepatic steatosis**

Limit consumption of fructose-enriched beverages

Weight loss

3–5% to improve steatosis; 7–10% to improve most **histopathology**, including **fibrosis**

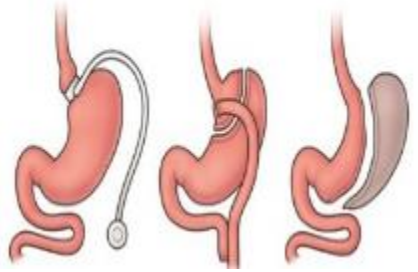
Exercise

May prevent or reduce steatosis

Ability to improve other aspects of liver histology unknown

Bariatric surgery

Can be considered in individuals with both NAFLD or NASH and obesity **who otherwise meet criteria for bariatric surgery**



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

Chalasani N, et al. Hepatology 2018;67(1):328–357

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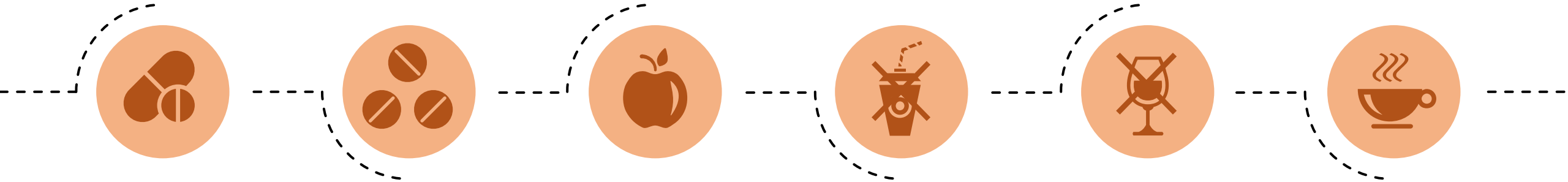
Management approaches for NASH (2/2)



NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

1. Chalasani N, et al. Hepatology 2018;67(1):328–357; 2. Simon TG, et al. Clin Gastroenterol Hepatol 2019;17:277–84. 3. https://www.nhs.uk/conditions/non-alcoholic-fatty-liver-disease/; 4. Calabrò A, et al. Hepatol Res 2020;6:69

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Evaluation of EPL in patients with NAFLD with or without relevant comorbidities (1/2)

Counselling provided to **advise on a standard diet and exercise**

Study drug: EPL

- **1800 mg** (six capsules) **a day** in three divided doses for 24 weeks

Followed by:

- **900 mg** (three capsules) **a day** in three divided doses for 48 weeks

Medications for comorbid conditions:

- Metformin
- Pioglitazone
- Atorvastatin
- Ezetimibe

Patients receiving insulin, DPP-4 inhibitors and GLP-1 RA were excluded

Patients receiving statins were included; however, those on fenofibrate were excluded

DPP-4, dipeptidyl peptidase-4; EPL, essential phospholipids; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NAFLD, non-alcoholic fatty liver disease

Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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Evaluation of EPL in patients with NAFLD with or without relevant comorbidities (2/2)

Summary of study results

Variable	Lone NAFLD	T2DM	Hyperlipidemia
Clinical	Significant improvement of clinical symptoms and signs (p<0.01)	Significant improvement of clinical symptoms and signs (p<0.01)	Significant improvement of clinical symptoms and signs (p<0.01)
Transaminases	Significant reduction (p<0.01)	Significant reduction (p<0.01)	Significant reduction (p<0.01)
Ultrasonography	Improvement in 29.2% of patients	Improvement in 23.4% of patients	Improvement in 20.2% of patients
Elastography	Change in liver stiffness measurement in 14.2% of patients	Change in liver stiffness measurement in 26.1% of patients	Change in liver stiffness measurement in 20.2% of patients

All changes in parameters are from pre-treatment to post-treatment assessments. EPL, essential phospholipids; NAFLD, non-alcoholic fatty disease; T2DM, type 2 diabetes mellitus
Dajani A, et al. Arab J Gastroenterol 2015;16:99–104

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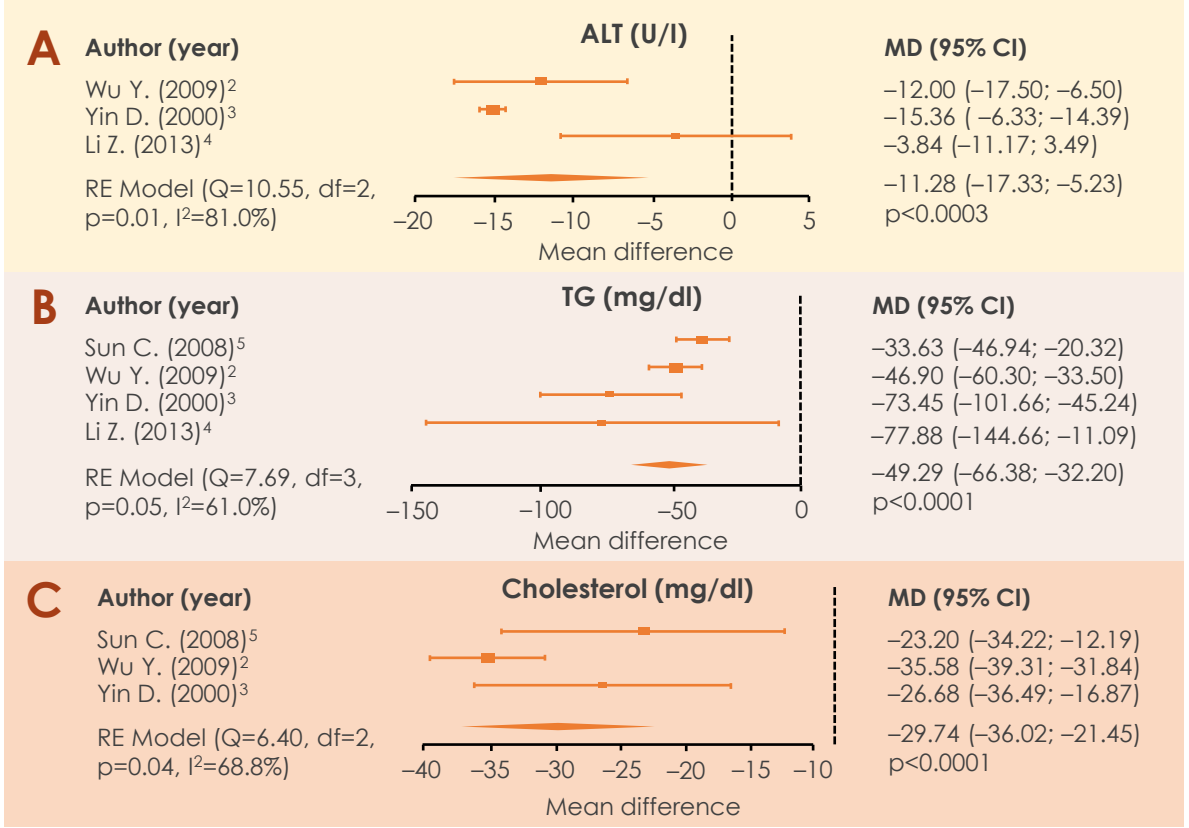
EPL for NAFLD associated with metabolic syndrome: A systematic review and network meta-analysis

Results of a direct meta-analysis of RCTs comparing the effect of treatment with EPL + AD vs AD therapy alone[1]:

A: Change in ALT: three studies[2–4] (N=371); mean treatment duration, 1.97 months

B: Change in TG levels: four studies[2–5] (N=445); mean treatment duration, 2.1 months

C: Change in total cholesterol levels: three studies[2,3,5] (N=359); mean treatment duration, 2.27 months



AD, anti-diabetic; ALT, alanine aminotransferase; CI, confidence interval; EPL, essential phospholipids; MD, mean difference; NAFLD, non-alcoholic fatty disease; RCT, randomised controlled trials RE, random effects; TG, triglycerides

1. Dajani A, et al. Poster presented at APASL 2020; PO-7-84; 2. Wu Y. J TCM Univ Hunan 2009;29:41–42; 3. Yin D, Kong L. Med JQ Illu 2000;15:277–278; 4. Li Z. J Tradit Chinese Med 2013;31:10–1; 5. Sun C, et al. Clin Focus 2008;23:1272–3

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Take-home messages

1. Clinical management challenges are:
   - Stratification of patients at higher risk of liver-related complications
   - Identifying predictive factors for progressive fibrosis in NAFLD, which is the most important parameter associated with patient outcomes
2. Non-invasive tests alone or in combination can be useful for fast identification of which patients with NAFLD require follow-up
3. Although no drugs are approved for the treatment of NAFLD, a growing evidence base shows that EPL treatment plays a beneficial role in the complex management of patients with NAFLD and metabolic comorbidities

EPL, essential phospholipids; NAFLD, non-alcoholic fatty liver disease

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