12th PHC, 14-15 January 2019

Cross paths liver/metabolism : the point of view of the hepatologist/ diabetologist

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1CHU Dijon, 2Institut du Thorax-Nantes

3Hôpitaux Universitaire de Strasbourg

Disclosures

JM Petit

- Novartis
- Novonodisk
- Lilly
- Astra-Zeneca

B Cariou

- Abbot
- Akcea
- Amgen
- Astra-Zeneca
- Genfit
- Gilead
- Novonordisk
- Sanofi
- MSD
- Lilly

L Serfaty

- Abbvie
- Allergan
- BMS
- Gilead
- Intercept
- MSD
- Sanofi

Clinical case

- 60-years-old man, with a 12 years history of type 2 diabetes was reffered to diabetology consultation for elevated HbA1c.

- In addition to type 2 diabetes, he had a history of hypertension myocardial infarction and hyperlipidemia

- his medical regimen included an ACE inhibitor, a statin, a sulfonylurea, a low dose of *aspirin* and the maximum dose of metformin.

- His height was 1.7 m, and his weight was 98 kg. His physical examination was normal. He had no retinopathy and no evidence of neuropathy.

- His glycated hemoglobin (HbA1c) level was 8.5% (normal <6.0%).

and a complete blood count revealed a white blood cell count of 7,200 and platelet count of 258,000. His liver function assessment revealed ALT 65 (NR: 13-56) and AST 34 (NR: 15-37).

- Alcool intake : 2 drinks maximum per day

Cross paths liver/metabolism

- Do we have to screen T2D patients for NASH ?
- How to screen and who to refer ?
- Treatment specificities in T2D patients with NASH ?

EPIDEMIOLOGY: a link between obesity, T2D and NAFLD

T2D

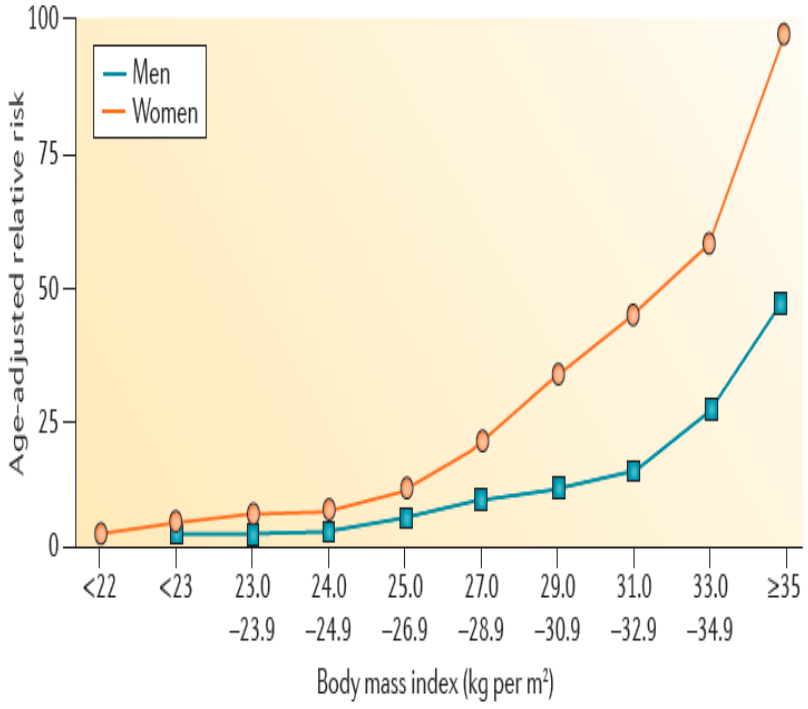


Figure 2 | **Association between BMI and T2DM.**

NAFLD

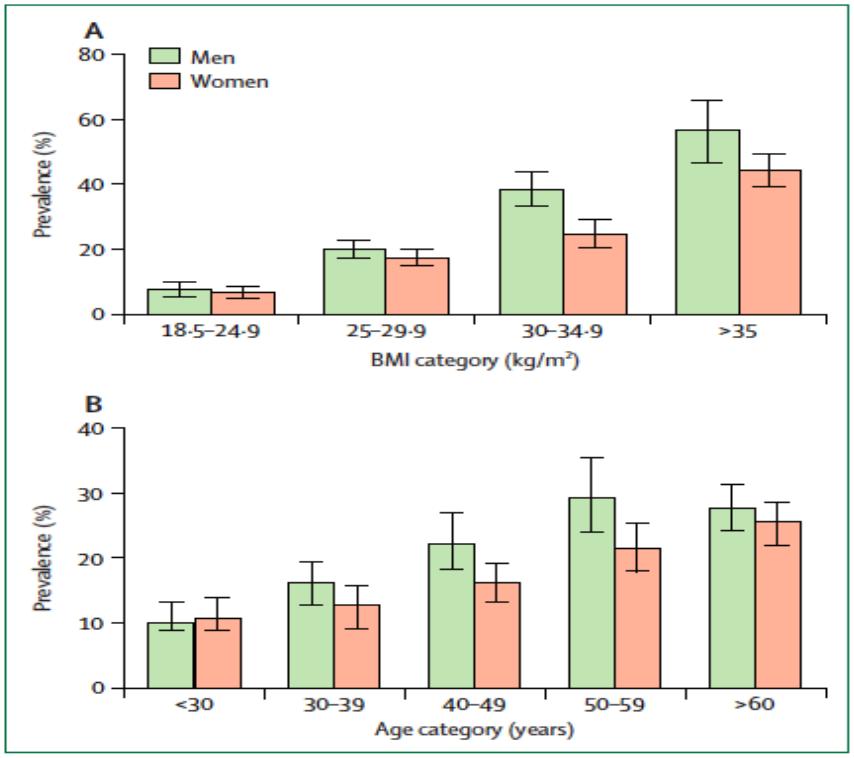


***Figure 3*: Prevalence of NAFLD according to BMI, age, and sex**

DeFronzo RA. et al. *Nat Rev Dis Primers* 2015; 1: 15019

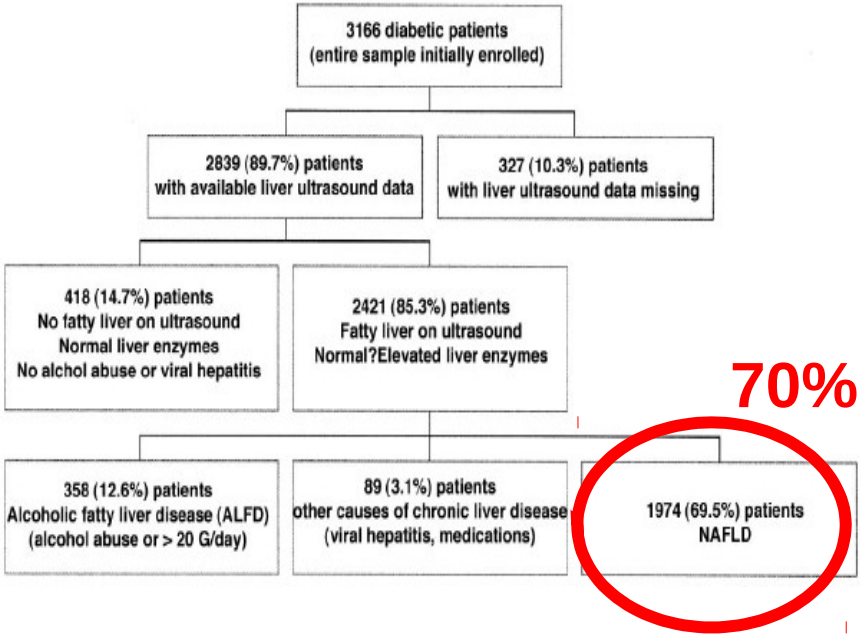
Yki-Järvinen H. et al. *Lancet Diabetes Endocrinol* 2014; 2: 901-1

WHAT IT IS THE PREVALENCE OF NAFLD in T2D?

Prevalence of Nonalcoholic Fatty Liver Disease and Its Association With Cardiovascular Disease Among Type 2 Diabetic Patients

GIOVANNI TARGHER, MD[1,2]
LORENZO BERTOLINI, MD[1]
ROBERTO PADOVANI, MD[1]
STEFANO RODELLA, MD[3]
ROBERTO TESSARI, MD[1]
LUCIANO ZENARI, MD[1]
CHRISTOPHER DAY, MD[4]
GUIDO ARCARO, MD[1]

Diabetes Care 30:1212–1218, 2007



70%

Epidemiology/Health Services Research
ORIGINAL ARTICLE

Prevalence of and Risk Factors for Hepatic Steatosis and Nonalcoholic Fatty Liver Disease in People With Type 2 Diabetes: the Edinburgh Type 2 Diabetes Study

RACHEL M. WILLIAMSON, MRCP[1]
JACKIE F. PRICE, MD, FFPH[2]
STEPHEN GLANCY, FRCR[3]
ELISA PERRY, MRCP, FRCR[3]
LISA D. NEE, GRADDIPPAPPSCI[3]
PETER C. HAYES, PHD, MD[4]
BRIAN M. FRIER, MD, FRCPE[5]
LIESBETH A.F. VAN LOOK, MRCP[1]
GEOFFREY I. JOHNSTON, PHD[6]
REBECCA M. REYNOLDS, PHD, FRCPE[7]
MARK W.J. STRACHAN, MD, FRCPE[1]
ON BEHALF OF THE EDINBURGH TYPE 2 DIABETES STUDY INVESTIGATORS

Diabetes Care 34:1139–1144, 2011

N=939 patients with T2

RESULTS—Hepatic steatosis was present in 56.9% of participants. After excluding those with a secondary cause for steatosis, the prevalence of NAFLD in the study population was 42.6%. Independent predictors of NAFLD were BMI, lesser duration of diabetes, HbA_{1c}, triglycerides, and metformin use. These remained unchanged after exclusion of participants with evidence of hepatic fibrosis from the group with no hepatic steatosis.

43%

...AND IN PRIMARY CARE?

AP&T Alimentary Pharmacology and Therapeutics

Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE

I. Doycheva*, J. Cui*, P. Nguyen*,†, E. A. Costa‡, J. Hooker‡, H. Hofflich§, R. Bettencourt¶, S. Brouha**, C. B. Sirlin‡ & R. Loomba*,†,¶

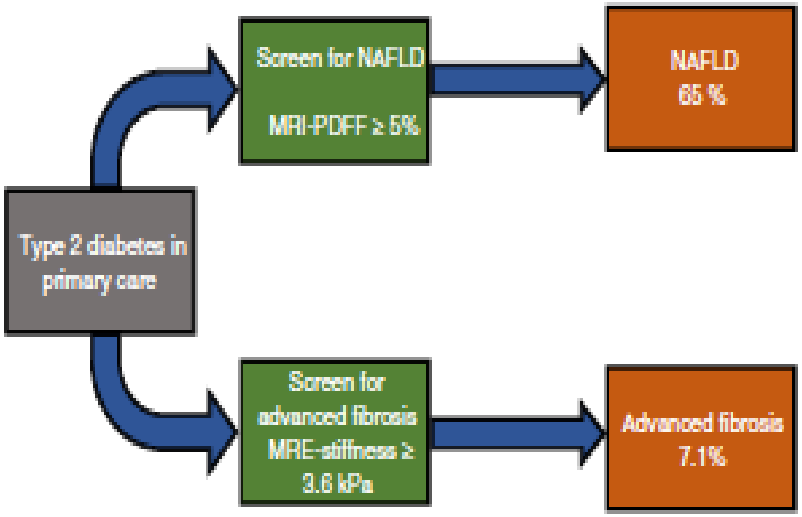
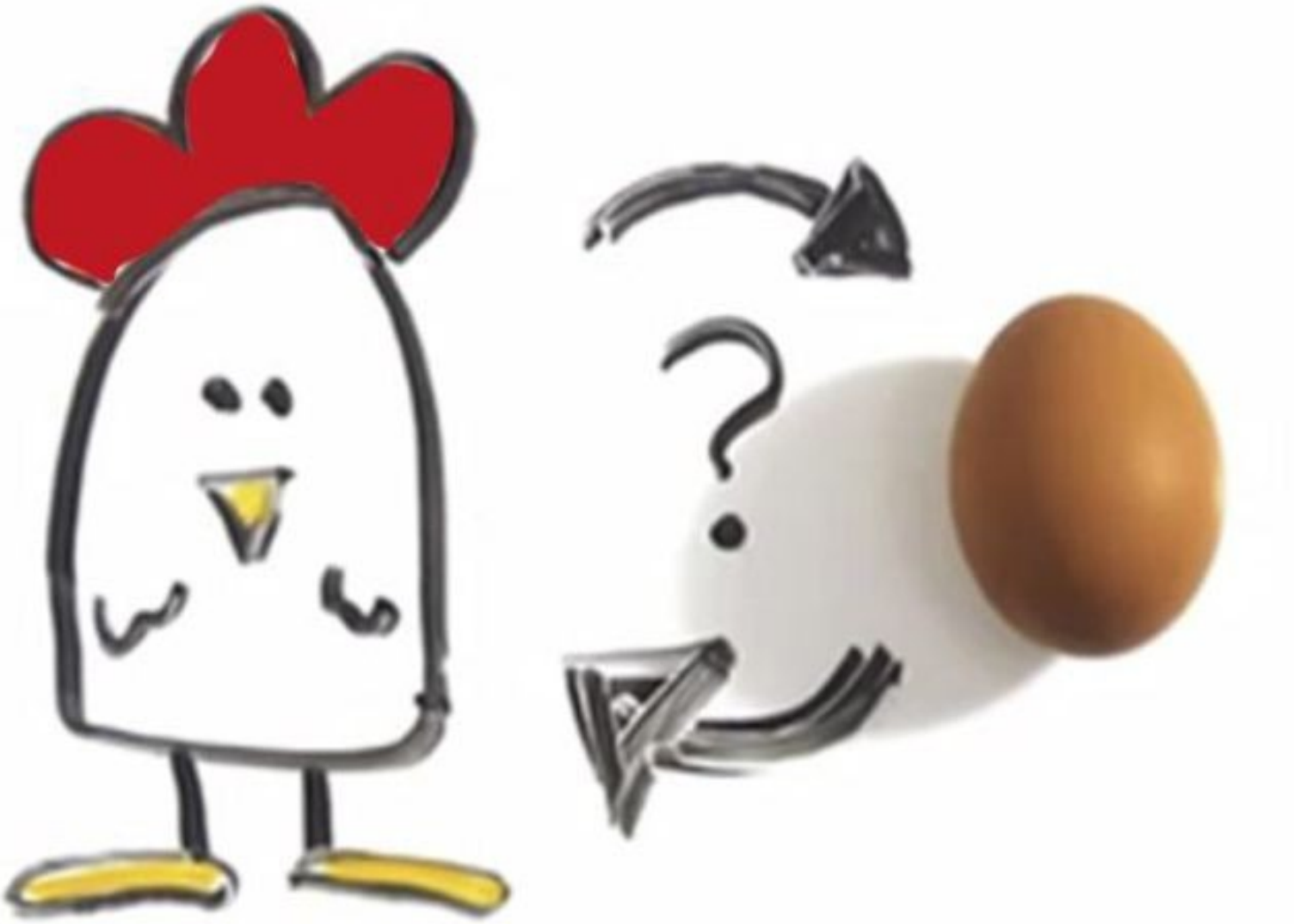


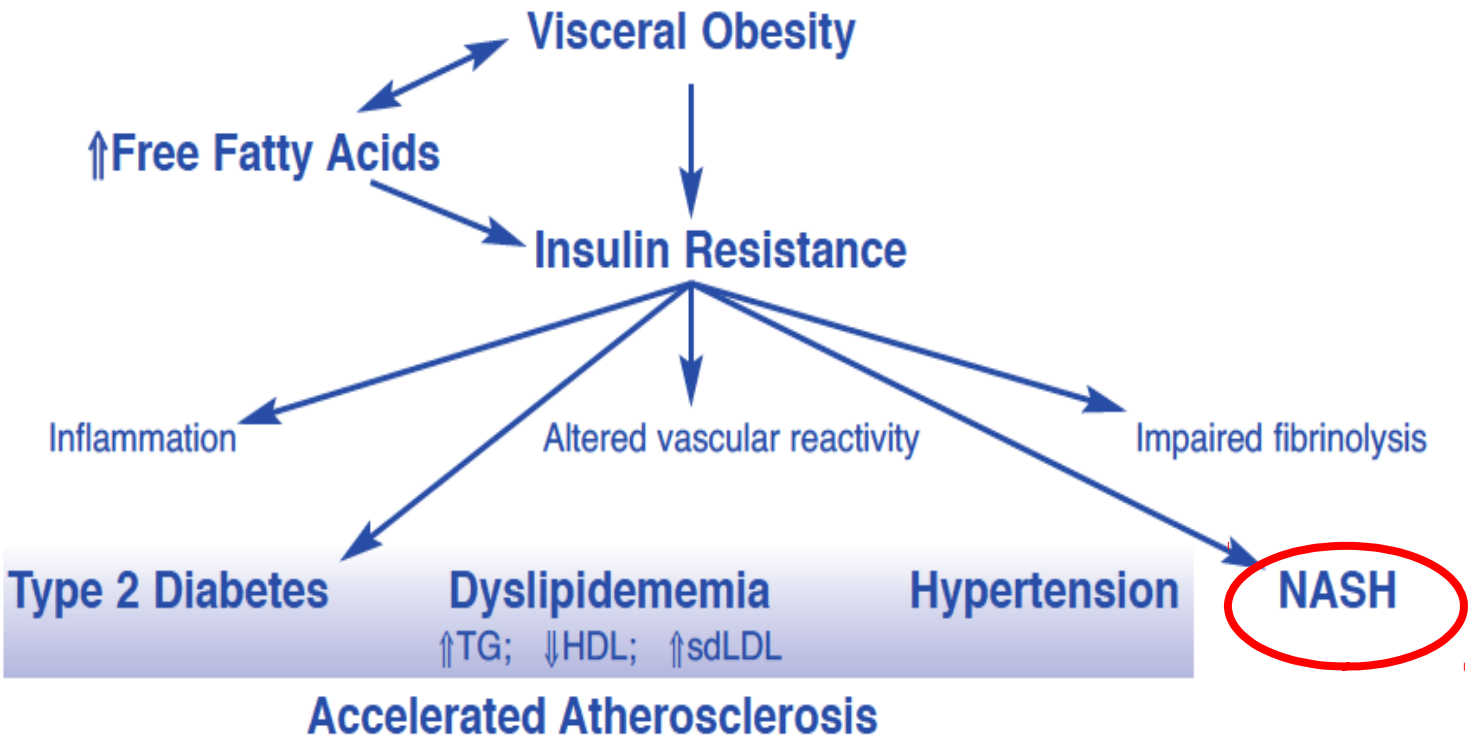
Figure 1 | Prevalence of NAFLD and advanced fibrosis among patients with type 2 diabetes in primary care. Patients with type 2 diabetes in the primary care setting were screened for NAFLD with magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF). NAFLD was defined by the presence of hepatic steatosis ≥5% on MRI-PDFF. Screening for advanced fibrosis was performed using magnetic resonance elastography (MRE) with a threshold of 3.6 kPa to identify those with advanced fibrosis.



NAFLD/NASH

INSULIN RESISTANCE/T2D

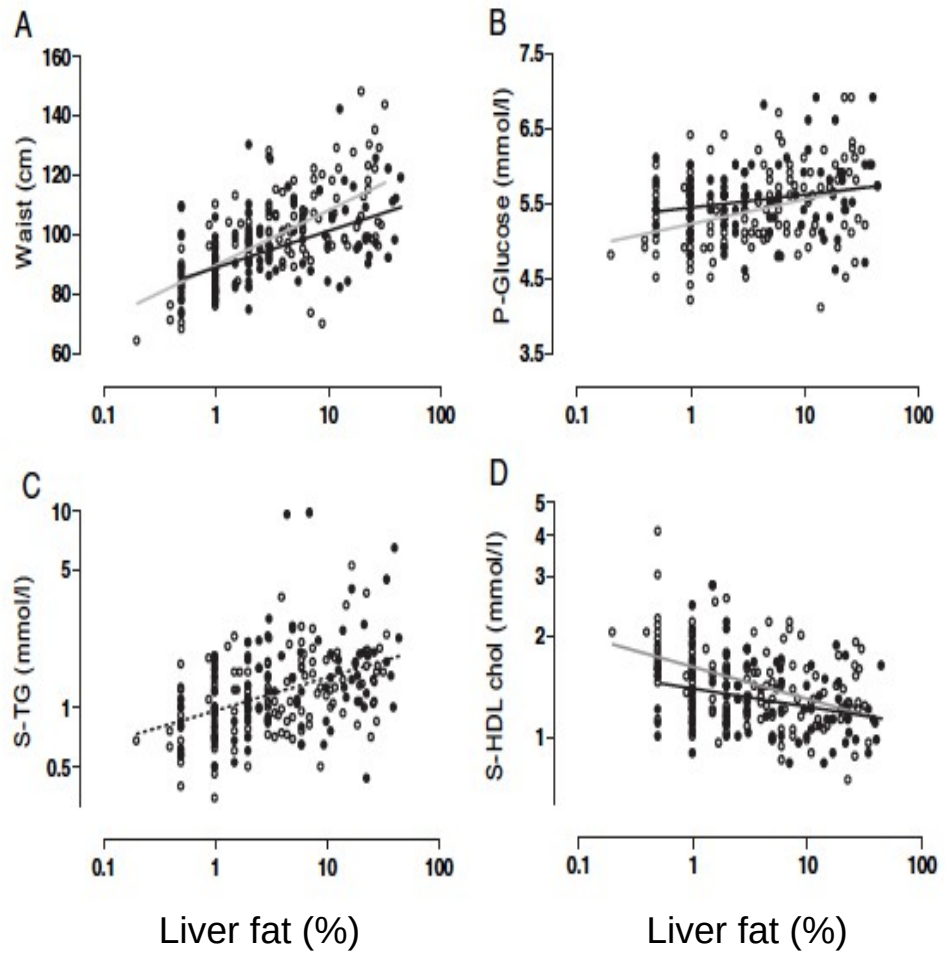
Insulin Resistance and Metabolic Syndrome



NASH = Nonalcoholic steatohepatitis
TG = Triglycerides; HDL = high-density lipoprotein; sdLDL = small dense LDL

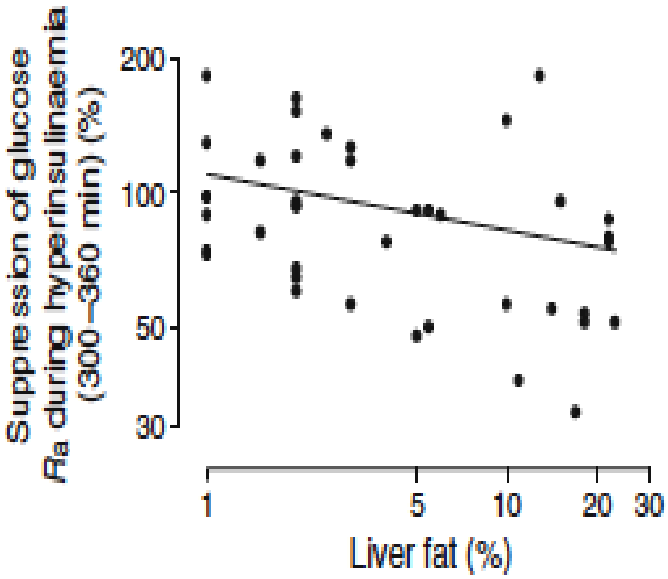
RELATION BETWEEN LIVER FAT AND COMPONENTS OF METABOLIC SYNDROME

271 non-diabetic subjects (162 women, 109 men)



Kotronen A. et al. *J Clin Endocrinol Metab* 2007; 92: 3490-97

45 non-diabetic men; hyperinsulinemic-euglycemic clamps



Kotronen A. et al. *Diabetologia 2008; 51: 130-38*

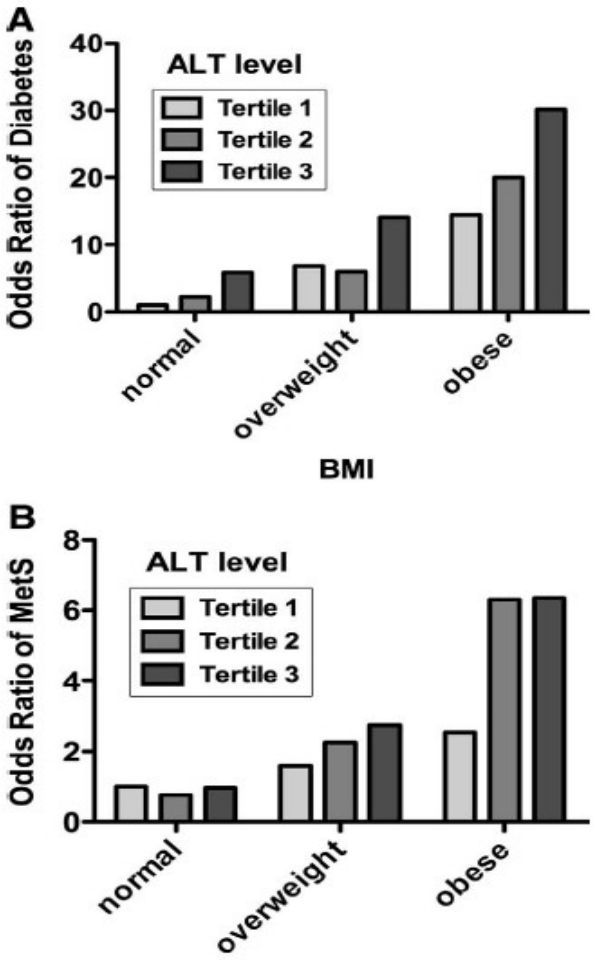
NAFLD is a risk factor for new onset type 2 diabetes

Framingham cohort – 20 years follow-up

Table 4. Baseline ALT and AST and the OR of Developing Incident DM Over 20 Years of Follow-Up

	Overall sample		AST or ALT in the normal range	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
AST				
Age/gender adjusted	1.41 (1.25–1.60)	< .0001	1.32 (1.12–1.55)	.001
MV adjusted[a]	1.33 (1.16–1.52)	< .0001	1.24 (1.04–1.48)	.02
+ glucose adjusted	1.25 (1.08–1.45)	.002	1.15 (0.96–1.39)	.13
+ interim weight change	1.33 (1.17–1.53)	< .0001	1.24 (1.04–1.48)	.02
ALT				
Age/gender adjusted	1.72 (1.51–1.94)	< .0001	1.62 (1.36–1.94)	.0001
MV adjusted[a]	1.48 (1.30–1.69)	< .0001	1.34 (1.11–1.61)	.002
+ glucose adjusted	1.42 (1.23–1.63)	< .0001	1.28 (1.05–1.55)	.01
+ interim weight change	1.48 (1.30–1.69)	< .0001	1.34 (1.11–1.61)	.002

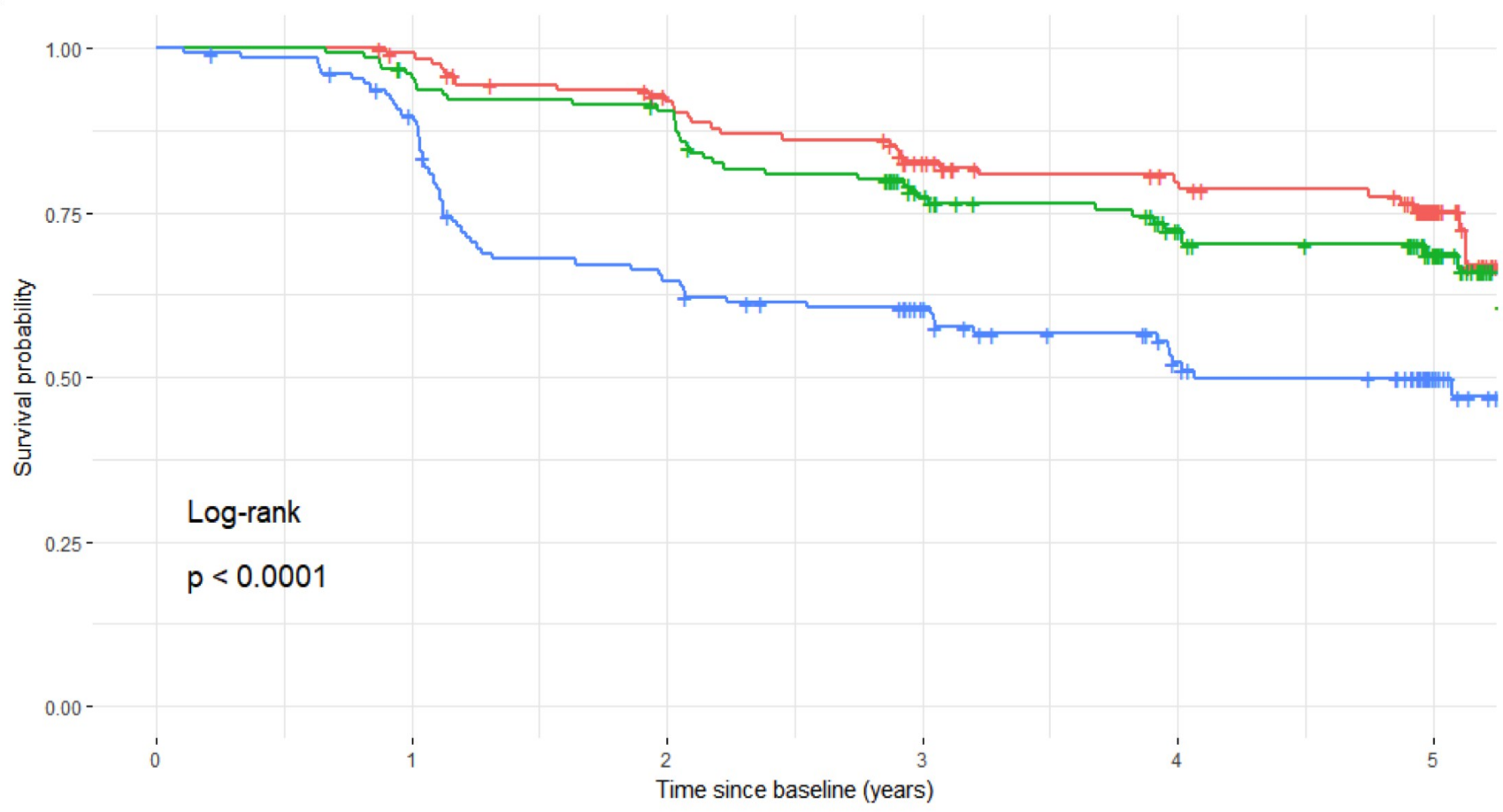
NOTE. The OR of developing incident DM was calculated per 1 gender-specific SD increase in log-transformed aminotransferase levels.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval; MV, multivariable.
[a]Adjusted for age, gender, smoking, menopause, alcohol use (g/day), BMI.



Goessling W et al. *Gastroenterology* 2008; 135: 1935-44

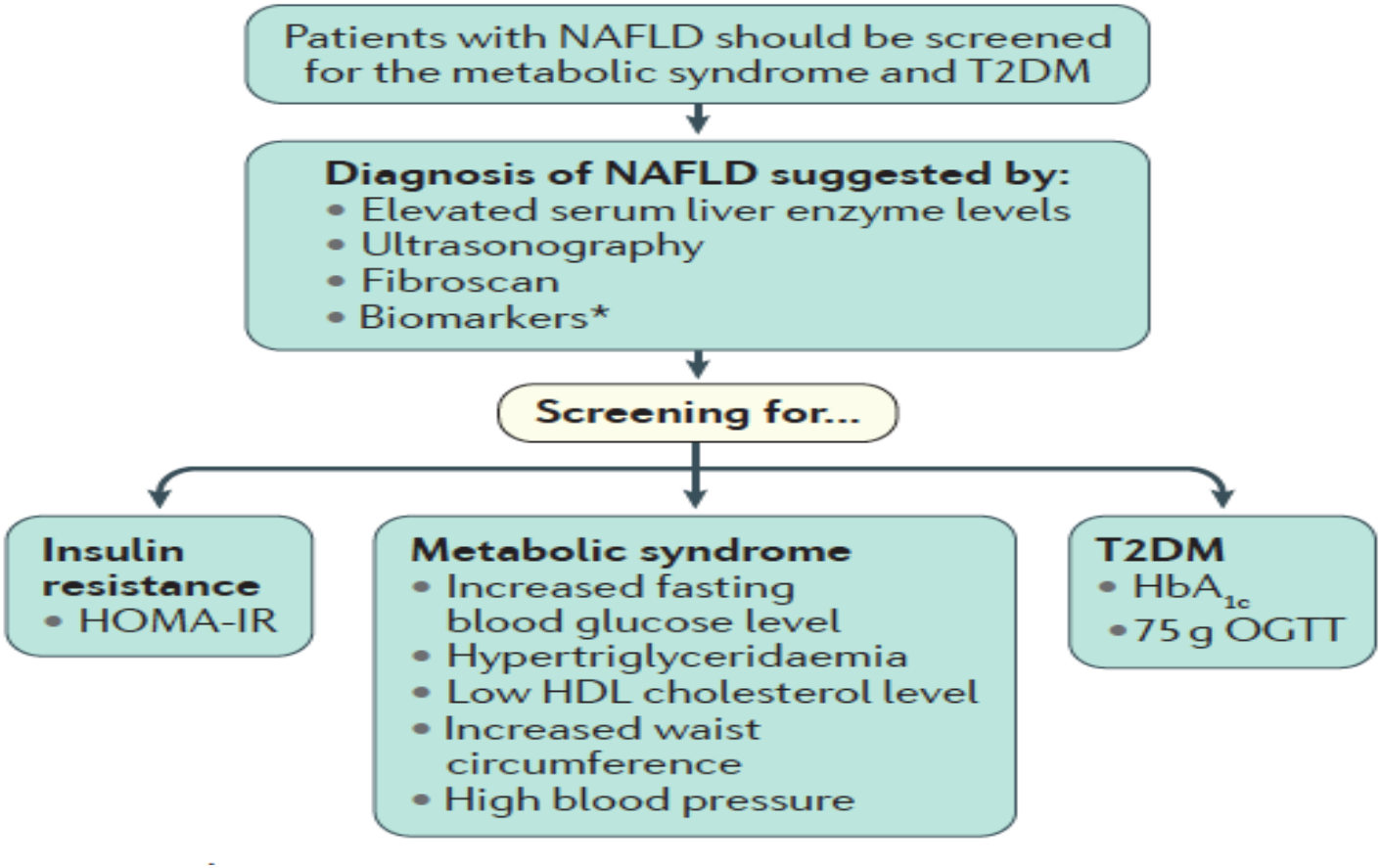
NAFLD is a risk factor for type 2 diabetes

DIAB study: 397 patients with pre-diabetes (IFG), 5 years follow-up, 33% new-onset diabe



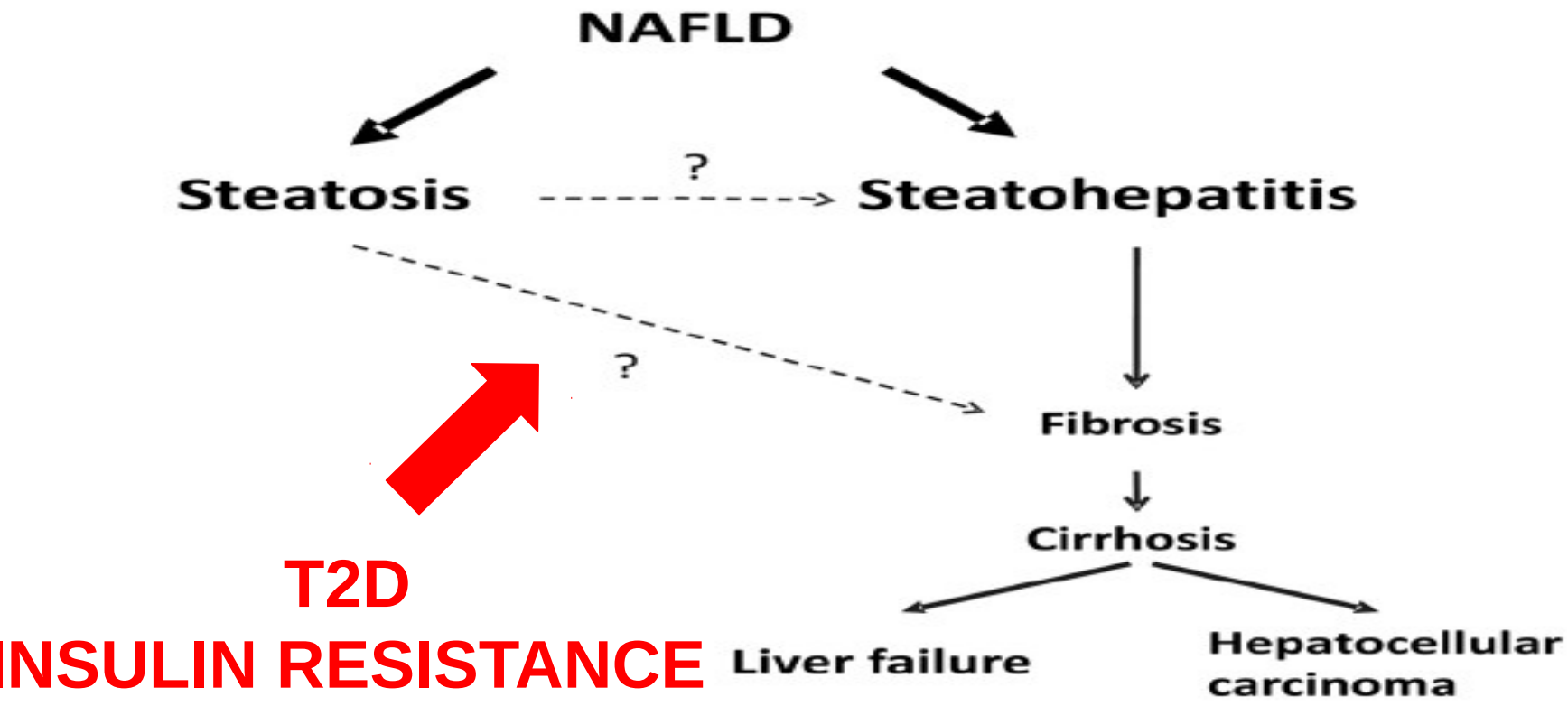
Wargny M, Cariou B (unpublished data)

TAKE HOME MESSAGE 1:
The hepatologist should screen for T2D in patients with NAFLD



=> In clinical practice: FPG (> 125 mg/dL) & HbA1C (>6.4%)

Type 2 diabetes and risk of liver fibrosis



Risk of Severe Liver Disease in Nonalcoholic Fatty Liver Disease with Normal Aminotransferase Levels: A Role for Insulin Resistance and Diabetes

Anna Ludovica Fracanzani,[1] Luca Valenti,[1] Elisabetta Bugianesi,[2] Marco Andreoletti,[3] Agostino Colli,[3] Ester Vanni,[2] Cristina Bertelli,[1] Erika Fatta,[1] Daniela Bignamini,[1] Giulio Marchesini,[4] and Silvia Fargion[1]

Table 5. Variables Significantly Associated with Fibrosis (≥2) in the Overall Series and in Patients Divided According to ALT Levels (Univariate Analysis)

Variables	*P* value		
	All Patients (n = 458)	Normal ALT (n = 63)	Increased ALT (n = 395)
Gender	0.01	NS	NS
Age (years)	0.001	0.03	0.002
BMI (kg/m^2)	0.02	NS	0.04
ALT (U/L)	0.01	NS	0.004
Serum ferritin (ng/mL)	0.001	NS	0.009
Fasting glucose (mg/dL)	0.002	NS	0.006
Fasting insulin (μU/mL)	NS	0.04	NS
Diabetes or glucose intolerance	0.04	0.03	0.001
HOMA-IR (%)	0.04	0.03	NS

NS, not significant.

(HEPATOLOGY 2008;48:792-798.)

Diabetes worsens the risk of fibrosis in patients with NAFLD

ETUDE CYTOL

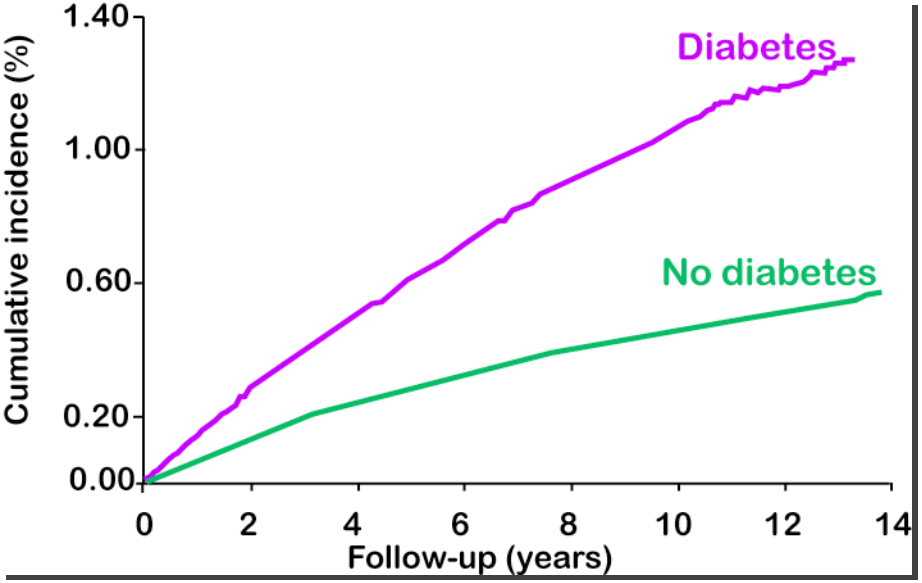
Table 5
Factors associated with significant fibrosis

Parameters	Odds ratio	95% confidence interval	*p*
Univariate analysis			
Age >40 years	2.04	1.06–3.93	0.03
Male gender	1.67	0.94–2.98	0.08
Tobacco use	2.64	1.48–4.71	0.001
Past history of alcohol abuse	3.03	1.29–7.12	0.01
Body mass index >25 (kg/m^2)	2.97	1.62–5.43	<0.0001
Diabetes	5.18	2.22–12.04	<0.0001
Multivariate analysis			
Age >40 years	1.72	0.85–3.49	0.13
Tobacco use	2.52	1.34–4.74	0.04
Past history of alcohol abuse	2.42	0.92–6.37	0.07
Body mass index >25 (kg/m^2)	2.49	1.31–4.73	0.005
Diabetes	4.41	1.73–11.29	0.002

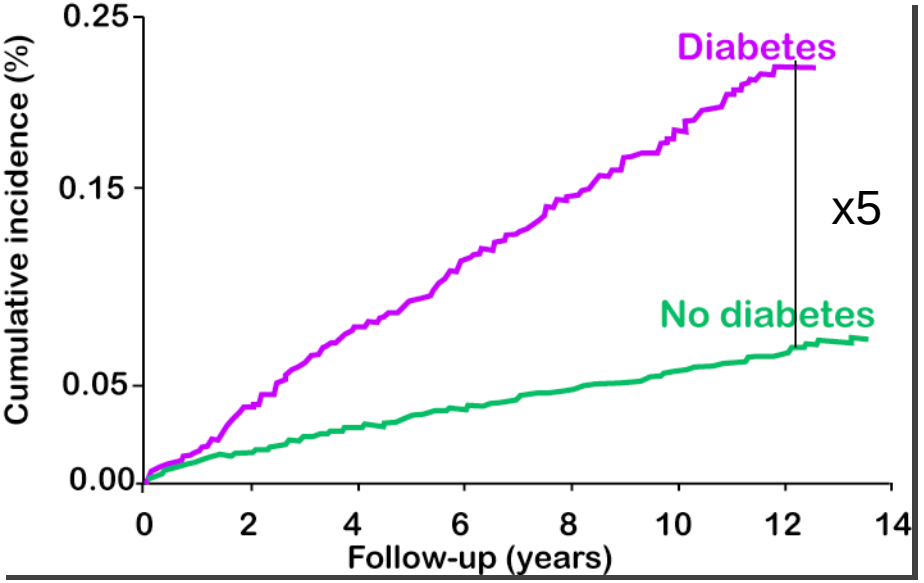
De Lédinghen V. et al. J Hepatol 2006

T2D is a risk factor for HCC

n = 173 643 veterans with diabetes
n = 650 620 veterans no diabetes



NAFLD



HCC

El-Serag, Gastroenterology 2004

TAKE HOME MESSAGE 2:
Diabetologist should screen for NASH

Diabetologia (2016) 59:1121–1140
DOI 10.1007/s00125-016-3902-y

CLINICAL PRACTICE GUIDELINES

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease

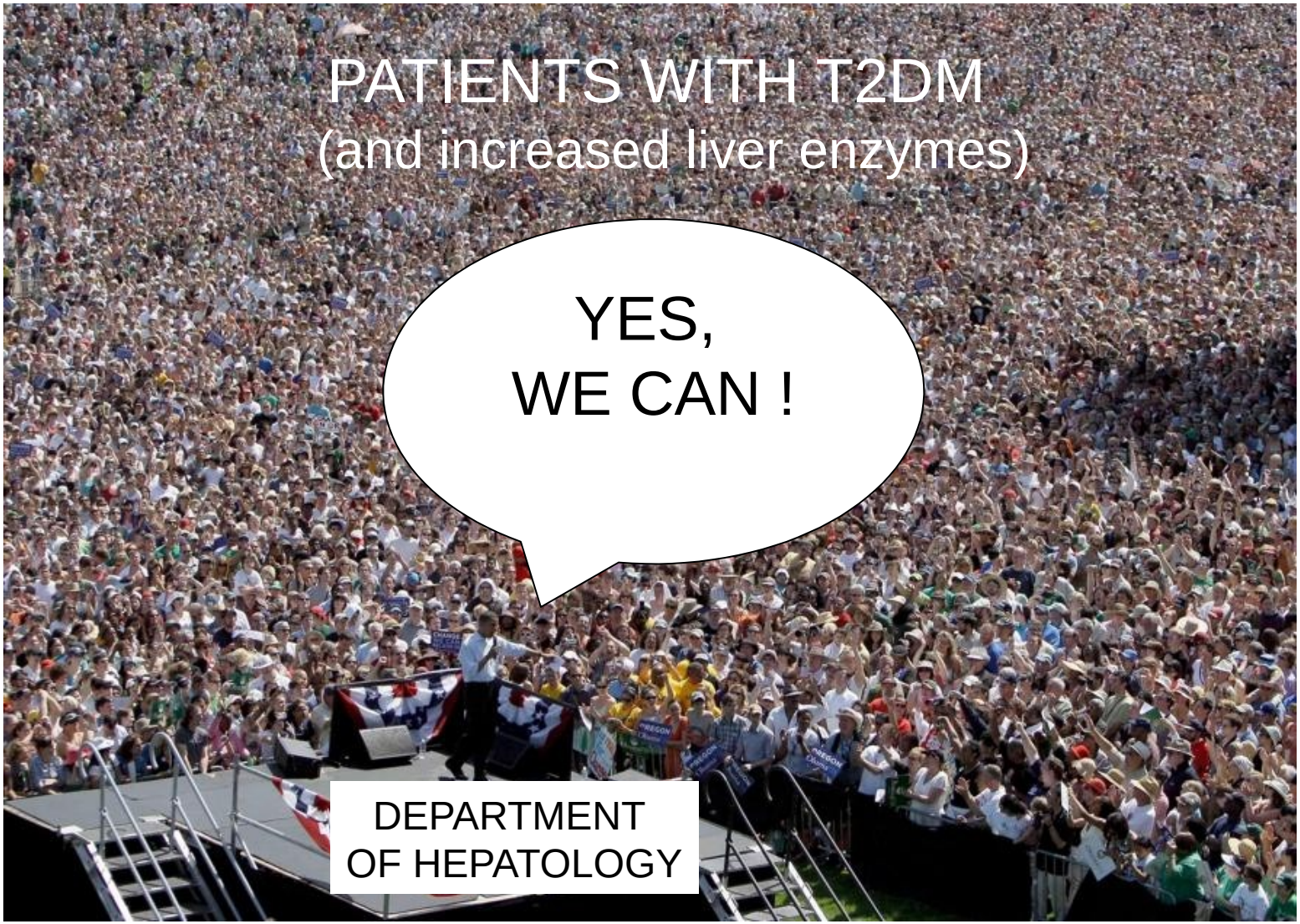
European Association for the Study of the Liver (EASL) · European Association for the Study of Diabetes (EASD) · European Association for the Study of Obesity (EASO)

Recommendations

- Patients with IR and/or metabolic risk factors (i.e. obesity or metabolic syndrome [MetS]) should undergo diagnostic procedures for the diagnosis of NAFLD, which relies on the demonstration of excessive liver fat (A1)

⇒**All patients with type 2 diabetes should be screened for NAFLD**

THE UNIVERSAL SCREENING FOR NASH



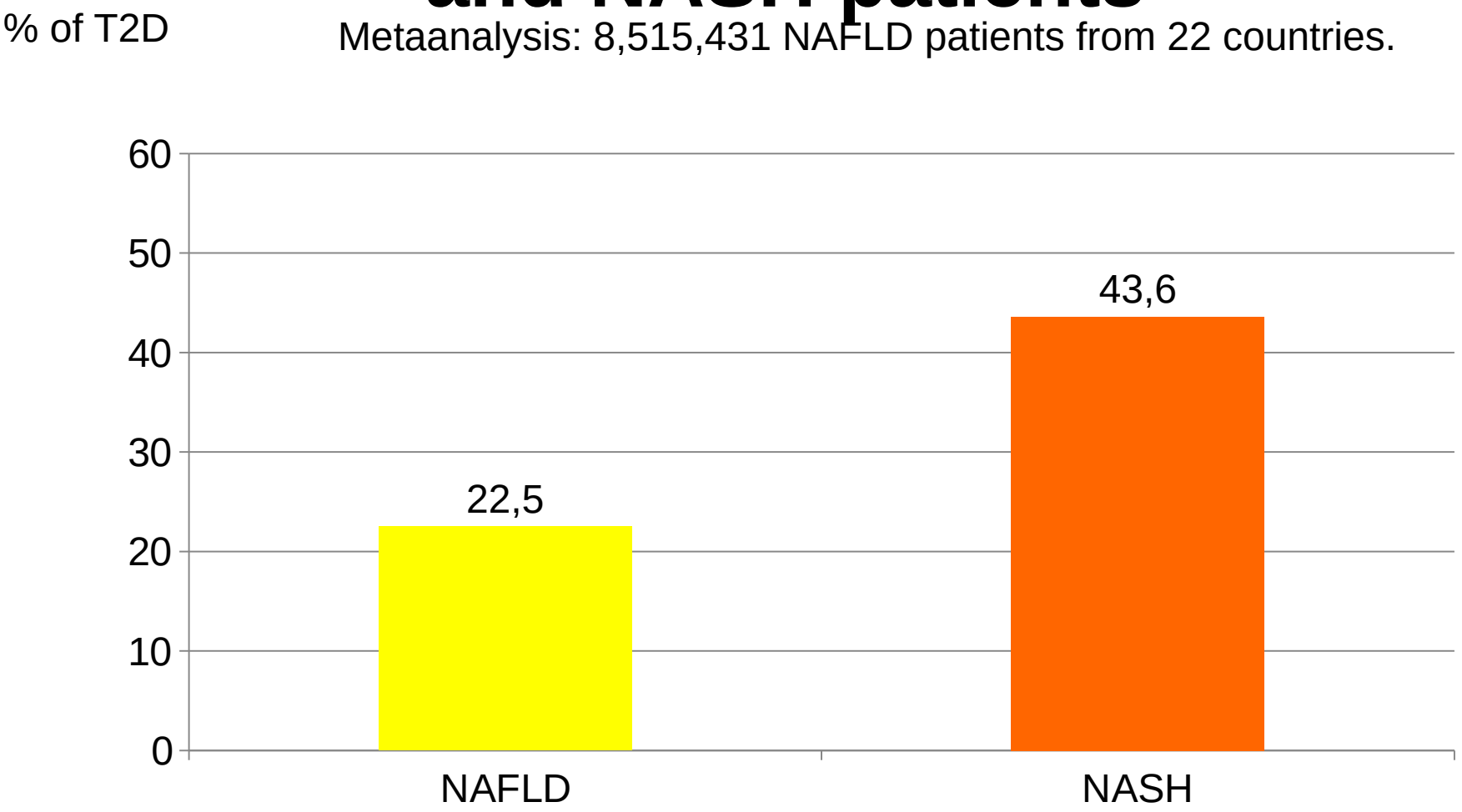
Screening of NASH in patients with type 2 diabetes

- What is the knowledge of diabetologists regarding NAFLD in T2D patients ?
- How to screen ? : the performance of non-invasive methods in T2D patients
- Which patients to refer to a liver clinic ?

What is the knowledge of diabetologists regarding NAFLD in T2D patients ?

High prevalence of diabetes among NAFLD and NASH patients

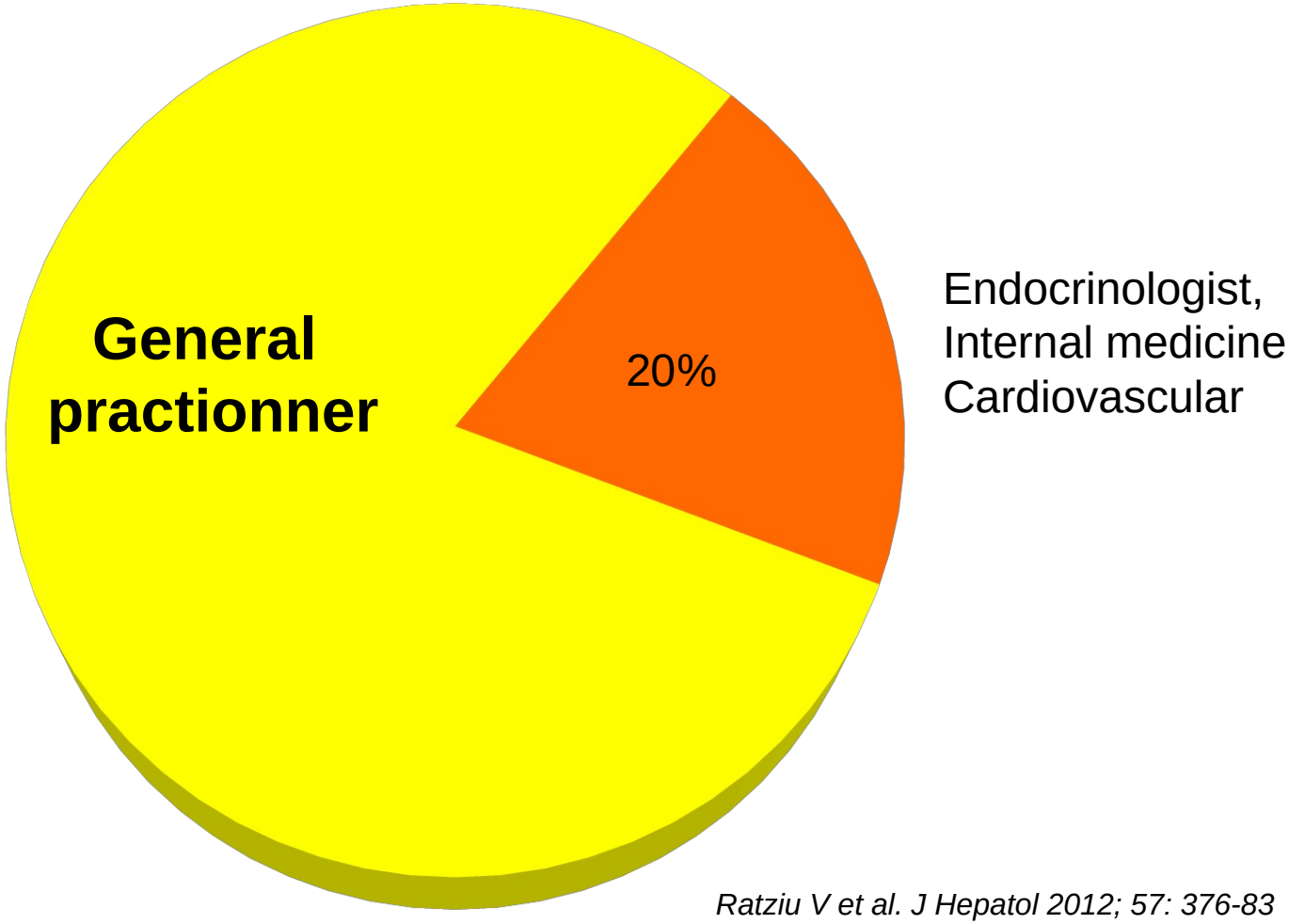
Metaanalysis: 8,515,431 NAFLD patients from 22 countries.



Younossi Z et al. Hepatology 2016

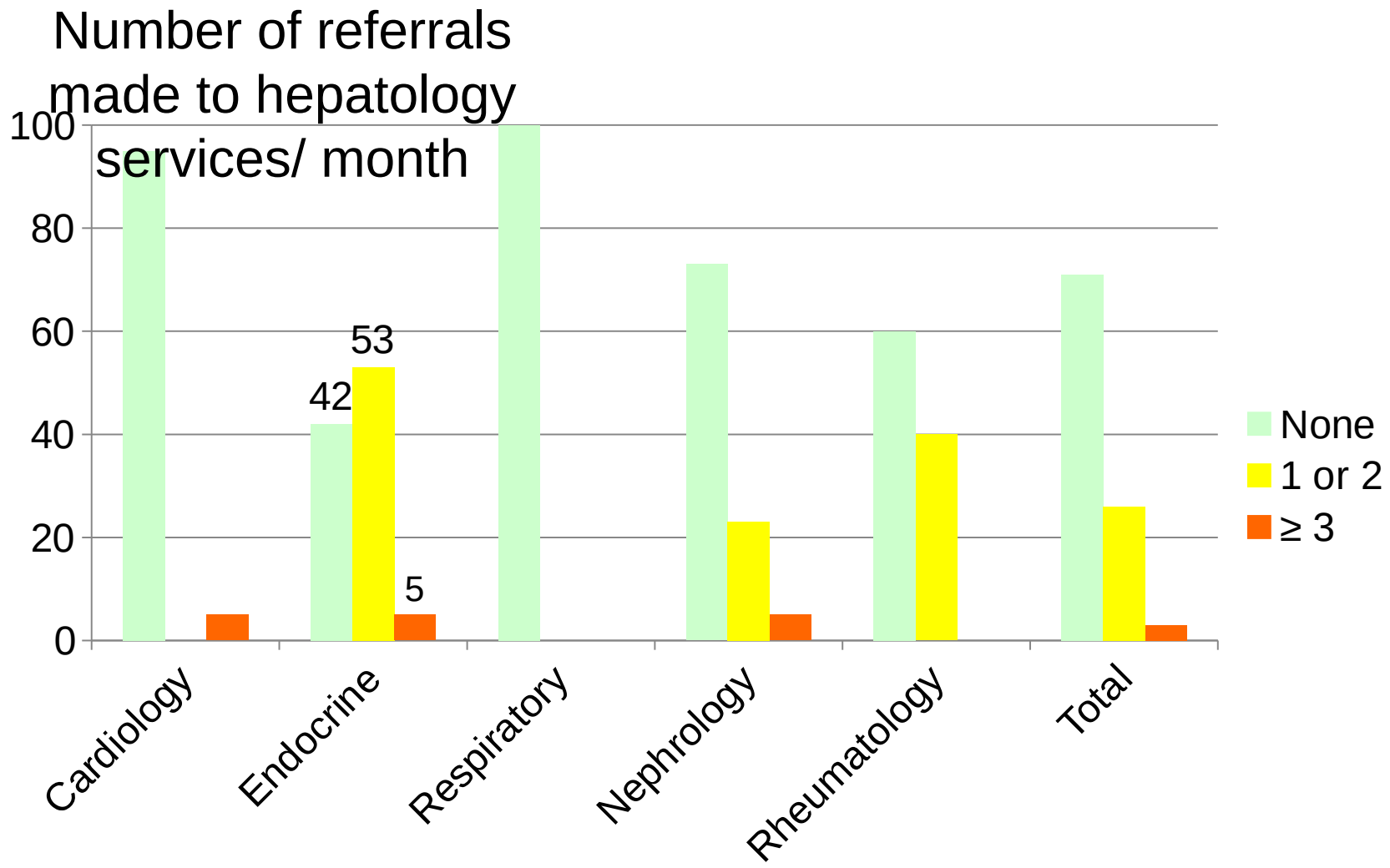
A minority of NAFLD patients are referred to the SP by a diabetologist

Practice survey among 352 French gastroenterologists



Ratziu V et al. J Hepatol 2012; 57: 376-83

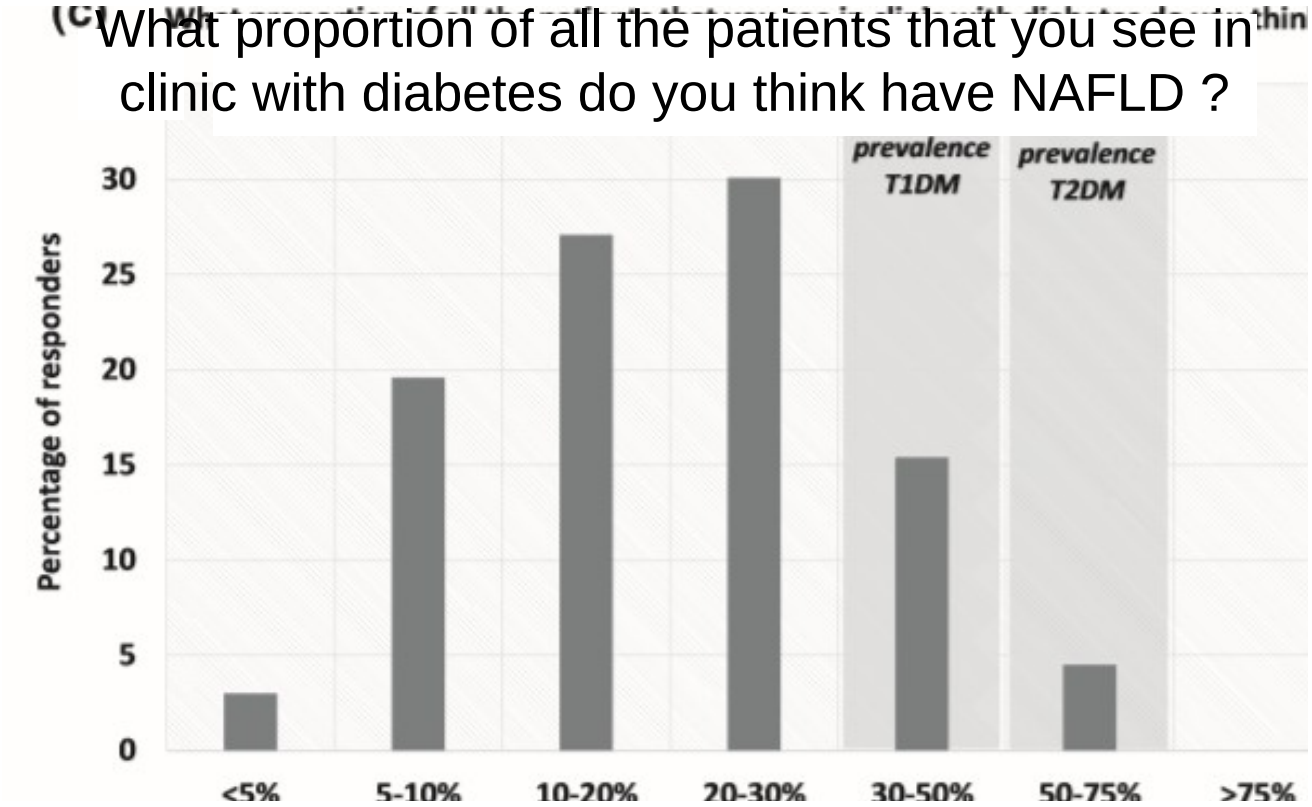
Referral practices among specialits



Bergqvist CJ et al. Intern Med J 2013; 43: 247-53

Prevalence and severity of NAFLD are underestimated among diabetologists

What proportion of all the patients that you see in clinic with diabetes do you think have NAFLD ?

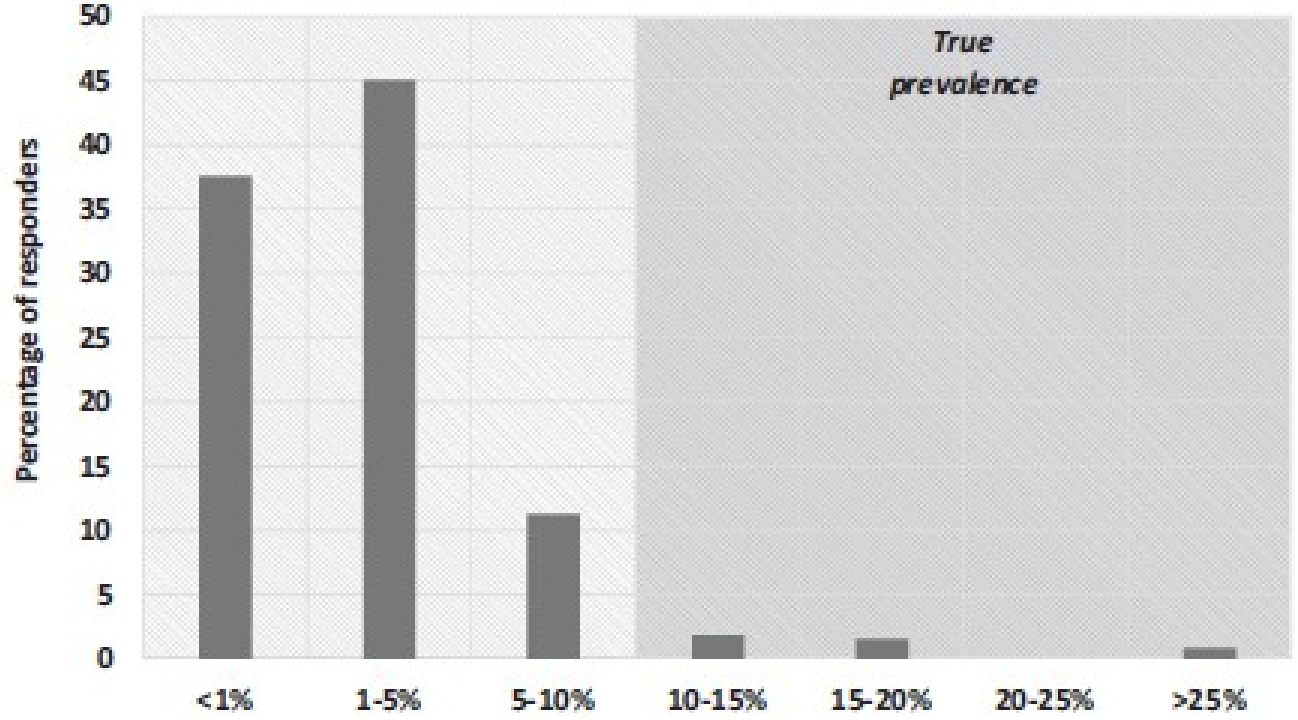


Less than 5 % of diabetogists give the right answer

Marjot T, et al. Diabetic medicine 2017

Prevalence and severity of NAFLD are underestimated among diabetologists

What proportion of all the patients that you see in clinic with diabetes do you think have advanced liver fibrosis or cirrhosis ?

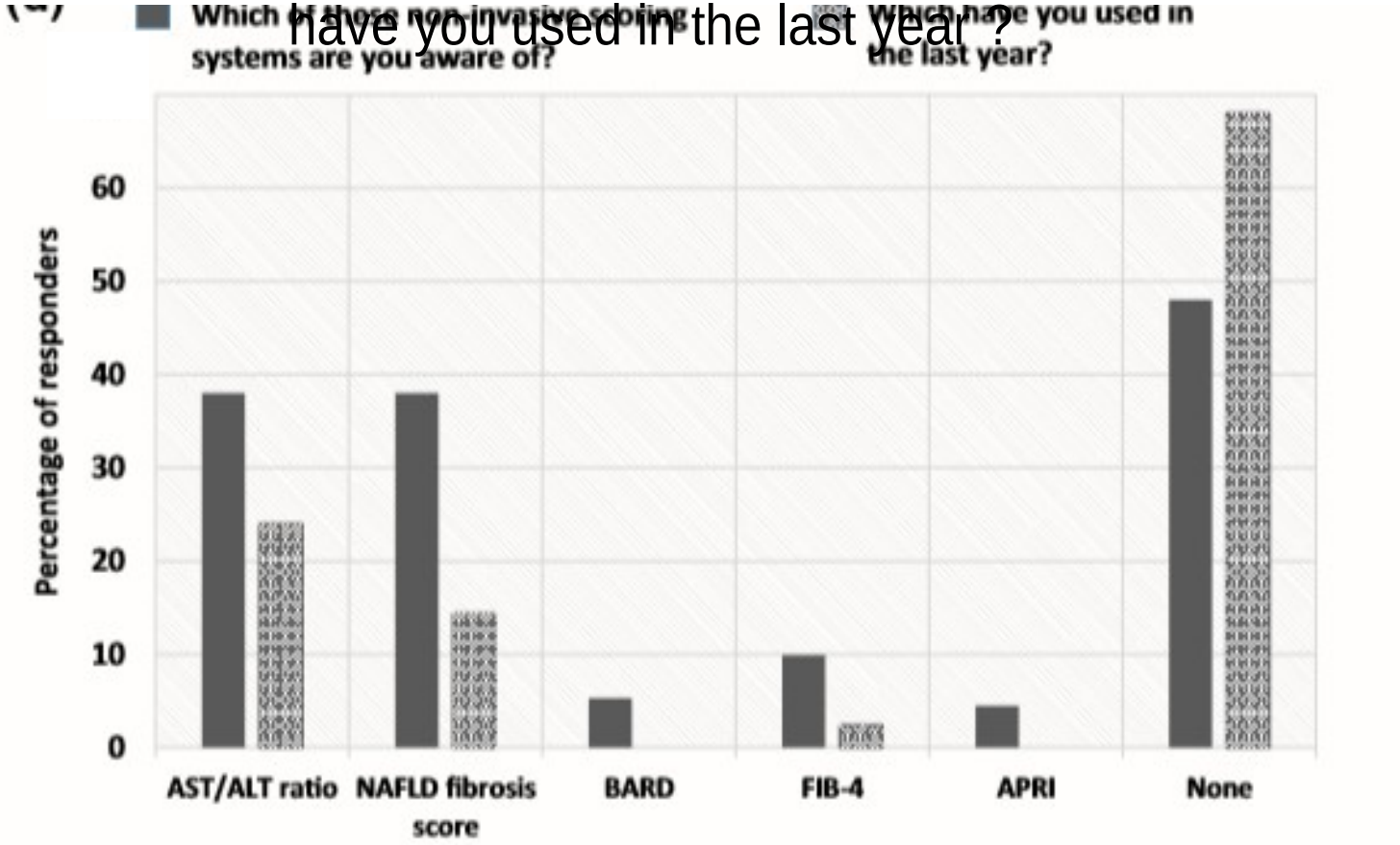


Less than 5 % of diabetogists give the right answer

Marjot T, et al. Diabetic medicine 2017

The use of non invasive methods by diabetologists

Which of these non-invasive scoring systemes have you used in the last year ?

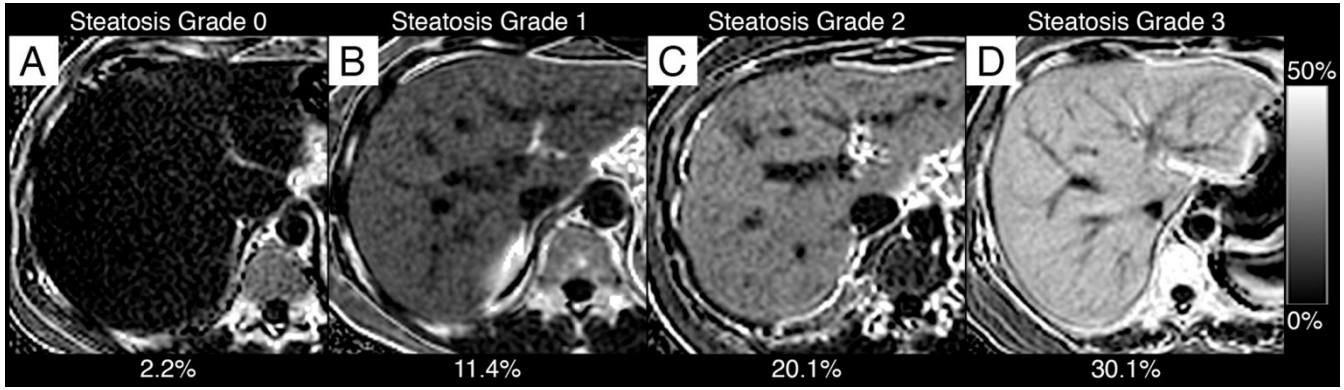


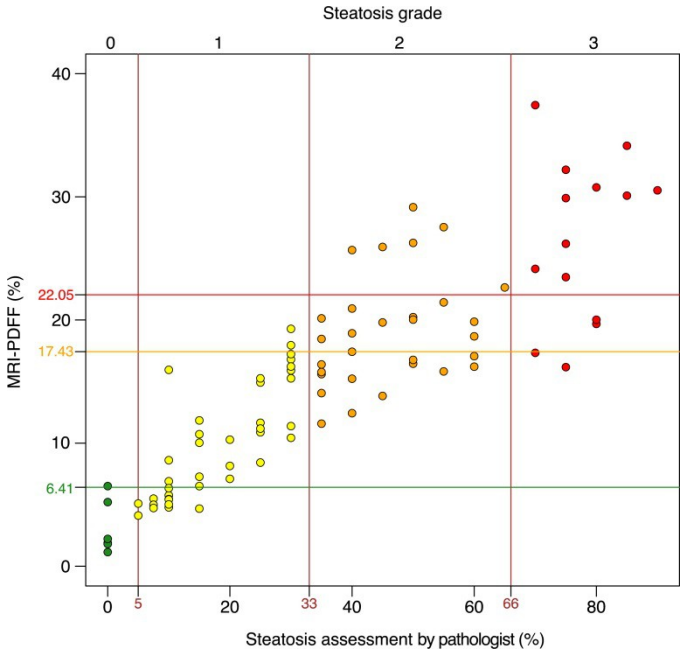
68 % of diabetologists had not used a non-invasive method to determine severity of disease.

Marjot T, et al. Diabetic medicine 2017

How to screen ?
The performance of non-invasive methods patients with type 2 diabetes

MR-based proton density fat fraction estimation of steatosis

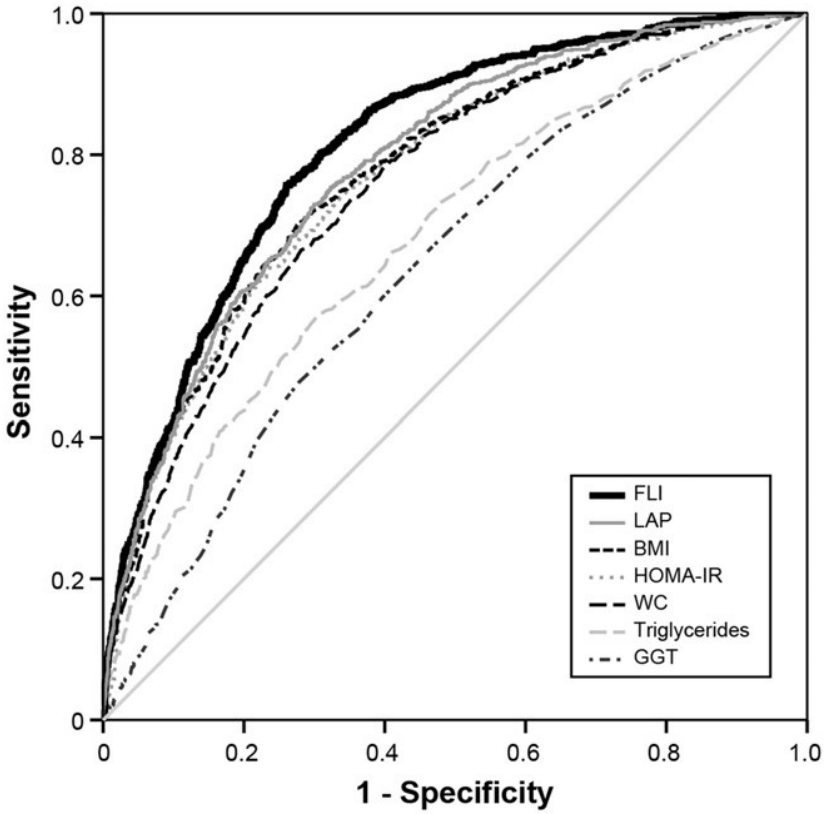




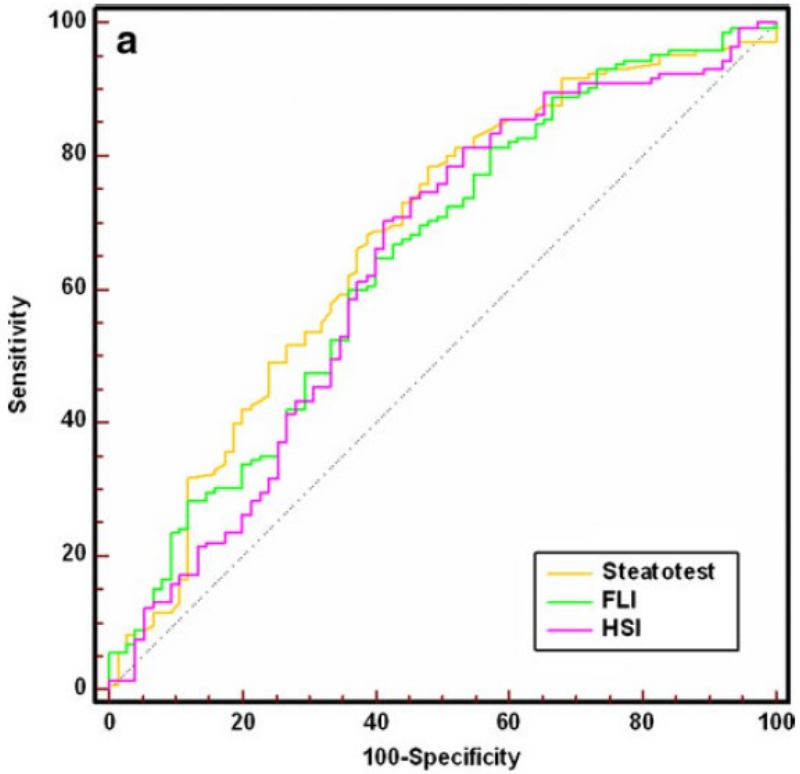
An Tang et al, Radiology, 2014

Biological tests for the prediction for steatosis

General population



T2D patients

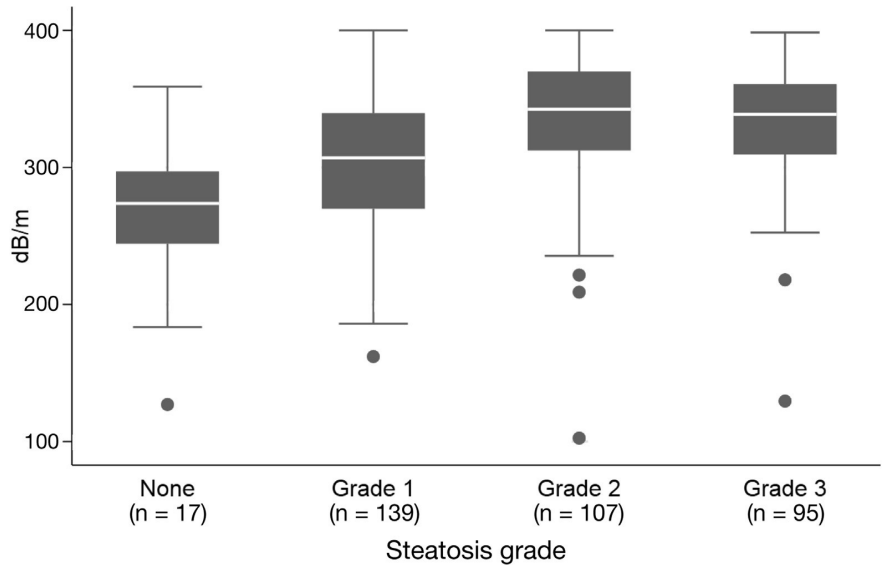


Koehler EM, et al. Clin Gastroenterol & Hepatol 2013

Guiu B, et al. Eur Radiol 2012

CAP for the prediction for steatosis

393 biopsy-proven NAFLD



AUROC 0.860.770.63

Metaanalysis

<u>Factors associated with dicrepencies between histological and CAP grading of steatosis</u>

BMI : *p<0.001*
Fibrosis staging : *p=0.98*
Diabetes : *p=0.48*

Siddiqui MS et al. Clin Gastroenterol & Hepatol 2019

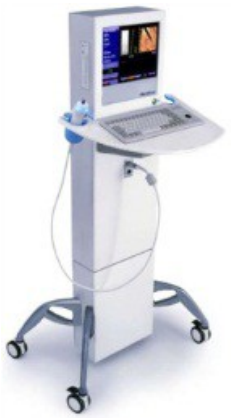
Karlas T et al. J Hepatol 2017

Non-invasive assessment of liver fibrosis

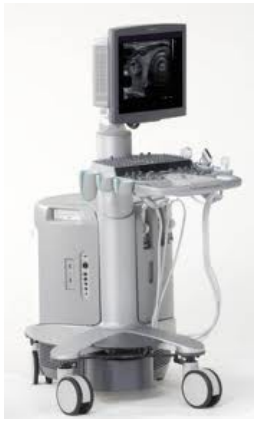
Blood tests

Generation	Characteristics	Virus	NAFLD
1st	Indirect markers Low cost Easy to calculate	APRI FIB4	FIB4 NAFLD Fibrosis Score
2nd	Indirect and/or direct markers Higher cost Computing calculation	Fibrotest Hepascore FibroMeterVirus	ELF FibroMeterNAFLD

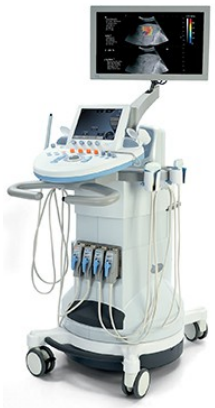
Elastography



Fibroscan



ARFI

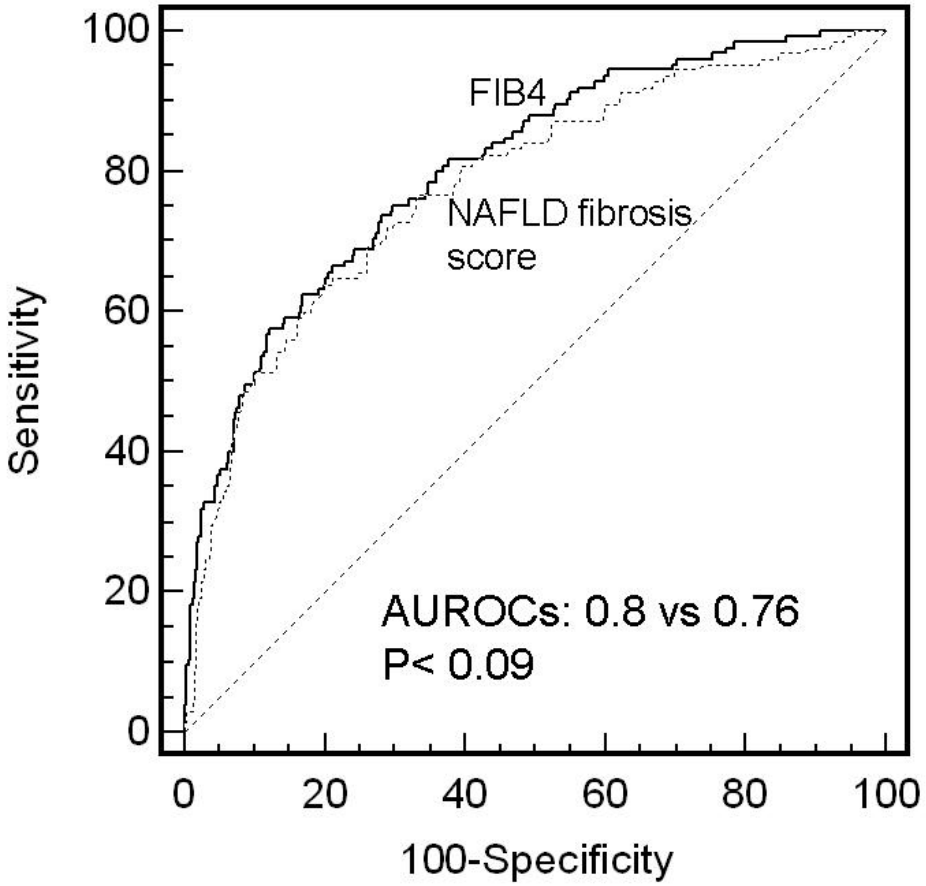


SSI

MRE
Magnetic Resonance Elastography

FIB-4: a first-line test to rule out patients with minimal fibrosis

ᵊge (yr) × AST (IU/L)/(platelet count (109/L) × √ALT (IU/L))



NPV=90%

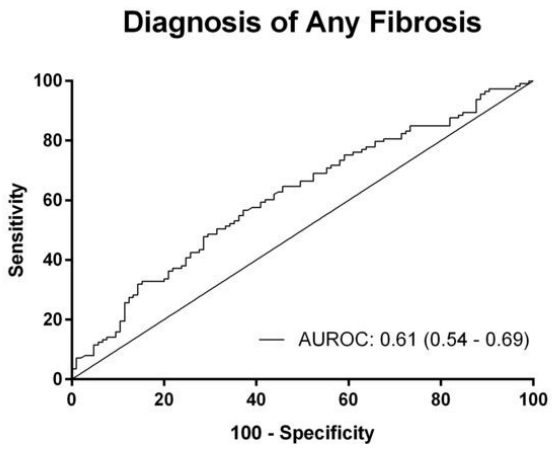
Shah et, Clin Gastroenterol Hepatol 2009

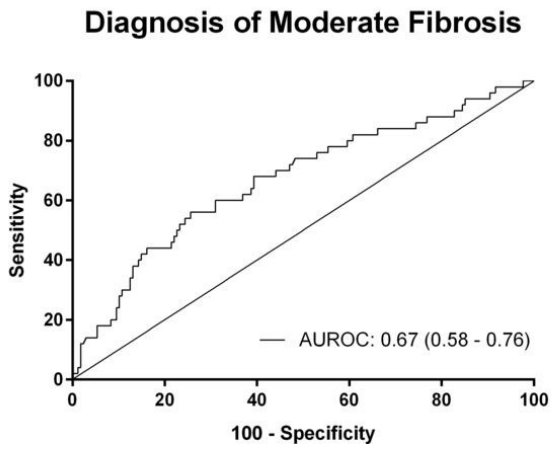
Performance of 1st line non invasive fibrosis test in T2D patients with NAFLD

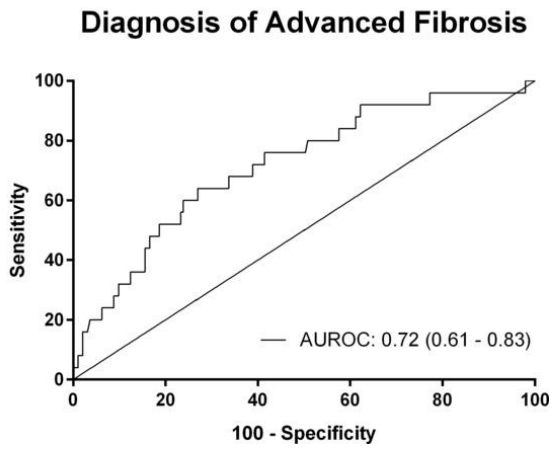
Overall AUC (95% CI)	Non-diabetics AUC (95% CI)	Diabetics AUC (95% CI)	Non-DM vs DM P value
0.87 (0.82 -0.92)	0.93 (0.89-0.98)	0.84 (0.77-0.91)	.03
0.82 (0.76-0.88)	0.87 (0.76-0.97)	0.79 (0.71-0.87)	.25
0.77 (0.70-0.83)	0.85 (0.75-0.95)	0.75 (0.66-0.83)	.13
0.72 (0.65-0.80)	0.70 (0.57-0.87)	0.67 (0.54-0.77)	.94
hosis)			
0.85 (0.78-0.93)	0.95 (0.91-0.99)	0.80 (0.69-0.90)	.005
0.86 (0.79-0.93)	0.96 (0.92-0.99)	0.80 (0.71-0.90)	.003
0.78 (0.70-0.86)	0.92 (0.85-0.98)	0.73 (0.63-0.83)	.002

Bertot LC, et al. Liver Int 2018

Performance of fibrotest in type 2 diabetic patients with biopsy proven NAFLD







Bril F, *et al*. *J Investig Med* 2018;

Liver stiffness measurement: factors associated with discordant results

Factors	M probe			XL probe		
	No discordance	Discordance	*P*	No discordance	Discordance	*P*
N	138	18		168	16	
Age (years)	50±11	49±12	0.72	52±12	49±11	0.44
Male gender	78 (57%)	15 (83%)	0.040	93 (55%)	12 (75%)	0.19
Body mass index (kg/m²)	27.5±3.7	31.8±5.1	<0.001	28.3±4.1	33.1±7.2	0.018
<30	109 (79%)	7 (39%)	<0.001	115 (69%)	7 (44%)	0.003
30–<35	24 (17%)	7 (39%)		42 (25%)	4 (25%)	
≥35	5 (4%)	4 (22%)		11 (7%)	5 (31%)	
Waist circumference (cm)	94±10	104±10	<0.001	96±11	103±13	0.032
<102	112 (81%)	8 (44%)	0.001	122 (73%)	8 (50%)	0.058
≥102	26 (19%)	10 (56%)		46 (27%)	8 (50%)	
Alanine aminotransferase (IU/l)	74±84	108±67	0.11	72±77	87±79	0.46
Type 2 diabetes	66 (48%)	10 (56%)	0.54	83 (49%)	9 (56%)	0.60
Hypertension	71 (51%)	9 (50%)	0.91	92 (55%)	6 (38%)	0.19
Metabolic syndrome	100 (73%)	18 (100%)	0.007	134 (76%)	11 (69%)	0.54
Length of liver specimen (mm)	24±6	25±4	0.69	24±6	23±4	0.38
Steatosis grade (1/2/3)	35/59/44 (25%/43%/32%)	2/9/7 (11%/50%/39%)	0.41	48/69/50 (29%/41%/30%)	2/6/7 (13%/38%/44%)	0.30

Wong V, et al. Am J Gastroenterol 2012

In summary

- Out of MRI, CAP is a good option to detect steatosis in T2D patients with suspected NAFLD
- FIB-4 should be the first line method to screen T2D patients for NASH
- Fibroscan as second line for detection of advanced fibrosis

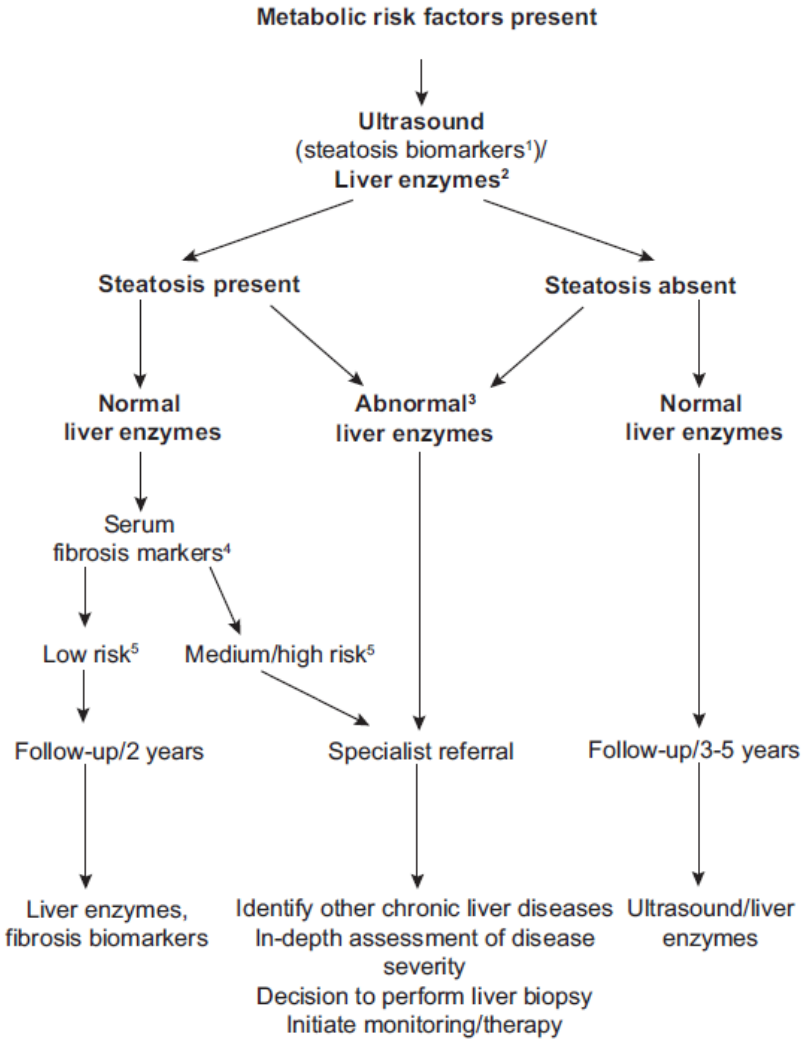
Which T2D patients to refer to a liver clinic ?

Discrepancy between European and American guidelines

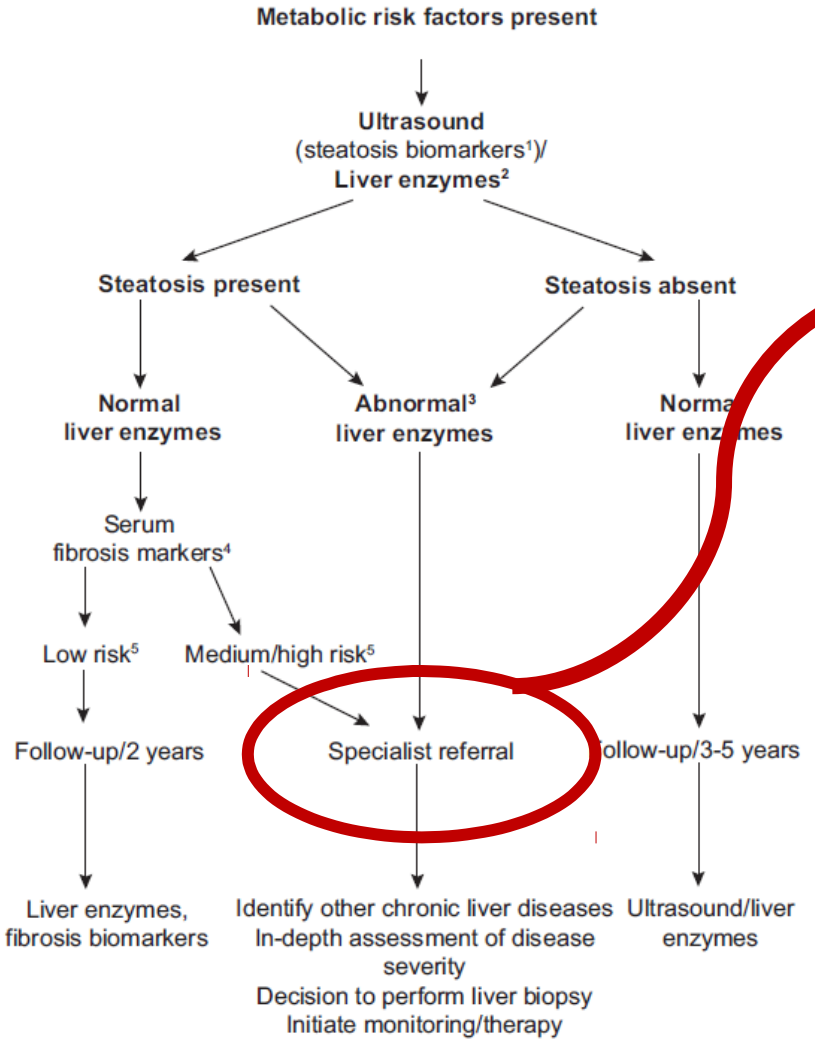
- The 2018 AASLD guidelines recommend against population screening (poor evidence for longer-term benefits and cost-effectiveness)

- The 2016 European clinical practice guidelines suggest screening patients older than 50 years with type 2 diabetes or metabolic syndrome for NAFLD

Application of the EASD-EASL-ESO guidelines

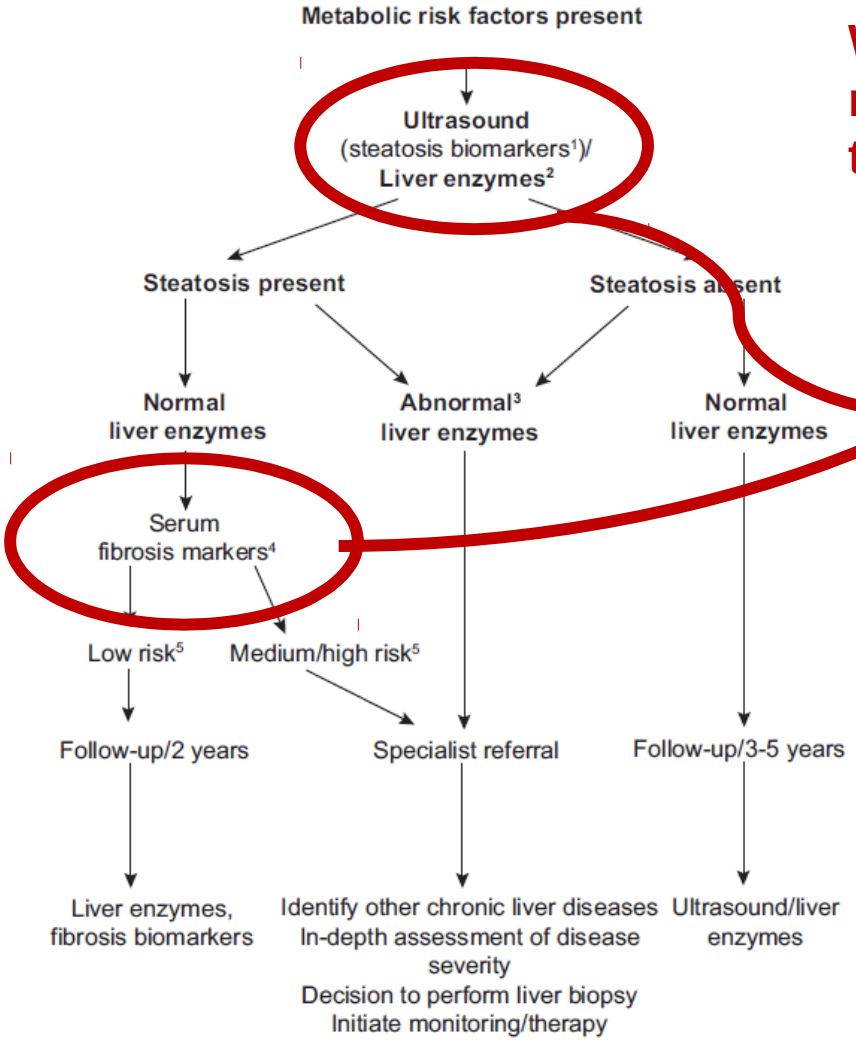


Application of the EASD-EASL-ESO guidelines



How many patients would be referred to a liver clinic ?

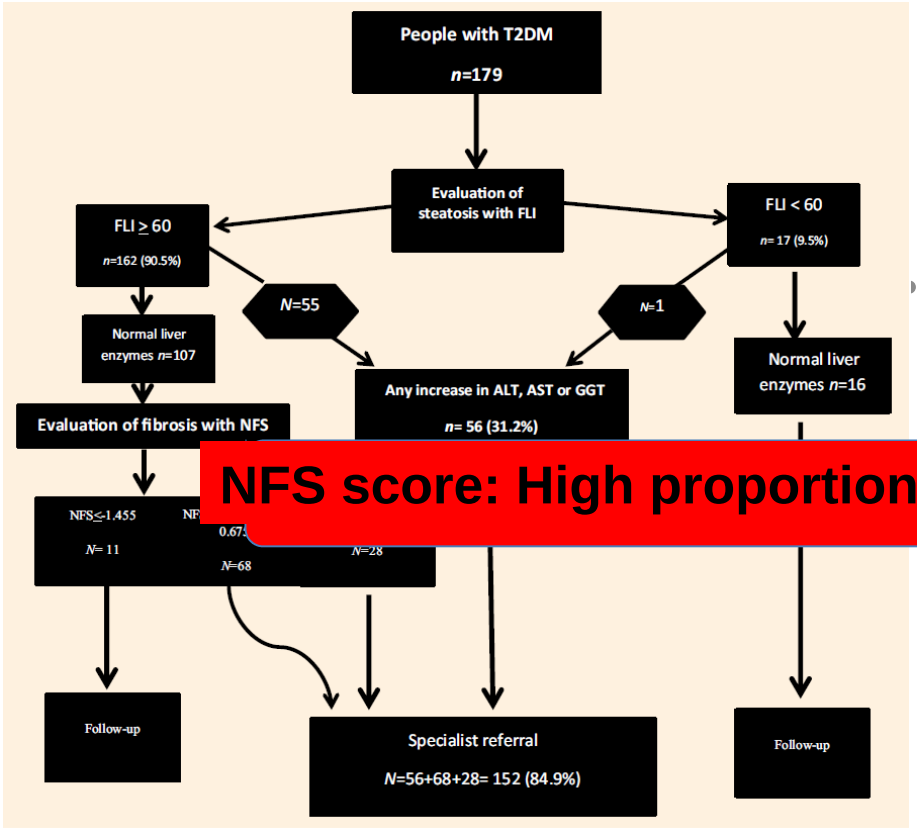
Application of the EASD-EASL-ESO guidelines

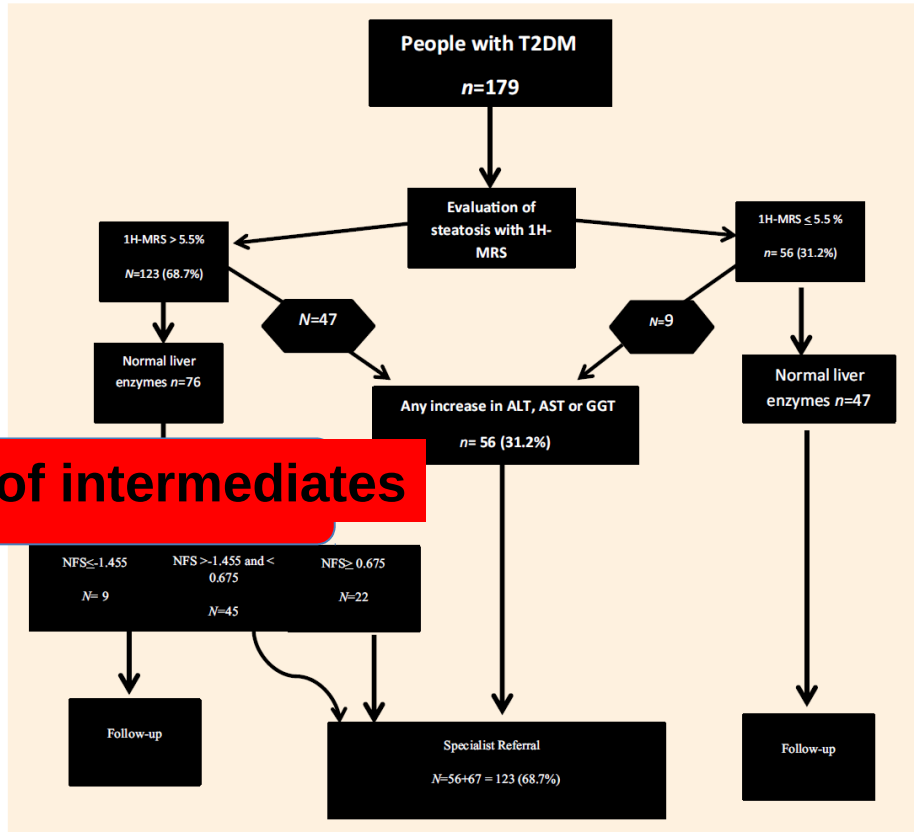


What is the impact of non invasive method that is used ?

The application of the European guidelines resulted in a referral to more than two-third people with T2D

- FLI + Nafld fibrosis score = **84,9 %**



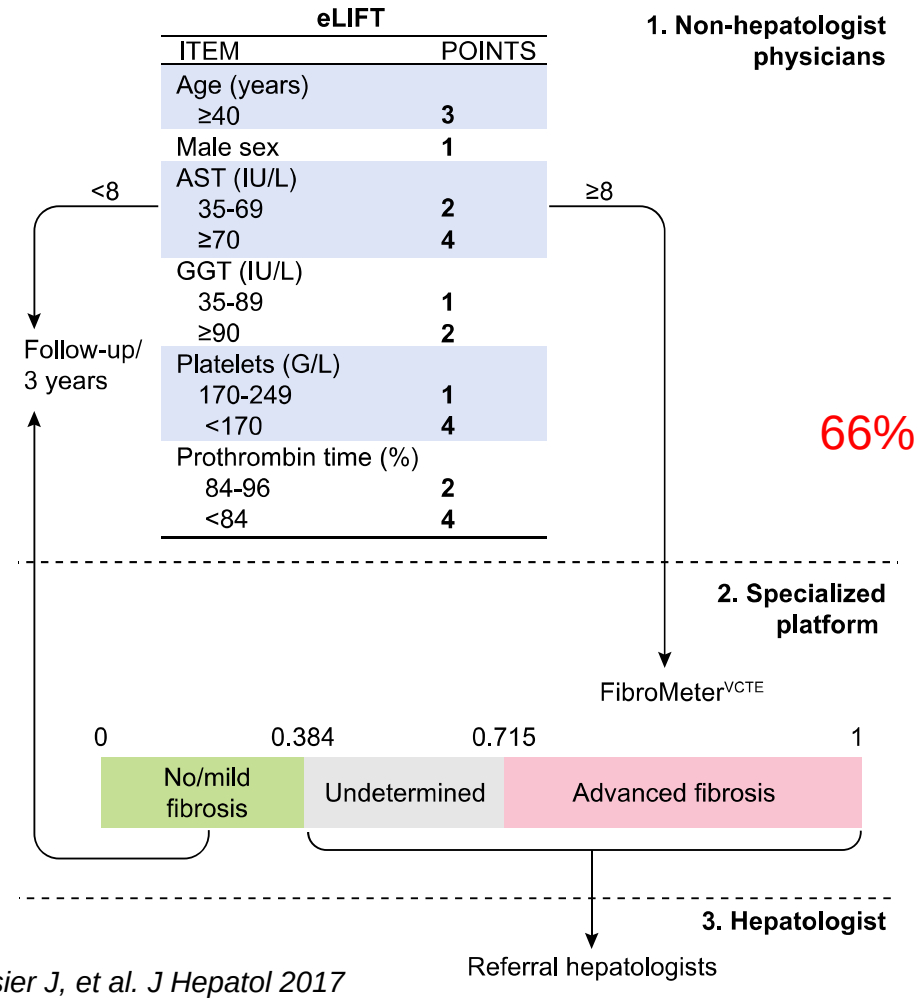


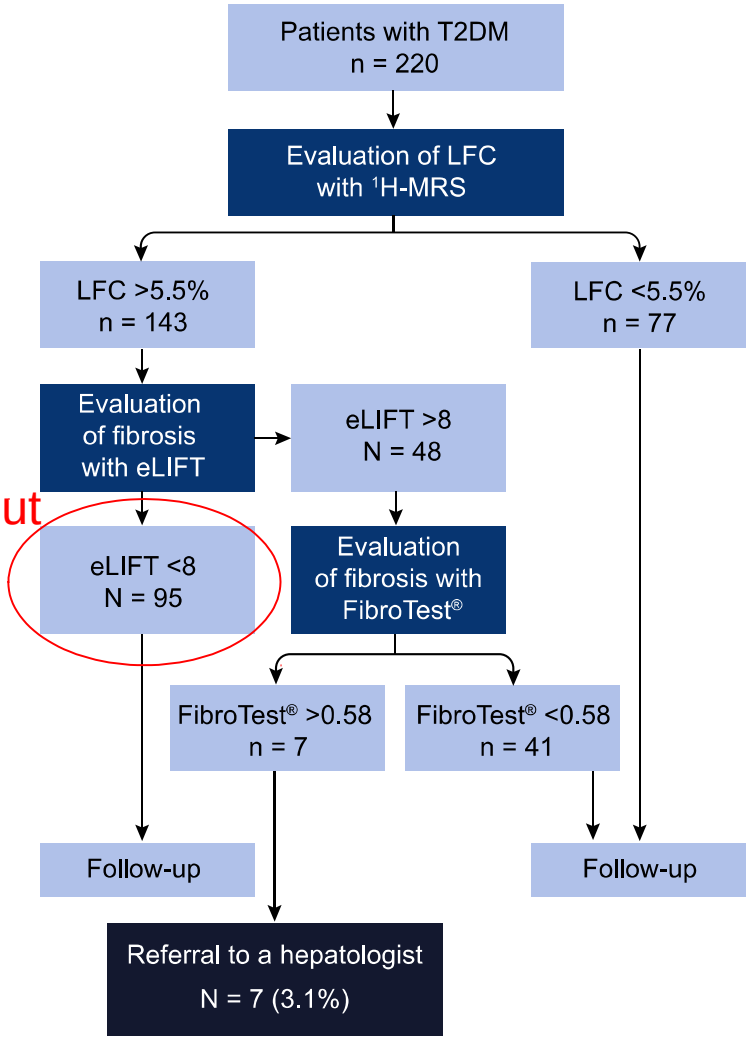
NFS score: High proportion of intermediates

Sberna AL et al. Diab Med 2018

Application of eLIFT algorithm in T2D

eLIFT-FM algorithm

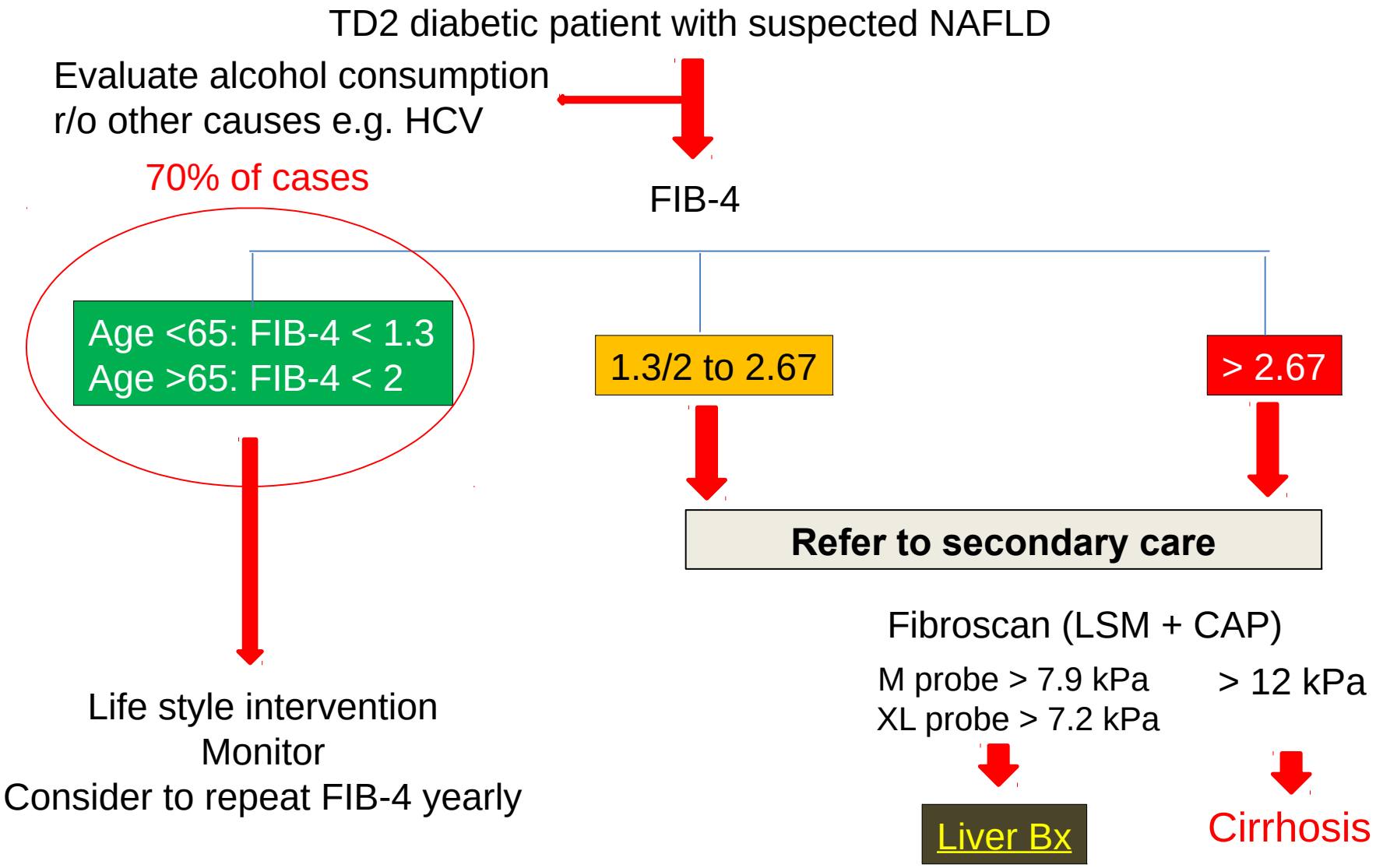




Boursier J, et al. J Hepatol 2017

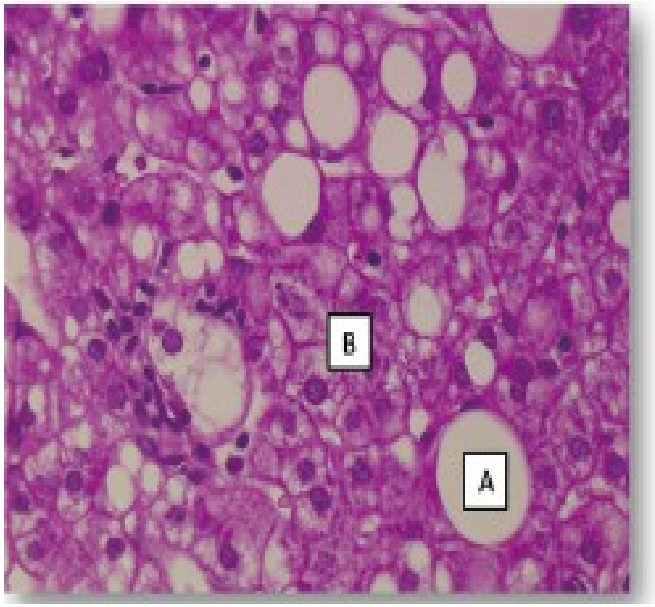
Petit JM, et al. J Hepatol 201

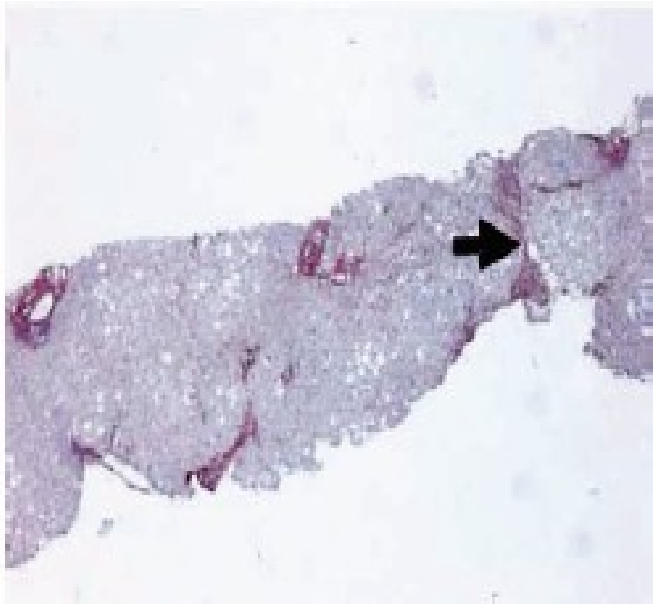
In summary: Triage and Risk stratification



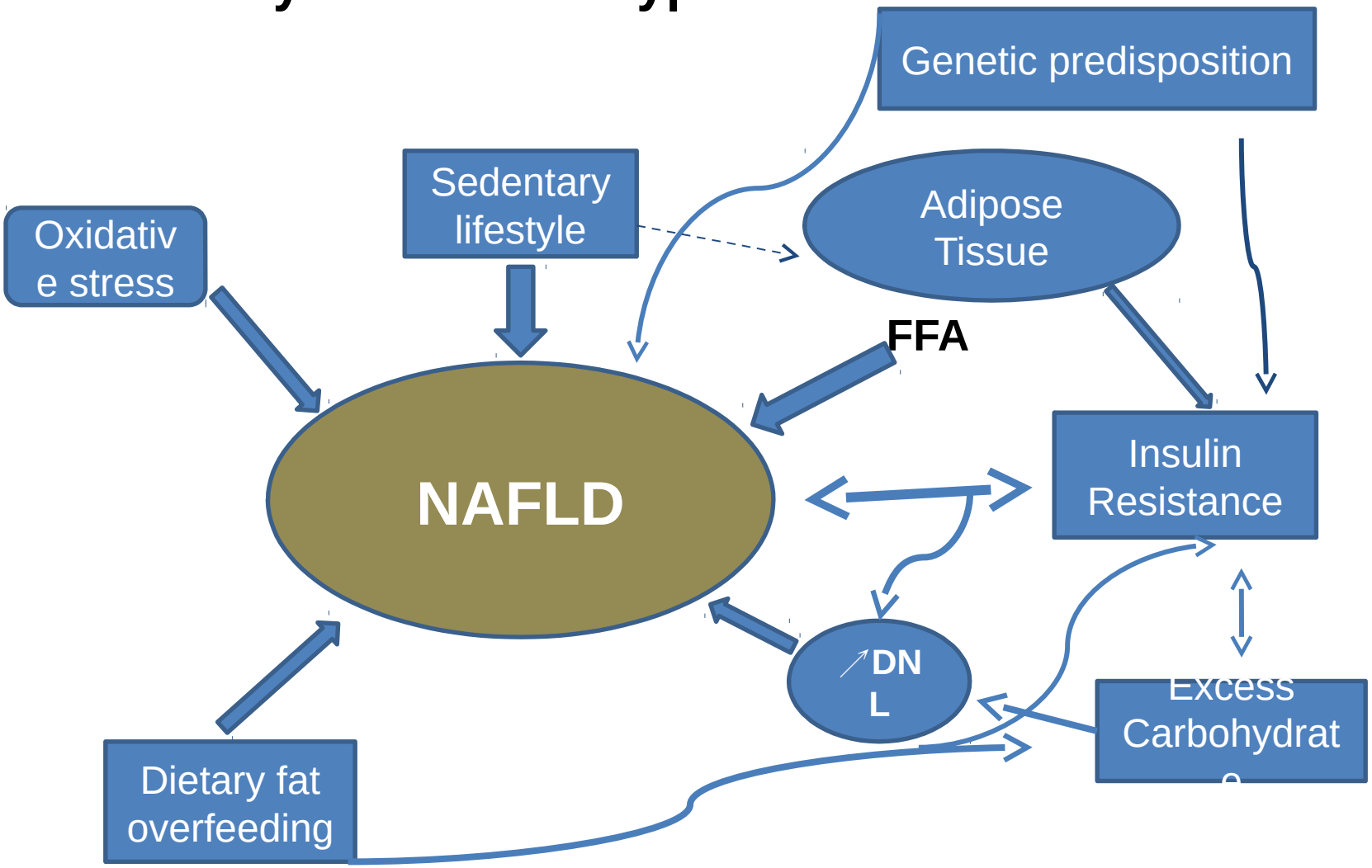
Clinical case

- FIB-4= 3
- Fibroscan= 9.2 kPa
- LB: NAS score= 6, Fibrosis F2



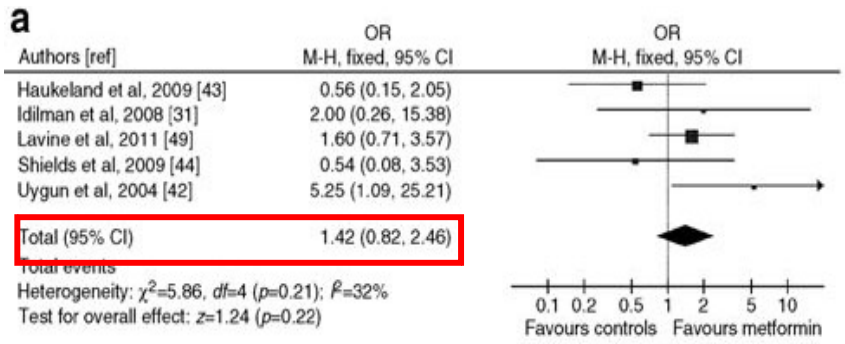


NAFLD shares common features with metabolic syndrome and type 2 diabetes

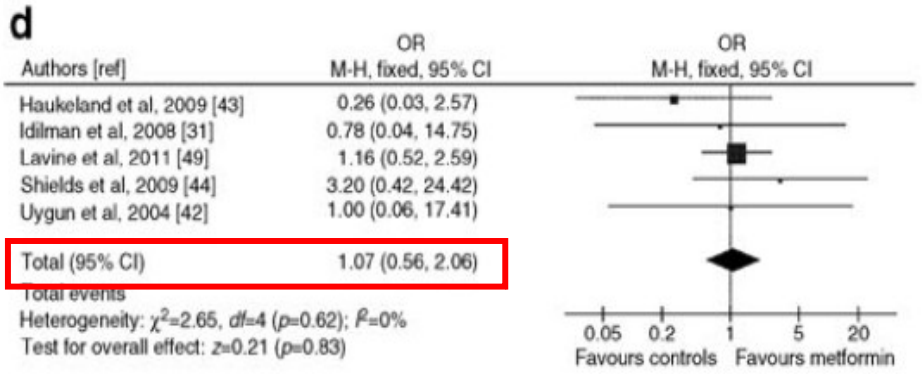


Metformin

No effect on steatosis

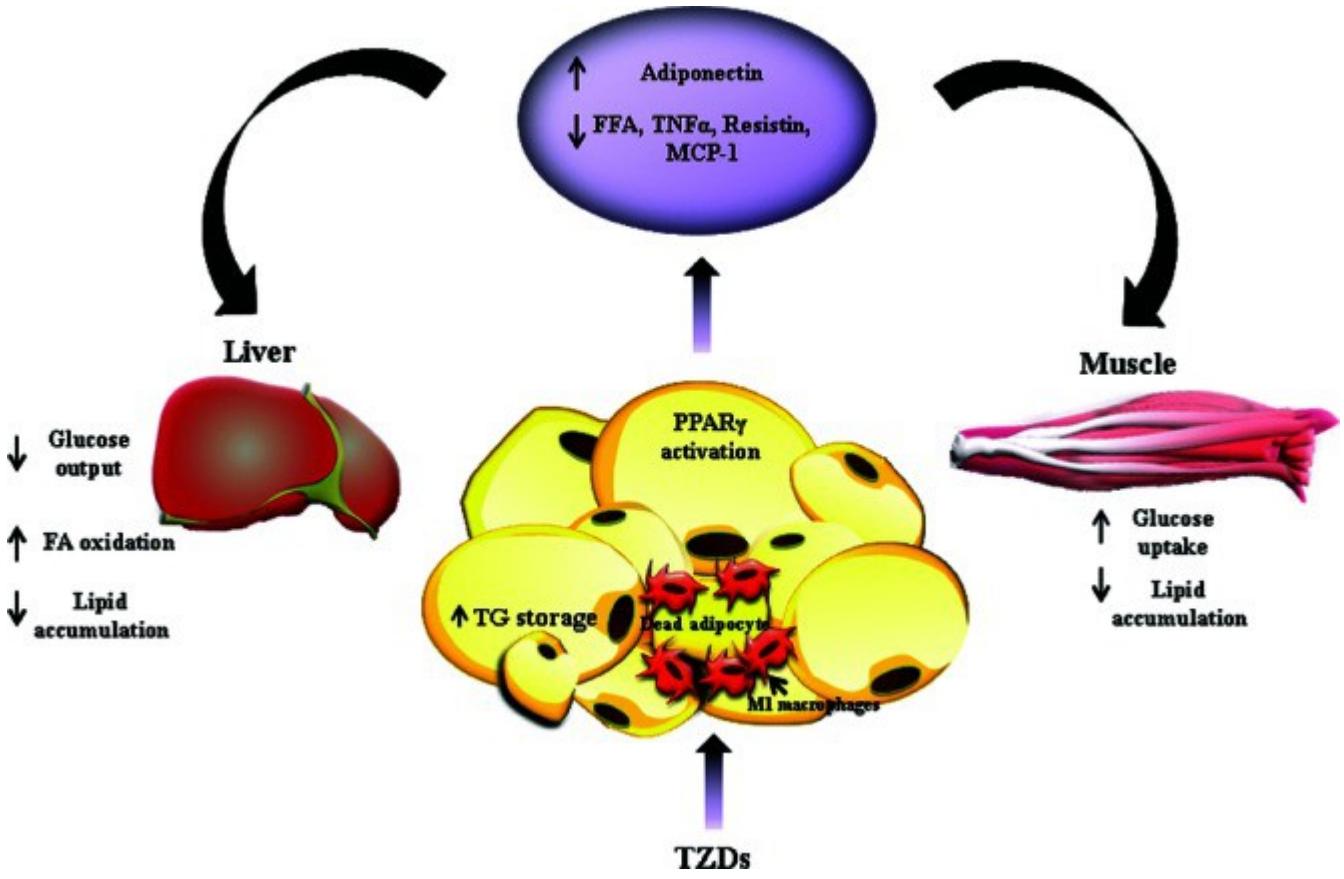


No effect on fibrosis



Musso *Diabetologia* 2012

TZD actions in vivo in human



Feng B et al Ann N Y Acad Sci. 2013; 1281: 160–177.

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

Table 2. Effect of 18 mo of Pioglitazone Treatment on Primary and Secondary Liver Histologic Outcomes*

Outcome	Placebo (n = 51)	Pioglitazone (n = 50)	Treatment Difference (95% CI)	P Value
Primary outcome				
≥2-point reduction in NAS (in 2 categories) without worsening of fibrosis, *n (%)*	9 (17)	29 (58)	41 (23 to 59)	<0.001
Secondary outcomes				
Resolution of NASH, *n (%)*†	10 (19)	26 (51)	32 (13 to 51)	<0.001
Steatosis				
≥1-point improvement, *n (%)*	13 (26)	35 (71)	44 (25 to 63)	<0.001
Mean change in score (SD)	−0.2 (0.8)	−1.1 (1.0)	−0.9 (−1.3 to −0.5)	<0.001
Inflammation				
≥1-point improvement, *n (%)*	11 (22)	25 (49)	27 (8 to 46)	0.004
Mean change in score (SD)	−0.1 (0.8)	−0.6 (0.9)	−0.6 (−0.9 to −0.2)	<0.001
Ballooning				
≥1-point improvement, *n (%)*	12 (24)	25 (51)	27 (7 to 47)	0.004
Mean change in score (SD)	−0.2 (0.7)	−0.6 (0.6)	−0.4 (−0.7 to −0.2)	0.001
Fibrosis				
≥1-point improvement, *n (%)*	13 (25)	20 (39)	14 (−6 to 34)	0.130
Mean change in score (SD)	0 (1.2)	−0.5 (1.0)	−0.5 (−0.9 to 0)	0.039

NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis.
* Multiple imputation was used to impute missing histologic data for patients who did not complete 18 mo of therapy (**Appendix**). Numbers of patients may not always seem to match the proportion because they were estimated from the combination of 40 imputed data sets.
† Defined as absence of NASH after 18 mo of therapy in patients with definite NASH at baseline.

Cusi K et al *Ann Intern Med.* 2016;165:305-315

Response to Pioglitazone in Patients With Nonalcoholic Steatohepatitis With vs Without Type 2 Diabetes

Fernando Bril,[*,‡] Srilaxmi Kalavalapalli,[*] Virginia C. Clark,[§] Romina Lomonaco,[*,‡] Consuelo Soldevila-Pico,[§] I-Chia Liu,[*] Beverly Orsak,[‖] Fermin Tio,[¶,#] and Kenneth Cusi[*,‡]

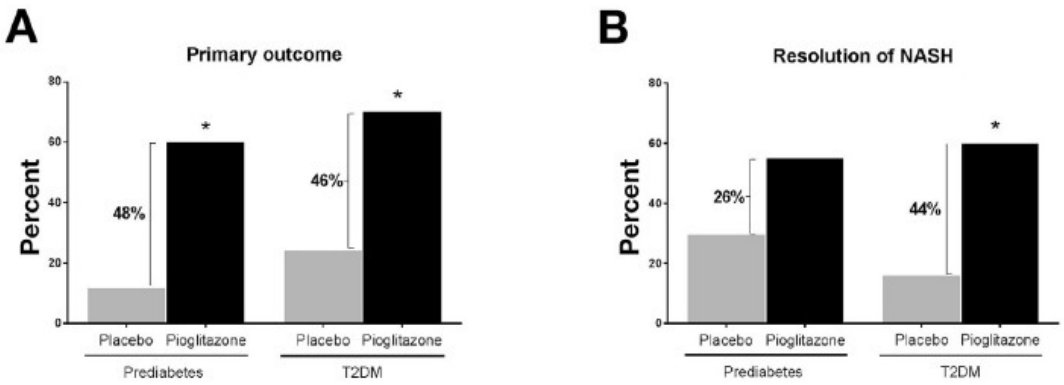
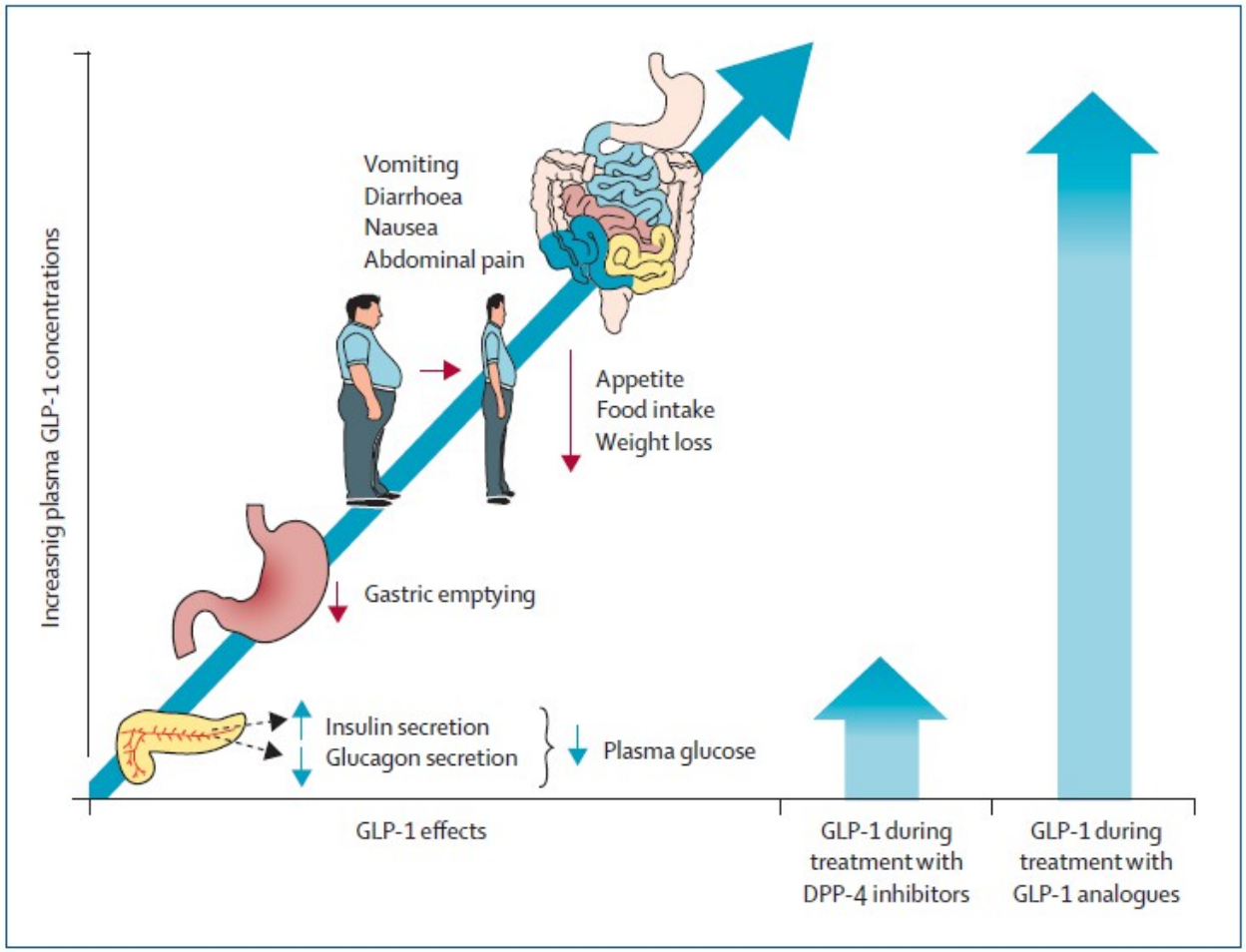


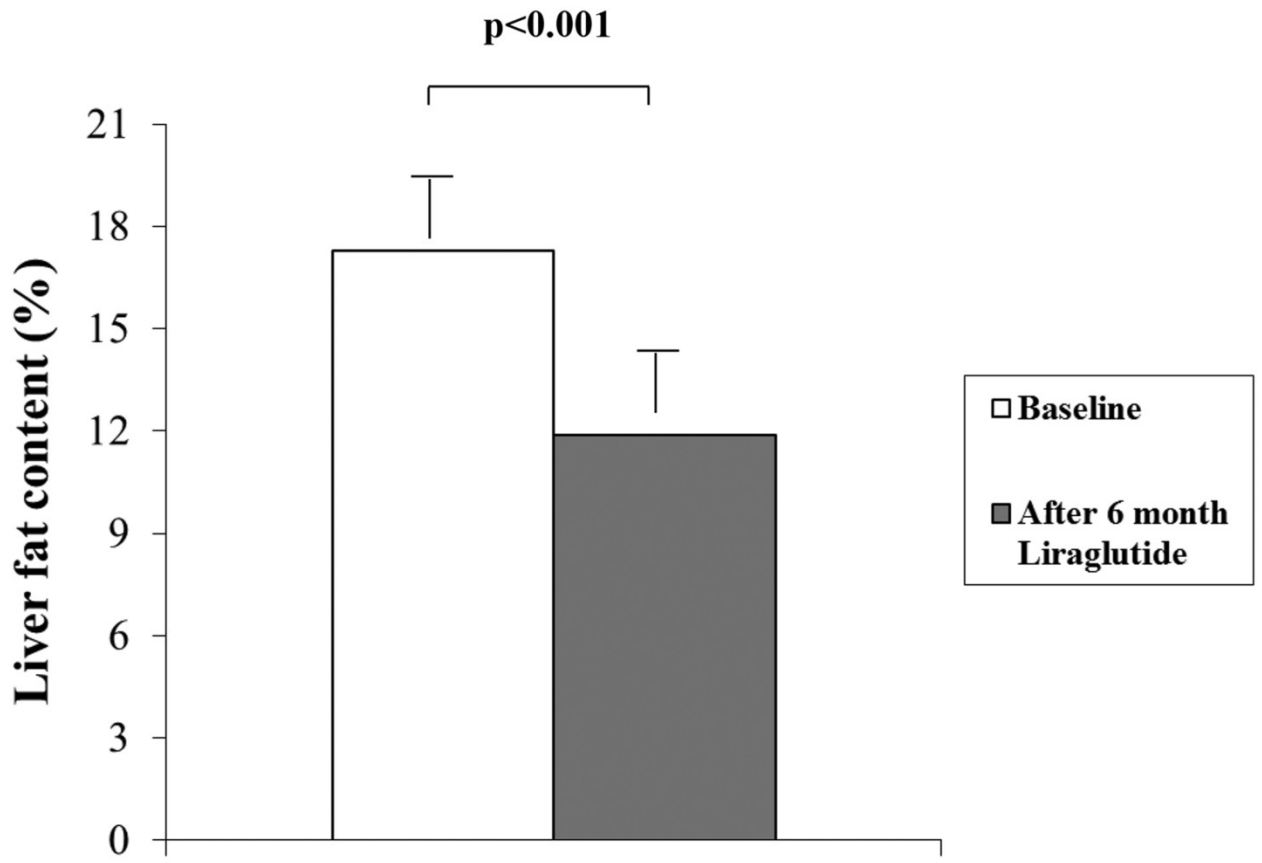
Figure 1. Histologic response after 18 months of pioglitazone therapy among patients with prediabetes vs T2DM. The primary outcome was improvement in the nonalcoholic fatty liver disease activity score ≥2 points (with improvement of at least 2 different parameters) without worsening of fibrosis. *$P < .05$ compared with baseline.

Effects of GLP1



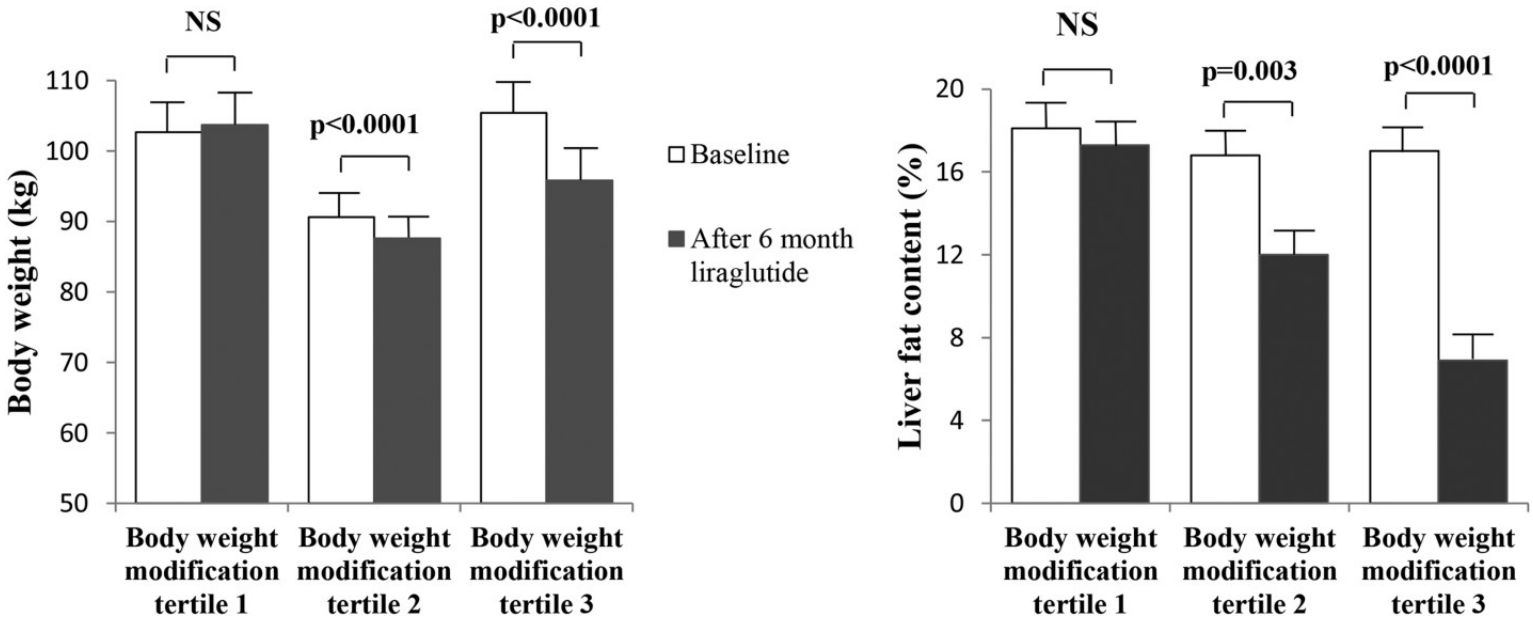
Madsbad S Lancet 2009

Effect of Liraglutide Therapy on Liver Fat Content in Patients With Inadequately Controlled Type 2 Diabetes: The Lira-NAFLD Study



Petit JM et al J Clin Endocrinol Metab. 2016;102(2):407-415.

Effect of Liraglutide Therapy on Liver Fat Content in Patients With Inadequately Controlled Type 2 Diabetes: The Lira-NAFLD Study

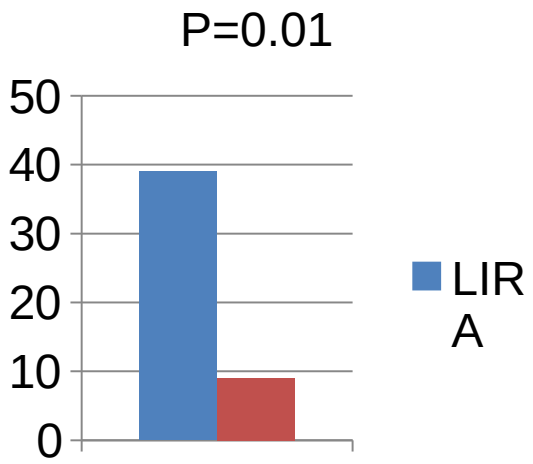


Petit JM et al J Clin Endocrinol Metab. 2016;102(2):407-415.

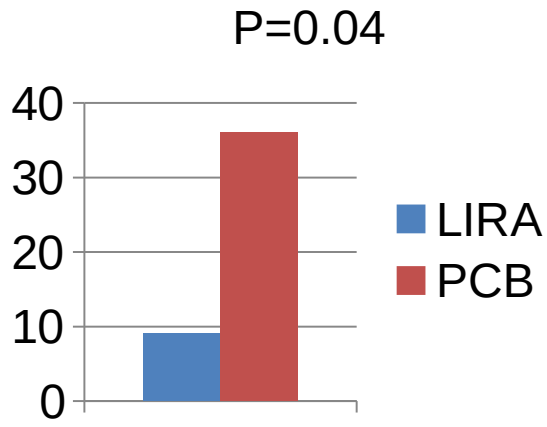
Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study

Matthew James Armstrong, Piers Gaunt, Guruprasad P Aithal, Darren Barton, Diana Hull, Richard Parker, Jonathan M Hazlehurst, Kathy Guo, LEAN trial team, George Abouda, Mark A Aldersley, Deborah Stocken, Stephen C Gough, Jeremy W Tomlinson, Rachel M Brown, Stefan G Hübscher, Philip N Newsome*

- 23 patients with NASH treated by liraglutide 1.8 mg daily 48 weeks vs 22 PCB
- 1/3 of patients with T2DM



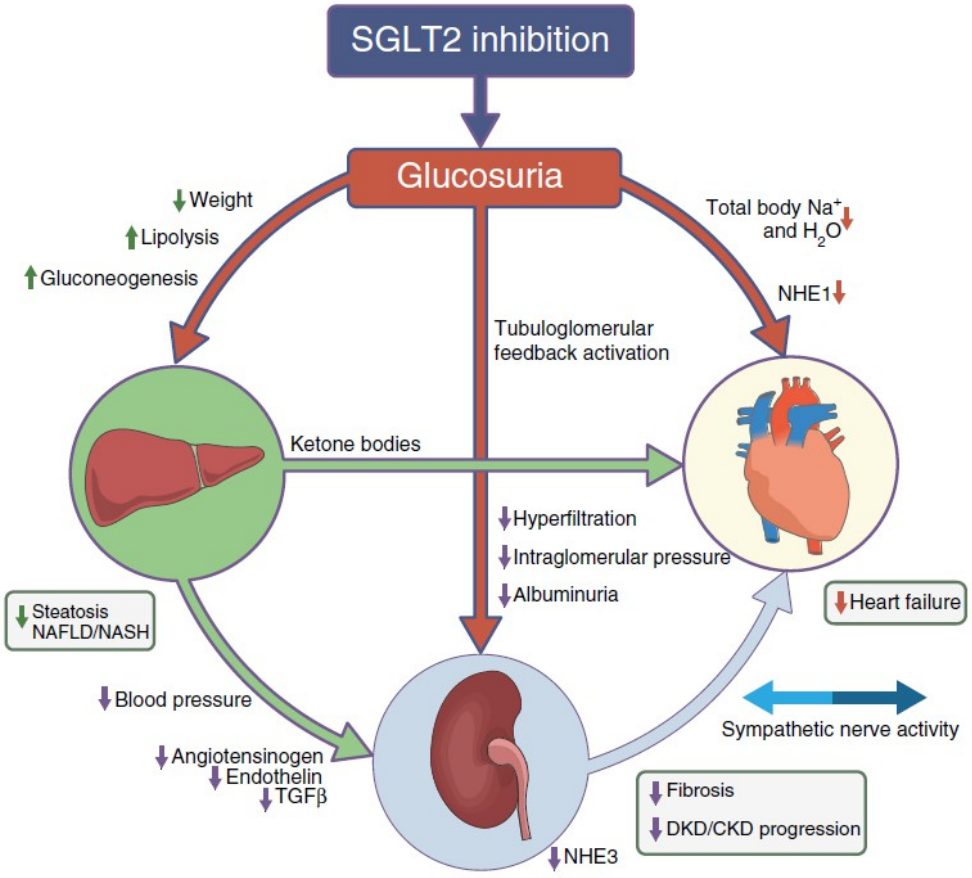
Percentage of patients with resolution of NASH



Percentage of patients with worsening fibrosis stage

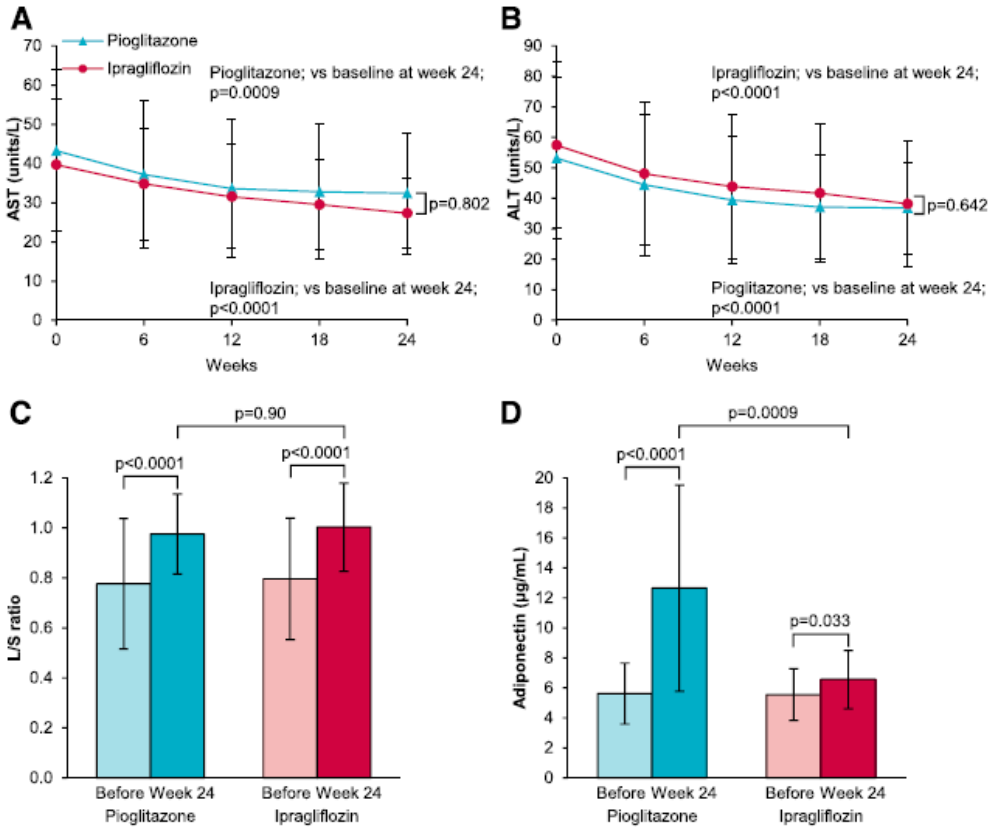
Lancet 2016

SGLT2 inhibition and NAFLD



Wanner and Marx Diabetologia (2018) 61:2134-2139

Comparison of Ipragliflozin and Pioglitazone effect on NAFLD in patients with T2DM



Ito D et al. Diabetes Care 2017; 40:1364-72

Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial)

Mohammad Shafi Kuchay,[1] Sonal Krishan,[2] Sunil Kumar Mishra,[1] Khalid Jamal Farooqui,[1] Manish Kumar Singh,[3] Jasjeet Singh Wasir,[1] Beena Bansal,[1] Parjeet Kaur,[1] Ganesh Jevalikar,[1] Harmendeep Kaur Gill,[1] Narendra Singh Choudhary,[4] and Ambrish Mithal[1]

Diabetes Care 2018;41:1801–1808 | https://doi.org/10.2337/dc18-0165

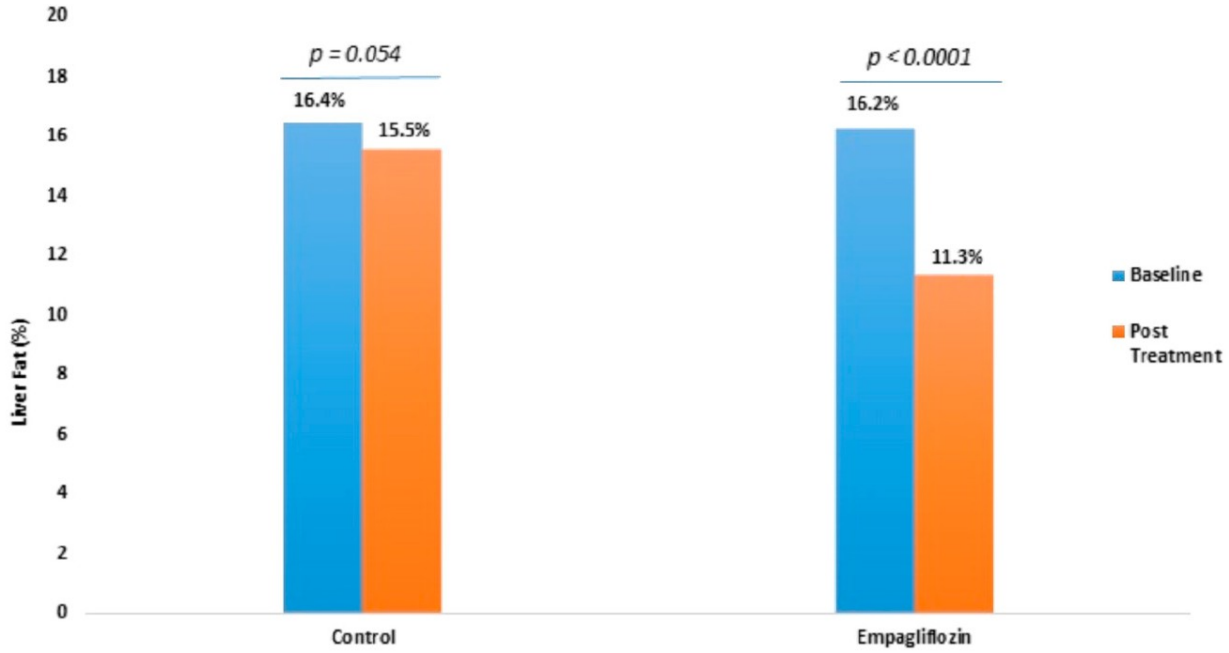
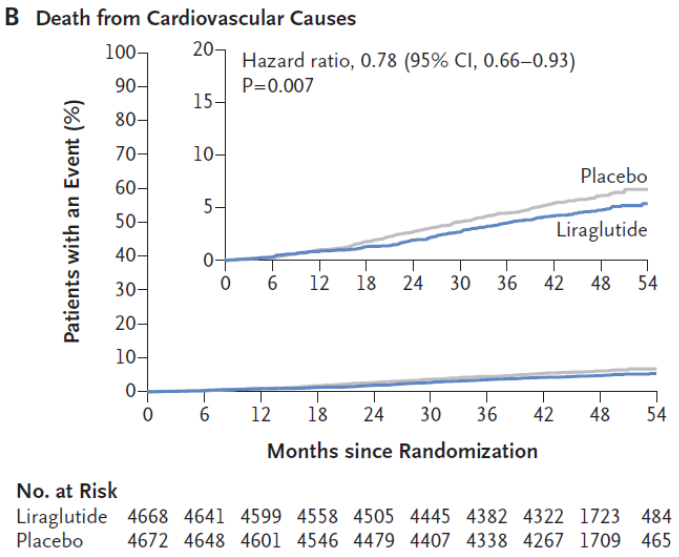


Figure 2—Baseline and posttreatment changes in liver fat in the empagliflozin and control groups as assessed by MRI-PDFF. Change in liver fat relative to baseline as assessed by MRI-PDFF. A significant difference was found in change in liver fat between the study groups ($P < 0.0001$).

Clinical case

- For this patients we decided to introduce a treatment by GLP1 analogues.

- objectives:
  - Improvement of HbA1C
  - Reduction of body weight
  - Improvement liver function
  - Past medical history of MI



Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Marso S et al. N Engl J Med. 2016 Jul 28;375(4):311-22

6 years later this patient developed cirrhosis

- Questions:
  - How does the diagnosis of cirrhosis affect diabetes management ?

Particularities of the management of diabetes in a patient with cirrhosis

- diagnosis and evaluation of glycemic control
- Antidiabetic drugs and hepatic impairment
- risk of hypoglycemia
- avoid aggravating undernutrition with diabetes treatment

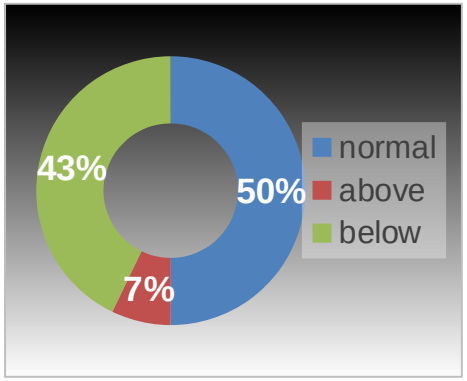
Diagnosis and evaluation of glycemic control

the diagnosis of diabetes is more difficult in patients with cirrhosis

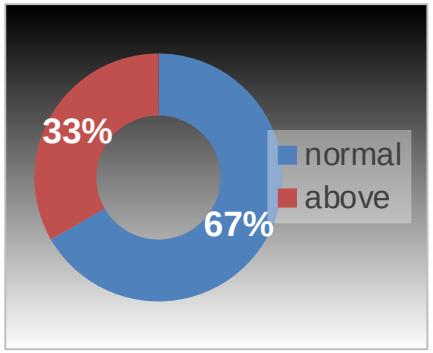
23.2% of patients with cirrhosis with glycemia in normal range had diabetes during OGTT

(Nishida T - A J Gastroenterol 2006)

HbA1c is falsely lowered in patients with cirrhosis



HbA1c

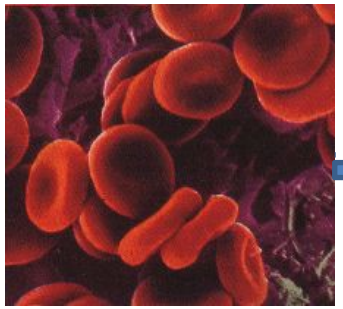


fructosamine

Lahousen et coll- World J Gastroeterology 2004

Measurement of glycated haemoglobin and fructosamine do not accurately reflect glycaemic status in patients with cirrhosis

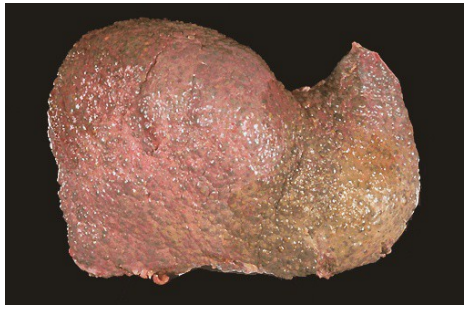
decrease of the lifespan of red blood cells



HbA1c falsely lowered

Anemia
Portal hypertension
Hemolysis
Nutritional deficiencies

increase in protein residence time



Decrease protein synthesis

Increase residence time

Increase protein glycation

↗ fructosamine

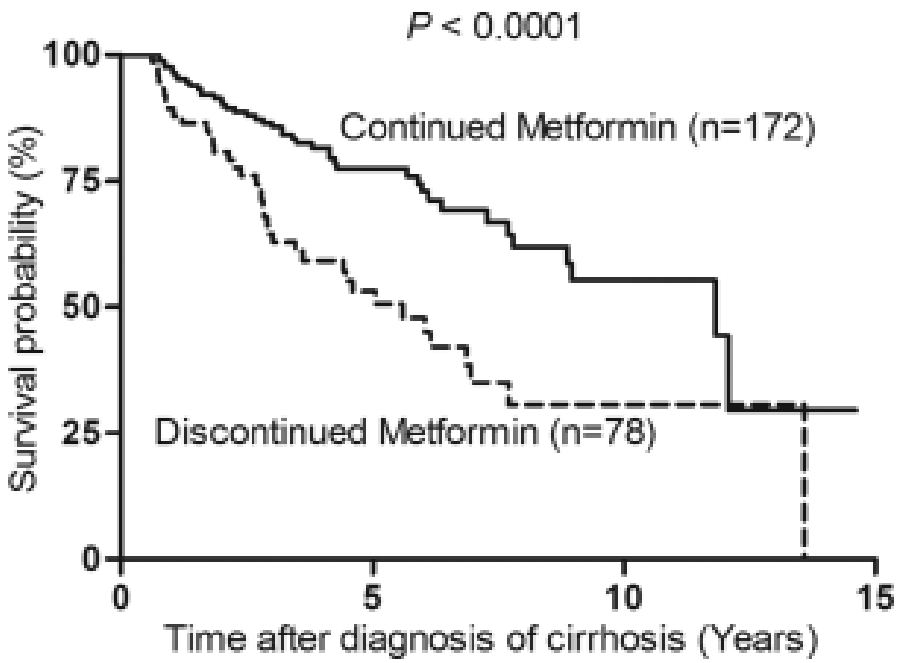
Glucose-lowering agents in diabetic patients with various degrees of hepatic impairment

Table 4. Clinical practice recommendations regarding the use of glucose-lowering agents in diabetic patients with various degrees of hepatic impairment (HI).

Medications	Mild HI	Moderate HI	Severe HI	Feared adverse event
Biguanides				
Metformin	Yes*	Caution	No use	Lactic acidosis§
Sulfonylureas				
Glibenclamide (glyburide), glimepiride, glipizide, gliclazide, gliquidone	Yes	Caution	No use	Hypoglycemia
Glinides				
Repaglinide, nateglinide	Yes	Caution	No use	Hypoglycemia
Alpha-glucosidase inhibitors				
Acarbose, miglitol, voglibose	Yes	Probably yes	Probably yes	Hyperamonemia
Thiazolidinediones				
Pioglitazone, rosiglitazone	Yes‡	Caution (check liver enzymes)	No use	Hepatotoxicity (?)
DPP-4 inhibitors				
Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin	Yes	Probably yes	Caution	Unknown (but no clinical experience)
SGLT2 inhibitors				
Dapagliflozin, canagliflozin, empagliflozin	Yes	Caution	No use	Unknown (but no clinical experience)
GLP-1 receptor agonists				
Exenatide, liraglutide, lixisenatide	Yes	Probably yes	Caution or no use	Unknown (but no clinical experience)
Insulin and insulin analogs	Yes	Yes	Yes with caution	Hypoglycemia

Scheen A Expert Opin Drug Metab Toxicol 2014

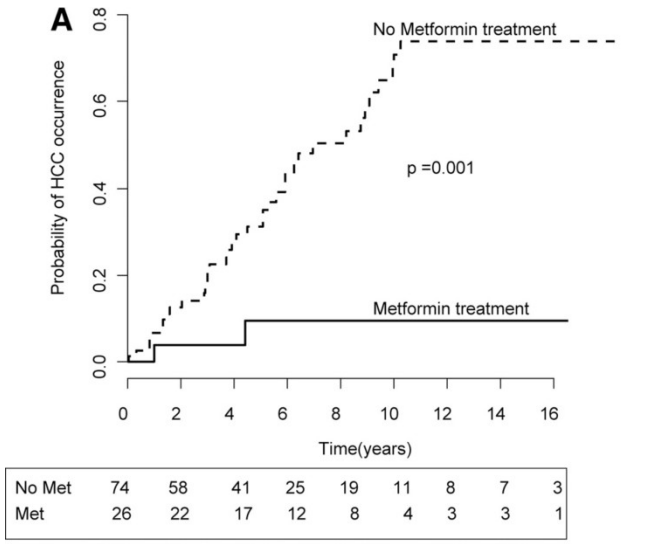
Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes



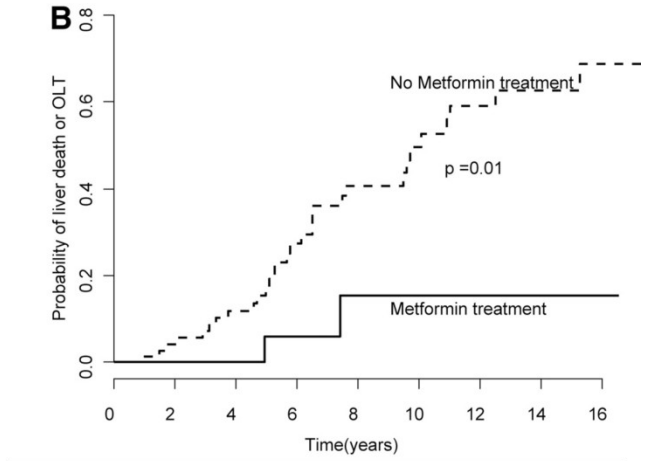
Continuation of metformin after cirrhosis diagnosis reduced the risk of death by 57%.

Zhang et Al Hepatology 2014

Impact of Metformin on the Prognosis of Cirrhosis Induced by Viral Hepatitis C in Diabetic Patients



No Met	74	58	41	25	19	11	8	7	3
Met	26	22	17	12	8	4	3	3	1



No Met	74	67	52	33	25	16	12	9	4
Met	26	23	18	14	8	4	3	3	1

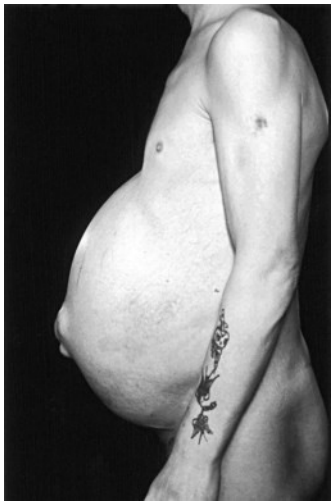
- **Observational prospective cohort**
- **100 consecutive diabetic patients with ongoing HCV cirrhosis**
- **and no contraindication for metformin**

- **In multivariate analysis, metformin treatment was independently associated with a decrease in HCC occurrence (HR, 0.19; *P* = 0.023)**

Nkontchou G et al. J Clin Endocrinol Metab. 2011;96:2601-2608.

Adverse effect of antidiabetic drugs in patient with cirrhosis

Low blood sugar



↗**risk of hypoglycemia**

↗ **prevalence of malnutrition**

Severe hypoglycemia in patients with known diabetes requiring emergency department care: A report from an Italian multicenter study

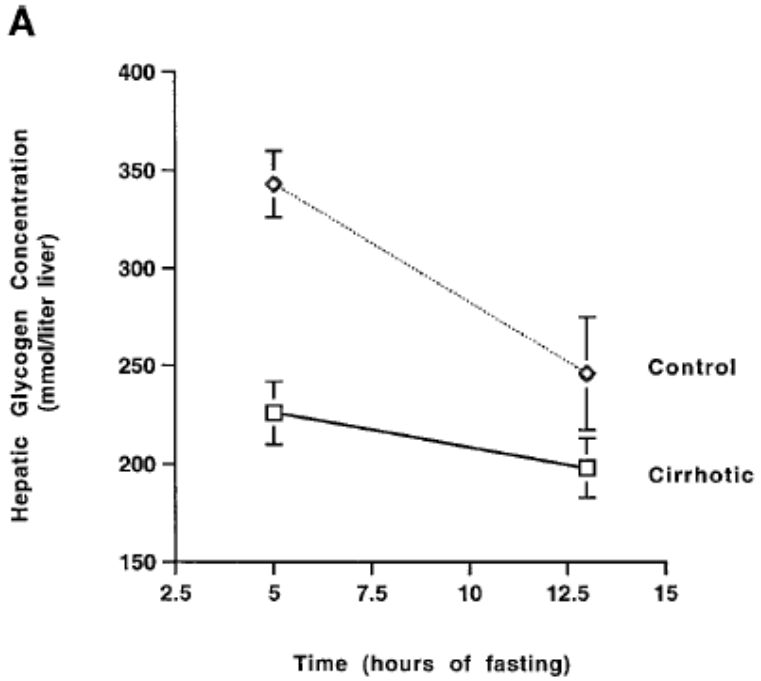
Severe hypoglycemia in 520 patients with known diabetes

Main predictors of hospital admission in patients with established diabetes requiring ED care for severe hypoglycemia

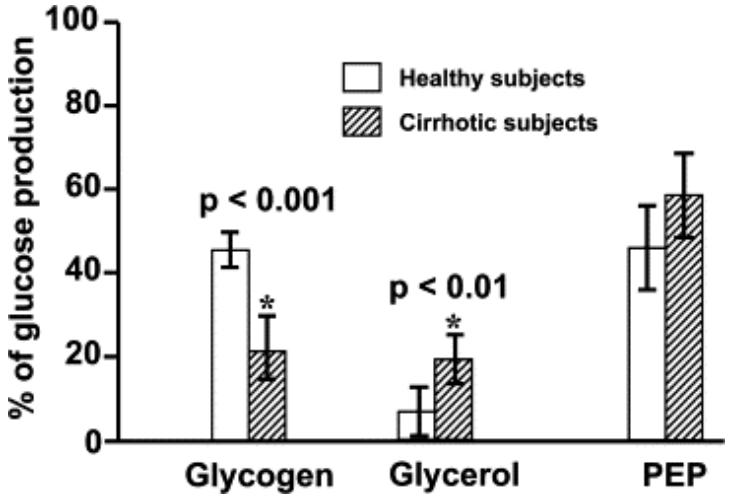
Multivariate logistic regression models	Odds ratio	95% CI	*P* value
Overall (n = 520)			
Age (years)	1.02	0.99–1.06	0.13
Sex (male *vs.* female)	0.89	0.42–1.87	0.76
Insulin users (yes *vs.* no)	0.61	0.13–2.81	0.53
Sulfonylurea alone users (yes *vs.* no)	1.61	0.32–8.02	0.56
Two or more oral glucose-lowering drug users (yes *vs.* no)	1.63	0.35–7.62	0.53
Ischemic heart disease (yes *vs.* no)	1.34	0.61–2.92	0.46
Cirrhosis (yes *vs.* no)	6.76	1.24–36.8	<0.05
Dementia (yes *vs.* no)	1.94	0.69–5.45	0.20
Chronic kidney disease (yes *vs.* no)	2.42	1.11–8.09	<0.05
Sapienza Hospital (yes *vs.* no)	3.70	1.57–8.69	<0.05

Mantovani J Clin trans Endocrinol 2016

hepatic glycogen concentrations were lower in the cirrhotic subjects.



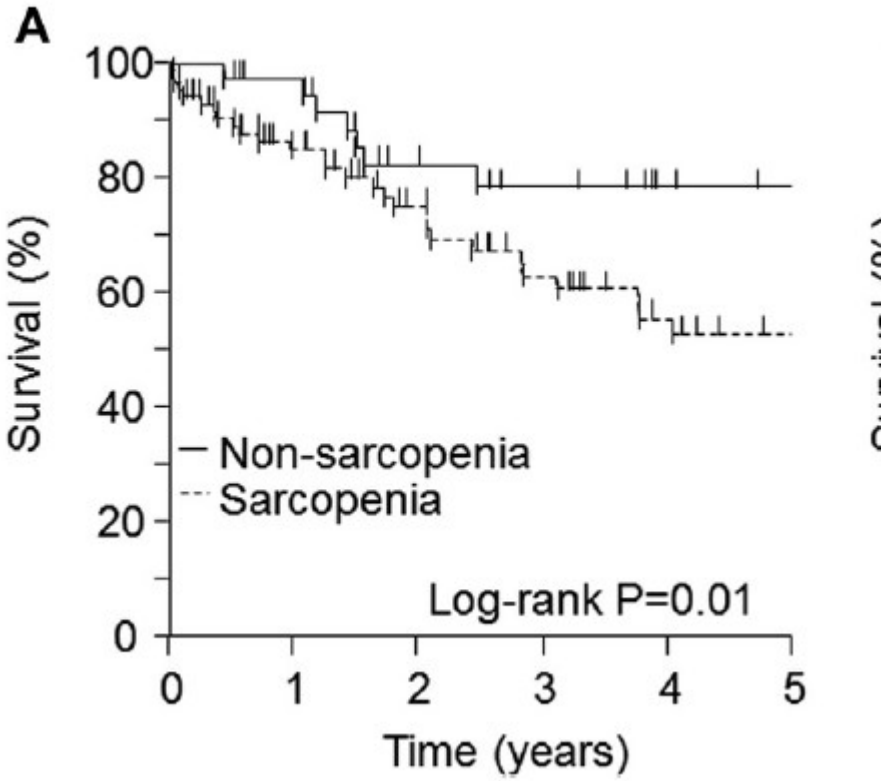
Hepatic glycogen concentration



Glucose production

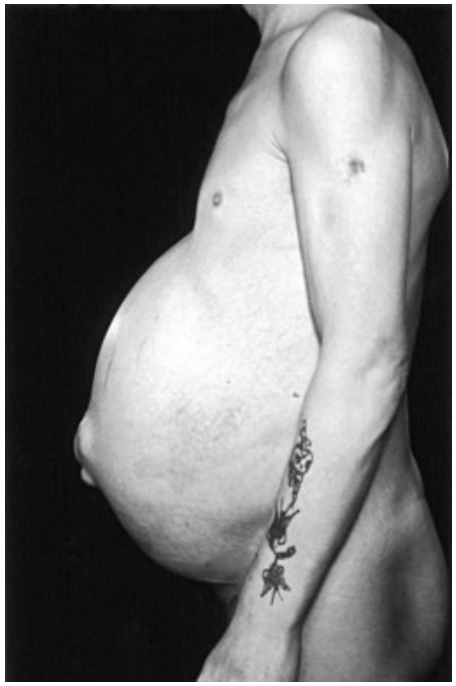
Petersen KF – Am J Physiology 1999

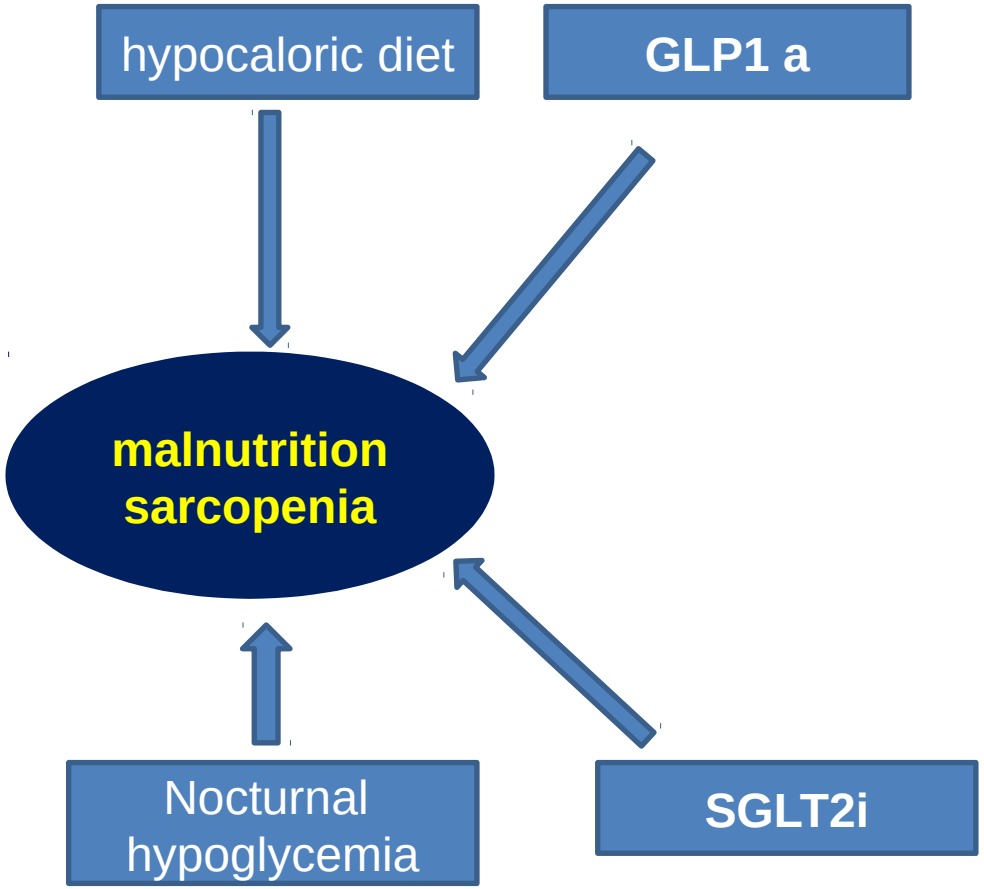
Sarcopenia Affect Survival in Cirrhosis



Hanai T et al. Nutrition 2015: 31; 193-199

Avoid aggravating sarcopenia with diabetes treatment





In summary

- In patient with diabetes antidiabetic drugs should be adapted to the diagnosis and the severity of NAFLD
  - Pioglitazone is effective for long-term treatment of patients with NASH with type 2 diabetes
  - GLP1 analogues and SGLT2i have benefit against NAFLD in patients with type 2 diabetes, but it seems that this effect is mainly driven by weight loss
- the diagnosis of cirrhosis should lead to change the management of diabetes
  - HbA1c measurement is not accurate in patients with cirrhosis
  - protective effect of metformin
  - Caution to adverse effects of diabetes therapy

International Think Tank

Paris NASH Meeting

SAVE THE DATE !

11 & 12 July, 2019

Institut Pasteur - Paris