Liver disease and diabetes

Dr Alberto Nascè

Prof François R. Jornayvaz

Department of Diabetology, Endocrinology, Nutrition and Patient Therapeutic Education of HUG, Geneva

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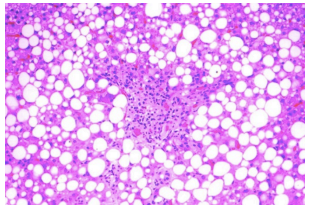
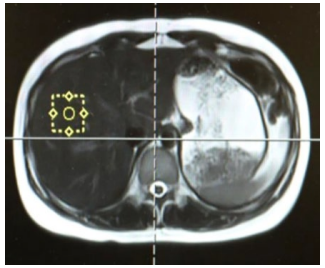
Disclosure

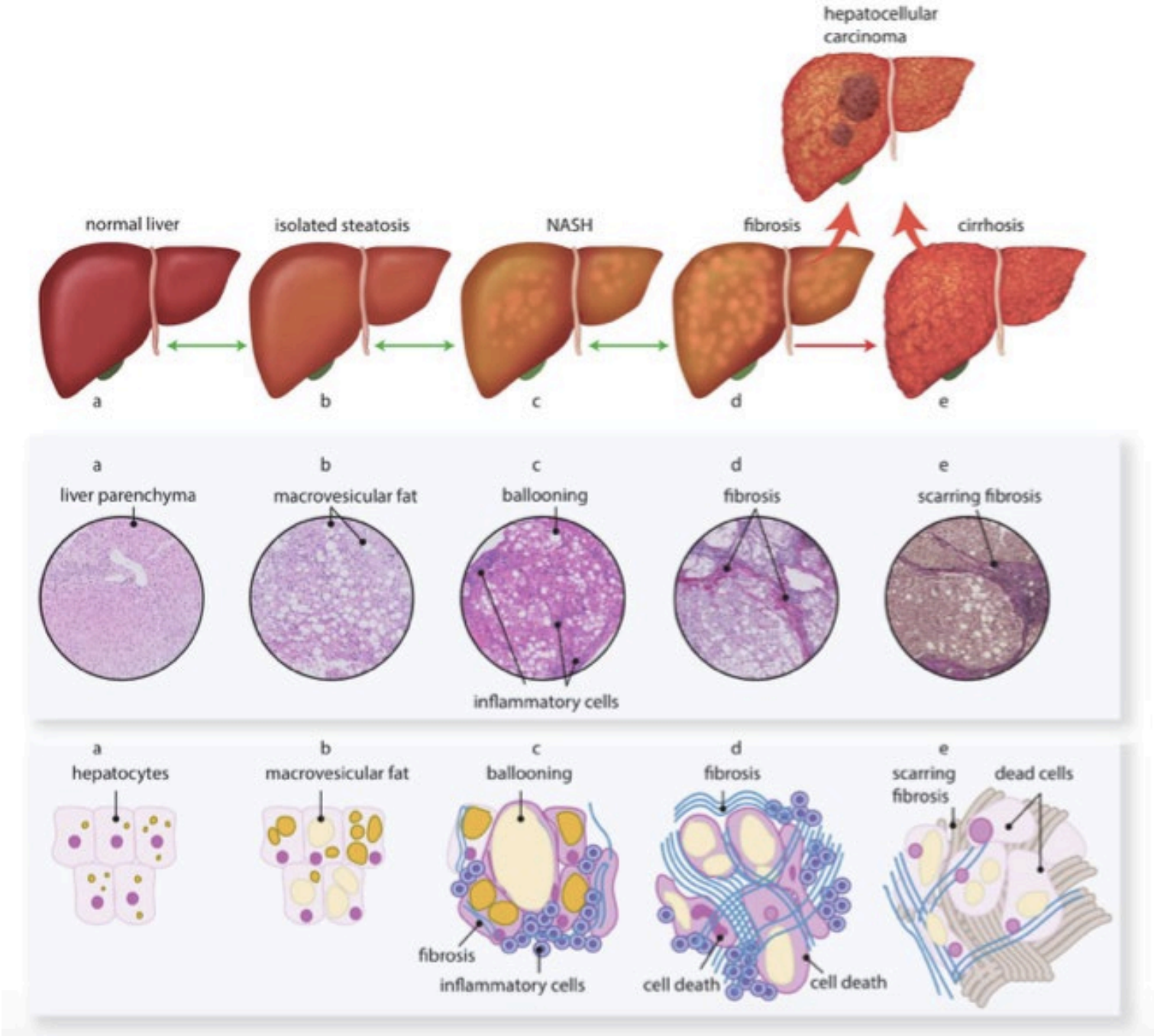
- No personal conflit of interest

NAFLD definition

- Excessive hepatic fat accumulation
- Steatosis in > 5% of hepatocytes according to
  - Histological analysis or 
  - Imaging (H-MRS, MRI) 
- Absence of other causes of hepatic steatosis (alcohol, certain metabolic conditions and drugs)

Journal of Hepatology 2016 vol. 64 j 1388–1402

NAFLD disease spectrum



European Journal of Endocrinology (2020) **183**, R57–R73

NAFLD epidemiology

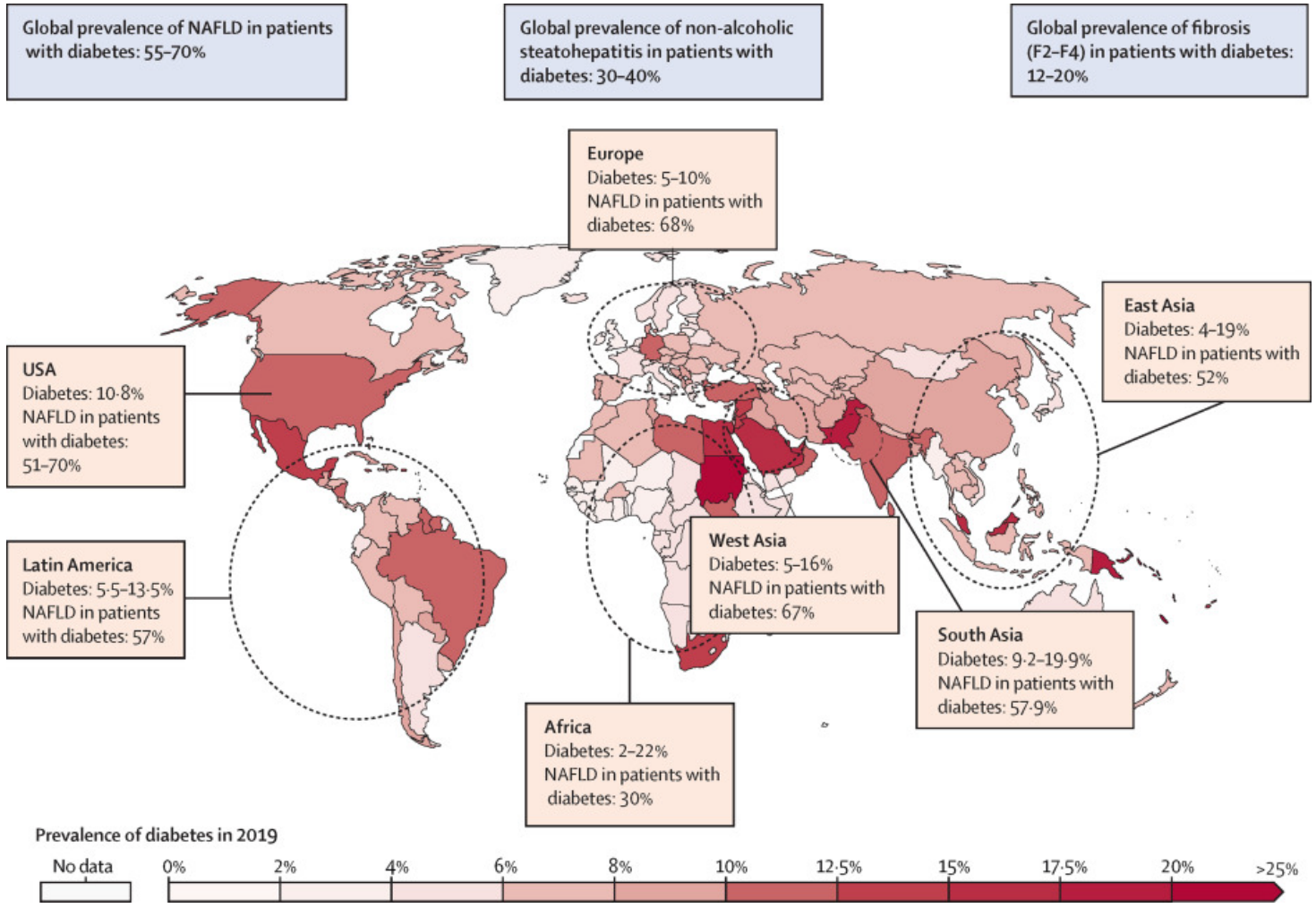
- Most common cause of chronic liver disease worldwide with a global prevalence of 25.2%
- NAFLD in lean/non-obese individuals 10-16%
- 3-10% of all children and 40% of children with obesity

- In the USA 
  - 75.1% of all chronic liver disease cases
  - 14.1% underlying cause for Hepatocellular Carcinoma (HCC)
  - Top 3 indications for liver transplantation

- In Switzerland 
  - Global increase in NAFLD prevalence to reach 24.3% in 2030
  - Higher increase in NASH than in NAFLD
  - Increase in mortality related to NAFLD and NASH

Younossi et al. Journal of Hepatology 2019 vol. 71 j 793–801
Goossens N *et al*. *Swiss Med Wkly* 2019;149:w20152

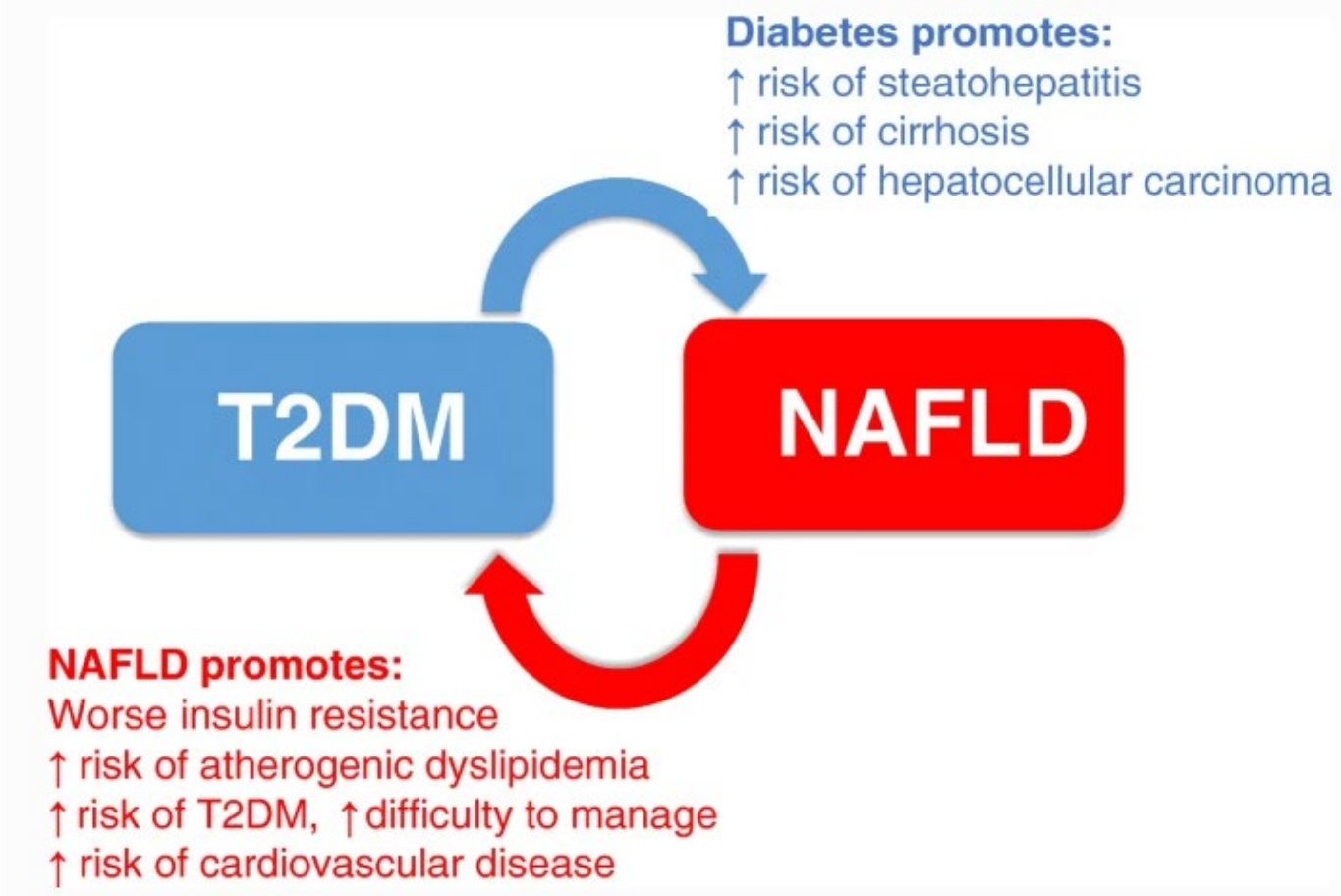
NAFLD and diabetes : epidemiology



Prevalence of NAFLD in patients with T2DM is more than 2-fold higher than in the general population

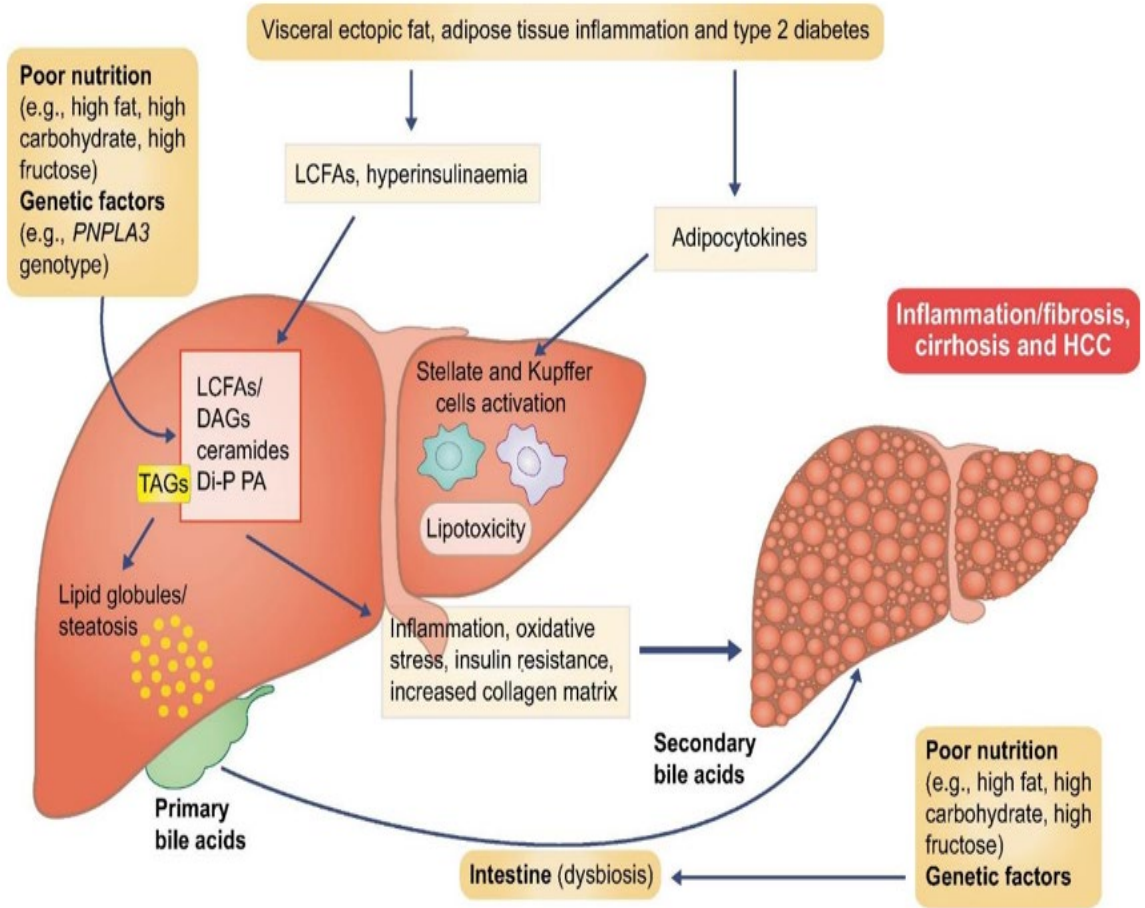
Stefan N,Lancet Diabetes Endocrinol. 2022 Apr;10(4):284-296.

NAFLD and T2DM : bad marriage



Budd & Cusi K. Current Diabetes Reports 2020; Oct 5;20(11): 59

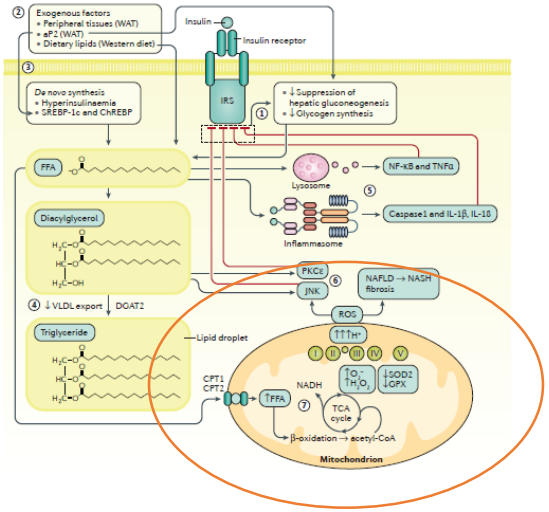
Pathophysiology : NAFLD and insulin resistance



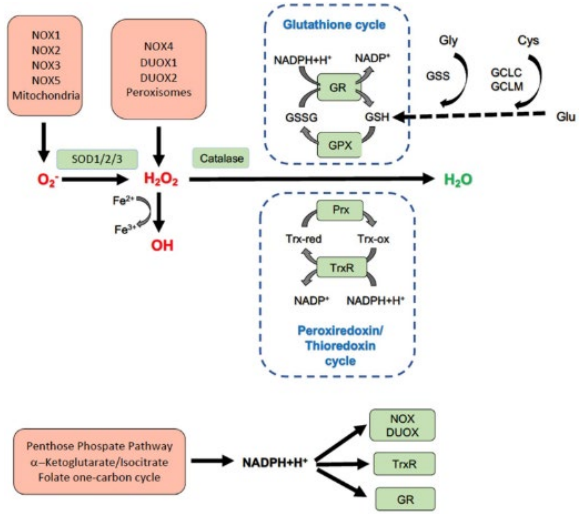
Byrne CD, Targher G. J Hepatol 2015;62:S47–64

Pathophysiology : oxidative stress

- Oxidative stress : inequity between the capacity of production and the elimination of Reactive Oxygen Species (ROS)
- NADPH oxidase enzymes (NOX) are one of the major hepatic ROS sources
- Excessive FFA -> uncontrolled NOX-derived ROS generation
  - NAFLD, IR and T2DM onset
  - Steatosis progression to fibrosis and HCC



Role of NOXes



Tilg H et al. Nature. January 2017. Vol 14

Nascè A et al. Antioxidants (Basel). 2022 Jun 9;11(6):1131.

NAFLD and T1DM

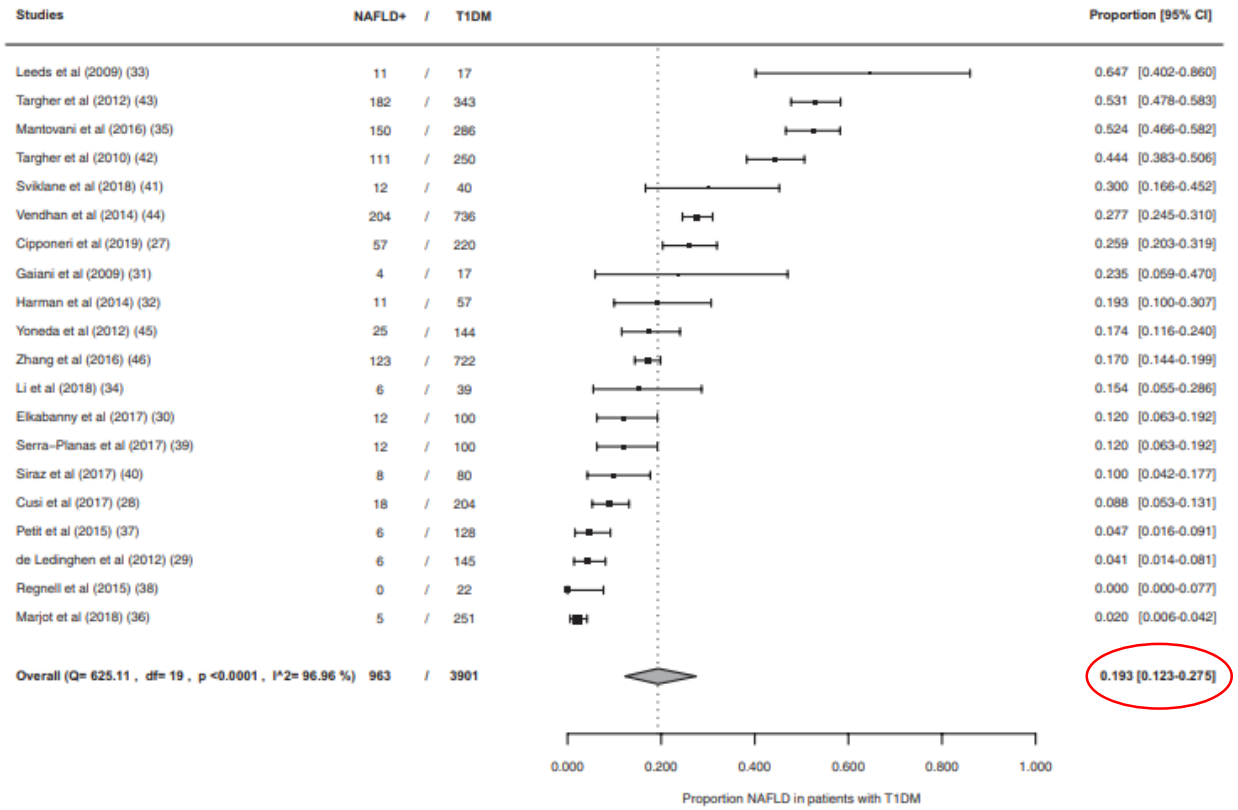


Figure 2. Forest plot overall NAFLD prevalence in patients with type 1 diabetes. NAFLD+, patients with nonalcoholic fatty liver disease; T1DM, type 1 diabetes mellitus.

- Insulin resistance and systemic hyperinsulinaemia as potential determinants of the pathophysiology
- More studies needed to understand their relationship

De Vries M et al. The Journal of Clinical Endocrinology and Metabolism 2020, Vol. 105, No.12

NAFLD : screening

- In order to prevent progression to NASH and associated fibrosis
- No NAFLD screening recommended in the general population
- Screening for NASH and significant fibrosis is advised for :
  - Obesity
  - T2DM > 10y duration or 50yo patients
  - Prediabetes or T2DM with steatosis or elevated ALT
  - Metabolic syndrome
- Previous evaluation for alternative or coexisting causes of liver disease

Kanwal F et al. Diabates Care 2021;44(9):2162-2172

NAFLD : screening. Non-Invasive Tests (NIT)

- Ultrasound
  - High accuracy for detection of moderate and severe steatosis
  - Suboptimal sensitivity for mild steatosis
  - If high pretests probability, no need for ultrasound
    - Directly to stratification
- Liver function tests
  - May be normal in most patients
  - Increased aminotransferases in 50% of patients with NAFLD and T2DM
- Vibration-controlled transient elastography
  - US waves to investigate the presence of advanced fibrosis
  - Specificity of 92%
- Patented serum tests
  - Measures of fibrogenesis (ELF, FibroMeter, FibroTest)

Kanwal F et al. Diabates Care 2021;44(9):2162-2172

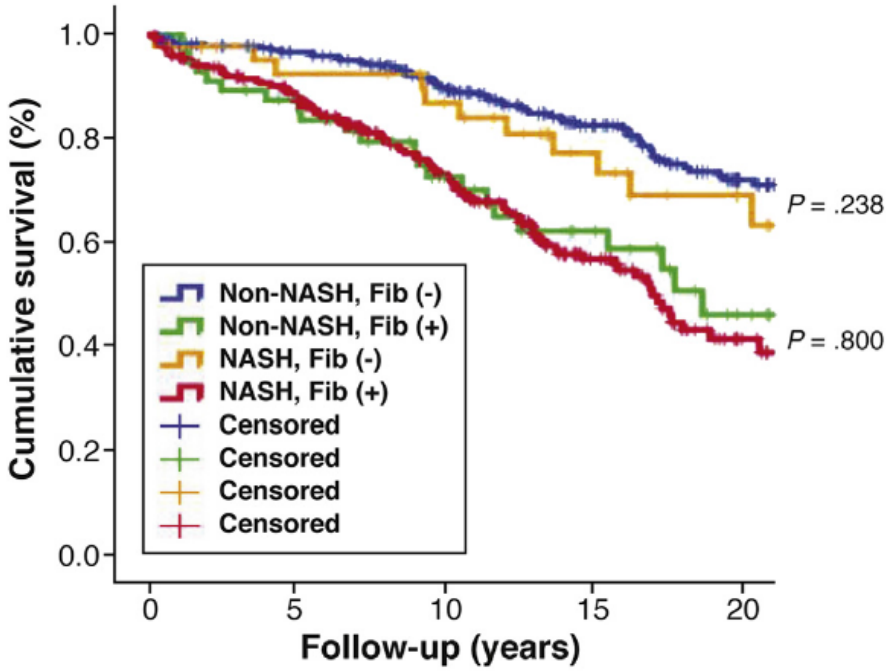
NAFLD : screening. Liver biopsy

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis
- NAFL encompasses
  - Steatosis alone plus ONE of lobular or portal inflammation OR ballooning
- NASH requires
  - Steatosis AND
  - Lobular or portal inflammation AND
  - Ballooning

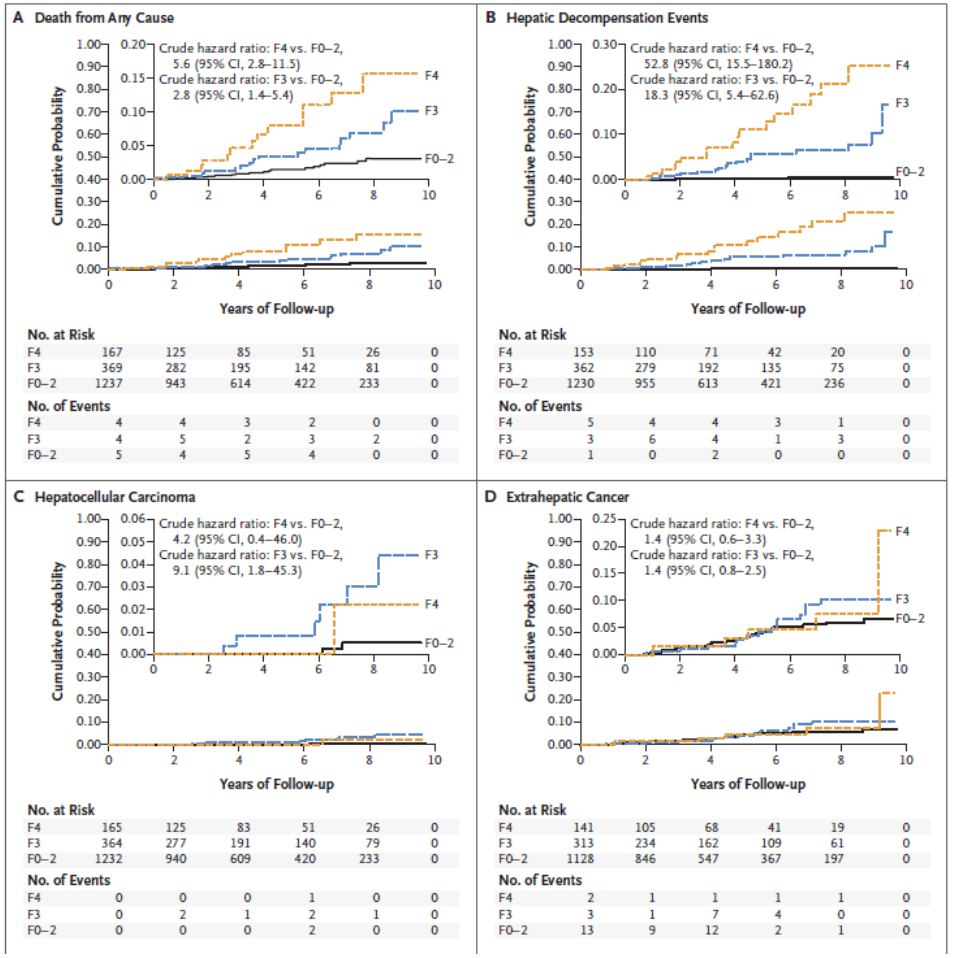
Recommendations	Grade of evidence	Grade of recommendation
NASH has to be diagnosed by a liver biopsy showing **steatosis, hepatocyte ballooning and lobular inflammation**	A	1

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Fibrosis : main mortality parameter

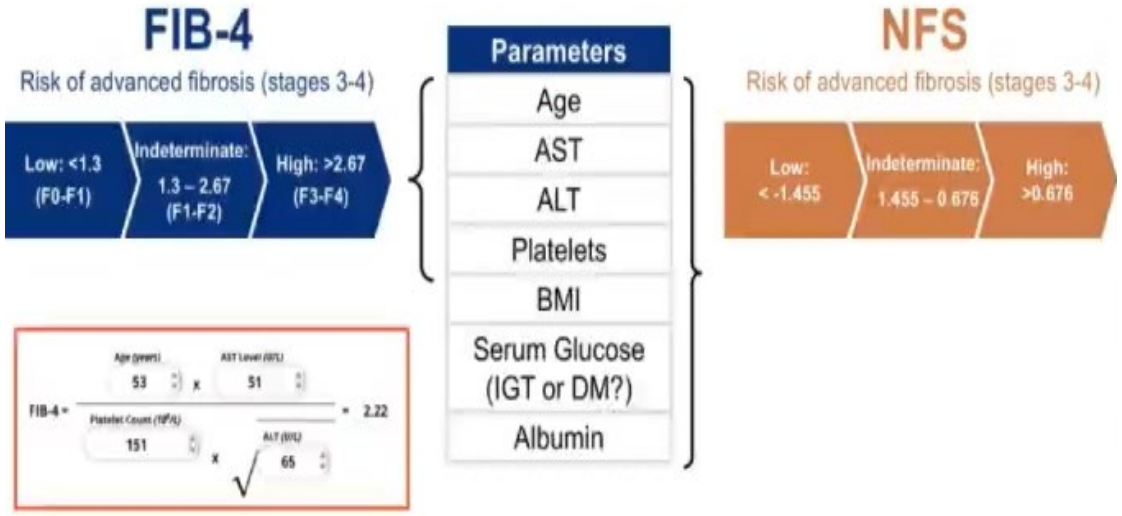


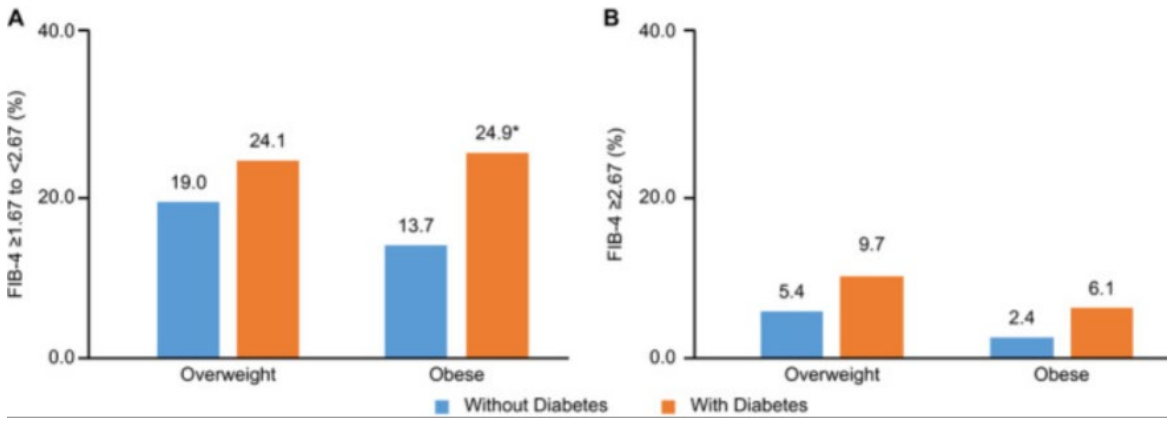
Angulo P *et al*. *Gastroenterology* 2015;149:389-397



Sanyal AJ et al. N Engl J Med 2021; 385:1559-1569

NAFLD : fibrosis scores



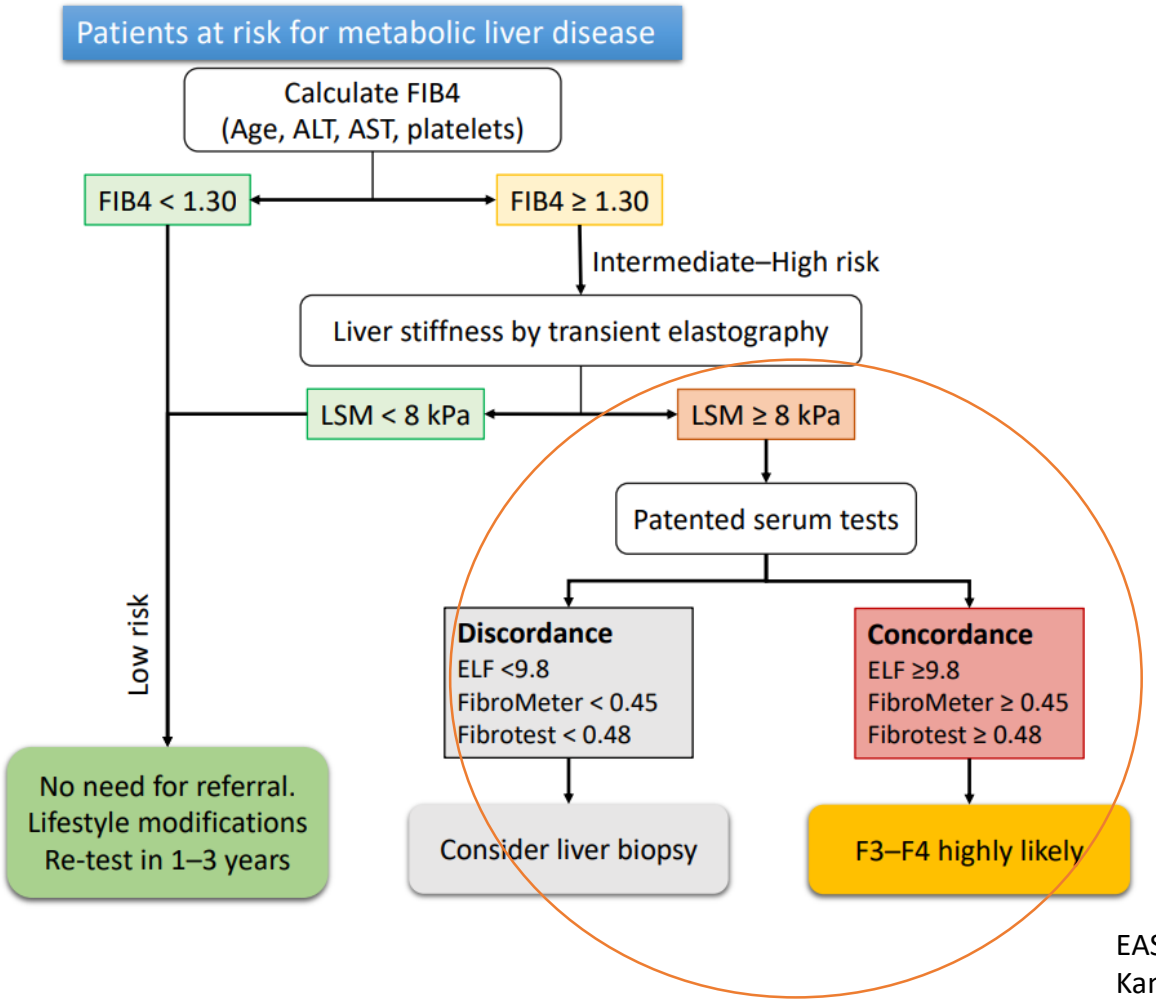


(**A**) Proportion of individuals at moderate risk (FIB-4 ≥ 1.67 to <2.67) of having NASH with liver fibrosis (risk of fibrosis stage F2), and (**B**) proportion of patients at high risk (FIB-4 ≥ 2.67) of having NASH with advanced liver fibrosis (risk of fibrosis stage F3 [advanced fibrosis] or F4 [cirrhosis]). *$p < 0.05$. *P* values were adjusted for multiple comparisons. FIB-4 = fibrosis-4 index; NASH = nonalcoholic steatohepatitis

Budd J & Cusi K. Am J Med 2020; May;133(5):536-43

Barb D et al. Obesity 2021 Nov;29(11): 1950-60

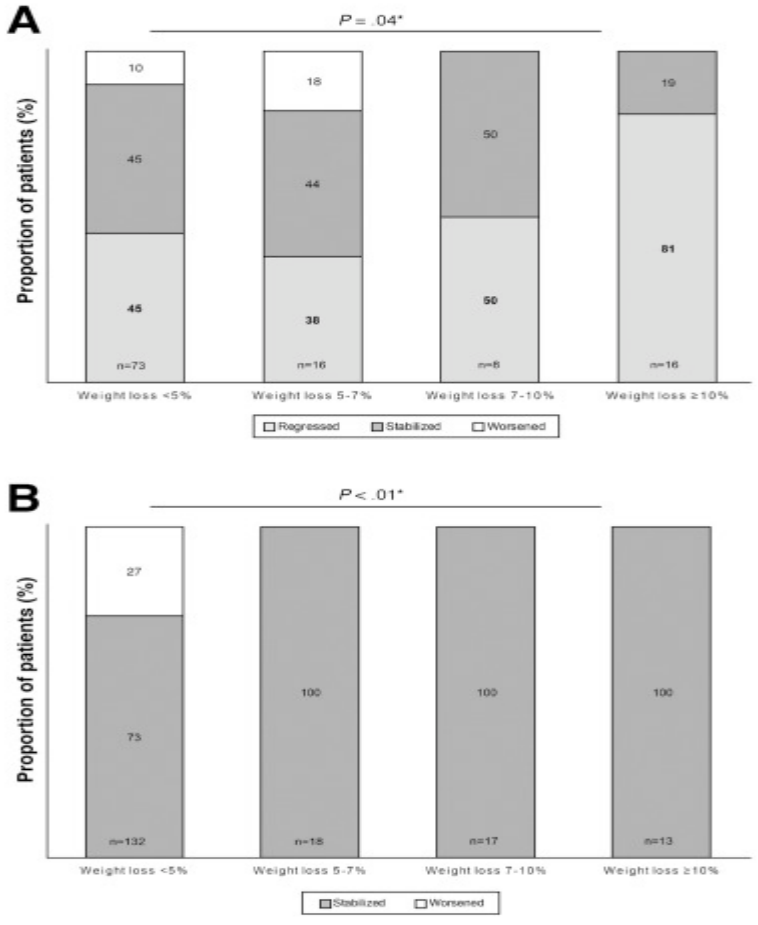
NAFLD diagnostic algorithm



Refer to a gastroenterologist or hepatologist

EASL 2021 update. Journal of Hepatology. 2021
Kanwal F et al. Diabates Care 2021;44(9):2162-2172

NAFLD treatment : lifestyle intervention



Clinical Practice Guidelines

Table 5. Elements of a comprehensive lifestyle approach to NAFLD treatment.

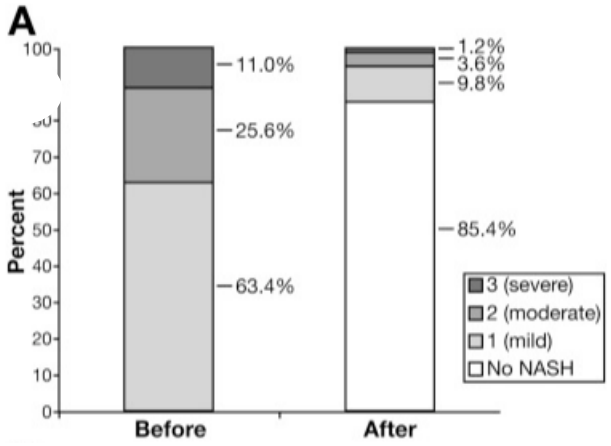
Area	Suggested intervention	Supportive literature
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week	Calorie restriction drives weight loss and the reduction of liver fat, independent of the macronutrient composition of the diet [107]
	• 7-10% total weight loss target	A 12-month intensive lifestyle intervention with an average 8% weight loss leads to significant reduction of hepatic steatosis [108]
	• Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment	Hepatic fat increases along with total body fat regain, but most of the beneficial metabolic effects are maintained and progression to T2DM is delayed [109].
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein	Adherence to the Mediterranean diet has been reported to reduce liver fat on ^{1}H-MRS, when compared with a low fat/ high carbohydrate diet in a cross-over comparison [110, 111]
Fructose intake	• Avoid fructose-containing beverages and foods	In the general population, an association has been reported between high fructose intake and NAFLD [9]
Alcohol intake	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women)	In epidemiological surveys, moderate alcohol intake (namely, wine) below the risk threshold is associated with lower prevalence of NAFLD, NASH and even lower fibrosis at histology [112-114]. Total abstinence is mandatory in NASH-cirrhosis to reduce the HCC risk [115]
Coffee drinking	• No liver-related limitations	Protective in NAFLD, as in liver disease of other aetiologies, reducing histological severity and liver-related outcomes [116]
Exercise/physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise	Physical activity follows a dose-effect relationship and vigorous (running) rather than moderate exercise (brisk walking) carries the full benefit, including for NASH and fibrosis [110, 117, 118] Any engagement in physical activity or increase over previous levels is however better than continuing inactivity

Conclusions: A greater extent of weight loss, induced by lifestyle changes, is associated with the level of improvement in histologic features of NASH. The highest rates of NAS reduction, NASH resolution, and fibrosis regression occurred in patients with weight losses ≥10%.

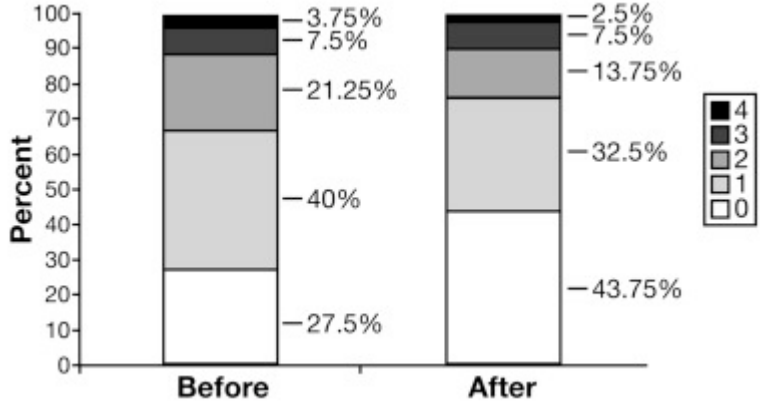
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Vilar-Gomez E et al. Gastroenterology. 2015 Aug;149(2):367-78.e5

NAFLD treatment : bariatric surgery



Distribution of NASH inflammatory activity grade (severity) before and 1 year after surgery, according to the Brunt score. *P* value for comparison of Brunt score before and after surgery <.0001

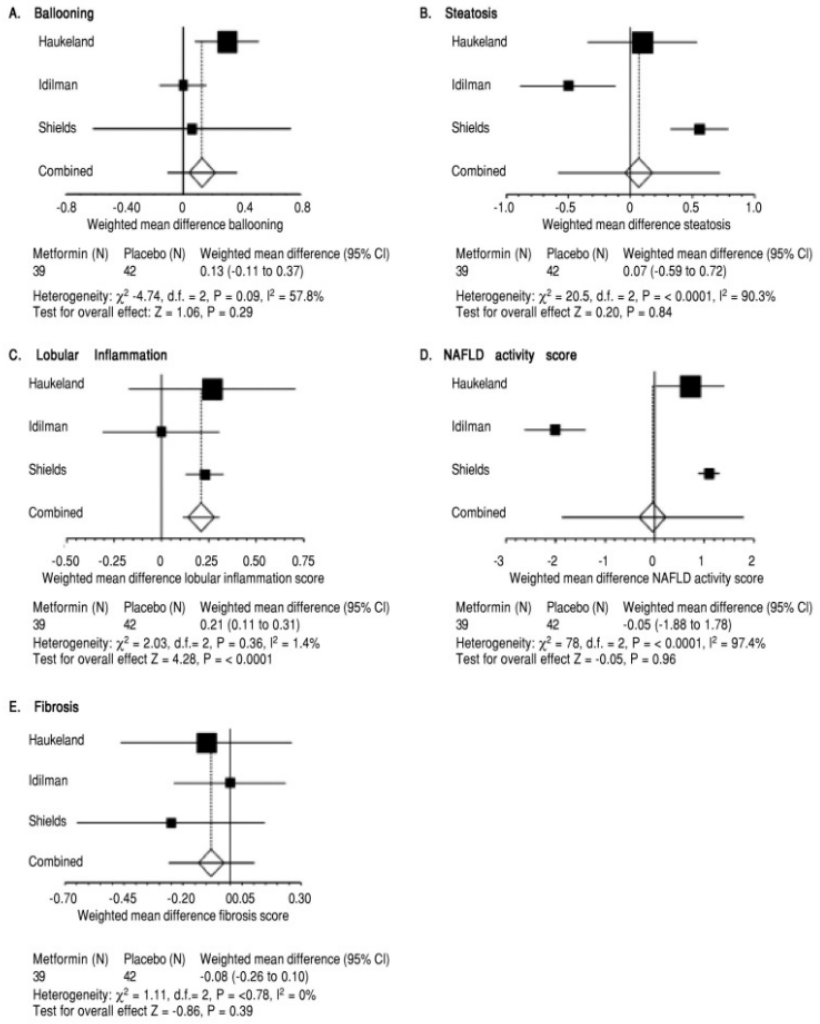


Distribution of fibrosis stage before and 1 year after surgery: Metavir score. Wilcoxon signed rank paired *t* test: *P* < .003.

Lassailly G et al. Gastroenterology. 2015 Aug;149(2):379-88;

Conclusions: Bariatric surgery induced the disappearance of NASH from nearly 85% of patients and reduced the pathologic features of the disease after 1 year of follow-up. It could be a therapeutic option for appropriate morbidly obese patients with NASH who do not respond to lifestyle modifications. More studies are needed to determine the long-term effects of bariatric surgery in morbidly obese patients with NASH.

NAFLD treatment : Metformin

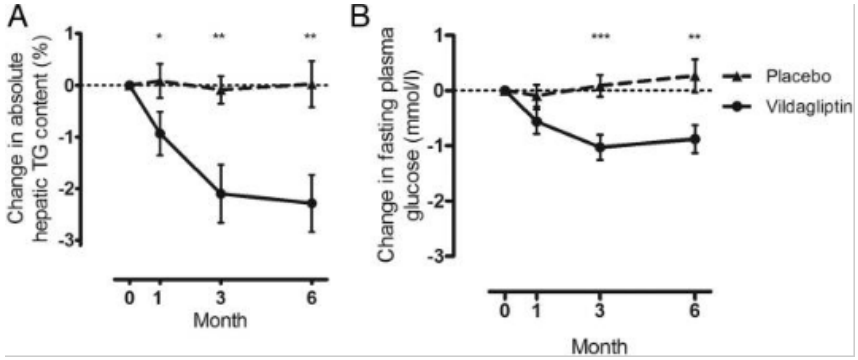


- Histological parameters including ballooning, fibrosis, steatosis and NAFLD score (NAS) did not significantly change with Metformin therapy
- Lobular inflammation significantly worsened after therapy (weighted mean increase 0.21, 95% CI 0.11 to 0.31, P < 0.0001).

Said A et al. Ann Hepatol. 2017 Jul-Aug;16(4):538-547.

NAFLD treatment : DPP4 inhibitors

- Vildagliptin but not sitagliptin reduced the MR-assessed liver fat content compared to placebo (Macauley M. et al. *J. Clin. Endocrinol. Metab.* **100**, 1578–1585(2015)



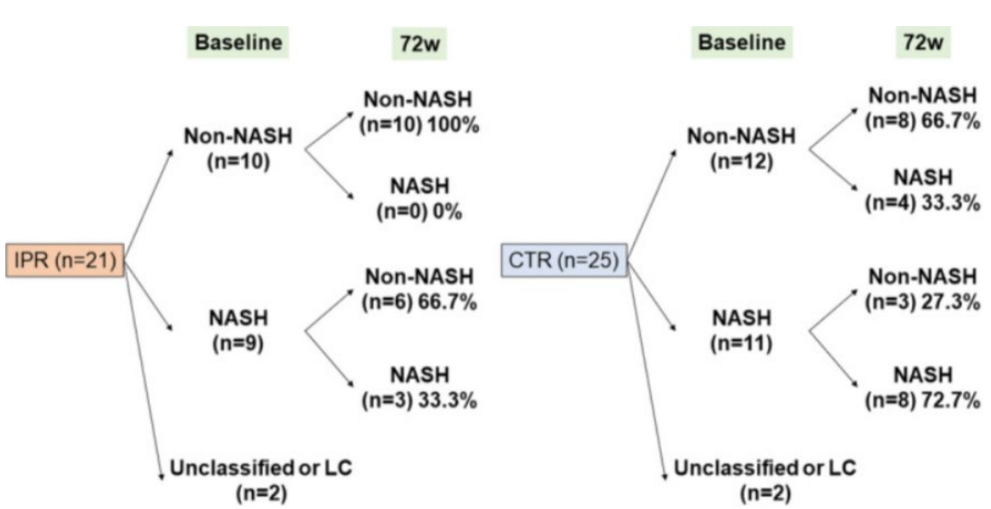
- Currently, no data are available for the effects of DPP4i on liver histology in NAFLD

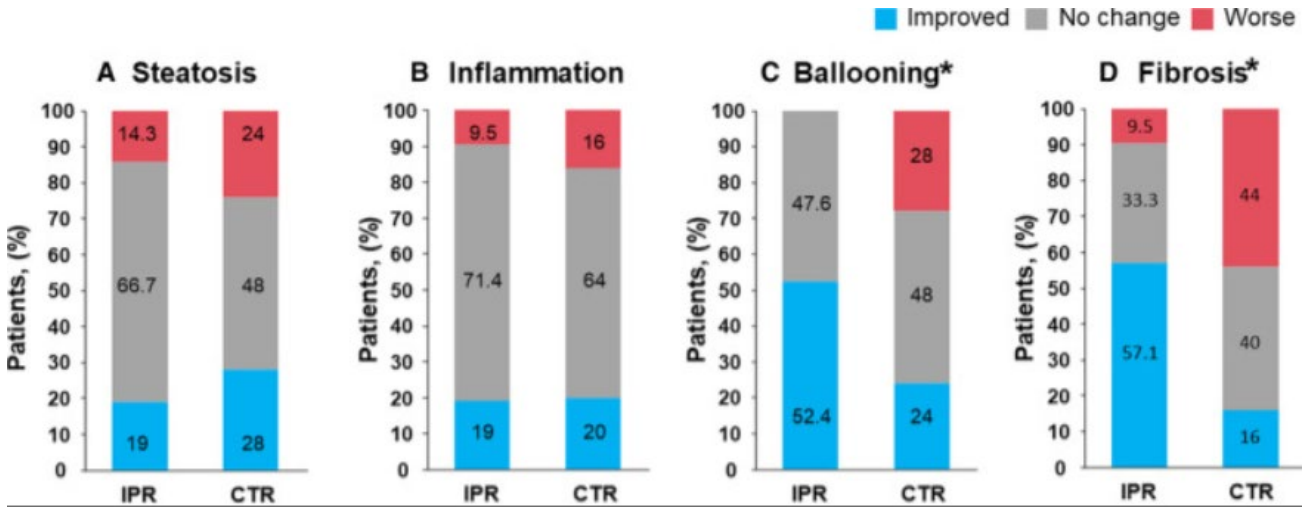
NAFLD treatment : SGLT2-inhibitors

Study/year	SGLT-2i	Study duration in weeks/n	Liver fat reduction (MRI)	Other outcome
Kuchay et al. 2018	Empagliflozin	20/50	↓4.0% (p = <0.0001)	↓ALT
Eriksson et al. 2018	Dapagliflozin + OM-3CA	12/84	↓3.2% (p = 0.046) ↓2.2% (Dapa group)	↓AST, ALT, GGT, CK 18-M65 (Dapa group only)
Cusi et al. 2019	Canagliflozin	24/56 (±NAFLD)	↓2.2% (overall) ↓3.1% (NAFLD group) (p = 0.04)	Hepatic insulin sensitivity improved, not muscle & adipose tissue IS
Latva-Rasku et al. 2019	Dapagliflozin	8/32	↓3.7% (p = <0.01)	↓IL-6, no change in tissue-level insulin sensitivity
Kahl et al. 2019	Empagliflozin	24/84 (±NAFLD)	↓1.8% (p = 0.02)	↑adiponectin, No change in tissue-specific insulin sensitivity

From these MRI-based studies, SGLT2-i reduce liver fat, improve liver enzymes and reduce some inflammatory and fibrosis markers

NAFLD treatment : SGLT2-inhibitors





patients with NAFLD. Thus, ipragliflozin might be effective for the treatment and prevention of NASH in patients with diabetes, as well as improving glycemic control and obesity. Therefore, SGLT2is may represent a therapeutic choice for patients with diabetes with NAFLD, but further larger studies are required to confirm these effects.

Takahashi H et al. Hepatol Commun. 2022 Jan;6(1):120-132.

NAFLD treatment : GLP1RA

Table 1. Summary of studies on the effect of GLP-1RA on hepatic steatosis by imaging or liver histology in patients with NAFLD

Primary outcome: relative reduction in liver fat on imaging[a]					
Author	GLP1-RA	n	Study design	Weight change[b]	Reduction in liver fat content
Vanderheiden et al, 2016	Liraglutide	71	RCT	↓ 2.2%	↓ 31%
Feng et al, 2017	Liraglutide	87	Open label	↓ 6.4%	↓ 19%
Petit et al, 2017	Liraglutide	68	Open label	↓ 4.4%	↓ 19%
Frossing et al, 2018	Liraglutide	72	RCT	↓ 5.7%	↓ 32%
Kuchay et al, 2020	Dulaglutide	52	Open label	↓ 2.6%	↓ 20%
Primary outcome: percentage of patients with resolution of NASH (by liver histology)[c]					
Author	GLP1-RA	n	Study design	Weight change[b]	NASH resolution
Armstrong et al, 2016	Liraglutide	52	RCT	↓ 4.8%	30%
Newsome et al, 2020	Semaglutide	320	RCT	↓ 4%-12%	19%-42%

Studies with a minimal treatment period of ≥24 weeks and ≥50 patients. Arrows indicate statistically significant changes vs comparator.
Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial.
[a] Placebo or comparator subtracted change in hepatic steatosis.
[b] Placebo or comparator subtracted weight loss.
[c] Placebo-subtracted change in number of patients with resolution of NASH.

Chandani Patel Chavez et al. *The Journal of Clinical Endocrinology & Metabolism*, Volume 107, Issue 1, January 2022, Pages 29–38

NAFLD treatment : GLP1RA

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide *vs* placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019
Changes from baseline in histopathological parameters				
Total NAFLD activity score				
Change in score	−1·3 (1·6)	−0·8 (1·2)	−0·5 (−1·3 to 0·3)	0·24
Patients with improvement	17 (74%)	14 (64%)	1·2 (0·8 to 1·7)	0·46
Hepatocyte ballooning score				
Mean change	−0·5 (0·7)	−0·2 (0·6)	−0·3 (−0·7 to 0·1)	0·15
Patients with improvement	14 (61%)	7 (32%)	1·9 (1·0 to 3·8)	0·05
Steatosis				
Change in score	−0·7 (0·8)	−0·4 (0·8)	−0·2 (−0·6 to 0·2)	0·32
Patients with improvement	19 (83%)	10 (45%)	1·8 (1·1 to 3·0)	0·009
Lobular inflammation				
Change in score	−0·2 (0·6)	−0·2 (0·5)	−0·01 (−0·3 to 0·3)	0·97
Patients with improvement	11 (48%)	12 (55%)	0·9 (0·5 to 1·6)	0·65
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	0·04†

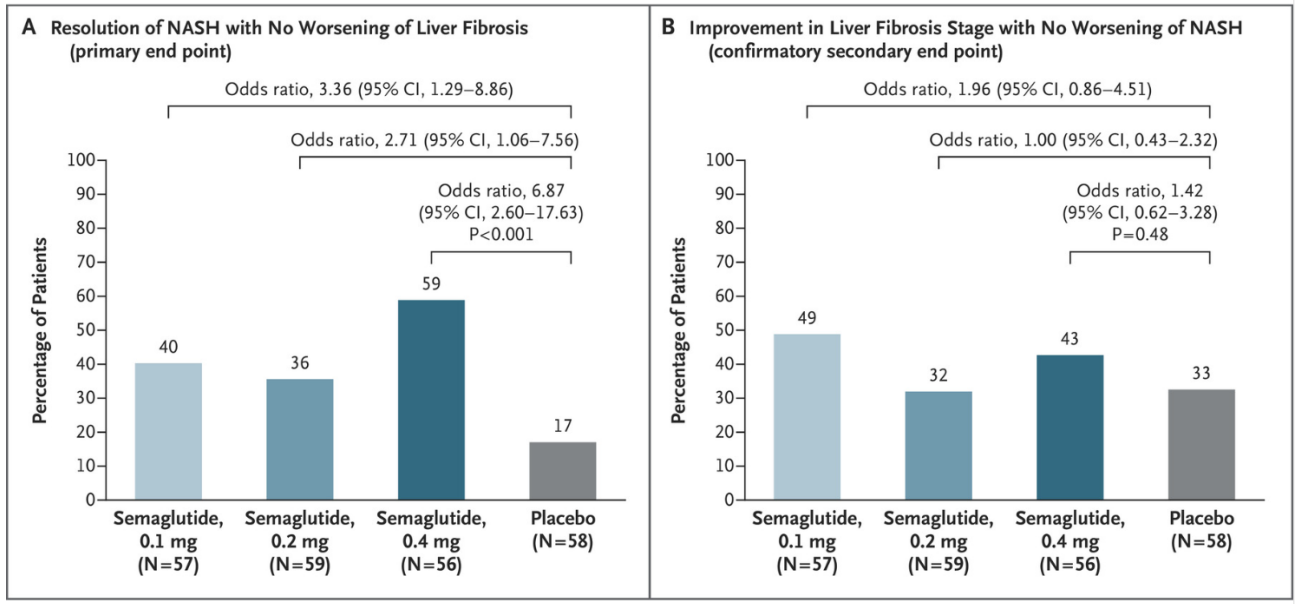
Data are n (%) or mean (SD). The mean of the two independent pathologists' scores for overall non-alcoholic fatty liver disease (NAFLD) activity score, steatosis, ballooning, inflammation, and fibrosis were used to compare the two treatment groups. The pathologists' agreement for overall NAFLD activity score using a weighted kappa was 0·854. *p values and mean changes from baseline were calculated by linear regression analysis using the baseline characteristic score and treatment as model covariates (equivalent to ANCOVA); for categorical comparisons, p values were determined by χ^2 analysis. †p value was determined by Fisher's exact test.

***Table 2*: Changes in liver histology after 48 weeks of treatment**

Fewer patients in the liraglutide group had progression of fibrosis than in the placebo group, and a greater proportion of patients in the liraglutide group had improvements in steatosis and hepatocyte ballooning compared with the placebo group (table 2). However, no differences were seen in lobular inflammation and overall NAFLD activity score (table 2).

Armstrong MJ et al. Lancet. 2016 Feb 13;387(10019):679-690.

NAFLD treatment : GLP1RA

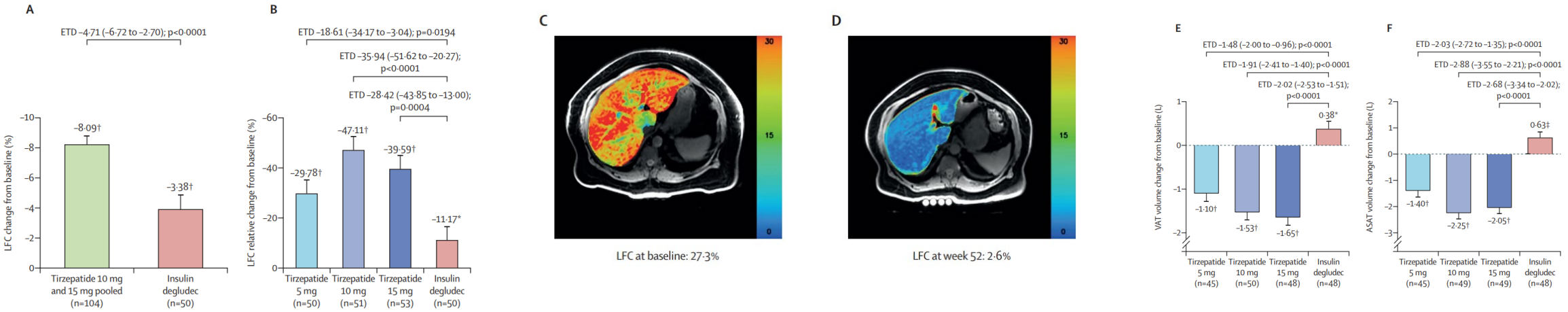


CONCLUSIONS

This phase 2 trial involving patients with NASH showed that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo. However, the trial did not show a significant between-group difference in the percentage of patients with an improvement in fibrosis stage. (Funded by Novo Nordisk; ClinicalTrials.gov number, NCT02970942.)

Newsome PN et al. N Engl J Med 2021; 384:1113-1124

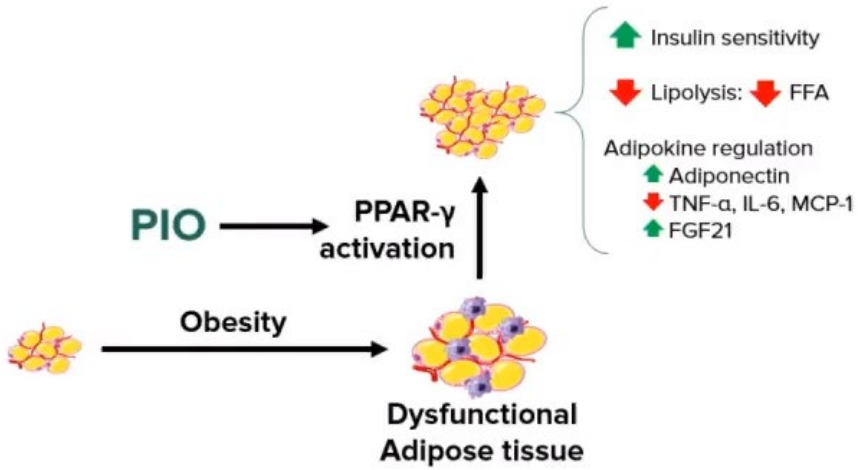
NAFLD treatment : GLP1RA/GIPRA



Interpretation Tirzepatide showed a significant reduction in LFC and VAT and ASAT volumes compared with insulin degludec in this subpopulation of patients with type 2 diabetes in the SURPASS-3 study. These data provide additional evidence on the metabolic effects of this novel dual GIP and GLP-1 receptor agonist.

Gastaldelli A et al. Lancet Diabetes Endocrinol. 2022 Jun;10(6):393-406.

NAFLD treatment : PPAR agonists



Combination with GLP-1 agonists and SGLT-2 inhibitors

Preventing weight gain.
Decreasing risk of HF hospitalization

?

Low-dose pioglitazone

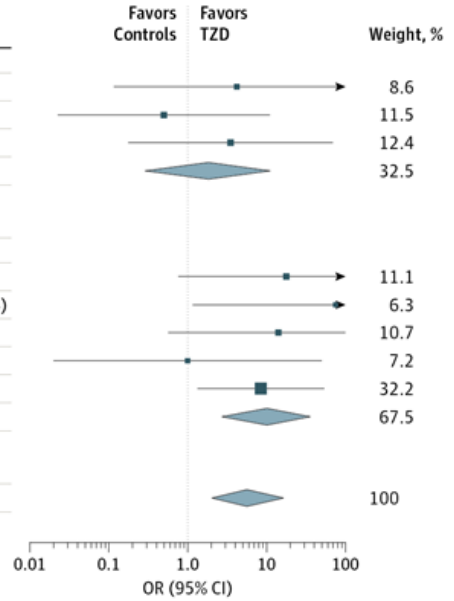
A new "improved" version of pioglitazone

$$$

Unknown safety; new AEs.

B Patients with NASH with advanced fibrosis at baseline

Source	TZD No. of Events	TZD No. of Patients	Control No. of Events	Control No. of Patients	Odds Ratio (95% CI)	Weight, %
Rosiglitazone maleate						
Idilman et al,[19] 2008	1	3	0	3	4.20 (0.12-151.97)	8.6
Omer et al,[21] 2010	1	7	1	4	0.50 (0.02-11.09)	11.5
Ratziu et al,[18] 2008	1	5	1	15	3.50 (0.18-69.34)	12.4
Total (95% CI)	3	15	2	22	1.84 (0.29-11.66)	32.5
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=1.06$; $P=.59$; $I^2=0\%$ Overall effect: $z=0.65$; $P=.52$						
Pioglitazone hydrochloride						
Aithal et al,[17] 2008	3	7	0	11	17.89 (0.76-420.49)	11.1
Belfort et al,[16] 2006	7	7	0	2	75.00 (1.16-4868.64)	6.3
Cusi et al,[12] 2016	4	7	0	5	14.14 (0.57-352.00)	10.7
Sanyal et al,[15] 2004	1	2	1	2	1.00 (0.02-50.40)	7.2
Sanyal et al,[20] 2010	6	12	2	19	8.50 (1.33-54.13)	32.2
Total (95% CI)	21	35	3	39	10.17 (2.83-36.54)	67.5
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=2.43$; $P=.66$; $I^2=0\%$ Overall effect: $z=3.55$; $P<.001$						
Total (95% CI)	24	50	5	61	5.84 (2.04-16.71)	100
Heterogeneity: $\tau^2=0.00$; $\chi^2_2=5.71$; $P=.57$; $I^2=0\%$ Overall effect: $z=3.29$; $P=.001$						

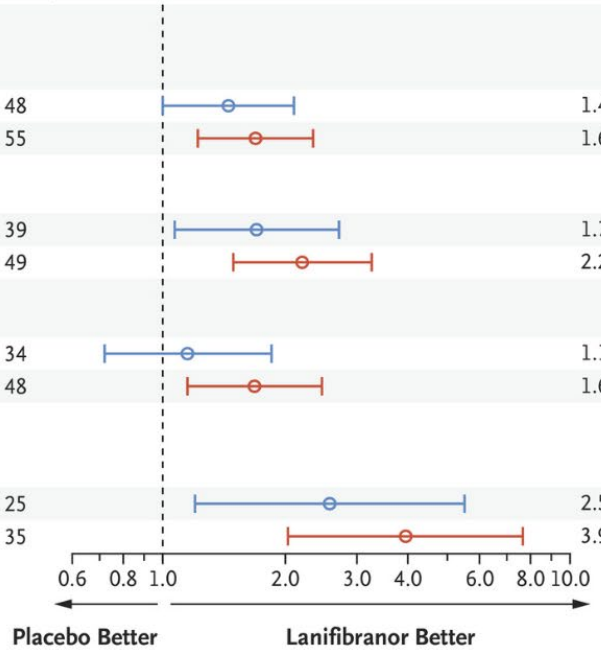


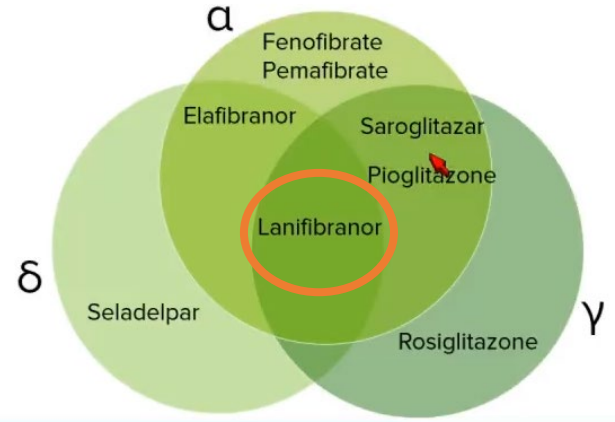
A, Improvement in advanced fibrosis (stage F3-F4) in patients with biopsy-proven NASH, defined as the number of patients with NASH whose fibrosis stage had changed from F3-F4 to F0-F2 at the end of treatment. B, Improvement in advanced fibrosis (stage F3-F4) in patients with NASH with advanced fibrosis, defined as the number of patients with NASH with advanced (F3-F4) fibrosis at baseline whose fibrosis stage had changed from F3-F4 to F0-F2 at the end of treatment. In contrast to A, only patients with NASH and advanced fibrosis were included as the denominator in B.

Musso G et al. JAMA Intern Med. 2017 May 1;177(5):747.

NAFLD treatment : PPAR agonists

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	





CONCLUSIONS

In this phase 2b trial involving patients with active NASH, the percentage of patients who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis was significantly higher with the 1200-mg dose of lanifibranor than with placebo. These findings support further assessment of lanifibranor in phase 3 trials. (Funded by Inventiva Pharma; NATIVE ClinicalTrials.gov number, NCT03008070.)

Francque SM et al. N Engl J Med 2021; 385:1547-1558

NAFLD treatment : emerging therapies

- Other insulin sensitizers
  - GLP-1/glucagon receptor dual agonists
  - Long-acting FGF21
- TG-lowering agents
  - ACCi
  - FASi
  - SCDI
  - DGAT2i
  - FXR agonists
  - Thyroid hormone receptor-beta agonists
- ROS-targeted therapies
  - Edaravone
  - Mitotherapy
  - NOX inhibitors (‘naxibs’)
- Genetic therapies (PNPLA3, TM6SF2…)

Nascè A et al. Antioxidants (Basel). 2022 Jun 9;11(6):1131.

NAFLD management

Table 3—Management of patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis

Variable	Lifestyle intervention[a]	Liver-directed pharmacotherapy	Diabetes care (in individuals with diabetes)	Cardiovascular risk reduction
NAFL	Yes	No	Standard of care	Yes
NASH with fibrosis stage 0 or 1 (F0, F1)	Yes	No	Standard of care	Yes
NASH with fibrosis stage 2 or 3 (F2, F3)	Yes	Yes	Pioglitazone, GLP-1 receptor agonists[b]	Yes
NASH cirrhosis (F4)	Yes	Yes	Individualize[c]	Yes

[a]All patients require regular physical activity and healthy diet and to avoid excess alcohol intake; weight loss recommended. [b]Among GLP-1 receptor agonists, semaglutide has the best evidence of benefit in patients with NASH and fibrosis. [c]Evidence for efficacy of pharmacotherapy in patients with NASH cirrhosis is very limited and should be individualized and used with caution.

Kanwal F et al. Diabates Care 2021;44(9):2162-2172

Take home messages

- Concerning NAFLD epidemic
- Intertwined NAFLD-diabetes relationship via insulin resistance and oxidative stress
- When screening
  - Select patients at high risk for NAFLD
  - Exclude secondary causes of liver disease
  - Promote NITs
- Treatment
  - Pivotal role of weight loss
  - Amongst antidiabetic drugs, GLP1RA and TZD the most promising
  - Several new classes ‘in the pipeline’

Merci pour votre attention!

Vielen Dank für Ihre Aufmerksamkeit!