Ordine dei
Medici Chirurghi
ed Odontoiatri di Crotone

Accademia Medica Pitagorica
dell'Ordine dei Medici Chirurghi ed Odontoiatri di Crotone

Giornate Mediche Pitagoriche

Stili di vita e "Bene-Essere"

I^a Edizione

Armonia - Salute - Disciplina

Crotone, 7 dicembre 2013
Lido degli Scogli

NAFLD e Malattia Aterosclerotica: Come accorgersene

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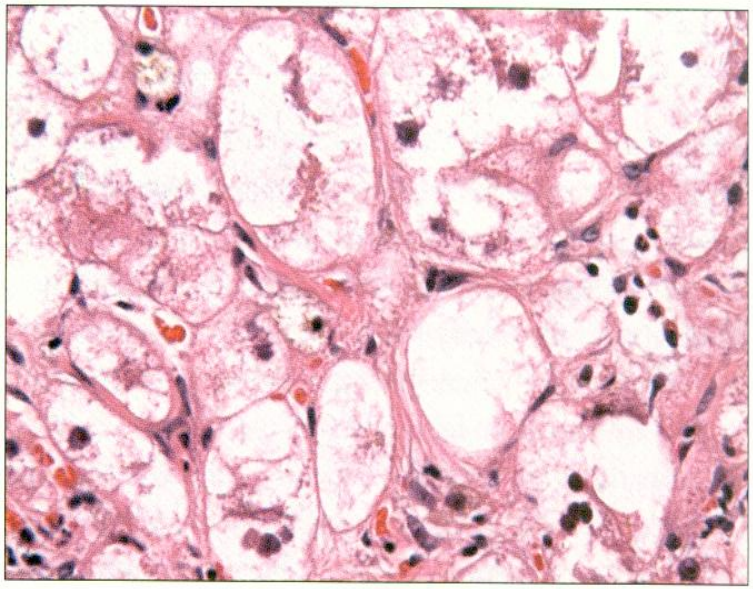
Steatosi



Steatosi (infiltrazione grassa) rappresenta una risposta caratteristica, e quasi monotona, del fegato a numerose noxae patogene (ipossiemia, tossine, infiammazioni sistemiche, digiuno, disturbi metabolici)

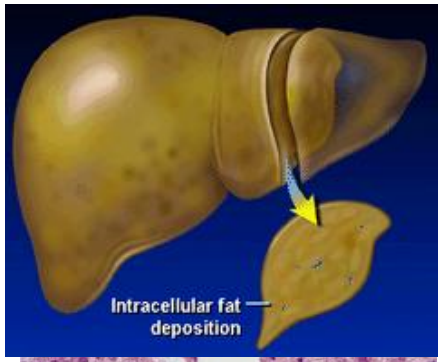
Non-Alcoholic Fatty Liver Disease (NAFLD)

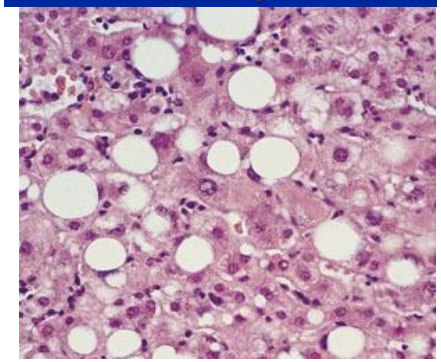
NAFL → **NonAlcoholic Steatohepatitis (NASH)**: → **Cirrosi**

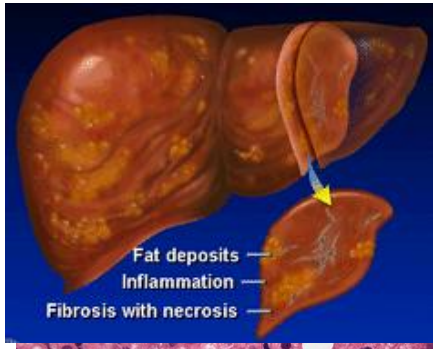
Steatosi (macrovescicolare)

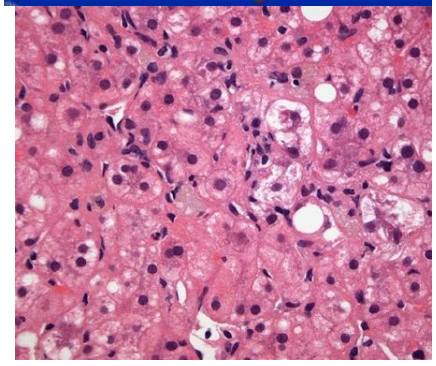
Steatosi,Infiam.Ballooning, ± Mallory hyaline,± Fibrosi

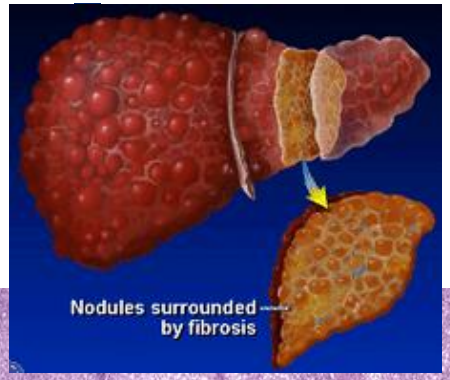
Infiammazione
Fibrosi Stadio IV
+ Steatosi

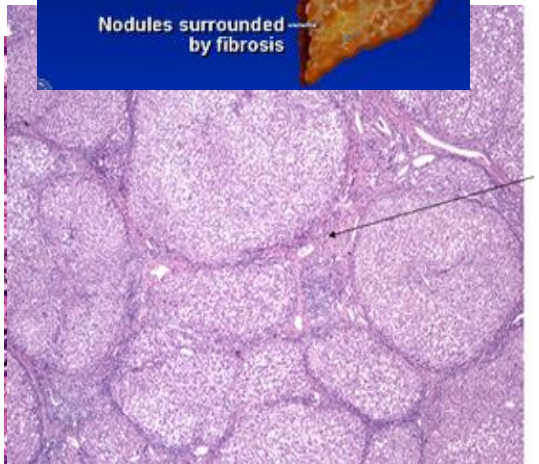












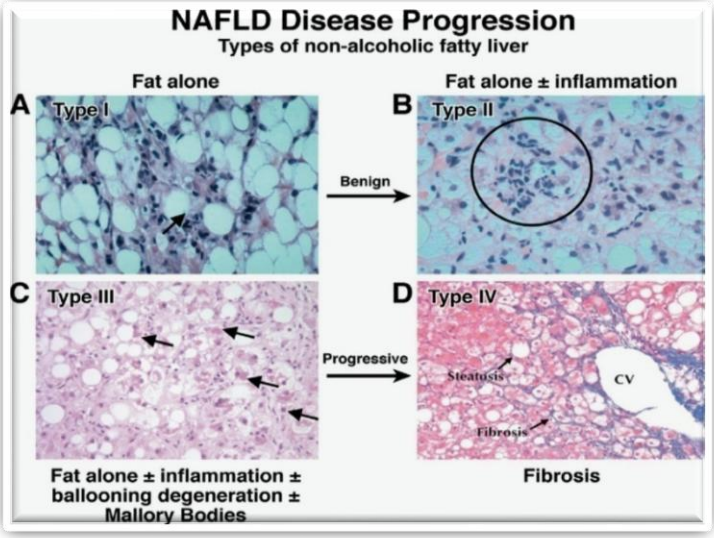
Nafld
- classificazione etiologica -

- **Primaria**
  - **Sindrome Metabolica (Obesità Centrale)**
- **Secondaria**
  - **Nutrizionale**
    - Malnutrizione
    - Digiuno
    - Nutrizione parenterale tot.
  - **Tossici ambientali**
    - Idrocarburi
    - Tossici fungini
    - Solventi organici
  - **Eredo-metaboliche**
    - Abetalipoproteinemia
    - Ipobetalipoproteinemia
    - Morbo di Wilson
    - Tirosinemia
  - **Iatrogenica**
    - Nimesulide
    - Amiodarone
    - Tamoxifene
    - Methotrexate
    - Ac. Valproico…etc
  - **Altri**
    - Malattie infiammatorie intestinali
    - HIV-HCV

NAFLD: Definizione

- La NAFLD è stata considerata per lungo tempo una malattia benigna e ancora oggi nella percezione comune, e anche tra gli addetti ai lavori, viene considerata tale

- Recenti studi hanno evidenziato che la NAFLD è una condizione cronica che comprende uno spettro di fenotipi anatomo-clinici che vanno dalla steatosi benigna a quadri più severi che includono infiammazione lobulare, ballooning epatocellulare, fibrosi e cirrosi (NASH)



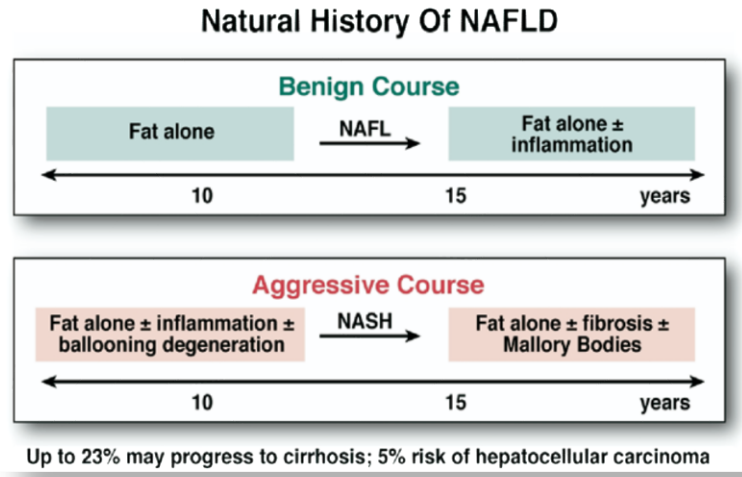
Category	Pathology	Clinicopathologic Correlations
Type 1	Simple steatosis	Known to be nonprogressive
Type 2	Steatosis plus lobular inflammation	Probably benign not considered to be NASH
Type 3	Steatosis, lobular inflammation, and ballooning degeneration	NASH without fibrosis; may progress to cirrhosis and liver failure
Type 4	Steatosis, ballooning degeneration, and fibrosis and/or Mallory bodies	NASH with fibrosis; may progress to cirrhosis and liver failure

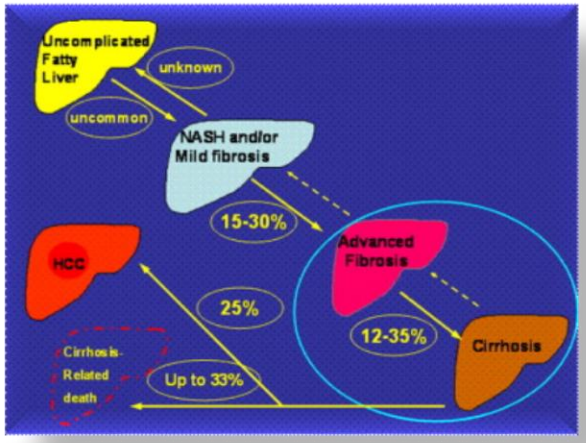
Epidemiologia

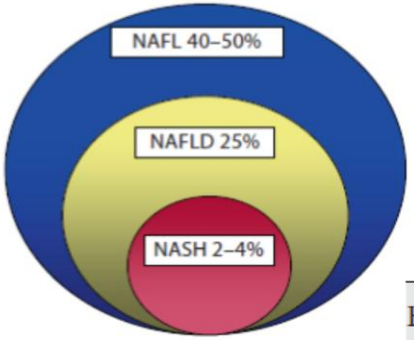
- 10 al 24 % della popolazione generale nei paesi occidentali
- 57.5 %-74 % negli obesi
- 100% negli obesi gravi e negli obesi diabetici
- 2.6 % giovani non obesi
- 22.5 %-52.8 % giovani obesi
- E' la principale causa di cirrosi criptogenetica

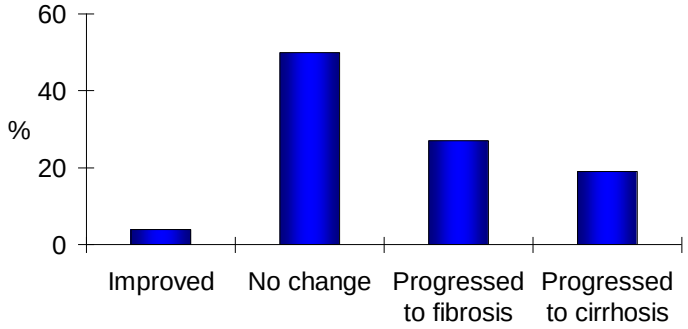
NAFLD:Evoluzione

- **La percentuale di soggetti con NAFLD che evolve verso la NASH non è ben conosciuta ma è stimata intorno al 5 al 10 %**
- **Numerosi studi indicano che l' 2%-4% della popolazione occidentale potrebbe avere la NASH**
- **La storia naturale della NAFLD è ancora poco conosciuta, ed in particolare, poco si sa perchè alcuni pazienti progrediscono verso la infiammazione, fibrosi e cirrosi ed altri invece no**







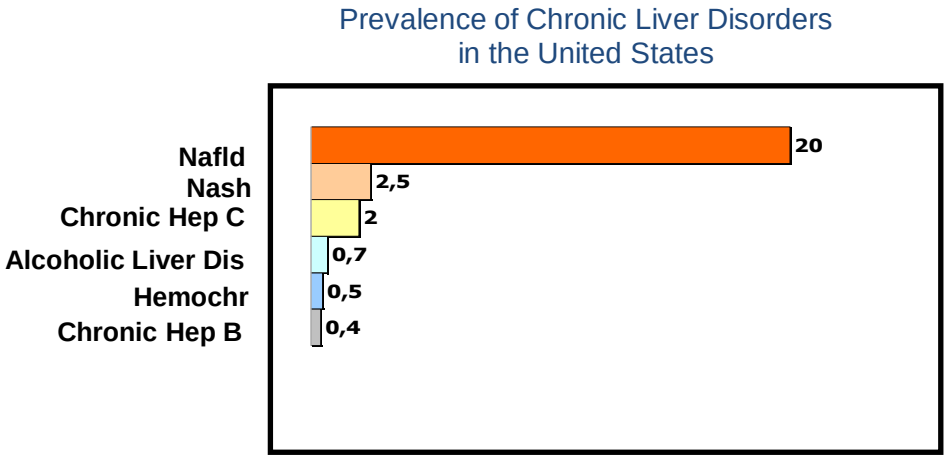


26 pazienti con NAFLD seguiti per 9 anni con biopsie epatiche seriali

Etiology	Alcoholic FL	NAFL
Cardiovascular diseases	9 (26%)	3 (38%)
Cancer	11 (31%)	3 (38%)
Cirrhosis/HCC	6 (17%)	1 (12.5%)

NAFLD: Definizione

- **Nonalcoholic fatty liver disease (NAFLD)**
- **E' attualmente la più comune forma di epatopatia cronica che colpisce sia gli adulti che i giovani in molte parti del mondo**
- **E' strettamente associata all'obesità e ad insulino-resistenza**
- **Viene considerata come un fattore di rischio indipendente per malattie cardiovascolari**



Nafld-IR

Autore	Metodica	Casi	Controlli	Caratteristiche pazienti	Risultati
Marchesini	Homa	46 NAFLD	92	Glicemia a digiuno norm.	↑ Insulino -resistenza
Chitturi	Homa	66 NASH	36 epatite cr. HCV + 20 controlli		Homa >75° percentile dei controlli nel 98% dei casi
Pagano	FSIGT	19 NASH		Non diabetici	↓ Sensibilità insulinica correlata al BMI circonf.vita e area sotto curva insulinemica
Comert	Clamp	13 NASH	12 sani	No DM2, obesità e dislipidemia	↓ Consumo di glucosio
Marchesini	Clamp	30 NAFLD	10 sani 10 DM2	No DM2 e obesità	Consumo glucosio = DM2 ↑FFA ↓Soppressione lipolisi ↓Soppressione glucogenesi
Sanyal	Clamp 2 livelli	10 NASH	6 controlli 6 steatosi pura	No DM2	↓Consumo di glucosio ↓ soppressione della lipolisi
Musso	Sens. Insulin. OGTT	25 NASH	25 controlli	No DM2 e obesità	↓Sensibilità insulinica

ATP III Definition of the Metabolic Syndrome

Defined by the presence of ≥3 risk factors

Risk factor	Abnormal level
Waist circumference	
Men	>102 cm
Women	>88 cm
Fasting blood glucose	≥110 mg/dl
Serum triglycerides	≥150 mg/dl, or under fibrates
Serum HDL cholesterol	
Men	<40 mg/dl
Women	<50 mg/dl
Arterial blood pressure	≥130/≥85 mmHg, or under pharmacologic treatment

Reprinted with permission from JAMA, 2001, vol. 285, p. 2493.

HDL-C=High-density lipoprotein cholesterol

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-2497

The new International Diabetes Federation (IDF) definition

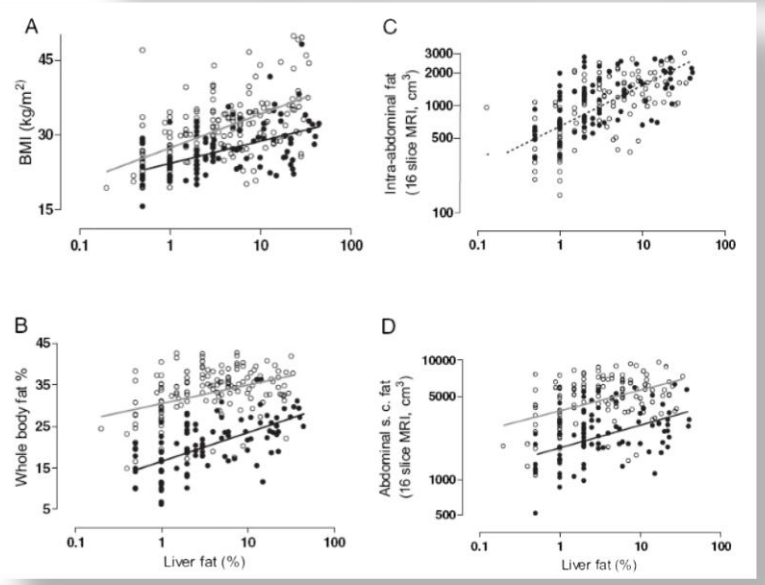
Central obesity (defined as waist circumference* with ethnicity specific values) **plus** any two of the following four factors:	
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) **or specific treatment for this lipid abnormality**
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females **or specific treatment for this lipid abnormality**
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg **or treatment of previously diagnosed hypertension**
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), **or previously diagnosed type 2 diabetes** If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

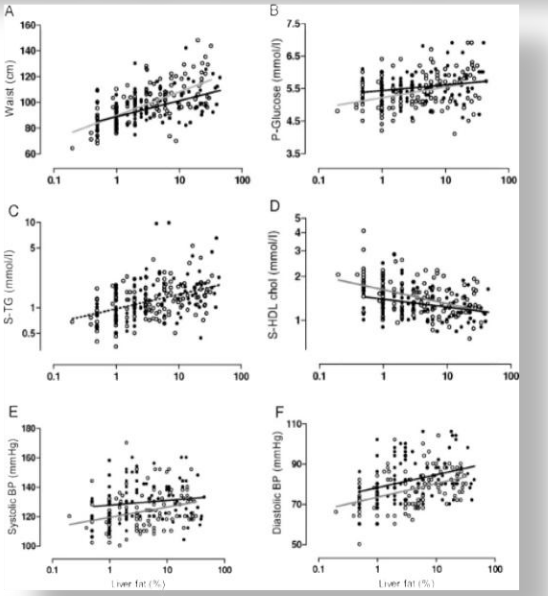
The new International Diabetes Federation (IDF) definition

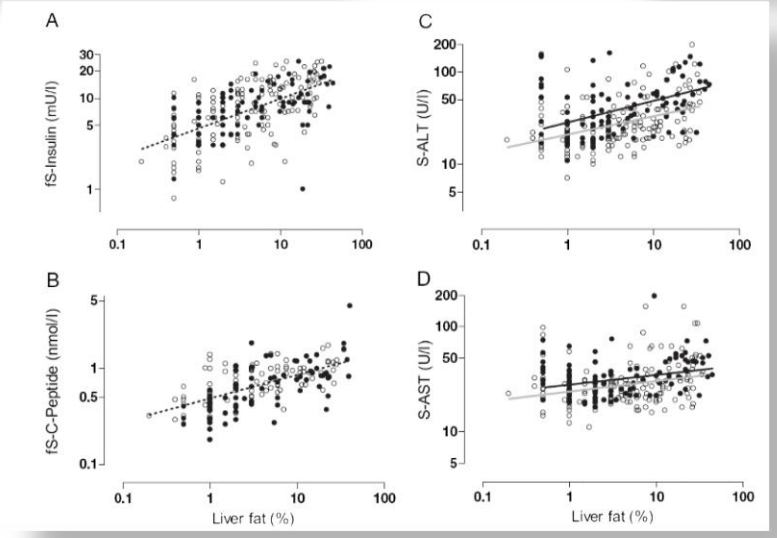
Ethnic specific values for waist circumference

Country/Ethnic group		Waist circumference
Europids* In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cm
	Female	≥ 80 cm
South Asians Based on a Chinese, Malay and Asian-Indian population	Male	≥ 90 cm
	Female	≥ 80 cm
Chinese	Male	≥ 90 cm
	Female	≥ 80 cm
Japanese**	Male	≥ 90 cm
	Female	≥ 80 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

Liver Fat in the Metabolic Syndrome







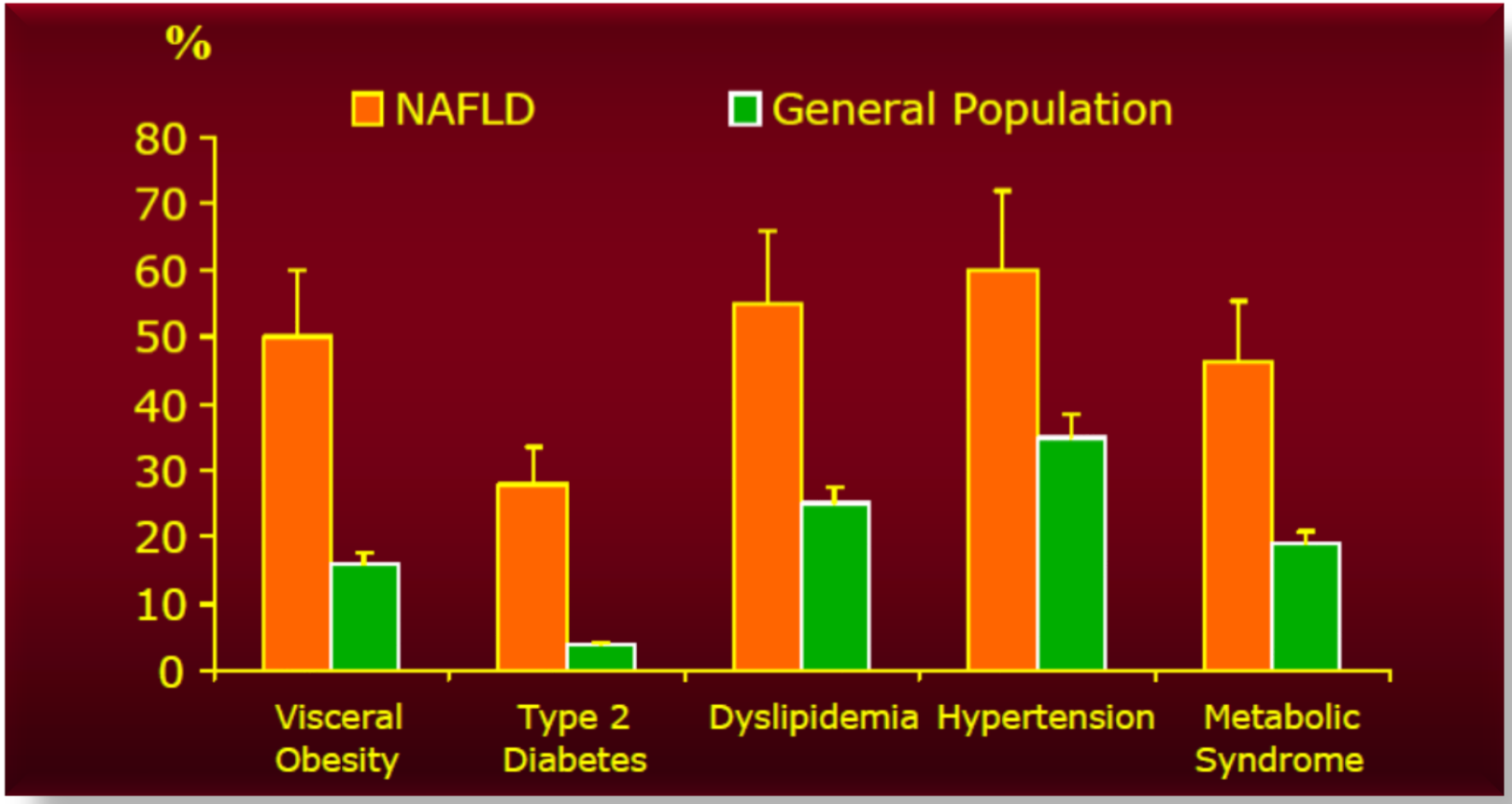
A. Kotronen; The Journal of Clinical Endocrinology & Metabolism 92(9):3490–3497; 2007

Other conditions associated with non-alcoholic fatty liver disease

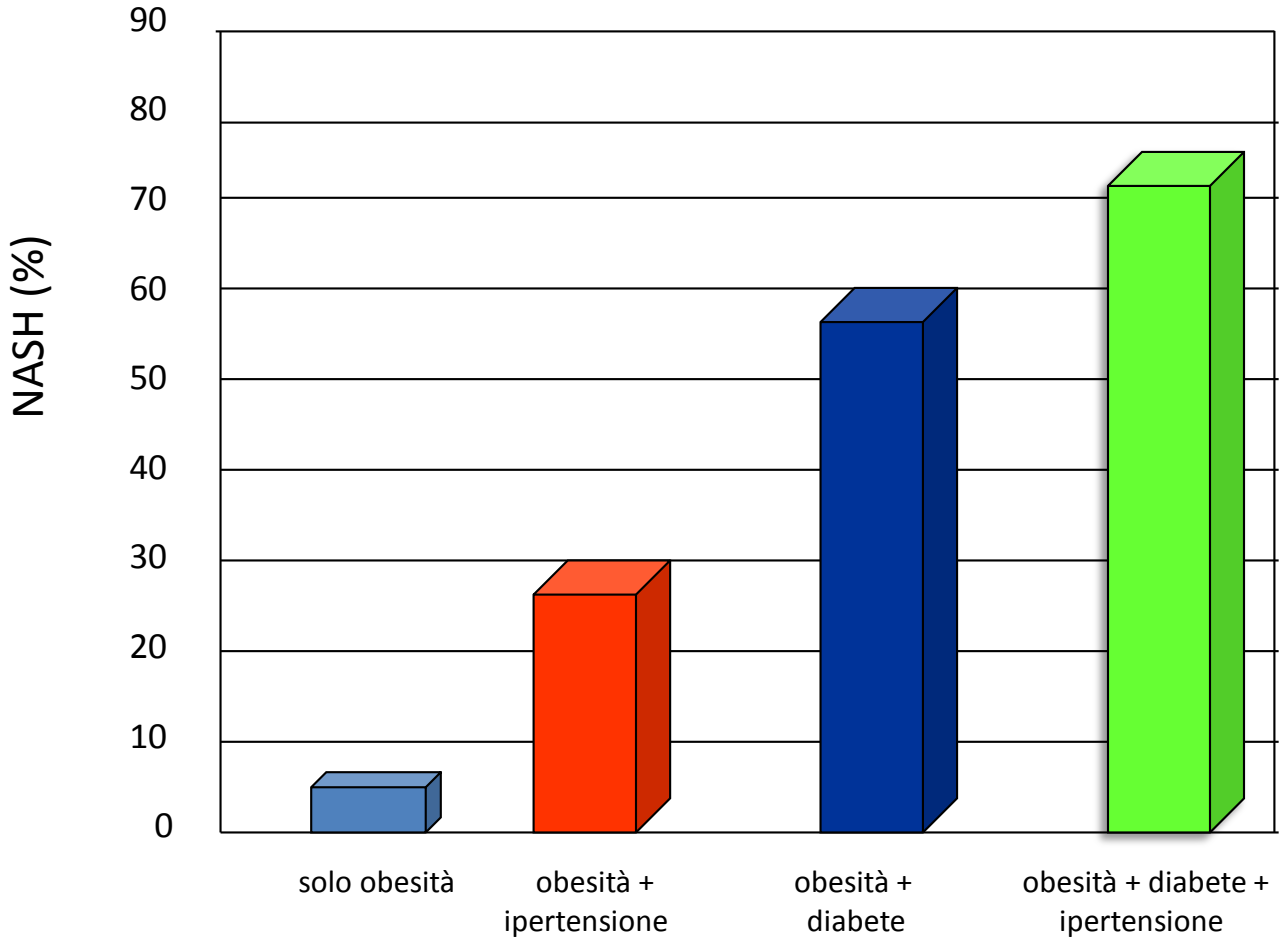
Author	No. of patients	Diabetes (%)	Obesity (%)	Hypertriglyceridaemia (%)
Ludwig (1980)	20	25	90	67
Diehl (1988)	39	88	71	–
Lee (1989)	49	51	69	4
Powell (1990)	42	36	93	81
Bacon (1990)	33	21	39	21
Matteoni (1999)	132	33	70	92
Angulo (1999)	144	28	60	27

Modified from McCullough.[45]

Prevalenza dei componenti della sindrome metabolica nella nafld



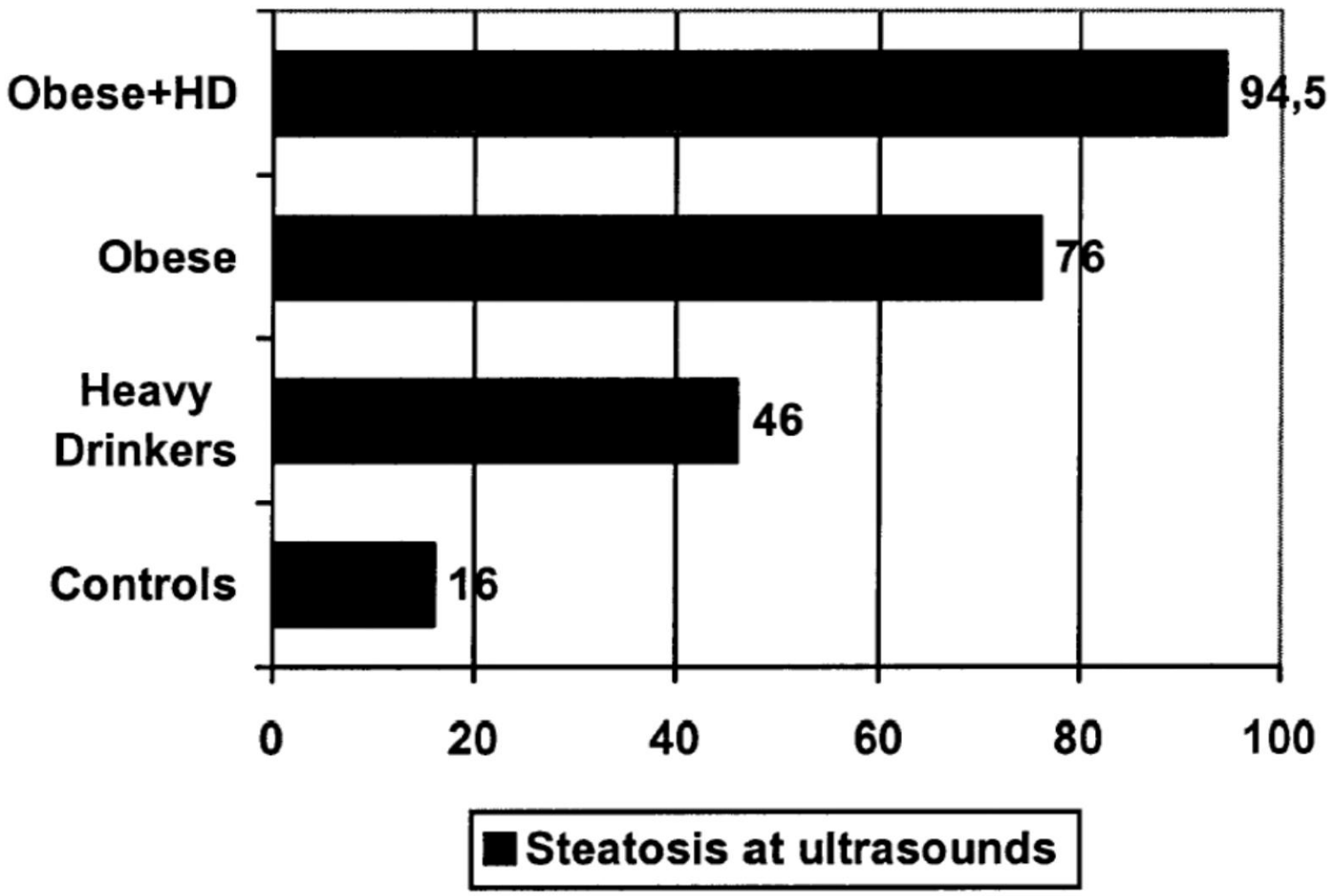
PREVALENZA DELLA NASH



105 grandi obesi in relazione alla coesistenza o meno di diabete e ipertensione

Dixon JB, Barthal PS, O'Brian PE. NAFLD : predictors of NASH in the severely obesity. Gastroenterolgy, 2001

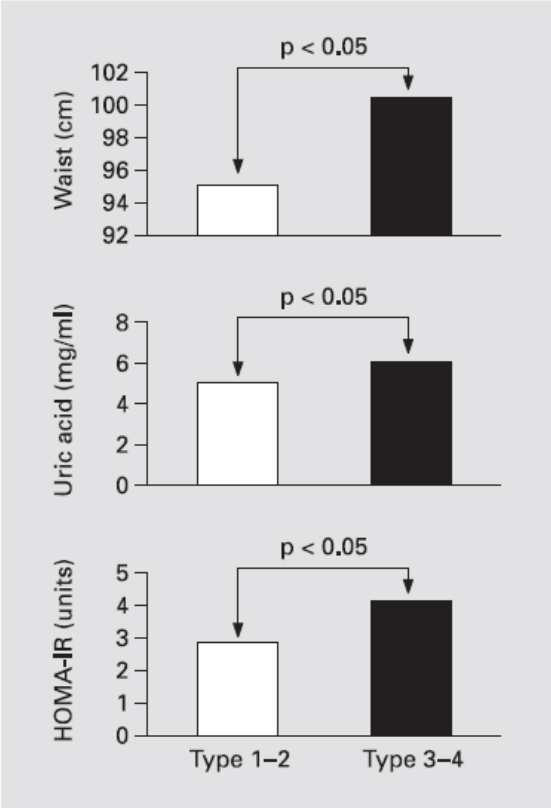
Prevalenza di steatosi all'ecografia nello studio Dionysos



Bellentani & Tiribelli, J Hepatol 2001

Is NAFLD a Liver Manifestation of Insulin Resistance?

Prevalence of metabolic alterations/ diseases in NAFLD.



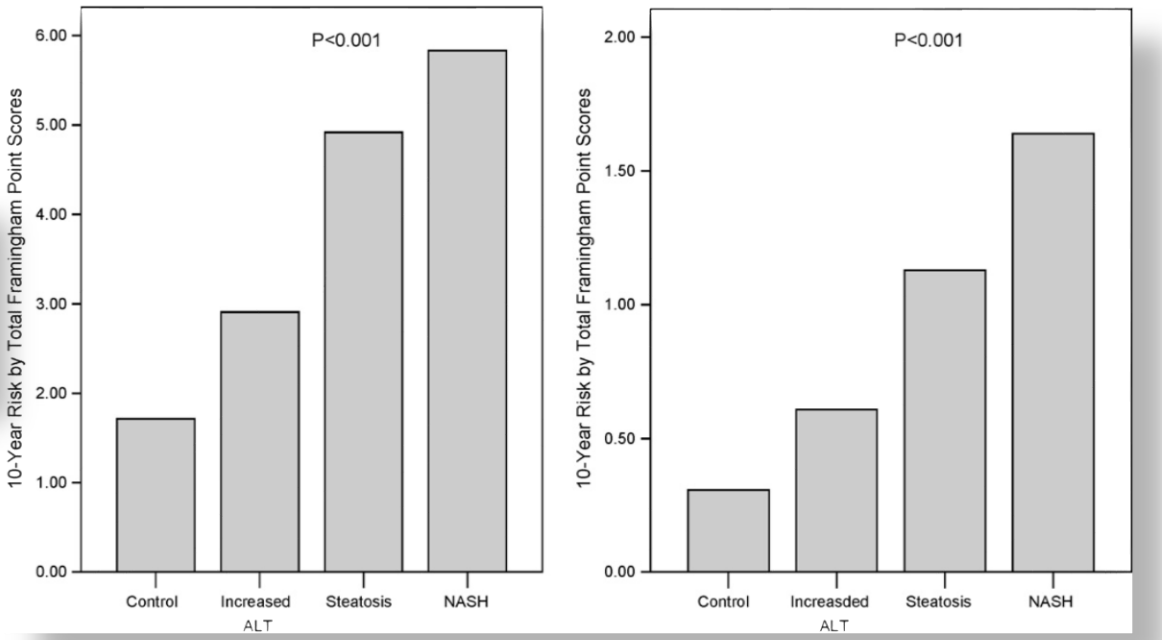
Evidence that IR associates with more advanced NAFLD types

Indices of IR in patients from the POLISTENA study are significantly more elevated in advanced (types 3 and 4) as compared to early (types 1 and 2) NAFLD

Dig Dis 2005;23:72–82

The severity of nonalcoholic fatty liver disease is associated with increased cardiovascular risk

Controlli
ALT aumentate senza steatosi
Steatosi con ALT normali (Nafld)
Steatosi con ALT alterate (Nash)



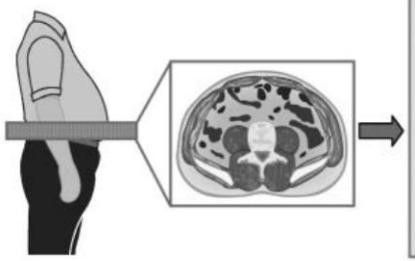
In una larga coorte (56.000) di popolazione, è stato dimostrato che:

- **La diagnosi e la severità della NAFLD è associata ai fattori tradizionali di rischio CV e ad un aumentato score di Framingham**
- **Una diagnosi clinica di NAFLD e particolarmente di NASH deve portare il medico a ricercare e ad individuare gli altri fattori di rischio per patologie cardiovascolari**

Sunga, Ryanb Atherosclerosis Oct. 2008

SINDROME METABOLICA

A CONCEPTUAL DEFINITION OF THE MOST PREVALENT FORM OF THE METABOLIC SYNDROME: ABDOMINAL OBESITY



- Atherogenic dyslipidemia
- Insulin resistance/ Glucose intolerance } may evolve to type 2 diabetes
- Proinflammatory profile
- Prothrombotic profile
- Raised blood pressure (in about 50% of patients)

B CLINICAL TOOLS TO FIND PATIENTS WITH THE METABOLIC SYNDROME

NCEP-ATP III	IDF	WHO	EGIR	AACE	HyperTG waist	Others
• Waist girth • HDL-cholesterol • Triglycerides • Blood pressure • Glucose	• Waist girth • HDL-cholesterol • Triglycerides • Blood pressure • Glucose	• Insulin* • Glucose • WHR, BMI • HDL-cholesterol • Triglycerides • Blood pressure • Microalbuminuria	• Insulin • Waist girth • Glucose • HDL-cholesterol • Triglycerides • Blood pressure	• Glucose • BMI • HDL-cholesterol • Triglycerides • Blood pressure • Other features of insulin resistance†	• Waist girth • Triglycerides	?

➢ **La Sindrome Metabolica è un cluster di F.R metabolici che predicono lo sviluppo di Diabete e di Malattie CV meglio di ognuno dei suoi componenti presi singolarmente**

Annals of Medicine. 2006; 38: 52–63

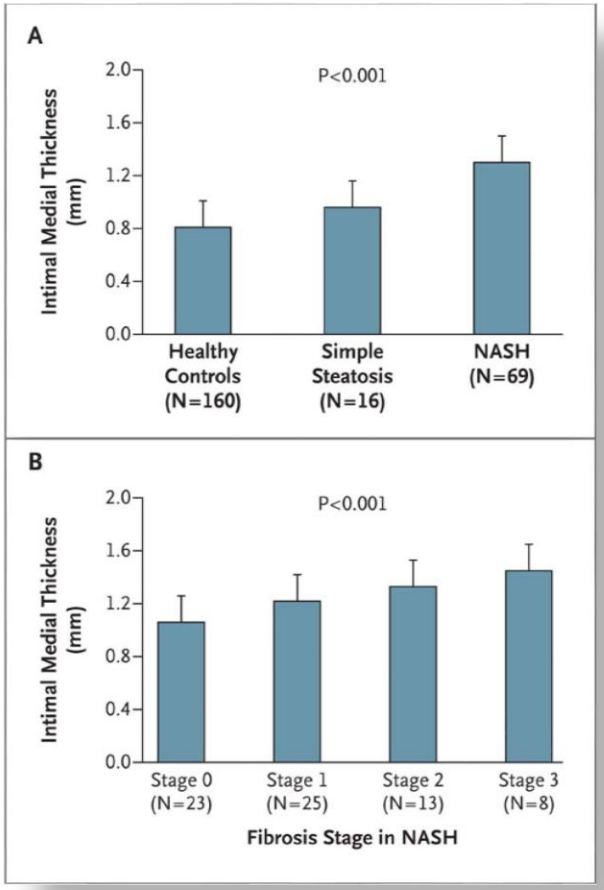
From the metabolic syndrome to NAFLD or vice versa?

NAFLD vs. la Sindrome Metabolica nelle Malattie CV

- **La Sindrome Metabolica aumenta il Rischio di Malattie CV approssimativamente di due volte**
- **La NAFLD lo aumenta di circa quattro volte**
- **Studi epidemiologici prospettici hanno dimostrato che la NAFLD predice lo sviluppo di MCV indipendentemente dal consumo di alcool o dei tradizionali FR CV, come per esempio LDL colesterolo**
- **Analisi multivariate di numerosi studi suggeriscono che la NAFLD e non la SM rappresenta un predittore indipendente di MCV**

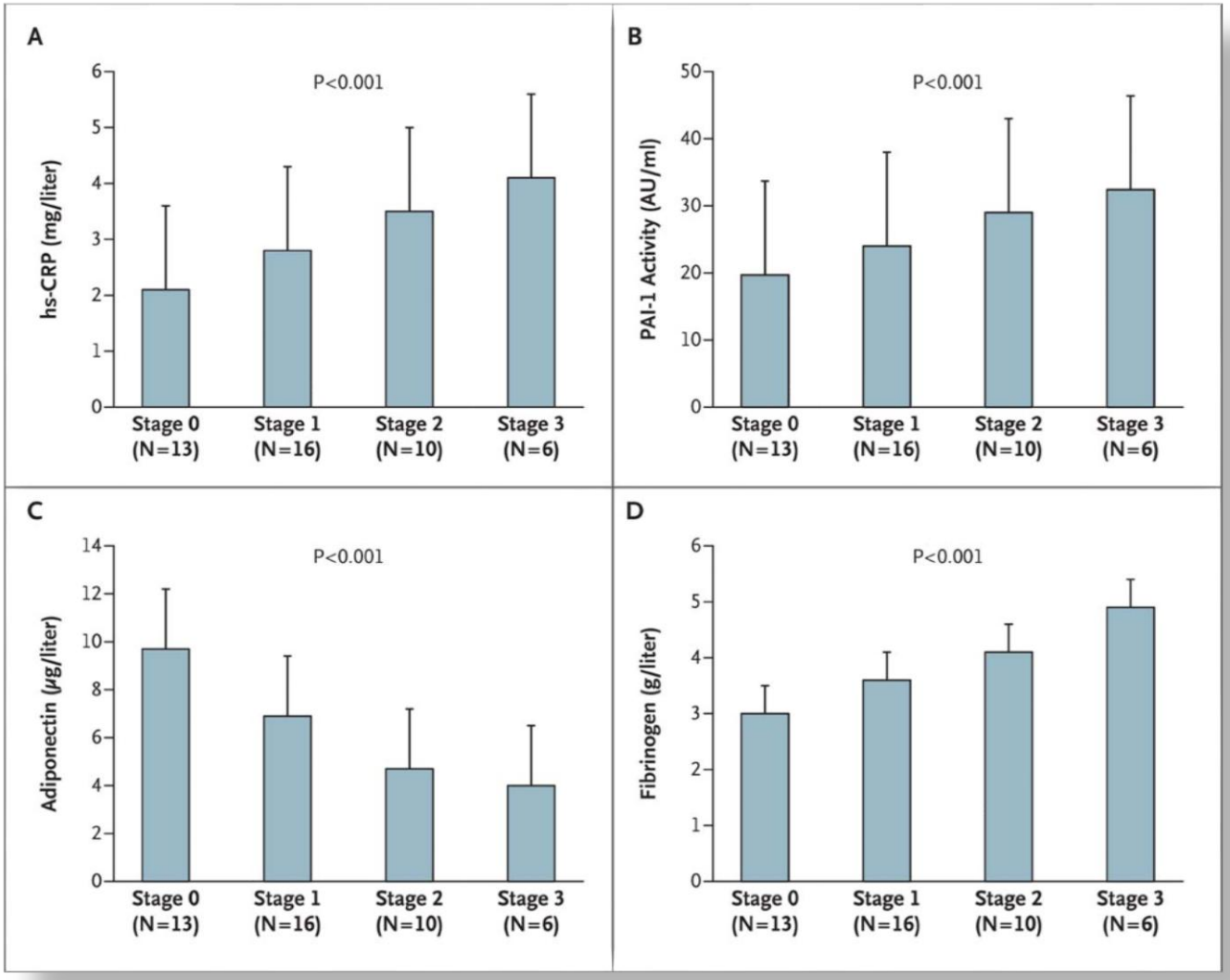
Digestive and Liver Disease 42 (2010) E Vannia, E Bugianesi, A Kotronen

Carotid-Artery Intimal Medial Thickness in Patients with Nonalcoholic Fatty Liver Disease



Targher G et al. N Engl J Med 2010;363:1341-1350

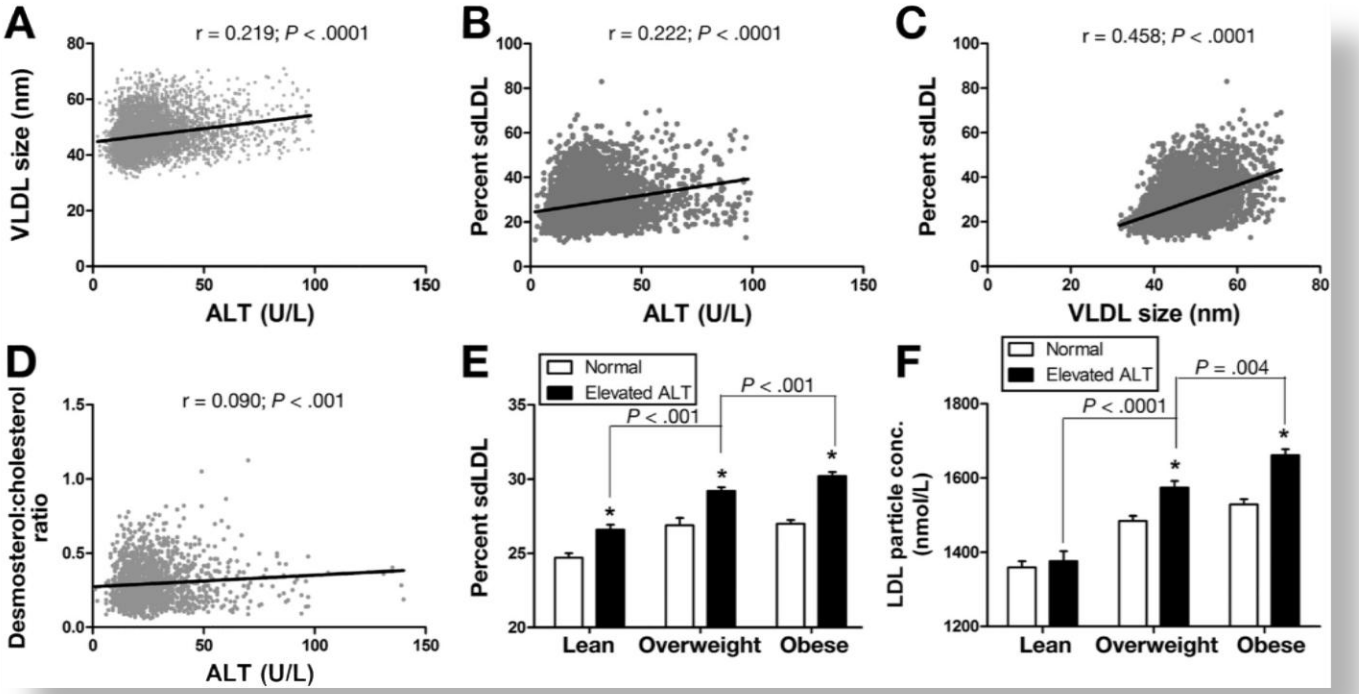
Inflammatory and Procoagulant Biomarkers in Patients with Nonalcoholic Steatohepatitis



Targher G et al. N Engl J Med 2010;363:1341-1350

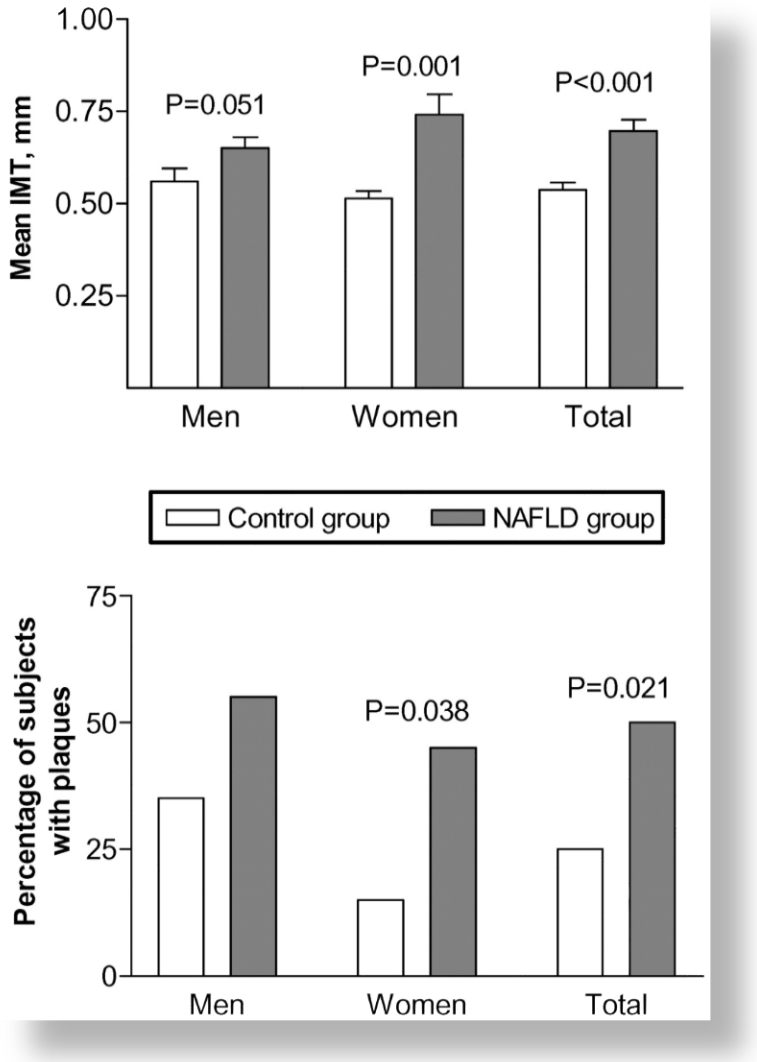
The NEW ENGLAND JOURNAL of MEDICINE

Association Between High-Normal Levels of Alanine Aminotransferase and Risk Factors for Atherogenesis



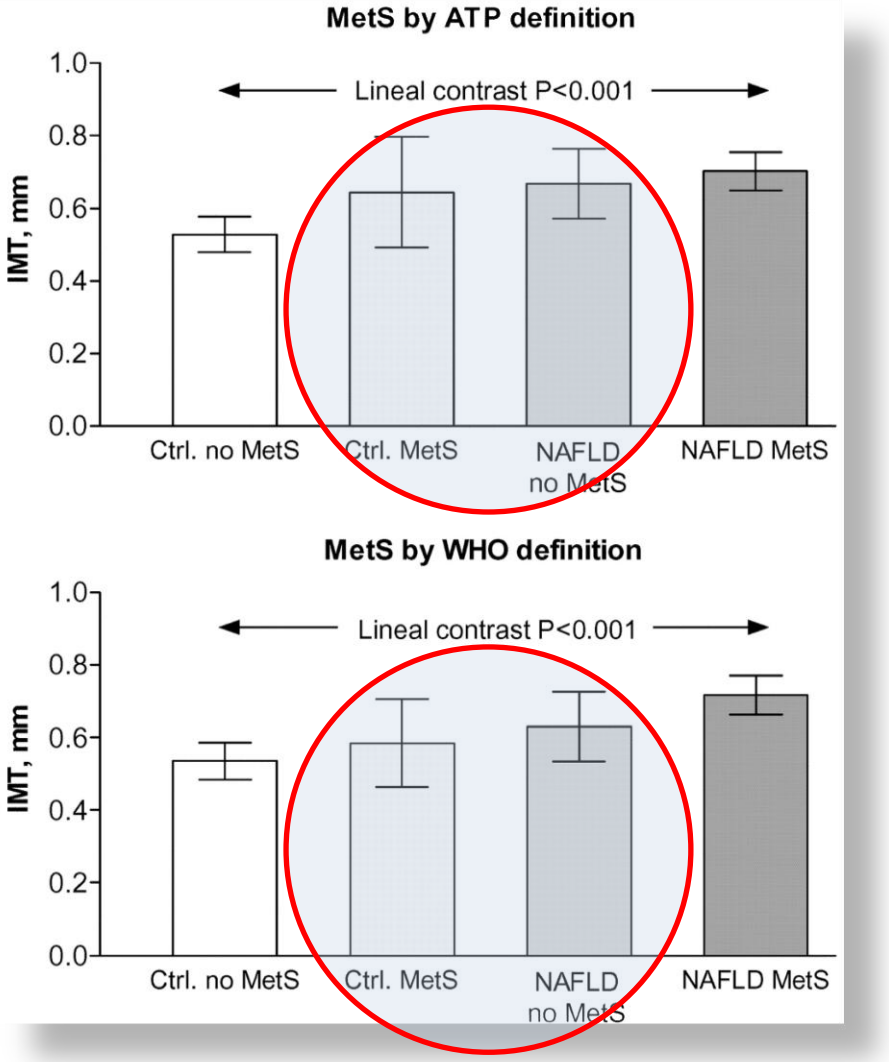
GASTROENTEROLOGY 2013;145:1271–1279

Comparisons of mean carotid IMT (top) and plaque frequency (bottom) in patients with NAFLD and control subjects



Brea, A. et al. Arterioscler Thromb Vasc Biol 2005;25:1045-1050

Sex- and age-adjusted mean carotid IMT in control (Ctrl) subjects and NAFLD patients with and without MetS by 2 definitions



Brea, A. et al. Arterioscler Thromb Vasc Biol 2005;25:1045-1050

Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: A systematic review.

- 3497 subjects (1427 patients and 2070 controls),

	NAFLD YES	NAFLD NO	
carotid IMT	0.51, 95%	0.44-0	p<0.01

13%

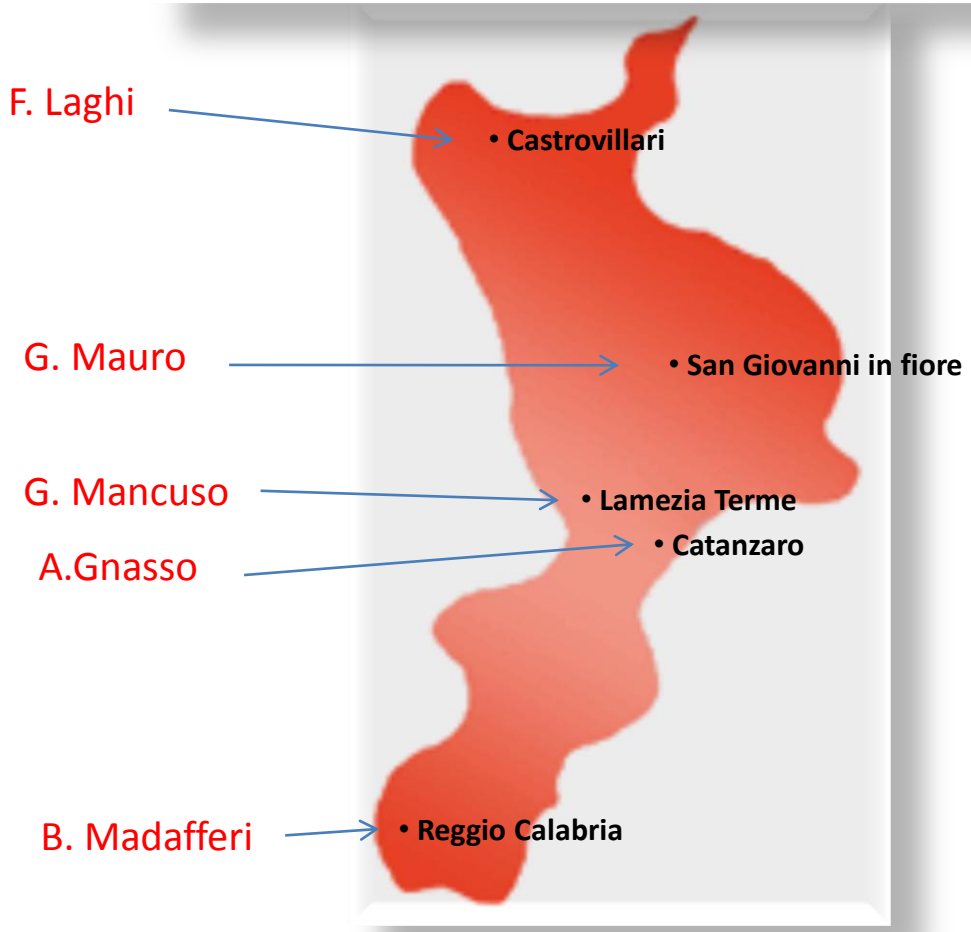
Sookoian S, Pirola CJ. J Hepatol. 2008 Oct;49(4):600-607. Epub 2008 Jul 2

J Gastroenterol
DOI 10.1007/s00535-009-0125-8

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Hepatic steatosis, carotid atherosclerosis and metabolic syndrome: the STEATO Study

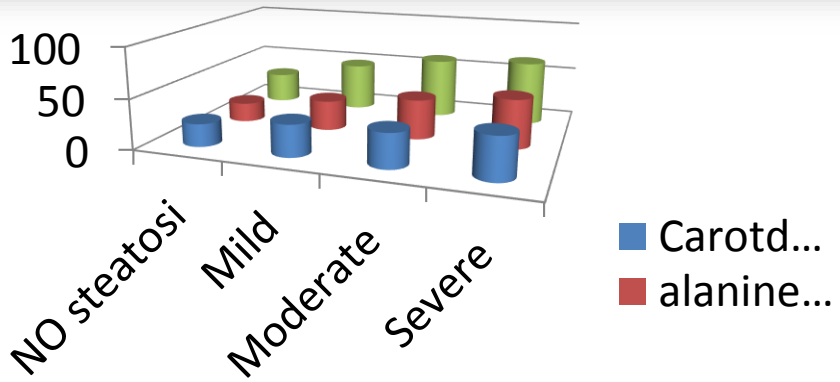
Claudio Carallo · Gerardo Mancuso · Gaetano Mauro · Ferdinando Laghi · Bruno Madafferi · Concetta Irace · Agostino Gnasso · Faustina Scavelli · Ferruccio Dell'Aquila · Mosè Bartone · Francesco Gullo · Maria Ferraro · Vitaliano Spagnuolo · Maria Belmonte · Antonio Ferrara · Antonio Silvano Rotondaro · Nicola Brandolino · Francesca Parasporo · Francesco Scopelliti



C Carallo, G Mancuso, GF Mauro, F Laghi, B Madafferi J Gastroenterol 2010

Degrees of bright liver with respect to transaminase values, prevalence of metabolic syndrome and carotid atherosclerosis

Steatosis degree	Alanine aminotransferase (U/L)*	Metabolic syndrome (%)°	Carotid plaques (%)°
No steatosis	19.5 ± 11.1	30.6	23.0
Mild	30.4 ± 20.6	48.1	32.2
Moderate	40.1 ± 26.1	60.2	34.4
Severe	49.3 ± 42.1	64.4	42.0

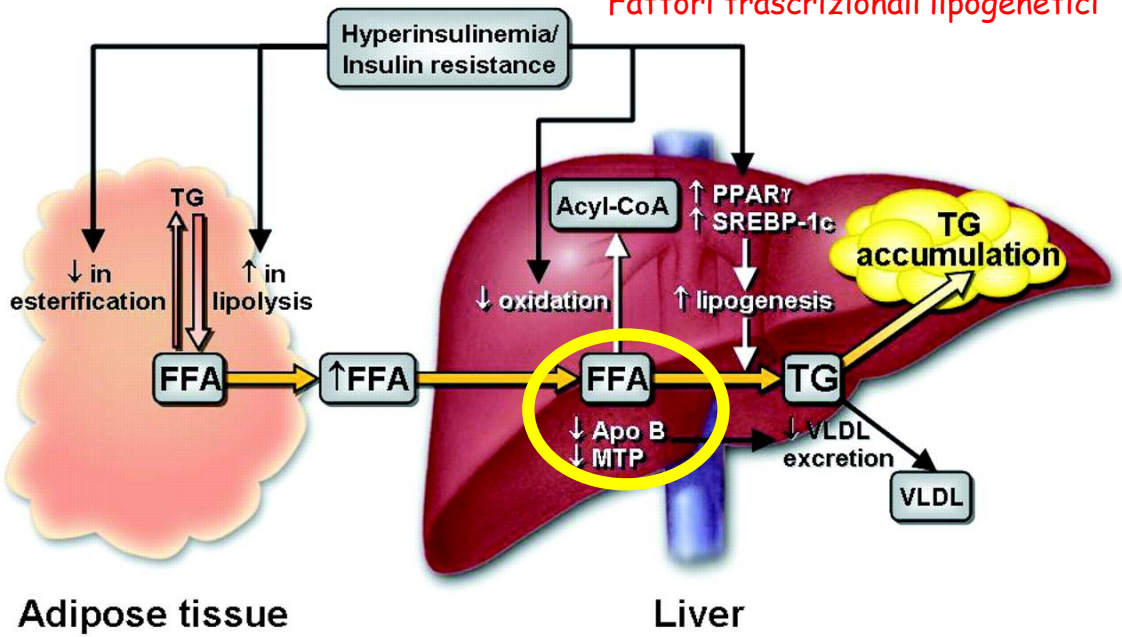


C Carallo, G Mancuso, GF Mauro, F Laghi, B Madafferi J Gastroenterol 2010

Sviluppo della steatosi (Nafl)

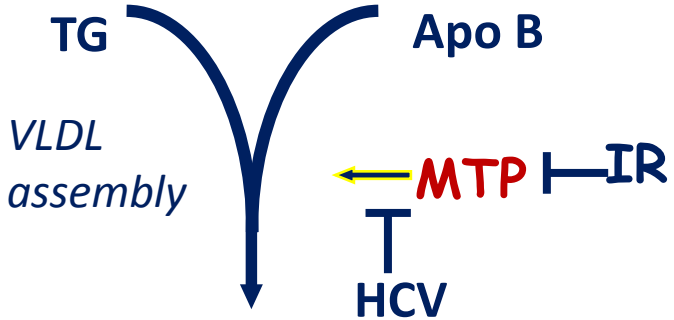
Non esiste un sistema che regola l'uptake degli FFA

Fattori trascrizionali lipogenetici



Sterol Regulatory Element-binding Protein-1c

MTP:Microsomal Triglyceride Transfer Protein



Alterata secrezione di VLDL

↓

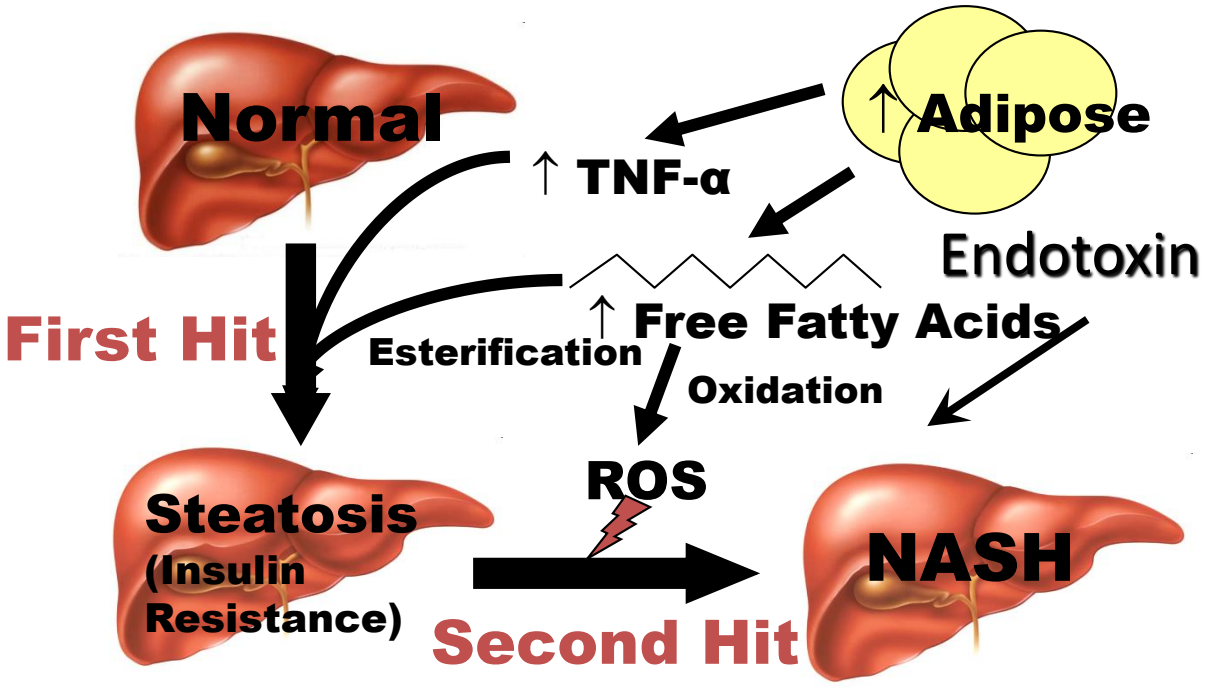
Accumulo intracitoplasmatico di TG

↓

STEATOSI

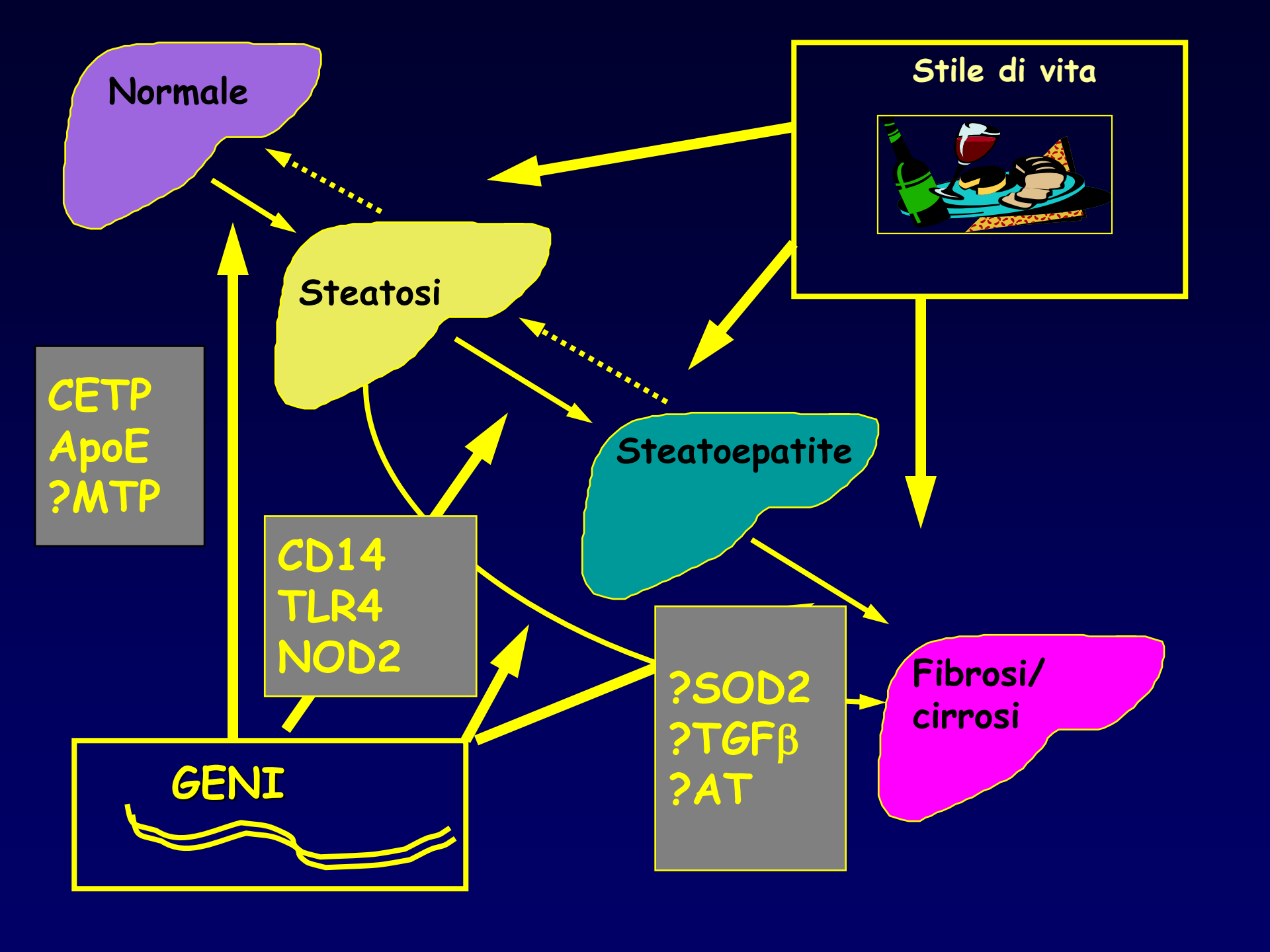
Adams, L. A. et al. CMAJ 2005;172:899-905

2-Hit Hypothesis



One of the burning questions in NAFLD remains which factors could be the driving forces toward a more progressive, inflammatory disease phenotype.

Day and colleagues presented more than a decade ago the so-called ‘‘two hit’’ model, suggesting that after a first hit (i.e., hepatic steatosis) another hit (e.g., gut-derived endotoxin) is needed to develop NASH

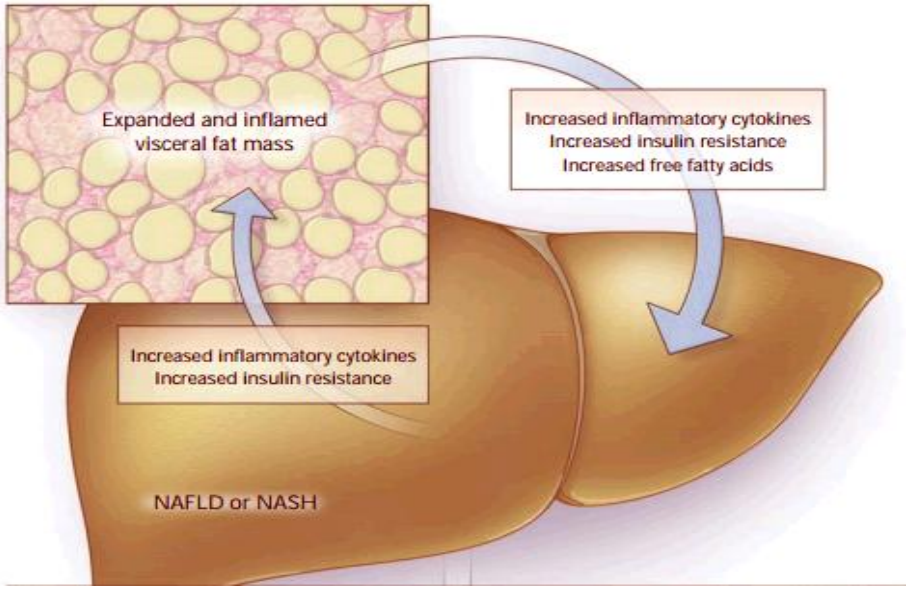

Normale
Stile di vita
Steatosi
CETP
ApoE
?MTP
Steatoepatite
CD14
TLR4
NOD2
?SOD2
?TGFβ
?AT
Fibrosi/
cirrosi
GENI

ADJUSTED ODDS RATIOS FOR SEVERE FIBROSIS (SEPTAL FIBROSIS OR CIRRHOSIS).*

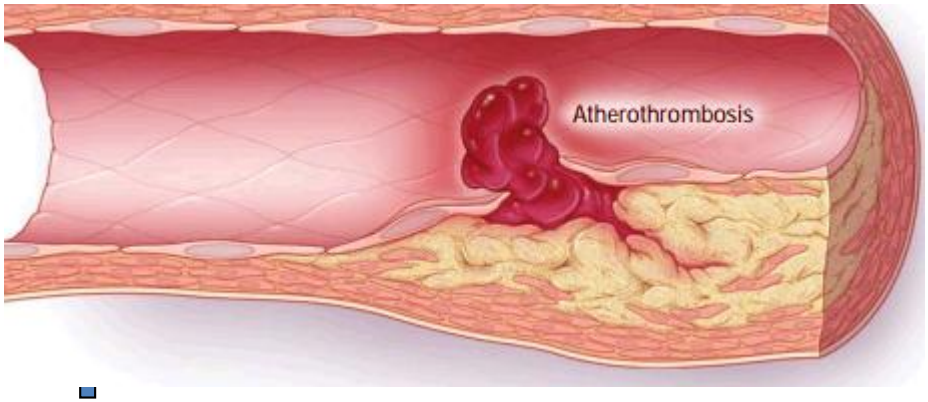
RISK FACTOR	ODDS RATIO (95% CI)
Age ≥45 yr	5.6 (1.5–21.7)
Obesity (body-mass index ≥30)	4.3 (1.4–13.8)
Aspartate aminotransferase:alanine aminotransferase ratio >1	4.3 (1.5–12)
Type 2 diabetes mellitus	3.5 (1.2–9.8)

*Adapted from Angulo et al.[14] with the permission of the publisher. CI denotes confidence interval.

Angulo, P. N Engl J Med 2002;346:1221-1231



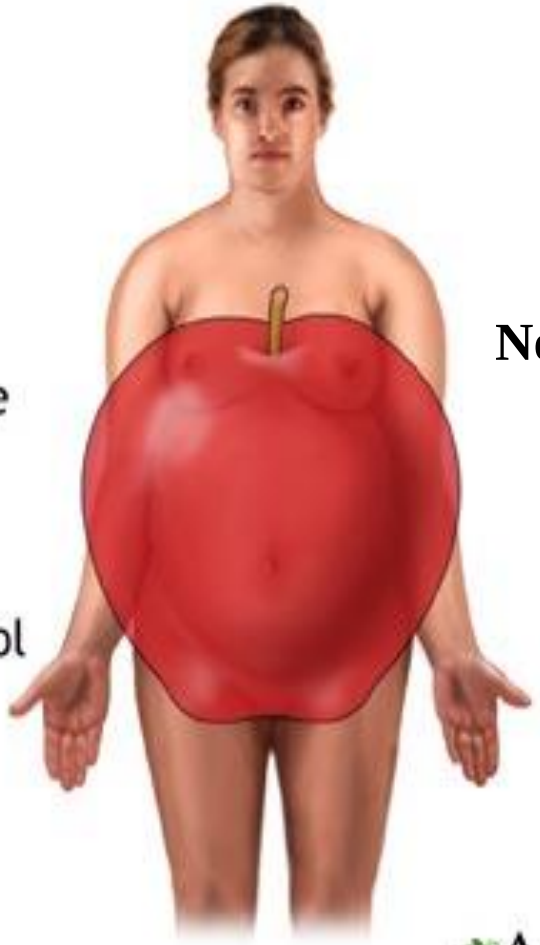
Chronic inflammation
(e.g., increases in PCR, interleukin-6, TNF
And other acute phase protein)
Hypercoafulation and hypofibrinolysis
(e.g., increases in fibrinogen, factor VII, plasminogen activator inhibitor 1,
And other coagualtion factors)
Atherogenic dyslipidemia
(e.g. increased TG, decreased HDL, increased small dense LDL, postprandial lipemia)
Dysglicemia and insulin resistance



METABOLIC SYNDROME

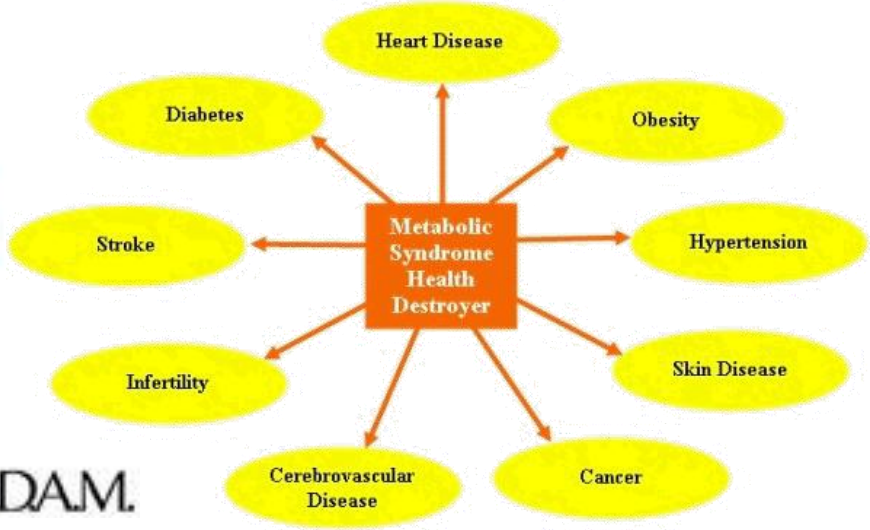
Metabolic syndrome
(Syndrome X)

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance



Common complications :

Cardiovascular diseases
Diabetes type II
Non-alcoholic fatty liver disease (NAFLD)
Non-alcoholic steatohepatitis (NASH)



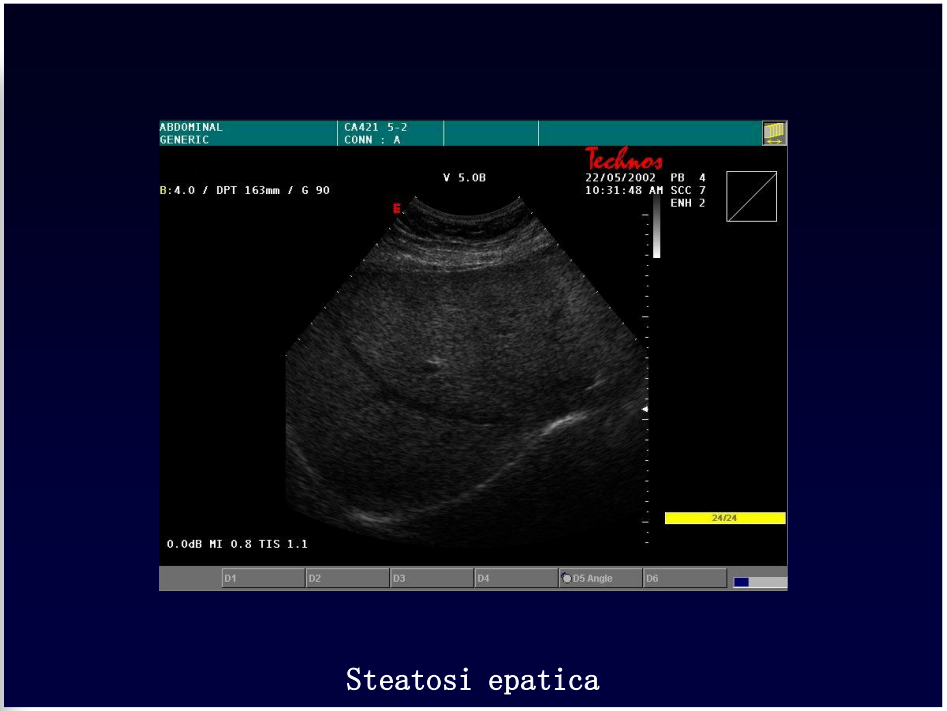
A.D.A.M.

Diagnosi di NAFLD

- **Steatosi Epatica**
  - **Ultrasonografia**
  - **RMN**
  - **RMN spectroscopy**
  - **Biopsia epatica**
- **Screening Negativi per altre eziologie**
  - **Marcatori Virali**
  - **Autoimmunità**
  - **Malattie genetiche (Ferro, a1-antitripsina, Rame)**
  - **Malattia celiaca**
- **Consumo alcolico trascurabile**
  - **< 20-40 g/die (< 210 g/sett.)**

VALUTAZIONE DELLA STEATOSI

- Le tecniche di immagine possono confermare la steatosi epatica ma non rilevano piccole quantità di grasso (steatosi)
- Non vi sono tecniche che confermano od escludono la diagnosi di steatoepatite

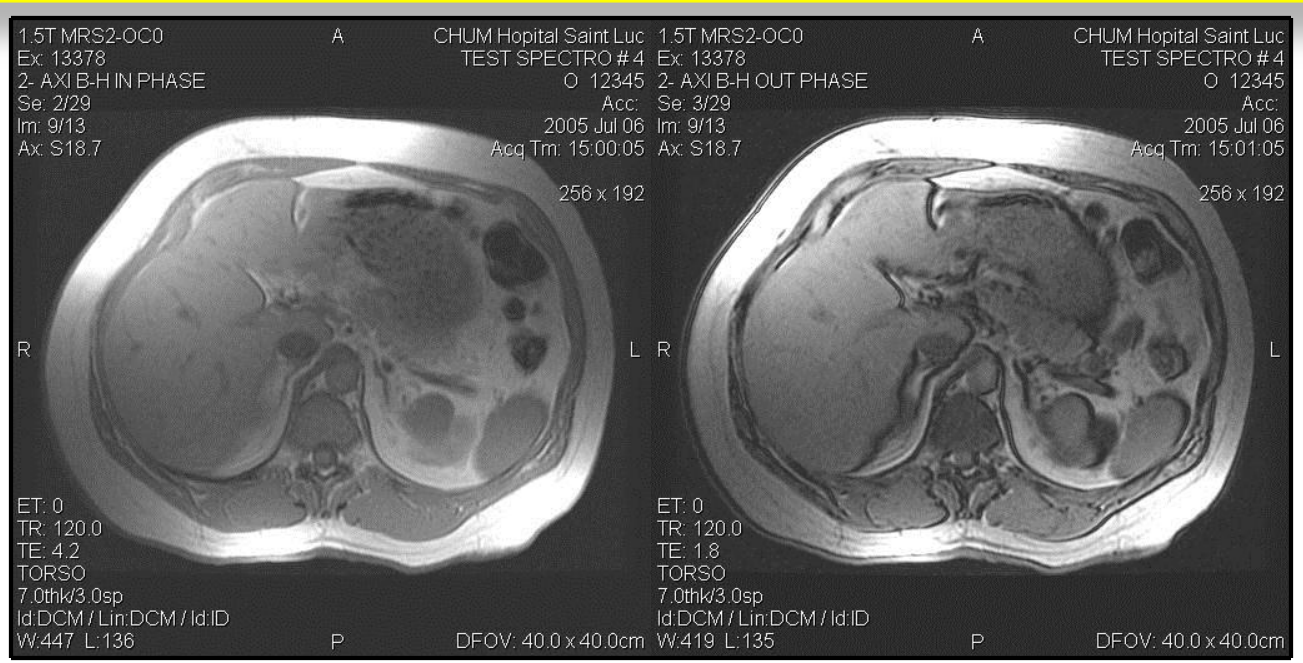


Steatosi epatica

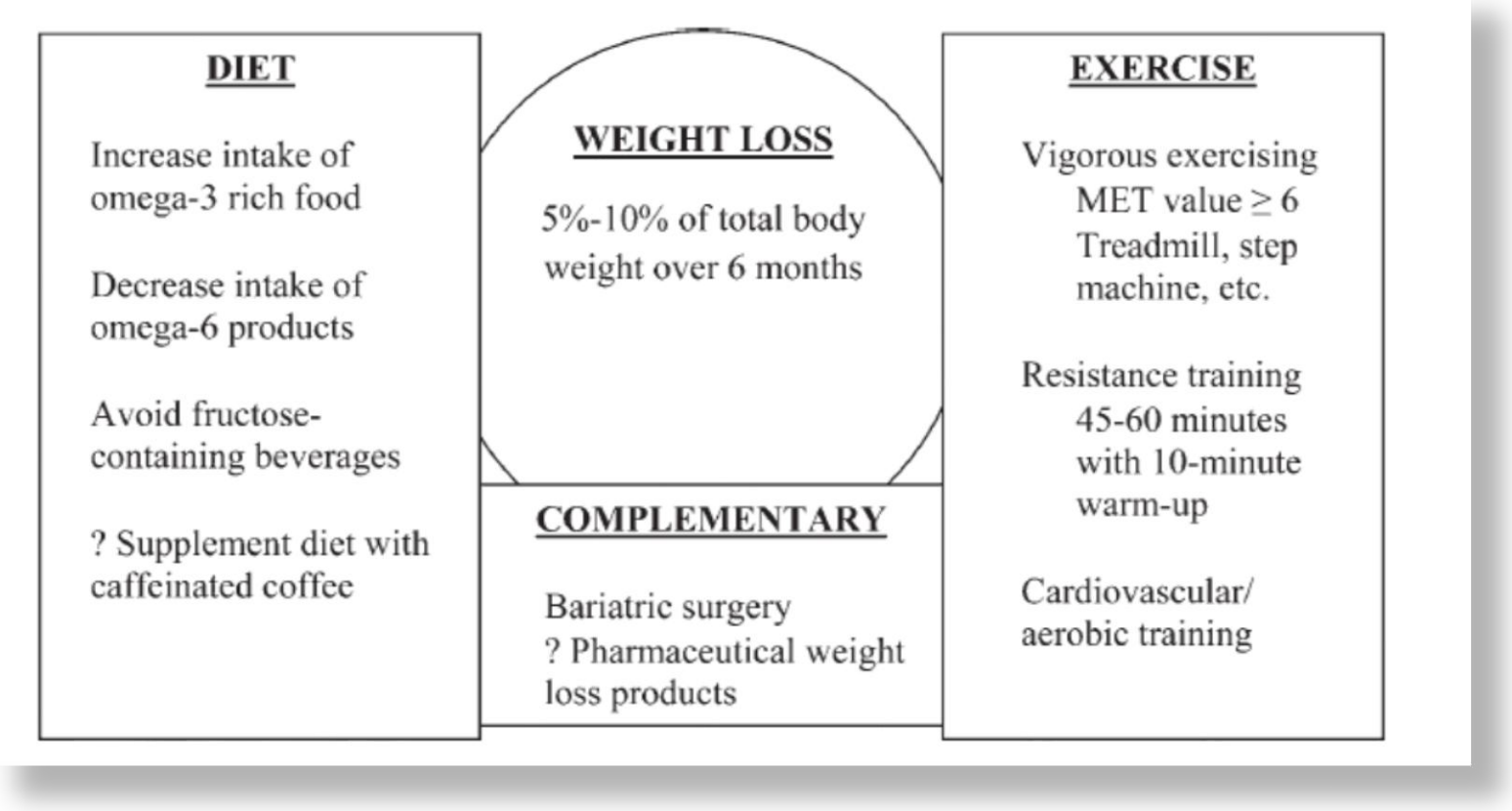
La Ecografia non evidenzia steatosi se < 33%

Diagnosi

- La MR spectroscopy misura accuratamente il contenuto epatico di trigliceridi
  - Ha vantaggi rispetto agli U/S, alla TAC ed alla MRI poichè da una misura quantitativa piuttosto che qualitativa



Integration of diet, exercise, and complementary medicine for the treatment of nonalcoholic fatty liver disease



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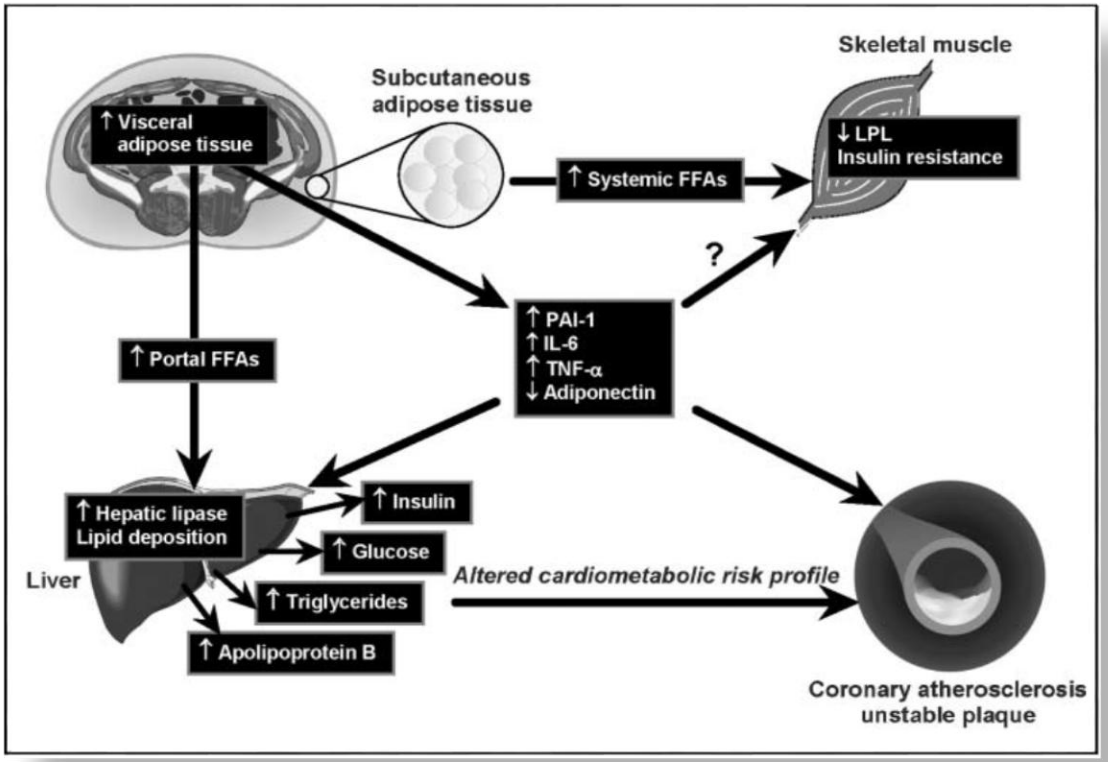
Conclusioni

- La NAFLD è associata ad una maggiore morbilità CV
- La NAFLD è strettamente associata con i marcatori di aterosclerosi come ad esempio un maggiore valore di spessore medio intimale
- La NAFLD può rappresentare un marcatore di danno cardiovascolare

GRAZIE PER L’ATTENZIONE

Obesità viscerale, Nafld e Sindrome Metabolica



- **La NAFLD rappresenta la manifestazione epatica della SM e frequentemente coesiste con Obesità, Diabete, dislipidemia, ipertensione e MCV**

Annals of Medicine. 2006; 38: 52–63