Maria Letizia Petroni
U.O. Riabilitazione Funzionale Bariatrica
Sol et Salus (RN)

Supporto nutraceutico alla gestione delle NAFLD (non alcoholic fatty liver diseases)

Dichiaro la assenza di conflitti di interesse

NAFLD

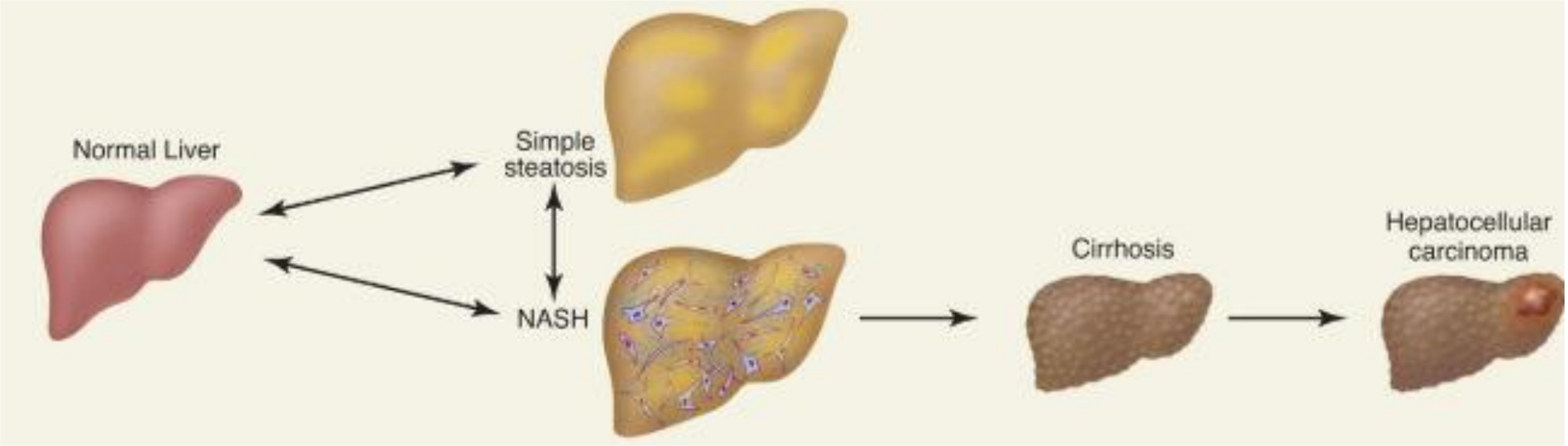
- La NAFLD è caratterizzata da eccessivo accumulo di lipidi nel fegato, associata ad insulino resistenza, e definita dalla presenza di **steatosi** in >5% degli epatociti

- E’ considerata la manifestazione epatica della **sindrome metabolica**

- La diagnosi di NAFLD richiede la **esclusione** sia di cause secondarie che di un consumo di alcool superiore a g 20/die per le donne, g 30/die per gli uomini

- La NAFLD include due condizioni distinte dal punto di vista istologico e clinico e con prognosi differenti: la non-alcoholic fatty liver (**NAFL**) e la non-alcoholic steatohepatitis (**NASH**)

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease, 2016



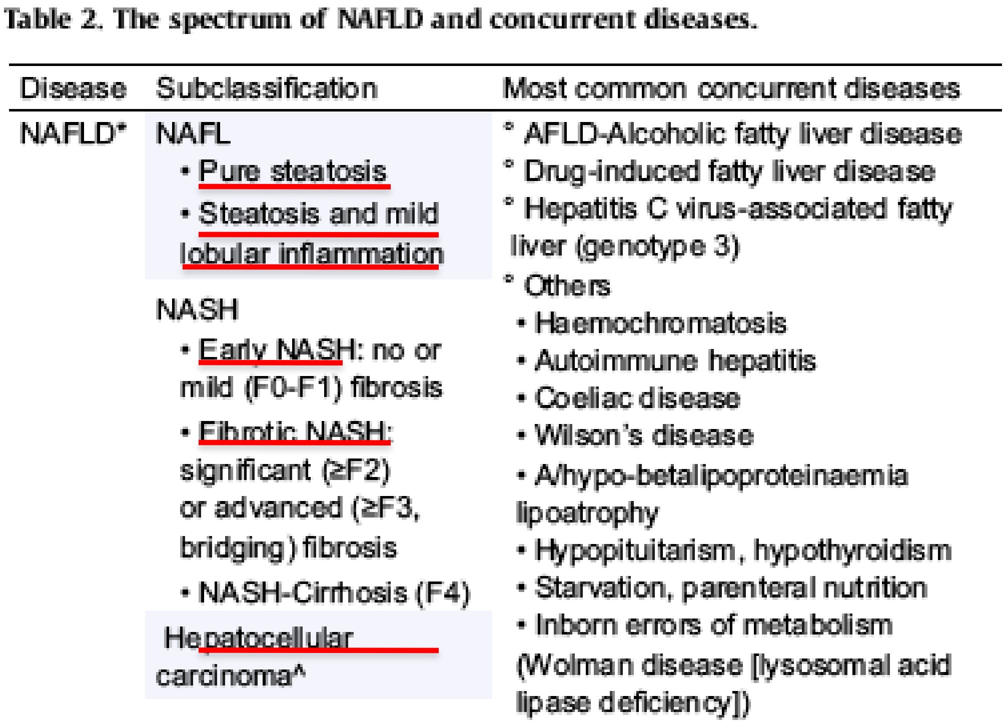


Table 2. The spectrum of NAFLD and concurrent diseases.

Disease	Subclassification	Most common concurrent diseases
NAFLD*	NAFL • Pure steatosis • Steatosis and mild lobular inflammation NASH • Early NASH: no or mild (F0-F1) fibrosis • Fibrotic NASH: significant (≥F2) or advanced (≥F3, bridging) fibrosis • NASH-Cirrhosis (F4) Hepatocellular carcinoma^	° 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])

NAFLD "primaria" = associata alle componenti della sindrome metabolica

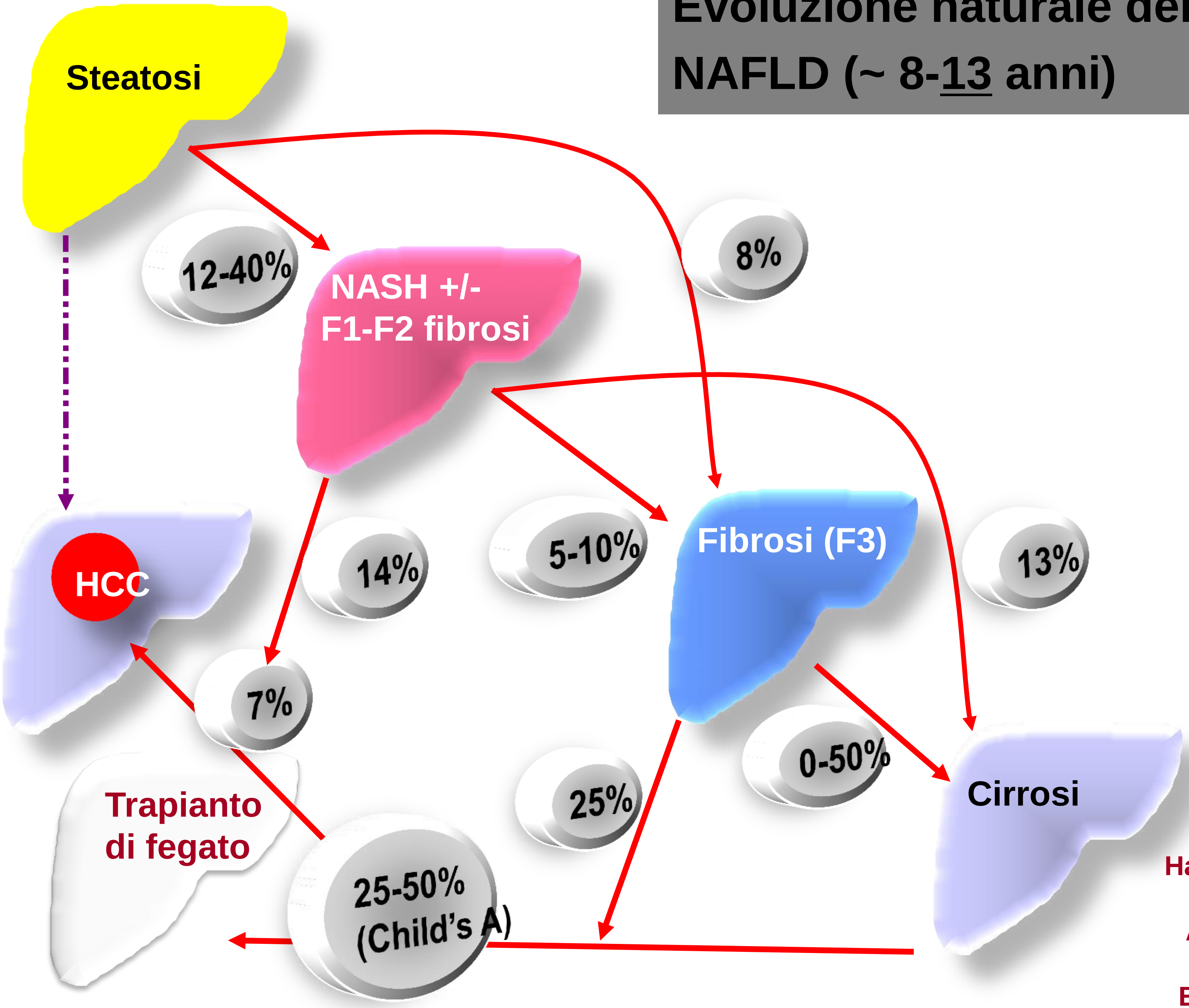
NAFLD ed AFDL possono coesistere

Stesso dicasi di NAFLD primaria e secondaria

HCC può verificarsi anche in assenza di cirrosi e addirittura di segni istologici di NASH in pz con sindrome metabolica "burned out NASH"

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease, 2016

Evoluzione naturale della NAFLD (~ 8-13 anni)



Steatosi

12-40%

NASH +/-
F1-F2 fibrosi

8%

5-10%

14%

Fibrosi (F3)

13%

HCC

7%

0-50%

25%

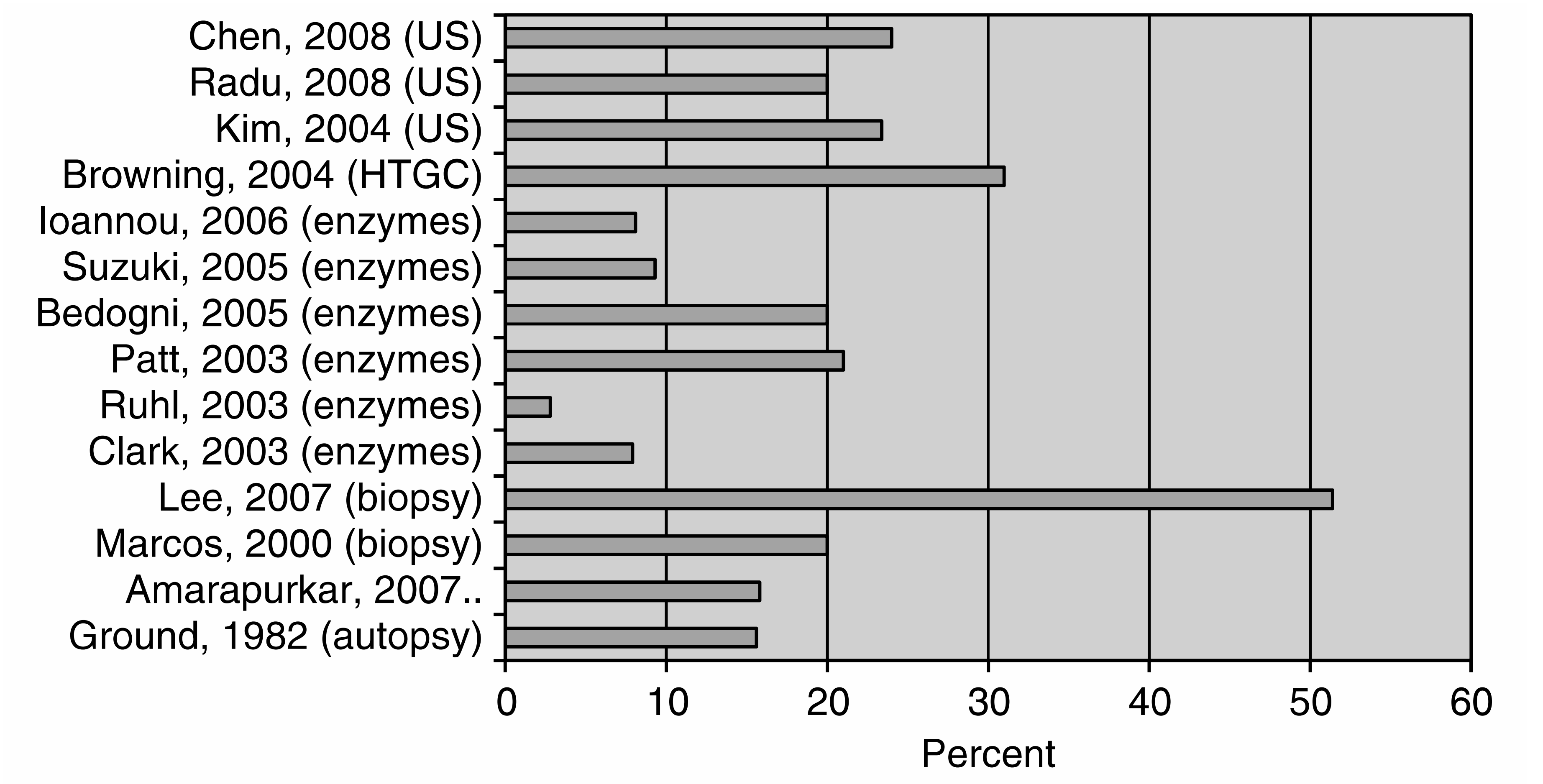
Cirrosi

Trapianto
di fegato

25-50%
(Child's A)

Ratziu 2002
Harrison 2003
Fassio 2004
Adams 2005
Sanyal 2006
Ekstedt 2006

Prevalenza della NAFLD



Vernon G, Baranova A, Younossi ZM (2011). Systematic review: the epidemiology and natural history of NAFLD and NASH in adults. Alimentary Pharmacology and Therapeutics 34:274-285

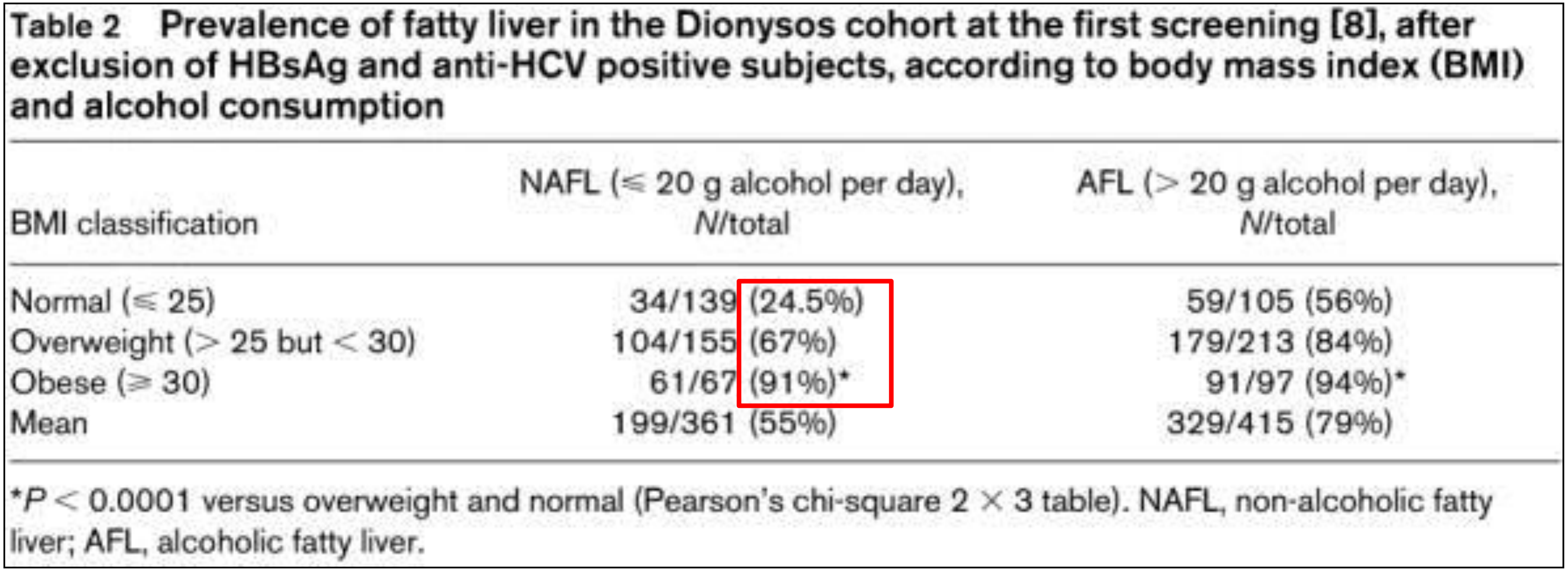
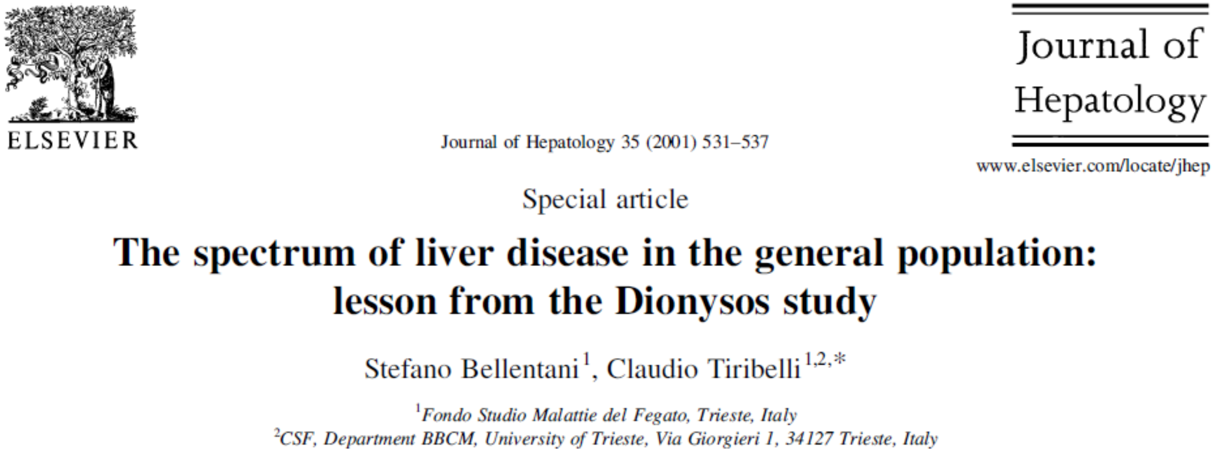


Table 2 Prevalence of fatty liver in the Dionysos cohort at the first screening [8], after exclusion of HBsAg and anti-HCV positive subjects, according to body mass index (BMI) and alcohol consumption

BMI classification	NAFL ($\leq$ 20 g alcohol per day), *N*/total	AFL ($>$ 20 g alcohol per day), *N*/total
Normal ($\leq$ 25)	34/139 (24.5%)	59/105 (56%)
Overweight ($>$ 25 but $<$ 30)	104/155 (67%)	179/213 (84%)
Obese ($\geq$ 30)	61/67 (91%)*	91/97 (94%)*
Mean	199/361 (55%)	329/415 (79%)

**P* $<$ 0.0001 versus overweight and normal (Pearson's chi-square 2 × 3 table). NAFL, non-alcoholic fatty liver; AFL, alcoholic fatty liver.



ELSEVIER

Journal of Hepatology 35 (2001) 531–537

Journal of Hepatology

www.elsevier.com/locate/jhep

Special article

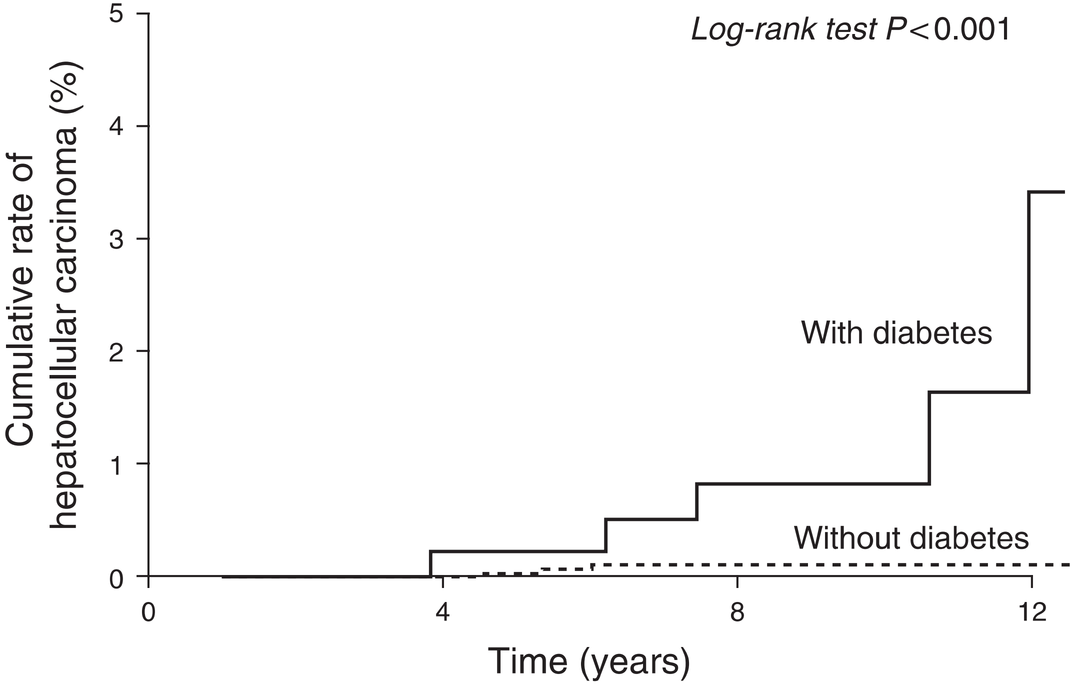
The spectrum of liver disease in the general population: lesson from the Dionysos study

Stefano Bellentani[1], Claudio Tiribelli[1,2,*]

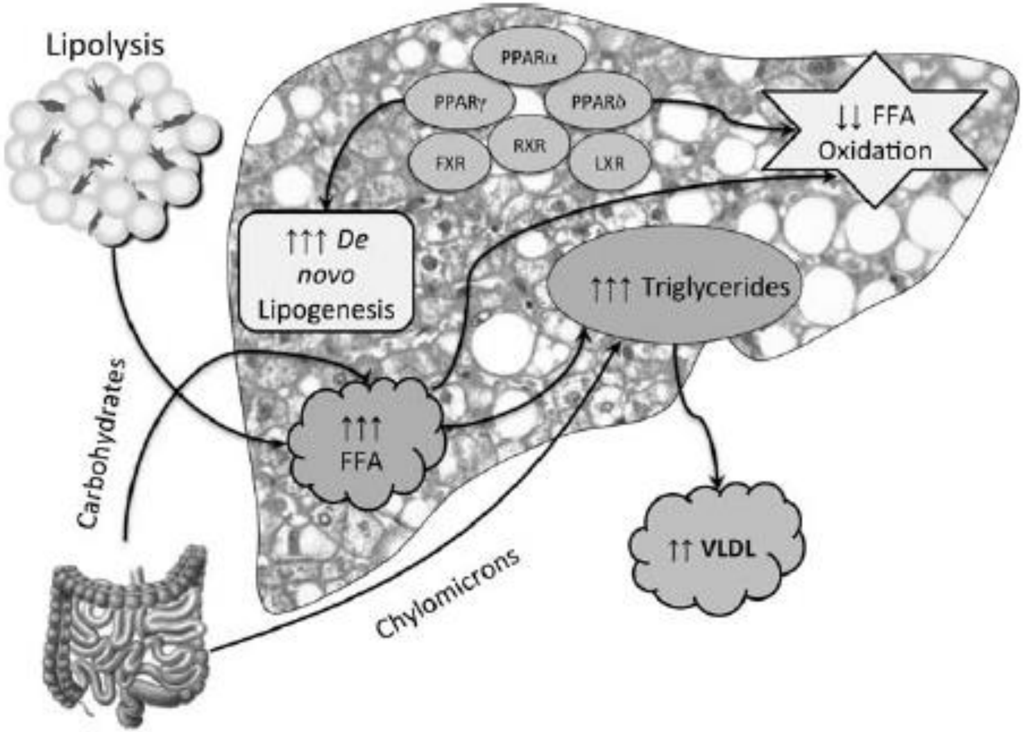
[1]*Fondo Studio Malattie del Fegato, Trieste, Italy*
[2]*CSF, Department BBCM, University of Trieste, Via Giorgieri 1, 34127 Trieste, Italy*

Inoltre, oltre il 50% dei bambini obesi hanno una NAFLD

NAFLD – rischio di HCC



Kawamura Y et al (2011). Large scale long term follow up study of Japanese patients with NAFLD for the onset of HCC. American Journal of Gastroenterology doi:10.1038/ajg.2011.327


Lipolysis
PPARα
PPARγ
PPARδ
RXR
FXR
LXR
↓↓ FFA Oxidation
↑↑↑ *De novo* Lipogenesis
↑↑↑ Triglycerides
↑↑↑ FFA
↑↑ VLDL
Carbohydrates
Chylomicrons

I trigliceridi accumulati nell’epatocita provengono da tre fonti:

1)Acidi grassi della **dieta (15%)**

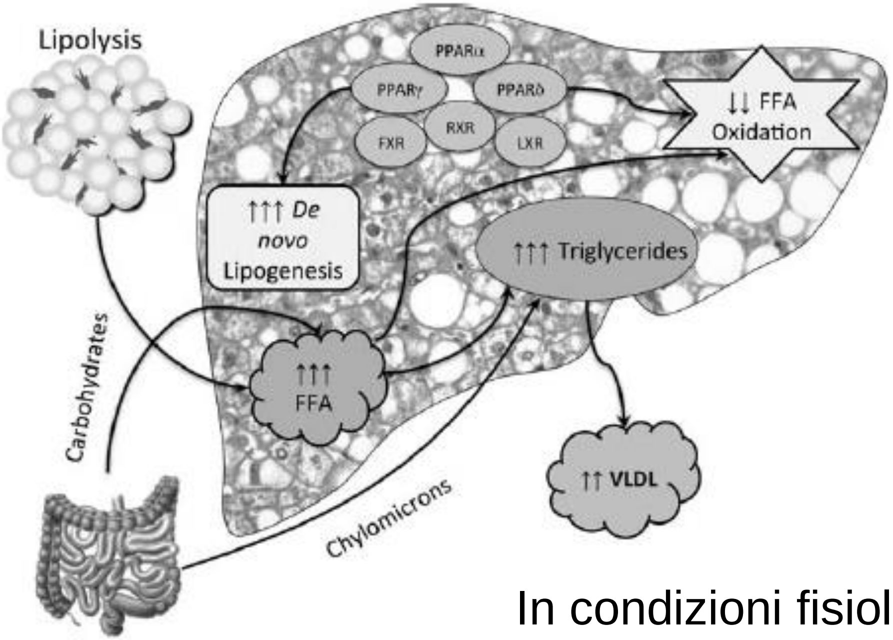
2)Acidi grassi rilasciati dalla **lipolisi del tessuto adiposo (60-80%)**

3) **Lipogenesi de novo** (26% NAFLD vs 5% fegato sano)

La **lipogenesi** de novo è strettamente regolata da diversi recettori nucleari e fattori di trascrizione citoplasmica: il liver X receptor (**LXR**) che media la sintesi epatica di acidi grassi; il farnesoid X receptor (**FXR**), che interferisce con l‘assemblaggio delle VLDL ed aumenta la clearance dei trigliceridi, la famiglia dei peroxisome proliferator activated receptors (**PPARs**). PPAR-alfa regola la ossidazione degli acidi grassi, PPAR-gamma ha una funzione antinfiammatoria, PPAR-delta sopprime la lipogenesi epatica e riduce la esprssione di geni pro-infiammatori e fibrotici.

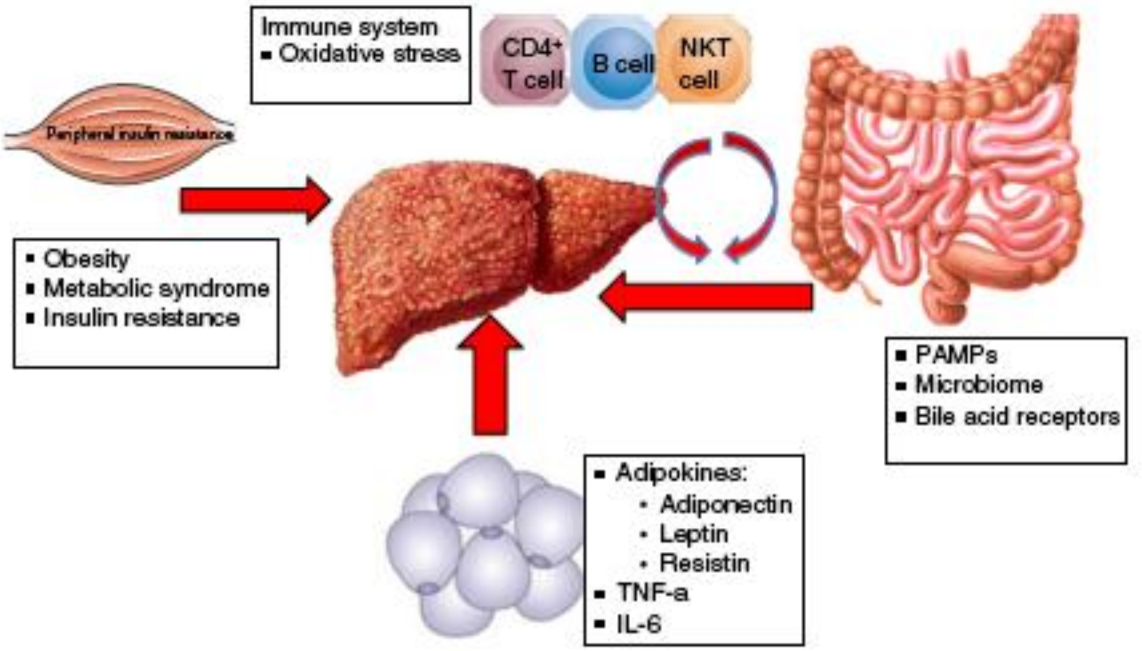
In corso di studio diversi farmaci che agiscono su questi recettori.

Marchesini G, Petta S, Dalle Grave G. Hepatology 2016


Lipolysis
PPARα
PPARγ
PPARδ
FXR
RXR
LXR
↓↓ FFA Oxidation
↑↑↑ *De novo* Lipogenesis
↑↑↑ Triglycerides
↑↑↑ FFA
↑↑ VLDL
Carbohydrates
Chylomicrons

In condizioni fisiologiche, la rimozione degli acidi grassi dall'epatocita è mediato sia dalla ossidazione mitocondriale degli acidi grassi che da dalla secrezione delle VLDL. Nei pazienti con NAFLD si assiste ad un aumento compensatorio dell'aumento della secrezione delle VLDL-TG , sia pure a livelli non adeguati a normalizzare il contenuto di lipidi intraepatici, mentre vi è una **ridotta capacità ossidativa mitocondriale**, che a sua volta determina accumulo di acidi grassi e **stress ossidativo.**

Marchesini G, Petta S, Dalle Grave G. Hepatology 2016

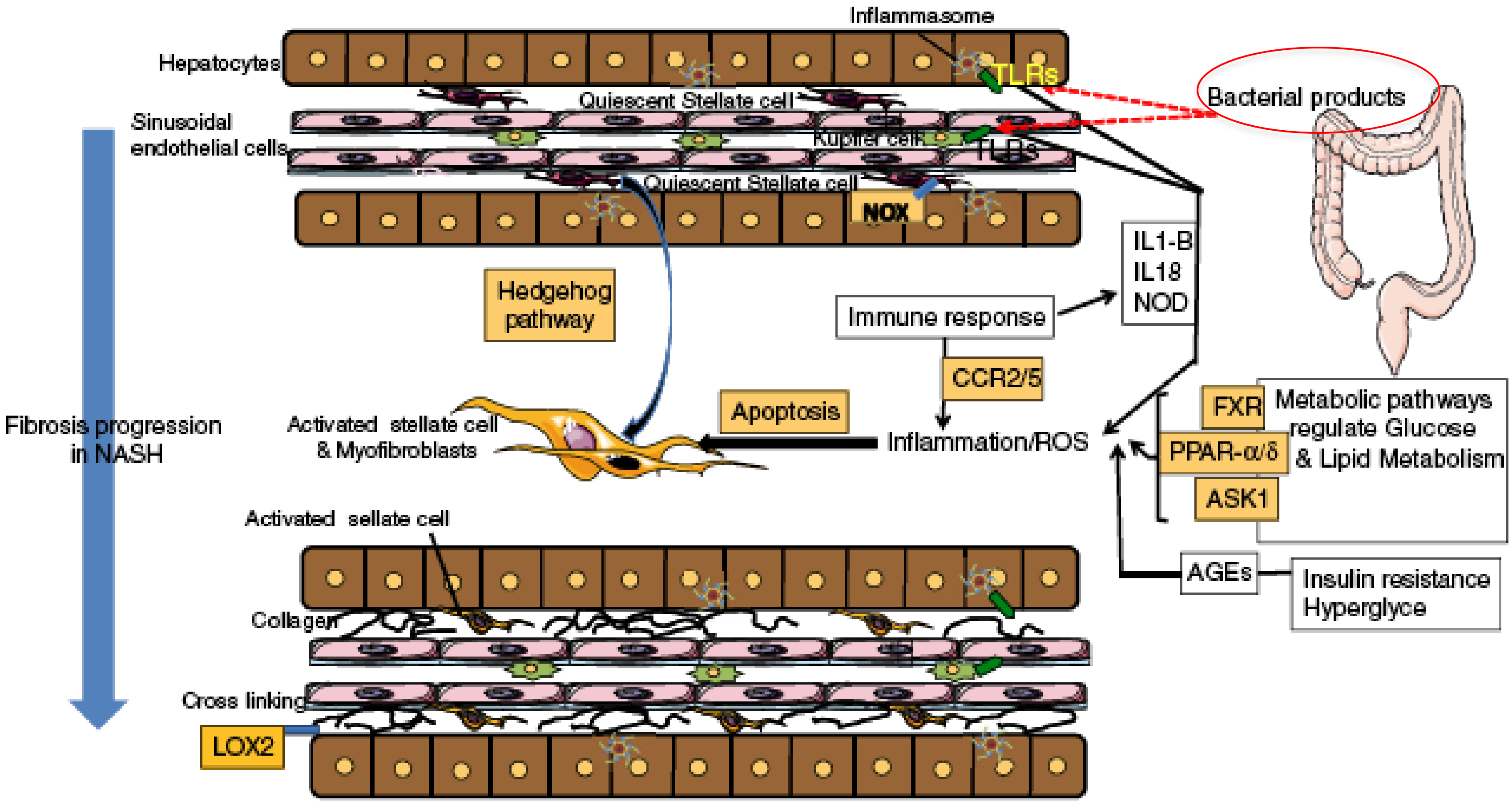

Immune system
▪ Oxidative stress
CD4+ T cell
B cell
NKT cell
Peripheral insulin resistance
▪ Obesity
▪ Metabolic syndrome
▪ Insulin resistance
▪ PAMPs
▪ Microbiome
▪ Bile acid receptors
▪ Adipokines:
• Adiponectin
• Leptin
• Resistin
▪ TNF-a
▪ IL-6

Stress ossidativo causato da:
-**Iperinsulinismo** (direttamente mediante produzione di ROS ed indirettamente mediante riduzione della capacità ossidativa mitocondriale da insulinoresistenza)
- Colesterolo libero (effetto lipotossico)
- **nei pazienti diabetici, i prodotti di glicosilazione** (AGEs, advanced glycation end products)

Alterazioni del microbiota intestinale e della permeabilità intestinale determinano una inappropriata attivazione delle cellule immunitarie, in particolare della immunità innata, con attivazione di citochine infiammatorie

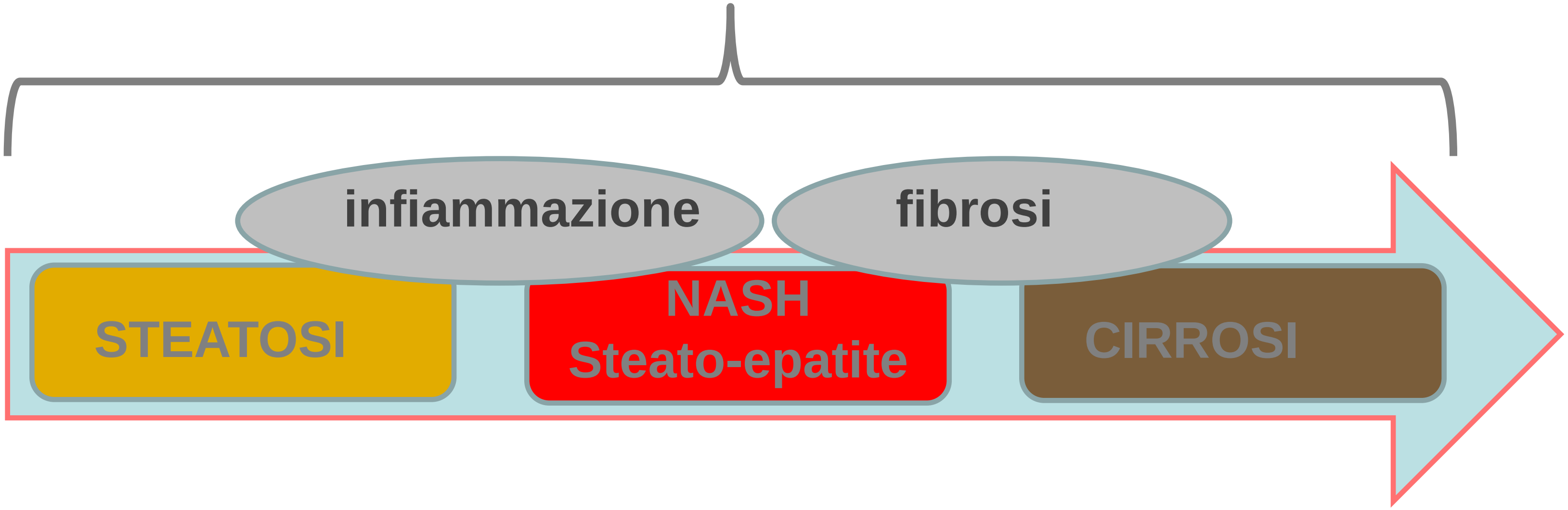
Noureddin M, Anstee QM, Loomba R, Aliment Pharmacol Ther 2016; 43: 1109–1123

Meccanismi multipli agiscono sulle cellule stellate nella genesi della fibrosi NASH-associata


Inflammasome
Hepatocytes
TLRs
Bacterial products
Quiescent Stellate cell
Sinusoidal endothelial cells
Kupffer cell
TLRs
Quiescent Stellate cell
NOX
IL1-B
IL18
NOD
Hedgehog pathway
Immune response
CCR2/5
Apoptosis
Fibrosis progression in NASH
Activated stellate cell & Myofibroblasts
Inflammation/ROS
FXR
PPAR-α/δ
ASK1
Metabolic pathways regulate Glucose & Lipid Metabolism
AGEs
Insulin resistance Hyperglyce
Activated sellate cell
Collagen
Cross linking
LOX2

Attivazione dei toll-like receptors dell’inflammasoma, generazione di citochine infiammatorie, aumentati livelli di signalling hedgehog, modifiche del metabolismo glicolipidico che generano stress ossidativo, danno epatocitario via apoptosi, morte cellulare che attiva meccanismi infiammatori e pro-fibrogenici nelle cellule non parenchimali e nelle cellule immunocompetenti. Tutti questi processi danno luogo ad **attivazione delle cellule stellate** che sono la causa di **eccessiva deposizione di matrice extracellulare** nel parenchima.

NAFLD



infiammazione

fibrosi

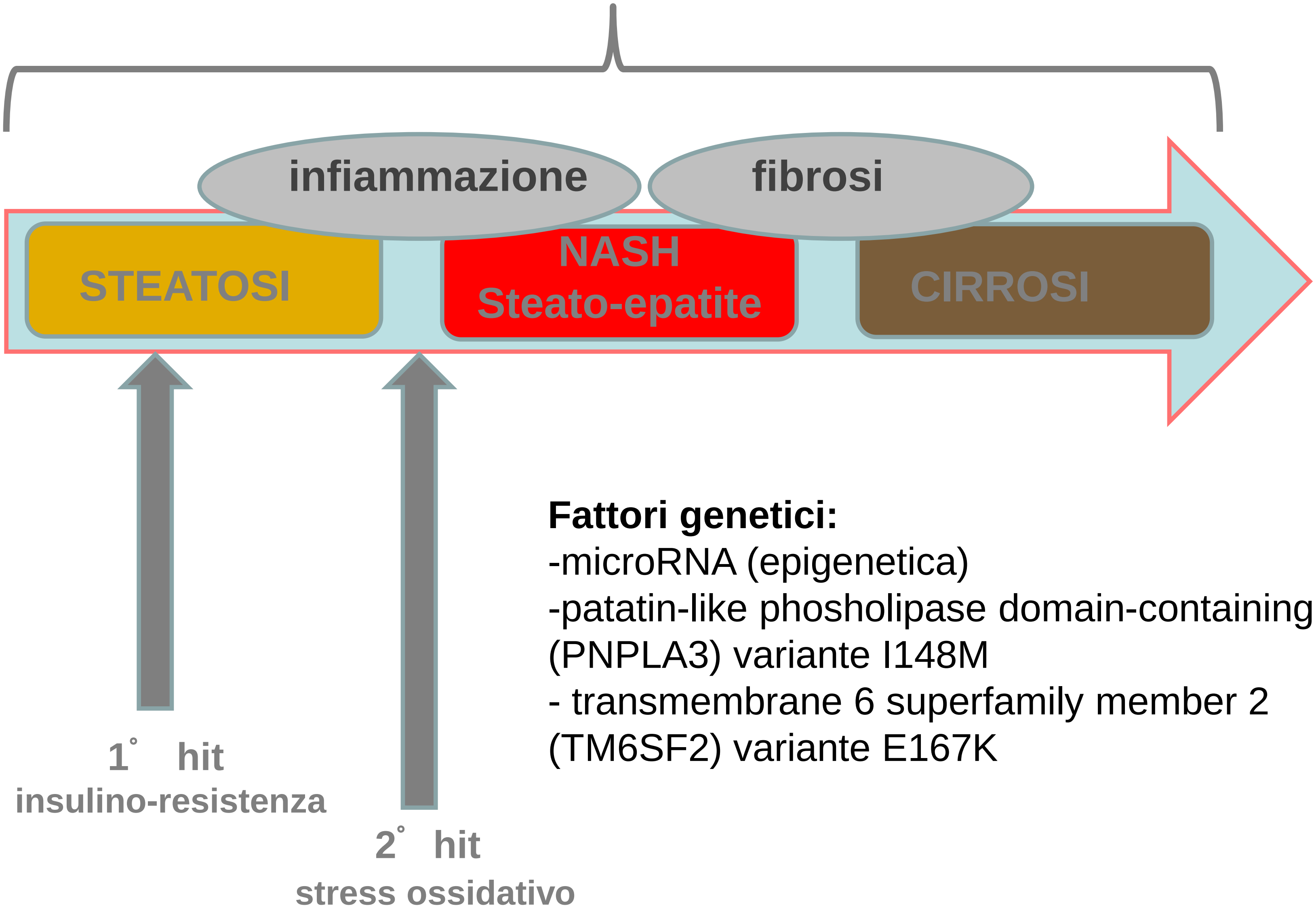
STEATOSI

NASH
Steato-epatite

CIRROSI

La ipotesi dei 2-hit (insulti) afferma che la disregolazione del metabolismo degli acidi grassi secondaria ad insulino resistenza dia luogo a steatosi, che è associata a diversi adattamenti cellulari ed alterazioni del signalling intra- ed extra cellulare che rendono gli epatociti vulnerabili ad un secondo hit. Quest’ultimo può essere causato da una o più perturbazioni ambientali o genetiche che causano necrosi ed infiammazione epatocitaria.
In una minoranza di casi viene attivata una cascata fibrogenica che conduce direttamente alla cirrosi.

NAFLD



infiammazione

fibrosi

STEATOSI

NASH
Steato-epatite

CIRROSI

1° hit
insulino-resistenza

2° hit
stress ossidativo

Fattori genetici:
-microRNA (epigenetica)
-patatin-like phosholipase domain-containing 3 (PNPLA3) variante I148M
- transmembrane 6 superfamily member 2 (TM6SF2) variante E167K

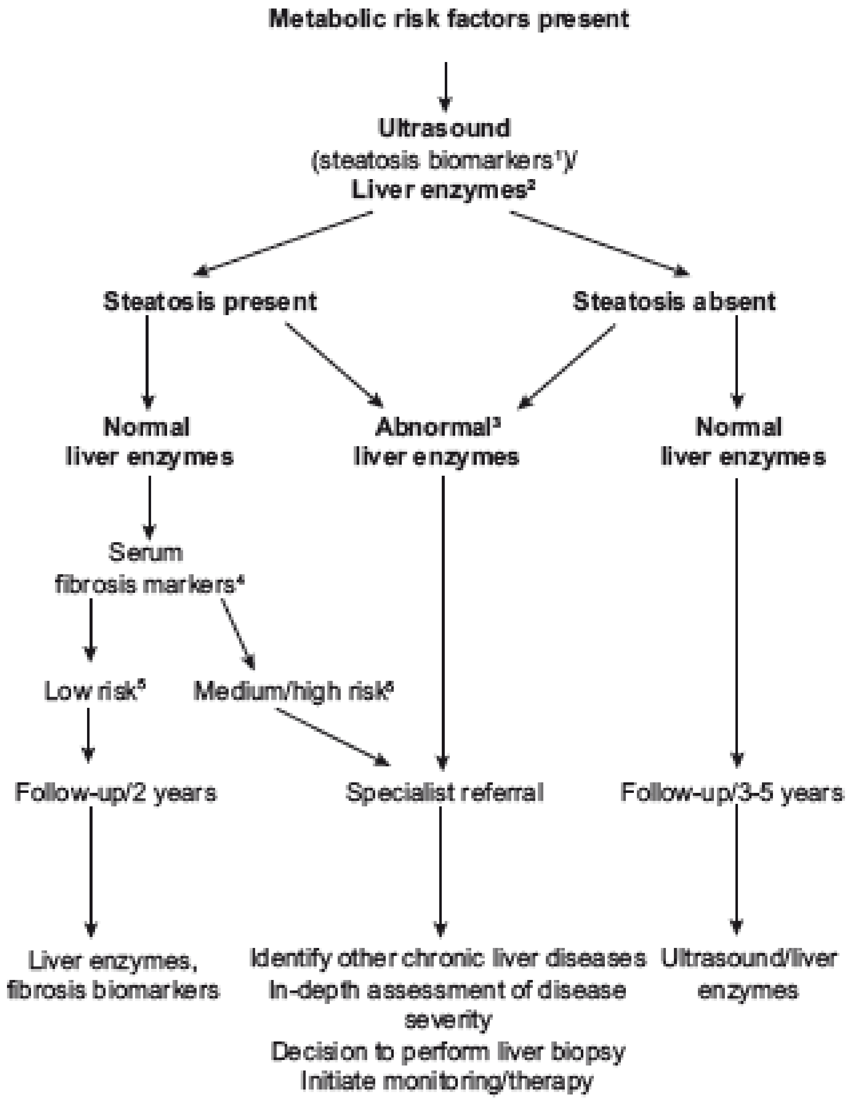
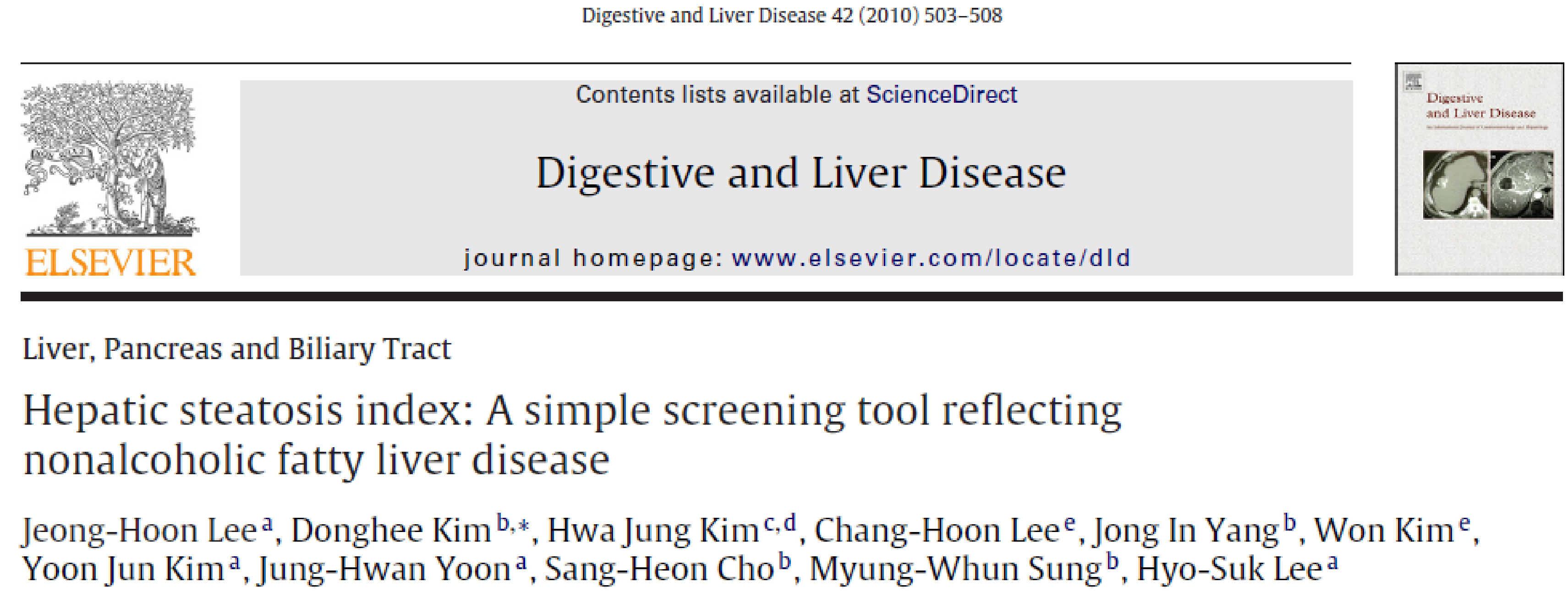

Metabolic risk factors present
Ultrasound
(steatosis biomarkers[1])/
Liver enzymes[2]
Steatosis present
Steatosis absent
Normal liver enzymes
Abnormal[3] liver enzymes
Normal liver enzymes
Serum fibrosis markers[4]
Low risk[5]
Medium/high risk[5]
Follow-up/2 years
Specialist referral
Follow-up/3-5 years
Liver enzymes, fibrosis biomarkers
Identify other chronic liver diseases
In-depth assessment of disease severity
Decision to perform liver biopsy
Initiate monitoring/therapy
Ultrasound/liver enzymes

Fig. 1. Diagnostic flow-chart to assess and monitor disease severity in the presence of suspected NAFLD and metabolic risk factors. [1]Steatosis biomarkers: Fatty Liver Index, SteatoTest, NAFLD Fat score (see Tables). [2]Liver tests: ALT AST, γGT. [3]Any increase in ALT, AST or γGT. [4]Serum fibrosis markers: NAFLD Fibrosis Score, FIB-4, Commercial tests (FibroTest, FibroMeter, ELF). [5]Low risk: indicative of no/mild fibrosis; Medium/high risk: indicative of significant fibrosis or cirrhosis (see Tables).


Digestive and Liver Disease 42 (2010) 503–508

Contents lists available at ScienceDirect

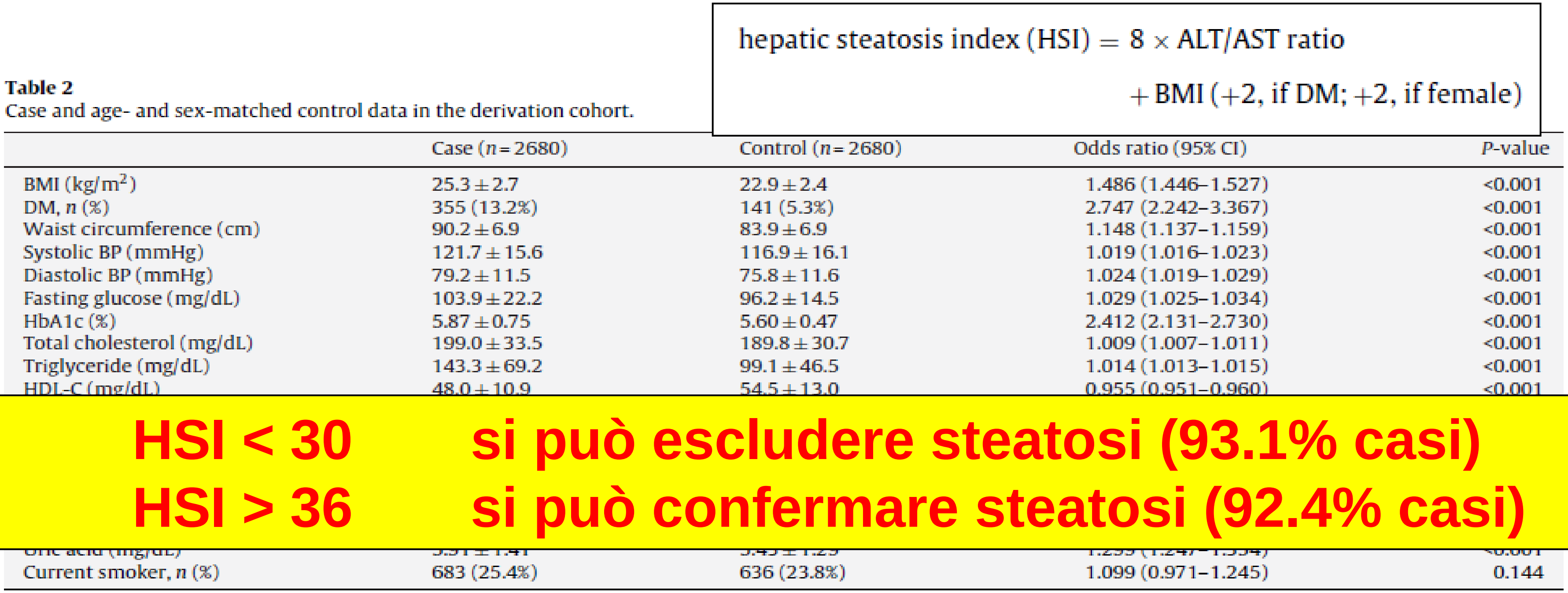
Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Hepatic steatosis index: A simple screening tool reflecting nonalcoholic fatty liver disease

Jeong-Hoon Lee[a], Donghee Kim[b,*], Hwa Jung Kim[c,d], Chang-Hoon Lee[e], Jong In Yang[b], Won Kim[e], Yoon Jun Kim[a], Jung-Hwan Yoon[a], Sang-Heon Cho[b], Myung-Whun Sung[b], Hyo-Suk Lee[a]

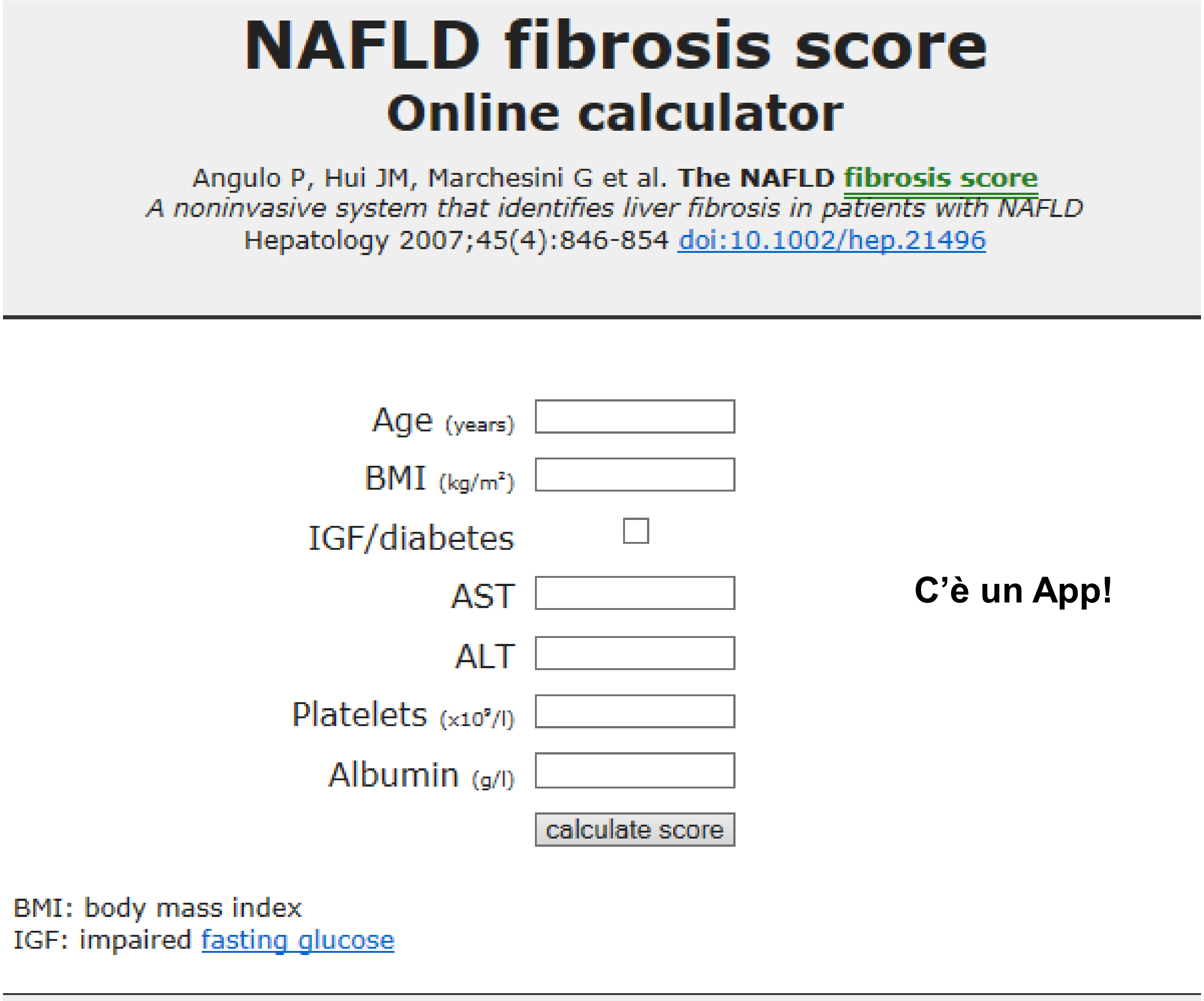


$$\text{hepatic steatosis index (HSI)} = 8 \times \text{ALT/AST ratio} + \text{BMI} (+2, \text{if DM}; +2, \text{if female})$$

Table 2
Case and age- and sex-matched control data in the derivation cohort.

	Case ($n = 2680$)	Control ($n = 2680$)	Odds ratio (95% CI)	*P*-value
BMI (kg/m^2)	25.3 ± 2.7	22.9 ± 2.4	1.486 (1.446–1.527)	<0.001
DM, *n* (%)	355 (13.2%)	141 (5.3%)	2.747 (2.242–3.367)	<0.001
Waist circumference (cm)	90.2 ± 6.9	83.9 ± 6.9	1.148 (1.137–1.159)	<0.001
Systolic BP (mmHg)	121.7 ± 15.6	116.9 ± 16.1	1.019 (1.016–1.023)	<0.001
Diastolic BP (mmHg)	79.2 ± 11.5	75.8 ± 11.6	1.024 (1.019–1.029)	<0.001
Fasting glucose (mg/dL)	103.9 ± 22.2	96.2 ± 14.5	1.029 (1.025–1.034)	<0.001
HbA1c (%)	5.87 ± 0.75	5.60 ± 0.47	2.412 (2.131–2.730)	<0.001
Total cholesterol (mg/dL)	199.0 ± 33.5	189.8 ± 30.7	1.009 (1.007–1.011)	<0.001
Triglyceride (mg/dL)	143.3 ± 69.2	99.1 ± 46.5	1.014 (1.013–1.015)	<0.001
HDL-C (mg/dL)	48.0 ± 10.9	54.5 ± 13.0	0.955 (0.951–0.960)	<0.001
Current smoker, *n* (%)	683 (25.4%)	636 (23.8%)	1.099 (0.971–1.245)	0.144

HSI < 30 si può escludere steatosi (93.1% casi)
HSI > 36 si può confermare steatosi (92.4% casi)



NAFLD fibrosis score

Online calculator

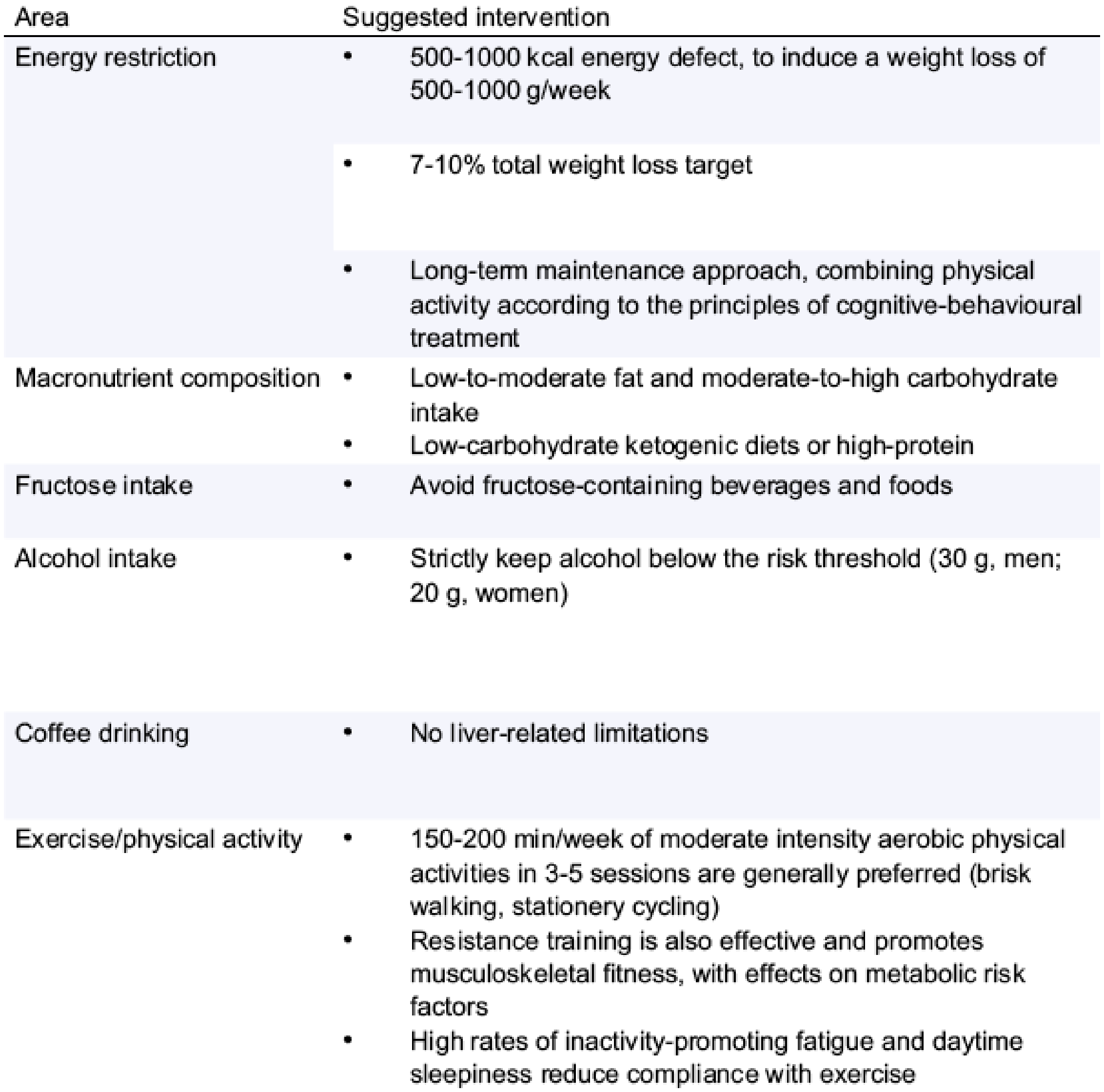
Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 doi:10.1002/hep.21496

Age (years)
BMI (kg/m²)
IGF/diabetes ☐
AST
ALT
Platelets (x10⁹/l)
Albumin (g/l)

BMI: body mass index
IGF: impaired fasting glucose

C’è un App!

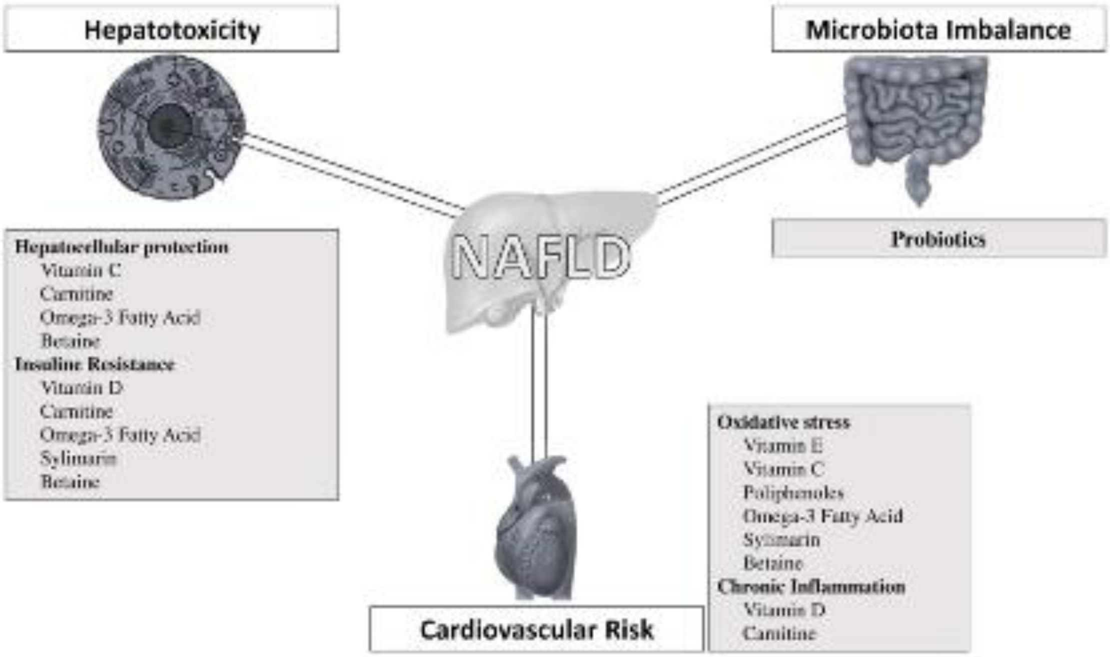
L’approccio dietetico e di modifica dello stile di vita rappresenta la prima linea di terapia



Area	Suggested intervention
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week • 7-10% total weight loss target • Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein
Fructose intake	• Avoid fructose-containing beverages and foods
Alcohol intake	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women)
Coffee drinking	• No liver-related limitations
Exercise/physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease, 2016

Potenzialità uso di nutraceutici nella NAFLD


Hepatotoxicity
Microbiota Imbalance
NAFLD
Probiotics
Cardiovascular Risk

Hepatocellular protection
- Vitamin C
- Carnitine
- Omega-3 Fatty Acid
- Betaine

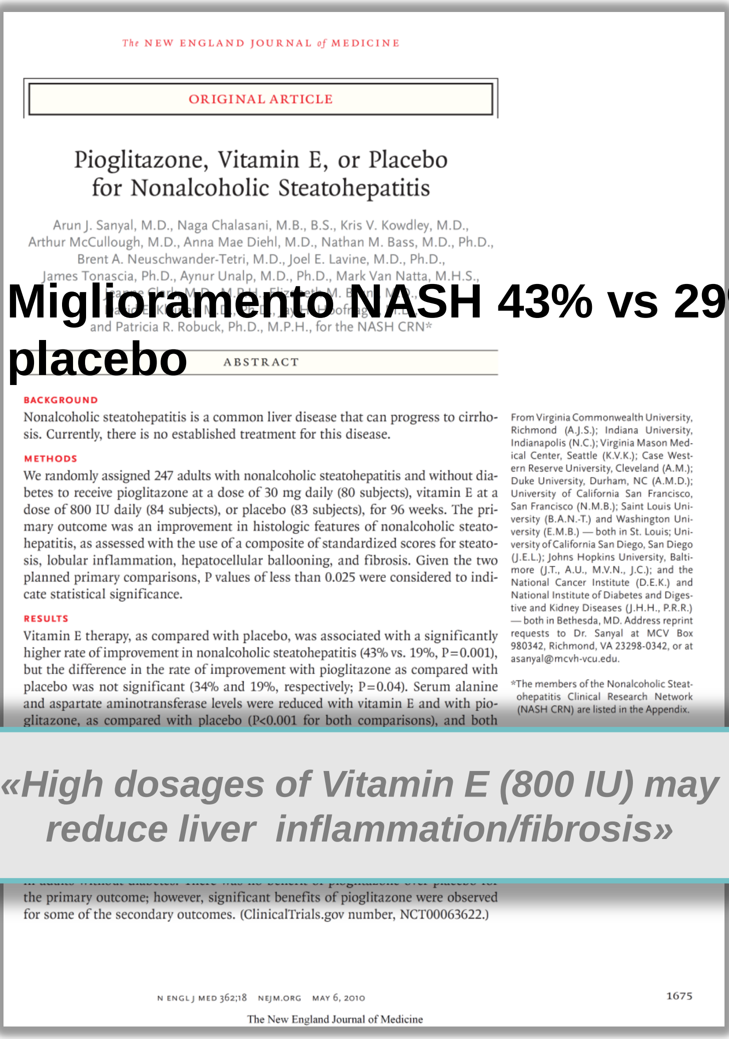
Insuline Resistance
- Vitamin D
- Carnitine
- Omega-3 Fatty Acid
- Sylimarin
- Betaine

Oxidative stress
- Vitamin E
- Vitamin C
- Poliphenoles
- Omega-3 Fatty Acid
- Sylimarin
- Betaine

Chronic Inflammation
- Vitamin D
- Carnitine

Angelico et al, Br J Pharmacol 2016

PIVENS Trial



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.,
[illegible]
[illegible]
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 indicate statistical significance.

RESULTS

Vitamin E therapy, as compared with placebo, was associated with a significantly higher rate of improvement in nonalcoholic steatohepatitis (43% vs. 19%, P=0.001), but the difference in the rate of improvement with pioglitazone as compared with placebo was not significant (34% and 19%, respectively; P=0.04). Serum alanine and aspartate aminotransferase levels were reduced with vitamin E and with pioglitazone, as compared with placebo (P<0.001 for both comparisons), and both

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 National Institute of Diabetes and Digestive and Kidney Diseases (J.H.H., P.R.R.) — both in Bethesda, MD. Address reprint requests to Dr. Sanyal at MCV Box 980342, Richmond, VA 23298-0342, or at asanyal@mcvh-vcu.edu.

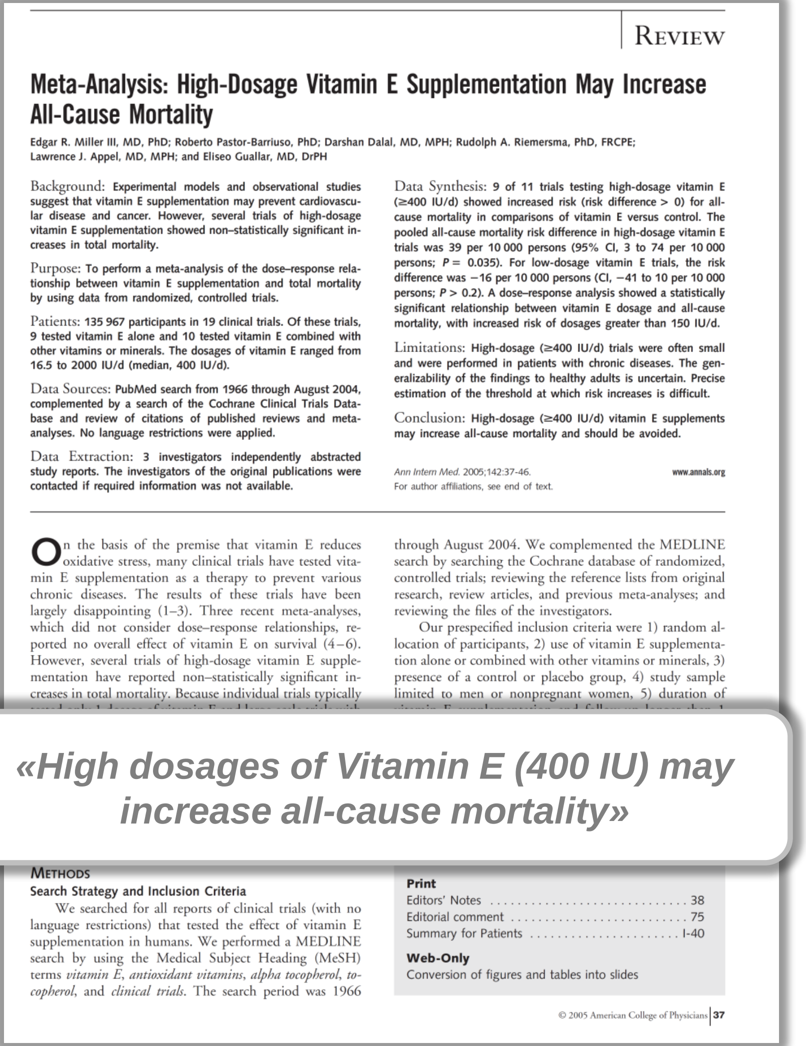
*The members of the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) are listed in the Appendix.

N ENGL J MED 362;18 NEJM.ORG MAY 6, 2010 1675

The New England Journal of Medicine

Miglioramento NASH 43% vs 29% placebo

«High dosages of Vitamin E (800 IU) may reduce liver inflammation/fibrosis»



REVIEW

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.

On the basis of the premise that vitamin E reduces oxidative stress, many clinical trials have tested vitamin E supplementation as a therapy to prevent various chronic diseases. The results of these trials have been largely disappointing (1–3). Three recent meta-analyses, which did not consider dose–response relationships, reported no overall effect of vitamin E on survival (4–6). However, several trials of high-dosage vitamin E supplementation have reported non–statistically significant increases in total mortality. Because individual trials typically

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 through August 2004. We complemented the MEDLINE search by searching the Cochrane database of randomized, controlled trials; reviewing the reference lists from original research, review articles, and previous meta-analyses; and reviewing the files of the investigators.

Our prespecified inclusion criteria were 1) random allocation of participants, 2) use of vitamin E supplementation alone or combined with other vitamins or minerals, 3) presence of a control or placebo group, 4) study sample limited to men or nonpregnant women, 5) duration of

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Web-Only
Conversion of figures and tables into slides

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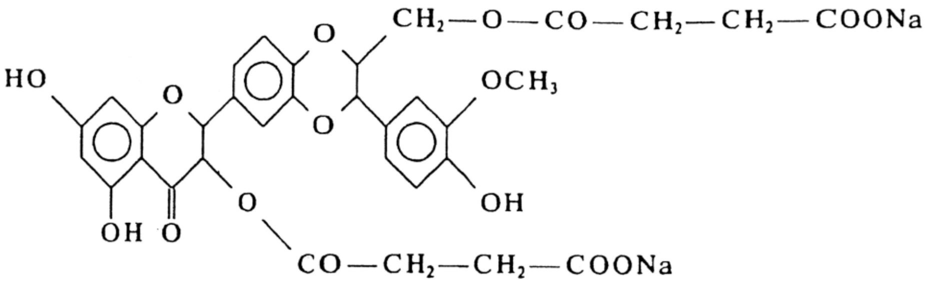
«High dosages of Vitamin E (400 IU) may increase all-cause mortality»

A causa del rischio connesso con la mortalità totale, da cause cardiovascolari e tumore prostatico le LG raccomandano di **usare la vitamina E ad alto dosaggio (800 IU/day, vs RDA 20 IU) come terapia di prima linea in non diabetici adulti con NASH diagnosticata mediante biopsia** ma raccomandano **cautela in pazienti diabetici o adulti non diabetici con NAFLD non biopsiati**

semi

estrazione

Silimarina


HO
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OH O
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O
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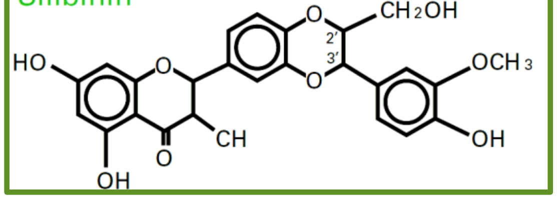
CH₂—O—CO—CH₂—CH₂—COONa
OCH₃
OH
CO—CH₂—CH₂—COONa

Silibinin-C-2';3 dihydrogensuccinate disodium salt is the hydrosoluble chemical derivative of pure silibinin (A and B), exclusively contained in Legalon®SIL for i.v.infusions

Silibinin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CH2OH
OCH3
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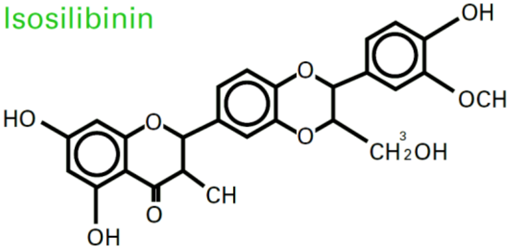
Isosilibinin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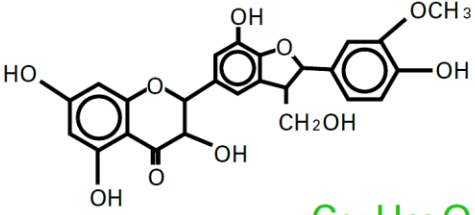
OCH
3
CH2OH

Silicristin


HO
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OH
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CH2OH
OCH3
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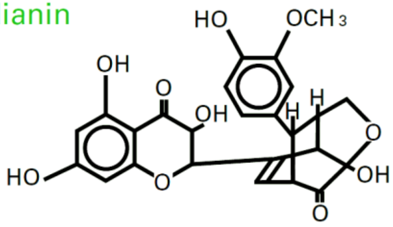
Silidianin


HO
OCH3
OH
O
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H
H
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HO
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OH
O

$C_{25}H_{22}O_{10}$: mol. wt. 482

Meccanismi potenziali di azione:
- **riduzione stress ossidativo**
- **riduzione infiammazione cronica**
- **insulinoresistenza**
- **protezione epatocellulare**

Miglioramento della biodisponibilità della silibinina dopo assunzione per os

Isosilibinin
Silicristin
Silibinina
Silidianin

Eurosil®85

60% silibinina

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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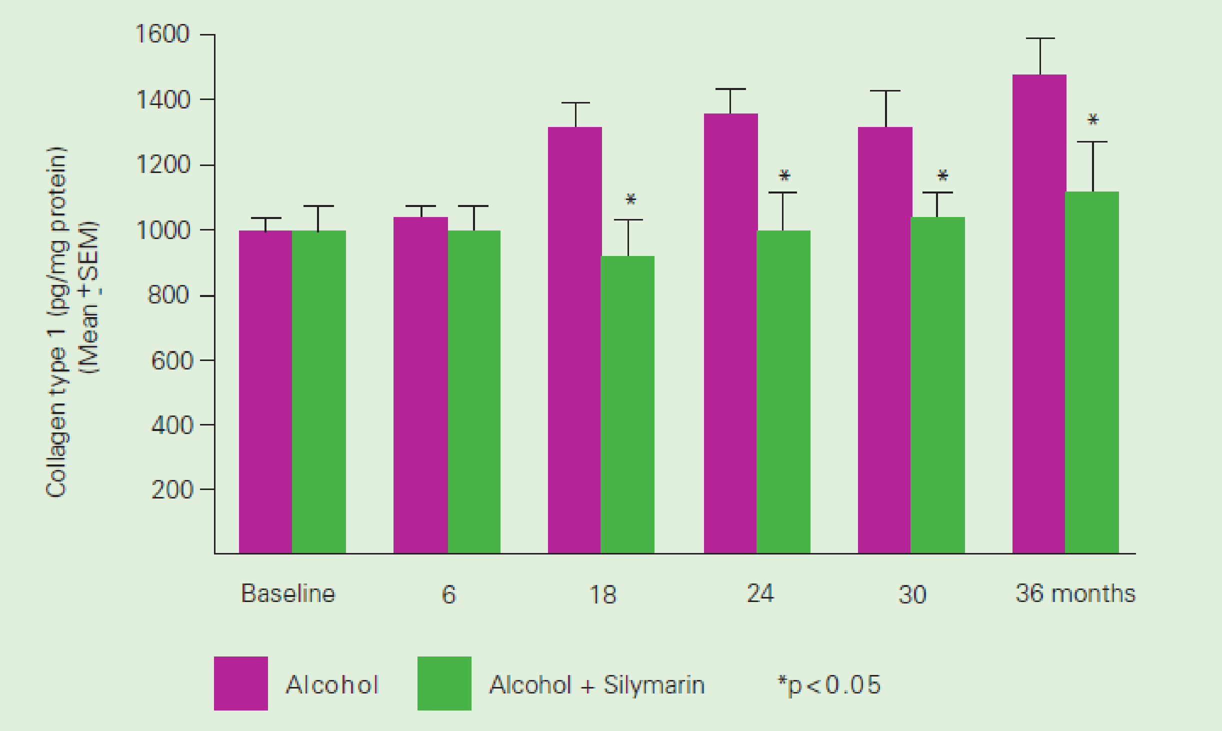
[2] *Dipartimento di Farmacologia Preclinica e Clinica, Università degli Studi di Firenze, Florence, Italy*
[3] *Dipartimento di Medicina e Oncologia Sperimentale, Università degli Studi di Torino, Turin, Italy*
[4] *IBI Istituto Biochimico Italiano Giovanni Lorenzini, Seconda Università di Napoli, Naples, Italy*
[5] *Dipartimento di Gastroenterologia, Seconda Università di Napoli, Naples, Italy*
[6] *Center for Research, High Education and Transfer DENOThe, University of Florence, Florence, Italy*

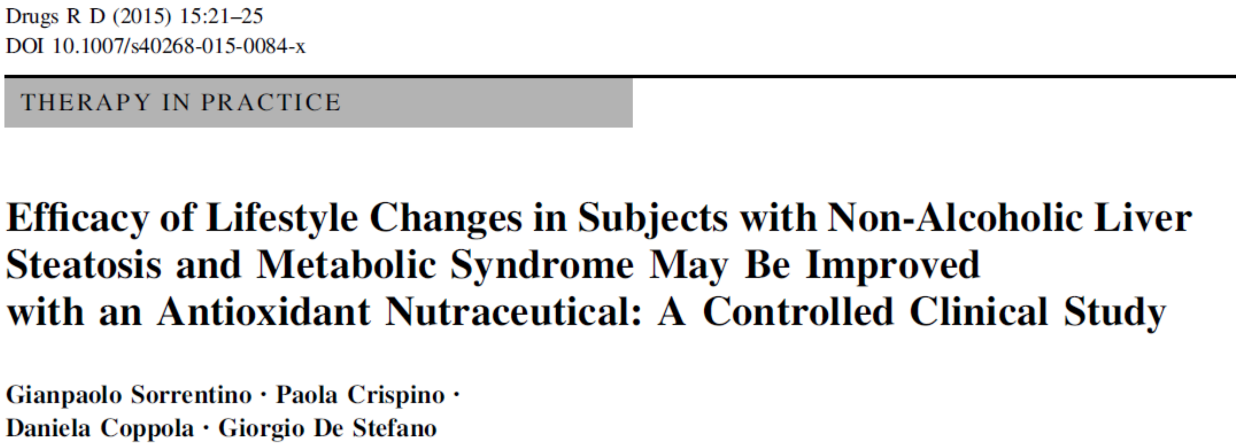
J. Clin Gastroenterol *Volume 37, Number 4, October 2003*

Silymarin Retards the Progression of Alcohol-Induced Hepatic Fibrosis in Baboons

Charles S. Lieber, MD, MACP, Maria A. Leo, MD, Qi Cao, MD, PhD, Chaoling Ren, MD, and Leonore M. DeCarli, BA

Legalon® prevents accumulation of collagen type I in a model of AFLD in baboons





Drugs R D (2015) 15:21–25
DOI 10.1007/s40268-015-0084-x

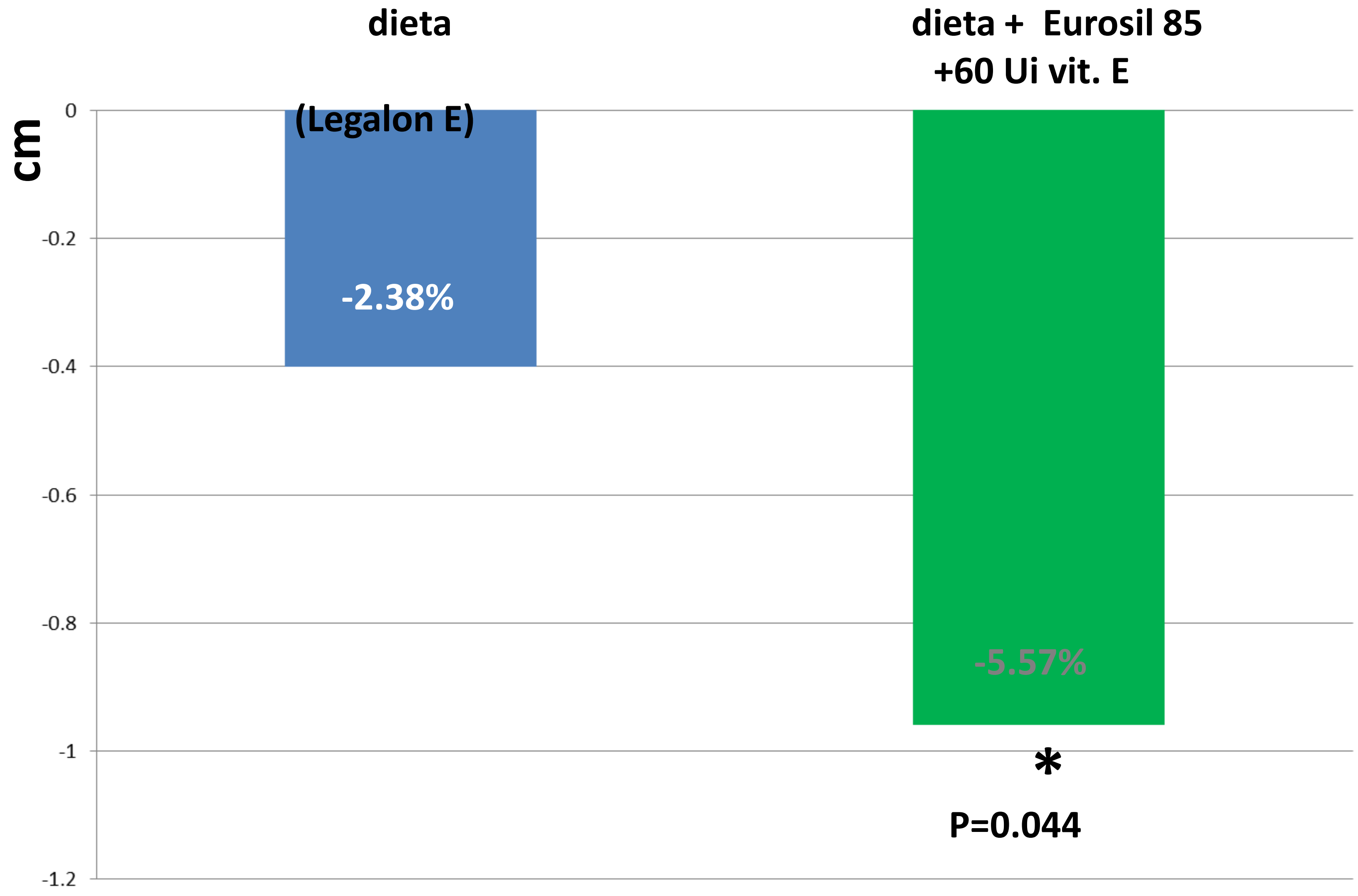
THERAPY IN PRACTICE

Efficacy of Lifestyle Changes in Subjects with Non-Alcoholic Liver Steatosis and Metabolic Syndrome May Be Improved with an Antioxidant Nutraceutical: A Controlled Clinical Study

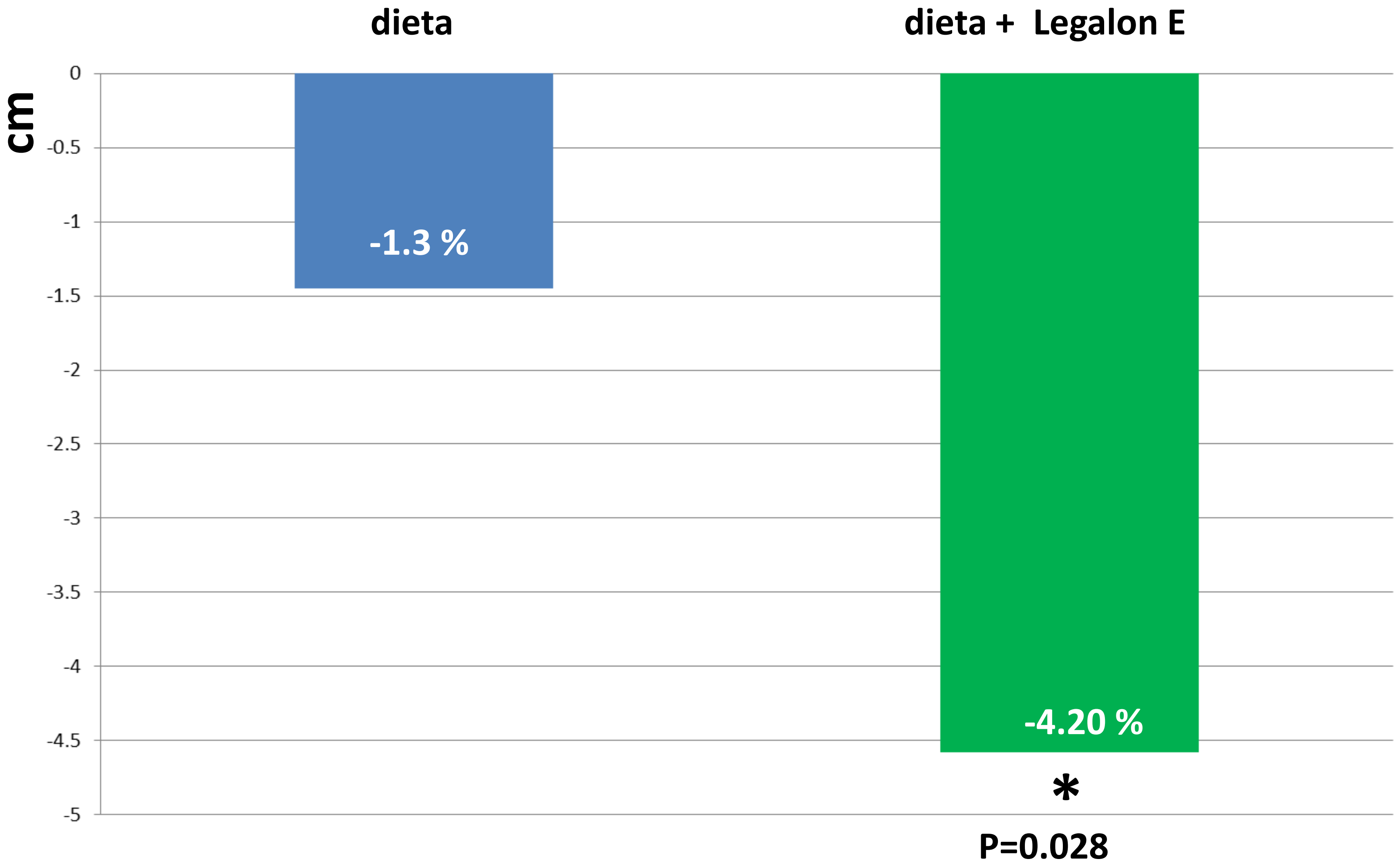
Gianpaolo Sorrentino · Paola Crispino ·
Daniela Coppola · Giorgio De Stefano

Parametri	Valori medi al basale
Lobo dx fegato	16.9 cm
ALT	32.15
AST	25.14
AST/ALT	0.88
γGT	38.33
TGL	174.18
glicemia	104.62
Hb glicata	4.32%
circonferenza vita	107.22 cm
BMI	31.78

Riduzione lobo dx fegato



Riduzione della circonferenza vita



Bedogni *et al. BMC Gastroenterology* 2010, **10**:98
http://www.biomedcentral.com/1471-230X/10/98

BMC Gastroenterology

RESEARCH ARTICLE **Open Access**

A simple index of lipid overaccumulation is a good marker of liver steatosis

LAP = (circonferenza – 65) x TGL mmol/l (maschio)
(circonferenza – 58) x TGL mmol/l (femmina)

Giorgio Bedogni[1,2*], Henry S Kahn[3], Stefano Bellentani[4], Claudio Tiribelli[1]

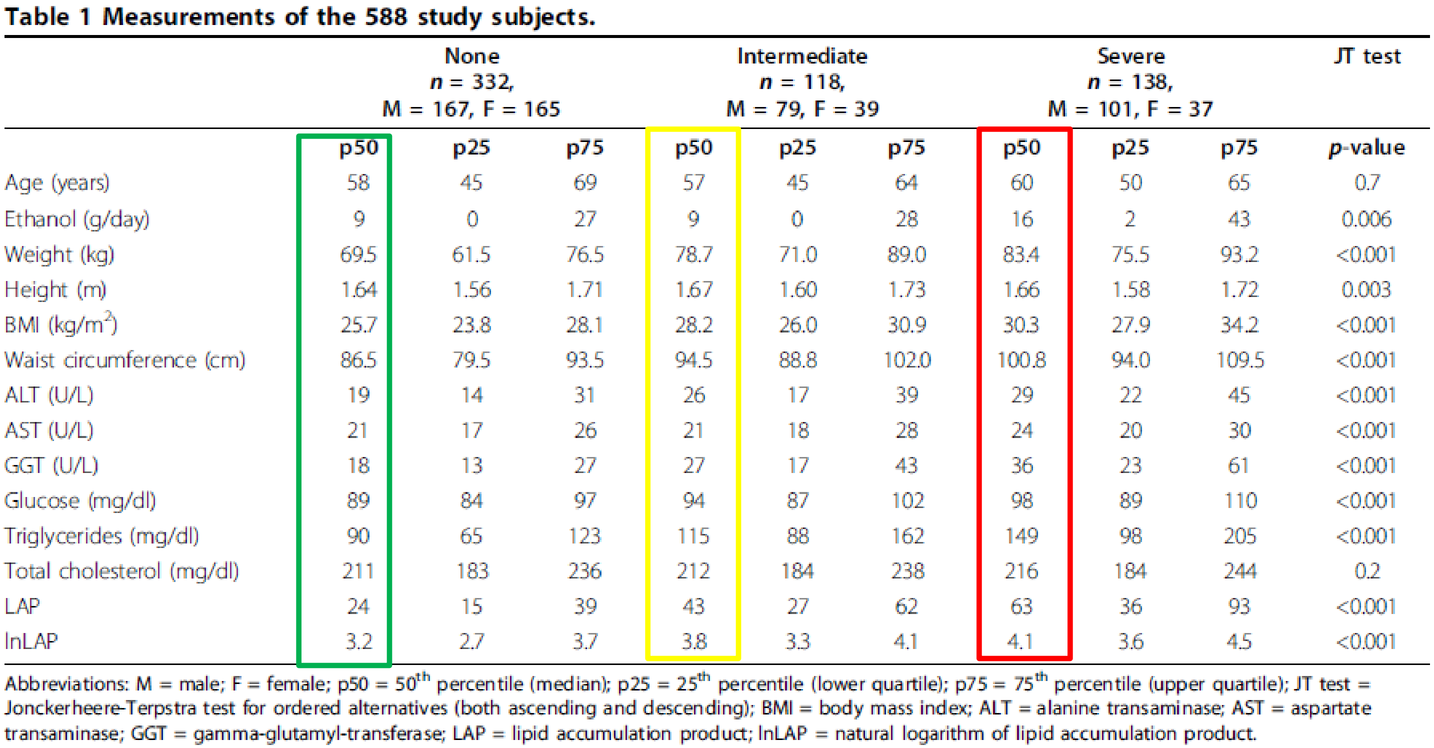
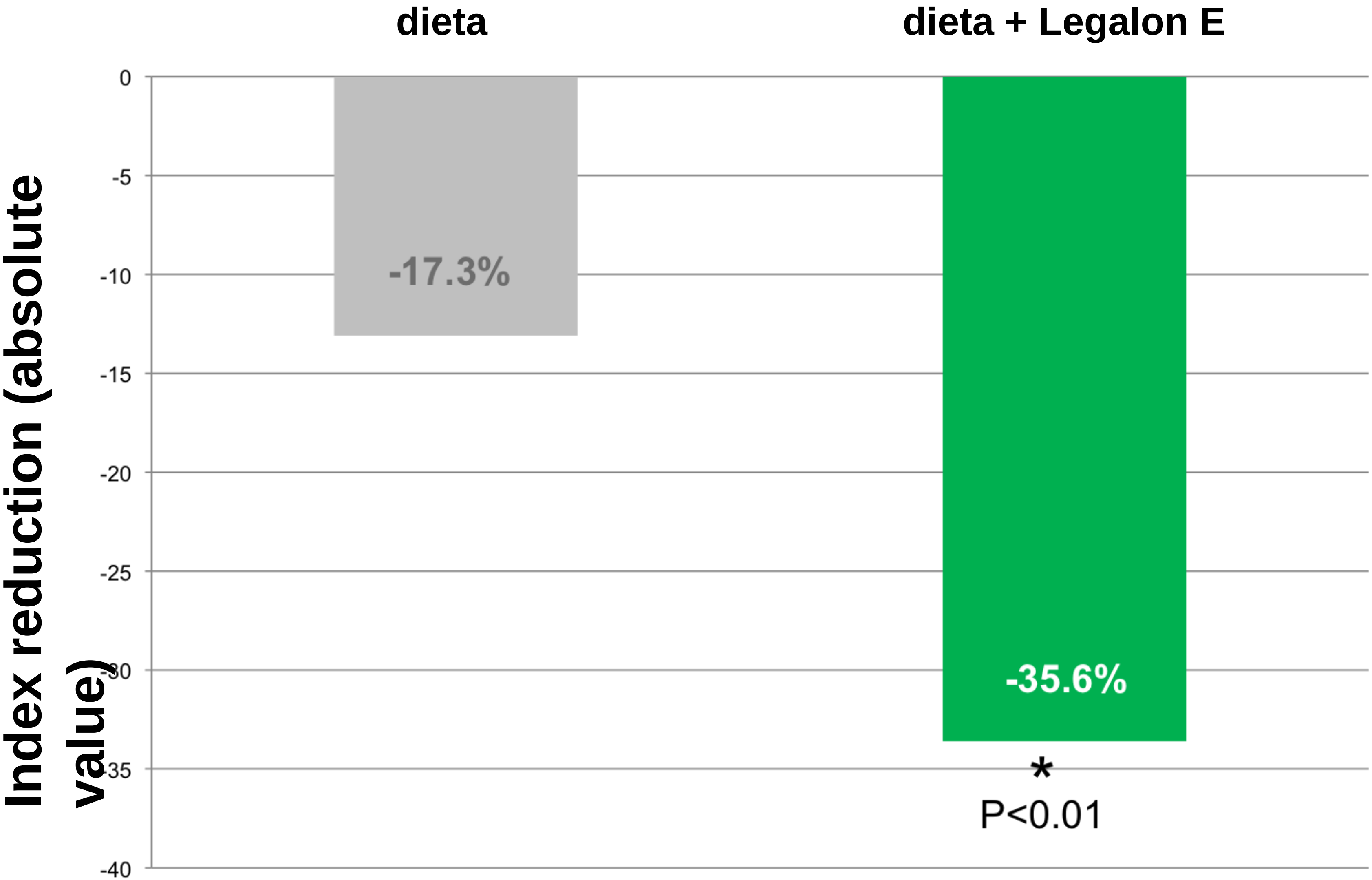


Table 1 Measurements of the 588 study subjects.

	None *n* = 332, M = 167, F = 165			Intermediate *n* = 118, M = 79, F = 39			Severe *n* = 138, M = 101, F = 37			JT test
	p50	p25	p75	p50	p25	p75	p50	p25	p75	*p*-value
Age (years)	58	45	69	57	45	64	60	50	65	0.7
Ethanol (g/day)	9	0	27	9	0	28	16	2	43	0.006
Weight (kg)	69.5	61.5	76.5	78.7	71.0	89.0	83.4	75.5	93.2	<0.001
Height (m)	1.64	1.56	1.71	1.67	1.60	1.73	1.66	1.58	1.72	0.003
BMI (kg/m^2)	25.7	23.8	28.1	28.2	26.0	30.9	30.3	27.9	34.2	<0.001
Waist circumference (cm)	86.5	79.5	93.5	94.5	88.8	102.0	100.8	94.0	109.5	<0.001
ALT (U/L)	19	14	31	26	17	39	29	22	45	<0.001
AST (U/L)	21	17	26	21	18	28	24	20	30	<0.001
GGT (U/L)	18	13	27	27	17	43	36	23	61	<0.001
Glucose (mg/dl)	89	84	97	94	87	102	98	89	110	<0.001
Triglycerides (mg/dl)	90	65	123	115	88	162	149	98	205	<0.001
Total cholesterol (mg/dl)	211	183	236	212	184	238	216	184	244	0.2
LAP	24	15	39	43	27	62	63	36	93	<0.001
lnLAP	3.2	2.7	3.7	3.8	3.3	4.1	4.1	3.6	4.5	<0.001

Abbreviations: M = male; F = female; p50 = 50th percentile (median); p25 = 25th percentile (lower quartile); p75 = 75th percentile (upper quartile); JT test = Jonckerheere-Terpstra test for ordered alternatives (both ascending and descending); BMI = body mass index; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl-transferase; LAP = lipid accumulation product; lnLAP = natural logarithm of lipid accumulation product.

Riduzione Indice LAP (Lipid Accumulation Product)



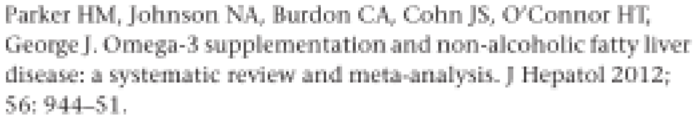
Basale 78 pz : 89.6

Omega-3

Meccanismi potenziali di azione:

- **riduzione accumulo acidi grassi nell'epatocita** (promuove attività PPAR alfa riduce la espressione degli enzimi che regolano la lipogenesi de novo**)**
- **riduzione stress ossidativo**
- **protezione epatocellulare**
- **riduzione insulinoresistenza**

Una recente metanalisi che includeva 5 RCTs e 355 soggetti ha concluso che la supplementazione con Omega-3 può ridurre gli indici di funzione epatica ed il contenuto lipidico del fegato, sia pure con un effetto modesto.
Non vi sono dati sul dosaggio ottimale, la durata della terapia e la sicurezza a lungo termine



Parker HM, Johnson NA, Burdon CA, Cohn JS, O'Connor HT, George J. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol 2012; 56: 944–51.

Long-Term Treatment with n-3 Polyunsaturated Fatty Acids as a Monotherapy in Children with Nonalcoholic Fatty Liver Disease

Mehmet Boyraz[1], Özgür Pirgon[2], Bumin Dündar[3], Ferhat Çekmez[4], Nihal Hatipoğlu[5]

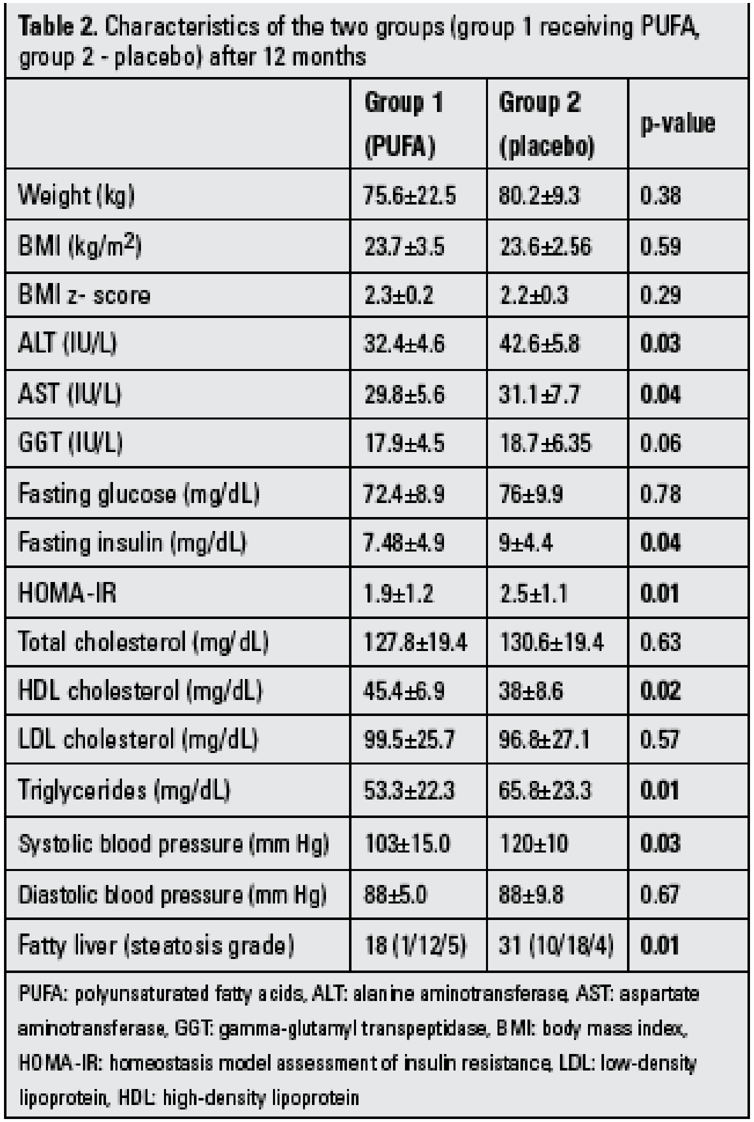


Table 2. Characteristics of the two groups (group 1 receiving PUFA, group 2 - placebo) after 12 months

	Group 1 (PUFA)	Group 2 (placebo)	p-value
Weight (kg)	75.6±22.5	80.2±9.3	0.38
BMI (kg/m^2)	23.7±3.5	23.6±2.56	0.59
BMI z- score	2.3±0.2	2.2±0.3	0.29
ALT (IU/L)	32.4±4.6	42.6±5.8	**0.03**
AST (IU/L)	29.8±5.6	31.1±7.7	**0.04**
GGT (IU/L)	17.9±4.5	18.7±6.35	0.06
Fasting glucose (mg/dL)	72.4±8.9	76±9.9	0.78
Fasting insulin (mg/dL)	7.48±4.9	9±4.4	**0.04**
HOMA-IR	1.9±1.2	2.5±1.1	**0.01**
Total cholesterol (mg/dL)	127.8±19.4	130.6±19.4	0.63
HDL cholesterol (mg/dL)	45.4±6.9	38±8.6	**0.02**
LDL cholesterol (mg/dL)	99.5±25.7	96.8±27.1	0.57
Triglycerides (mg/dL)	53.3±22.3	65.8±23.3	**0.01**
Systolic blood pressure (mm Hg)	103±15.0	120±10	**0.03**
Diastolic blood pressure (mm Hg)	88±5.0	88±9.8	0.67
Fatty liver (steatosis grade)	18 (1/12/5)	31 (10/18/4)	**0.01**

PUFA: polyunsaturated fatty acids, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transpeptidase, BMI: body mass index, HOMA-IR: homeostasis model assessment of insulin resistance, LDL: low-density lipoprotein, HDL: high-density lipoprotein

1 g omega-3/die
o placebo

intervento stile di vita

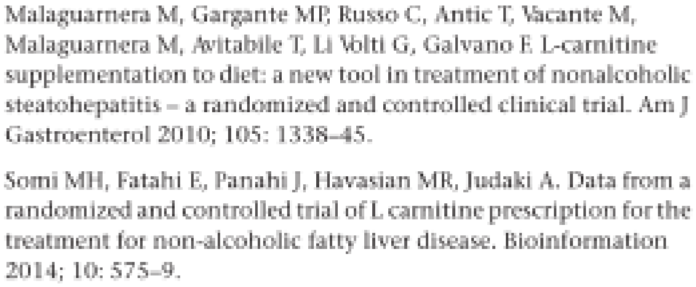
J Clin Res Pediatr Endocrinol 2015;7(2):121-127

L-carnitina

Meccanismi potenziali di azione:
- **riduzione insulinoresistenza**
- **riduzione infiammazione cronica**
- **protezione epatocellulare**
- **riduzione dislipidemia**

Dati contrastanti:
al dosaggio di 2 g/die miglioramento istologico (steatosi e fibrosi) e bioumorale (ALT, HOMA) in pazienti con NASH

Al dosaggio di 1 g/die non miglioramenti bioumorali di pazienti con NAFLD non sottoposti a biopsia



Malaguarnera M, Gargante MP, Russo C, Antic T, Vacante M, Malaguarnera M, Avitabile T, Li Volti G, Galvano F. L-carnitine supplementation to diet: a new tool in treatment of nonalcoholic steatohepatitis – a randomized and controlled clinical trial. Am J Gastroenterol 2010; 105: 1338–45.

Somi MH, Fatahi E, Panahi J, Havasian MR, Judaki A. Data from a randomized and controlled trial of L carnitine prescription for the treatment for non-alcoholic fatty liver disease. Bioinformation 2014; 10: 575–9.

Polifenoli (resveratrolo)

Meccanismi potenziali di azione:
- **aumento ossidazione acidi grassi**
- **riduzione stress ossidativo**
- **protezione epatocellulare**
- **riduzione insulinoresistenza**

Evidenze in prevenzione primaria da studi epidemiologici
Non disponibili trials clinici

Curcumina

Meccanismi potenziali di azione:

- **riduzione stress ossidativo**
- **riduzione insulinoresistenza**

Dati in forma di abstract mostrano una potenzialità di azione su IR e transaminasi

Conclusioni

La NAFLD primaria rappresenta una espressione della sindrome metabolica
Caratterizzata da notevole eterogeneità nella evoluzione, a causa di fattori
genetici, ambientali e dalla presenza o meno di diabete.

Sono disponibili linee guida che forniscono algoritmi per il follow-up
In setting cure primarie e per l’invio allo specialista

La terapia dietetica e le modifiche dello stile di vita rappresentano la prima linea di cura. Tuttavia questa può essere integrata da un approccio nutraceutico.

Mentre la vitamina E ad alto dosaggio è da riservarsi agli specialisti,
la silibinina associata a basse dosi di vitamina E può essere utilizzata nell’ambito delle cure primarie.

Altri nutraceutici promettenti sono rappresentati da carnitina ad alto dosaggio, omega-3, curcumina.