NAFLD COME FATTORE DI RISCHIO DI MALATTIE DISMETABOLICHE E CARDIOVASCOLARI

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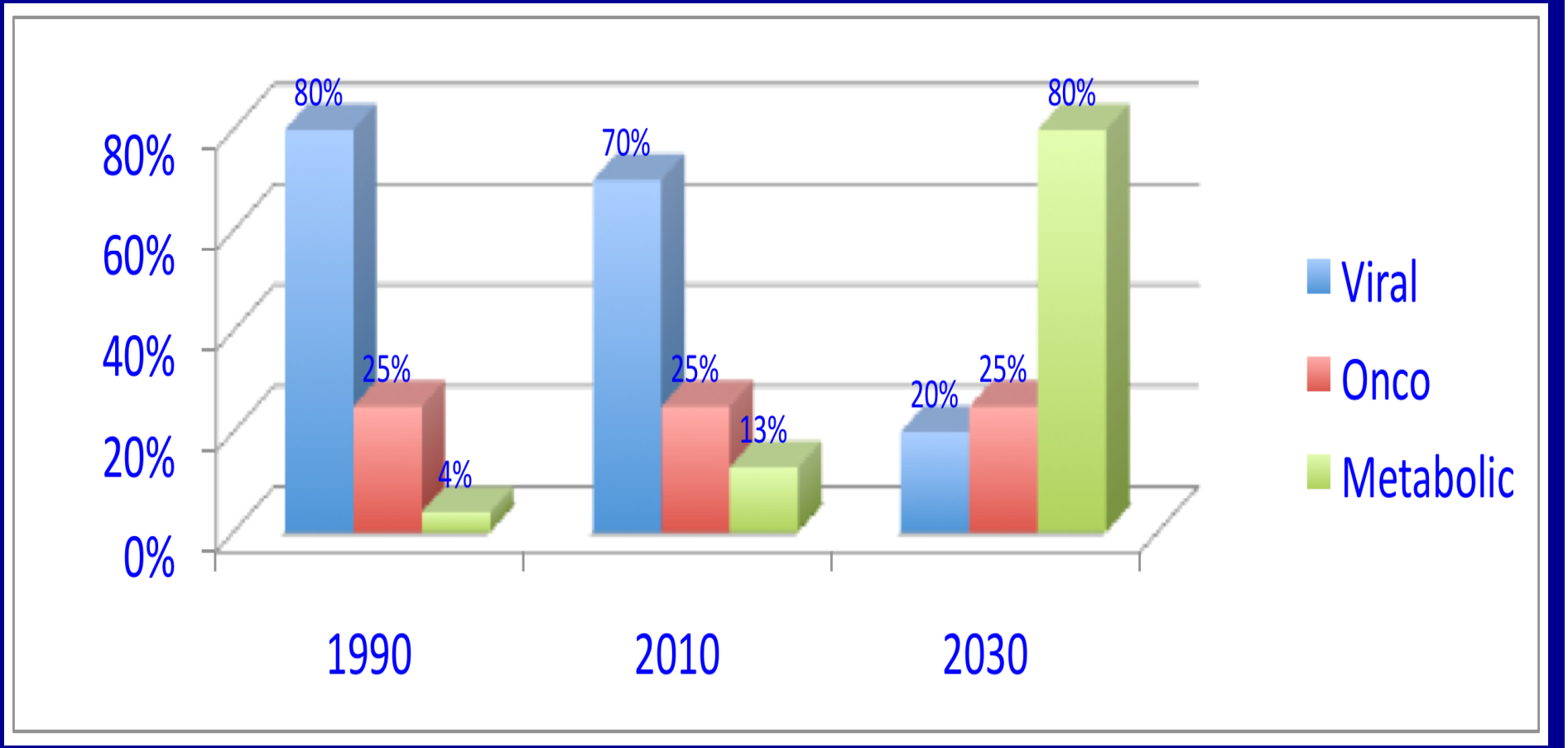
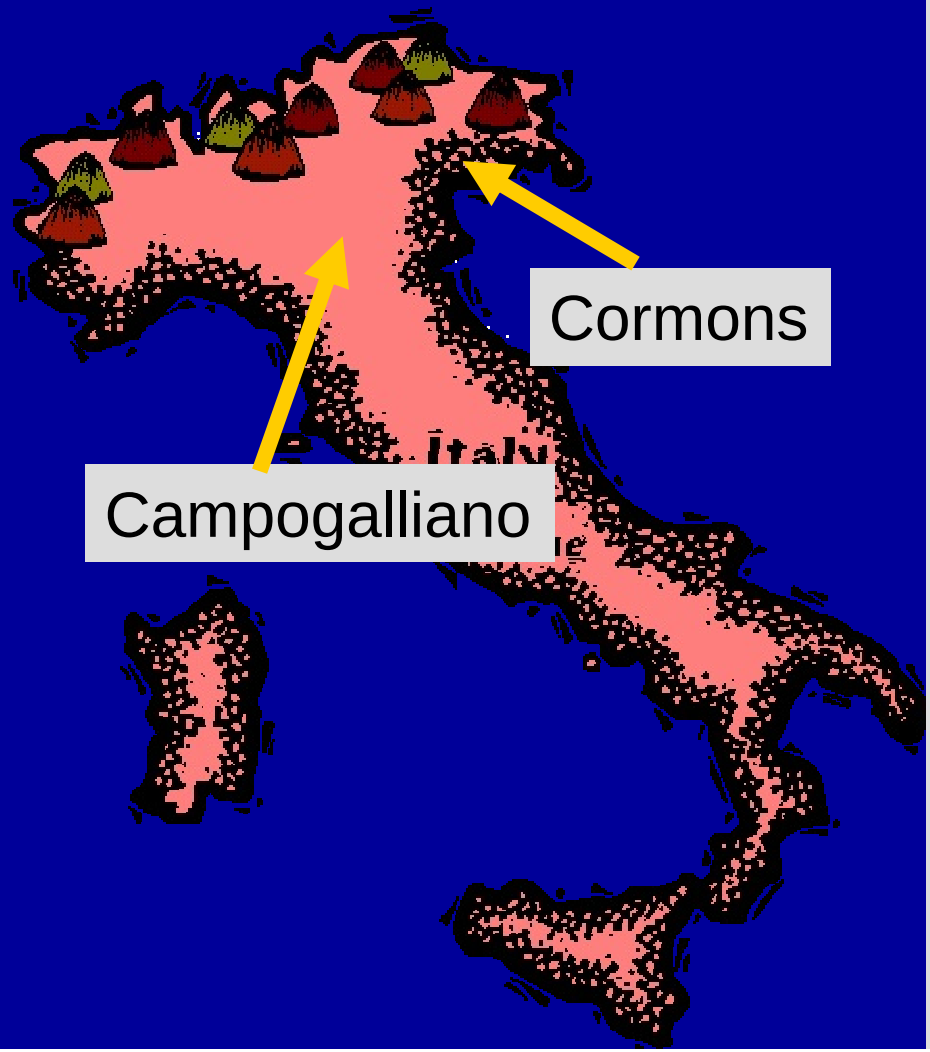
EZIOLOGIE DELLE EPATOPATIE CRONICHE: PASSATO, PRESENTE E FUTURO



Progetto Dionysos (1992-2002)



- Screening della popolazione generale (range età 12-65 anni);
- Città comparabili in termini di reddito pro-capite e caratteristiche demografiche;
- 6841 soggetti esaminati nel 1992 e 6781 nel 2002 (68% e 60% dei soggetti arruolati);
- Valutazione introito alcolico ed alimenti con diario dei 7 giorni e questionario semiquantitativo illustrato;
- AST, ALT, GGT, MCV, piastrine, HBsAg, Anti-HCV;
- Anamnesi farmacologico e storia di epato-patie;
- Esame obiettivo, BMI;

Italy: The Dionysos Study

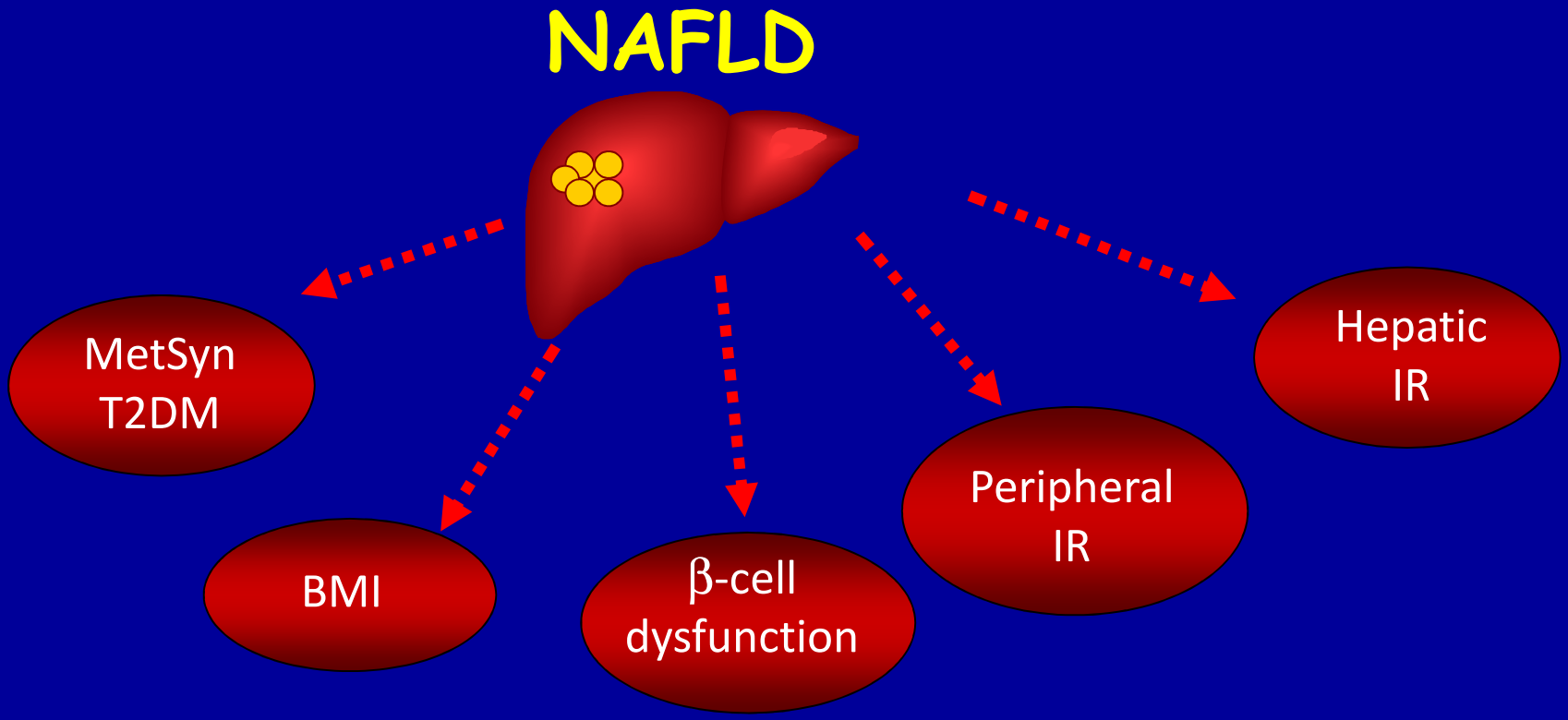
	Condition Prevalence	Liver disease Prevalence	
		Among exposed	*General Population*
HCV	**3,2%** (221/6917)	50% (110/221)	**1,6%** (110/6917)
HBV	**1,2%** (83/6917)	25% (21/83)	**0,3%** (21/6917)
Alcohol*	**21%** (1349/6917)	5,5% (74/1349)	**1,1%** (74/6917)
NAFLD	**25%** **(1729/6917)**	**7,9-11,9%** **(138-207/1729)** **estimated**	**2-3%** **(138-207/6917)** **estimated**

**Risk threshold for developing liver disease (> 30 gr/day x both sexes)*

Bellentani S et al, Dig Dis 2010
Bedogni G et al, Hepatology 2005
Bellentani S et al, Gut 1999
Bellentani S et al, Gut 1997
Bellentani S et al, Hepatology 1994

Cosa è la NAFLD (Steatosi Epatica Non Alcolica)

- NAFLD è una malattia cronica del fegato caratterizzata da accumulo di grasso intraepatico in assenza di abuso di alcol (<20-30 g/giorno) & altre cause identificabili
- NAFLD è associata a insulino-resistenza
- NAFLD rappresenta la manifestazione epatica della sindrome metabolica



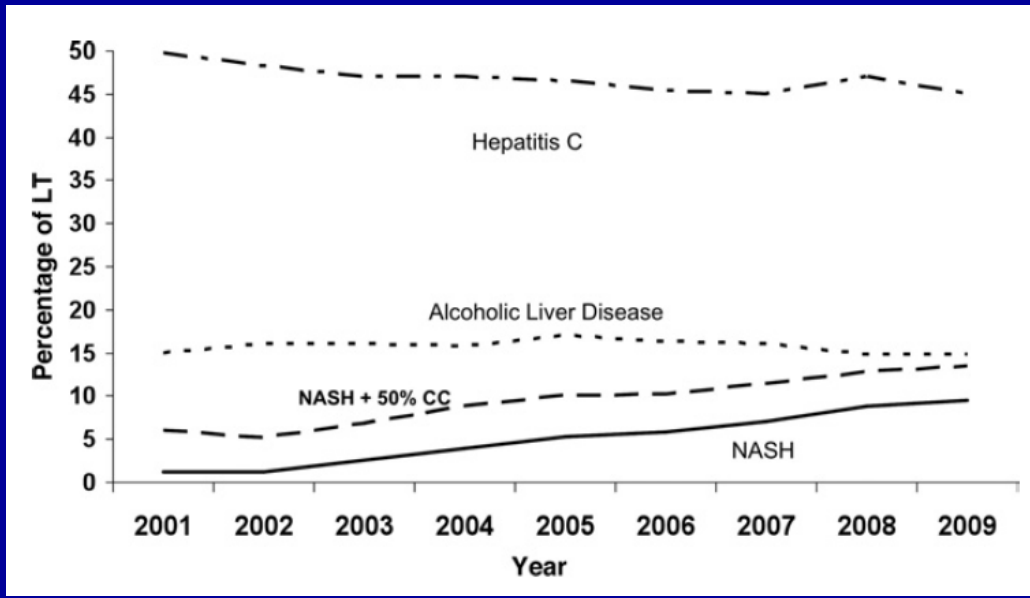
PREVALENZA DELLE EPATOPATIE IN POPOLAZIONE GENERALE

Eziologia dell'epatopatia	**Prevalenza**
NAFLD	Fino al 33%
HCV	2%
Epatopatia alcolica	1%
HBV	0,3-0,4%
Emocromatosi da mutazioni del gene *HFE*	1:200-1:400
Epatopatie autoimmuni	Fino a 17/100.000
Deficit di α1-antitripsina	1/1500-1/7600
Malattia di Wilson	1/30.000

Loria P, Dig Liver Dis. 2010;42:272-82.

"NASH è oggi la terza indicazione al trapianto epatico in USA ed è in incremento costante tanto da diventare tra breve la cuasa piu' comune."

Charlton MR, Gastroenterology. 2011;141:1249-53.



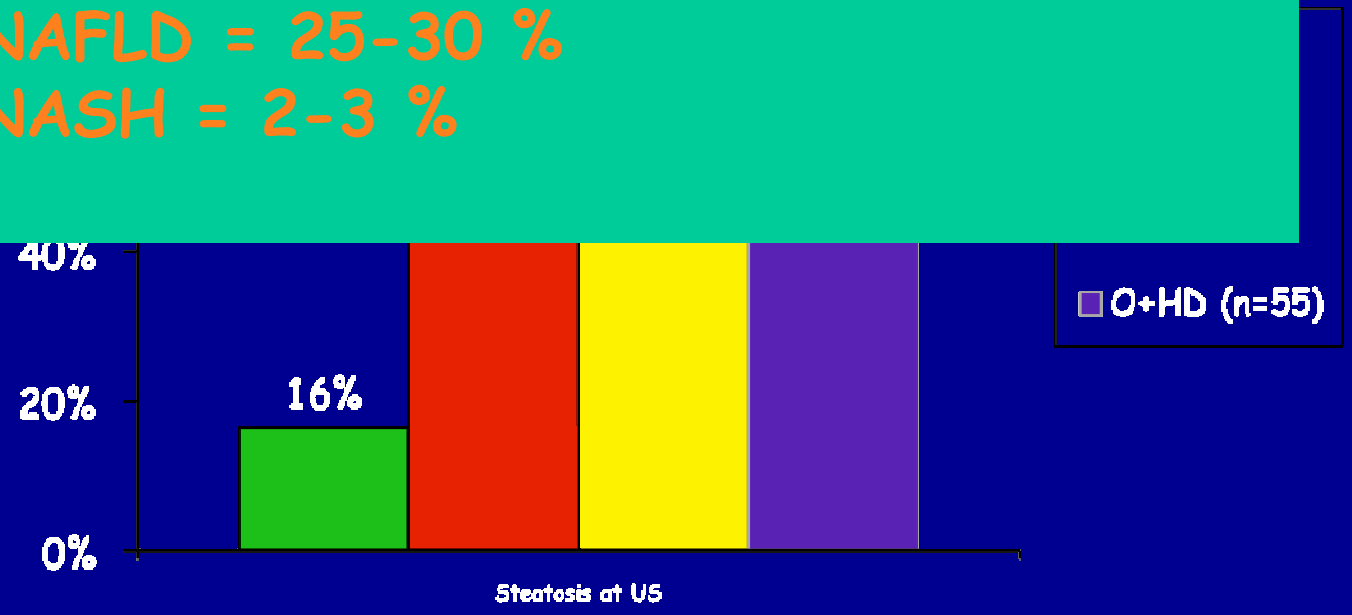
Fegato grasso nello studio Dionysos

Prevalenza

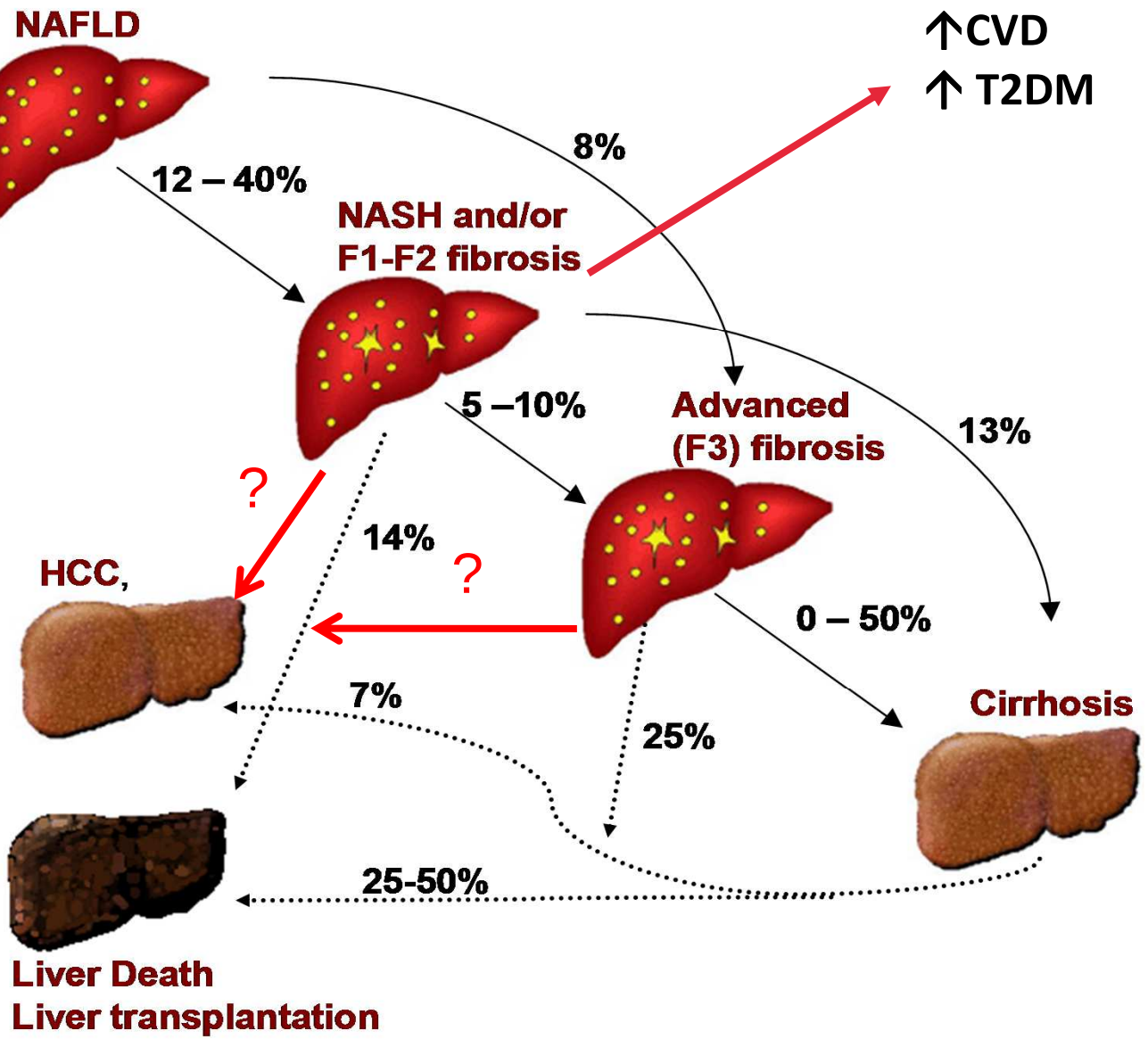
FL = 58.3%

PREVALENZA NELLA POPULAZIONE GENERALE IN ITALIA:

NAFLD = 25-30 %
NASH = 2-3 %

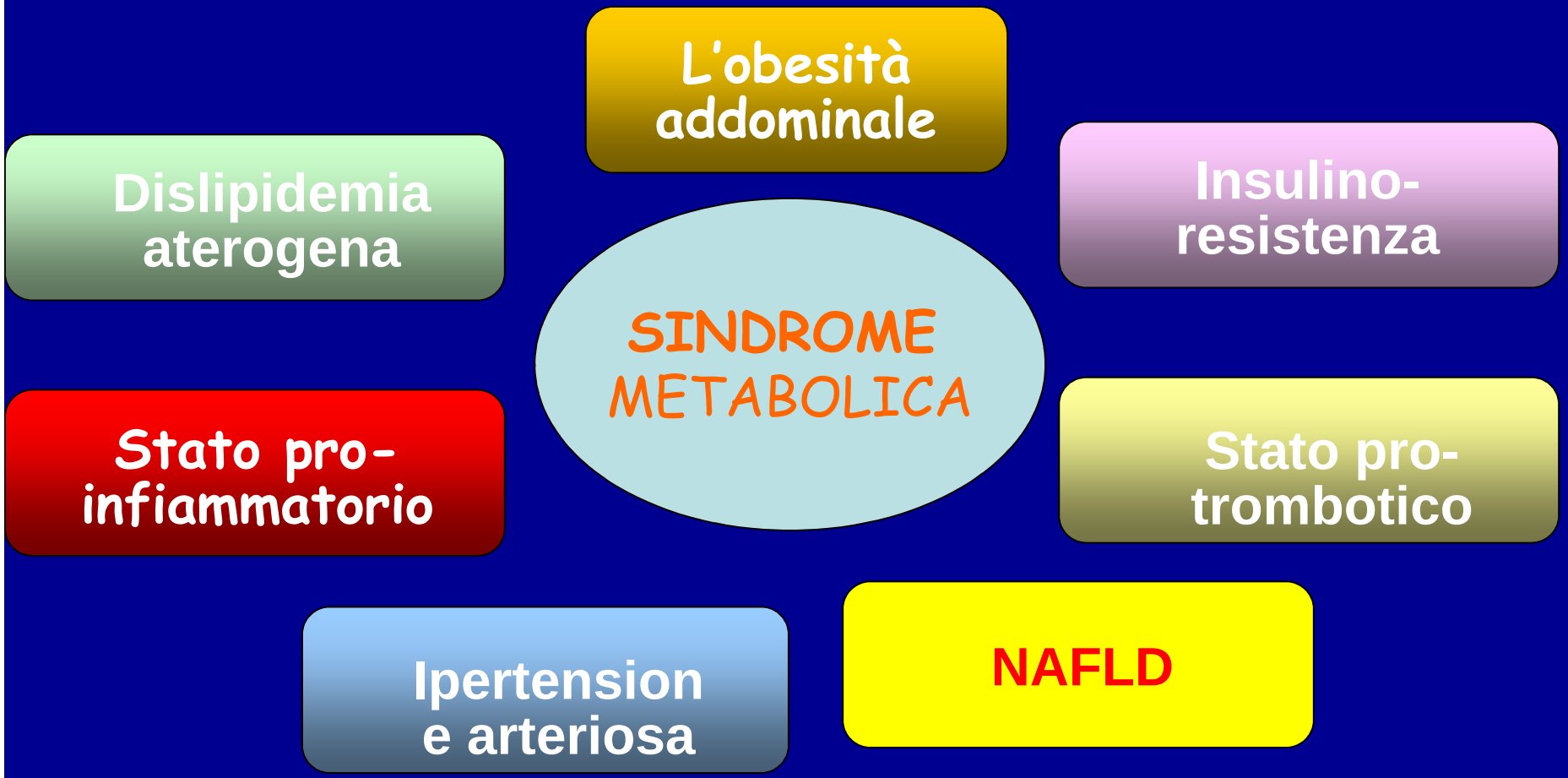


Bellentani et al., Ann.Int.Med., 2000



de Alwis and C Day, J Hepatol, 2008, S104

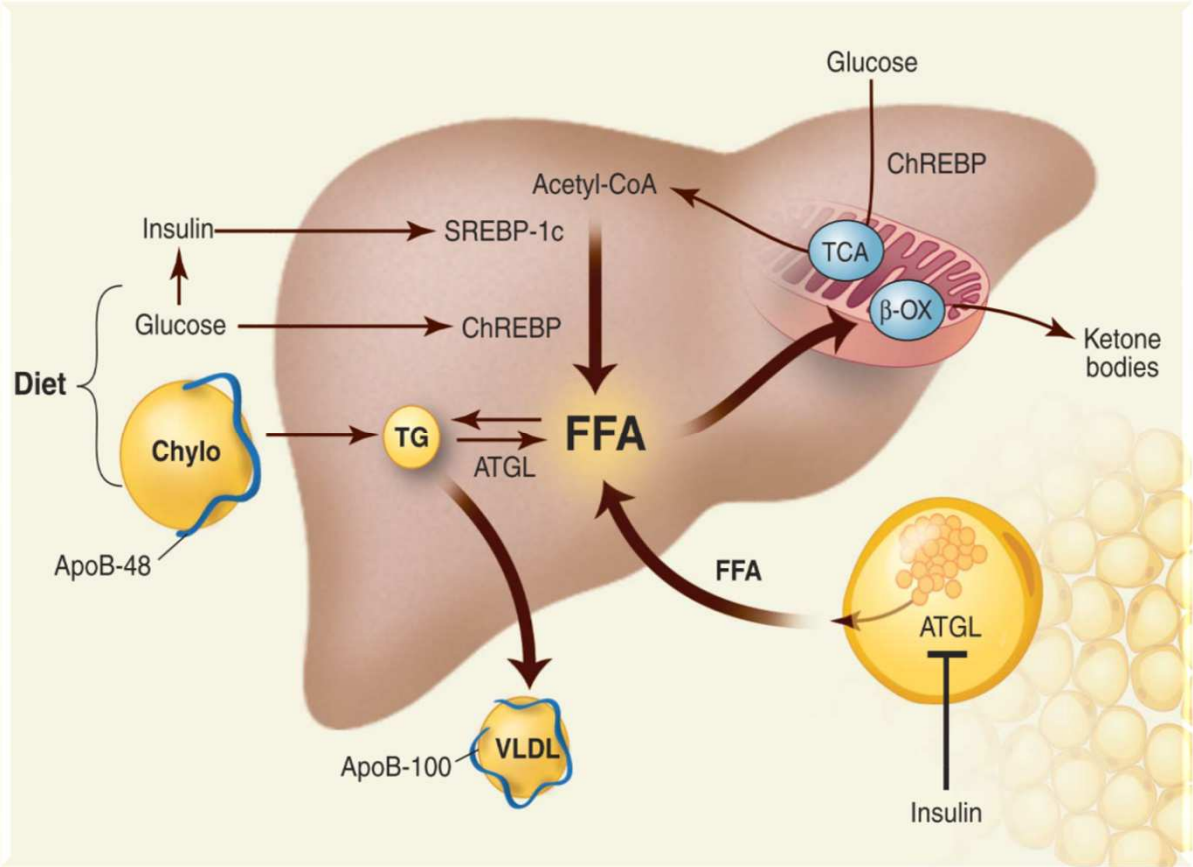
COMPONENTI DELLA SINDROME METABOLICA



National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III)

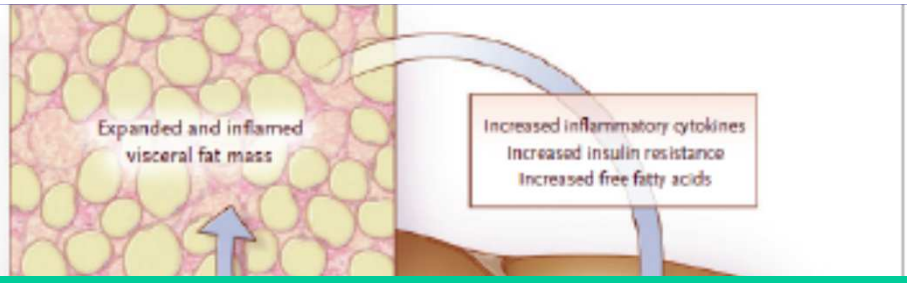
Dunque è sul fattore obesità viscerale e insulino-resistenza che bisogna porre l'attenzione?

NAFLD e insulino-resistenza



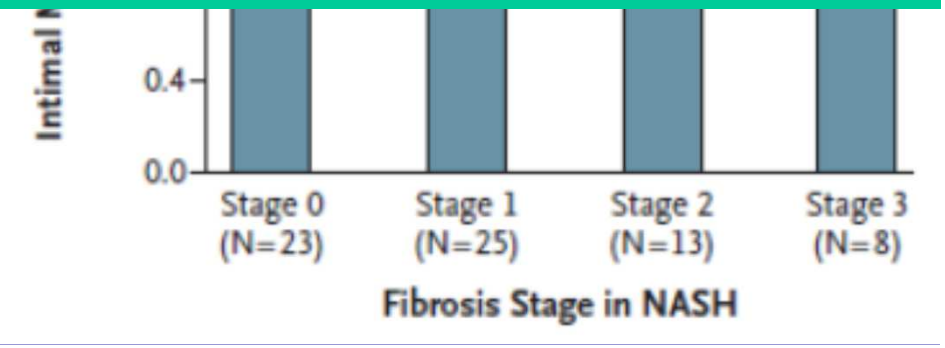
- Aumentata sintesi TGL (steatosi)
- Aumentata ossidazione (stress ossidativo)

Cohen JC et al. Science 2011



"Le evidenze attuali suggeriscono di mettere in atto pe
la NAFLD strategie di monitoraggio per le malattie
cardiovascolari.
I pazienti con NAFLD, specialmente quelli con NASH,
sono candidati ad un precoce ed aggressivo trattament
non solo della loro epatopatia ma anche dei rischi
associati di MCV, perchè molti di loro svilupperanno in
futuro eventi CV maggiori o moriranno di MCV prima ch
si sviluppi una cirrosi epatica o un HCC."

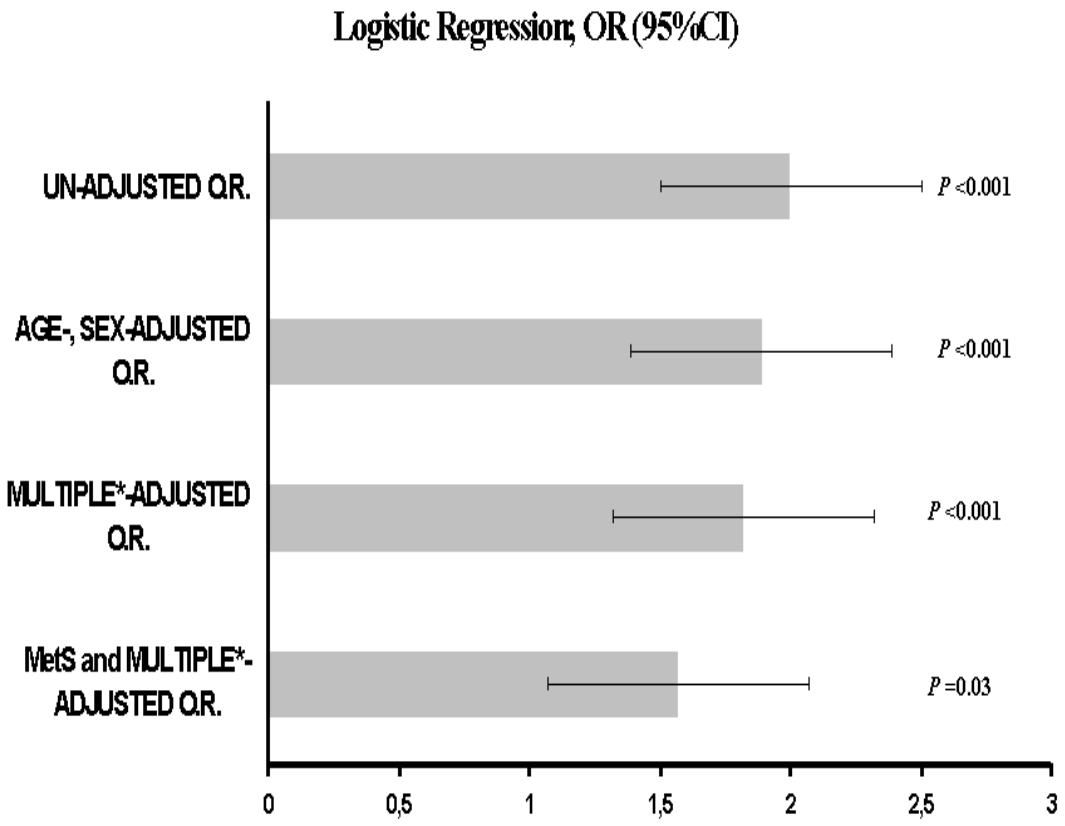
Targher et al., NEJM, 2010



Fattori di rischio per NAFLD/NASH

- Il piu' documentato e' l'obesità viscerale (WC): 30% degli obesi ha NAFLD;
- Età > 45
- Sesso maschile
- Ipertensione
- Iperlipidemia
- Diabete tipo 2 o IR
- Sindrome metabolica
- Grado di infiammazione alla biopsia iniziale
- Fruttosio nella dieta

La NAFLD è un fattore di rischio cardiovascolare indipendentemente dal T2DM



2,839 T2DM

81.5%: NAFLD (Ecografia)

NAFLD *vs* non-NAFLD

(p<0.001):

-↑ malattia coronarica

(26.6 vs. 18.3%)

- ↑ malattia cerebrovascolare

(20.0 vs. 13.3%)

- ↑ vasculopatia periferica

(15.4 vs. 10.0%)

Targher et al Diabetes Care 2007

NAFLD E MCV : SUMMARY

L'insulino resistenza *"per se"* è sufficiente per indurre dislipidemia e aterosclerosi nell'animale sperimentale.

Nell'uomo la NAFLD è associata con:

1- Disfunzione dell' endotelio vascolare

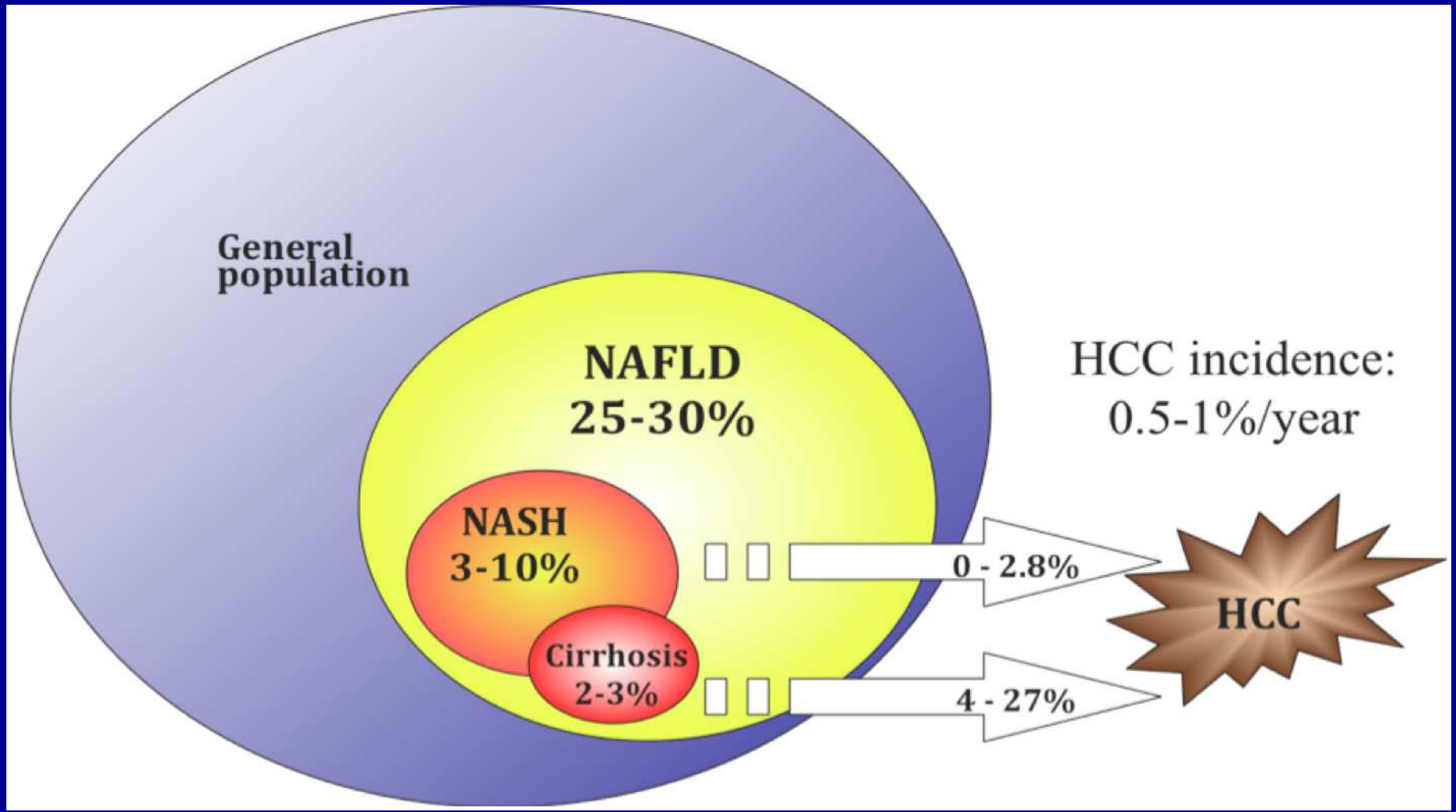
2- Alterazione dei markers surogati di aterosclerosi

3- Alterazione del metabolismo energetico del ventricolo sinistro

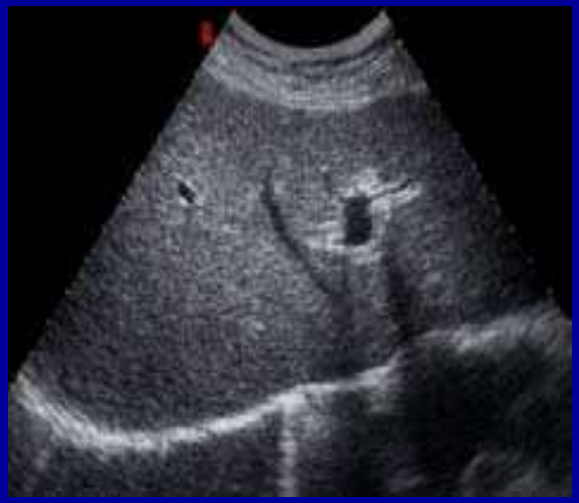
4- Aumeto della espressione di mediatori dell'infiammazione

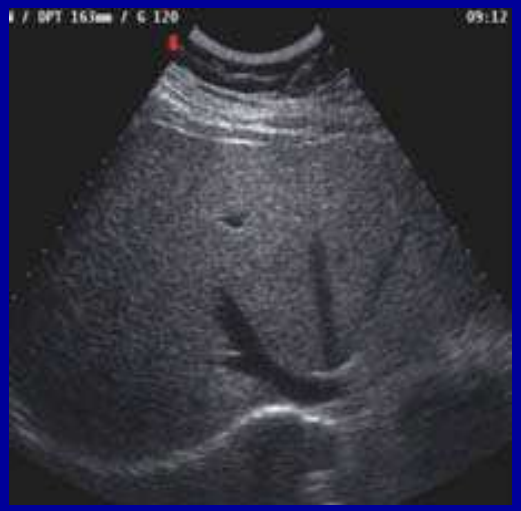
Ratziu V, Bellentani S et al. EASL NAFLD/NASH Position Paper J.Hepatol., 2010

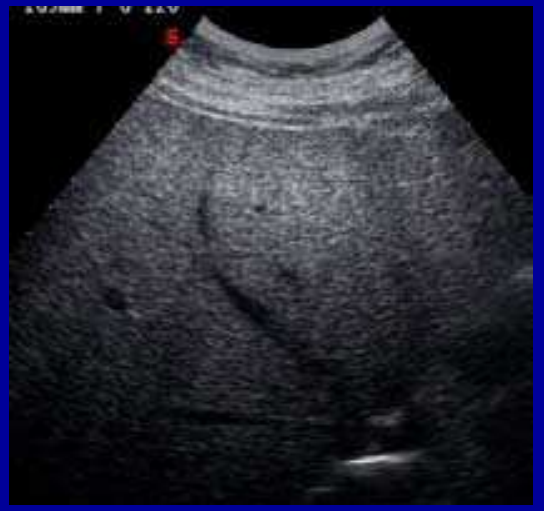
L'EPIDEMIA DI NAFLD/NASH E DI NASH-CIRROSI E PREVALENZA DI HCC NELLA POPOLAZIONE GENERALE

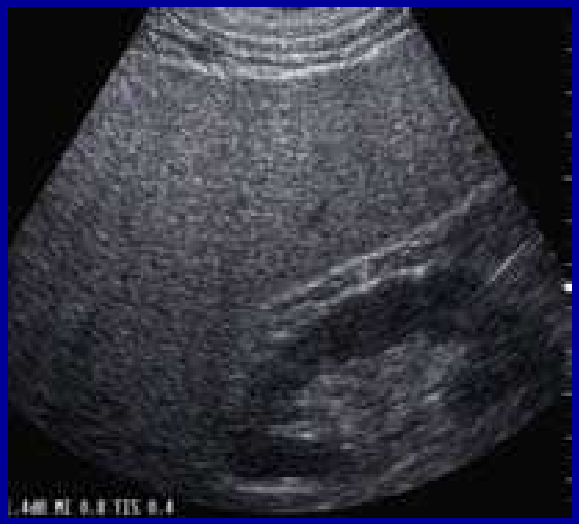


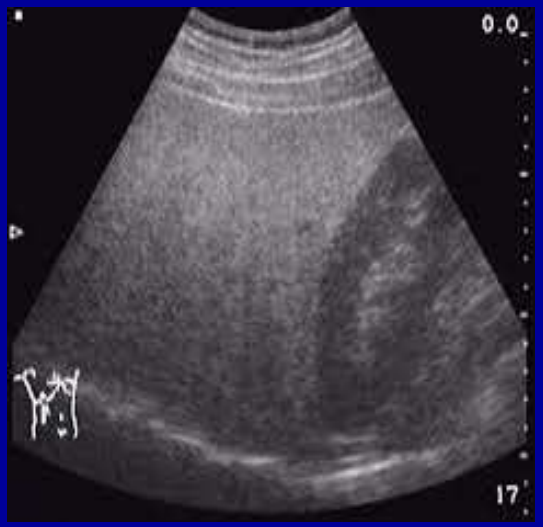
STABILIRE LA DIAGNOSI DI NAFLD: DIAGNOSI DI STEATOSI

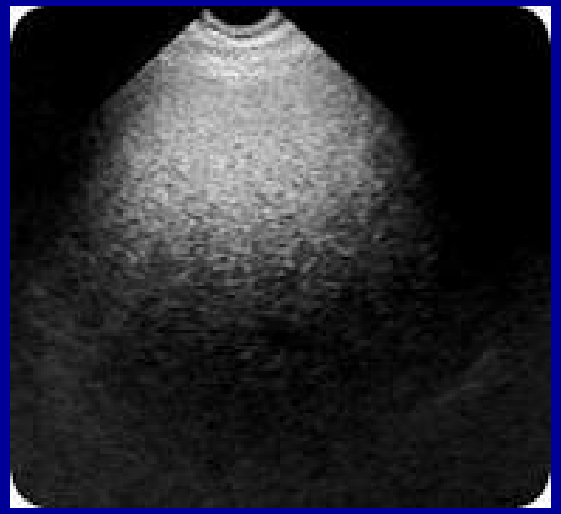








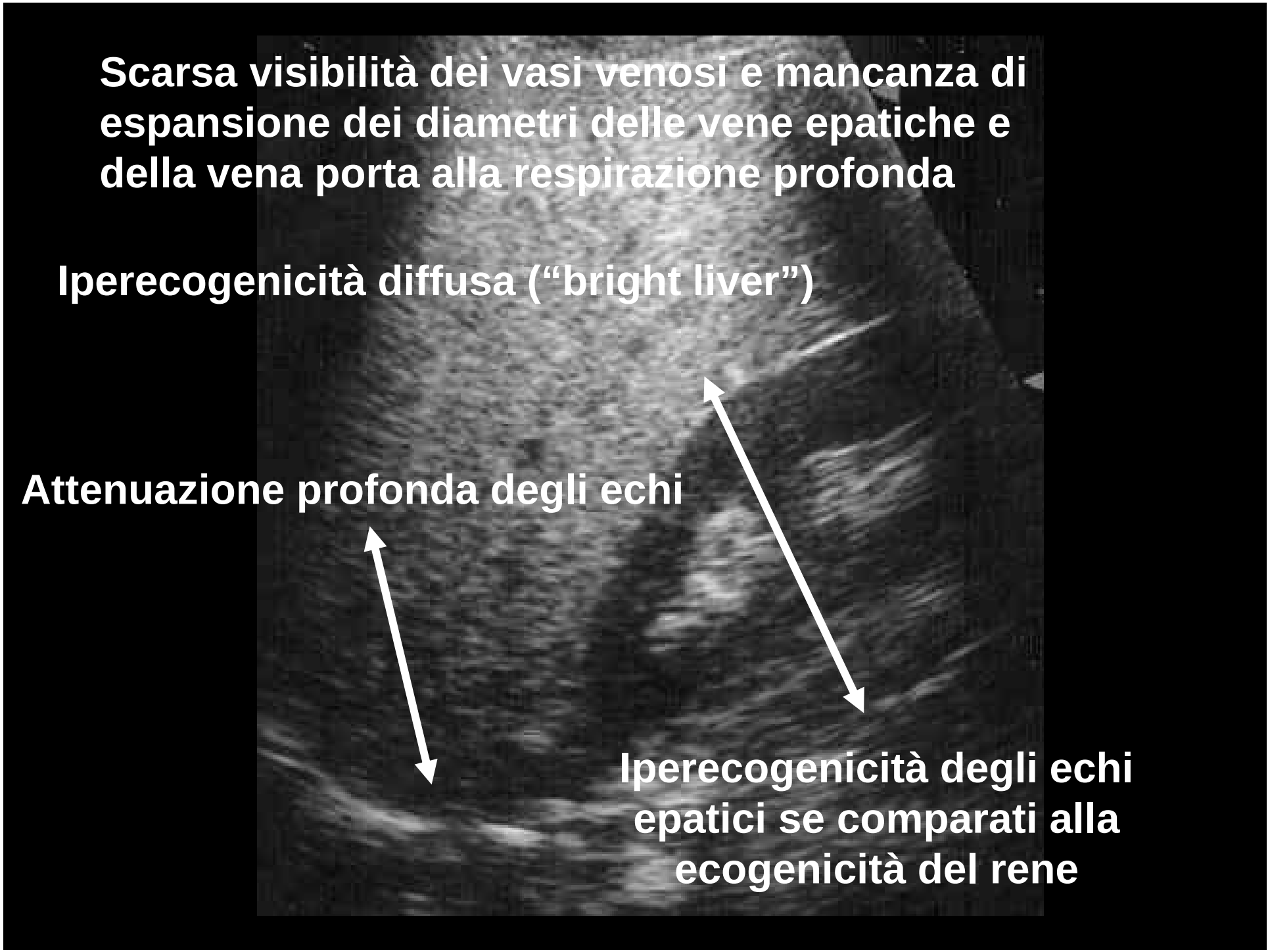


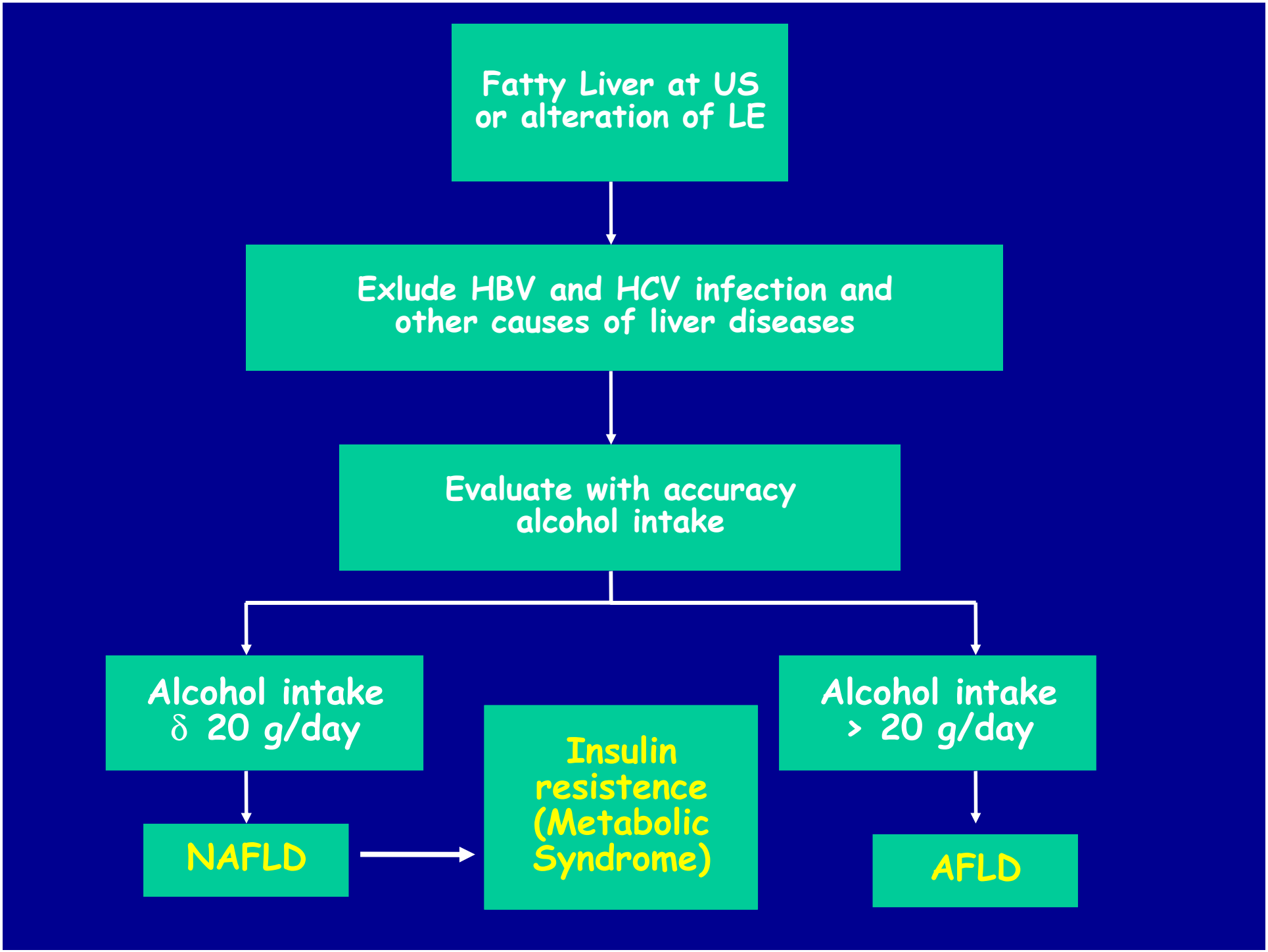


Lieve

Moderata

Severa


Scarsa visibilità dei vasi venosi e mancanza di espansione dei diametri delle vene epatiche e della vena porta alla respirazione profonda
Iperecogenicità diffusa (“bright liver”)
Attenuazione profonda degli echi
Iperecogenicità degli echi epatici se comparati alla ecogenicità del rene


Fatty Liver at US
or alteration of LE
Exlude HBV and HCV infection and
other causes of liver diseases
Evaluate with accuracy
alcohol intake
Alcohol intake
δ 20 g/day
Alcohol intake
> 20 g/day
NAFLD
Insulin
resistence
(Metabolic
Syndrome)
AFLD

NAFLD/NASH DIAGNOSI

Importante per il paziente in Primary Care identificare i predittori di:

Steatosi (FLI, …. CAP NEL FIBROSCAN)

IR e NASH (FLI, biopsia epatica …)

Fibrosi (Fibroscan, Score di fibrosi)

HCC (Ecografia … a chi ?)

DIAGNOSIS OF FATTY LIVER: THE FLI INDEX

www.amicidelfegato.it

	Predictors	logits
Triglicerydes (mg / dL)	200	5,049
BMI (Body Mass Index) (kg / m^2)	27	3,753
GGT (U / L)	45	2,733
Waist Circumference (cm)	98	5,194
Constant	**********	-15,745
Sum	**********	0,984

Fatty Liver Index (FLI) is **73**

Use this table for interpretation of FLI:

If FLI is > 60 you have > 85% probability of FL

If FLI is < 30 you have > 86% probability of NON having FL

Bedogni G et al.,BMC Gastroenterol. ,2006

FLI NELL'AMBULATORIO DEL MMG COME PREDITTORE

- Steatosi epatica (Bedogni et al., BMC Gastroenterol. 2006)
- Insulino-resistenza (Gastaldelli et al., Hepatology 2009)
- Malattia cardiovascolare (Gastaldelli et al., Hepatology 2009)
- Diabete (Balkau et al., BMC Gastroenterology, 2010)
- Mortalità generale

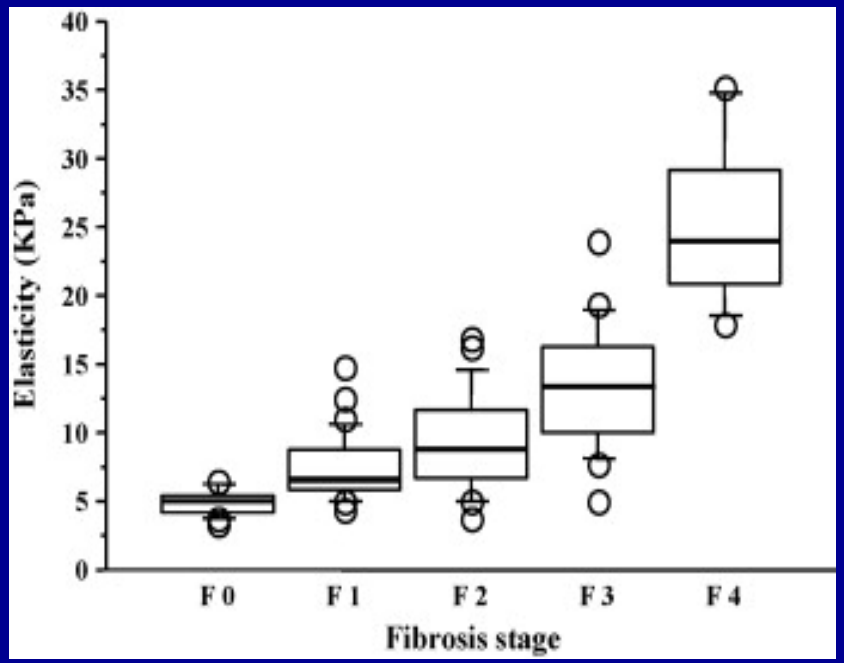
TEST PREDITTORI DI FIBROSI E NASH

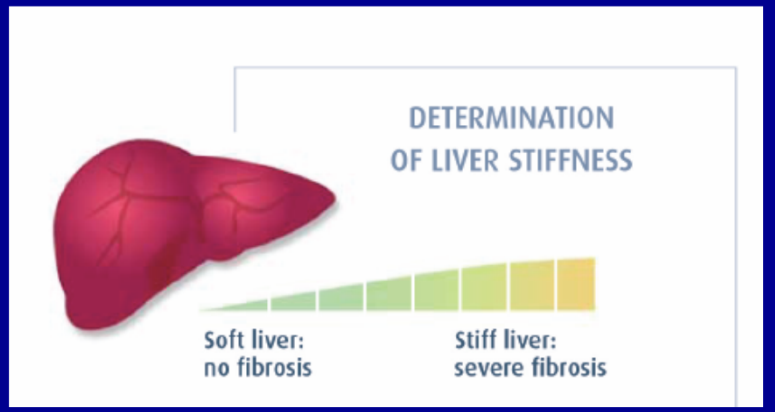
- Imaging: nessuna tecnica imaging è in grado di diagnosticare NASH o fibrosi in assenza di cirrosi
- Score ed algoritmi per fibrosi

- ELASTOGRAFIA (FIBROSCAN, ARFI ???)

- Biopsia Rimane il "Gold" o "Best" standard

Elastografia (Fibroscan) nella NAFLD





(Yoneda, 2008)

Perché fare la biopsia epatica nella NAFLD ?

Steatosi vs. NASH

↓

DIAGNOSI

NASH
Grading/Staging

↓

PROGNOSI

QUANDO FARE LA BIOPSIA EPATICA ?

Key Issues nel paziente con NAFLD/NASH per la prevenzione della progressione della malattia

- Valutazione non-invasiva del passaggio da NAFLD a NASH (FLI, CAP ???)
- Valutazione non invasiva del grado di fibrosi (NAFLD-fibrosi score ? Fibroscan ?
- Valutazione del rischio cardiovascolare (calcolo con tabelle, TSA)
- Valutazione del rischio metabolico (pattern lipidico, obesità viscerale (WC), pressione arteriosa, IR)
- Valutazione della funzionalità renale e screening Ca colon-retto e per HCC (colonscopia ed ecografia)

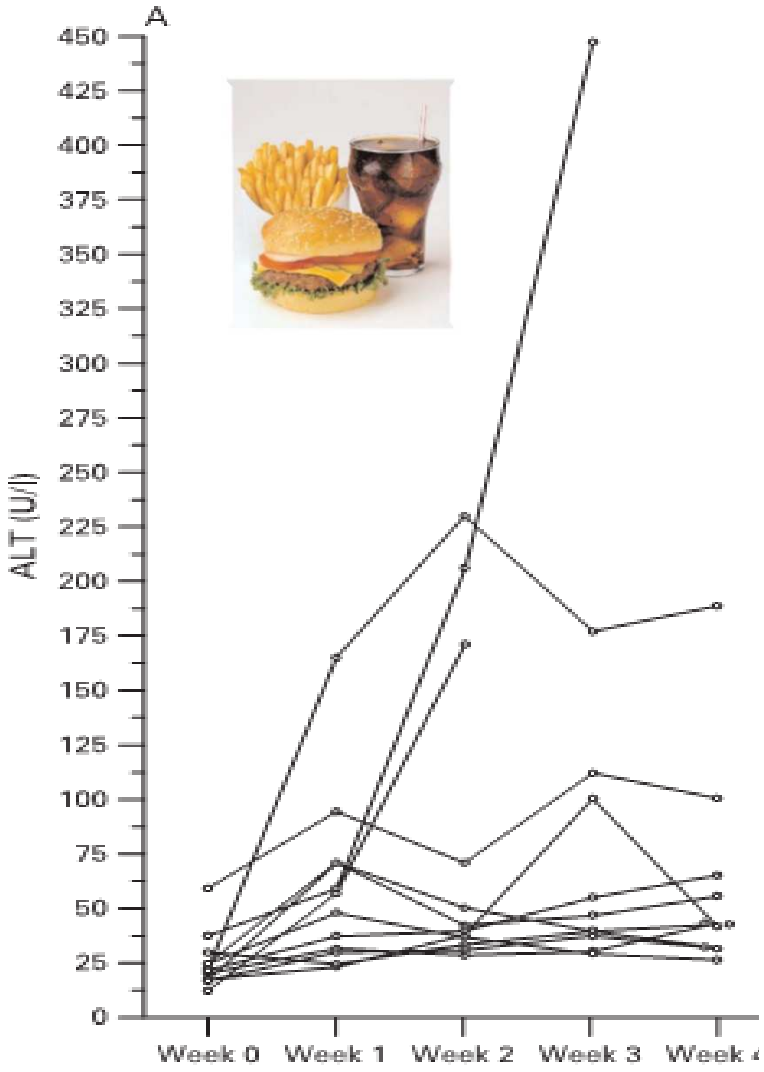
QUALE TRATTAMENTO PER LA NASH ?

- C’è necessità di un trattamento ?
- Quale tipo di trattamento ?
  - Non farmacologico (dieta, cambio stile di vita, nutraceutici)
  - Farmacologico: abbiamo bisogno di farmaci ?
  - Chirurgico
- Quali farmaci utilizzare ? Ne esistono di efficaci ?
- Ci sono ricerche o RCT in corso ?


DIET

Effetto del “Fast Food” sul fegato grasso

18 soggetti sani in4 settimane



- ✓ Doubled caloric intake by a fast food-based diet
- ✓ Limited physical activity <5000 steps/day

RESULTS:

- ✓ +6.4 kg, 10% weight gain in 4 weeks
- ✓ Serum ALT, on average from 22 U/L to 68 (+220%)
- ✓ Liver fat (MRS), 1.1% to 2.8 (+155%)

Kechagias et al, Gut 2008

‘..con un poco di zucchero ..’

- Sciroppo di acero ad alto contenuto di fruttosio:
  - Cibo piu’ palatabile
  - Riduce senso di sazietà centrale (effetto sulla grelina)
- Dieta ad alto indice glicemico
- Il caramello usato come colorante in molte salse e’ ricco in prodotti terminali ad alto contenuto di glicati.
- Aumentato consumo di carne rossa

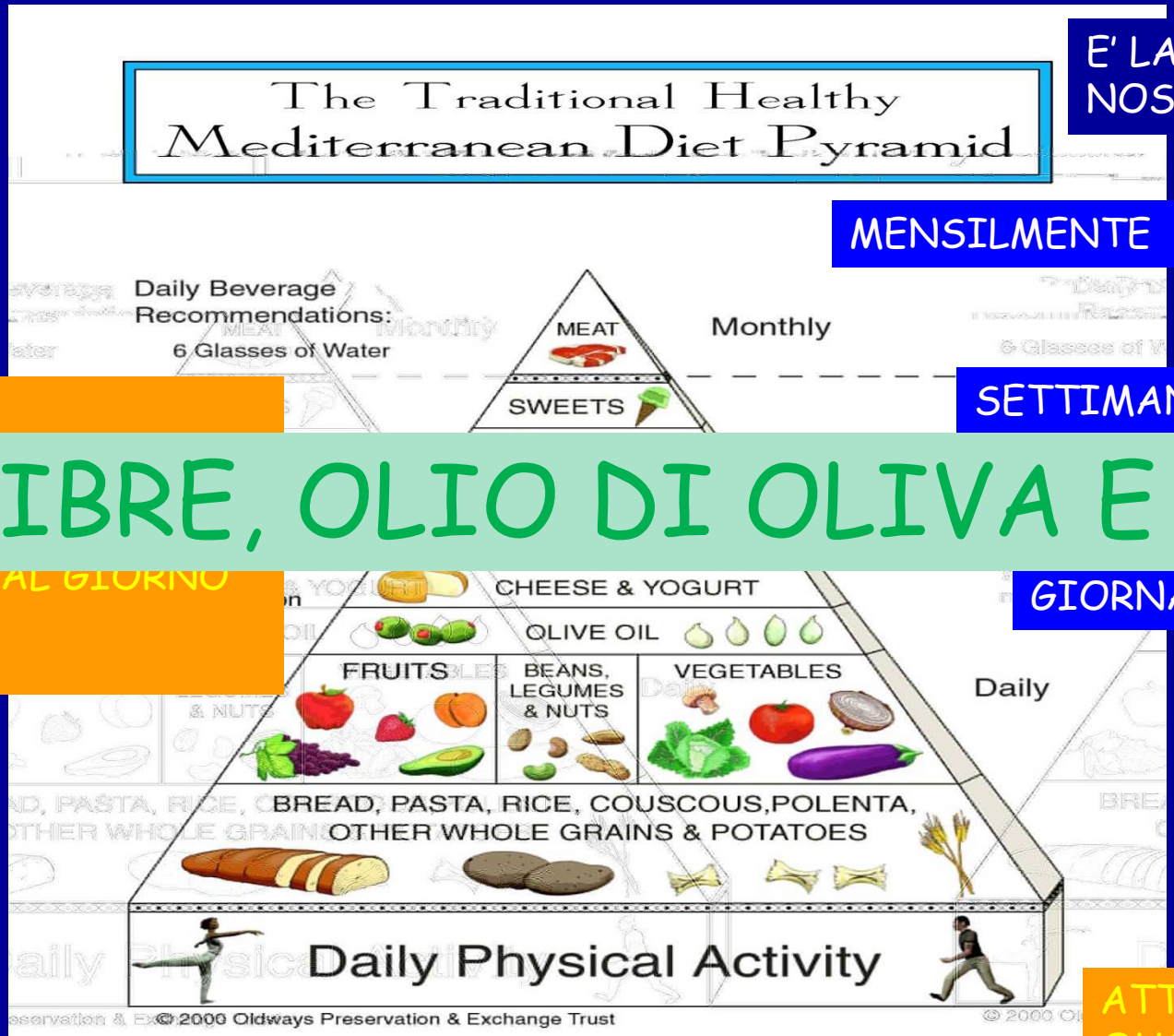

COMMENT

The toxic truth about sugar

Added sweeteners pose dangers to health that justify controlling them like alcohol, argue Robert H. Lustig, Laura A. Schmidt and Claire D. Brindis.

Lustig RH el al, Nature 2012

PIRAMIDE ALIMENTARE della dieta mediterranea "salutistica"



E' LA DIETA DEI NOSTRI AVI!!

MENSILMENTE

SETTIMANALMENTE

FIBRE, OLIO DI OLIVA E NOCI

AL GIORNO

GIORNALMENTE

ATTIVITA' FISICA QUOTIDIANA

Table 1 Main studies on Mediterranean diet in the treatment of non-alcoholic fatty liver disease

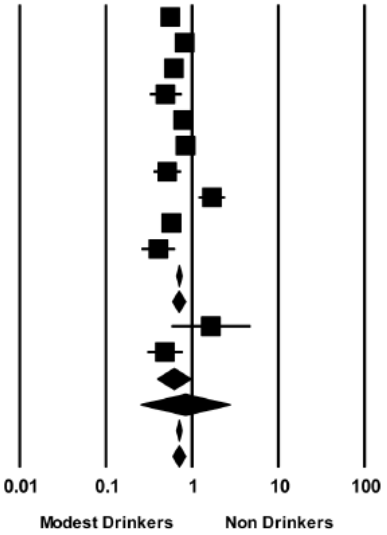
Ref.	Patients	Nutritional protocol	Metabolic and histological changes
Shai *et al*[75]	322 obese patients (277 males)	Low-fat diet MD Low-carbohydrate diet	Weight loss (kg): 2.9 low-fat diet, 4.4 MD, 5.5 low-carbohydrate diet TC/HDL reduction (20%) in the low-carbohydrate diet; decrease in fasting plasma glucose levels and HOMA-IR in MD Changes in adiponectin, leptin, ALP, ALT similar in all diet group
Tzima *et al*[76]	1514 males 1528 females	MD	Higher MD score was associated with lower likelihood of having the metabolic syndrome In patients without or with moderate adherence to the MD an increase in the AST/ALT ratio was associated with lower likelihood of having the metabolic syndrome In patients with greater adherence to the MD AST/ALT ratio was not associated with the presence of the metabolic syndrome
Pérez-Guisado *et al*[77]	31 obese patients (22 males)	Spanish ketogenic MD	Improvement in body weight Steatosis degree Reduction in BMI, systolic blood pressure and diastolic blood pressure, total cholesterol, triacylglycerols, glucose and LDLc Increase in HDLc
Ryan *et al*[78]	12 non-diabetic patients (6 males) with NAFLD	MD control diet (low fat-high carbohydrate diet)	Weight loss with both diets Significant reduction in hepatic steatosis with MD Insulin sensitivity improved with MD
Kontogianni *et al*[79]	73 overweight NAFLD patients (50 males)	MD	MD score was negatively correlated to serum alanine aminotransferase, insulin levels, insulin resistance index and severity of steatosis MD score was positively correlated to serum adiponectin levels
Trovato *et al*[80]	90 non-alcoholic non-diabetic patients (44 males)	MD	Significant decrease of bright liver score (BLS) Adherence to MD change and body mass index changes (multiple linear regression model) independently explain the variance of decrease of fatty liver involvement

NAFLD: Non-alcoholic fatty liver disease; MD: Mediterranean diet; TC: Total-cholesterol; HOMA-IR: Homeostasis model assessment for insulin resistance; ALP: Alkaline phosphatase; AST: Aspartate amino-transferase; ALT: Alanine amino-transferase; LDLc: Low density lipoprotein-cholesterol; HDLc: High density lipoprotein-cholesterol; BMI: Body mass index

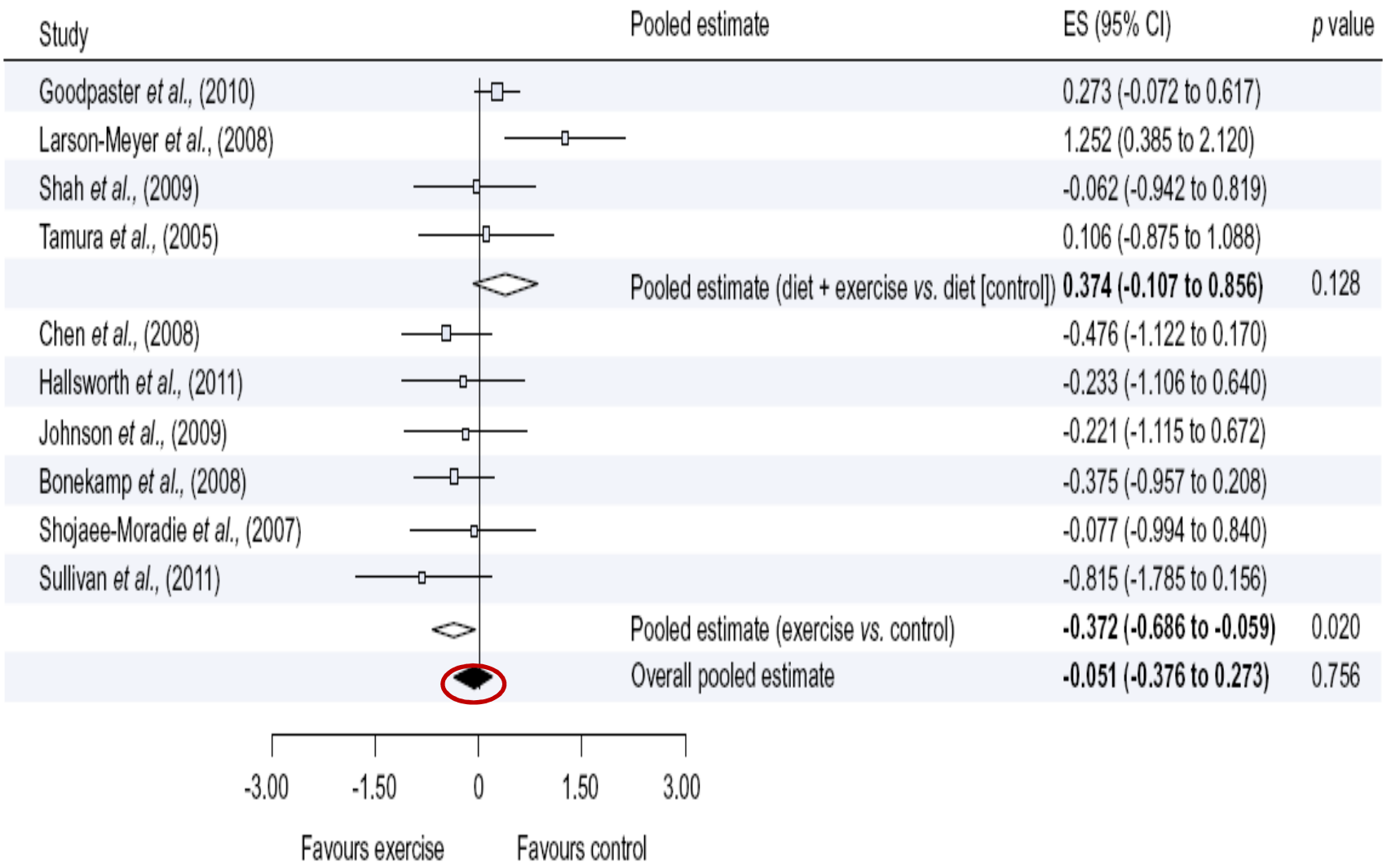
Un consumo di alcol moderato diminuisce il rischio di NAFLD: meta-analisi di 43 175 individui.

"A seconda della prevalenza della NAFLD e della NASH, gli enzimi epatici e i markers sierici di infiammazione erano piu' bassi nei soggetti che assumono una modesta quantità di alcol rispetto agli astemi"

Model	Group by Subgroup within study	Study name	Popul	Outcome	Statistics for each study: Odds ratio	Lower limit	Upper limit	p-Value
	GP	Dunn W et al, 2008	GP	NAFLD	0.561	0.443	0.712	0.0000018
	GP	Gunji T et al, 2009	GP	NAFLD	0.824	0.683	0.994	0.0431493
	GP	Hamaguchi Met al, 2012	GP	NAFLD	0.618	0.548	0.696	0.0000000
	GP	Hamaguchi Met al, 2012b	GP	NAFLD	0.493	0.319	0.764	0.0015209
	GP	Hiramine Y et al, 2011	GP	NAFLD	0.788	0.680	0.914	0.0015862
	GP	Mbriya A et al, 2011	GP	NAFLD	0.844	0.697	1.023	0.0834293
	GP	Mbriya A et al, 2011b	GP	NAFLD	0.515	0.351	0.755	0.0006678
	GP	Wong VW et al, 2012	GP	NAFLD	1.698	1.171	2.461	0.0051890
	GP	Yamada T et al, 2010	GP	NAFLD	0.576	0.481	0.691	0.0000000
	GP	Yamada T et al, 2010b	GP	NAFLD	0.406	0.255	0.646	0.0001416
Fixed	GP				0.690	0.647	0.735	0.0000000
Random	GP				0.686	0.578	0.813	0.0000139
	HB	Cotrim HP et al., 2009	HB	NAFLD	1.655	0.569	4.811	0.3546589
	HB	Sookoian S et al, 2013	HB	NAFLD	0.486	0.298	0.792	0.0038201
Fixed	HB				0.601	0.385	0.938	0.0248711
Random	HB				0.815	0.249	2.671	0.7354566
Fixed	Overall				0.688	0.646	0.733	0.0000000
Random	Overall				0.688	0.581	0.814	0.0000137



exercise vs. Control effect on liver fat



Informazione a cura del Gruppo Attività Fisica – Diabete Italia

Migliora l'umore, la qualità della vita e l'autostima!

Riduce del 15% il rischio di infarto

Riduce del 20% la glicemia

Riduce in media la pressione di 10 mmHg

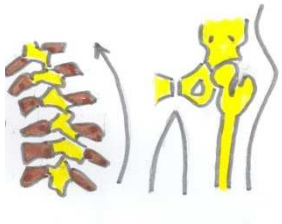
CAMMINARE TUTTI I GIORNI PER 4-5 KM

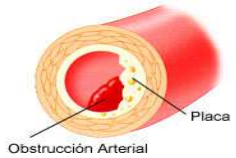
Riduce in media la circonferenza vita di 5 cm e il peso di 3 kg

Riduce l'osteoporosi e il rischio di fratture

Ritarda e ottimizza l'uso dei farmaci

Riduce del 30% i grassi del sangue





A te, cosa ti ha prescritto il Prof. Bellentani per il fegato grasso ?

Cento giri
al giorno
attorno al
suo ambulatorio,
senza entrarci.

the main difference between Europe and USA

Nutraceutici : Vitamina E

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN*

ABSTRACT

BACKGROUND

Nonalcoholic steatohepatitis is a common liver disease that can progress to cirrhosis. Currently, there is no established treatment for this disease.

METHODS

We randomly assigned 247 adults with nonalcoholic steatohepatitis and without diabetes to receive pioglitazone at a dose of 30 mg daily (80 subjects), vitamin E at a dose of 800 IU daily (84 subjects), or placebo (83 subjects), for 96 weeks. The primary outcome was an improvement in histologic features of nonalcoholic steatohepatitis, as assessed with the use of a composite of standardized scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis. Given the two planned primary comparisons, P values of less than 0.025 were considered to indi-

and P<0.001 for pioglitazone) and lobular inflammation (P=0.02 for vitamin E and P=0.004 for pioglitazone) but not with improvement in fibrosis scores (P=0.24 for vitamin E and P=0.12 for pioglitazone). Subjects who received pioglitazone gained more weight than did those who received vitamin E or placebo; the rates of other side effects were similar among the three groups.

CONCLUSIONS

Vitamin E was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes. There was no benefit of pioglitazone over placebo for the primary outcome; however, significant benefits of pioglitazone were observed for some of the secondary outcomes. (ClinicalTrials.gov number, NCT00063622.)

From Virginia Commonwealth University, Richmond (A.J.S.); Indiana University, Indianapolis (N.C.); Virginia Mason Medical Center, Seattle (K.V.K.); Case Western Reserve University, Cleveland (A.M.); Duke University, Durham, NC (A.M.D.); University of California San Francisco, San Francisco (N.M.B.); Saint Louis University (B.A.N.-T.) and Washington University (E.M.B.) — both in St. Louis; University of California San Diego, San Diego (J.E.L.); Johns Hopkins University, Baltimore (J.T., A.U., M.V.N., J.C.); and the National Cancer Institute (D.E.K.), and

N Engl J Med 2010;362:1675-85.

«Alti dosaggi di Vitamina E (800UI) potrebbero ridurre la fibrosi epatica»

Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality

Edgar R. Miller III, MD, PhD; Roberto Pastor-Barriuso, PhD; Darshan Dalal, MD, MPH; Rudolph A. Riemersma, PhD, FRCPE; Lawrence J. Appel, MD, MPH; and Eliseo Guallar, MD, DrPH

Background: Experimental models and observational studies suggest that vitamin E supplementation may prevent cardiovascular disease and cancer. However, several trials of high-dosage vitamin E supplementation showed non–statistically significant increases in total mortality.

Purpose: To perform a meta-analysis of the dose–response relationship between vitamin E supplementation and total mortality by using data from randomized, controlled trials.

Patients: 135 967 participants in 19 clinical trials. Of these trials, 9 tested vitamin E alone and 10 tested vitamin E combined with other vitamins or minerals. The dosages of vitamin E ranged from 16.5 to 2000 IU/d (median, 400 IU/d).

Data Sources: PubMed search from 1966 through August 2004, complemented by a search of the Cochrane Clinical Trials Database and review of citations of published reviews and meta-analyses. No language restrictions were applied.

Data Extraction: 3 investigators independently abstracted study reports. The investigators of the original publications were contacted if required information was not available.

Data Synthesis: 9 of 11 trials testing high-dosage vitamin E (≥400 IU/d) showed increased risk (risk difference > 0) for all-cause mortality in comparisons of vitamin E versus control. The pooled all-cause mortality risk difference in high-dosage vitamin E trials was 39 per 10 000 persons (95% CI, 3 to 74 per 10 000 persons; $P = 0.035$). For low-dosage vitamin E trials, the risk difference was −16 per 10 000 persons (CI, −41 to 10 per 10 000 persons; $P > 0.2$). A dose–response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d.

Limitations: High-dosage (≥400 IU/d) trials were often small and were performed in patients with chronic diseases. The generalizability of the findings to healthy adults is uncertain. Precise estimation of the threshold at which risk increases is difficult.

Conclusion: High-dosage (≥400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided.

Ann Intern Med. 2005;142:37-46. www.annals.org
For author affiliations, see end of text.

«Alti dosaggi di Vitamina E (400UI) possono aumentare la mortalità per tutte le cause»

On the basis of the premise that vitamin E reduces oxidative stress, many clinical trials have tested vita-

through August 2004. We complemented the MEDLINE search by searching the Cochrane database of randomized,

response meta-analysis to evaluate a potential dose-dependent effect of vitamin E supplementation. We focused on all-cause mortality because this end point has unambiguous clinical relevance and, in contrast to cause-specific events such as cardiovascular morbidity or death, is resistant to miscoding.

The restriction to include studies with follow-up longer than 1 year and at least 10 deaths was determined a priori because we anticipated that many small trials did not collect mortality data. We contacted the investigators of the original studies if information required to establish inclu-

Methods

Search Strategy and Inclusion Criteria

We searched for all reports of clinical trials (with no language restrictions) that tested the effect of vitamin E supplementation in humans. We performed a MEDLINE search by using the Medical Subject Heading (MeSH) terms *vitamin E*, *antioxidant vitamins*, *alpha tocopherol*, *tocopherol*, and *clinical trials*. The search period was 1966

See also:

Print
Editors' Notes 38
Editorial comment 75
Summary for Patients I-40

Web-Only
Conversion of figures and tables into slides

Nutraceutici

ELSEVIER

Journal of Hepatology 50 (2009) 1102–1111

Journal of Hepatology

www.elsevier.com/locate/jhep

Silybin, a component of sylimarin, exerts anti-inflammatory and anti-fibrogenic effects on human hepatic stellate cells☆

Marco Trappoliere[1], Alessandra Caligiuri[1], Monika Schmid[1], Cristiana Bertolani[1], Paola Failli[2], Francesco Vizzutti[1], Erica Novo[3], Carlo di Manzano[4], Fabio Marra[1,6], Carmela Loguercio[5], Massimo Pinzani[1,6,*]

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[2] *Dipartimento di Farmacologia Preclinica e Clinica, Università degli Studi di Firenze, Florence, Italy*
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Nutraceutici

STUDIO MULTICENTRICO SILIMET

Farmaci o nutraceutici normo-lipemizzanti

SILIMARINA
VITAMINA E

QUALE TRATTAMENTO PER LA NASH ?

DAVVERO ABBIAMO NECESSITA' DI UN TRATTAMENTO PER LA NASH ?

CHE TIPO DI TRATTAMENTO ? ?

L'UNICO DISPONIBILE E AUTORIZZATO OGGI E' IL TRATTAMENTO NON FARMACOLOGICO:

QUALI FARMACI ? (Tutti per ora "out of label", "non prescrivibile")

Che tipo di nutraceutico o farmaco ?

Ci sono studi clinici controllati in corso ?

Trattamento chirurgico (Chirurgia Bariatrica)

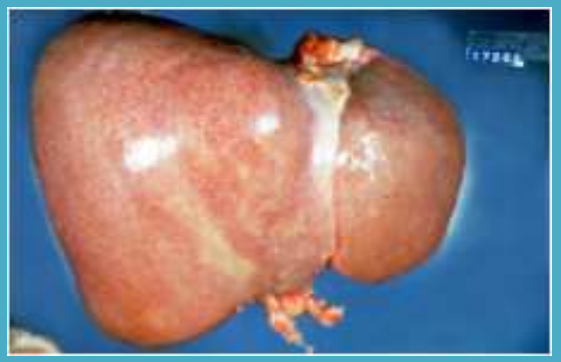
	Effects on Cardiometabolic Risk	*Hepatic Effects*
Lifestyle changes (diet ± physical exercise)	***Physical activity may ↓ excess CVD morbidity/mortality associated with raised CRP levels in T2D***	***A 5–10% weight loss reduces steatosis. Up to a 10% weight loss is needed to improve the necro-inflammation.***
Statins	***↓ cardiovascular events of ~ 30%. ↑ T2D risk***	***↓ steatosis and transaminases. Potential for HCC prevention.***
Ezetimibe	The CV benefits of combining statins + ezetimibe have been largely reported in the literature.	Not tested in RCTs. Preliminary evidence suggests some improvement in liver histology in NAFLD
Fibrates	statins + fibrates provides clinical benefits over treatment with statins alone but increased risks, (hepatic or renal side effects)	↓ Liver tests withouth affecting liver histology
Vitamin D3	RCTs are needed	RCTs are needed
UDCA	None	Histological improvement of fibrosis remains unproven
Pentoxyphylline	no data on whether it ↓ cardiovascular events	PTX significantly improved steatosis and lobular inflammation. No effects in hepatocellular ballooning nor fibrosis

	Effects on Cardiometabolic Risk	*Hepatic Effects*
Sartans	Significantly ↓ blood pressure and may ↑ glucose tolerance, thus ↓ CVD events through prevention of new-onset T2D	Telmisartan was associated with some improvement in NASH histology in a small study
Insulin	Patients with T2D who show pronounced weight gain during insulin therapy have a less favourable cardiometabolic risk profile. Hypoglycemic episodes ↑ CV events	Possibly ↑ HCC risk
Metformin	***The superior anti-diabetic therapy based on CVR profiles. Cardioprotection mediated by the Reperfusion Injury Salvage Kinase (RISK) pathway, AMPK and ↑adenosine. Potential to improve CV outcome even in non-T2D***	***Marginal benefit on aminotransferase levels without improving liver histology. ↓HCC risk.***
Glytazones	The lack of benefits on CV system, suggests that the ↓ of CV risk needs a more global approach than just glucose control	↓ systemic IR and improve hepatic steatosis and necro-inflammation. These effects vanish after drug discontinuation
GLP-1 analogues	possible cardio-protective effect	↓ steatosis and aminotrasferases in T2D patients
Vitamin E	vitamin E supplementation associated with with a ↓risk of myocardial infarction, only in RCTs in which supplements were supplied by the pharmaceutical industry	Superior to placebo for the treatment of NASH in adults without diabetes. Does not improve fibrosis

la NAFLD …..

SLOGAN PER EXPO 2015:

GUARDA IL TUO FEGATO



E' LO SPECCHIO DELLA TUA SALUTE !

GRAZIE PER L'ATTENZIONE !

Stefano Bellentani, MD, PhD

bellentanistefano@gmail.com

SEVENTH FRAMEWORK PROGRAMME

flip fatty liver inhibition of progression

Dott. STEFANO BELLENTANI