IL MANAGEMENT DELLA NAFLD NEL PAZIENTE DIABETICO

Relatore:

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Specializzando in Medicina Interna

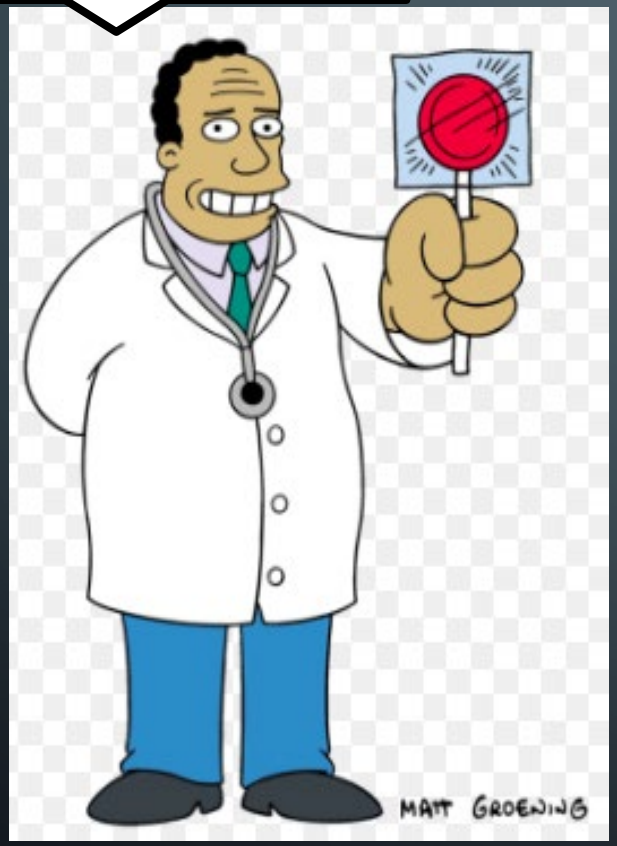


- Il Dott. Mastino dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

CASO CLINICO

Ma no è solo un po' di fegato grasso, stia tranquillo, deve solo dimagrire

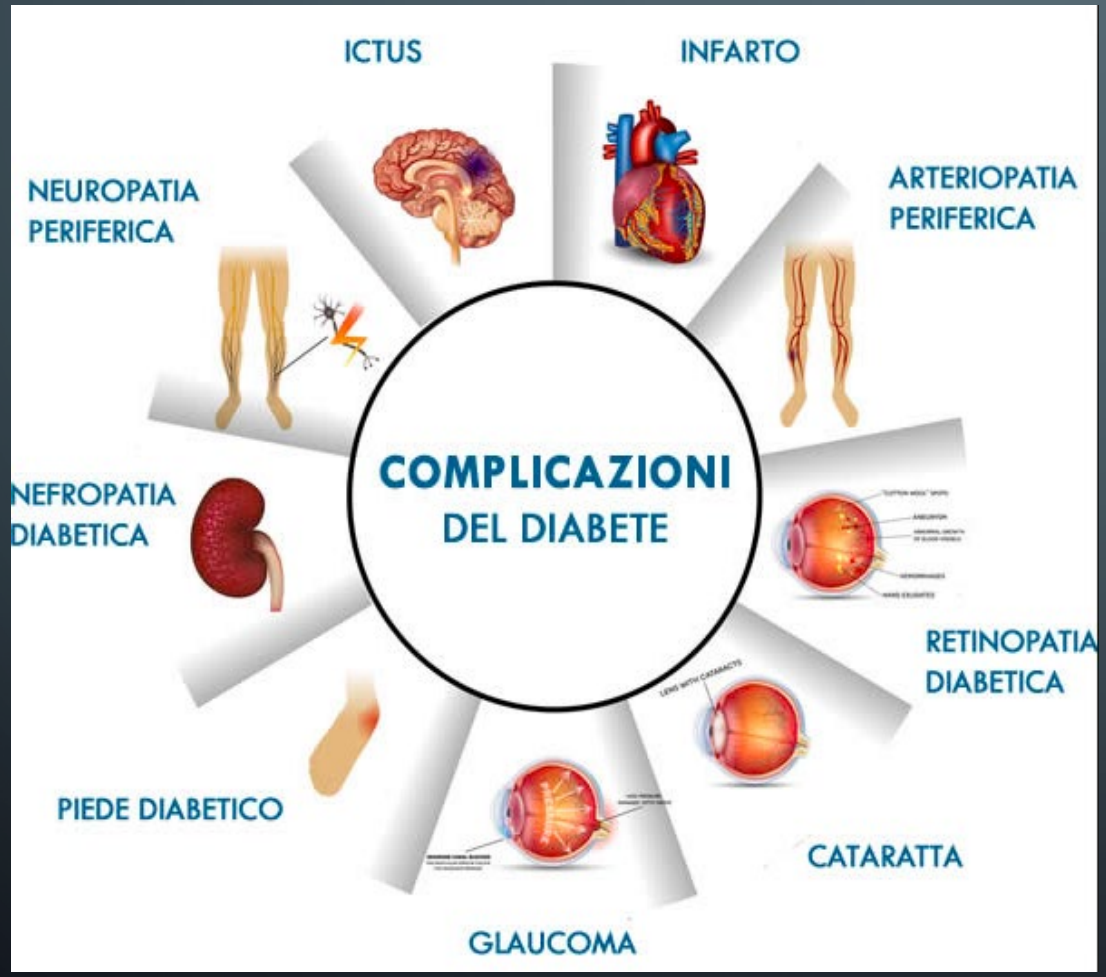


Età (anni)	55
HbA1c (%)	7,7
AST (U/L)	40
ALT (U/L)	45
Conta piastrinica (cell/mm^3)	189000
BMI (Kg/m^2)	32,6
Eco Addome	Steatosi moderata

Dottore ma questa «steatosi» è una cosa grave?



COMPLICANZE DEL DIABETE MELLITO



+



FACCIAMO CHIAREZZA: DEFINIZIONI

Table 2. The spectrum of NAFLD and concurrent diseases.

Disease	Subclassification	Most common concurrent diseases
NAFLD*	NAFL • Pure steatosis • Steatosis and mild lobular inflammation	° AFLD-Alcoholic fatty liver disease ° Drug-induced fatty liver disease ° Hepatitis C virus-associated fatty liver (genotype 3) ° Others • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson's disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism (Wolman disease [lysosomal acid lipase deficiency])
	NASH • Early NASH: no or mild (F0-F1) fibrosis • Fibrotic NASH: significant (≥F2) or advanced (≥F3, bridging) fibrosis • NASH-Cirrhosis (F4)	
	Hepatocellular carcinoma^	

Marchesini, Giulio, et al. "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease." *Journal of Hepatology* 64.6 (2016): 1388-1402.

FACCIAMO CHIAREZZA: DEFINIZIONI

Table 1 Diagnostic criteria for non-alcoholic fatty liver disease according to the various guidelines

	EASL	NICE	Asia-Pacific	AISF	AASLD
Required criteria	Steatosis in > 5% of hepatocytes by either imaging or histology No other causes of steatosis Insulin resistance	Excessive fat in the liver No other causes of steatosis No significant alcohol consumption	Hepatic steatosis by either imaging or histology No other causes of steatosis No significant alcohol consumption	Hepatic steatosis on either imaging or histology No other causes of steatosis No significant alcohol consumption	Evidence of hepatic steatosis either by imaging or histology No other causes of steatosis No significant alcohol consumption No coexisting chronic liver disease
Alcohol consumption threshold (men)	30 g/d	30 g/d	2 standard drink/d 140 g/wk	30 g/d	21 standard drink/wk 294 g/wk
Alcohol consumption threshold (women)	20 g/d	20 g/d	1 standard drink/d 70 g/wk	20 g/d	14 standard drink/wk 196 g/wk

Leoni, Simona, et al. "Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis." *World journal of gastroenterology* 24.30 (2018): 3361.

ISTOLOGIA: NAFLD, NASH, FIBROSI

CARATTERISTICHE ISTOLOGICHE

1. ***STEATOSI***
2. ***GRADO DI ATTIVITÀ INFIAMMATORIA***
3. ***FIBROSI***

ISTOLOGIA: NAFLD, NASH, FIBROSI

Grado	Brunt	Nash CRN	SAF
STEATOSI			
0	No	< 5%	< 5%
1	< 33%	5-33%	5-33%
2	33-66%	33-67%	33-67%
3	> 66%	> 67%	> 67%
INFIAMMAZIONE LOBULARE			
0	No foci	No foci	No foci
1	1-2 foci per 20 campi	< 2 foci x 20	< 2 foci per 20 campi
2	2-4 foci per 20 campi	2-4 foc per 20 campii	> 2 foci per 20 campi
3	> 4 foci per 20 campi	> 4 foci per 20 campi	
INFIAMMAZIONE PORTALE			
0	No	No	
1	Lieve	Lieve	
2	Moderato	Maggiore di lieve	
3	Severo		

Kleiner, David E., et al. »Histology of NAFLD and NASH in adults and children." *Clin Liver Dis*. 2016 May ; 20(2): 293–312.

ISTOLOGIA: NAFLD, NASH, FIBROSI

Grado	BRUNT	NASH CRN	SAF
BALLOONING			
0	No	No	No
1	Lieve, zona 3	Lieve	Lieve
2	Moderato, zona 3	Abbondante	Abbondante
3	Severo, zona 3		
FIBROSI			
0	No	No	No
1	Perisinusoidale, zona 3	Perisinusoidale o periportale	Perisinusoidale o periportale
2	Perisunsoidale e periportale, zona 3	Perisinusoidale e periportale	Perisinusoidale e periportale
3	Bridging	Bridging	Bridging
4	Cirrosi	Cirrosi	Cirrosi

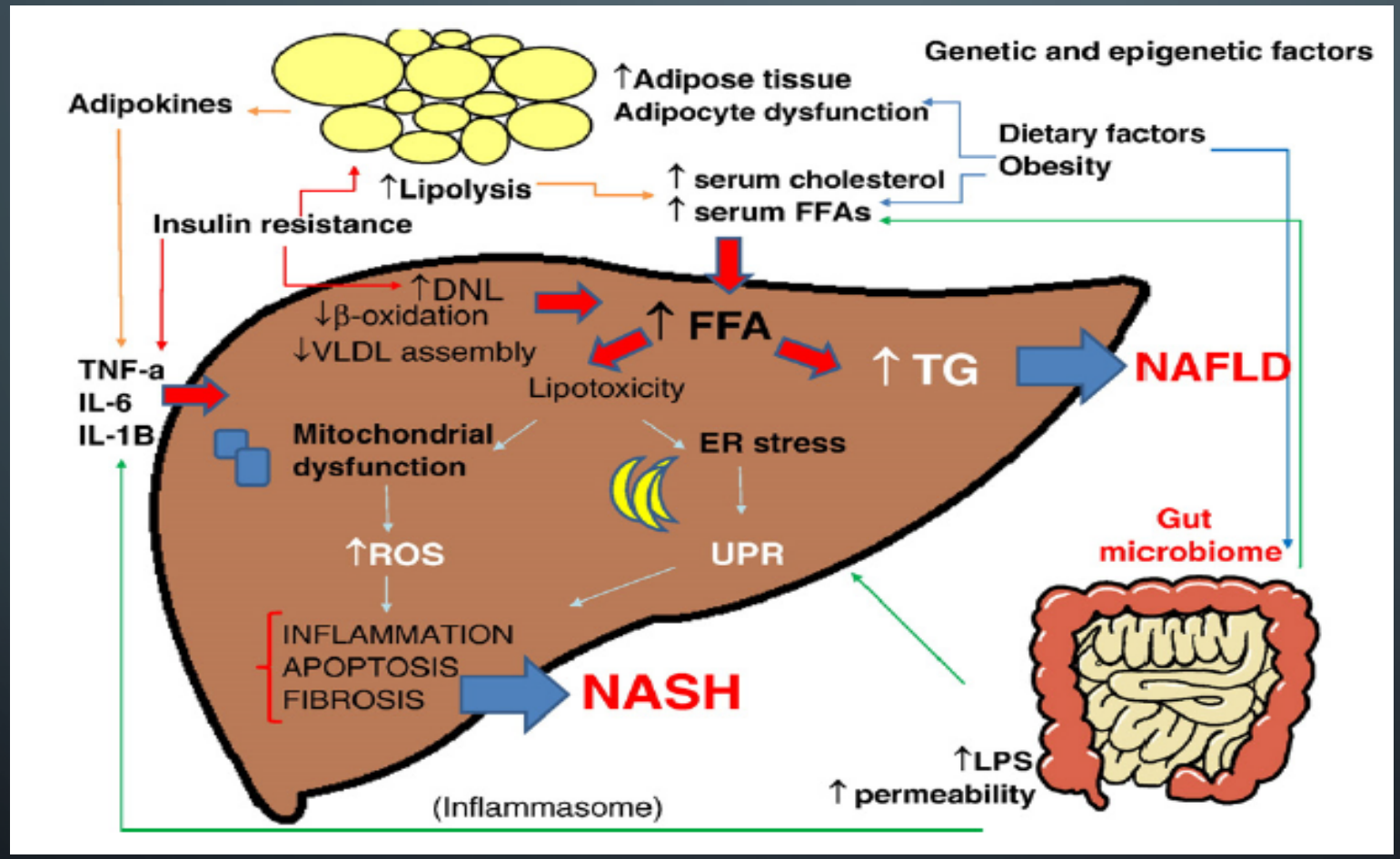
Kleiner, David E., et al. »Histology of NAFLD and NASH in adults and children." *Clin Liver Dis*. 2016 May ; 20(2): 293–312.

ISTOLOGIA: NAFLD, NASH, FIBROSI

SAF SCORE				
STEATOSI	**INFIAMMAZIONE LOBULARE**	**BALLOONING**	**SCORE DI ATTIVITÀ**	**DIAGNOSI**
0	0, 1, 2	0, 1, 2	0-4	**Altro**
1, 2, 3	0	0	0	**NAFL**
		1	1	**NAFL**
		2	2	**NAFL**
	1	0	1	**NAFL**
		1	2	**NASH**
		2	3	**NASH**
	2	0	2	**NAFL**
		1	3	**NASH**
		2	4	**NASH**

NAFLD ACTIVITY SCORE (NAS)				
STEATOSI	**INFIAMMAZIONE LOBULARE**	**BALLOONING**	**SCORE DI ATTIVITÀ**	**DIAGNOSI**
0, 1, 2, 3	0, 1, 2, 3	0, 1, 2	< 4	**NAFL**
			4-5	**Borderline NASH**
			> 5	**NASH**

FISIOPATOGENESI

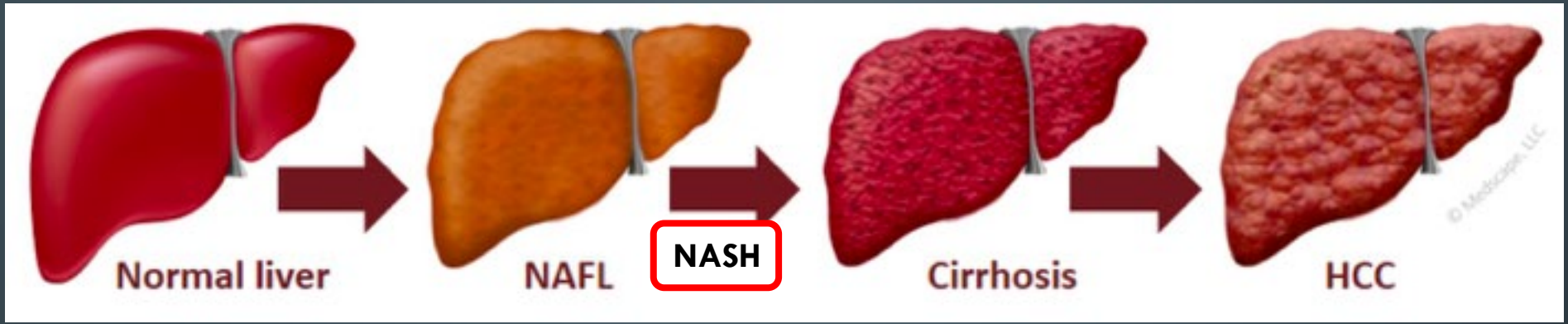


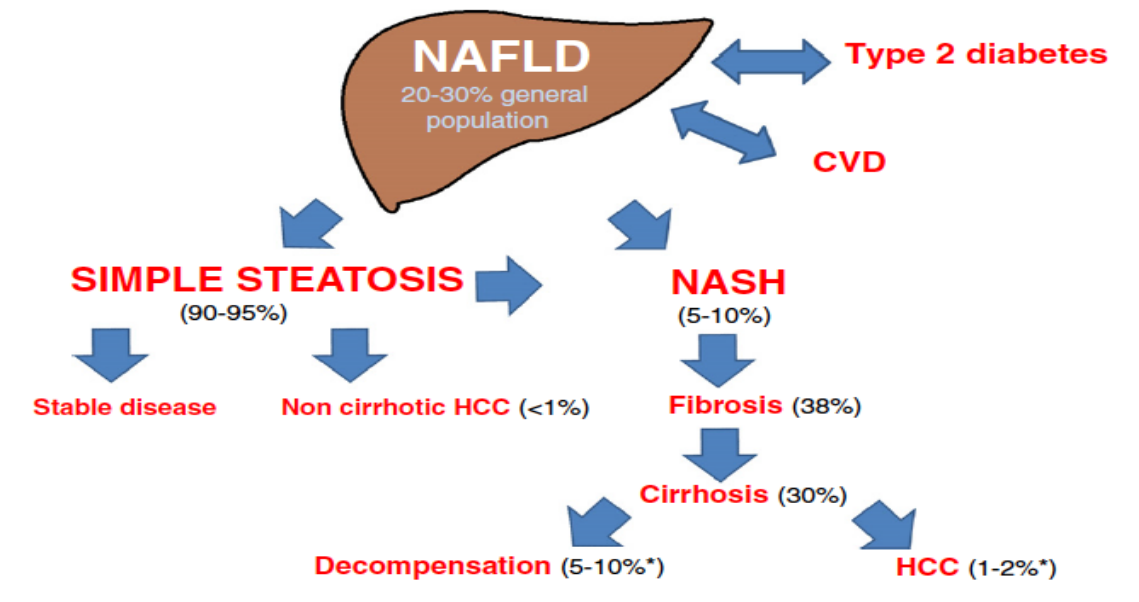
Multiple hits hypotesis

- Insulino-resistenza
- Disfunzione adipociti
- Fattori genetici ed epigenetici
- Fattori dietetici
- Disbiosi intestinale

Buzzetti, Elena, et al.. "The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD)." *Metabolism* 65.8 (2016): 1038-1048.

STORIA NATURALE

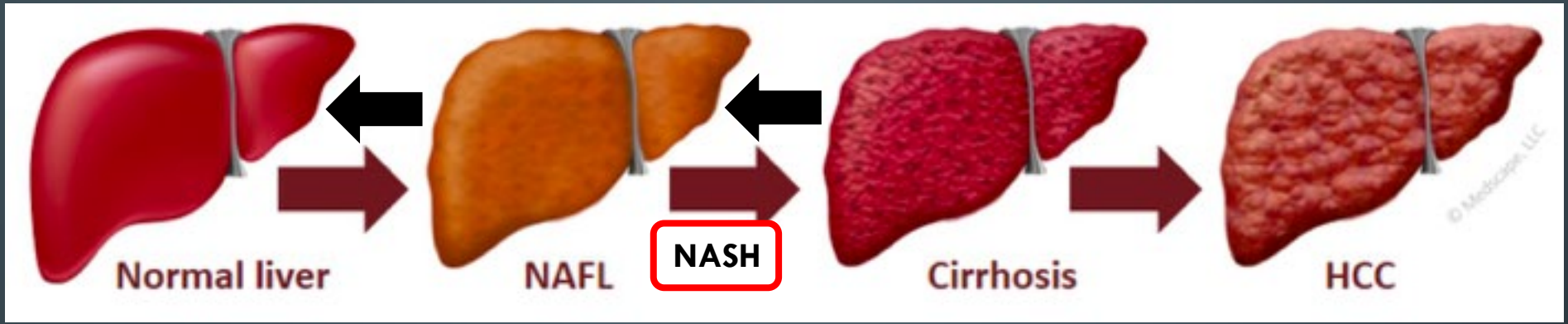


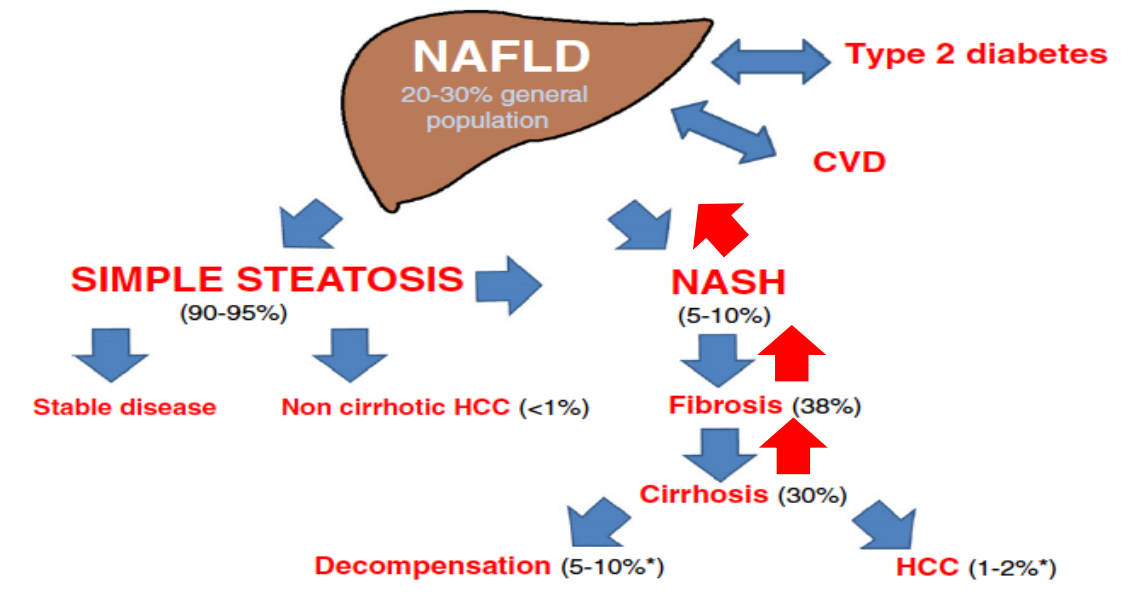


Brunt, Elizabeth M., et al. "Nonalcoholic fatty liver disease." *Nature reviews Disease primers* 1 (2015): 15080.

Buzzetti, Elena, et al.. "The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD)." *Metabolism* 65.8 (2016): 1038-1048.

STORIA NATURALE





Brunt, Elizabeth M., et al. "Nonalcoholic fatty liver disease." *Nature reviews Disease primers* 1 (2015): 15080.

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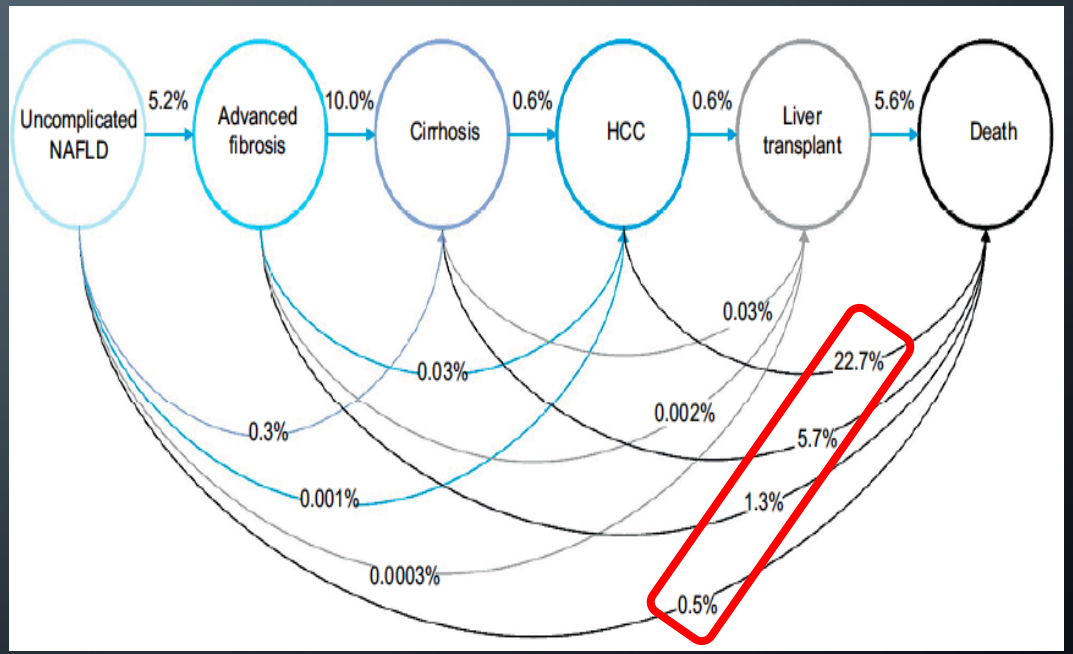
PERCHÉ É IMPORTANTE DIAGNOSTICARE NAFLD/NASH?

- ***ELEVATA PREVALENZA***
- ***AUMENTATO RISCHIO DI MORTALITÀ CARDIOVASCOLARE***
- ***POSSIBILE EVOLUZIONE VERSO COMPLICANZE (CIRROSI, HCC)***
- ***RACCOMANDAZIONI TERAPEUTICHE SPECIFICHE***

SU COSA CI DOBBIAMO CONCENTRARE?

L'aumentata mortalità in presenza di NAFLD è correlata esclusivamente ai *gradi più avanzati di fibrosi*. Nessuna correlazione con la presenza di NASH anche di entità severa.

Model	HR (95% CI of HR)	*P* Value
Fibrosis, stage 0	1 (reference)	
Fibrosis, stage 1	2.07 (1.40, 3.08)	<.0001
Fibrosis, stage 2	3.02 (2.0, 4.56)	<.0001
Fibrosis, stage 3	3.97 (2.50, 6.30)	<.0001
Fibrosis, stage 4	11.97 (6.47, 22.12)	<.0001

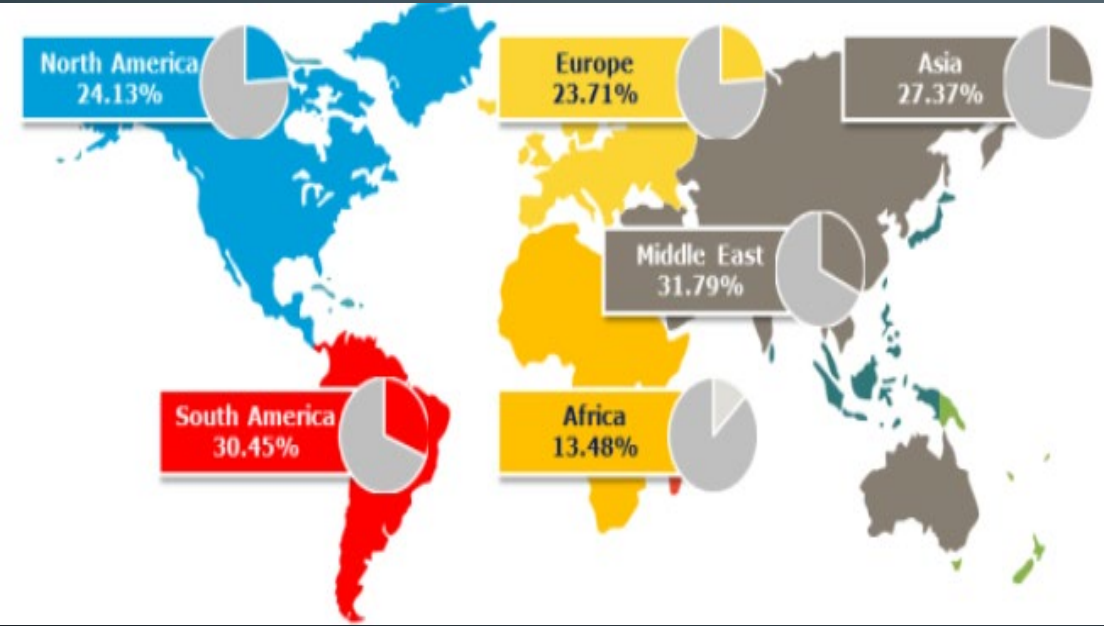


Angulo, Paul, et al. "Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease." *Gastroenterology* 149.2 (2015): 389-397.

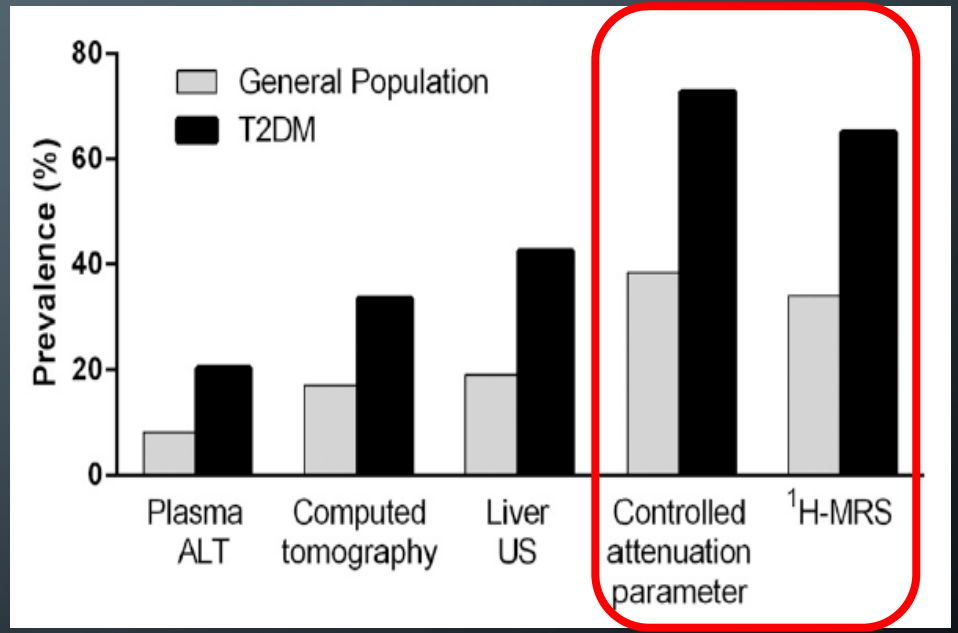
Simeone, Jason C., et al. "Clinical course of nonalcoholic fatty liver disease: an assessment of severity, progression, and outcomes." *Clinical epidemiology* 9 (2017): 679.

EPIDEMIOLOGIA NAFLD/NASH NEL DIABETE MELLITO

POPOLAZIONE GENERALE



DIABETICI TIPO 2



Younossi, Zobair, et al. "Global Perspectives on Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis." *Hepatology* (2018).

IMPATTO ECONOMICO NAFLD/NASH

TABLE 5. Annual Predicted Economic Burden of NAFLD by Country

	United States	Germany	France	Italy	United Kingdom
Total costs (in billions)					
Direct costs	$103.31	€4.33	€11.40	€11.95	£5.24
Societal costs	$188.88	€51.94	€64.31	€44.14	£26.03
Total costs	$292.19	€56.27	€75.72	€56.09	£31.26
Total costs (per patient)					
Direct costs	$1,612.18	€354	€784	€1,163	£357
Societal costs	$2,947.36	€4,240	€4,421	€4,297	£1,773
Total costs	$4,559.54	€4,593	€5,205	€5,460	£2,130
Costs (in millions) due to					
NAFL	$86,564.2	€3,492.43	€9,163.92	€9,776.54	£4,326.86
NASH no FB	$5,483.6	€244.07	€759.79	€701.42	£301.79
NASH FB	$1,866.3	€87.86	€242.90	€250.94	£110.21
CC	$6,573.3	€312.74	€916.78	€900.07	£362.66
DCC	$1,765.5	€90.33	€268.63	€260.60	£103.06
HCC	$522.7	€31.30	€25.78	€15.50	£17.60
LT	$161.6	€30.09	€18.24	€15.25	£11.09
PLT	$375.7	€43.97	€8.08	€30.35	£4.26

USA = *$103 mld/anno*

GERMANIA = *€4,5 mld/anno*

FRANCIA = *€11,5 mld/anno*

ITALIA = *€12 mld/anno*

UK = *€5,5 mld/anno*

Nei prossimi 10 anni tenendo conto dell'incremento della prevalenza di Obesità, Sindrome metabolica e NAFLD si stima che la spesa sanitaria per NAFLD risulti di:

- **USA:** *$1.050 miliardi*
- **GERMANIA, FRANCIA, ITALIA, UK:** *€334 miliardi*

Younossi, Zobair M., et al. "The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe." *Hepatology* 64.5 (2016): 1577-1586.

EPIDEMIOLOGIA COMPLICANZE NAFLD/NASH NEL PAZIENTE DIABETICO

La presenza di NAFLD nel diabetico tipo 2 aumenta il rischio di complicanze microvascolari (soprattutto nefropatia diabetica)

La presenza di NAFLD nel diabetico tipo 2 aumenta il rischio cardiovascolare

Figure 3: Prevalence of diabetic nephropathy and retinopathy in patients with type 2 diabetes mellitus.

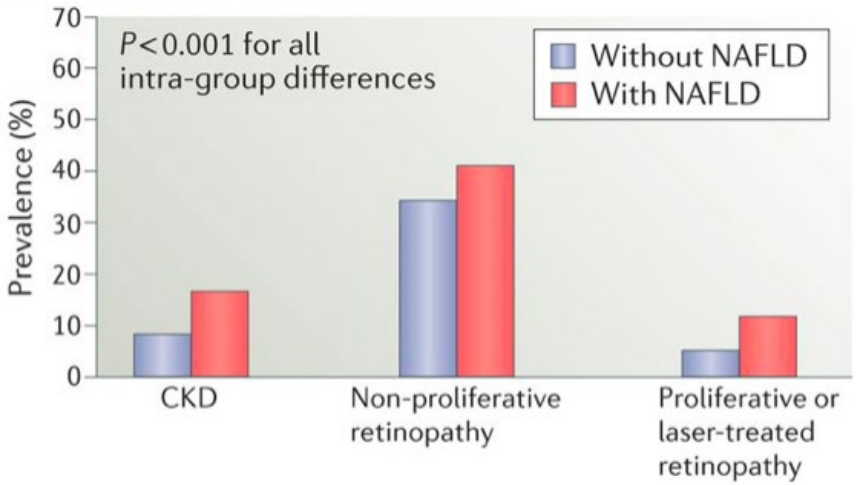
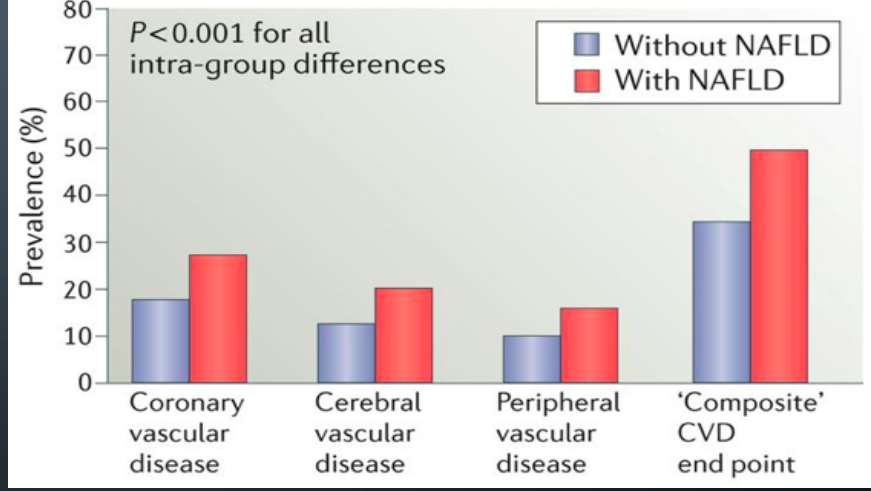


Figure 2: Prevalence of clinically manifest cardiovascular disease in patients with type 2 diabetes mellitus.



Targher, Giovanni, Amedeo Lonardo, and Christopher D. Byrne. "Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus." *Nature Reviews Endocrinology* 14.2 (2018): 99.

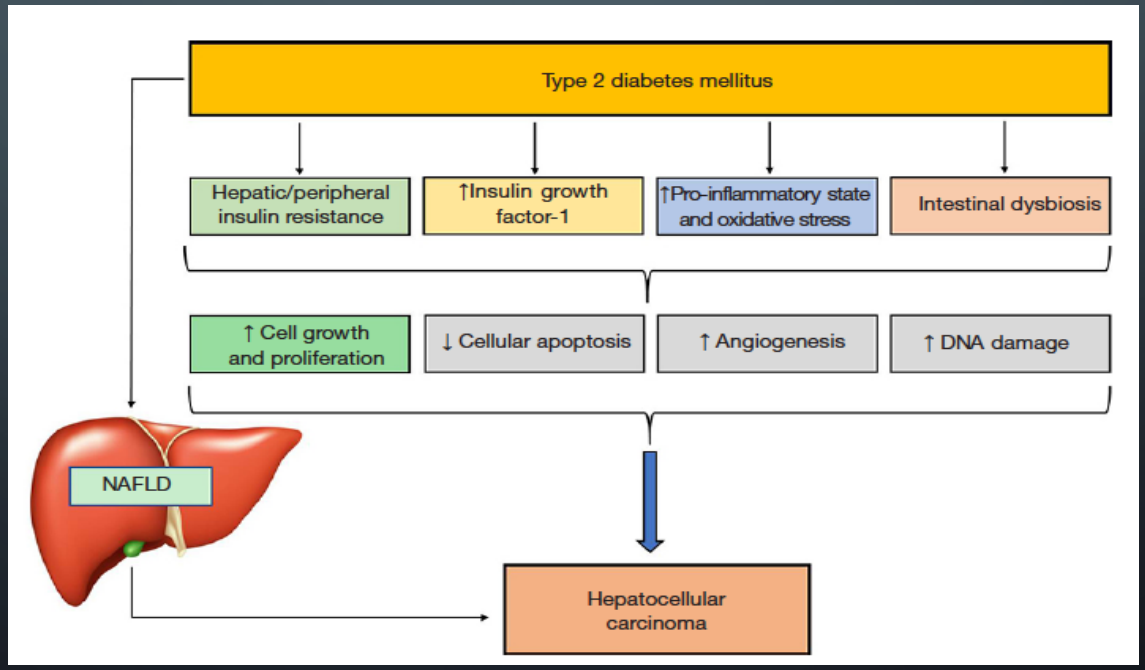
EPIDEMIOLOGIA COMPLICANZE NAFLD/NASH NEL PAZIENTE DIABETICO

Nel diabetico tipo 2, la NAFLD è spesso caratterizzata da gradi più avanzati di NASH e fibrosi

Arab, Juan P., et al. "High prevalence of undiagnosed liver cirrhosis and advanced fibrosis in type 2 diabetic patients." *Annals of hepatology* 15.5 (2017): 721-728.

Nel diabetico tipo 2, il rischio di sviluppare HCC secondario a NAFLD è 2 volte maggiore

Mantovani, Alessandro, and Giovanni Targher. "Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease." *Annals of translational medicine*5.13 (2017).



DOBBIAMO SCREENARE I NOSTRI PAZIENTI CON DIABETE TIPO 2?

Table 2 Comparative analysis of the recommendations regarding the screening for non-alcoholic fatty liver disease

	EASL	NICE	Asia-Pacific	AISF	AASLD
Systematic screening	No	No	No	No	No
Screening in high-risk groups	Yes Obesity Metabolic syndrome Abnormal liver enzymes	Yes Obesity Type II Diabetes	Yes Obesity Type II Diabetes	Not mentioned	No[1]
Screening modality	Yes liver enzymes	No liver enzymes Yes ultrasonography	No liver enzymes Yes ultrasonography Yes transient elastography		

Leoni, Simona, et al. "Current guidelines for the management of non-alcoholic fatty liver disease: A systematic review with comparative analysis." *World journal of gastroenterology* 24.30 (2018): 3361.

COME DIAGNOSTICARE LA NAFLD?

- **ECOGRAFIA**
- **FATTY LIVER INDEX**
  (BMI, GGT, TG, CV)
- **RM EPATICA**



COME SCREENARE I NOSTRI PAZIENTI PER FIBROSI NAFLD-RELATA?

PARAMETRI CLINICO-LABORATORISTICI SEMPLICI	PARAMETRI CLINICO-LABORATORISTICI COMPLESSI	DIAGNOSTICA PER IMMAGINI
AST/platelet ratio index (APRI)	NASH FibroSure	Vibration controlled transient elastography (VCTE)
NAFLD Fibrosis score	Fibrospect NASH	Shear wave elastography (SWE)
FIB-4 index	ELF score	Risonanza magnetica elastografica (MRE)
BARD score	HepaScore	Liver acoustic radiation force impulse (ARFI)

COME SCREENARE I NOSTRI PAZIENTI PER FIBROSI NAFLD-RELATA?

PARAMETRI CLINICO-LABORATORISTICI SEMPLICI	PARAMETRI CLINICO-LABORATORISTICI COMPLESSI	DIAGNOSTICA PER IMMAGINI
AST/platelet ratio index (APRI)	NASH FibroSure	**Vibration controlled transient elastography (VCTE)**
NAFLD Fibrosis score	Fibrospect NASH	Shear wave elastography (SWE)
FIB-4 index	ELF score	Risonanza magnetica elastografica (MRE)
BARD score	HepaScore	Liver acoustic radiation force impulse (ARFI)

PARAMETRI CLINICI E SCORE DIAGNOSTICI

PARAMETRI
Età (anni)
AST (U/L)
ALT (U/L)
Conta piastrinica
BMI (Kg/m^2)
Albumina (g/L)
IFG/IGT o T2DM (si/no)

NAFLD FIBROSIS SCORE[1]

CUT-OFFS	STADIO FIBROSI
< -1,455	F0-F2
-1,455 – 0,676	Indeterminato
> 0,676	F3-F4

FIB-4 INDEX[2]

CUT-OFFS	STADIO FIBROSI
< 1,45	F0-F2
1,45 – 3,25	Indeterminato
> 3,25	F3-F4

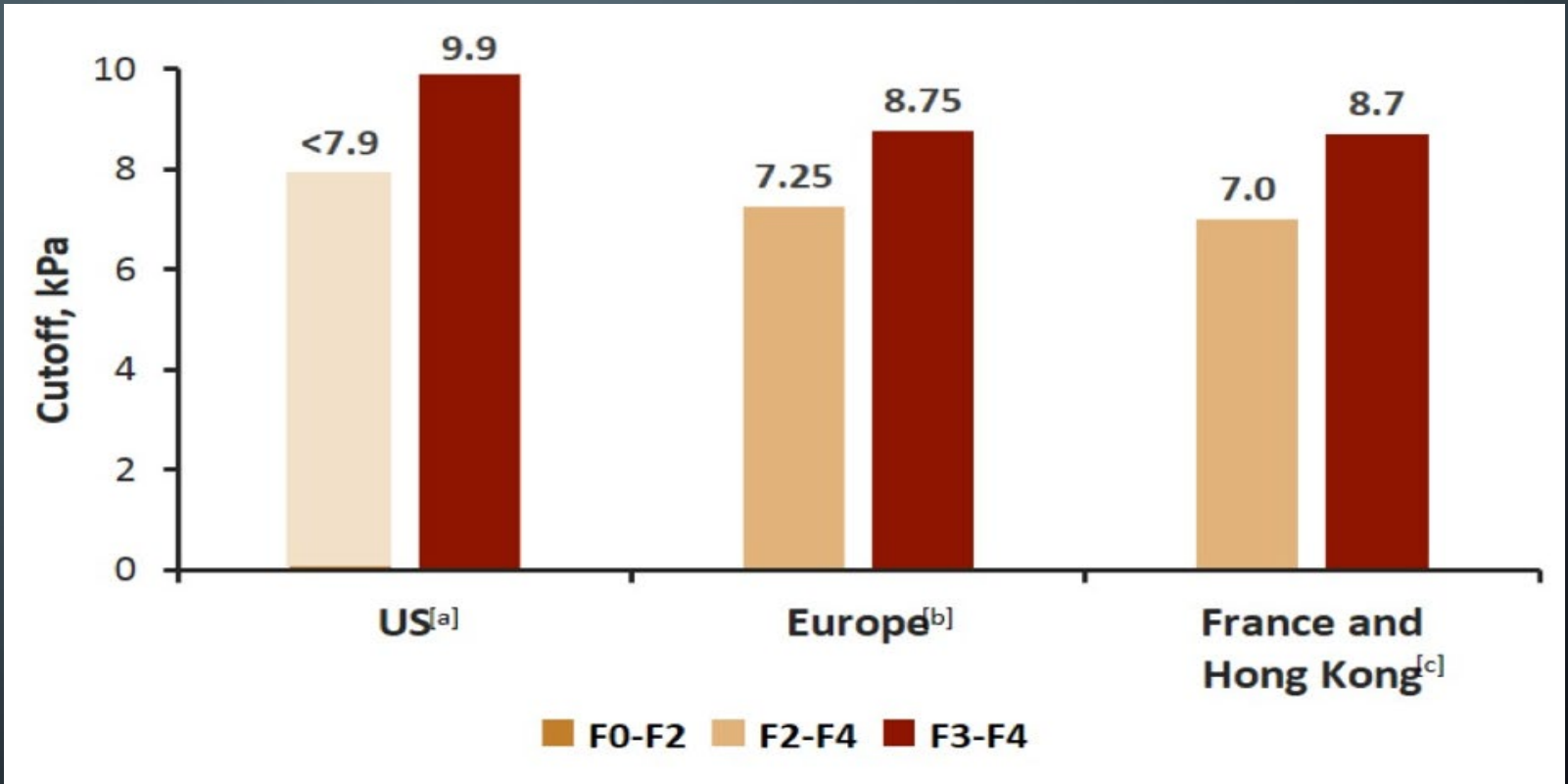
[1]Angulo, Paul, et al. "The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD." *Hepatology* 45.4 (2007): 846-854.
[2]Sterling, Richard K., et al. "Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection." *Hepatology* 43.6 (2006): 1317-1325.

DIAGNOSTICA PER IMMAGINI: ELASTOGRAFIA EPATICA (VCTE)

- Metodica poco costosa, non invasiva, facilmente ripetibile
- Utile per diagnosticare e valutare il grado di severità della fibrosi
  - Più accurata per gradi avanzati di fibrosi
  - Meno utile per valutare il grado di steatosi o la presenza di NASH
- Può predire il rischio di scompenso o complicanze
- Correla bene con la pressione portale
- Diversi cut-offs in base alla popolazione
- Metodica operatore-dipendente
- Possibili fattori interferenti
  - Obesità; Paziente non a digiuno; Eccessiva assunzione di alcolici; Colelitiasi; Congestione epatica

DIAGNOSTICA PER IMMAGINI: ELASTOGRAFIA EPATICA (VCTE)



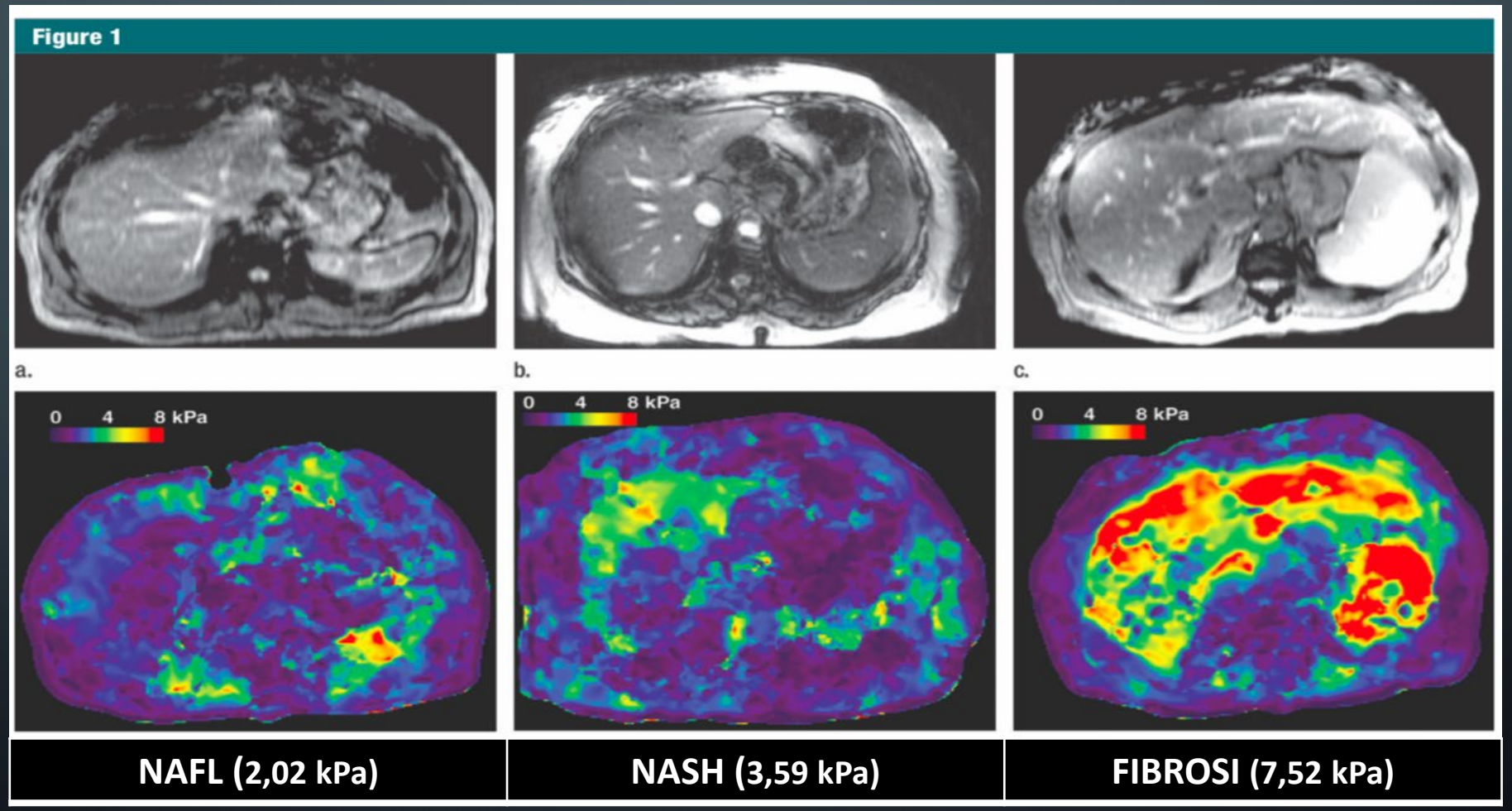


[a]Tapper, Elliot B., et al. "The performance of vibration controlled transient elastography in a US cohort of patients with nonalcoholic fatty liver disease." *The American journal of gastroenterology* 111.5 (2016): 677.

[b]Petta, Salvatore, et al. "Reliability of liver stiffness measurement in non-alcoholic fatty liver disease: the effects of body mass index." *Alimentary pharmacology & therapeutics* 33.12 (2011): 1350-1360.

[c]Wong, Vincent Wai-Sun, et al. "Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease." *Hepatology* 51.2 (2010): 454-462.

DIAGNOSTICA PER IMMAGINI: RISONANZA MAGNETICA

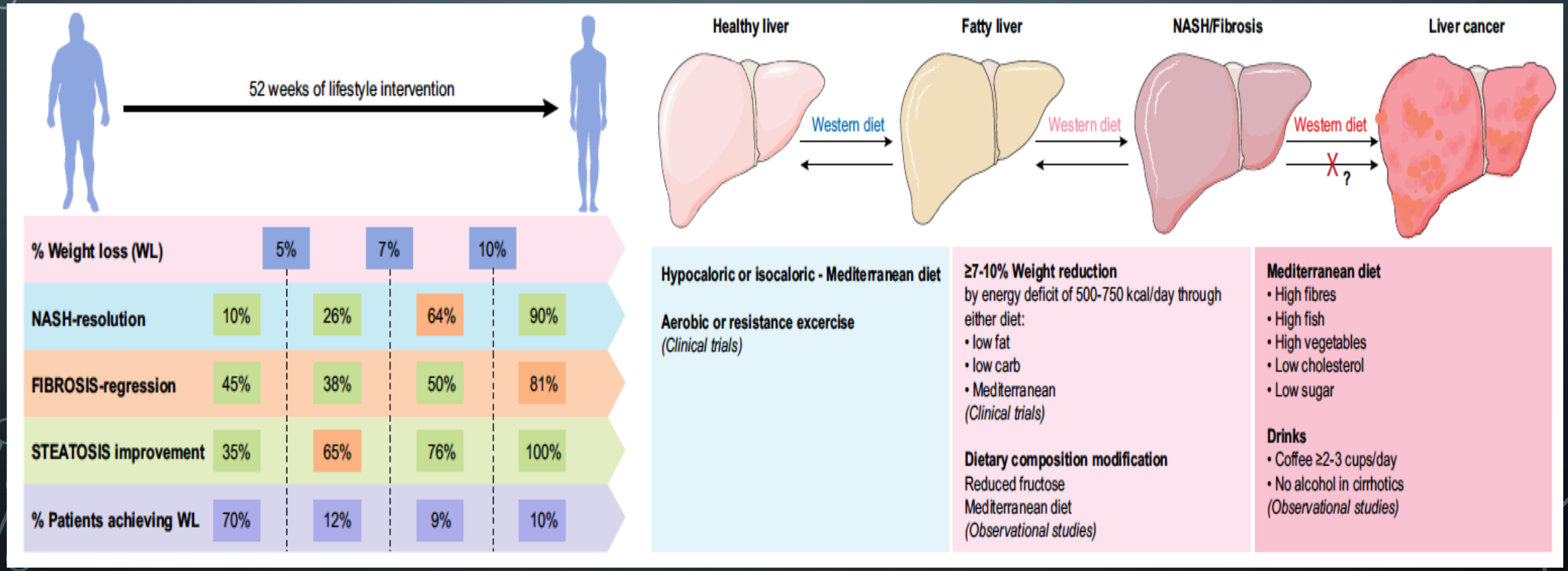


Chen, Jun, et al. "Early detection of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease by using MR elastography." *Radiology* 259.3 (2011): 749-756.

QUANDO INVIARE ALL'EPATOLOGO?

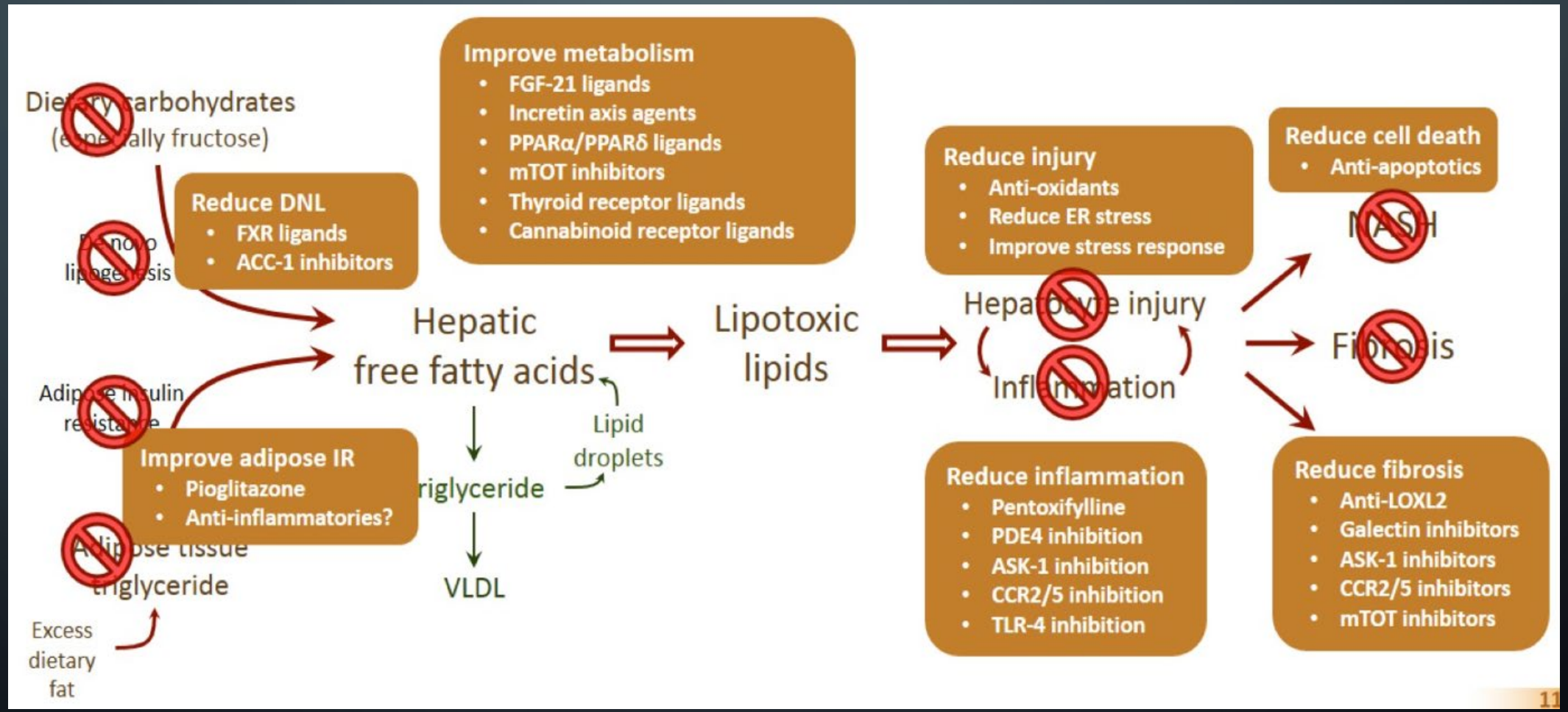
- ❑ Esami diagnostici non invasivi indicativi di rischio intermedio o elevato per *fibrosi in stadio avanzato (F3-F4)* per definizione diagnostica (biopsia epatica) e presa in carico
- ❑ Paziente con diagnosi istologica di NASH, per presa in carico e monitoraggio
- ❑ Epatopatia ad eziologia dubbia: NAFLD + altra causa (etilismo, HBV, HCV, farmaci, emocromatosi, ecc.)
- ❑ **Biopsia epatica** è il gold standard per la diagnosi, ma è indicata solo se:
  - Eziologia dubbia
  - Metodi di screening non invasivi per fibrosi avanzata con risultati indeterminati

MODIFICHE DELLO STILE DI VITA UNICA TERAPIA «APPROVATA» PER NAFLD



Romero-Gómez, Manuel, Shira Zelber-Sagi, and Michael Trenell. "Treatment of NAFLD with diet, physical activity and exercise." *Journal of hepatology* 67.4 (2017): 829-846.

TARGET TERAPIA FARMACOLOGICA: POSSIBILI TARGET



Neuschwander-Tetri, Brent A. "Non-alcoholic fatty liver disease." *BMC medicine* 15.1 (2017): 45.

TERAPIA FARMACOLOGICA: RACCOMANDAZIONI SCIENTIFICHE

NON ESISTE ALCUNA TERAPIA FARMACOLOGICA CON APPOSITA INDICAZIONE PER NAFLD. TUTTE LE TERAPIE SONO OFF-LABEL

OPZIONI TERAPEUTICHE ATTUALI

PIOGLITAZONE

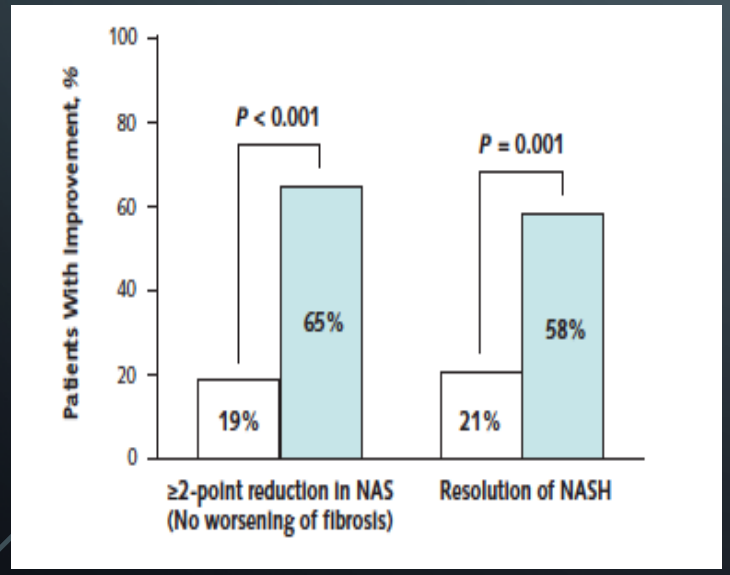
Annals of Internal Medicine

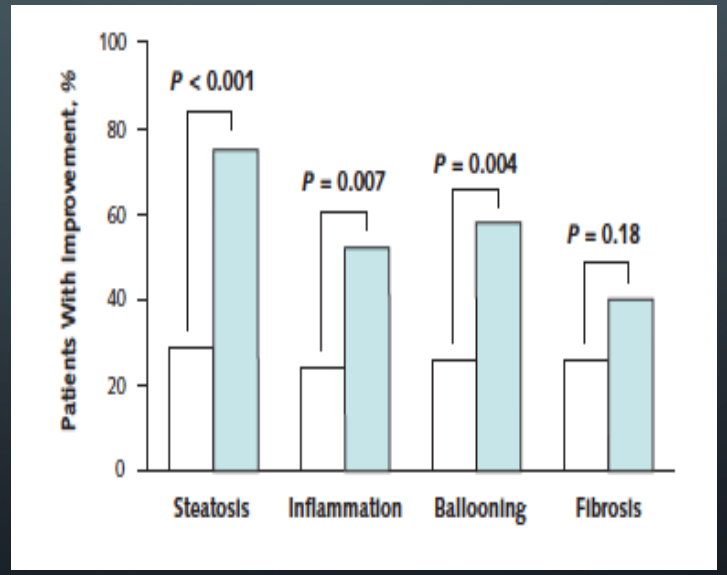
ORIGINAL RESEARCH

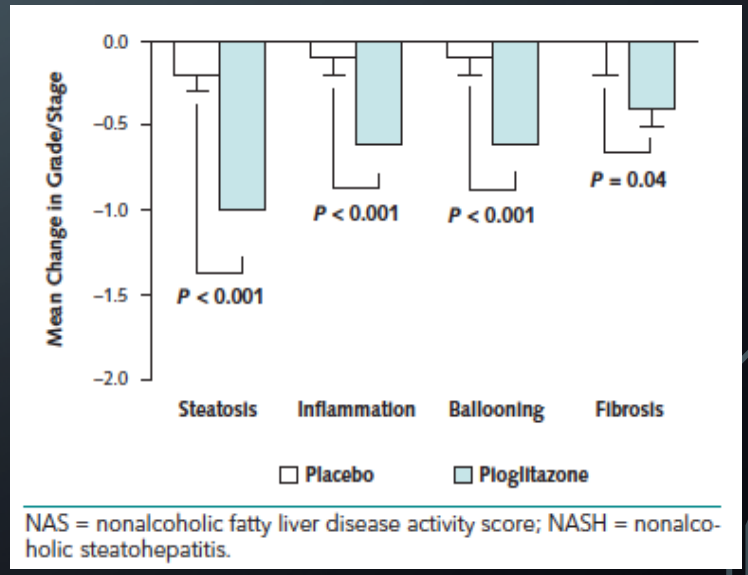
Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus

A Randomized Trial

Kenneth Cusi, MD; Beverly Orsak, RN; Fernando Bril, MD; Romina Lomonaco, MD; Joan Hecht, RN; Carolina Ortiz-Lopez, MD; Fermin Tio, MD; Jean Hardies, PhD; Celia Darland, RD; Nicolas Musi, MD; Amy Webb, MD; and Paola Portillo-Sanchez, MD







NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis.

OPZIONI TERAPEUTICHE ATTUALI

VITAMINA E: PIVENS trial

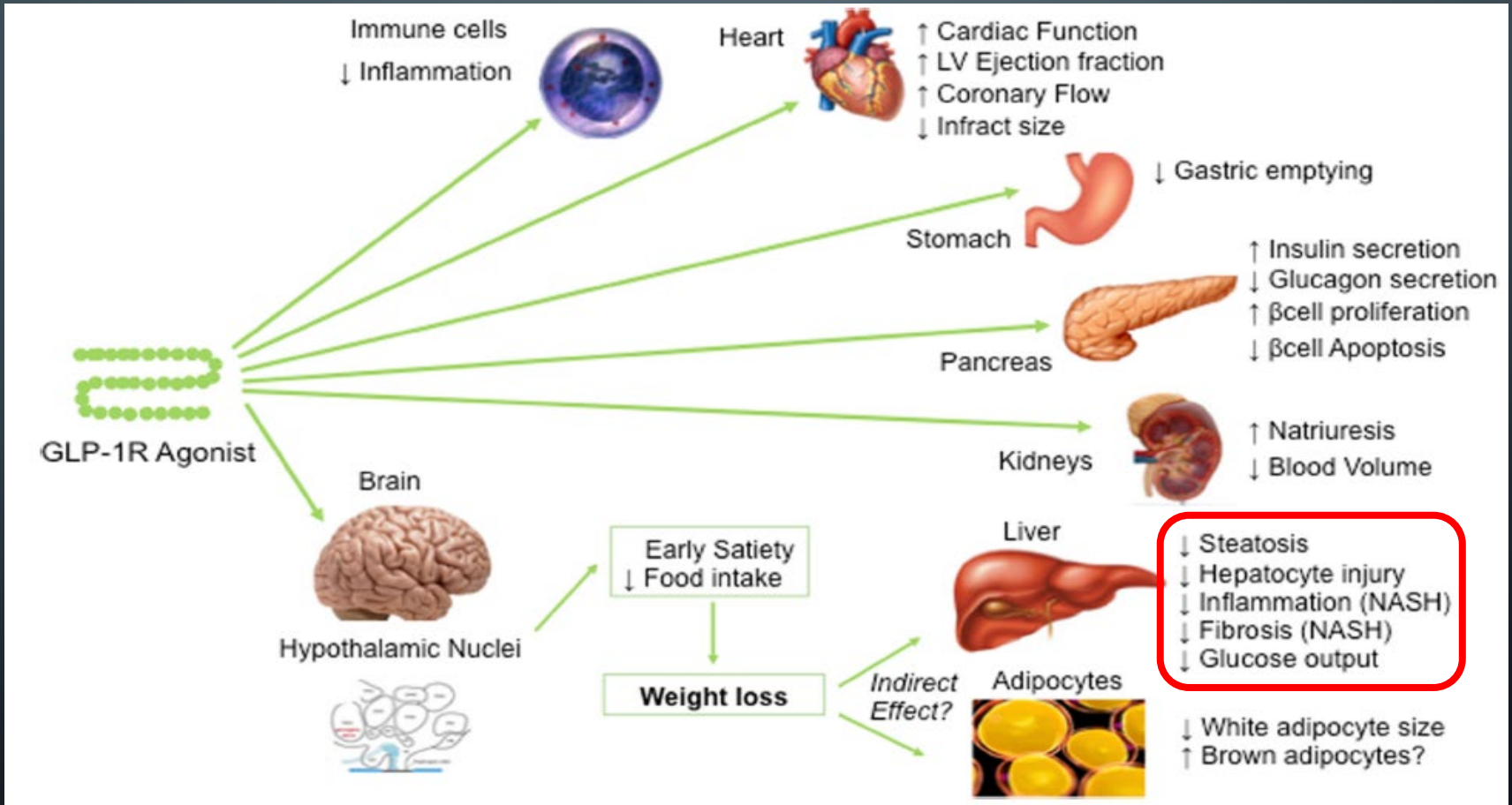
Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

Variable	Placebo	Vitamin E Pioglitazone	Pioglitazone	P Value*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	−0.1	−0.7	−0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.004
Mean change in score	−0.2	−0.6	−0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	−0.2	−0.5	−0.4	0.03	0.01
Total NAFLD activity score (mean change)	−0.5	−1.9	−1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	−0.1	−0.3	−0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

Sanyal, Arun J., et al. "Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis." *New England Journal of Medicine*362.18 (2010): 1675-1685.

OPZIONI TERAPEUTICHE ATTUALI

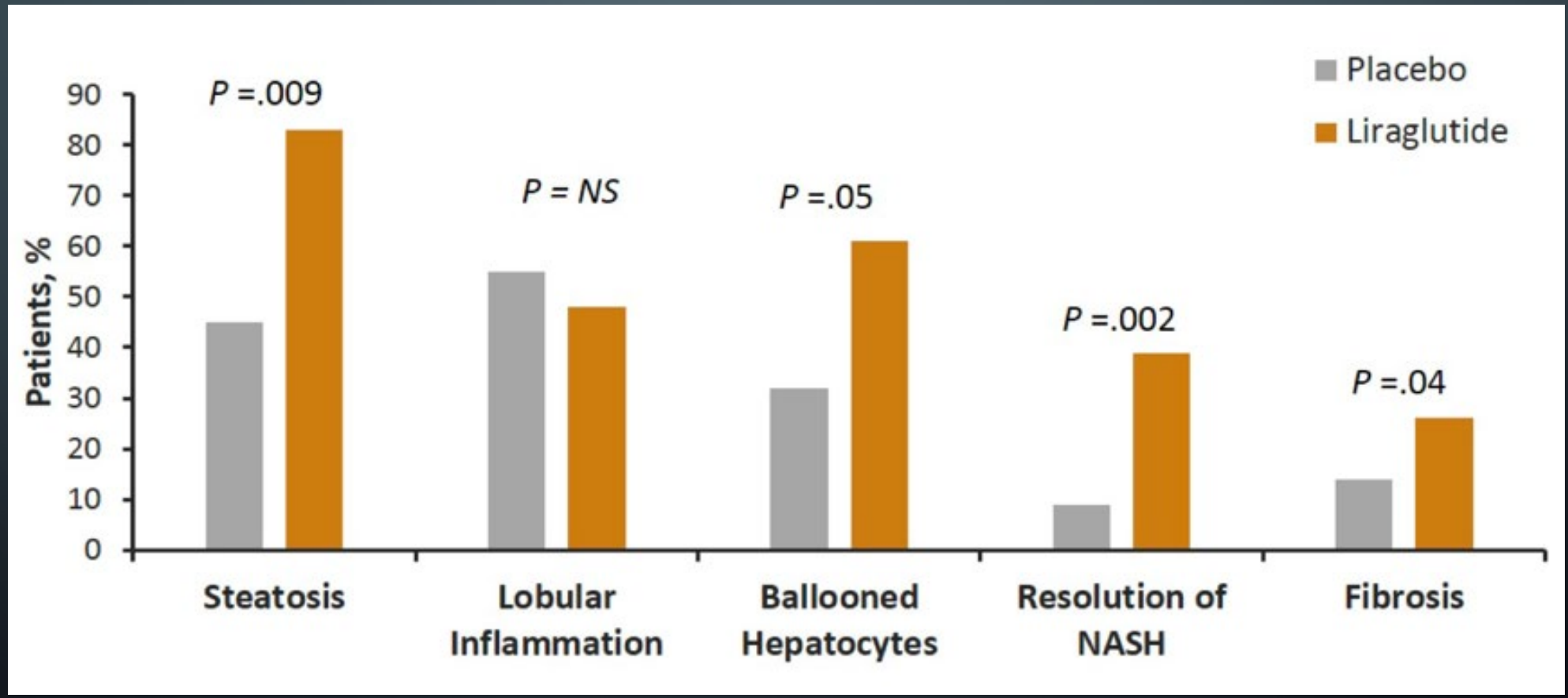
GLP-1 RA



Dhir, Gauri, and Kenneth Cusi. "Glucagon like peptide-1 receptor agonists for the management of obesity and non-alcoholic fatty liver disease: a novel therapeutic option." *Journal of Investigative Medicine* 66.1 (2018): 7-10.

OPZIONI TERAPEUTICHE ATTUALI

LIRAGLUTIDE: LEAN study



Armstrong, Matthew James, et al. "Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study." *The Lancet* 387.10019 (2016): 679-690.

OPZIONI TERAPEUTICHE ATTUALI

INIBITORI SGLT-2

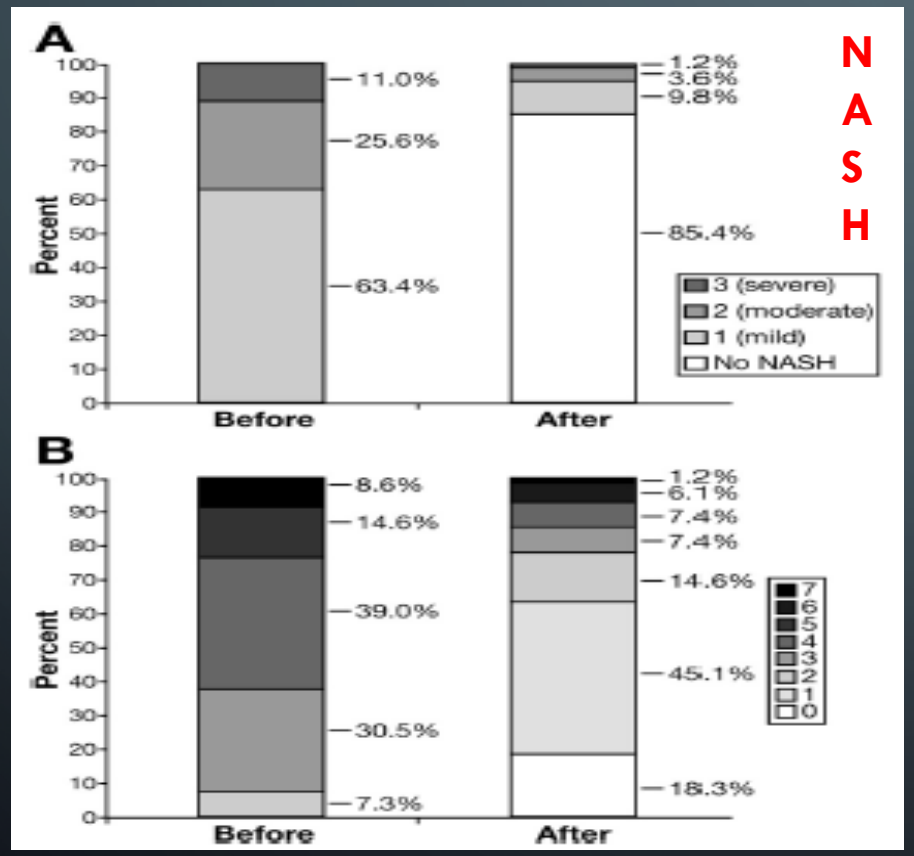
Author (nation, year)	Study design	Subjects	N	Drug	Dose	Treatment period	Evaluation	Liver	Others	Correlated factor with ALT reduction level
Ohki (Japan, 2016)	Case series	T2DM with NAFLD resistant to DDP-4 inhibitors/	24	Ipragliflozin	50mg/d	320 days (median)	Biochemistry	↓ ALT ↓ FIB4 index	↓ BW	Not shown
Komiya (Japan, 201										respective of W reduction
Leiter (Canada, 2										orrelation ith HbA1c nd BW eductions ot shown
Iizuka (Japan, 201										
Takase (Japan, 201										ot shown Changes in LI correlated with A1c reductions)
Seko (Japan, in press)	Two centers, retrospective	T2DM with biopsy-proven NAFLD	24	Canagliflozin Ipragliflozin (vs. DPP-4 inhibitor)	100mg/d 50mg/d	24wk	Biochemistry InBody	↓ AST, ALT ↓ γGT	↓ Body fat	Inespective of BW and HbA1c reduction

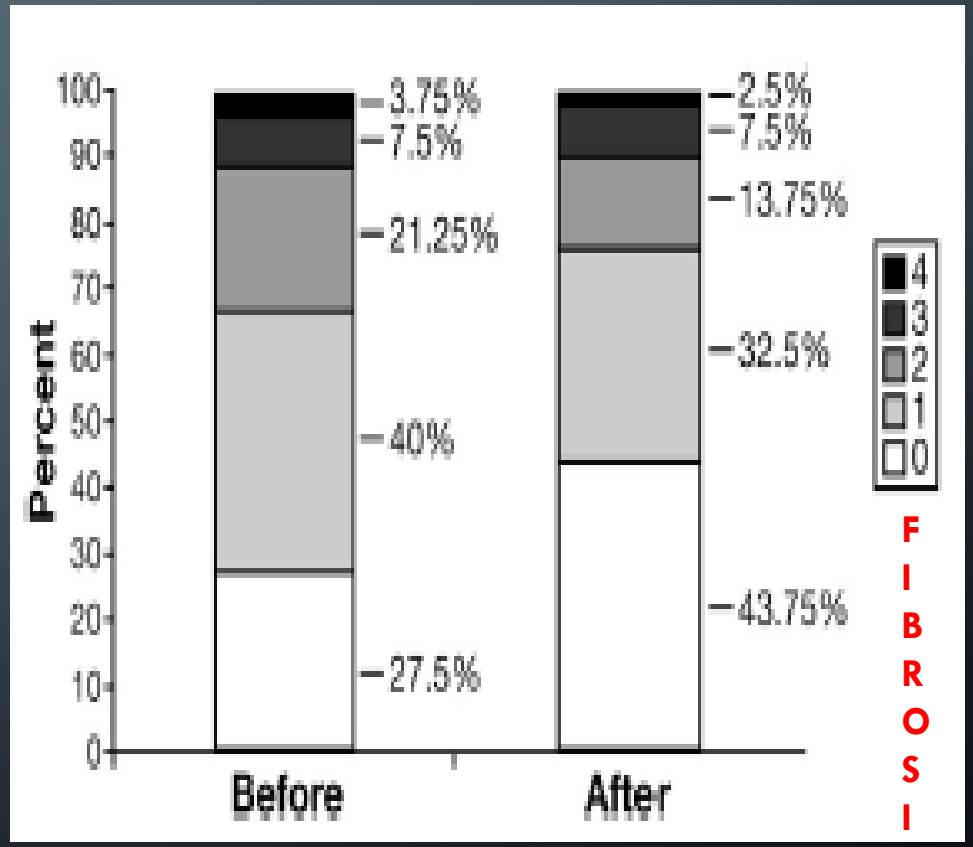
NESSUN DATO SU EVENTUALI MIGLIORAMENTI A LIVELLO ISTOLOGICO

Sumida, Yoshio, et al. "Novel antidiabetic medications for non-alcoholic fatty liver disease with type 2 diabetes mellitus." *Hepatology Research* 47.4 (2017): 266-280.

OPZIONI TERAPEUTICHE ATTUALI

CHIRURGIA BARIATRICA





Lassailly, Guillaume, et al. "Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients." *Gastroenterology* 149.2 (2015): 379-388.

OPZIONI TERAPEUTICHE ATTUALI

STATINE

- **Nessuno studio dimostra in maniera diretta la capacità delle statine di rallentare la progressione o favorire la risoluzione di NAFLD (3 RCTs risultati contrastanti, 1 RCT non ha raggiunto l'endpoint primario).**

- **L'utilizzo delle statine in pazienti diabetici con epatopatia cronica secondaria a NAFLD è sicuro**

	Patients Newly Started on a Statin (n = 19)		
Variable	**At Enrollment**	**After 18 Months**	***P* Value**
BMI, kg/m^2	35.1 ± 0.9	34.6 ± 0.9	0.06
Liver fat by ^{1}H-MRS, %	13 ± 2	8 ± 2	<0.001
ALT, IU/L	66 ± 8	38 ± 5	<0.001
AST, IU/L	48 ± 6	31 ± 3	0.006
Patients with ALT > 40 IU/L, %	67	39	0.10
Hemoglobin A1c, %	6.2 ± 0.2	6.2 ± 0.2	0.86
Total cholesterol, mg/dL	201 ± 11	148 ± 10	<0.001
Triglycerides, mg/dL	166 (132–210)	141 (94–189)	0.04
HDL-C, mg/dL	37 ± 2	41 ± 2	0.01
LDL-C, mg/dL	127 ± 8	77 ± 6	<0.001
Muscle insulin sensitivity (*Rd*, mg/kg LBM per min)	5.8 ± 0.7	5.5 ± 0.6	0.45
Suppression of EGP, %	43 ± 5	37 ± 5	0.34
Suppression of FFA, %	41 ± 5	49 ± 4	0.02
NAFLD activity score	3.9 ± 0.3	3.7 ± 0.5	0.40
Steatosis grade	1.7 ± 0.2	1.4 ± 0.2	0.10
Inflammation grade	1.5 ± 0.1	1.6 ± 0.2	0.50
Ballooning grade	0.8 ± 0.1	0.7 ± 0.1	0.43
Fibrosis stage	0.6 ± 0.2	0.5 ± 0.2	0.50

Bril, Fernando, et al. "Liver safety of statins in prediabetes or T2DM and nonalcoholic steatohepatitis: post hoc analysis of a randomized trial." *The Journal of Clinical Endocrinology & Metabolism* 102.8 (2017): 2950-2961.

OPZIONI TERAPEUTICHE ATTUALI

ALTRE TERAPIE

- **Acido ursodesossicolico (UDCA) non efficace**

  Lindor, Keith D., et al. "Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial." *Hepatology* 39.3 (2004): 770-778.

- **Acidi grassi omega-3 non efficaci**

  Sanyal, Arun J., et al. "No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial." *Gastroenterology* 147.2 (2014): 377-384.
  Scorletti, Eleonora, et al. "Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: results from the Welcome* study." *Hepatology* 60.4 (2014): 1211-1221.

- **Silymarin: efficace, ma farmaco non presente in Italia**

  Kheong, Chan Wah, Nik Raihan Nik Mustapha, and Sanjiv Mahadeva. "A randomized trial of silymarin for the treatment of nonalcoholic steatohepatitis." *Clinical Gastroenterology and Hepatology* 15.12 (2017): 1940-1949.

- **Alcolici:** «bicchiere di vino ai pasti» protettivo tranne in caso di fibrosi avanzata (F3-F4)

PROSPETTIVE FUTURE

Phase 2 Studies

- Acarbose
- Amlexanox
- Aramchol
- ARI-3037MO
- ASP9831
- Atorvastatin + L-carnitine
- AZ compound
- AZD4076
- Beta glucosylceramide
- Betaine
- BI 1467335
- BMS-986036
- Cenicriviroc (ORION)
- CF102
- Colesevelam
- Cysteamine bitartrate
- Deferasirox
- DHA
- DS102
- Emricasan
- EPA-E
- Epanova + fenofibrate
- Exenatide
- Ezetimibe
- Ezetimibe-ursodiol
- Foralumab
- GFT505
- Glucamannan
- GR-MD-02
- GS-0976
- GS-4497
- GS-9450
- GS-9674
- Hepar-P
- HL tablet
- IDN-6556
- INT-747
- IVA337
- JKB-121
- LCQ908
- Levothyroxine
- LIK066
- Liraglutide
- LJN452
- LMB763
- MB12066
- Metformin
- Metreleptin
- MGL-3196
- MitoQ
- MN-001
- MSDC 0602K
- MT-3995
- n-3 PUFA
- NGM282
- NLR972
- NS-0200
- OCA (FLINT)
- OCA + statins OKT3 (CONTROL)
- Oltipraz
- Omega-3 carboxylic acids + dapagliflozin
- Oral insulin
- Pentoxiphylline
- PF-05221304
- PF-0635919
- Pioglitazone
- Pioglitazone + berberine
- Polyunsaturated fatty acids
- Px-104
- Recombinant leptin
- Resveratrol
- Rofumalast + pioglitazone
- Rosiglitazone
- Runihol
- Saroglitazar magnesium
- Selonsertib
- Semaglutide
- Siliphos
- Silymarin
- Simtuzumab
- Sitagliptin
- Solythromycin
- Spironolactone
- Testosterone (TEREPINS)
- Tipekulast
- TRO19611
- Ursodesoxycholic acid
- VK2809
- Vitamin D
- Vitamin E
- Volixibat

ClinicalTrials.gov website. Non-alcoholic Steatohepatitis

PROSPETTIVE FUTURE

Phase 3 Studies

Pharmacologic Agents	Plant and Food	Supplements	Other
Aramchol	Trigonella Foenum-graecum seed extract	Synbiotics supplement	Lifestyle changes
Cenicriviroc (AURORA)	Coffee main constituents (caffeine and chlorogenic acid)	Omega 3 fish oil supplements	CPAP
Cysteamine bitartrate		Flaxseed supplement	
Diacerein		DHA + choline + vitamin E	
Diamel		Resveratrol supplement	
Elafibranor		Curcumin supplement	
Eltrombopag		Ginger supplement	
Exenatide			
Liraglutide + bariatric surgery			
Losartan			
Metadoxine			
Metformin			
Obetacholic acid			
Oltipraz			
Pentoxiphylline			
Pentoxiphylline + vitamin E			
Pioglitazone vs vitamin E (PIVENS)			
Rimonabant			
S-adensyl-L-methionine			
Saroglitazar + pioglitazone			
Selonsertib			
Vitamin D			
Vitamin E			

ClinicalTrials.gov website. Non-alcoholic Steatohepatitis

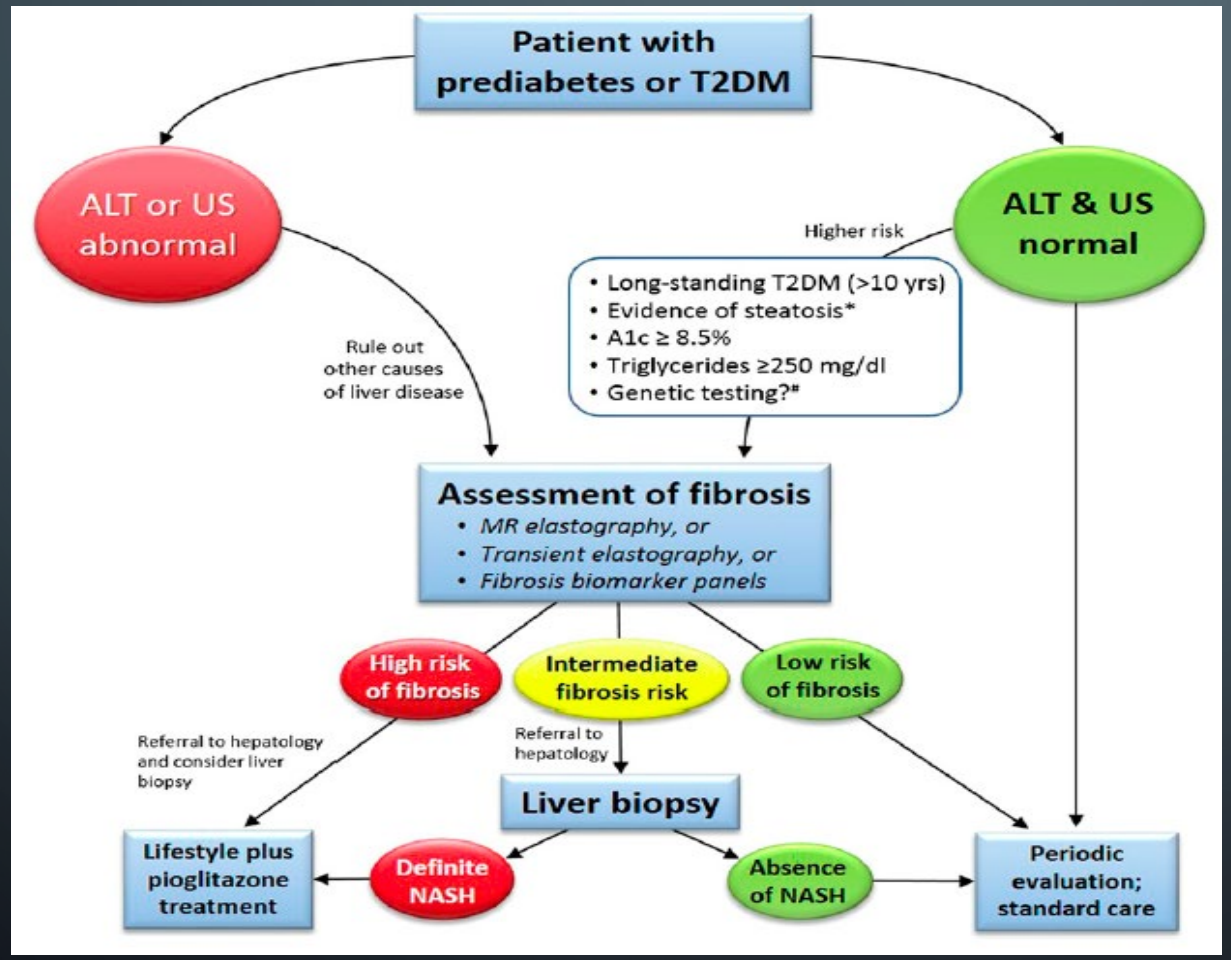
PROSPETTIVE FUTURE

Classe	Farmaco
GLP-1 analoghi	Semaglutide; Liraglutide; Exenatide
SGLT-2 inibitori	Canagliflozin; Ipragliflozin
PPAR α/δ	Elafibranor; Saroglitazar
Agonisti FXR	Acido obeticolico (OCA)
Anti-lipogenetici	Agonisti THR-β
Anti-ossidanti	Vitamina E; Cistamina
Anti-apoptotici	Selonsertib (inibitore ASK-1); Emricasan (inibitore caspasi)
Anti-infiammatori	Cenicriviroc (antagonista CCR2/CCR5)
Anti-fibrotici	Simtuzumab (anti-LOXL2); GR-MD-02 (inibitore galectina)

PROSPETTIVE FUTURE

Classe	Farmaco
GLP-1 analoghi	**Semaglutide; Liraglutide**; Exenatide
SGLT-2 inibitori	Canagliflozin; Ipragliflozin
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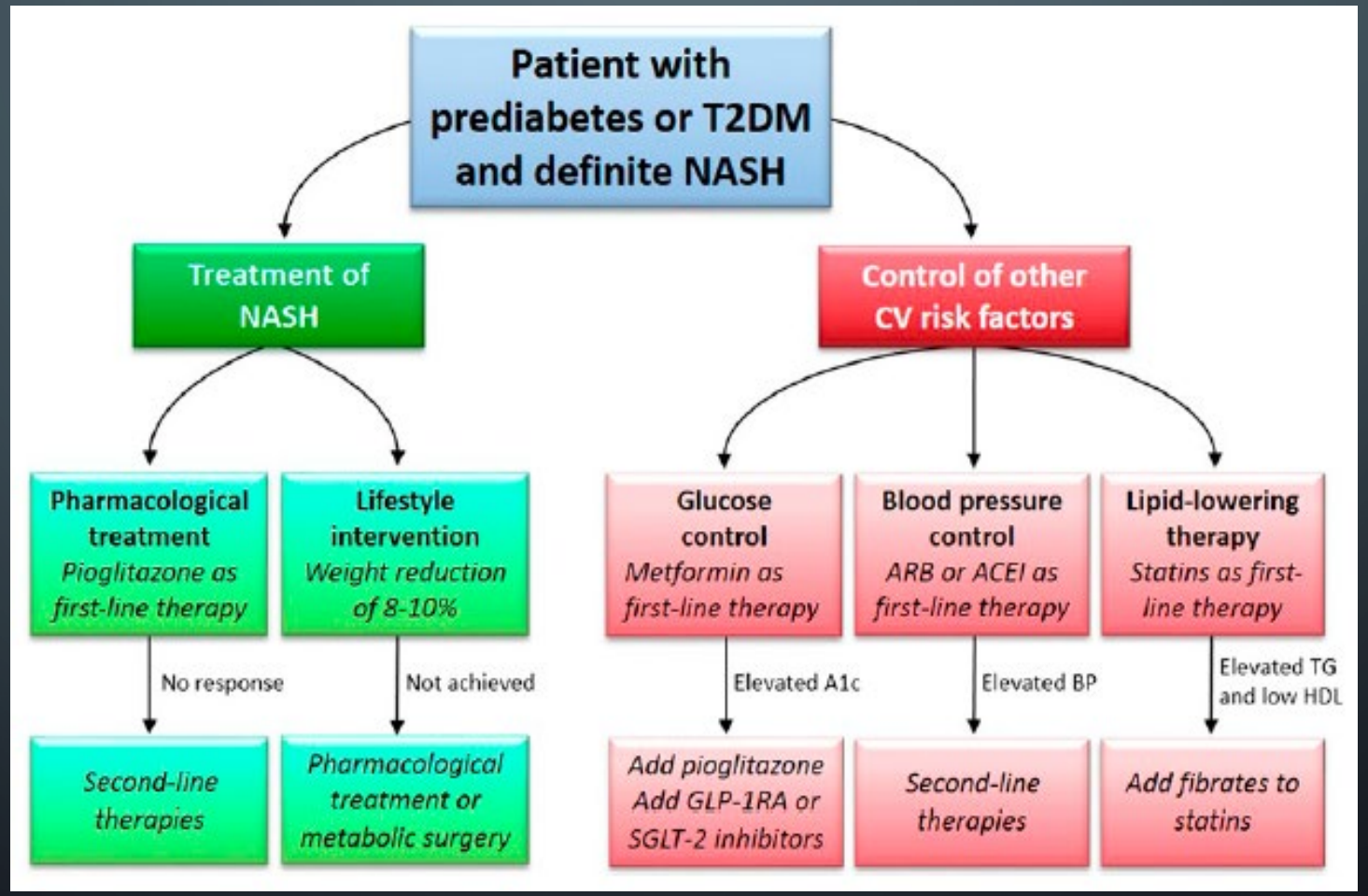
ALGORITMO MANAGEMENT NAFLD NEL PAZIENTE CON DIABETE TIPO 2



Fibrosi	Follow-up (ecografia, esami laboratorio)
Basso rischio	Ogni 2 anni
Moderato/Alto rischio o diagnosi accertata	Ogni anno
Cirrosi	Ogni 6 mesi (sorveglianza HCC)

Bril, Fernando, and Kenneth Cusi. "Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action." *Diabetes Care* 40.3 (2017): 419-430.

ALGORITMO MANAGEMENT NAFLD NEL PAZIENTE CON DIABETE TIPO 2



Bril, Fernando, and Kenneth Cusi. "Management of nonalcoholic fatty liver disease in patients with type 2 diabetes: a call to action." *Diabetes Care* 40.3 (2017): 419-430.

CASO CLINICO

DOPO 6 MESI

Età (anni)	56
HbA1c (%)	6,8
AST (U/L)	37
ALT (U/L)	34
Conta piastrinica (cell/mm^3)	176000
BMI (Kg/m^2)	31,5



CASO CLINICO

DOPO 6 MESI

Età (anni)	56
HbA1c (%)	6,8
AST (U/L)	37
ALT (U/L)	34
Conta piastrinica (cell/mm^3)	176000
BMI (Kg/m^2)	31,5
Albumina (g/dL)	3,8
NAFLD Fibrosis Score	0,77



CASO CLINICO

DOPO 7 ANNI

Età (anni)	63
HbA1c (%)	7,4
AST (U/L)	58
ALT (U/L)	75
Conta piastrinica (cell/mm^3)	130000
BMI (Kg/m^2)	32,7
Eco Addome	Steatosi severa



CASO CLINICO

DOPO 7 ANNI

Albumina (g/dL)	3,7
NAFLD Fibrosis Score	1,49
Elastografia epatica	12 kPa
Biopsia	NASH (NAS = 6) + Fibrosi F3



TAKE HOME MESSAGES

1. NAFLD complicanza frequente nel paziente con T2DM
2. NAFLD può evolvere verso forme che incrementano la mortalità malattia-specifica (cirrosi, HCC), cardiovascolare e per tutte le cause (Fibrosi F3-F4)
3. Utilizzare NAFLD Fibrosis Score o Fib-4 Index per diagnosticare fasi avanzate di fibrosi
4. Indirizzare all'epatologo per presa in carico, diagnosi e monitoraggio
5. Sottolineare l'importanza delle modifiche dello stile di vita
6. Valutare terapie specifiche per NAFLD e trattamento del diabete con Pioglitazone
7. Non dimentichiamoci della chirurgia bariatrica/metabolica

ATTUALI LINEE GUIDA SID-AMD 2018

H. EPATOPATIA STEATOSICA NON ALCOLICA (NAFLD)

Tutti i pazienti affetti da diabete mellito e/o sindrome metabolica per verificare la presenza di eventuale steatosi epatica devono essere sottoposti all'ecografia epatica (o altre tecniche di imaging radiologico), che potrà essere ripetuta periodicamente (ogni 2-3 anni) sulla base del giudizio clinico. *I A*

In tutti i pazienti affetti da diabete e NAFLD deve essere periodicamente esclusa la presenza delle forme più severe di NAFLD (NASH con fibrosi e cirrosi) mediante l'uso di biomarkers/scores non invasivi di fibrosi avanzata (FIB-4 score, NAFLD fibrosis score) e/o elastografia epatica (Fibroscan). *I B*

Un programma strutturato volto a modificare lo stile di vita deve essere sempre raccomandato nei pazienti affetti da diabete con NAFLD. *III B*

L'intervento dietetico-nutrizionale dovrebbe essere ipocalorico (nella maggior parte dei pazienti se obesi od in sovrappeso) e possibilmente strutturato secondo la composizione tipica della dieta mediterranea, evitando alimenti processati e quelli contenenti fruttosio. *I B*

Sia l'esercizio fisico aerobico che di resistenza possono contribuire a migliorare la NAFLD e la scelta tra le due tipologie di esercizio dovrebbe essere basata sul quadro clinico e le preferenze individuali del paziente. *II B*

GRAZIE PER L'ATTENZIONE!!!

RICETTA

SECONDI PIATTI

FOIE GRAS D'ANATRA DORATO, CRUMBLE ALLE MELE, GELATINA DI FRAGOLE

DI ALESSANDRO FUMAGALLI



INGREDIENTI

Per il crumble alle mele

Farina
100 gr, bianca

Zucchero
50 gr

Burro
50 gr

Spezie
1 cucchiaio, per pan pepato

Mela
1, Golden Delicious

Per la gelatina di fragole

Fragole
220 gr, polpa

Agar agar
10 gr

Per il Foie Gras

Foie gras
8 scaloppe, di 50 gr ciascuna

Sale
Pepe

Olio
1 cucchiaio, di semi

INFO BOX

Tempo di preparazione
30 m

Tempo di cottura
2 h

Categoria ricetta
Secondi Piatti

Porzioni
4