Bambino Gesù
OSPEDALE PEDIATRICO

SAPIENZA
UNIVERSITÀ DI ROMA

La Sindrome Metabolica

Prof. Valerio Nobili

Disclosure of speaker's interests	
(Potential) conflict of interest	None
Potentially relvant company relationships in connection with event [1]	Alexion, Entercept, Squibb, Novartis, Gilead, Nestle'
• Sponsorship or research funding[2] • Fee or other (financial) payment[3] • Shareholder[4] • Other relationship, i.e. …[5]	• • • •

Original Paper

Annals of Nutrition & Metabolism

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Published online: May 24, 2014

Metabolic Syndrome in Overweight and Obese Adolescents: A Comparison of Two Different Diagnostic Criteria

Denise Tavares Giannini[a] Maria Cristina Caetano Kuschnir[a] Moyses Szklo[b]

[a]Pedro Ernesto University Hospital, Rio de Janeiro State University, Rio de Janeiro, Brazil; [b]Department of Epidemiology, Johns Hopkins University, Baltimore, Md., USA

Table 1. Definition of MS according to the NCEP-ATPIII and IDF criteria

MS components	NCEP-ATPIII	IDF	
		10 < 16 years	≥16 years
Obesity	WC >75th percentile for age and sex	WC ≥90th percentile	Boy WC ≥90 cm Girl WC ≥80 cm
Fasting glucose	≥110 mg/dl	≥100 mg/dl	≥100 mg/dl
TG	≥100 mg/dl	≥150 mg/dl	≥150 mg/dl
HDL	500 mg/dl, except boys from 15 to 18 years, whose cutoff point was <45 mg/dl	<40 mg/dl	Boy <40 mg/dl Girl <50 mg/dl
Blood pressure	SBP >90th percentile for age and sex	SBP ≥130 or DBP ≥85	SBP ≥130 or DBP ≥85

SBP = Systolic blood pressure; DBP = diastolic blood pressure.

GUT ONLINE

Gut 2008;**57**:1283–1287.

Hepatology

Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis

M Manco,[1] G Bedogni,[2] M Marcellini,[1] R Devito,[3] P Ciampalini,[4] M R Sartorelli,[1] D Comparcola,[1] F Piemonte,[5] V Nobili[1]

Table 2 Frequency of the metabolic syndrome and its components in the 197 children with non-alcoholic fatty liver disease (NAFLD)

	n (%)
Large waist	166 (84.26)
Low HDL-cholesterol	99 (50.25)
Hyper-triglyceridaemia	25 (12.69)
Hypertension	26 (13.20)
Impaired fasting glucose or diabetes	10 (5.08)
⩾ 3 of the above (metabolic syndrome)	20 (10.15)

HDL, high-density lipoprotein.

International Diabetes Federation (IDF) Criteria for the Classification of Metabolic Syndrome in Children

	Age		
	6 - 10 years	10 – 16 years	> 16 years
Definition of adiposity	WC > 90th percentile	WC > 90th percentile	WC > 90th percentile
Blood glucose	No set value	FBG >100 mg/dL	FBG > 100 mg/dL
Dyslipidemia	No set value	TG > 150 mg/dL HDL < 40 mg/dL	TG > 150 mg/dL HDL < 40 mg/dL
Blood Pressure	No set value	Systolic >130 mm Hg Diastolic >85 mm Hg	Systolic >130 mm Hg Diastolic >85 mm Hg

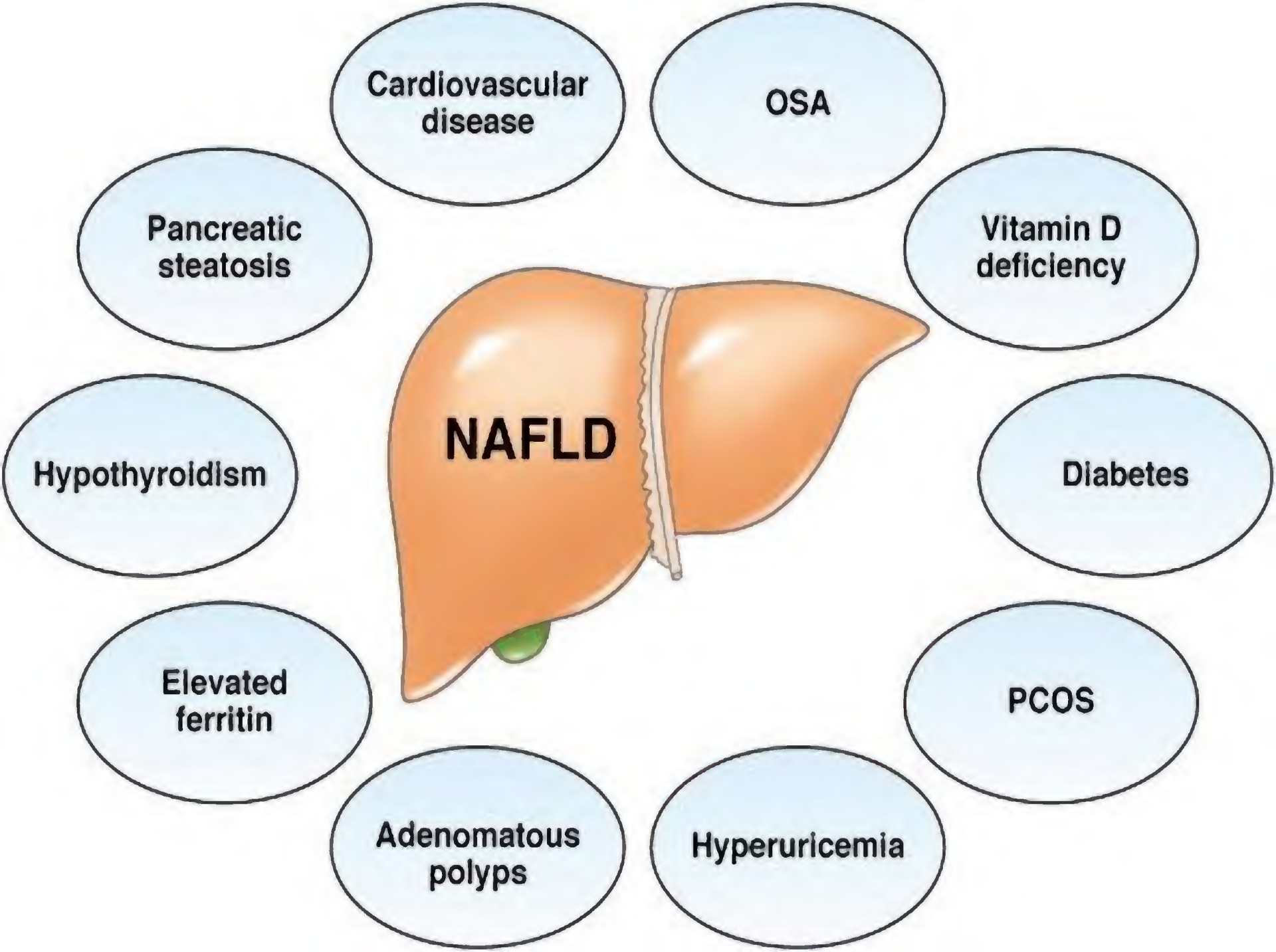
TABLE 2 INTERNATIONAL DIABETES FEDERATION CONSENSUS DEFINITION OF PEDIATRIC METABOLIC SYNDROME

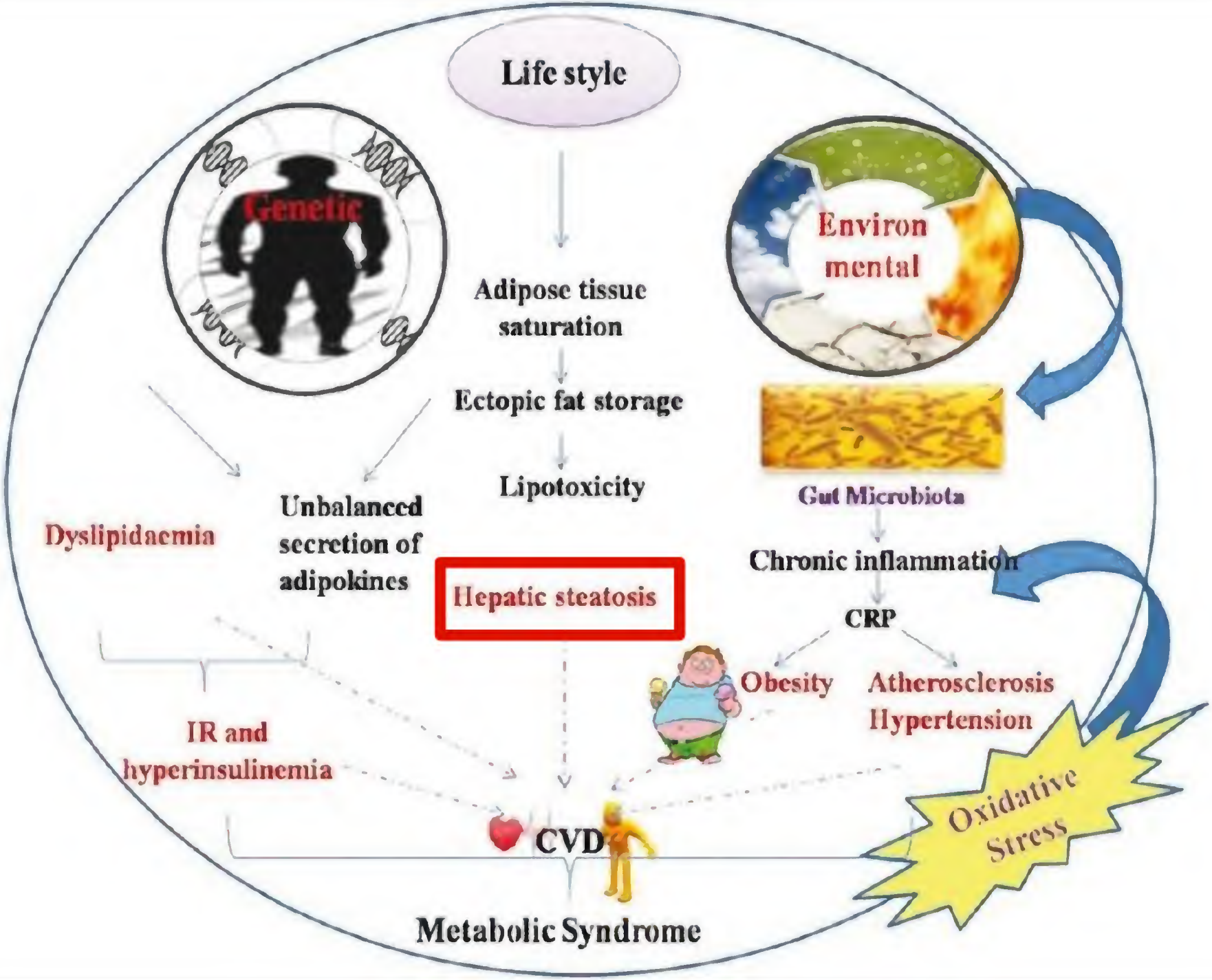
AGE GROUP (YEARS)	OBESITY[A] (WC)	TRIGLYCERIDES	HDL-C	BLOOD PRESSURE	GLUCOSE (MMOL/L) OR KNOWN T2DM
6-<10	≥90th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension, and/or obesity.			
10-<16 metabolic syndrome	≥90th percentile or adult cutoff if lower	≥1.7 mmol/L (≥150 mg/dL)	<1.03 mmol/L (<40 mg/dL)	Systolic ≥130/ diastolic ≥85 mm Hg	≥5.6 mmol/L (100 mg/dL) (If ≥5.6 mmol/L [or known T2DM] recommend an OGTT)
16+ metabolic syndrome	Use existing IDF criteria for adults, ie: Central obesity (defined as WC ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnicity specific values for other groups[a]) plus any 2 of the following 4 factors: ○ Raised triglycerides: ≥1.7 mmol/L ○ Reduced HDL-C: <1.03 mmol/L (<40 mg/dL) in males and <1.29 mmol/L (<50 mg/dL) in females, or specific treatment for these lipid abnormalities ○ Raised BP: systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension ○ Impaired fasting glycemia (IFG): fasting plasma glucose (FPG) ≥5.6 mmol/L (≥100 mg/dL), or previously diagnosed T2DM				

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WC, waist circumference.

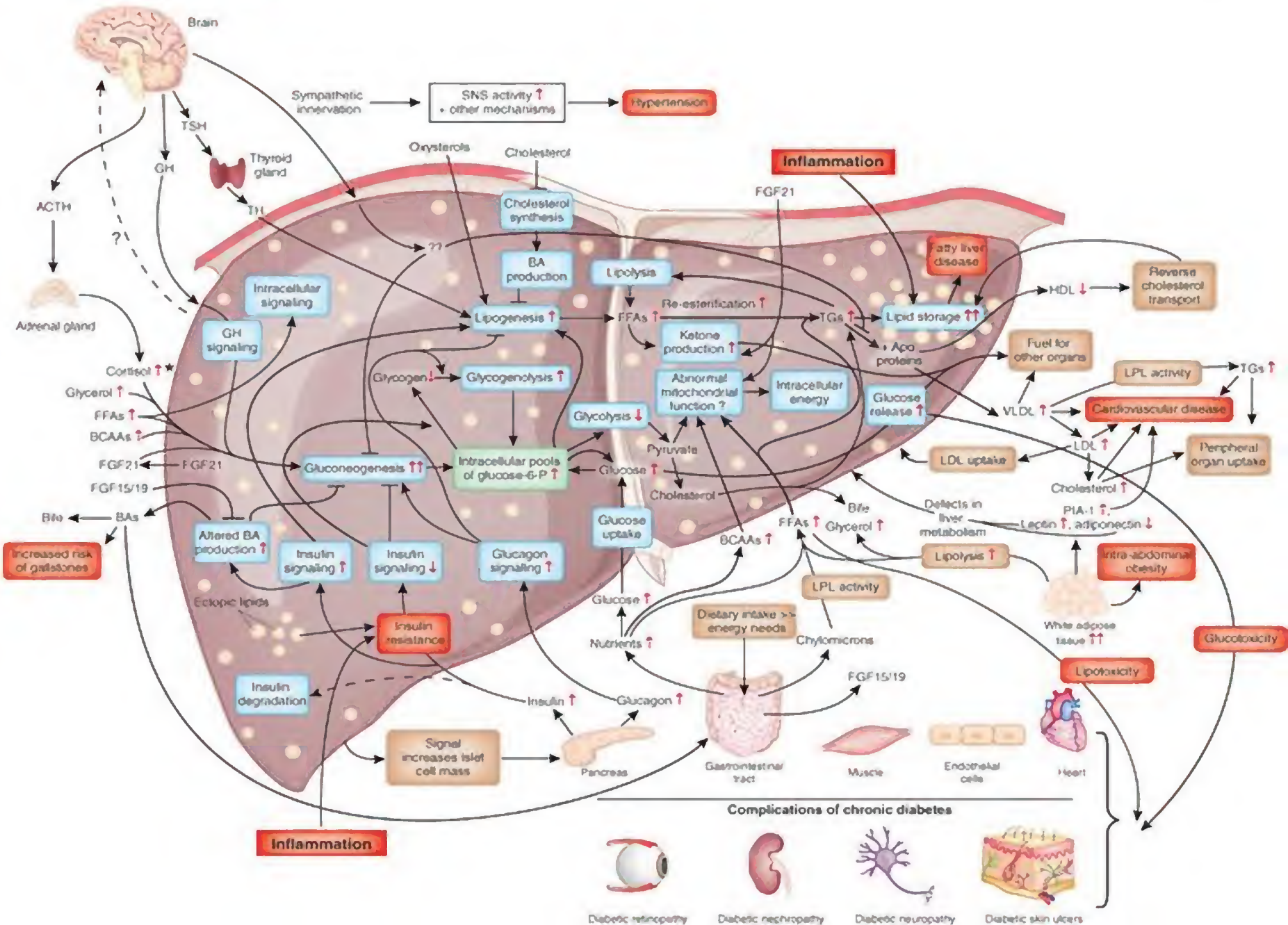
[a]The IDF Consensus group recognizes that there are ethnic, gender, and age differences, but research is still needed on outcomes to establish risk.

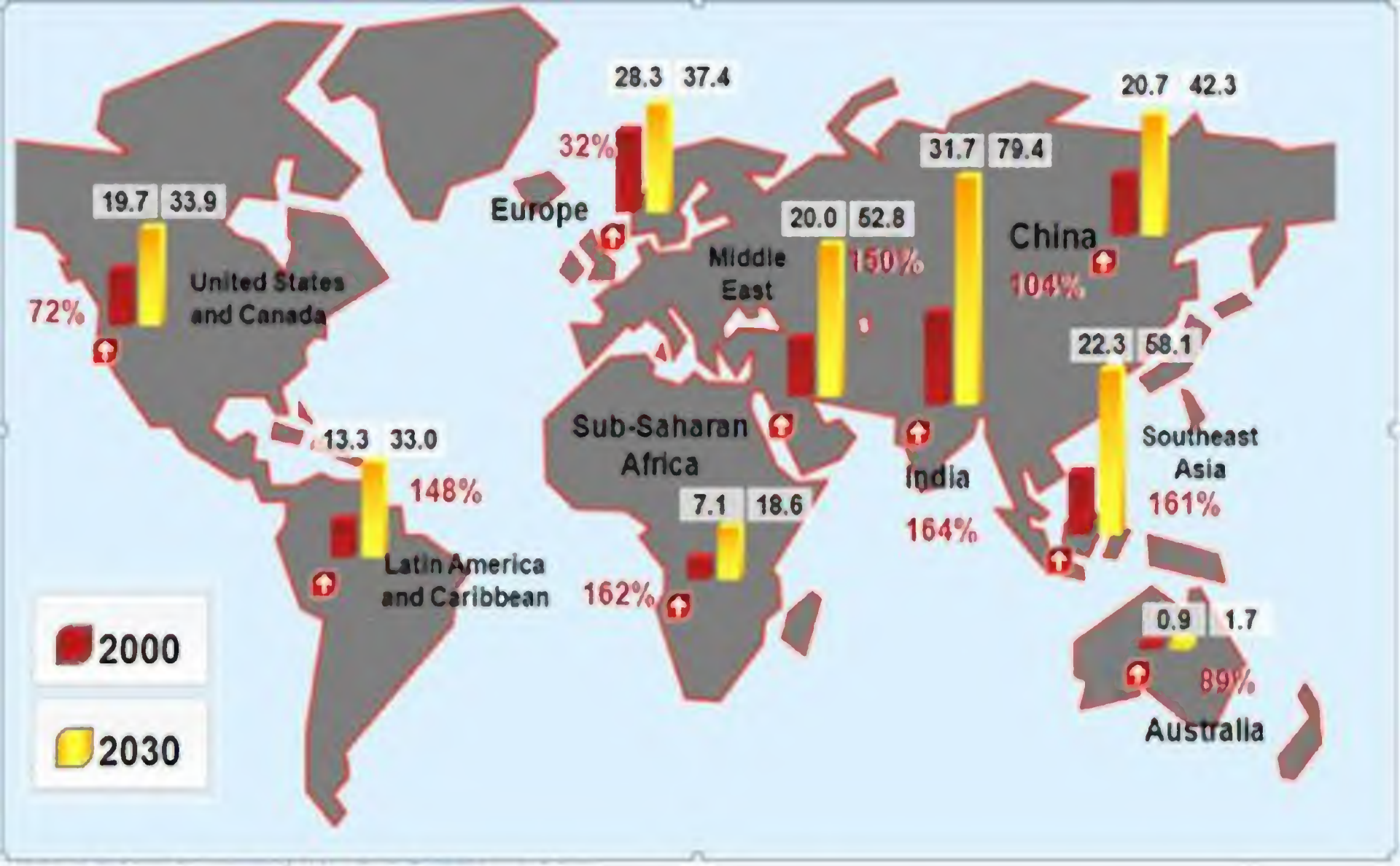
From: Alberti G, Zimmet P. The IDF consensus definition of the metabolic syndrome in children and adolescents. Brussels, Belgium: International Diabetes Federation; 2007.


NAFLD
Cardiovascular disease
OSA
Pancreatic steatosis
Vitamin D deficiency
Hypothyroidism
Diabetes
Elevated ferritin
PCOS
Adenomatous polyps
Hyperuricemia


Life style
Genetic
Environ
mental
Adipose tissue
saturation
Ectopic fat storage
Lipotoxicity
Gut Microbiota
Dyslipidaemia
Unbalanced
secretion of
adipokines
Hepatic steatosis
Chronic inflammation
CRP
Obesity
Atherosclerosis
Hypertension
IR and
hyperinsulinemia
Oxidative
Stress
CVD
Metabolic Syndrome

nature medicine





WORLDWIDE PREVALENCE OF DIABETES, WHICH IS LIKELY TO MIRROR FATTY LIVER DISEASE (MILLIONS), ADAPTED FROM HOSSAIN P ET.AL, NEW ENGLAND J. MEDICINE 2007, 356, 213-5.

The Results of the Mismatch Between Genes and the Environment

Obesity
Metabolic Syndrome
Celiac
Intestinal Permeability
Type 2 Diabetes

Cardiovascular Disease
Hypertension
Some Cancers

Caries

Malocclusion

Sleep Apnea

Asthma
Autism
Asperger's
Alzheimers
ADD/ADHD
Depression
Chronic Back Pain
Osteoporosis

Chronic Non-Communicable Diseases of Civilization
Western Lifestyle Diseases

METABOLIC SYNDROME IN PAEDIATRIC POPULATION: IS IT TIME TO THINK BACK ON DIAGNOSIS CRITERIA?

Claudia Della Corte, Anna Alisi, *Valerio Nobili

Hepatometabolic Department, "Bambino Gesù" Children's Hospital, Rome, Italy

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Citation: EMJ Hepatol. 2015;3[1]: - .

OUTLOOK · 22 NOVEMBER 2017

Fatty liver disease

Herb Brody

PDF version

Credit: Neil Webb

A healthy adult liver is a thing of beauty – a 1.5-kilogram, reddish-brown biochemical processing plant of extraordinary versatility and efficiency. From inside the abdomen, it performs an array of tasks: manufacturing proteins, metabolizing drugs, detoxifying the blood and secreting the bile that is needed for digestion. And especially high on the liver's to-do list is regulating the amounts of sugar, protein and fat that enter the bloodstream.

Unfortunately, the increasing prevalence of obesity in the past few decades has led to a surge in non-alcoholic fatty liver disease (NAFLD), in which liver cells become

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Diagnostics: Missing the point

Disease progression: Divergent paths

When a condition commonly associated with a lifetime of alcohol abuse — severe scarring of the liver, or cirrhosis — starts to show up in children as young as eight, something is very wrong.

"I had a teenage patient, who wasn't even being evaluated for liver disease but was getting surgery for weight loss, and was incidentally found to have cirrhosis," says Jennifer Woo Baidal, a paediatric gastroenterologist at Columbia University Medical Center in New York.

or obese — with non-alcoholic fatty liver disease (NAFLD), as well as its more serious

It is also more common in those of Hispanic ethnicity and in boys.

persuade all the operators about the danger-ousness of this condition, and about the need

Mann says that, to his knowledge, there has not yet been a case of NAFLD in a child or adolescent that has progressed so far as to require a liver transplant. "The feeling is that, even at its worst, it would progress over twenty years, probably," he says. "The way I think about it is: *we're doing our job to help ease the burden on the adult hepatologists."*

livers tend to have more fat and inflammation

liver transplant. "The feeling is that, even at its

Australia.

But paediatric gastroenterologist Valerio Nobili, at the Bambino Gesù Paediatric Hospital in Rome, proposes that all overweight or obese children should be screened for NAFLD to identify the condition while there is still time to address it.

“Strategic in this fight against NAFLD is to persuade all the operators about the dangerousness of this condition, and about the need to act as soon as possible before the disease becomes irreversible,” Nobili says

Nobili says that vitamin E, omega-3 fatty acids and the diabetes drug metformin have all showed some minimal effects in clinical trials, but the results so far are “unsatisfactory”. Yet thanks to the renewed focus on NAFLD in children, he remains optimistic. “The attention on the paediatric NAFLD problem is today so high,” he says, “that I remain confident about important progress during the next years”

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor* N ENGL J MED 377;21 NEJM.ORG NOVEMBER 23, 2017

Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis

Anna M. Diehl, M.D., and Christopher Day, M.D.

FATTY LIVER DISEASE IS THE MOST COMMON LIVER DISEASE IN THE WORLD. About 25% of adults in the United States have fatty livers in the absence of excessive alcohol consumption, a condition termed nonalcoholic fatty liver disease. More than a quarter of adults with nonalcoholic fatty liver disease are presumed to have nonalcoholic steatohepatitis on the basis of elevated serum aminotransferase levels and an absence of other identifiable causes of liver injury.[1] A definitive diagnosis of nonalcoholic steatohepatitis is currently based on histologic evidence not only of fat accumulation (steatosis) in hepatocytes but also of liver-cell injury and death and accumulation of inflammatory cells (Fig. 1A and 1B). Because livers with nonalcoholic steatohepatitis are more damaged than livers

From the Department of Medicine, Duke University, Durham, NC (A.M.D); and Newcastle University Medical School, Newcastle upon Tyne, United Kingdom (C.D.). Address reprint requests to Dr. Diehl at the Snyderman Bldg., Suite 1073, Duke University, Durham, NC 27710, or at annamae.diehl@duke.edu.

N Engl J Med 2017;377:2063-72.
DOI: 10.1056/NEJMra1503519
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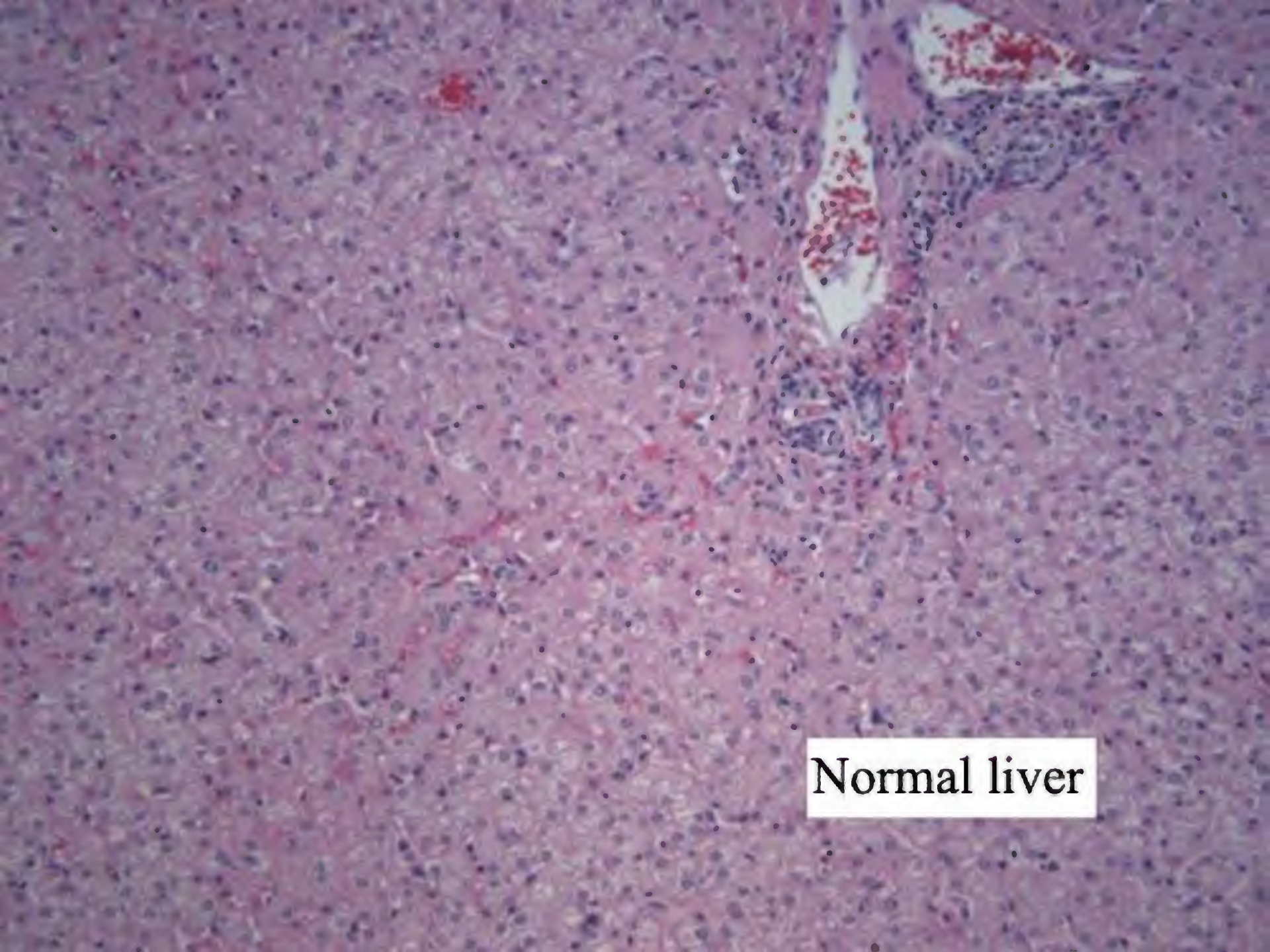
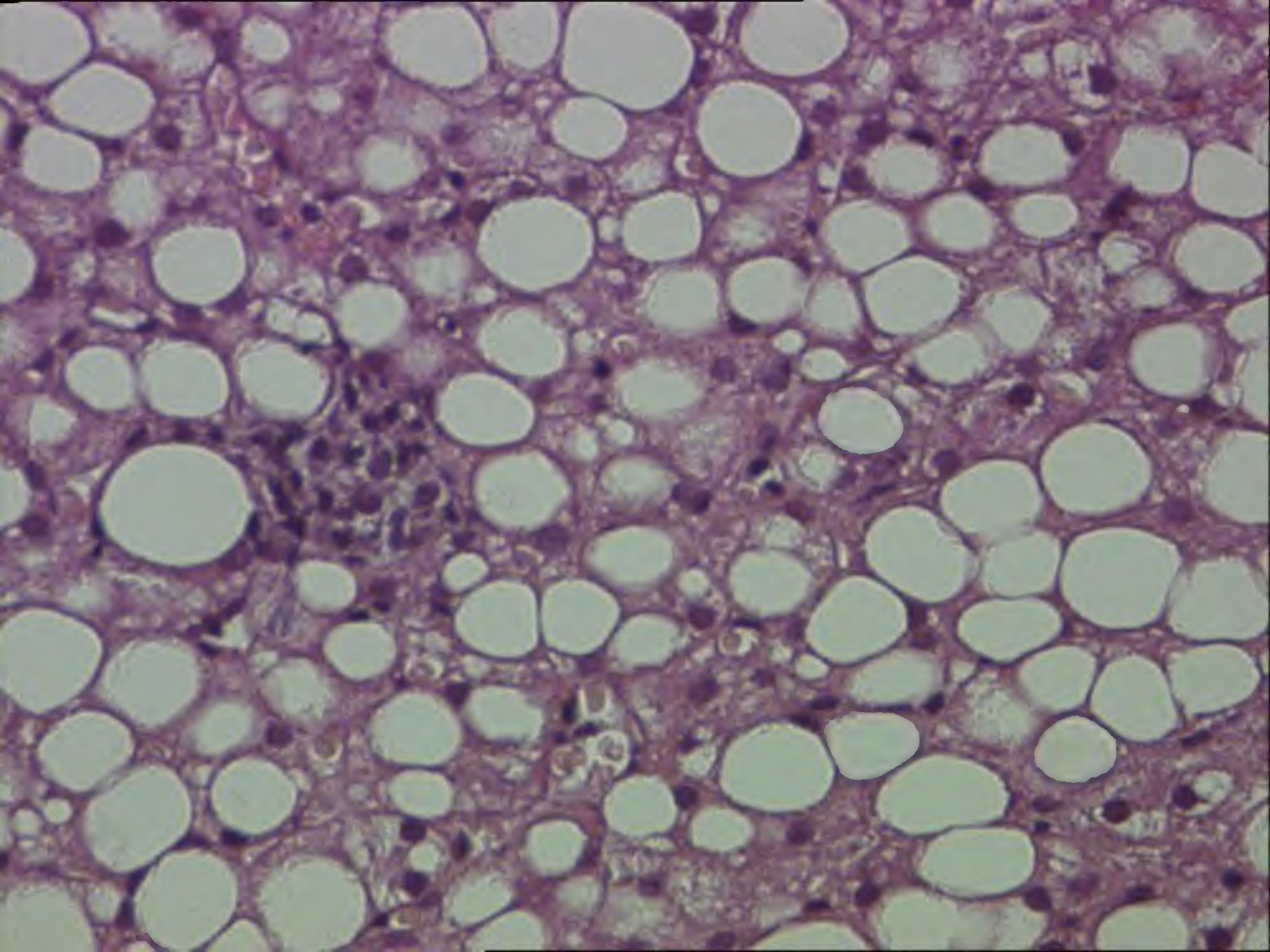
The prevalence of nonalcoholic steatohepatitis in the United States approaches that of type 2 diabetes, and annual medical costs directly attributable to nonalcoholic fatty liver disease already exceed $100 billion, much of which is attributable to nonalcoholic steatohepatitis, underscoring the importance of developing interventions to prevent and treat this disease. A number of


Normal liver

"What we're finding in these patients is that there's so much fat in their liver cells, the fat actually pushes the nucleus aside"

Ludwig 1980



"13% percent of normal weight children, and 30% of obese children now have non-alcoholic fatty liver disease. This is a disease that wasn't even described until 1980. It is the biggest epidemic in the history of the world."

ROBERT H. LUSTIG, MD
PEDIATRIC ENDOCRINOLOGIST

Nonalcoholic fatty liver disease (NAFLD) is a common disorder characterized by the accumulation of macrovesicular fat in hepatocytes. The condition of

HEPATOLOGY 2006

LIVER DISEASE

NAFLD in Children: A Prospective Clinical-Pathological Study and Effect of Lifestyle Advice

Valerio Nobili,[1] Matilde Marcellini,[1] Rita Devito,[2] Paolo Ciampalini,[3] Fiorella Piemonte,[4] Donatella Comparcola,[1] Maria Rita Sartorelli,[1] and Paul Angulo[5]

disease."[2] Within a few years, the first cases of pediatric NASH were reported.[3] NASH is currently defined as fatty liver disease in which there is also inflammation and varying degrees of hepatic fibrosis. In recent years, much

NAFLD

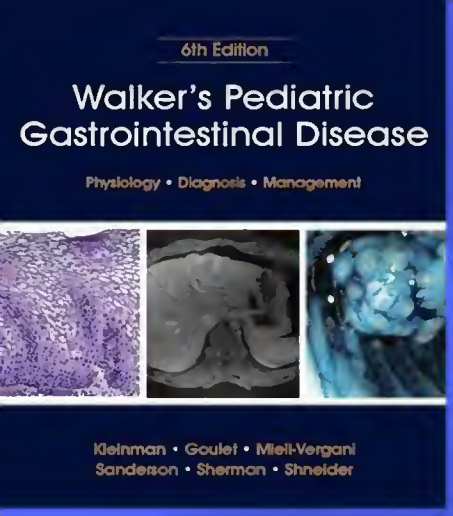
Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis.

NAFL

Presence of hepatic steatosis with no evidence of hepaocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is nominal.

NASH

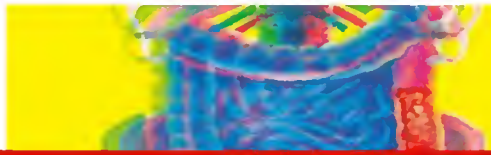
Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.
This can progress to cirrhosis, liver failure and, rarely, liver cancer.



Walker's Pediatric Gastrointestinal Disease, 6th ed., Vol. 2. Edited by R. Kleinman, O. Goulet, G. Mieli-Vergani, et al. (Shelton, CT: People's Medical Publishing House—USA, **March 2018**

Giorgio V, Alisi A, Villani A, Nobili V.

"Fatty Liver Disease in Children"



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Reference: 1. Molodecky NA, et al. Gastroenterology. 2012;142(1):46-54.
Date of preparation: March 2016 Item code: GLO/EYV/2016-00047

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Reuters Health Information

One in Four People Worldwide Have Nonalcoholic Fatty Liver Disease

By Laura Newman

March 09, 2016

REUTERS HEALTH INFORMATION

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Pathology of Nonalcoholic Steatohepatitis

Liver Disease and Pregnancy

Fatty Liver

NEW YORK (Reuters Health) - As the global obesity epidemic continues to fuel development of metabolic disorders, the clinical and economic burden of nonalcoholic fatty liver disease (NAFLD) and its more severe form, nonalcoholic steatohepatitis (NASH), will become "enormous," researchers warn in a new paper.

"People with NASH are going on to have cirrhosis and liver-related cancers, creating an immense clinical and economic burden," Dr. Zobair M. Younossi, of Inova Health System in Falls Church, Virginia, told Reuters Health in a telephone interview. This burden is expected to grow astronomically.

In a meta-analysis, published online February 22 in Hepatology, Dr. Younossi and colleagues reviewed several databases worldwide for papers published between 1989 and 2015 that addressed the epidemiology and progression of NAFLD and NASH.

They excluded papers that exclusively recruited the morbidly obese, children, or people with diabetes. All studies that did not report results on screening for alcohol consumption were also excluded, as were papers with patients with hepatitis B and hepatitis C virus. Histological diagnosis through liver biopsy was used to establish NASH.

The initial search pulled 729 papers, and 86 were included in the analysis. Altogether more than 8.5

Alternative NAFLD and NASH Screening Methods

Estimated Global Prevalence of NAFLD

World population: **7.5 billion**

People with NAFLD: **1.8 billion**

Prevalence rate: **~25%**

Stages and Occurrence of NAFLD Progression

25% of the global population has NAFLD

59% progresses to → NASH

41% develops into → Fibrosis

40% becomes → Cirrhosis

Increases risk of:
- Liver transplant
- Cardiovascular disease
- Mortality

Are Biomarkers a Suitable Screening Alternative?

Gold Standard
Liver Biopsy

- High direct and indirect costs per surgery
- Invasive
- Risky and painful

Biomarkers

- Noninvasive
- No special equipment
- Cost effective
- Rapid turn around time

Imaging

- Noninvasive
- Excessive body fat presents limitation
- Not optimized

Emerging Biomarkers

- Adiponectin
- TNF-α
- Leptin
- C-Reactive Protein
- IL-6
- IL-17
- Oxidized-LDL

For references, see www.alpco.com/alternative-nafld-and-nash-screening-methods

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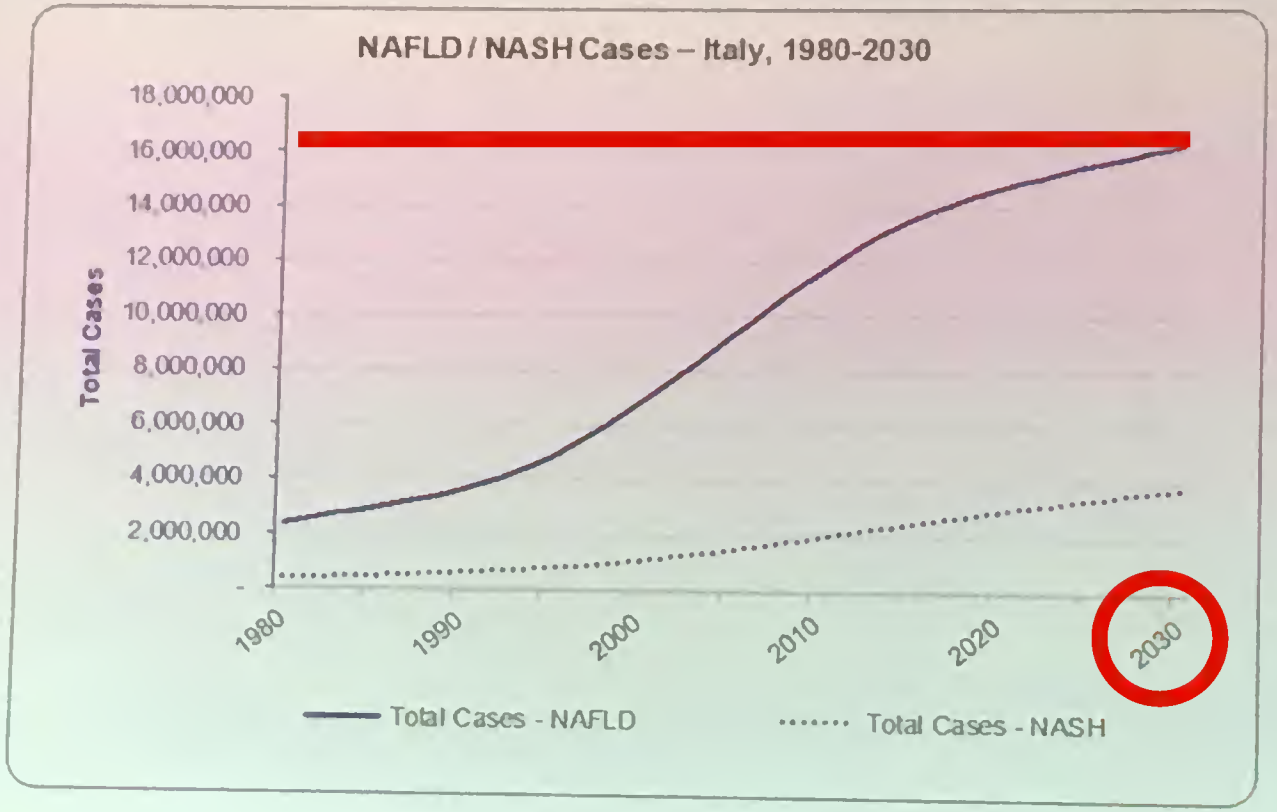
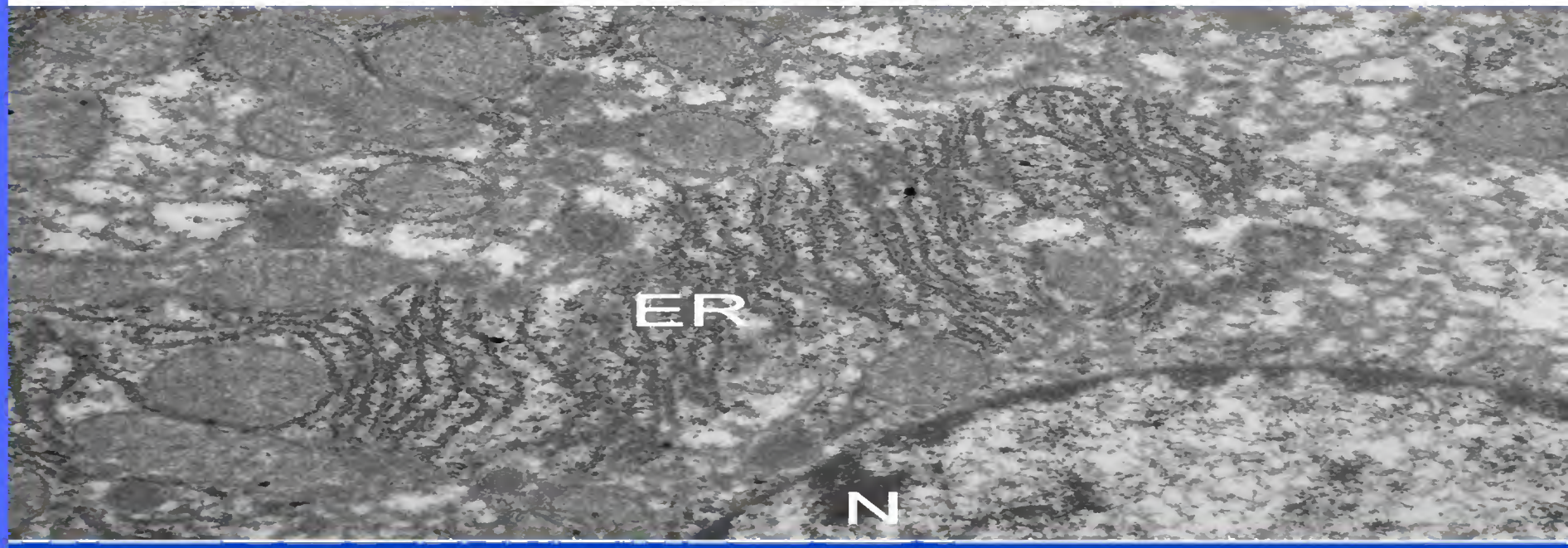
Relative Incidence of NAFLD (Italy)

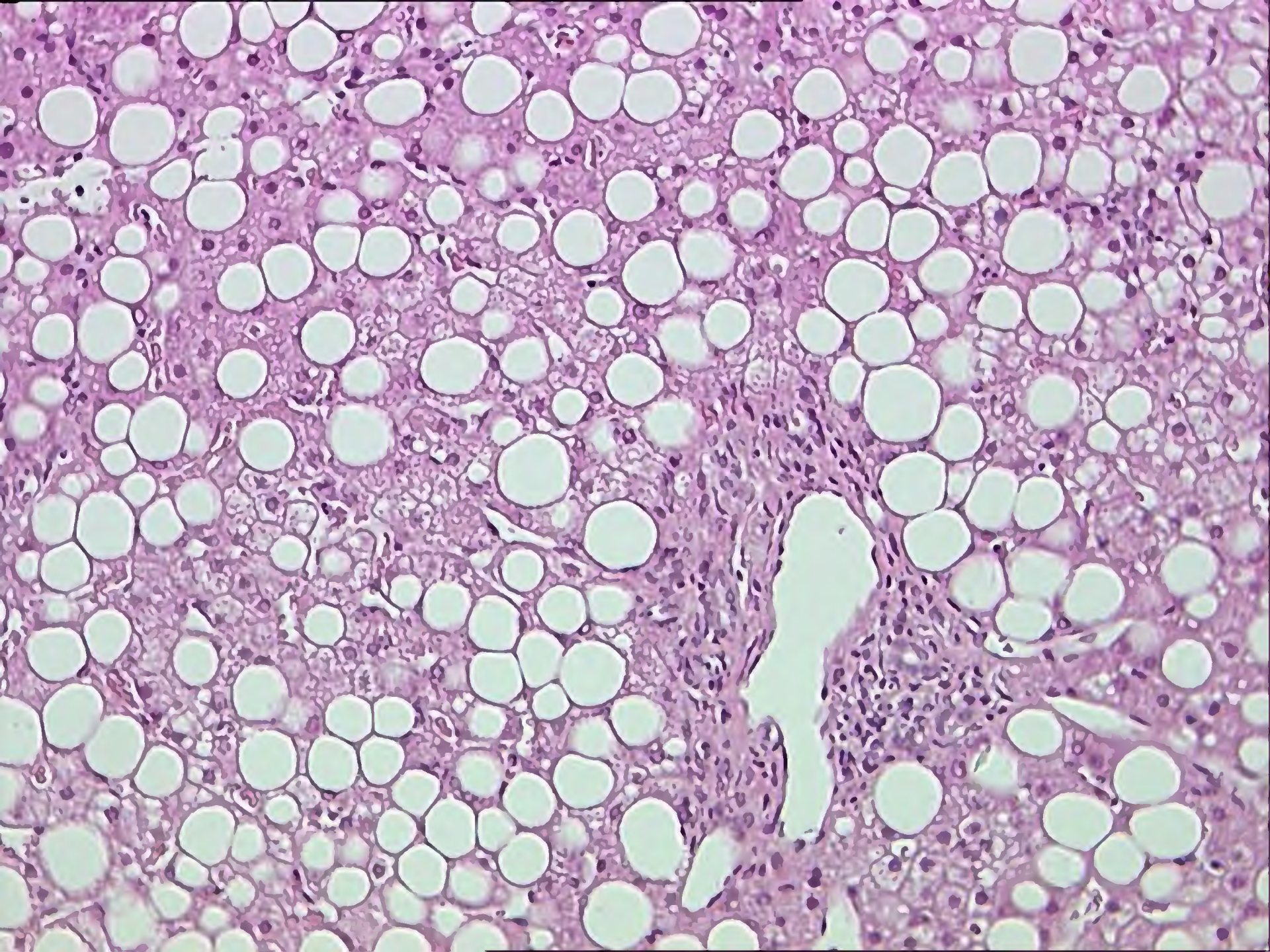


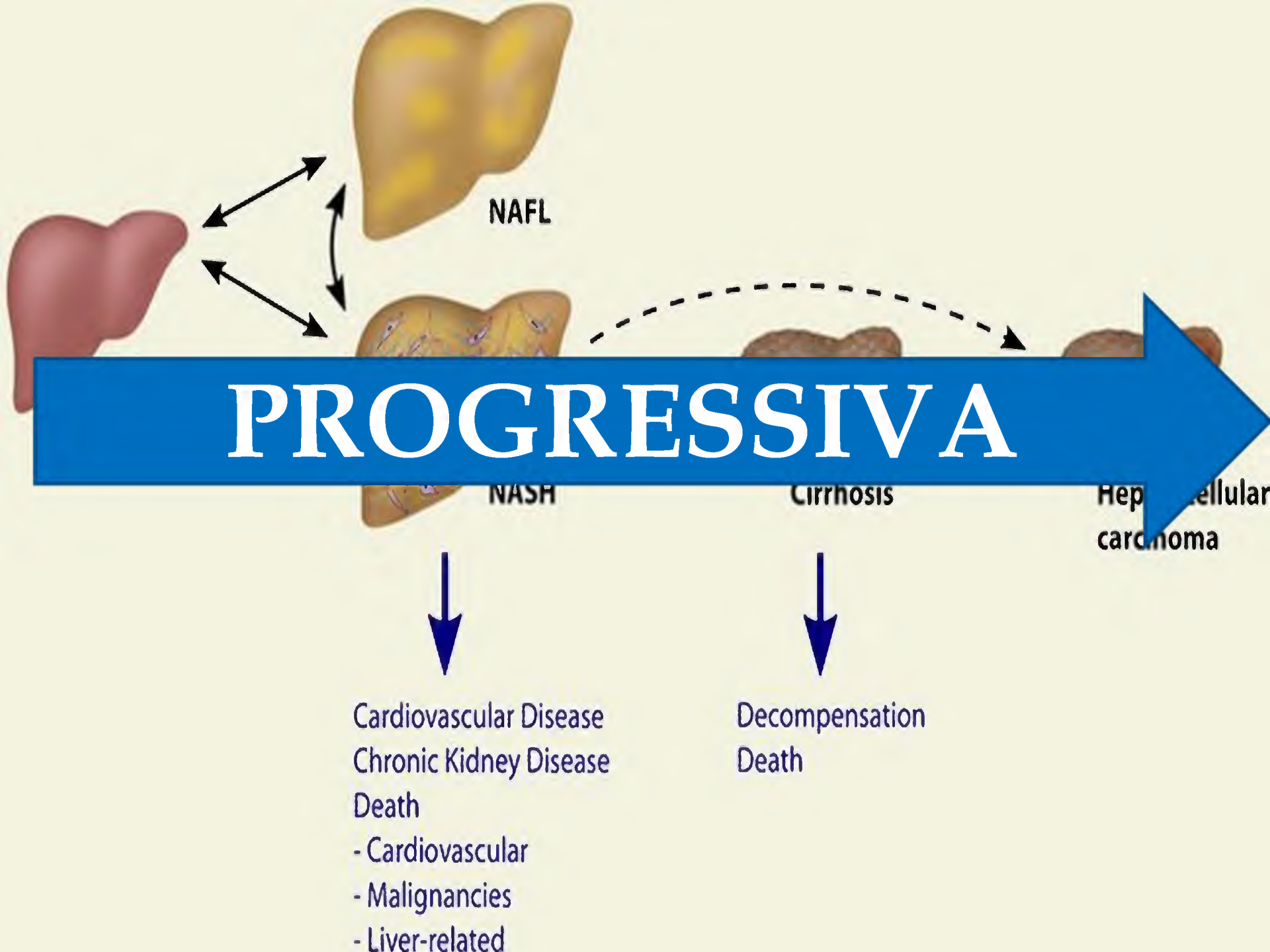
- An estimated 13.6 million NAFLD cases in 2015 will increase to 16.2 million by 2030 .
- An estimated 2.5 million NASH cases in 2015 will increase to 3.8 million by 2030.

Stima del numero di bambini di 6-11 anni sovrappeso e obesi

Normal liver cell

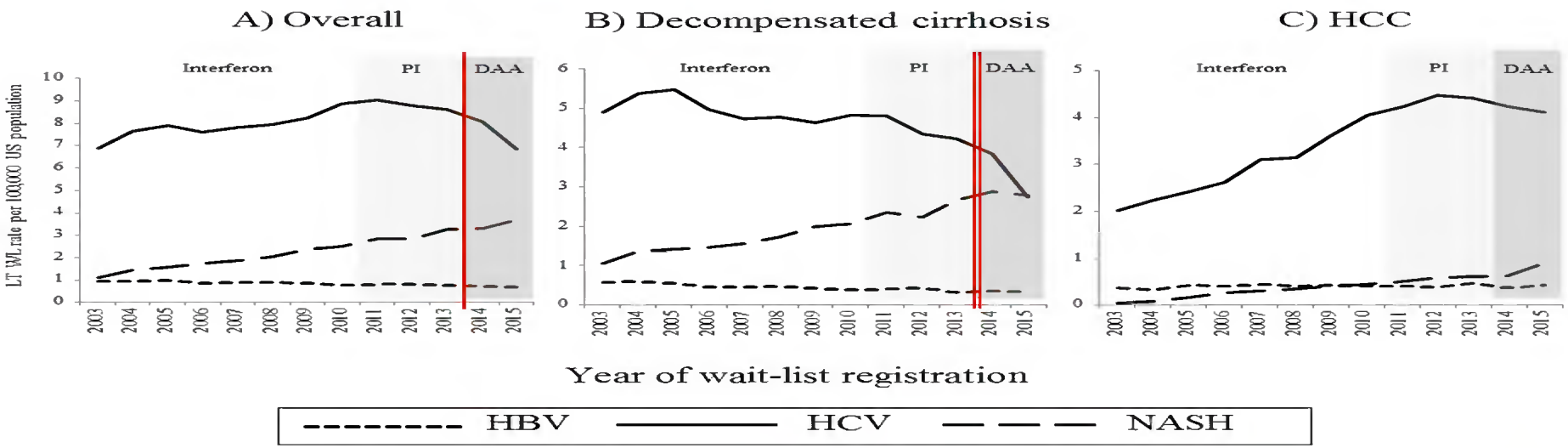





NAFL
PROGRESSIVA
NASH
Cirrhosis
Hep ellular
carcinoma
Cardiovascular Disease
Chronic Kidney Disease
Death
- Cardiovascular
- Malignancies
- Liver-related
Decompensation
Death

"If even 1% of children with NAFLD in the USA progress to end-stage liver disease that would require liver tx, we shall need cadaver donor organs by more than 10-fold"

Schwimmer J.B. Semin Liver Dis 2007



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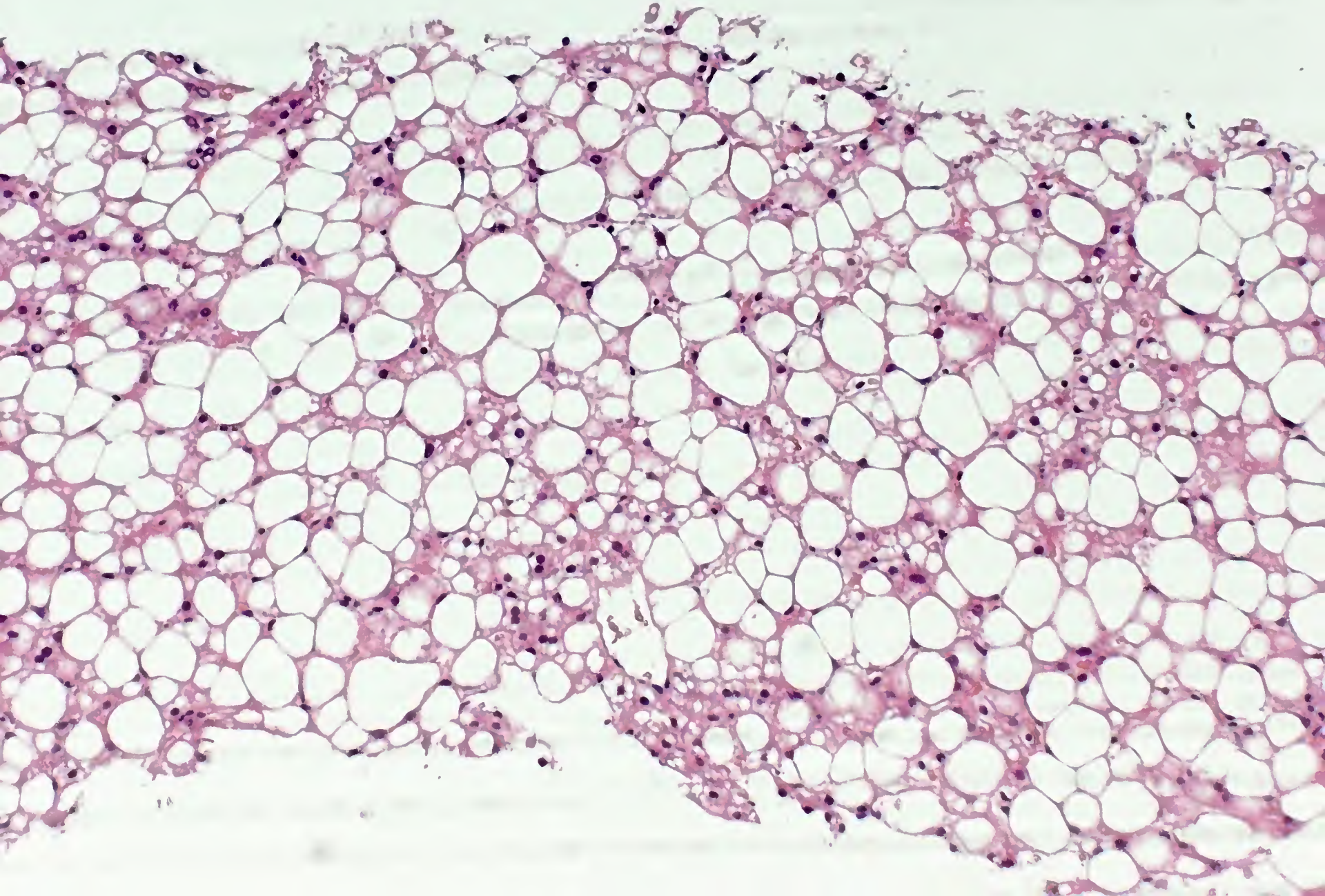

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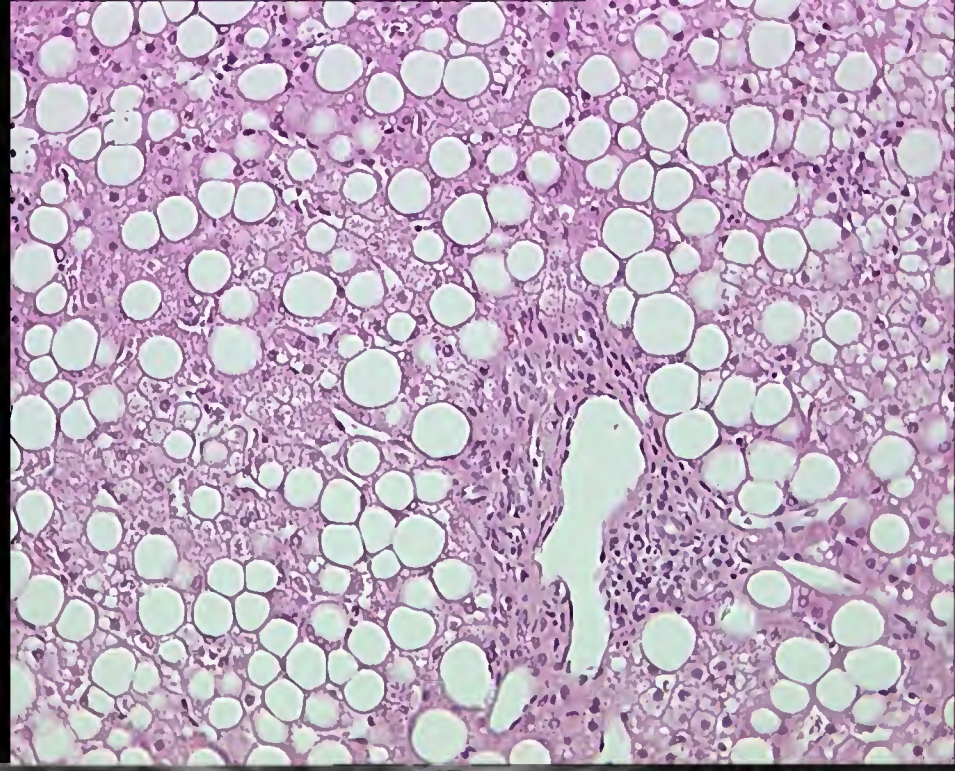


Diffuse hyperechoic echotecture ("bright liver")

Increased liver echotexture compared with the kidney

MARCH 2011

Ultrasonographic Quantitative Estimation of Hepatic Steatosis in Children with Nonalcoholic Fatty Liver Disease (NAFLD)

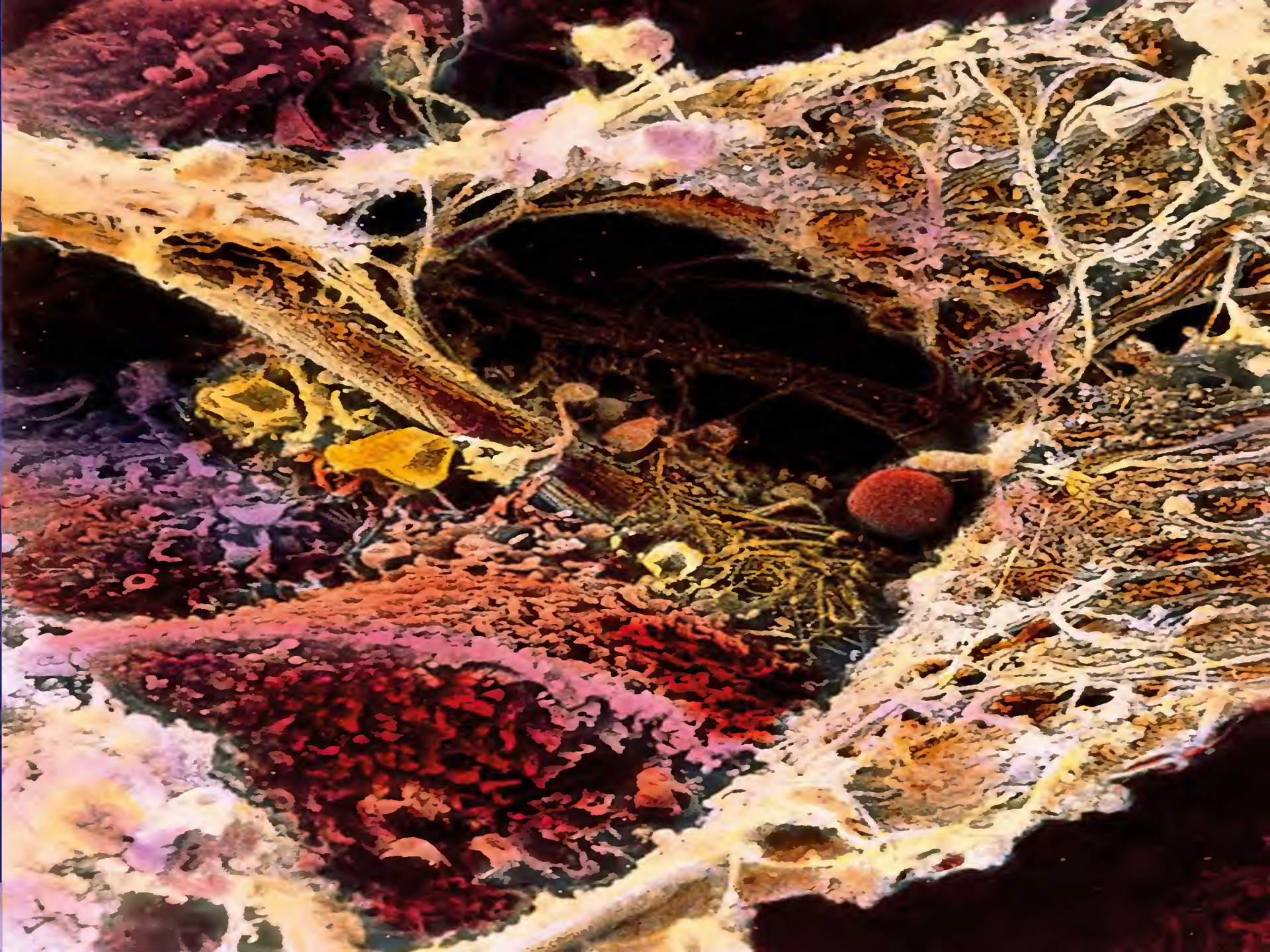
The ultrasonographic steatosis score (USS) was calculated as follows:

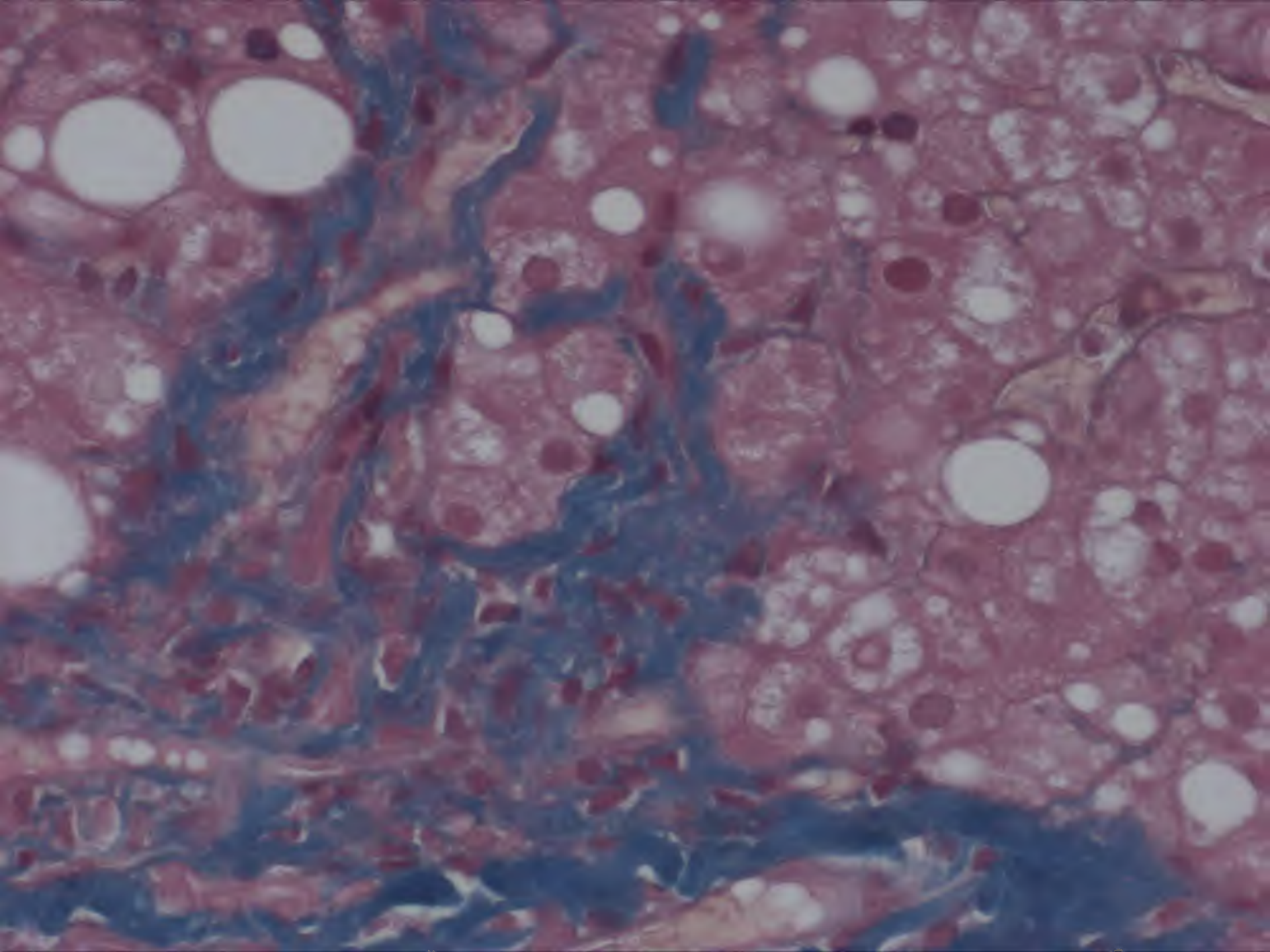
absent (score 0) steatosis was defined as normal liver echotexture;

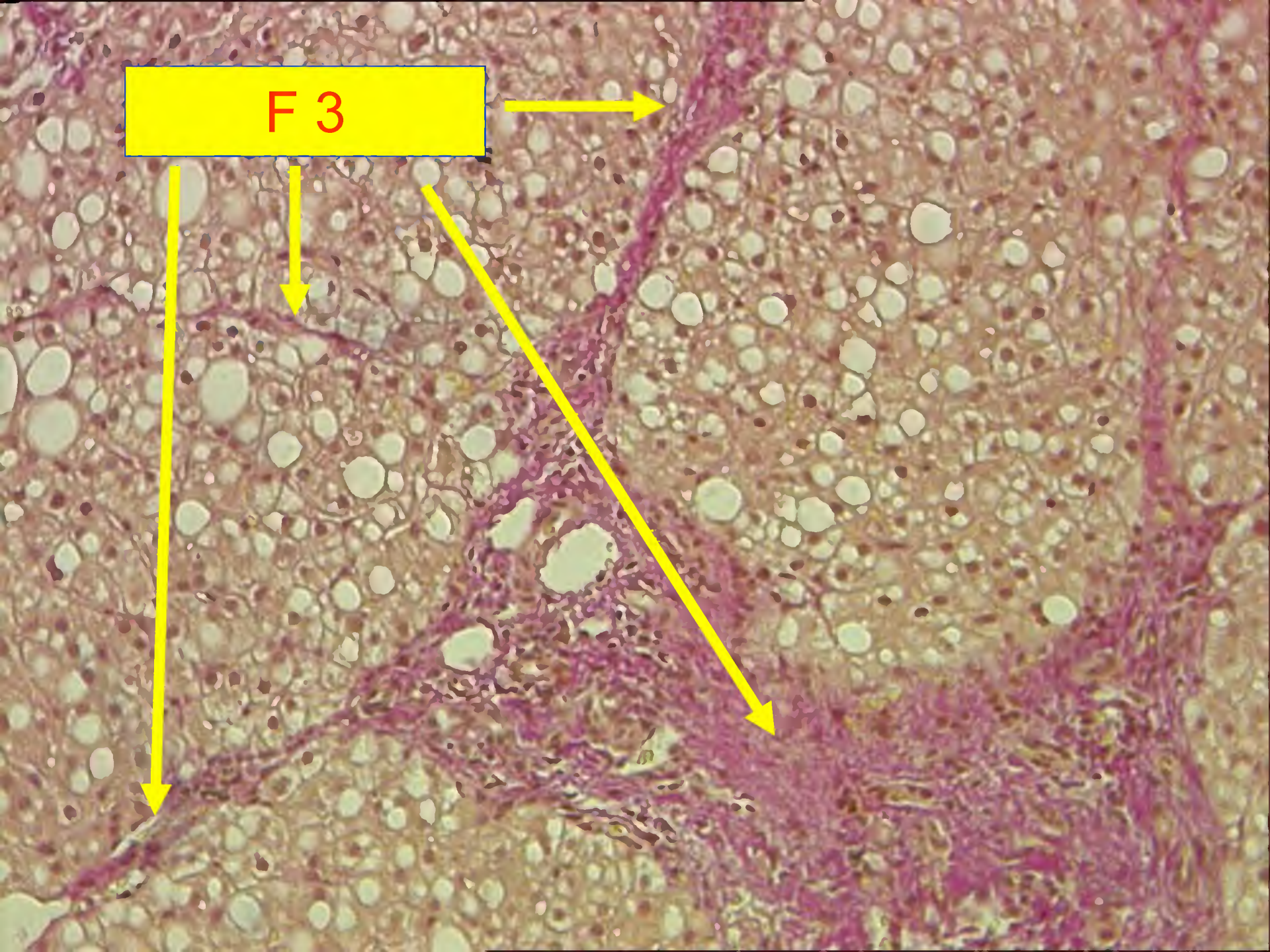
mild (score 1) steatosis as slight and diffuse increase in fine parenchymal echoes with normal visualization of diaphragm and portal vein borders;

moderate (score 2) steatosis as moderate and diffuse increase in fine echoes with slightly impaired visualization of portal vein borders and diaphragm;

severe (score 3) steatosis as fine echoes with poor or no visualization of portal vein borders, diaphragm, and posterior portion of the right lobe



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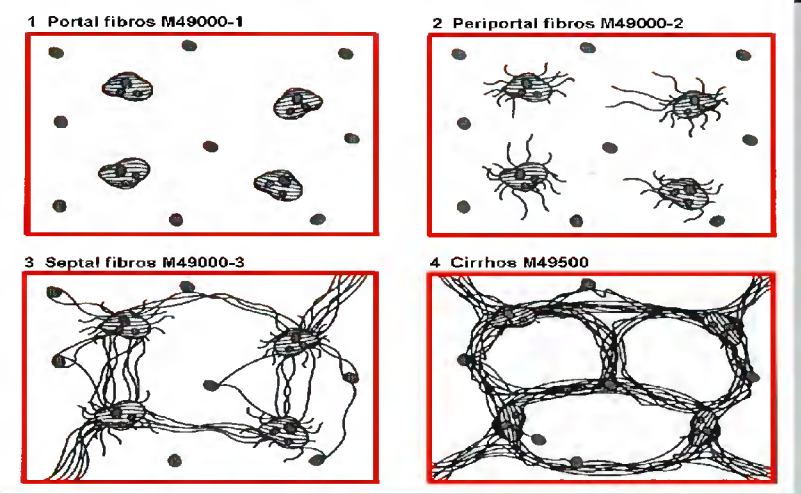

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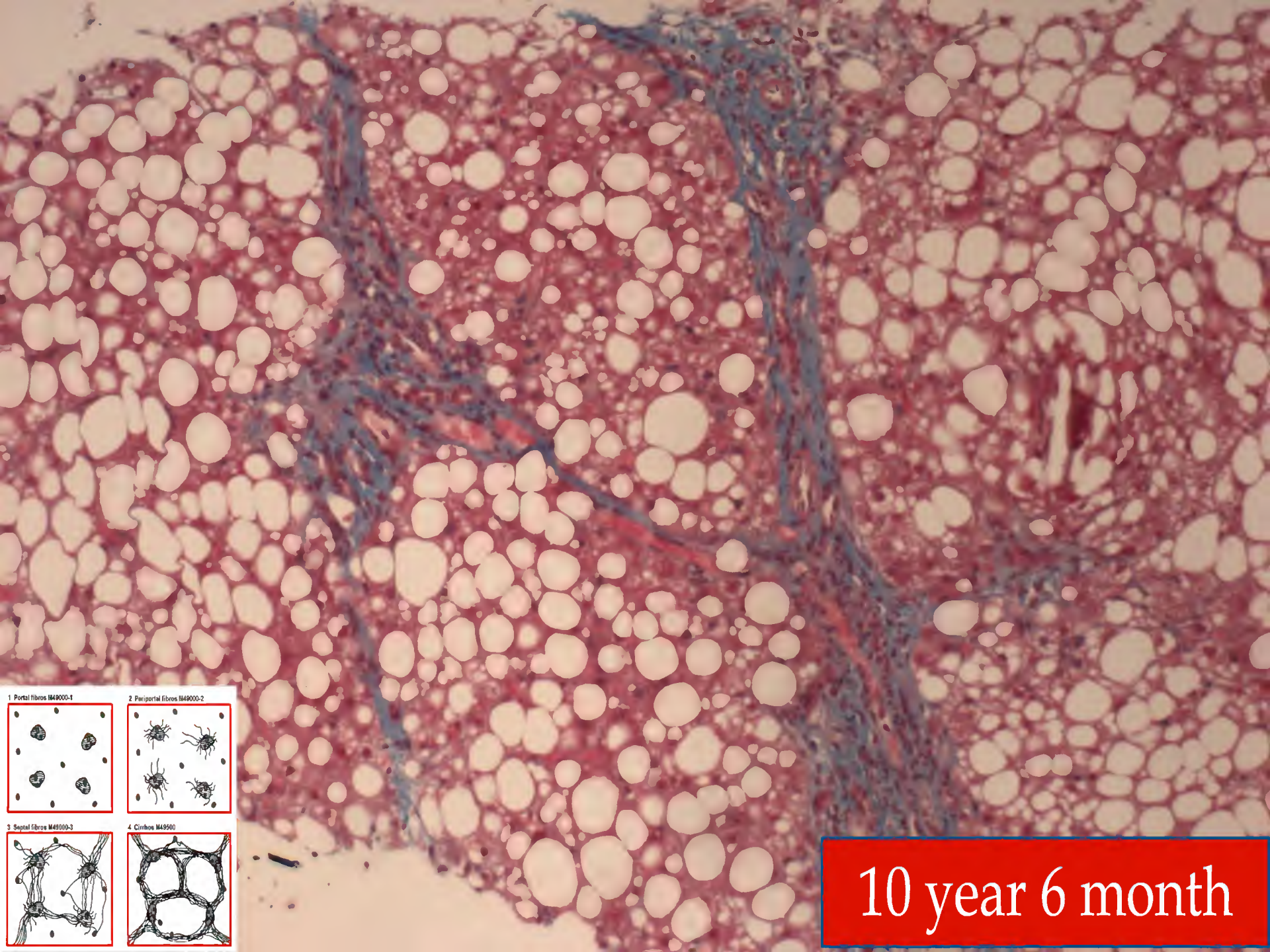
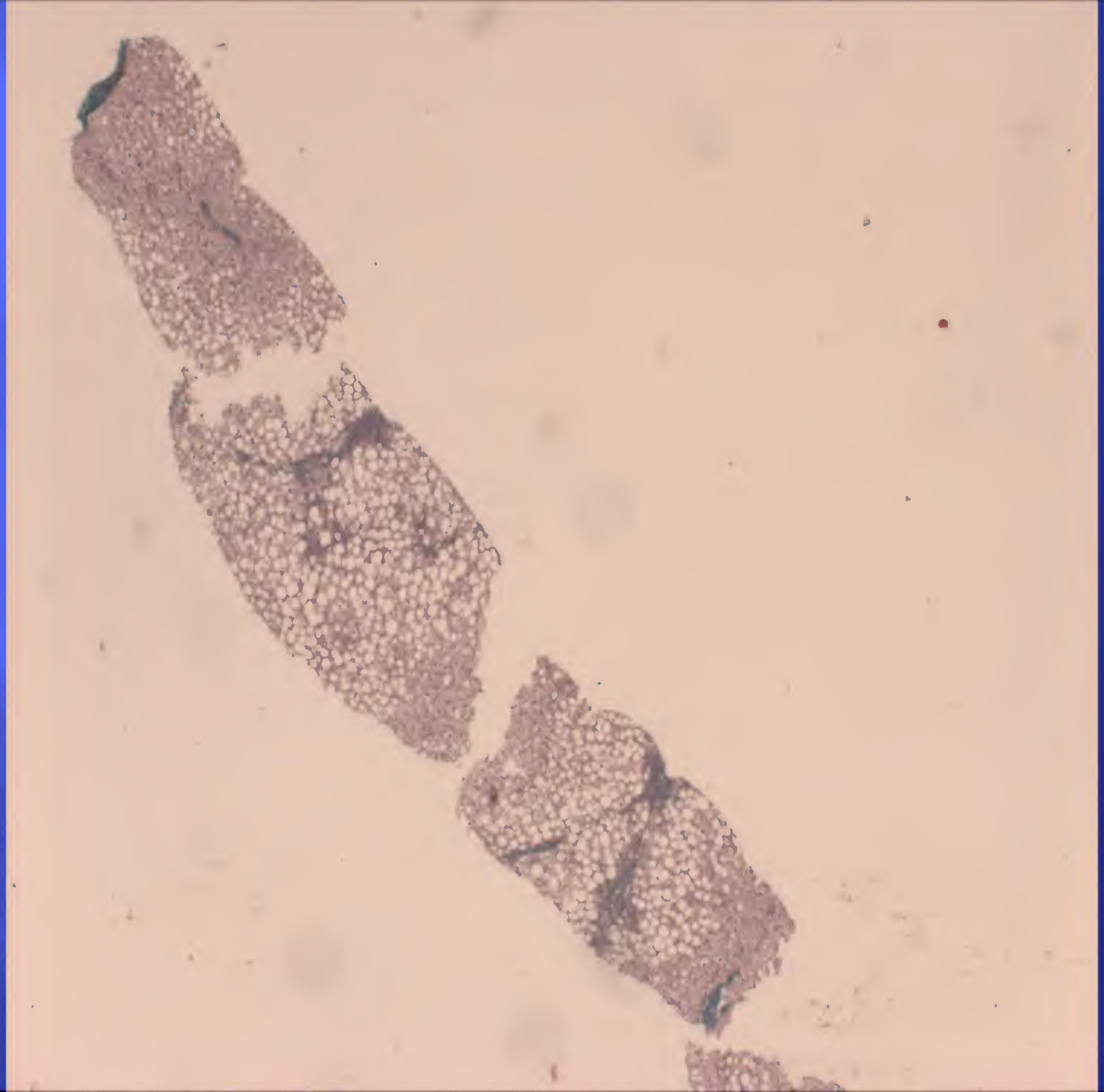
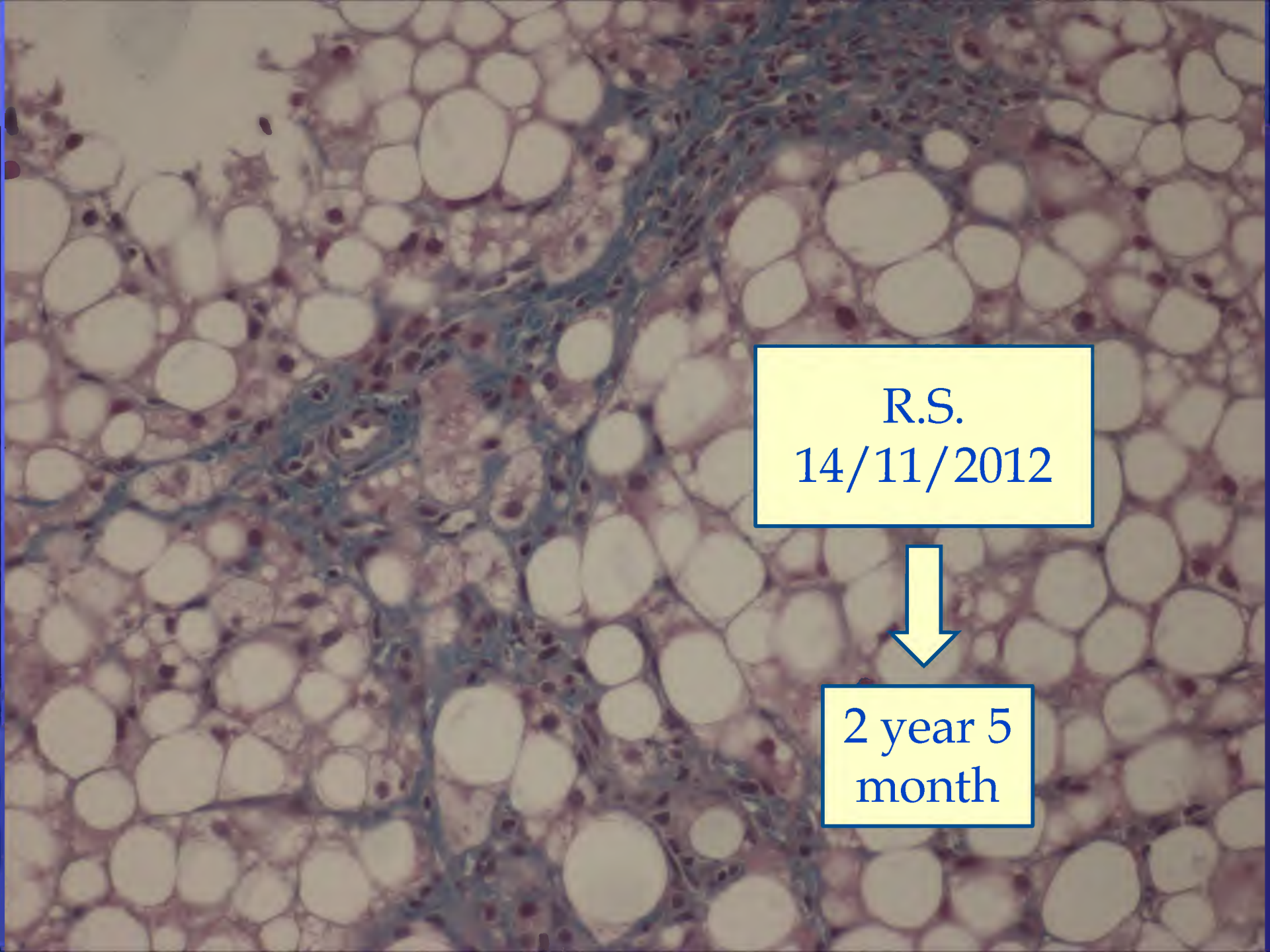
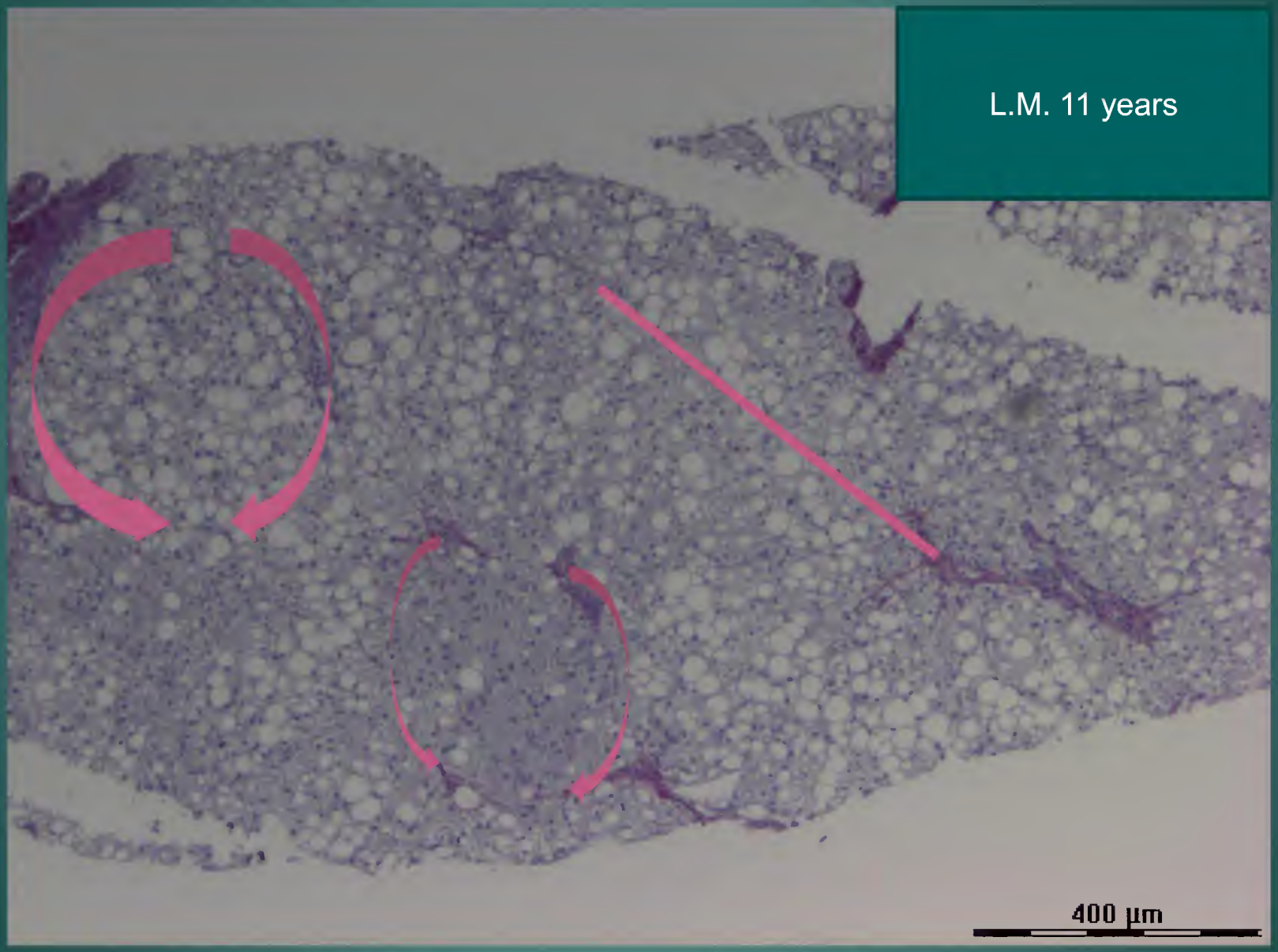
PRE-CIRRHOTIC/CIRRHOTIC CONDITION !!!

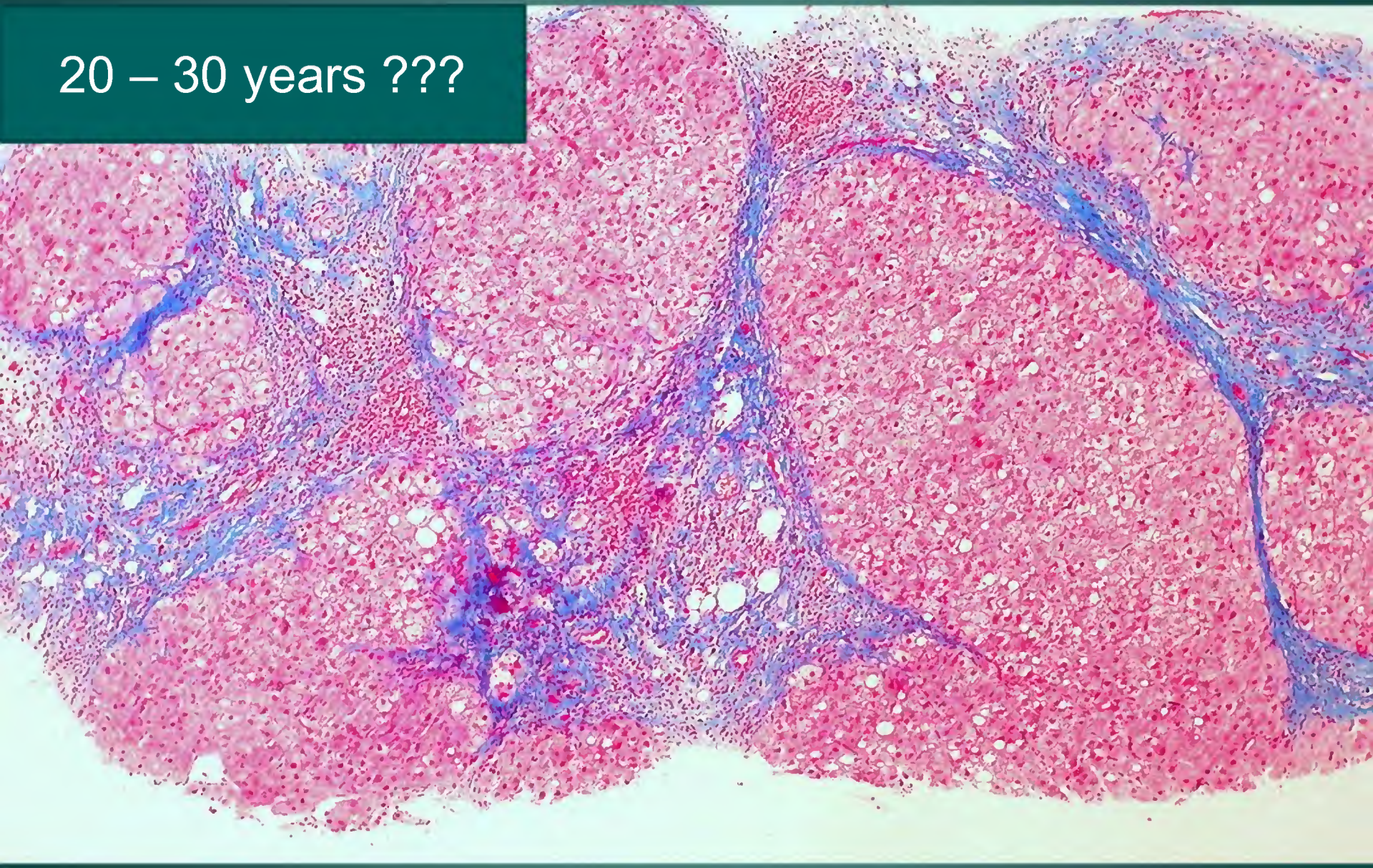

1 Portal fibros M49000-1
2 Periportal fibros M49000-2
3 Septal fibros M49000-3
4 Cirrhos M49500
10 year 6 month

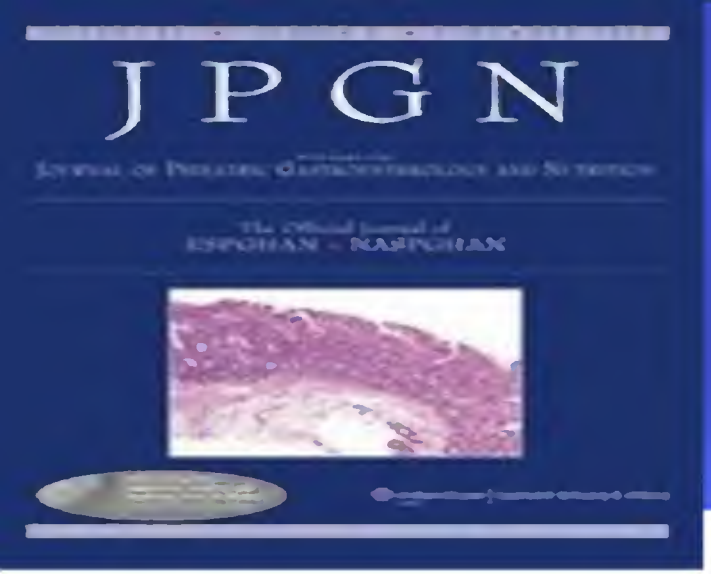



R.S.
14/11/2012
2 year 5
month


L.M. 11 years
400 µm

20 – 30 years ???



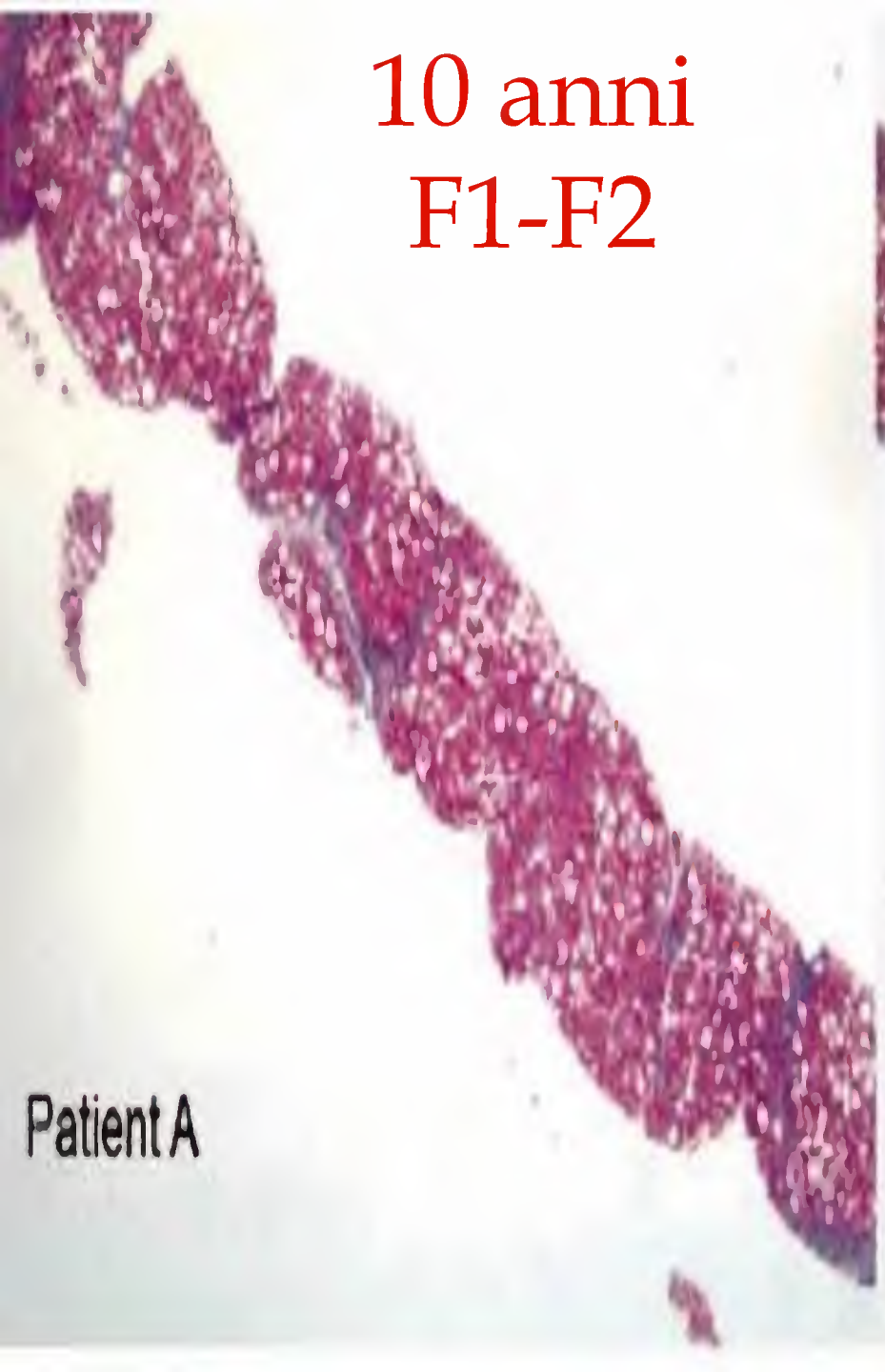


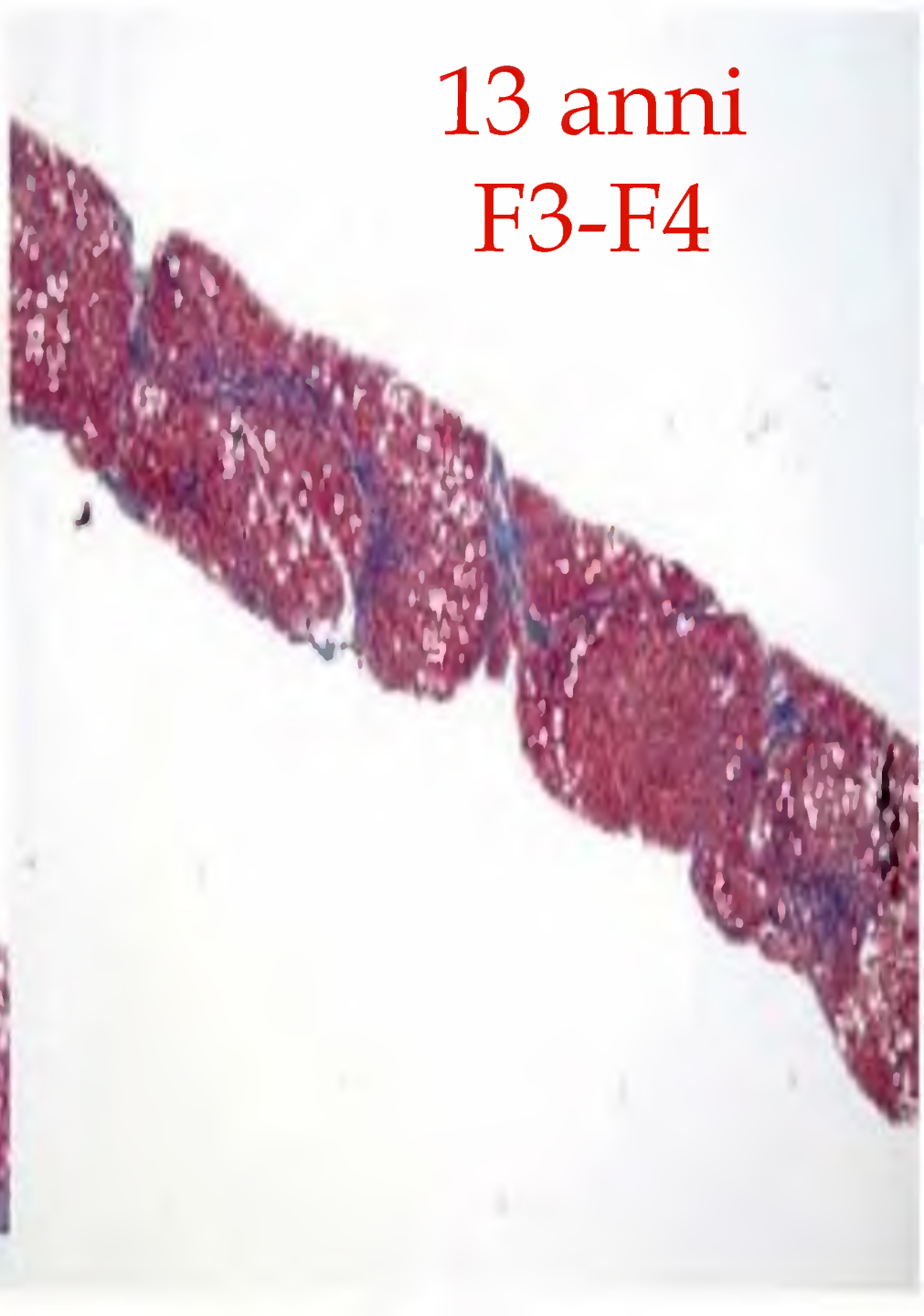
May 2010

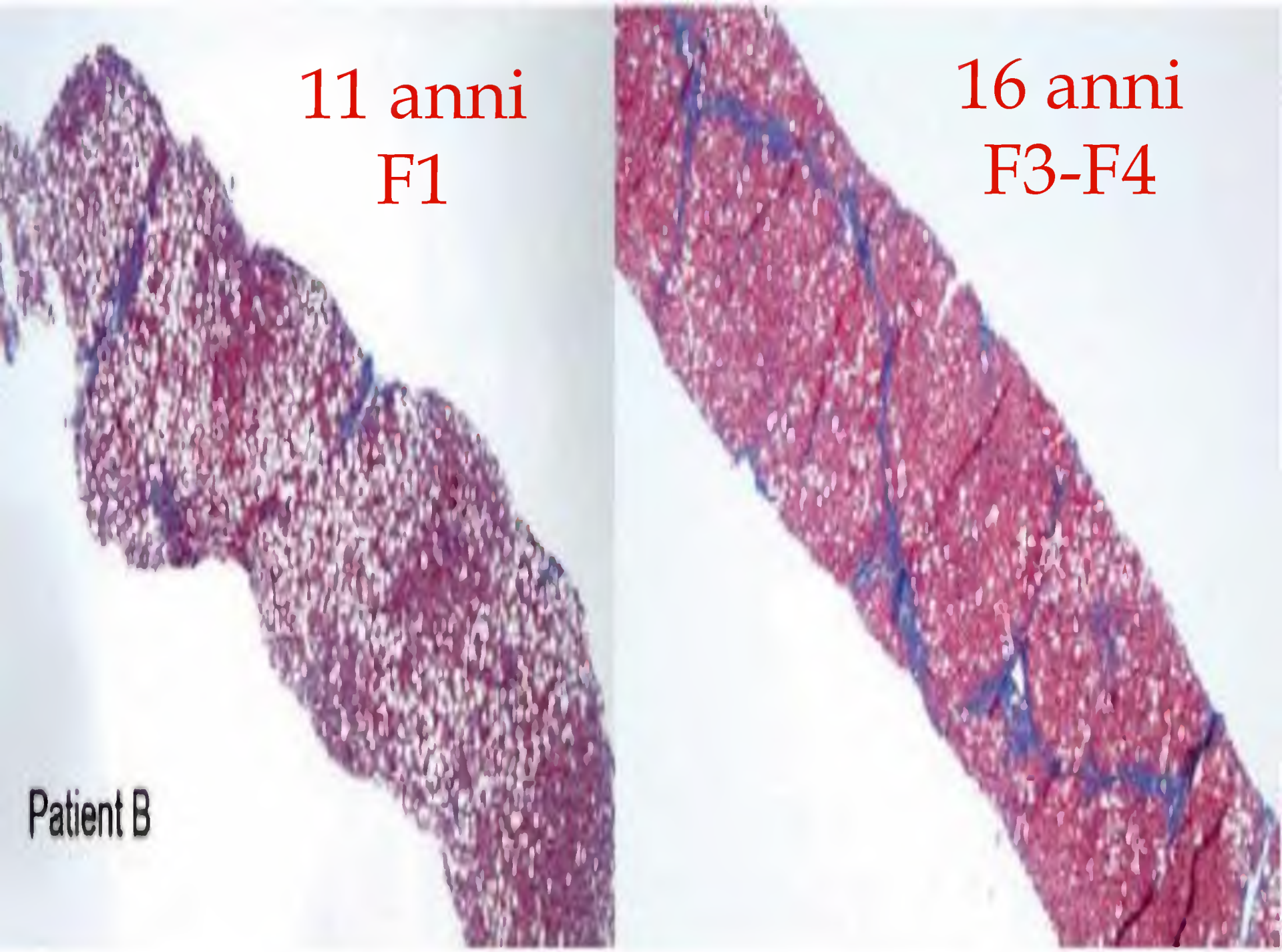
CASE REPORT

Rapid Progression of NASH in Childhood

*Rohit Kohli, †Todd Boyd, *Kathleen Lake, *Kim Dietrich, *Lynda Nicholas, *William F Balistreri, ‡Dawn Ebach, §Harohadli Shashidhar, and *Stavra A. Xanthakos


10 anni
F1-F2
Patient A


13 anni
F3-F4


11 anni
F1
16 anni
F3-F4
Patient B

Nonalcoholic Fatty Liver Disease in Children

Hepatic and Extrahepatic Complications

Praveen Kumar Conjeevaram Selvakumar, MD[a], Mohammad Nasser Kabbany, MD[a], Valerio Nobili, MD[b], Naim Alkhouri, MD[c,*]

Pediatr Clin North Am. June 2017

Poor Quality of Life

- Poor physical and mental health scores
- Depression

Dyslipidemia

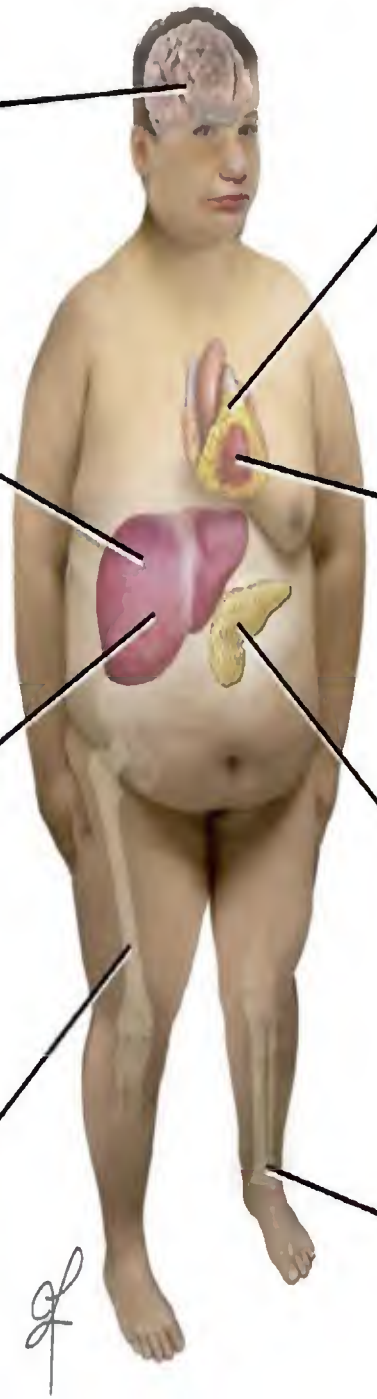
- Hypercholesterolemia, hypertriglyceridemia, low HDL
- Worse atherogenic lipid profile with more severe liver disease

Cirrhosis / Hepatocellular Cancer

- Very rare in childhood
- Liver transplantation still reported in children and young adults

Bone Disease / Osteopenia

- Low bone mineral density Z-scores independent of age, gender and BMI
- Negative correlation of bone mineral density Z-scores with severity of liver disease



Hypertension

- Reported in about 20%–30% of children with NAFLD
- Masked hypertension (systolic nondippers)

Cardiovascular Disease

- Early development of left ventricular structural abnormalities
- Left ventricular systolic and diastolic dysfunction

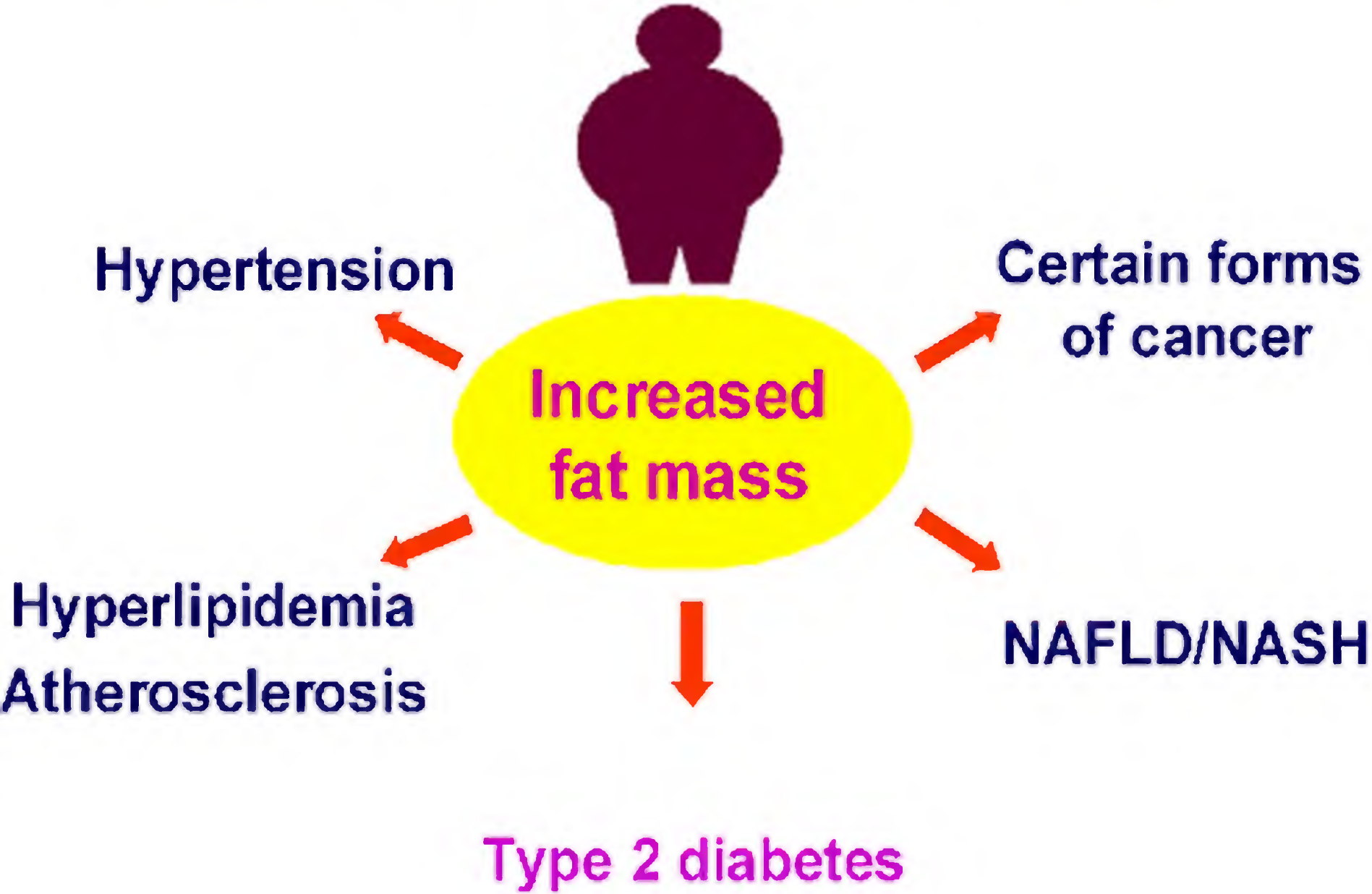
Diabetes

- Estimated prevalence of about 6%–7% in children with NAFLD
- Higher risk of progression of liver disease

Vitamin D Deficiency

- Extremely common in children with NAFLD
- May correlate with severity of liver disease.

Obesity and Metabolic Syndrome



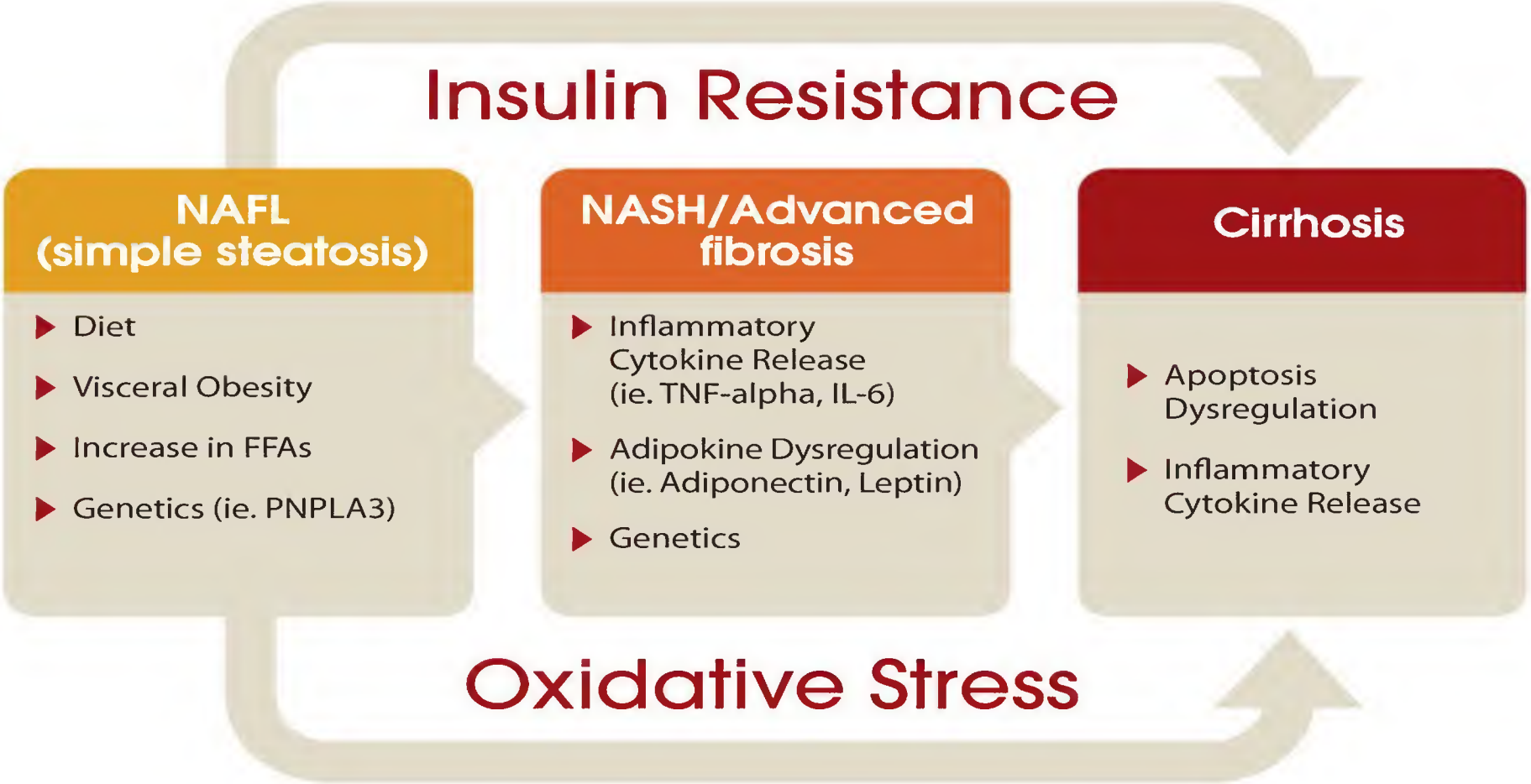


Figure 1. Pathogenesis of NAFLD. The development and progression of NAFLD occurs through 'multiple hits' involving a complex interaction between genetic factors and the release of free fatty acids (FFAs), inflammatory cytokines and adipokines. Insulin resistance and oxidative stress represent key pathogenic features in the progression toward advanced fibrosis and cirrhosis. NAFL = Non-alcoholic fatty liver; NASH = Non-alcoholic steatohepatitis.

Data di Stampa: 02/10/2014 Ore: 14:56 Pag.: 1

Id.:01011004 Sig.ra
Data Nascita: 12/02/2003 Età: 11 Anni Provenienza: 35 MALATTIE EPATO METAB
Sesso F

Routine

Richiesta: 10024283 02/10/2014 Ore: 08:00

Esame	*Esito*	*U.M.*	*Valori Riferimento*
ENDOCRINOLOGIA2			
Insulina Basale (met. Chemilum.)	**44.83** >	mU/L	3.00 - 25.00
	basale?		
Insulina punto 4	**332.7**	mU/L	
	Valore ottenuto con diluizione del campione		
CHIMICA CLINICA DI BASE			
CARICO/STIMOLO GLICEMICO			
Glicemia Basale	**67**	mg/dl	55 - 110
Glicemia +120	**109**	mg/dl	

Id.:01011004 Sig.ra
Nosologico: **2015134145**
Data Nascita: **12/02/2003** Età: 12 Anni
Sesso F

Provenienza: 000004671010 RM Malattie Epato-Metaboliche RO

Routin

Richiesta: 09303498 **30/09/2015** Ore: 08:00

Esame	*Esito*	*U.M.*	*Valori Riferimento*
ENDOCRINOLOGIA2			
Insulina Basale (met. Chemilum.)	**62.58** >	mU/L	3.00 - 25.00
Insulina punto 4	**1 139.3**	mU/L	
	Valore ottenuto con diluizione del campione		
CHIMICA CLINICA DI BASE			
CARICO/STIMOLO GLICEMICO			
Glicemia Basale	**73**	mg/dL	55 - 110
Glicemia +120	**162**	mg/dL	

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
2013
American Association for the Study of Liver Diseases
AASLD

STEATOHEPATITIS/METABOLIC LIVER DISEASE

Left Ventricular Dysfunction in Obese Children and Adolescents With Nonalcoholic Fatty Liver Disease

Lucia Pacifico,[1,2] Michele Di Martino,[3] Antonio De Merulis,[1] Mario Bezzi,[3]
John Frederick Osborn,[4] Carlo Catalano,[3] and Claudio Chiesa[2]

Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 72–74

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Available online at www.sciencedirect.com

SciVerse ScienceDirect

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

Nutrition, Metabolism & Cardiovascular Diseases

SHORT COMMUNICATION

Early left ventricular abnormality/ dysfunction in obese children affected by NAFLD

D. Fintini [a,*,1], M. Chinali [b,1], G. Cafiero [c], C. Esposito [b], U. Giordano [c], A. Turchetta [c], S. Pescosolido [d], G. Pongiglione [b], V. Nobili [e]

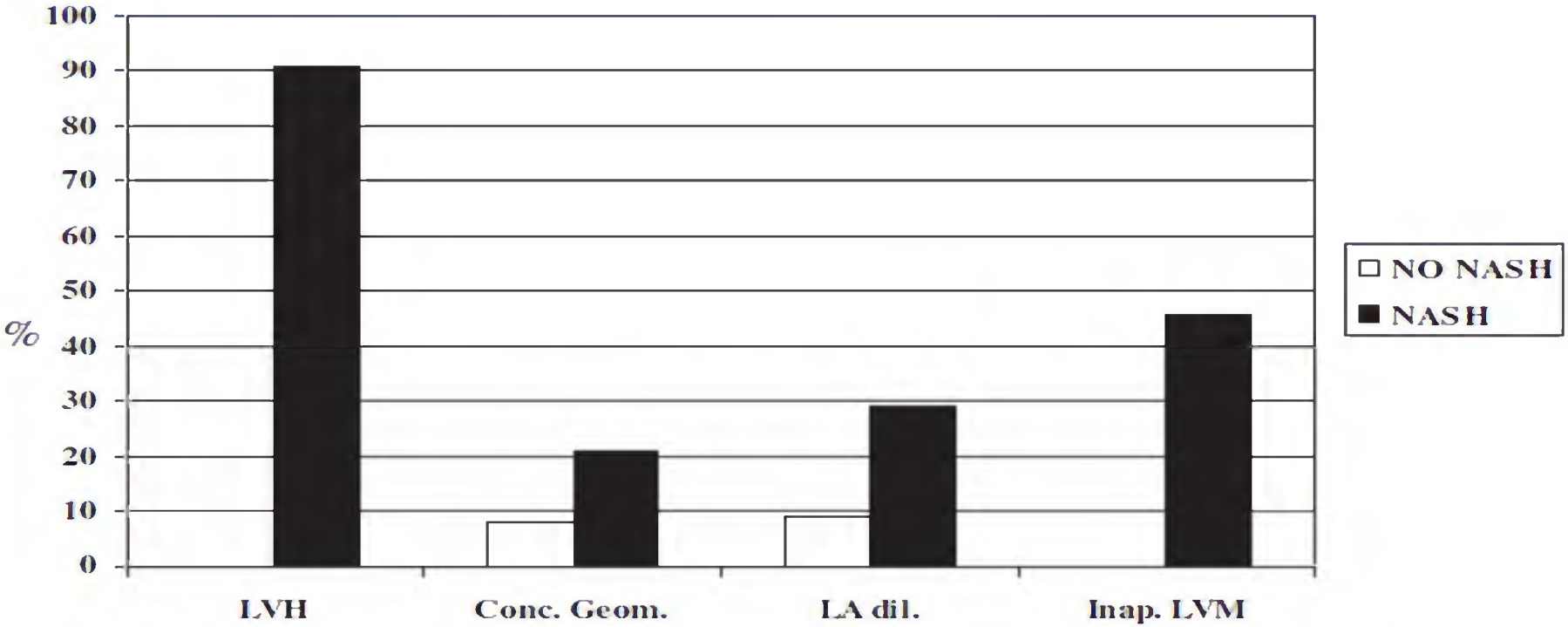


Figure 1 In this figure are shown echocardiografic LV geometry abnormalities according to NASH class (NASH (NAS score >5) — non NASH (NAS score ≤5) (LVH = left ventricular hypertrophy; ConcGeo = concentric geometry; SYSdys = systolic dysfunction; DYSdys = diastolic dysfunction; Ladil = left atrial dilatation; NASH = non alcoholic steatohepatitis; LVH = left ventricular hypertrophy; ConcGeo = concentric geometry; LAdil = left atrial dilatation; InapLVM = inappropriate left ventricular mass).

Bambino Gesù
OSPEDALE PEDIATRICO

Dipartimento di Medicina Pediatrica
Unità Operativa Complessa di Broncopneumologia
Dott. Renato Cutrera, Responsabile

Direttore Dott. Renato Cutrera
Medici di riferimento M. Pavone, E.Verrillo
Infermiera Serena Soldini
Tecnico Antonietta Piliero
Tel. 0668592009- 0668592020

POLISONNOGRAFIA NOTTURNA

Data esame: 24/03/2015	**Codice: 259bis/2015**
Data referto: 25/03/2015	
Cognome e nome: **Ran**	Data di nascita: 14/08/2010
Età: 5 anni	
Reparto: Malattie epatometaboliche	
Motivo dell'esame: obesità, disturbo del comportamento.	
Condizioni di esecuzione dell'esame: Respiro spontaneo FiO2=0.21	

Risultati

Parametri	Valori
Tempo Totale di Sonno (h)	7.25
SaO_2 media (%)	94 (*)
SaO_2 minima (%)	81 (*)
SaO_2 < 90 % (% tempo)	9.1 (*)
Indice di desaturazione >3%	6.5 (*)
Frequenza media del polso (bpm)	116
MOHAI (Indice di ipopnea ostruttiva+mista) (N°/h)	13.8
Indice di Apnea Centrale(N°/h)	0.0

(*) valore non completamente attendibile

Conclusioni

Lo studio cardiorespiratorio risulta condizionato dalla particolare ricchezza di artefatti relativi al segnale della saturazione di ossigeno (SaO_2). Con i limiti sopra riportati, si evidenzia la presenza di apnee/ipopnee ostruttive e miste in numero significativo. La saturazione non è giudicabile a causa di numerosi artefatti di registrazione. Numerosi episodi di risveglio e/o movimento. Frequenza respiratoria normale. Quadro compatibile con apnee/ipopnee ostruttive durante il sonno di entità grave.
Si consiglia valutazione broncopneumologica.

Dott. Martino Pavone
Dirigente Medico I livello

Dott. Renato Cutrera
Responsabile Unità Operativa Complessa
Broncopneumologia

ORIGINAL ARTICLE 2014

Obstructive Sleep Apnea Syndrome Affects Liver Histology and Inflammatory Cell Activation in Pediatric Nonalcoholic Fatty Liver Disease, Regardless of Obesity/Insulin Resistance

Valerio Nobili[1]*, Renato Cutrera[2]*, Daniela Liccardo[1], Martino Pavone[2], Rita Devito[3], Valentina Giorgio[1], Elisabetta Verrillo[2], Giuseppe Baviera[4], and Giovanni Musso[5]

[1]HepatoMetabolic Diseases Unit, [2]Pneumology Unit, Sleep and Noninvasive Ventilation Laboratory, and [3]Pathology Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [4]Family pediatrician, Rome, Italy; and [5]Gradenigo Hospital, Turin, Italy

In pediatric NAFLD, OSAS is associated with biochemical, immunohistochemical, and histological features of NASH and fibrosis. The impact of hypoxemia correction on liver disease severity warrants evaluation in future trials

American Journal of Respiratory and Critical Care Medicine Volume 189 Number 1
January 2014

Metabolic Complications and Obstructive Sleep Apnea in Obese Children: Time to Wake Up!

Obstructive sleep apnea (OSA) is highly prevalent in pediatric obesity. It affects 13 to 59% of obese children, depending on the definitions used (1). Repetitive apneas and hypopneas cause intermittent hypoxia and sleep fragmentation, resulting in increased local and systemic inflammation and sympathetic activity. OSA is an independent risk factor for the metabolic syndrome and several of its components, including dyslipidemia, insulin resistance, and cardiovascular comorbidities (2–4). However, the link between OSA and full-blown manifestations of end-organ damage in pediatrics such as diabetes or daytime hypertension has not been established. Although the association between OSA during childhood and premature onset of these

Editorials

Kim Van Hoorenbeeck, M.D., Ph.D.
Stijn L. Verhulst, M.D., Ph.D.
Department of Pediatrics
Antwerp University Hospital
Edegem, Belgium

The high prevalence of obesity and OSA in this population makes this a public health priority: it is time to wake up and be active!

Apnee Ostruttive Del Sonno

Email address...

GIOVEDÌ 18 LUGLIO 2013

L'OSAS, 3 Miliardi di euro all'anno tra mancata diagnosi e trattamento.

Raccogliendo informazioni in giro per il web, ci siamo imbattuti in diversi articoli che parlavano di costi legati al trattamento ed alla mancata diagnosi della Sindrome delle Apnee Ostruttive Del Sonno.

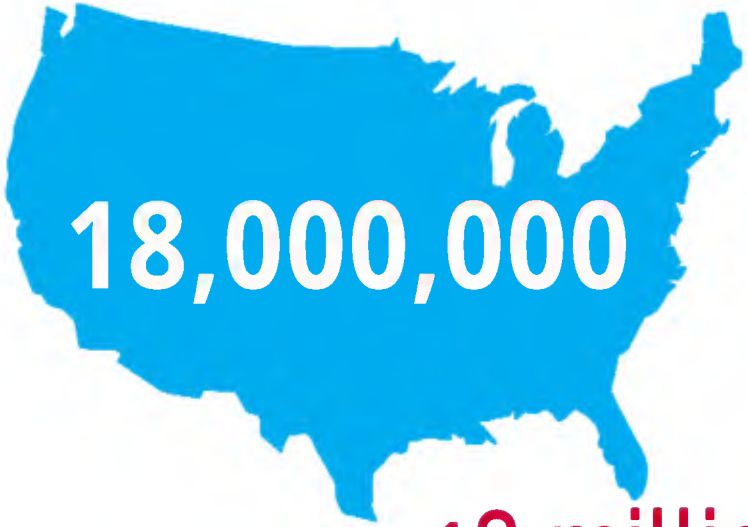
Ci siamo poi divertiti a "sistemare" questi numeri ed a fare alcune somme;

Abbiamo sommato alcune stime, tra costi sanitari diretti (ovvero quelli spesi per il trattamento delle Apnee Ostruttive Del Sonno) e indiretti, verificando che, ***un'adeguata diagnosi e trattamento, potrebbe portare ad un risparmio di circa 3 Miliardi di euro all'anno*** (La famosa IMU dello scorso anno, è stata una manovra da 4 Miliardi di Euro).

iHateSNORINGMD

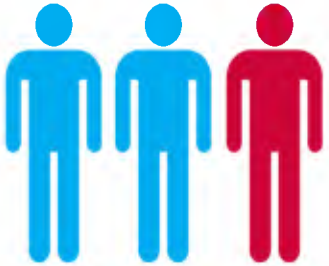
Sleep Apnea 101

Sleep apnea is the ***involuntary cessation of breathing*** that occurs during sleep.



1 in 50 Americans suffering from sleep apnea are ***undiagnosed***.

1 in 3 people over the age of 15 is at ***risk*** for sleep apnea.



An estimated **18 million** Americans (**1 in 15**) have sleep apnea.

DID YOU KNOW?

80%

of moderate to severe sleep apnea cases go undiagnosed.

"Sleep apnea affects males and females of all ages, particularly those who are overweight," says **Krishna Sundar, M.D.**, medical director of the Sleep-Wake Center at University of Utah Health Care.

Symptoms may include:

- Snoring, suspended breathing and gasping for air during sleep
- Daytime exhaustion and sleepiness
- Sore throat

Discuss with your doctor what lifestyle changes or treatments are right for you.

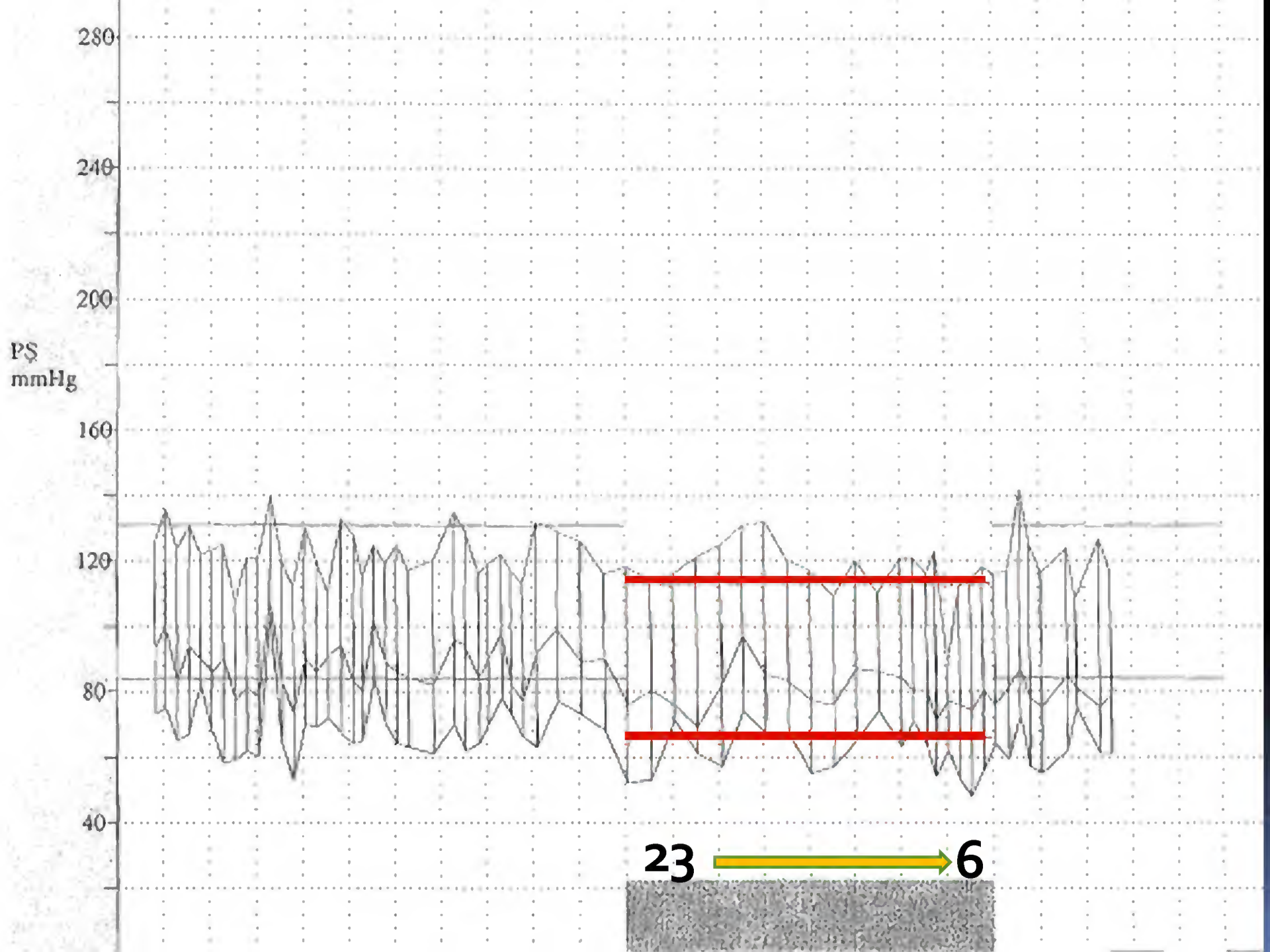
UNIVERSITY OF UTAH HEALTH CARE

healthfeed.uofuhealth.org

MAY 2014

Association between Nocturnal Blood Pressure Dipping and Insulin Resistance in Children Affected by NAFLD

Ugo GIORDANO, Claudia DELLA CORTE, Giulia CAFIERO, Daniela LICCARDO, Attilio TURCHETTA, Kazem Mohammad HOSHEMAND, Danilo FINTINI, Giorgio BEDOGNI, Maria Chiara MATTEUCCI, and Valerio NOBILI.


280
240
200
PS
mmHg
160
120
80
40
23
6

RESULTS

The anthropometric and metabolic measurements of the 101 children with NAFLD were as follow. 76 children (75.3%) were systolic non-dippers and 23 of them were also diastolic non-dippers (30.3%).

As compared to systolic dippers, systolic non-dippers had higher medians of mean nocturnal SBP, OGTT glucose at 0, 60 and 120 min, OGTT insulin at all time points, HOMA and ISI.

OSP. PEDIATRICO BAMBINO GESU'
U.O.C. MEDICINA CARDIORESPIRATORIA E DELLO SPORT

Informazioni paziente

Sesso: Femmina
Altezza: 160 Centimetri
Peso: 76 Chilogrammi
Razza: Caucasica
Medico: Giordano,Ugo
Infermiera/Tecnico:
Durata: 20:44
Inizio scansione: 26/05/2014 13:50 Lu.
Fine scansione: 27/05/2014 10:34 Ma.
Lettura(e) riuscita(e): 64 94%

Età: 13 Anni
Farmaci: Dose: Ora:

Indicazioni:
OBESITA'

Riepilogo globale

	MED	STD		MIN	MAX	Dipping
Sistolica:	121	8.66	mmHg	88 (07:04 Ma.)	142 (08:36 Ma.)	3.3%
Diastolica:	65	8.94	mmHg	48 (07:34 Ma.)	103 (16:19 Lu.)	9.0%
PAM:	84	8.16	mmHg	69	109	7.0%
Pressione polso:	56	9.71	mmHg	26	69	
Frequenza cardiaca:	78	15.10	bpm	53	130	

	Letture	Ora
Percentuale di Sistolica oltre i limiti:	34.4%	39.8 %
Percentuale di Diastolica oltre i limiti:	10.9%	14.4 %

Periodi di veglia 08:00 - 00:00

	MED	STD		MIN	MAX
Sistolica:	122	8.00	mmHg	107 (15:34 Lu.)	142 (08:36 Ma.)
Diastolica:	67	8.80	mmHg	53 (16:49 Lu.)	103 (16:19 Lu.)
PAM:	86	8.08	mmHg	73	109
Pressione polso:	55	9.29	mmHg	33	69
Frequenza cardiaca:	82	12.92	bpm	57	130

	Letture	Ora
Percentuale delle letture di Sistolica >131mmHg:	13.6%	11.5 %
Percentuale delle letture di Diastolica >84mmHg:	2.3%	1.6 %

Numero di letture Periodi di veglia:44

Periodi di sonno 00:00 - 08:00

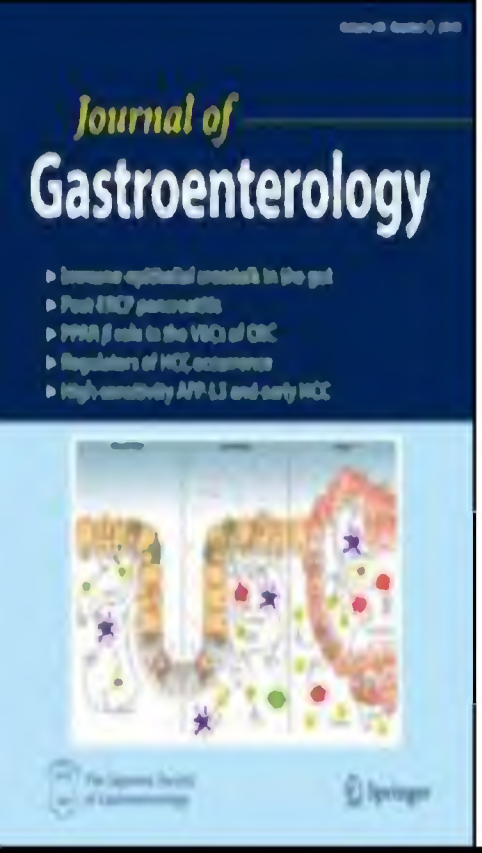
	MED	STD		MIN	MAX
Sistolica:	118	9.14	mmHg	88 (07:04 Ma.)	132 (03:04 Ma.)
Diastolica:	61	7.80	mmHg	48 (07:34 Ma.)	74 (02:34 Ma.)
PAM:	80	6.27	mmHg	69	97
Pressione polso:	58	10.79	mmHg	26	69
Frequenza cardiaca:	67	13.80	bpm	53	101

	Letture	Ora
Percentuale delle letture di Sistolica >113mmHg:	80.0%	80.4 %
Percentuale delle letture di Diastolica >66mmHg:	30.0%	35.5 %

Numero di letture Periodi di sonno:20

Interpretazione

I VALORI RILEVATI HANNO EVIDENZIATO IPERTENSIONE SISTOLICA NOTTURNA DI GRADO LIEVE-LIEVE/MODERATO.
CALO FISIOLOGICO NOTTURNO MARCATAMENTE RIDOTTO.
NELLA NORMA I VALORI NEL PERIODO DIURNO.
BRACCIALE 24/32 SX



The Association between Retinal Microvascular Changes, Metabolic Risk Factors, and Liver Histology, in Paediatric Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)

Liccardo D[1], Mosca A[1], Petroni S[2], Valente P[2], Giordano U[3], Mico' A.G.A[4], Pescosolido S[5], Buzzonetti L[2], and Nobili V[1]

Affiliations:

[1]Unit of Hepato-Metabolic Diseases, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[2] Ophthalmology Departments, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

[3] Sport Medicine Unit, Bambino Gesù Children's Hospital - IRCCS, Rome, Italy.

[4]ASL RM C, Rome, Italy

[5]ASL RM D, Rome, Italy

In summary, our findings suggest that the effects of metabolic parameters (such as HOMA IR and triglycerides) and nocturnal (non dipping) blood pressure, on the retinal microvasculature, are evident in overweight and obese children with NAFLD.

Further longitudinal studies will be needed to clarify, whether structural changes of the retinal microvasculature in overweight and obese children with NAFLD, can predict the clinical onset of severe metabolic complications that are obesity related in adulthood

NORMAL BLOOD VESSELS

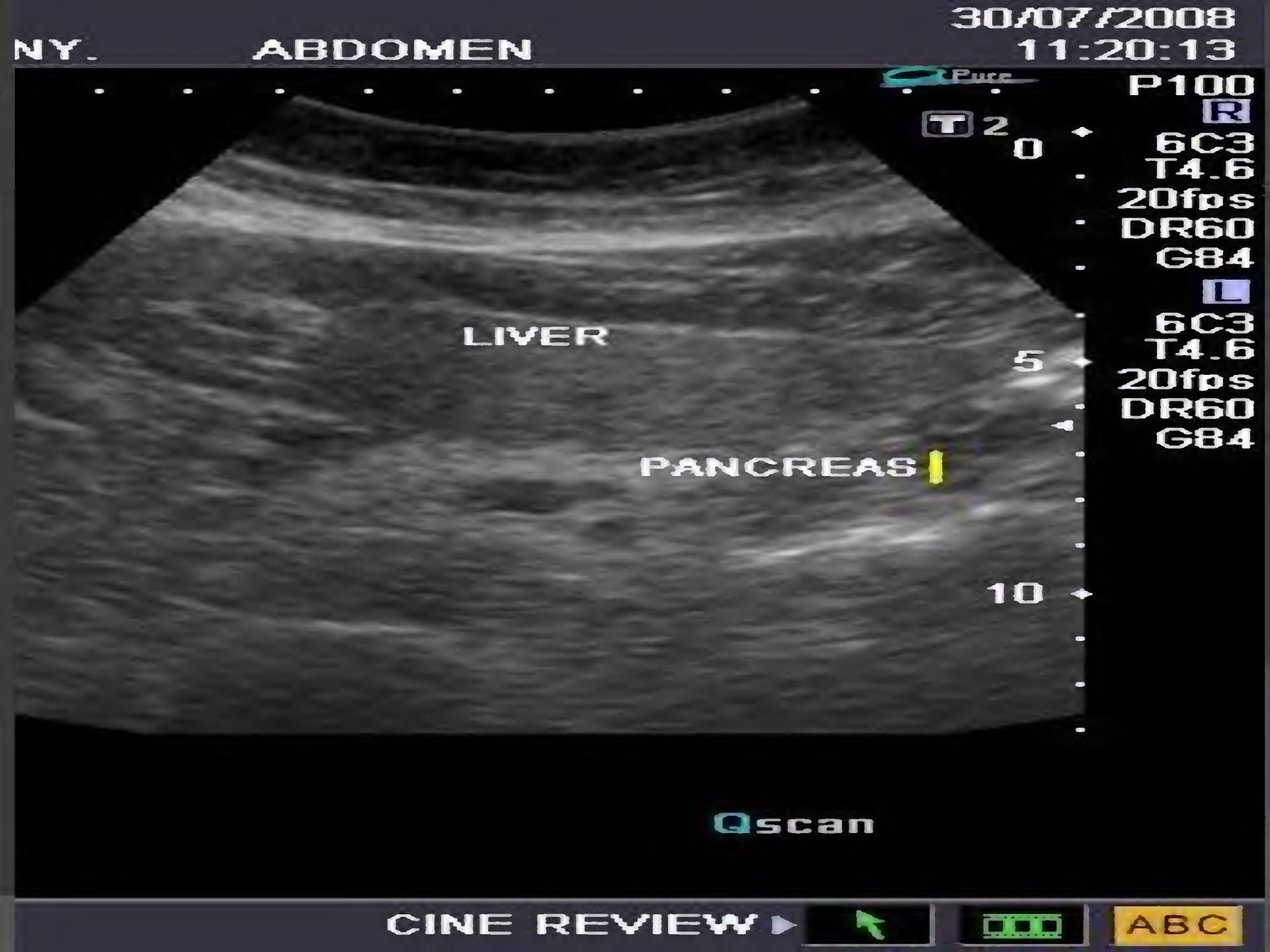
11 anni
MILD BLOOD VESSELS
TORTUOSITY

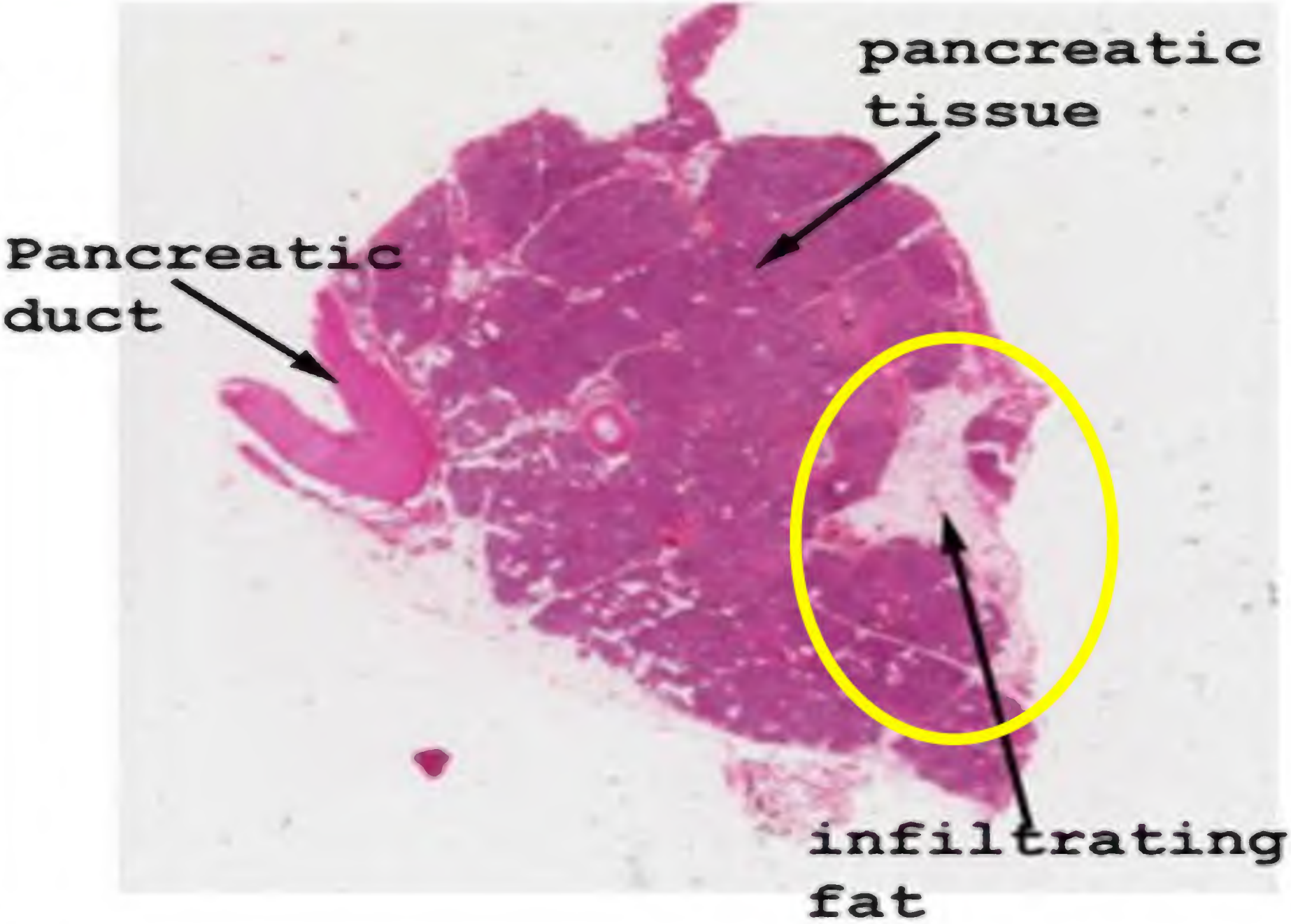
13 anni
SEVERE BLOOD VESSELS
TORTUOSITY

Accepted on
JULY 2015

Non-alcoholic fatty pancreas disease and Non-alcoholic fatty liver disease: more than ectopic fat

Della Corte C, Mosca A, Majo F, Lucidi V, Panera N, Giglioni E, Monti L, Stronati L, Alisi A, Nobili V


NY.
ABDOMEN
30/07/2008
11:20:13
Pure
P100
R
T 2
0
6C3
T4.6
20fps
DR60
G84
L
6C3
T4.6
20fps
DR60
G84
LIVER
5
PANCREAS
10
Qscan
CINE REVIEW
ABC


pancreatic
tissue
Pancreatic
duct
infiltrating
fat

	No-NAFPD (63)	NAFPD (58)	*p*
Insulin, mU/L (mean± SD)	18.11 (9.47)	24.29 (11.99)	***0.001****
Insulin -120' (mean± SD)	109.15 (107.99)	124.85 (84.40)	0.36
HOMA-IR (mean± SD)	3.72 (2.03)	4.86 (2.39)	***0.01****
ISI (mean± SD)	4.91(2.97)	3.06(1.72)	***0.004****

	Population	No-NAFDP	NAFDP	
Fibrosis				
0	17(25.3)	14(37.85)	3(10)	0.01*
1	35(52.3)	21(56.75)	14(46.66)	0.09
2	12(17.8)	2(5.4)	10(33.34)	0.002*
3	3(4.6)	/	3(10)	/

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nature REVIEWS ENDOCRINOLOGY

NATURE REVIEWS ENDOCRINOLOGY | RESEARCH HIGHLIGHT

PANCREAS

Fatty pancreas linked to increased BMI and insulin resistance in children

Tim Geach

Nature Reviews Endocrinology (2015) | doi:10.1038/nrendo.2015.131
Published online 11 August 2015

Nonalcoholic fatty pancreas disease (NAFPD), the ectopic accumulation of fat in the pancreas, is associated with obesity and metabolic dysfunction in adults; however, little is known about its pathogenic consequences in children.

In a new study, investigators from the Bambino Gesù Children's Hospital, in Rome, Italy, enrolled 121 children (mean age 13.16 years) who had evidence of hepatic steatosis. The patients were then divided into two groups: those who had evidence of NAFPD (n = 58), and those who did not (n = 63), to evaluate how NAFPD affects metabolic parameters.

Compared with patients who only had hepatic steatosis, those individuals with NAFPD had significantly higher BMI (27.51 vs. 29.29 kg/m^2; P = 0.04), higher insulin levels (18.11 vs. 24.29 mU/l; P = 0.001) and insulin resistance (HOMA index 3.72 vs. 4.86; P = 0.01).

nature

EBOLA: THE LONG GAME

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Assistant Professor in Human Genetics
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NATURE REVIEWS GASTROENTEROLOGY & HEPATOLOGY | RESEARCH HIGHLIGHT

PANCREAS

Fatty pancreas linked to increased BMI and insulin resistance in children

Tim Geach

Nature Reviews Gastroenterology & Hepatology (2015) | doi:10.1038/nrgastro.2015.143
Published online 11 August 2015

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Nonalcoholic fatty pancreas disease (NAFPD), the ectopic accumulation of fat in the pancreas, is associated with obesity and metabolic dysfunction in adults; however, little is known about its pathogenic consequences in children.

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Of the original 121 patients, 67 underwent a liver biopsy. In these patients the presence of NAFPD

nature

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Image credit: Centre for Infections/Public Health England/SPL

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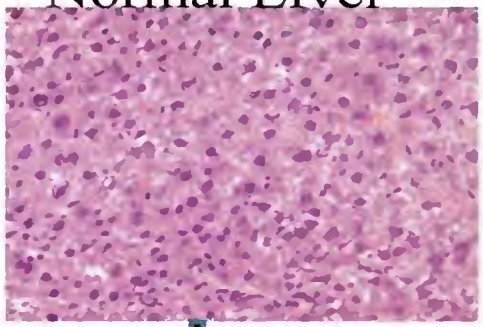
Most read

NAFLD Progression **Risk factors**

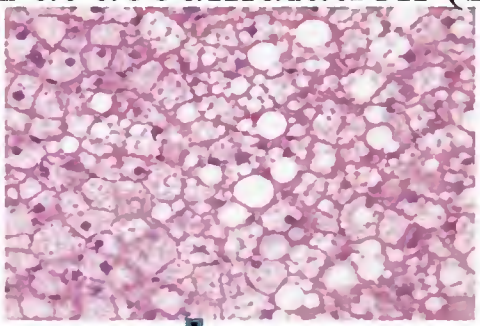
Normal Liver



Genetic predisposition: SNPs, especially PNPLA3

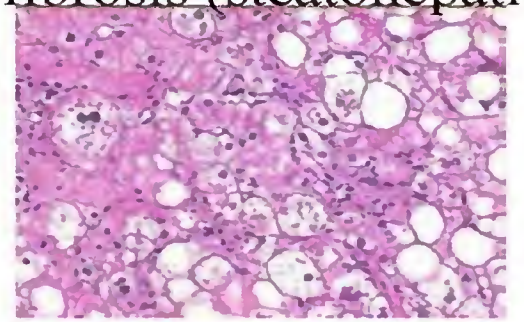
Environmental: Western diet, lack of activity
Obesity
Metabolic syndrome
Insulin resistance

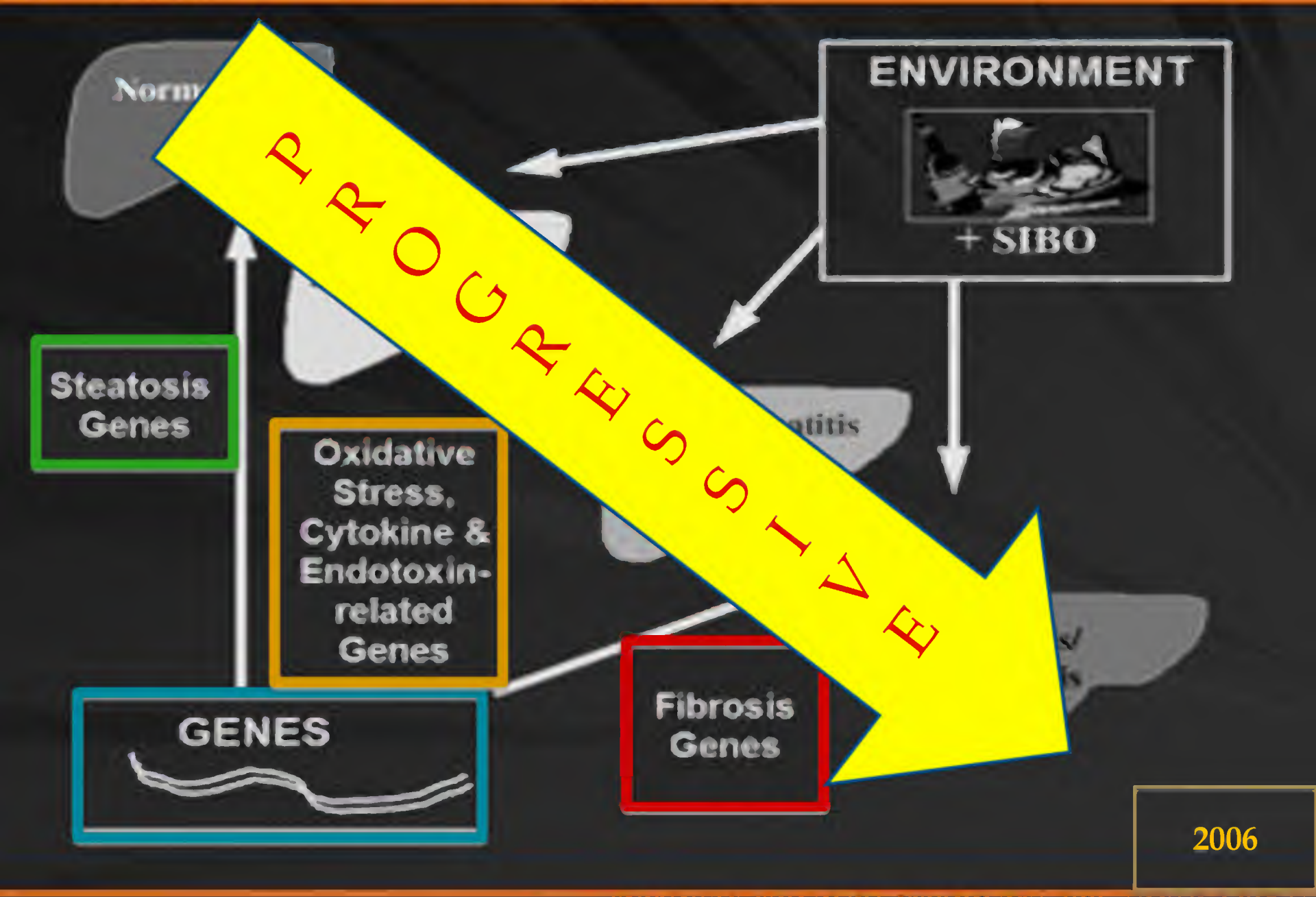
Fat accumulation (steatosis)



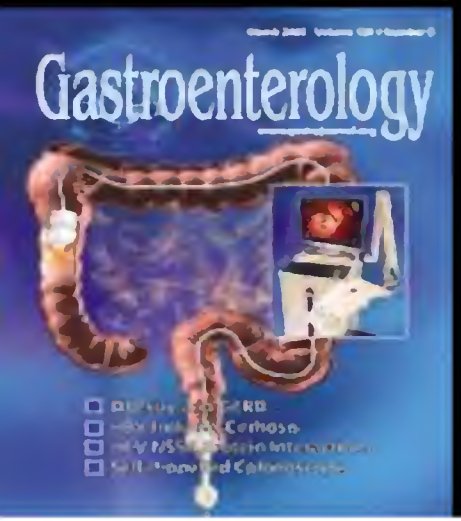
Free fatty acids (lipotoxicity)
Oxidative stress: ROS, lipid peroxidation
Adipokine/cytokines
Gut microbiota/endotoxin
Mitchondrial dysfunction
Lipid peroxidation
Stellate cell activation

Inflammation and/or fibrosis (steatohepatitis)





Source: Liver Int © 2006 Blackwell Publishing



Gastroenterology. 2008 Jul;135(1):282-291

The Kruppel-Like Factor 6 Genotype Is Associated With Fibrosis in Nonalcoholic Fatty Liver Disease

LUCA MIELE,[*,‡,§] GARY BEALE,[*,‡] GILLIAN PATMAN,[*,‡] VALERIO NOBILI,[‖] JULIAN LEATHART,[‡,#] ANTONIO GRIECO,[§] MARILENA ABATE,[¶] SCOTT L. FRIEDMAN,[**] GOUTHAM NARLA,[‡‡] ELISABETTA BUGIANESI,[¶] CHRISTOPHER P. DAY,[‡,#] and HELEN L. REEVES[*,‡]

[*]Northern Institute for Cancer Research, [‡]The Liver Group, Newcastle University, Newcastle upon Tyne, United Kingdom, and [§]Department of Internal Medicine, Policlinico Gemelli Hospital and Catholic University of the Sacred Heart, Rome, Italy; [‖]Liver Unit, Bambino Gesu' Hospital, Rome, Italy; [¶]Department of Gastroenterology, University of Turin, Turin, Italy; [#]The Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; and [**]Division of Liver Diseases, and [‡‡]Department of Medicine and Genetics and Genomic Sciences, The Mount Sinai School of Medicine, New York, New York

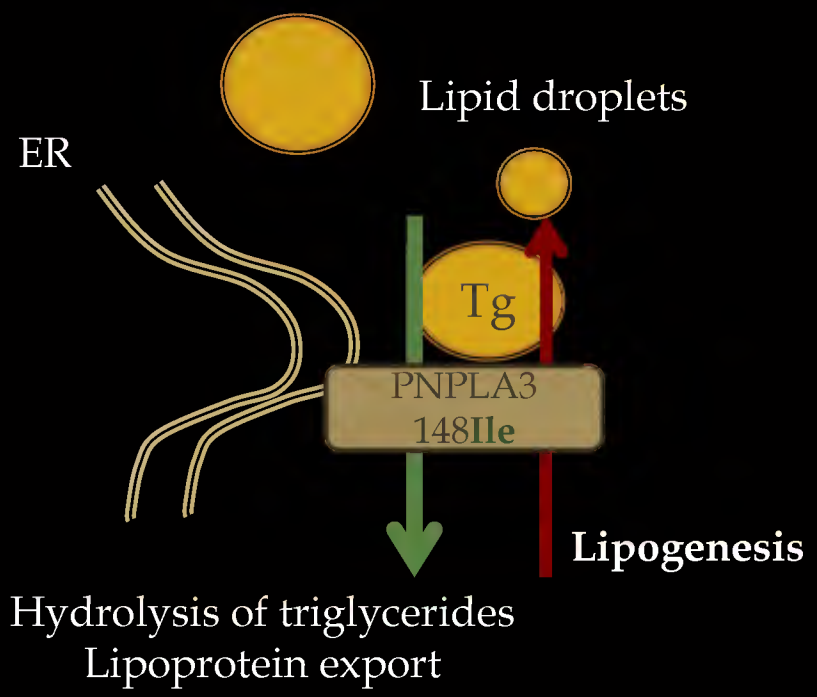
Hepatology. 2010 Oct;52(4):1274-80

I148M Patatin-Like Phospholipase Domain-Containing 3 Gene Variant and Severity of Pediatric Nonalcoholic Fatty Liver Disease

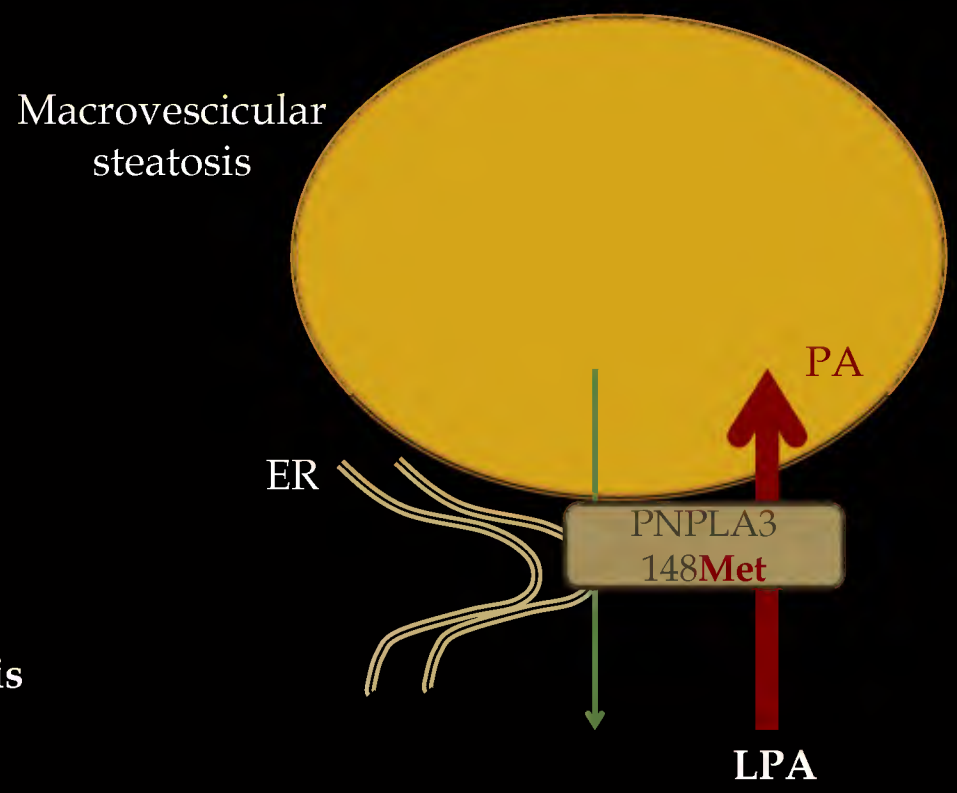
Luca Valenti,[1] Anna Alisi,[2] Enrico Galmozzi,[1] Andrea Bartuli,[3] Benedetta Del Menico,[1] Arianna Alterio,[2] Paola Dongiovanni,[1] Silvia Fargion,[1] and Valerio Nobili[2]

Mechanisms of steatosis associated with I148M PNPLA3

Equilibrium:
Hepatocellular fat content
0-5%

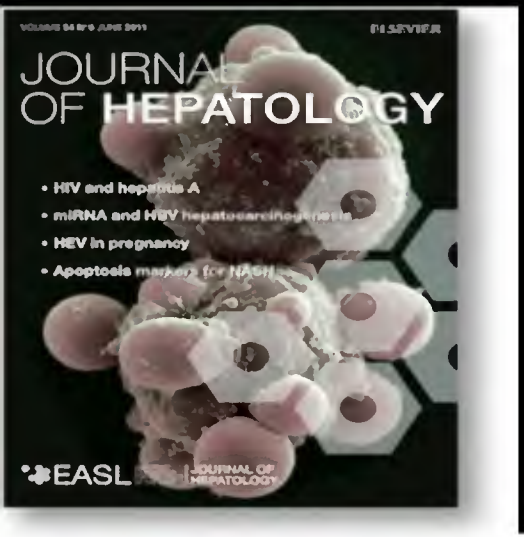


Equilibrium:
Hepatocellular fat content
6% →



He, J Biol Chem 2010
Kumari, Cell Metab 2012
Pirazzi, J Hepatol 2012

Zhong Li, J Clin Invest 2012
Hyysalo, Diabetes 2013



J Hepatol. 2012 Feb;56(2):448-54

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

The *SOD2* C47T polymorphism influences NAFLD fibrosis severity: Evidence from case-control and intra-familial allele association studies

Ahmad Al-Serri[1], Quentin M. Anstee[1,*], Luca Valenti[3], Valerio Nobili[2], Julian B.S. Leathart[1], Paola Dongiovanni[3], Julia Patch[1], Anna Fracanzani[3], Silvia Fargion[3], Christopher P. Day[1], Ann K. Daly[1]

[1]*Institute of Cellular Medicine, Newcastle University Medical School, Newcastle upon Tyne, UK;* [2]*Liver Unit, Bambino Gesù Children's Hospital and Research Institute, Rome, Italy;* [3]*Department of Internal Medicine, UO Medicina Interna IB, University of Milano, Ospedale Policlinico Mangiagalli e Regina Elena Fondazione IRCCS, Milano, Italy*

J Pediatr Gastroenterol Nutr. 2012 May;54(5):588-93

ORIGINAL ARTICLE: HEPATOLOGY AND NUTRITION

LPIN1 rs13412852 Polymorphism in Pediatric Nonalcoholic Fatty Liver Disease

*Luca Valenti, *Benedetta Maria Motta, †Anna Alisi, †Rita Sartorelli, *Giulia Buonaiuto, *Paola Dongiovanni, *Raffaela Rametta, *Serena Pelusi, *Silvia Fargion, and †Valerio Nobili

FLT

Fatty Liver Test

- PNPLA3 (Hepatology 2010)
- LPIN – 1 (JPGN 2012)
- KLF – 6 (Gastroenterology 2008)
- SOD – 2 (J of Hepatology 2012

MARZO 2015

FLT Fatty Liver Test

CE IVD

Real Time PCR Kit

Kit per la genotipizzazione dei principali polimorfismi correlati con Steatosi epatica, NASH e Fibrosi epatica

JPGN
Journal of Pediatric Gastroenterology and Nutrition

J Pediatr Gastroenterol Nutr 2014 May;58(5):632-6

ORIGINAL ARTICLE: HEPATOLOGY AND NUTRITION

A 4-Polymorphism Risk Score Predicts Steatohepatitis in Children With Nonalcoholic Fatty Liver Disease

*Valerio Nobili, †Benedetta Donati, *Nadia Panera, †Apirom Vongsakulyanon, *Anna Alisi, ‡Bruno Dallapiccola, and †Luca Valenti

TABLE 3. Independent genetic predictors of NASH evaluated by a multivariate logistic model in 152 Italian pediatric patients with NAFLD

	OR	95% CI
PNPLA3 148MM	52.6	9.9–984
SOD2 49VV	0.5	0.2–1.2
LPIN1 TT	0.3	0.02–2.1
KLF6 AG/AA	1.8	0.6–5.1

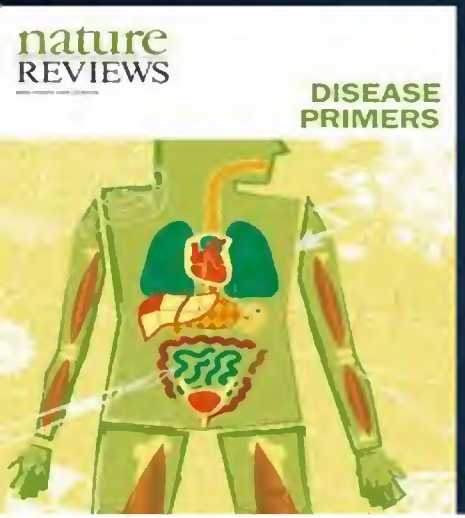
TABLE 5. Independent clinical predictors of NASH evaluated by a multivariate logistic model in 152 Italian pediatric patients with NAFLD

	OR	95% CI
Age, y	0.9	0.8–1.0
Diastolic BP, mmHg	1.04	1.01–1.05
AST, IU/mL	1.01	1.00–1.02

Table 4 Independent predictors of ultrasonographic severity of steatosis in 200 overweight adolescents with suspected NAFLD

	Estimate	SE	p value
Age (years)	+0.21	0.08	1.7×10^{-2}
WC centile	+0.15	0.06	1.6×10^{-2}
I148M alleles	+4.32	0.50	2.0×10^{-18}
Physical exercise hours	−1.78	0.61	3.4×10^{-3}
I148M × sodas	+0.76	0.35	2.3×10^{-2}
I148M × vegetables	−1.31	0.62	3.4×10^{-2}

WC waist circumference



2 | 2015 | VOLUME 1

Published online 17 December 2015

PRIMER

Nonalcoholic fatty liver disease

Elizabeth M. Brunt[1], Vincent W.-S. Wong[2], Valerio Nobili[3], Christopher P. Day[4], Silvia Sookoian[5], Jacquelyn J. Maher[6], Elisabetta Bugianesi[7], Claude B. Sirlin[8], Brent A. Neuschwander-Tetri[9] and Mary E. Rinella[10]

Metabolic syndrome
- Diabetes
- Obesity
- Dyslipidaemia
- Arterial hypertension

SNPs
- *PNPLA3*
- *KLF6*
- *TM6SF2*

- Gender
- Ethnicity
- Family history

NAFLD

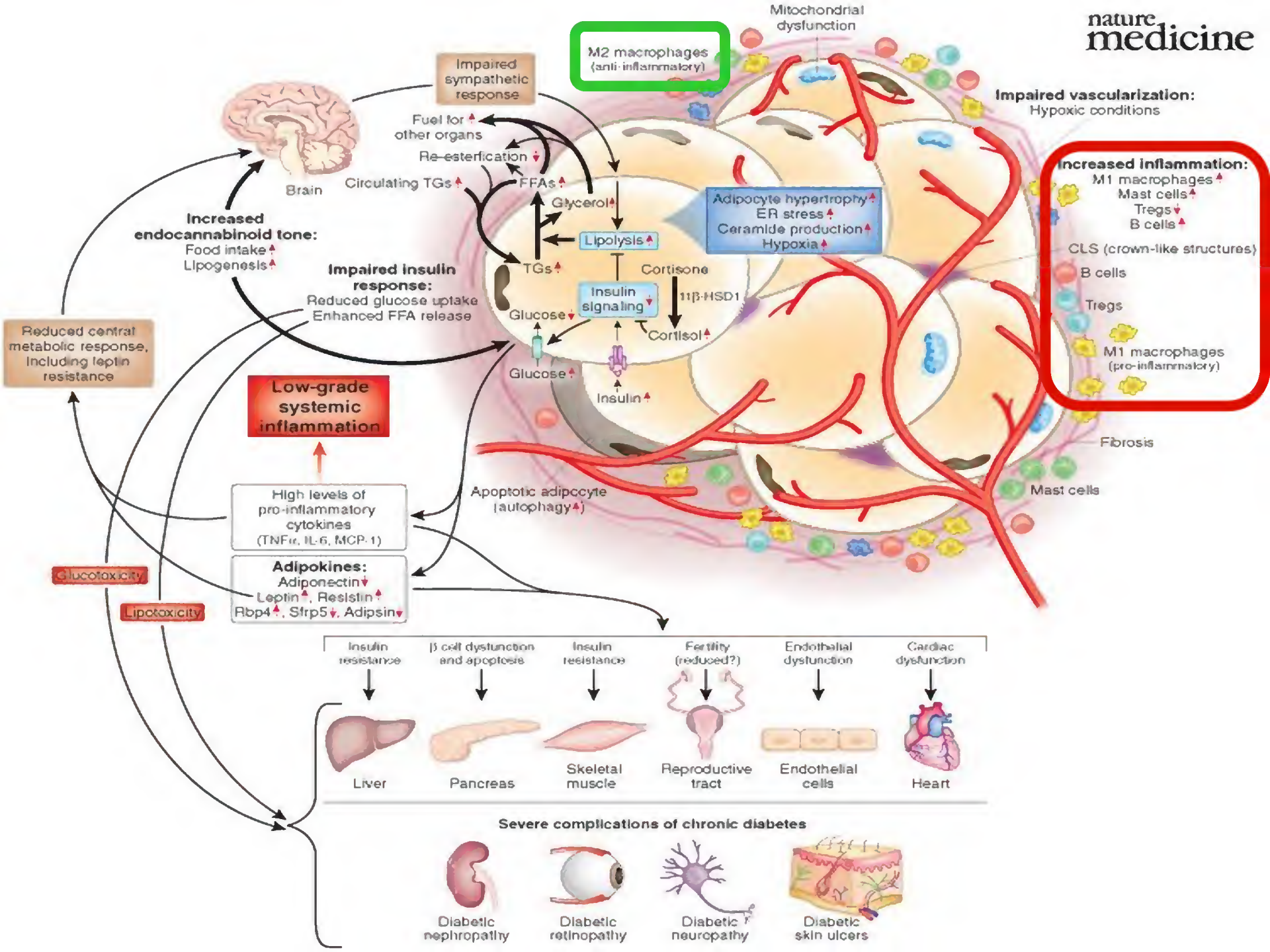
NAFL NASH **Cirrhosis HCC**

- Intrauterine environment
- Early infant feeding

- Sedentary lifestyle

Diet
- High saturated FA intake
- High cholesterol intake
- High fructose intake
- High carbohydrate intake
- Low polyunsaturated FA intake
- Low antioxidant, zinc and fibre intake

nature medicine



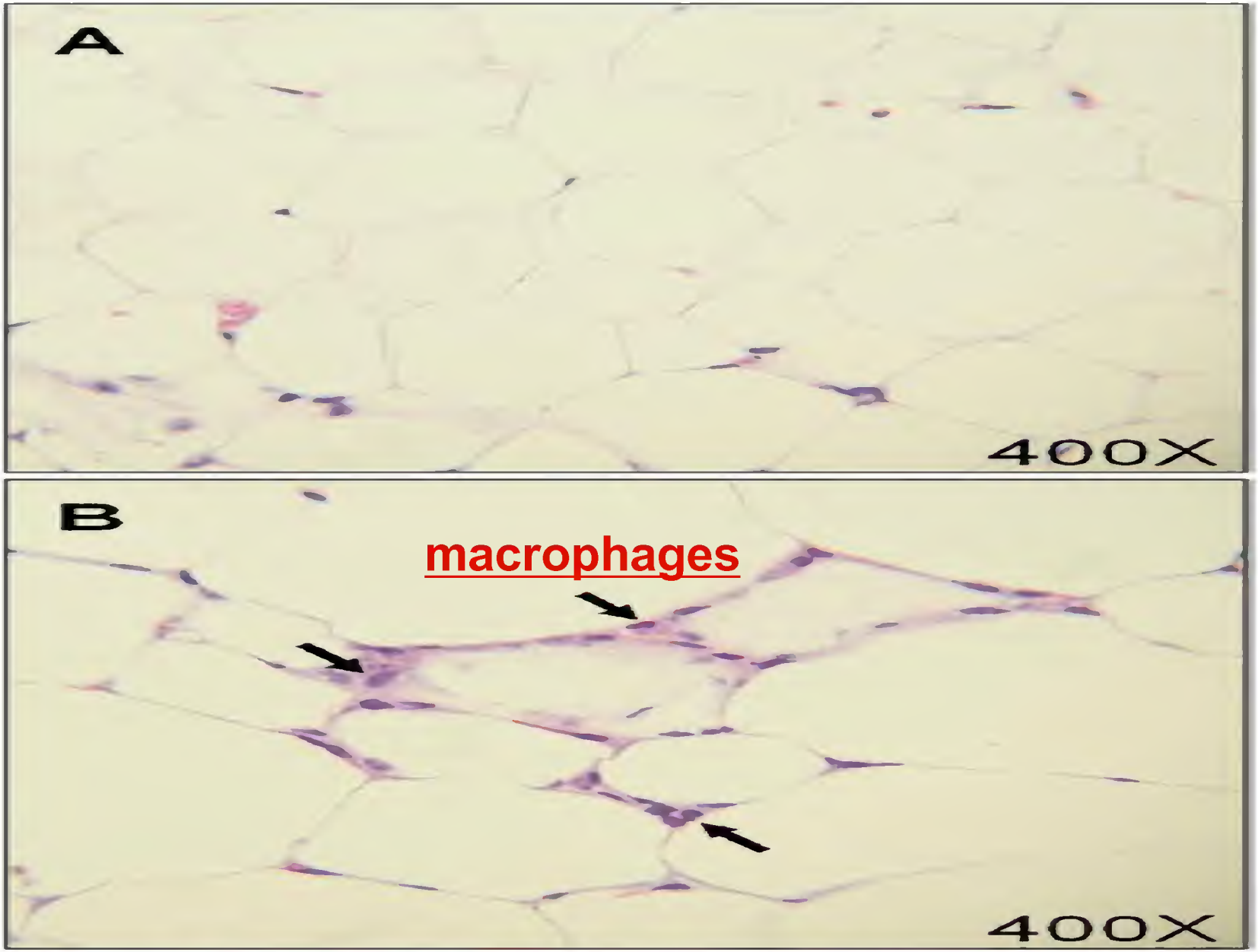
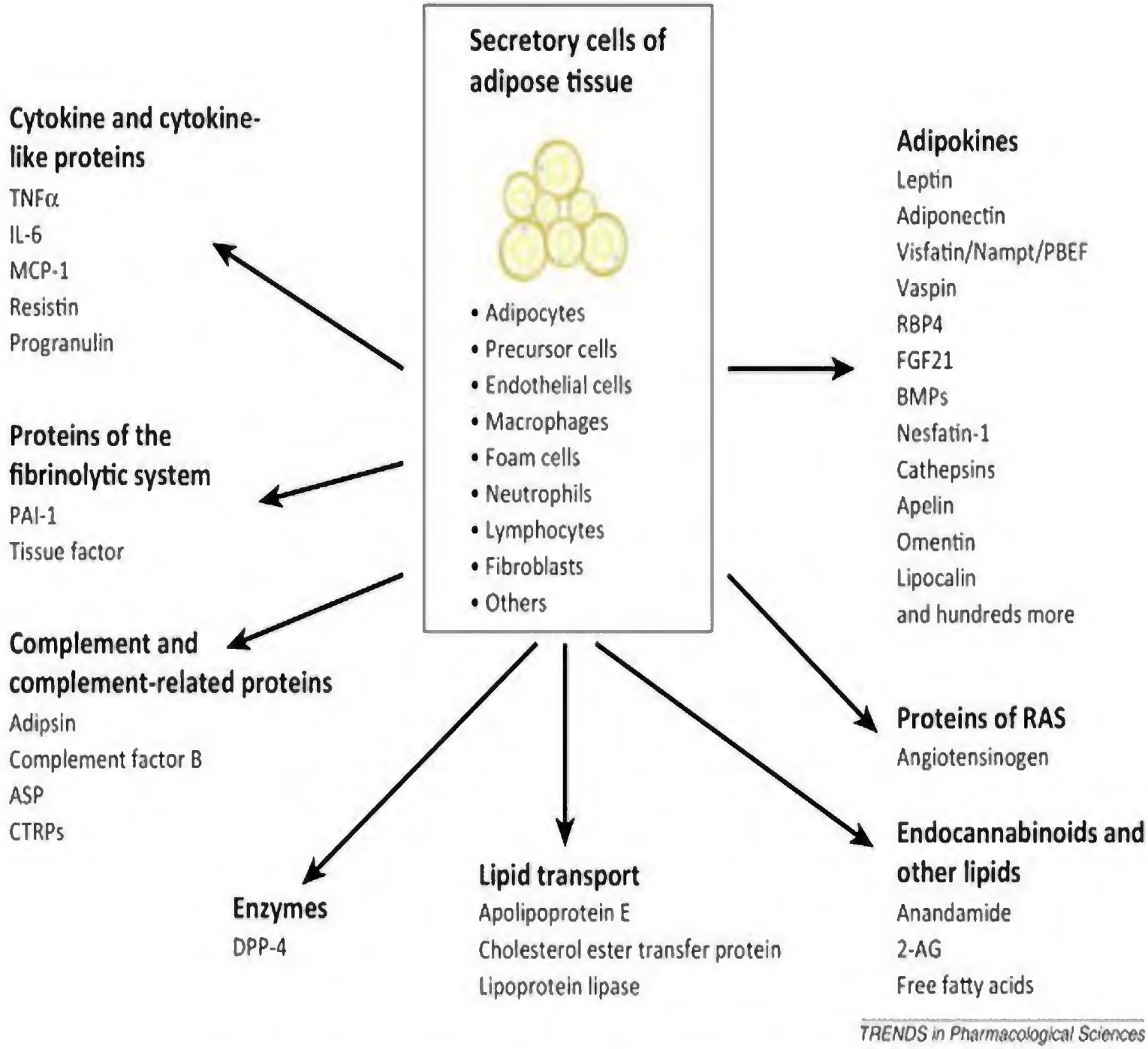
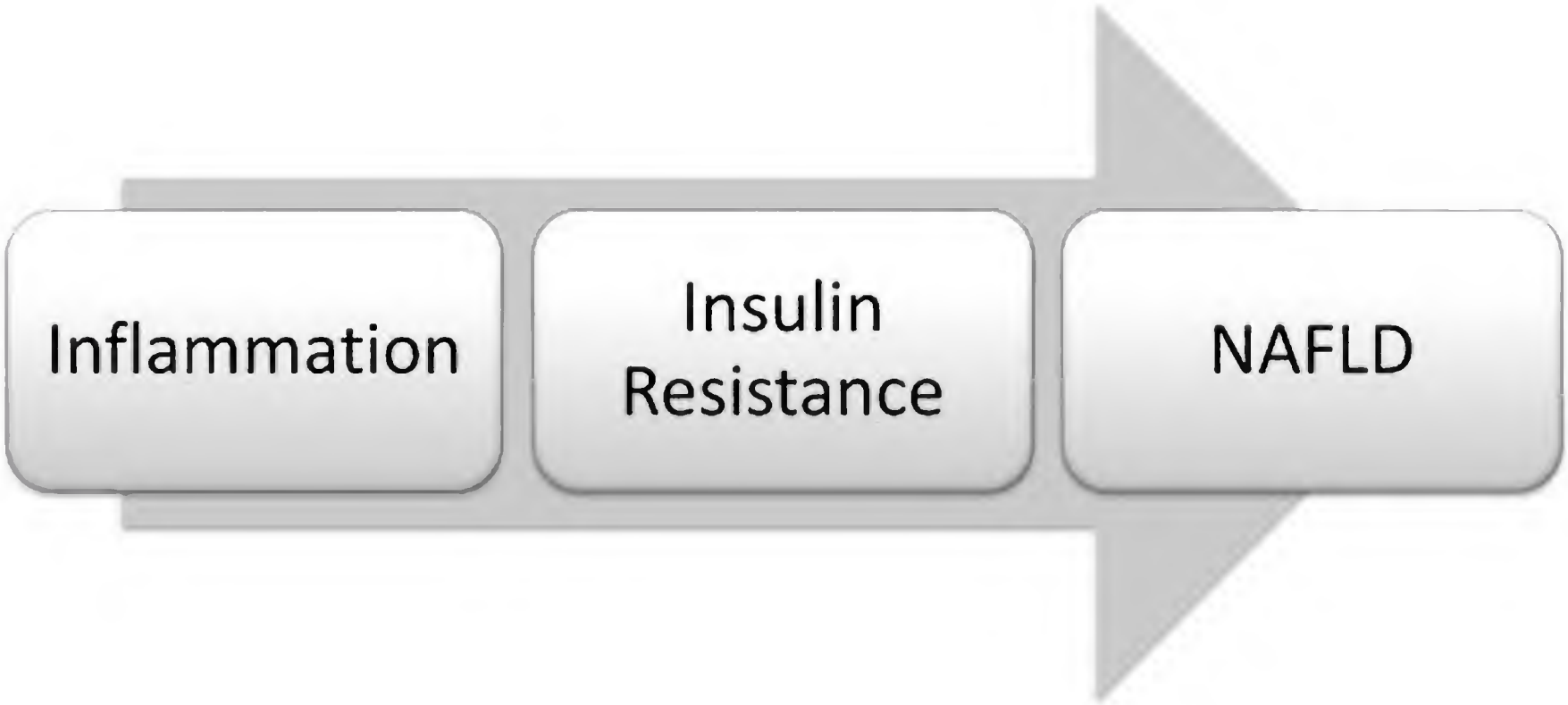
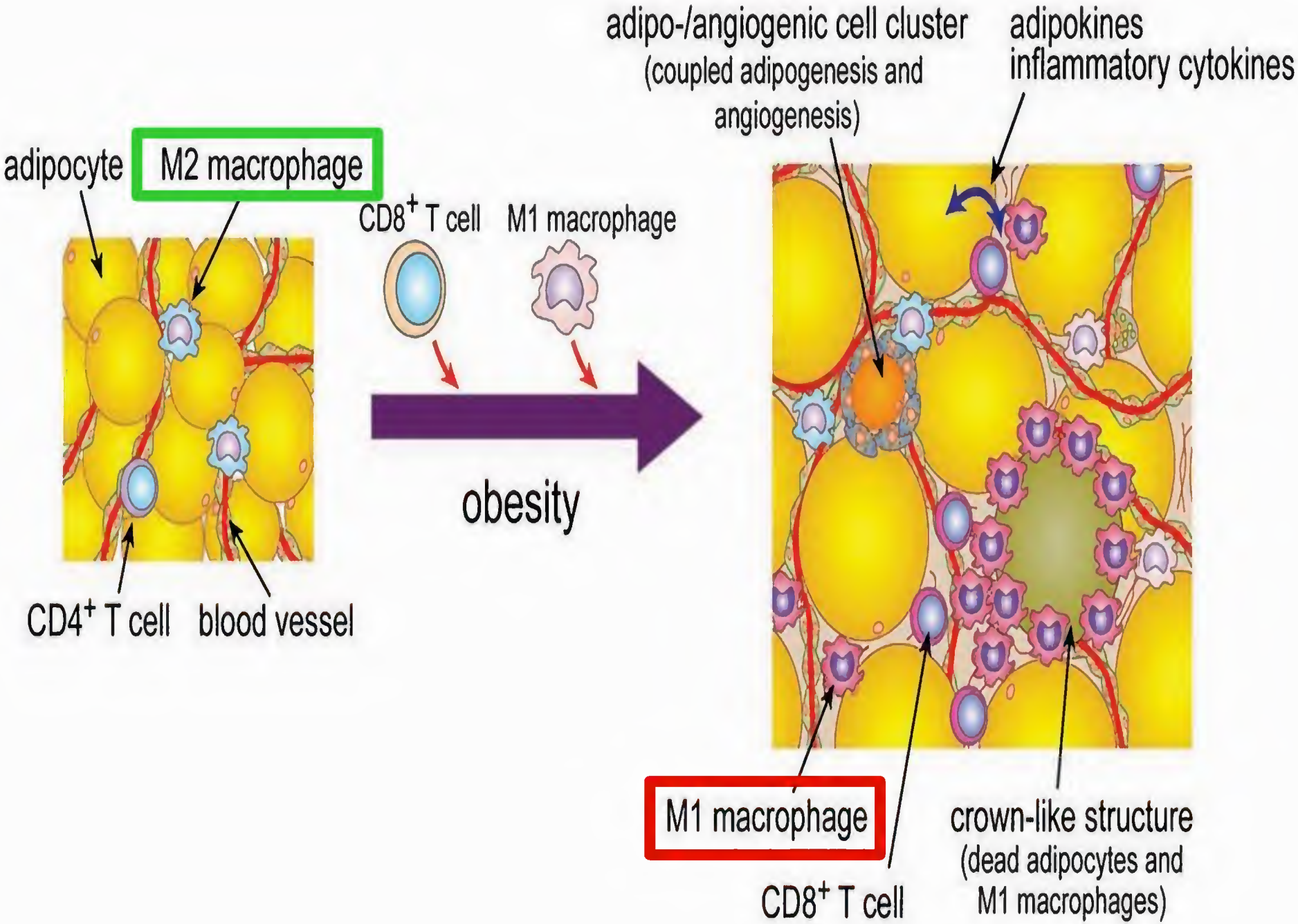


Figure 2. Adipose tissue inflammation. H&E-stained sections are shown from the epididymal adipose tissue of 14-week-old (*A*) wt C57Bl/6 mice and (*B*) obese *ob/ob* mice. The increase in fat cell size seen in *ob/ob* mice is accompanied by the increased infiltration of immune cells including macrophages (*arrows*).


Secretory cells of adipose tissue
• Adipocytes
• Precursor cells
• Endothelial cells
• Macrophages
• Foam cells
• Neutrophils
• Lymphocytes
• Fibroblasts
• Others
Cytokine and cytokine-like proteins
TNFα
IL-6
MCP-1
Resistin
Progranulin
Proteins of the fibrinolytic system
PAI-1
Tissue factor
Complement and complement-related proteins
Adipsin
Complement factor B
ASP
CTRPs
Enzymes
DPP-4
Lipid transport
Apolipoprotein E
Cholesterol ester transfer protein
Lipoprotein lipase
Adipokines
Leptin
Adiponectin
Visfatin/Nampt/PBEF
Vaspin
RBP4
FGF21
BMPs
Nesfatin-1
Cathepsins
Apelin
Omentin
Lipocalin
and hundreds more
Proteins of RAS
Angiotensinogen
Endocannabinoids and other lipids
Anandamide
2-AG
Free fatty acids
TRENDS in Pharmacological Sciences

Adipocyte is an Endocrine Organ




adipocyte
M2 macrophage
CD4+ T cell
blood vessel
CD8+ T cell
M1 macrophage
obesity
adipo-/angiogenic cell cluster
(coupled adipogenesis and angiogenesis)
adipokines
inflammatory cytokines
M1 macrophage
CD8+ T cell
crown-like structure
(dead adipocytes and M1 macrophages)

On line March 2012

INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 00: 0-00, 0000

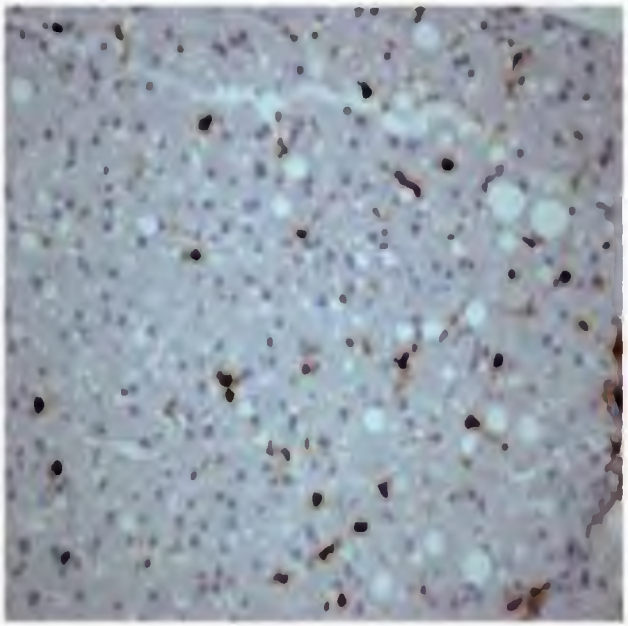
Markers of activated inflammatory cells correlate with severity of liver damage in children with nonalcoholic fatty liver disease

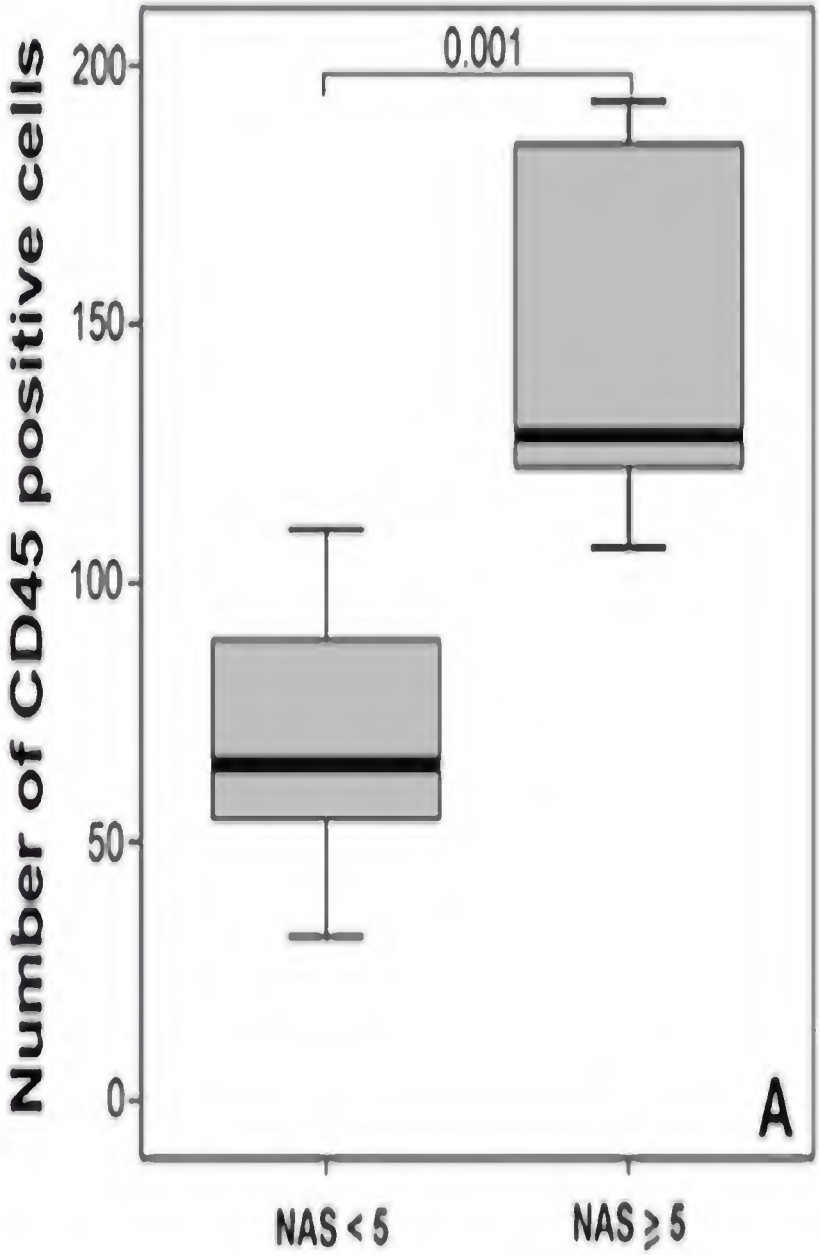
RITA De VITO[1*], ANNA ALISI[2*], ANDREA MASOTTI[3], SARA CECCARELLI[2], NADIA PANERA[2], ARIANNA CITTI[1], MICHELE SALATA[4], LUCA VALENTI[5], ARIEL E. FELDSTEIN[6,7] and VALERIO NOBILI[2,6]

[1]Unit of Pathology, [2]Unit of Liver Research, [3]Gene Expression-Microarrays Laboratory, [4]Department of Pediatrics of 'Bambino Gesù' Children's Hospital, IRCCS, Rome; [5]Department of Internal Medicine, Università degli Studi, Ospedale Maggiore Policlinico 'Ca' Granda' IRCCS, Milan, Italy; Departments of [6]Pediatric Gastroenterology and [7]Cell Biology, Cleveland Clinic, Cleveland, OH, USA

CD45

NAS < 5




Number of CD45 positive cells
200
150
100
50
0
0.001
A
NAS < 5
NAS ≥ 5

Original Article
PEDIATRIC OBESITY

Obesity

Macrophages and Fibrosis in Adipose Tissue are Linked to Liver Damage and Metabolic Risk in Obese Children

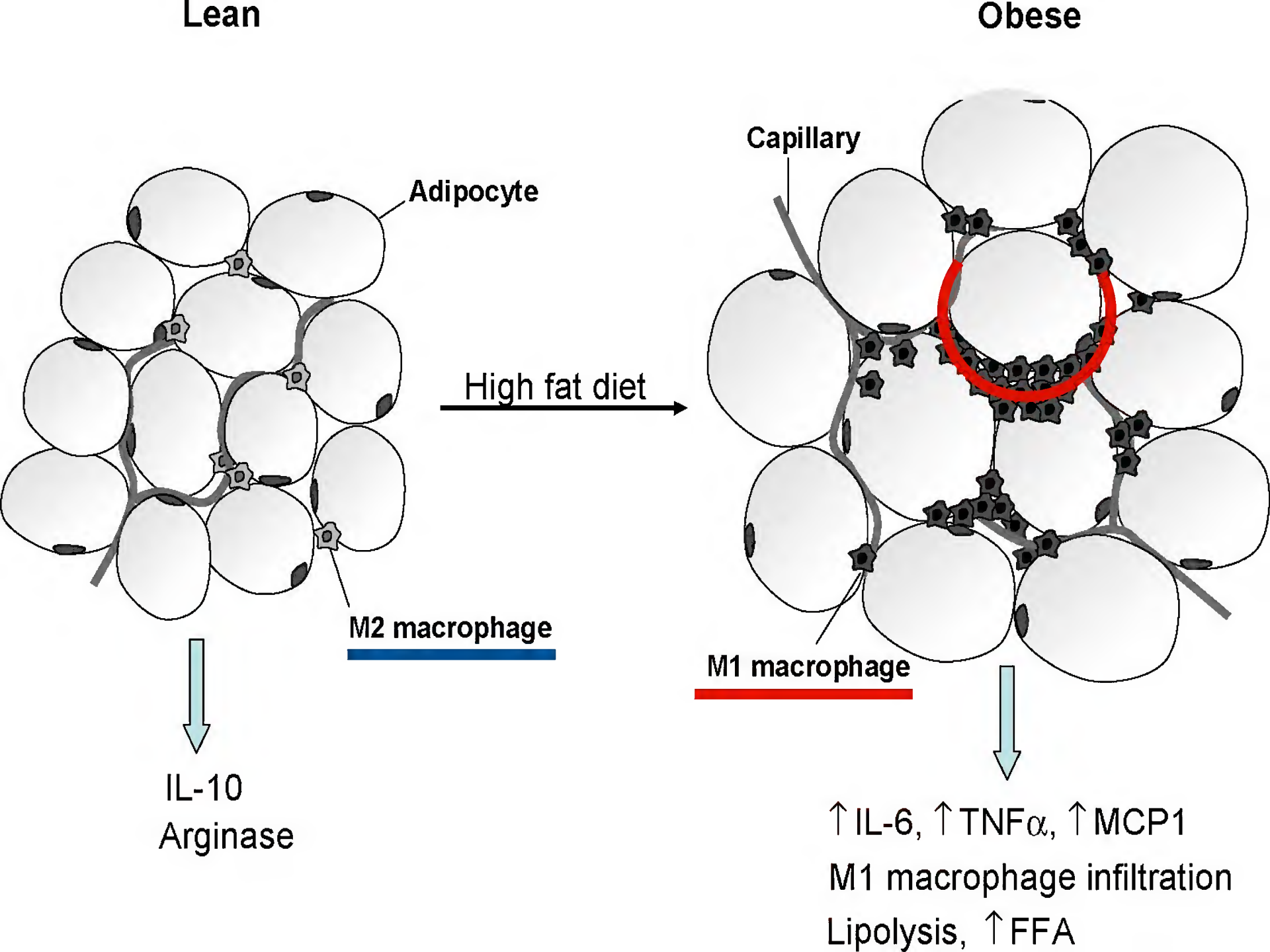
Ryan W. Walker[1], Hooman Allayee[2], Alessandro Inserra[3], Rodolfo Fruhwirth[4], Anna Alisi[5], Rita Devito[6], Magalie E. Carey[2], Frank Sinatra[7], Michael I. Goran[2] and Valerio Nobili[5,8]

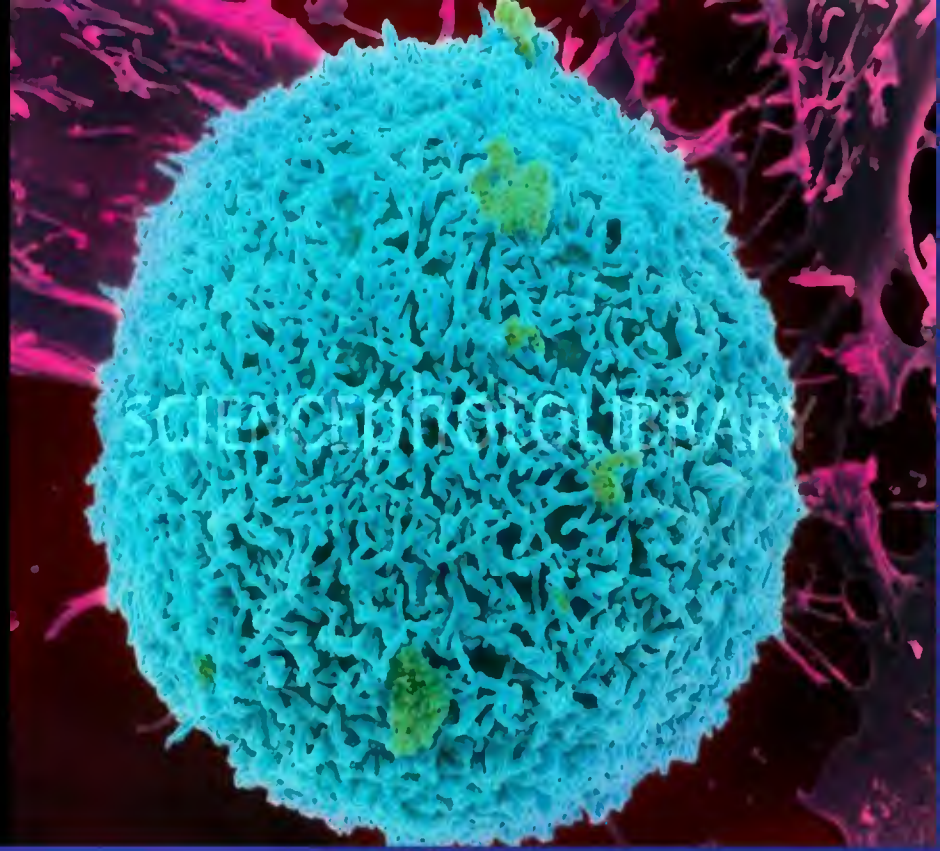
[1] Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine, Mount Sinai, New York, USA [2] Preventive Medicine, University of Southern California, Los Angeles, USA [3] General Surgery, Bambino Gesu Children Hospital, Rome, Italy [4] Interventional Radiology, Bambino Gesu Children Hospital, Rome, Italy [5] Liver Research Laboratory, Bambino Gesu Children Hospital, Rome, Italy. Correspondence: Valerio Nobili (valerio.nobili@opbg.net and nobili66@yahoo.it) [6] Pathology Department, Bambino Gesu Children Hospital, Rome, Italy [7] Department of Pediatrics, University of Southern California, Los Angeles, USA [8] Hepatometabolic Unit, Bambino Gesu Children Hospital, Rome, Italy

Funding agency: Portions of this study were supported by The Ruth L. Kirschstein National Research Service Award NIH grant number 2T32ES013678-06 (analysis, interpretation of the data, preparation and review of the manuscript).

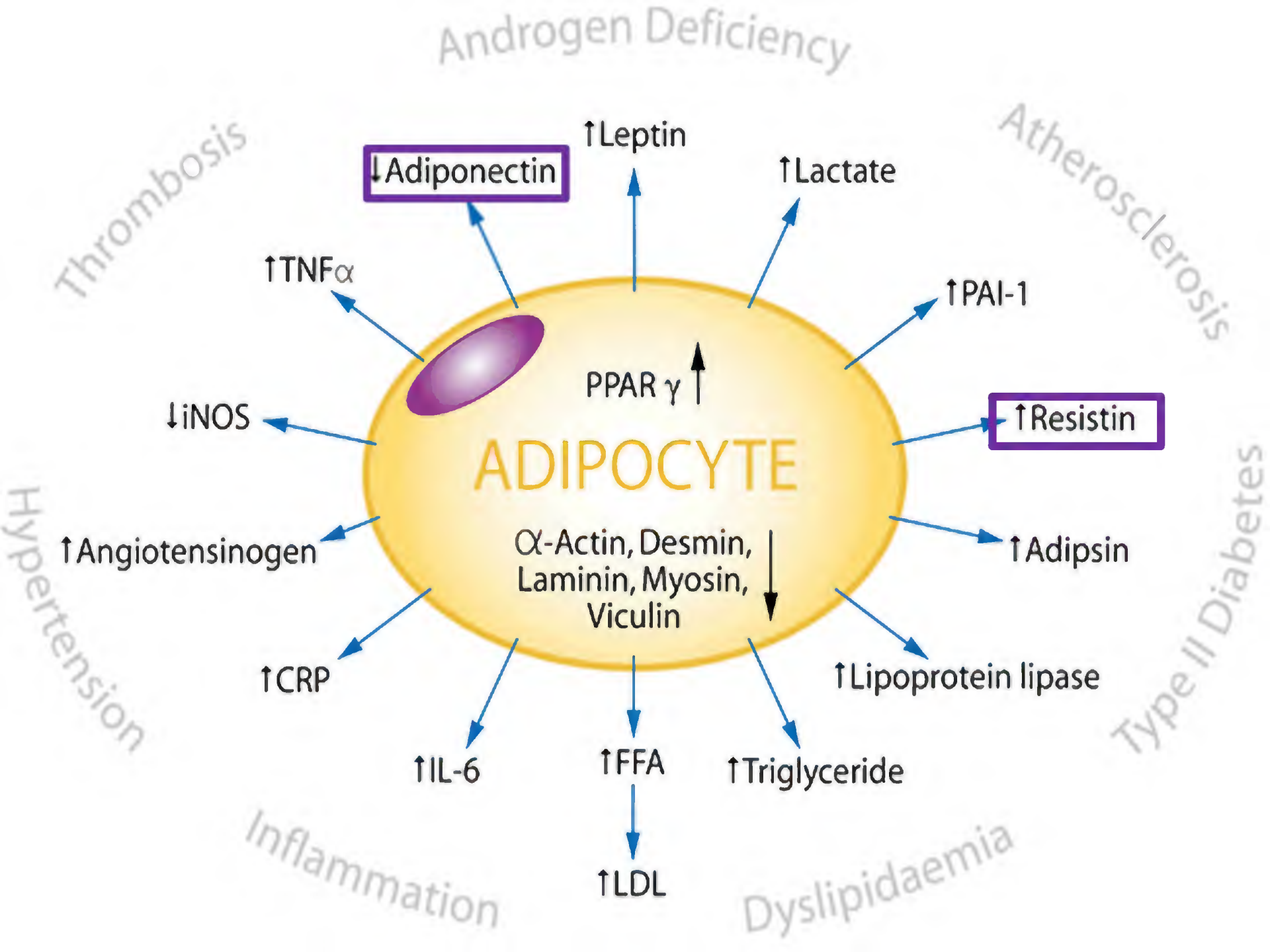
Disclosure: The authors declare no conflicts of interest.

Received: 20 October 2013; **Accepted:** 13 February 2014; **Published online 25 February 2014. doi:10.1002/oby.20730**


Lean
Obese
Adipocyte
Capillary
High fat diet
M2 macrophage
M1 macrophage
IL-10
Arginase
↑IL-6, ↑TNFα, ↑MCP1
M1 macrophage infiltration
Lipolysis, ↑FFA



ADIPOCYTE HEPATOCYTE

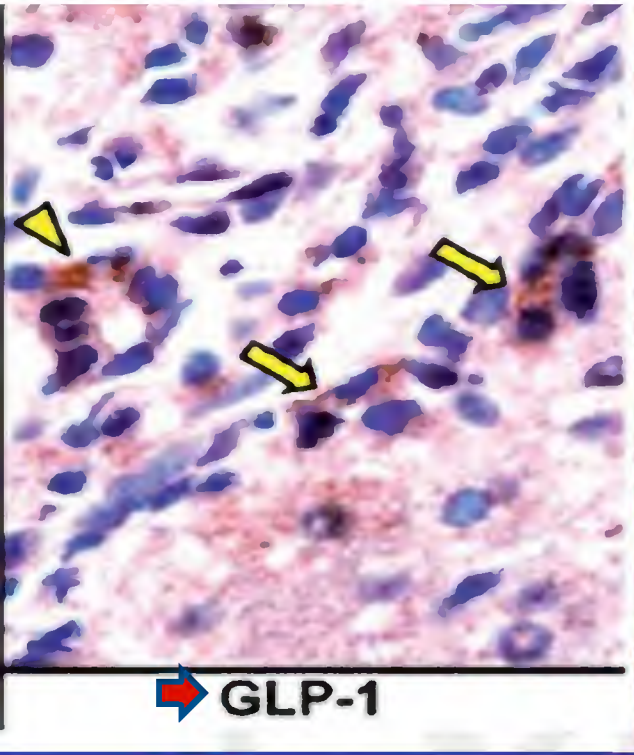

Androgen Deficiency
Atherosclerosis
Type II Diabetes
Dyslipidaemia
Inflammation
Hypertension
Thrombosis
↓Adiponectin
↑Leptin
↑Lactate
↑TNFα
↑PAI-1
PPAR γ ↑
↓iNOS
↑Resistin
ADIPOCYTE
↑Angiotensinogen
α-Actin, Desmin,
Laminin, Myosin,
Viculin ↓
↑Adipsin
↑CRP
↑Lipoprotein lipase
↑IL-6
↑FFA
↑Triglyceride
↑LDL

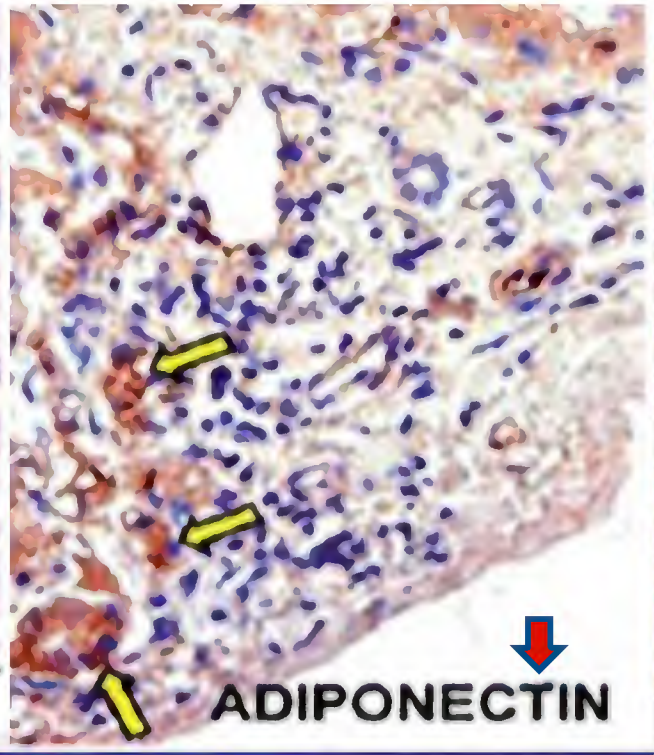
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
December 2012
AASLD

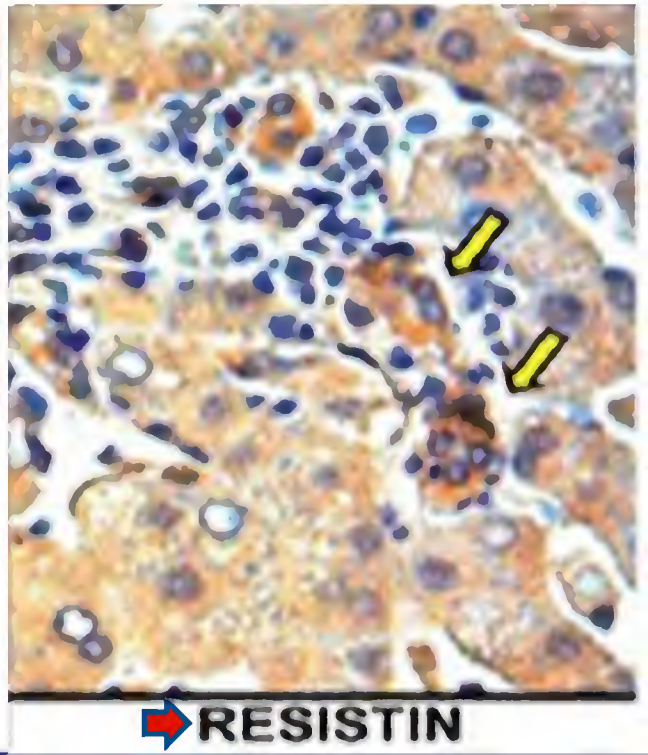
STEATOHEPATITIS/METABOLIC LIVER DISEASE

Hepatic Progenitor Cells Activation, Fibrosis, and Adipokines Production in Pediatric Nonalcoholic Fatty Liver Disease

Valerio Nobili,[1]* Guido Carpino,[2]* Anna Alisi,[1] Antonio Franchitto,[3,4] Gianfranco Alpini,[5] Rita De Vito,[6] Paolo Onori,[7] Domenico Alvaro,[4,8] and Eugenio Gaudio[3]







HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

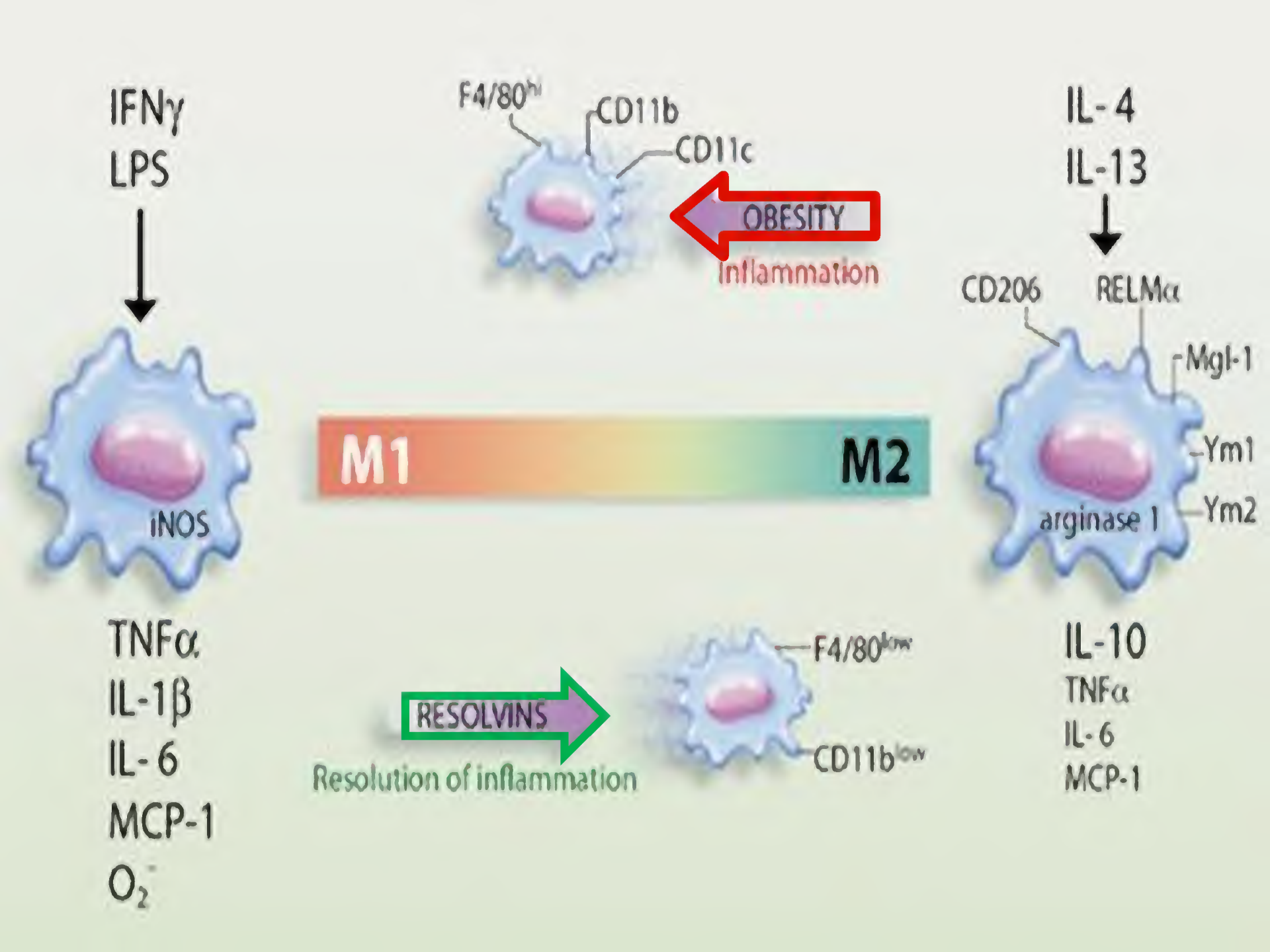
EDITORIALS

Hepatic Progenitor Cells: Another Piece in the Nonalcoholic Fatty Liver Disease Puzzle

DAWN M. TORRES, STEPHEN A. HARRISON

Hepatology Dec 2012

Nobili et al. open new perspectives on the pathophysiology of NAFLD, proposing a novel paracrine mechanisms for the liver's cells and suggest several therapeutic hypotheses to be tested.


IFNγ
LPS
iNOS
TNFα
IL-1β
IL-6
MCP-1
O_2^-
F4/80hi
CD11b
CD11c
OBESITY
Inflammation
M1
M2
IL-4
IL-13
CD206
RELMα
Mgl-1
Ym1
Ym2
arginase 1
IL-10
TNFα
IL-6
MCP-1
RESOLVINS
Resolution of inflammation
F4/80low
CD11blow

PLOS | ONE

Published: June 16, 2016

RESEARCH ARTICLE

Macrophage Activation in Pediatric Nonalcoholic Fatty Liver Disease (NAFLD) Correlates with Hepatic Progenitor Cell Response via Wnt3a Pathway

Guido Carpino[1], Valerio Nobili[2], Anastasia Renzi[3], Cristiano De Stefanis[2], Laura Stronati[4], Antonio Franchitto[3], Anna Alisi[2], Paolo Onori[3], Rita De Vito[5], Gianfranco Alpini[6], Eugenio Gaudio[3]*

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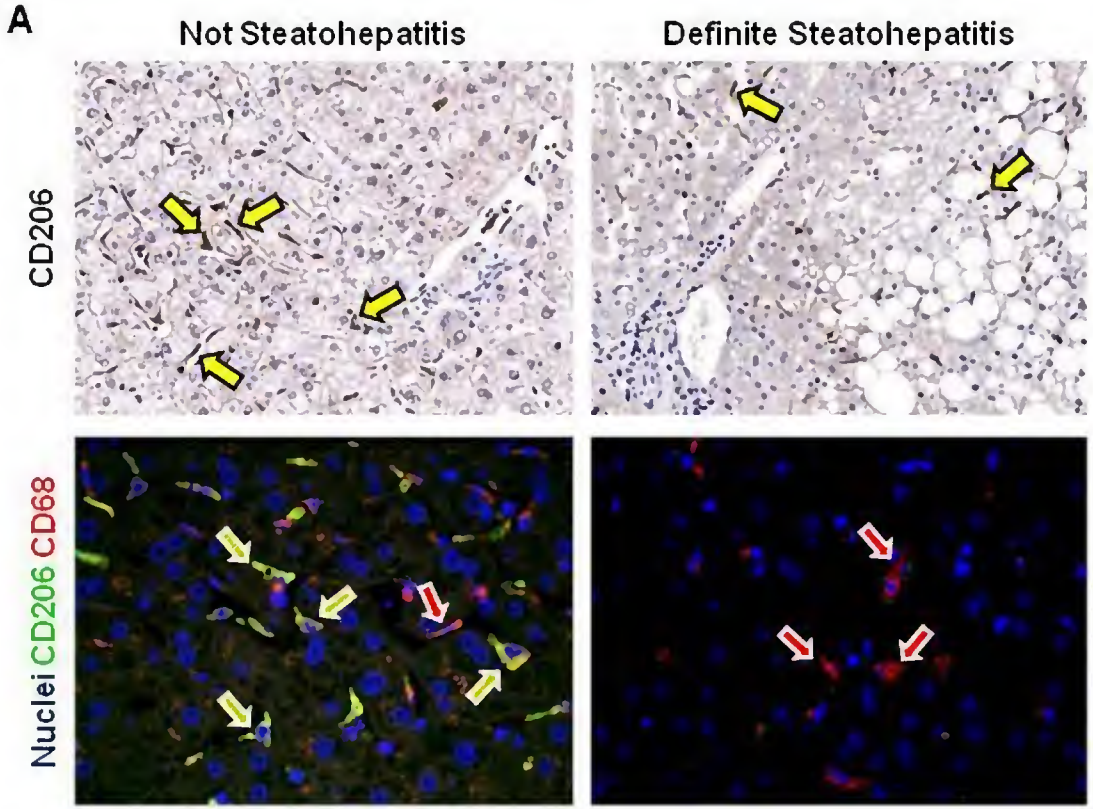
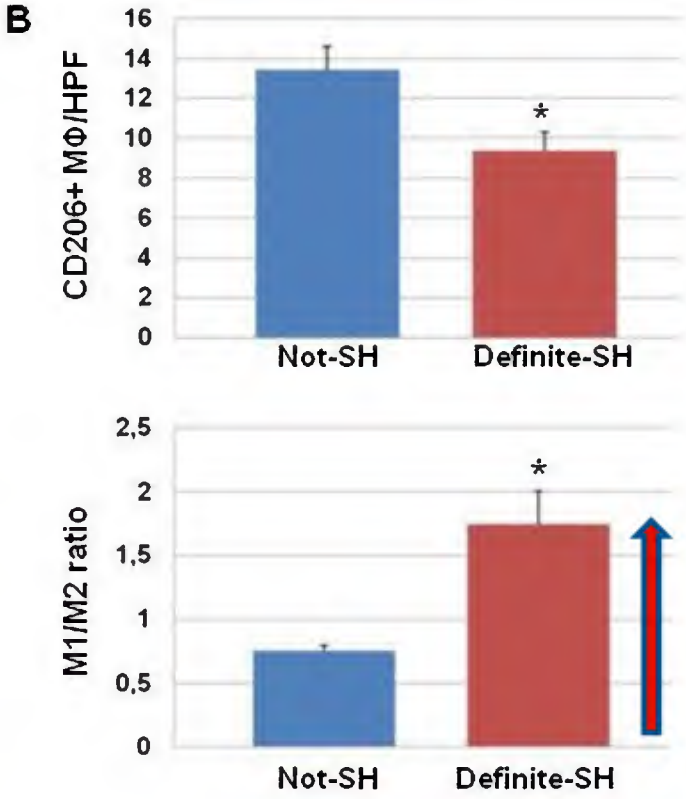
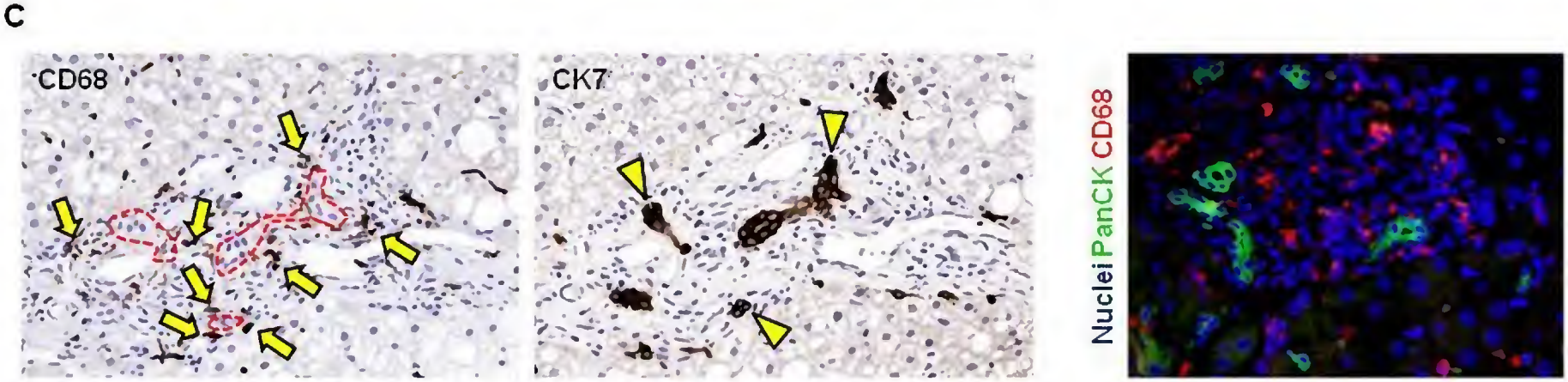
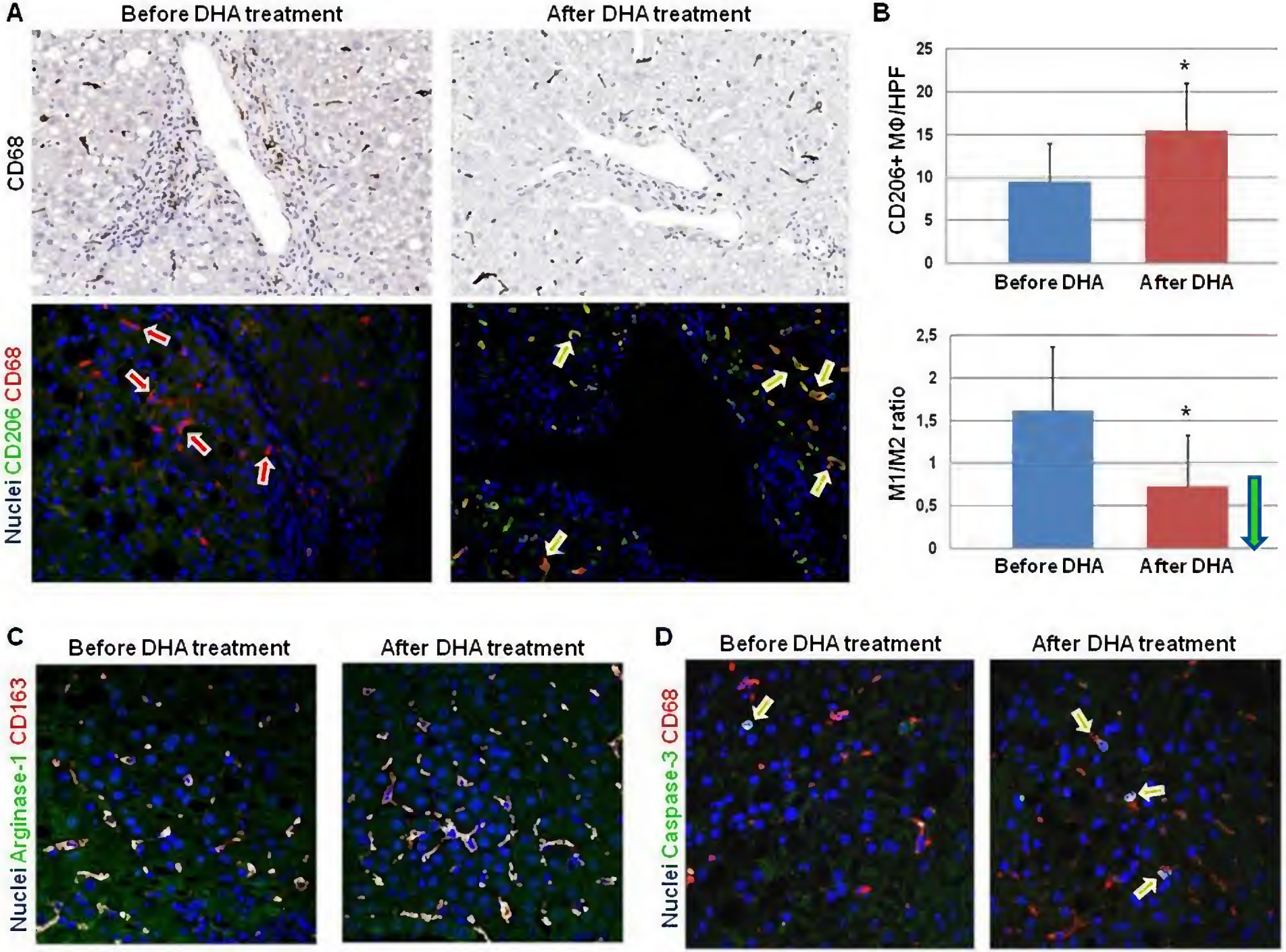

A
Not Steatohepatitis
Definite Steatohepatitis
CD206
Nuclei CD206 CD68


B
CD206+ MΦ/HPF
16
14
12
10
8
6
4
2
0
*
Not-SH
Definite-SH
M1/M2 ratio
2,5
2
1,5
1
0,5
0
*
Not-SH
Definite-SH


C
CD68
CK7
Nuclei PanCK CD68


A
Before DHA treatment
After DHA treatment
CD68
Nuclei CD206 CD68
B
CD206+ MΦ/HPF
25
20
15
10
5
0
*
Before DHA
After DHA
M1/M2 ratio
2,5
2
1,5
1
0,5
0
*
Before DHA
After DHA
C
Before DHA treatment
After DHA treatment
Nuclei Arginase-1 CD163
D
Before DHA treatment
After DHA treatment
Nuclei Caspase-3 CD68

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Volume 2017, Article ID 8162421, 15 pages
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Review Article

The Role of Tissue Macrophage-Mediated Inflammation on NAFLD Pathogenesis and Its Clinical Implications

Anna Alisi,[1] Guido Carpino,[2] Felipe L. Oliveira,[3] Nadia Panera,[1] Valerio Nobili,[4] and Eugenio Gaudio[5]

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Correspondence should be addressed to Valerio Nobili; vnobili66@gmail.com

Received 26 September 2016; Revised 22 November 2016; Accepted 4 December 2016; Published 1 January 2017

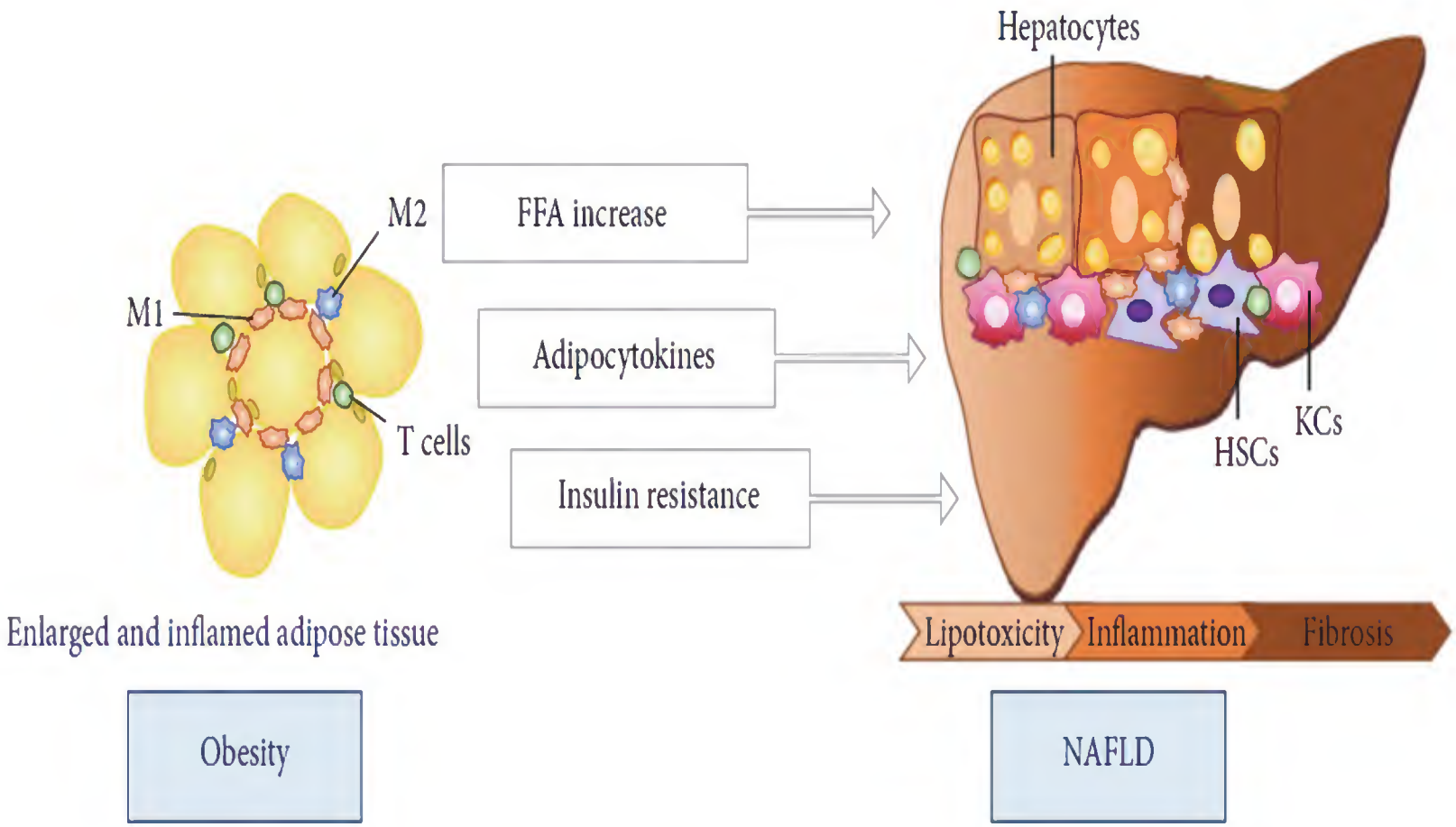


FIGURE 1: The crosstalk between adipose tissue macrophages and the liver cells in NAFLD.

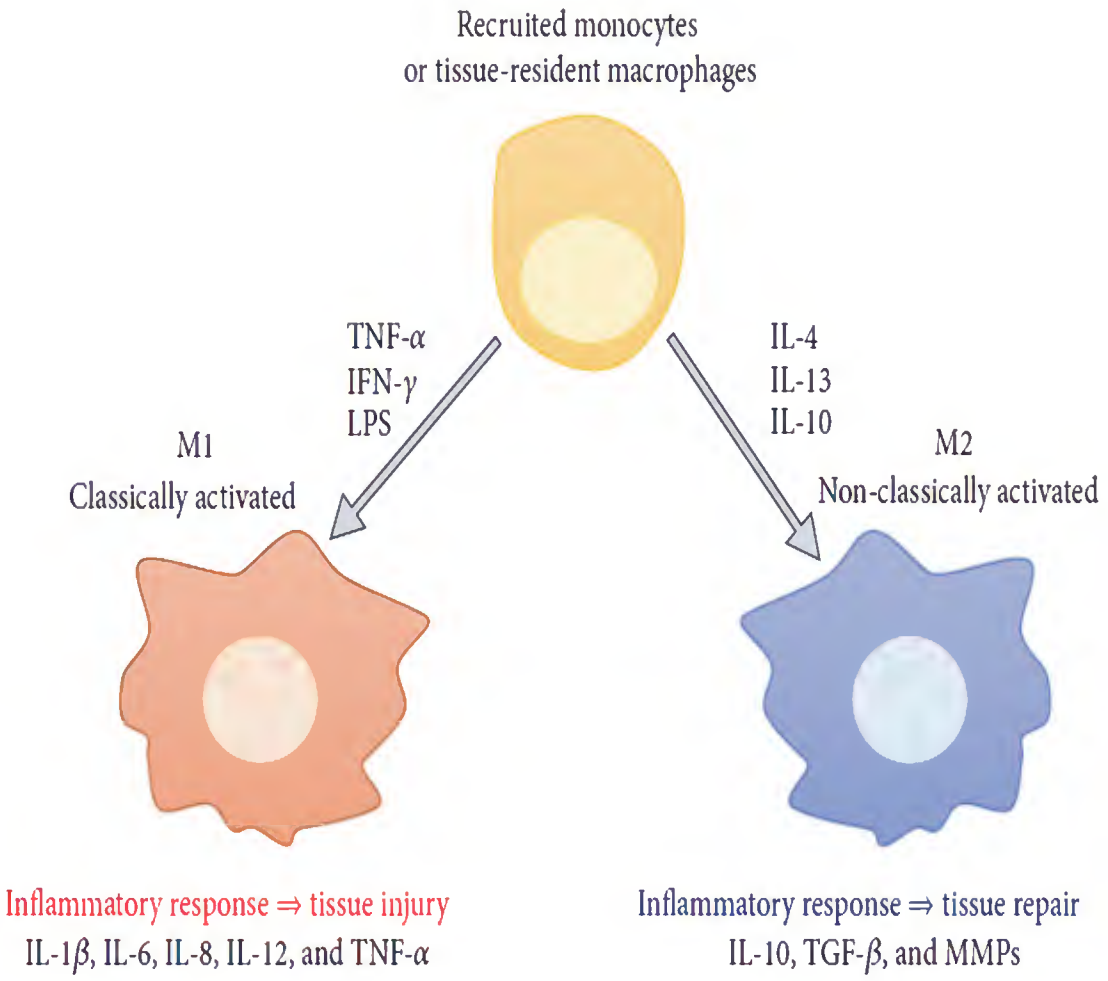


FIGURE 2: Schematic summary of macrophage polarization. Monocytes from peripheral blood differentiate in response to mediators in tissues, giving rise to different subsets: classically (M1) or alternatively (M2) activated macrophages that, respectively, lead to "bad" or "good" proinflammatory response.

JOURNAL OF HEPATOLOGY
Official Journal of the European Association for the Study of the Liver

J Hepatol. 2012 Dec 10. pii: S0168-8278(12)00922-1

Review

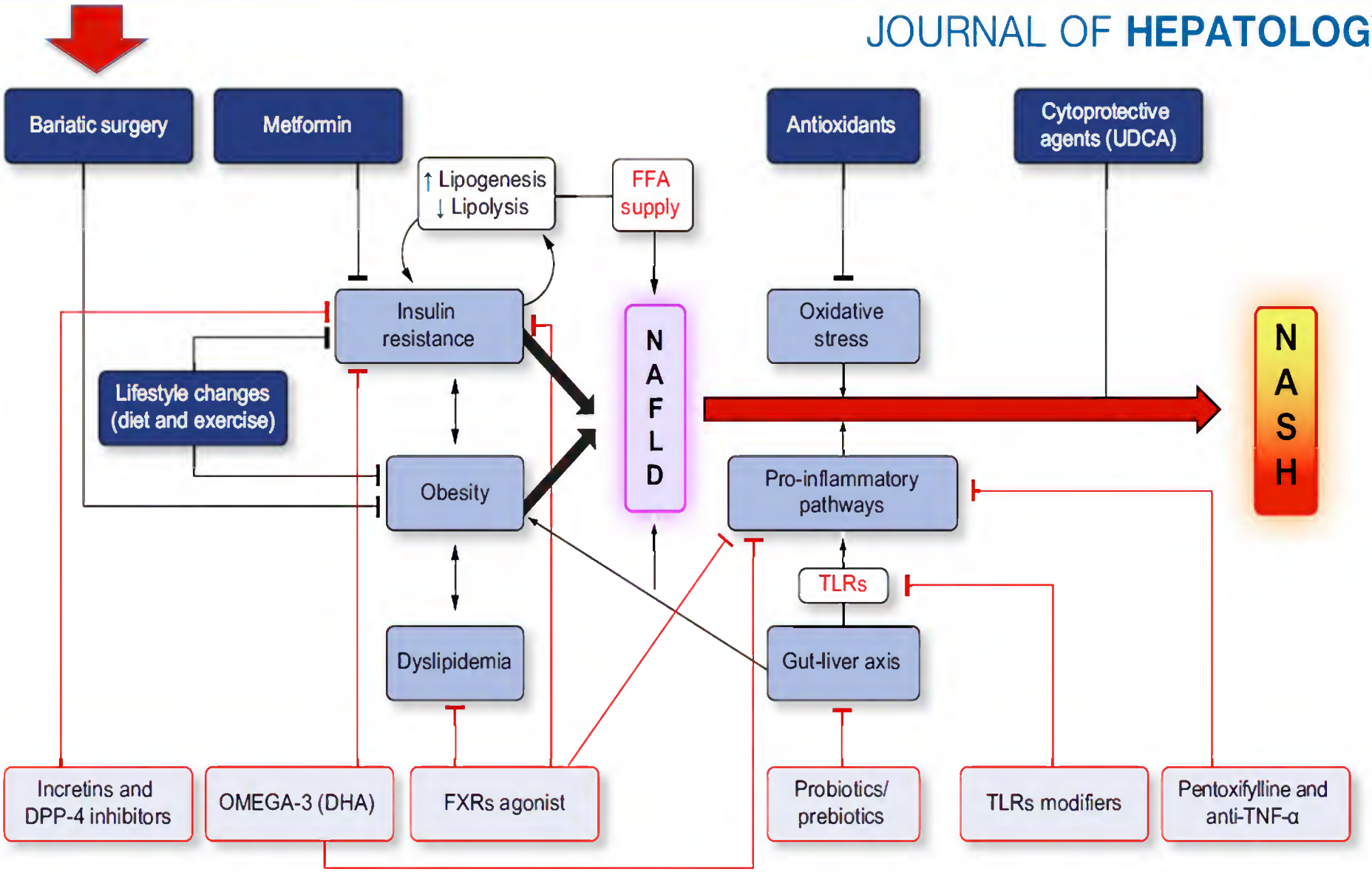
EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

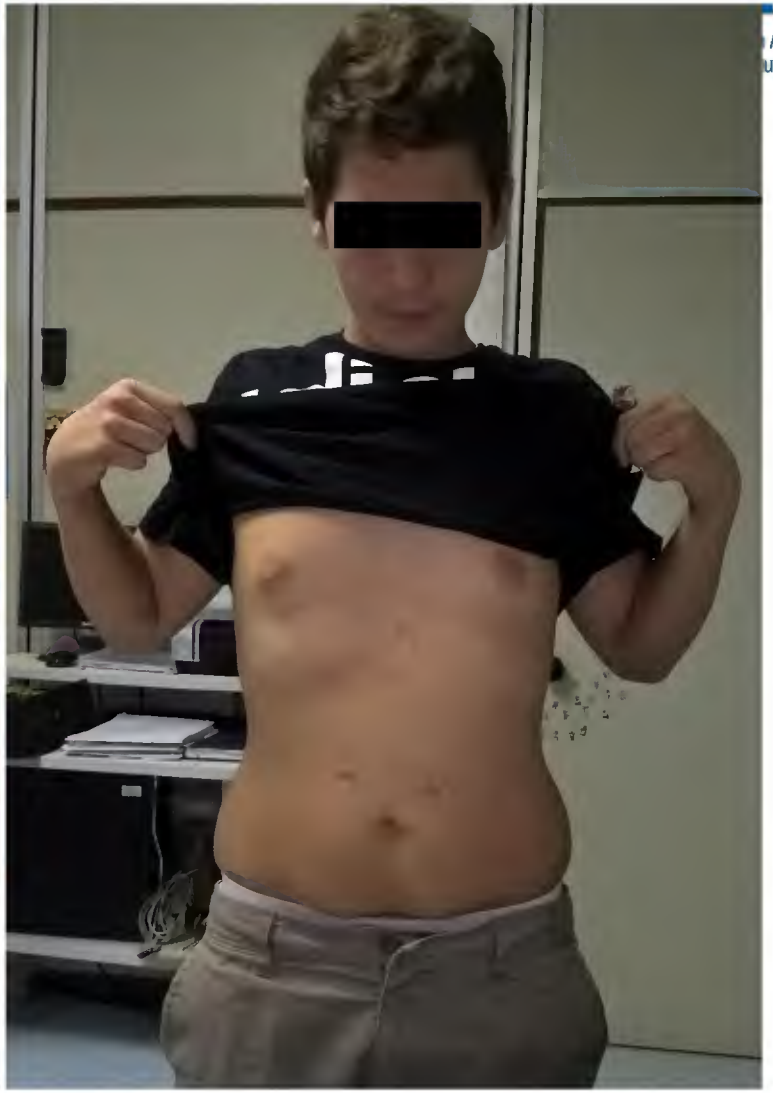
A 360-degree overview of paediatric NAFLD: Recent insights

Valerio Nobili[1,*], Gianluca Svegliati-Baroni[2], Anna Alisi[1], Luca Miele[3], Luca Valenti[4], Pietro Vajro[5]

[1]*Hepato-metabolic Disease Unit and Liver Research Unit, "Bambino Gesù" Children's Hospital, IRCCS, P.le S. Onofrio 4, 00165 Rome, Italy;* [2]*Department of Gastroenterology, Polytechnic University of Marche, Ancona, Italy;* [3]*Department of Medical Sciences, Policlinico Gemelli Hospital, Catholic University of Rome, Italy;* [4]*Department of Pathophysiology and Transplantation, Section of Internal Medicine, Università degli Study di Milano, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy;* [5]*Department of Medicine and Surgery, University of Salerno, Italy*

JOURNAL OF HEPATOLOGY





Association
udy of the Liver

September 2016

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

The Benefit of Sleeve Gastrectomy in Obese Adolescents on Nonalcoholic Steatohepatitis and Hepatic Fibrosis

Melania Manco, MD, PhD, FACN[1], Antonella Mosca, MD[2], Francesco De Peppo, MD[3], Romina Caccamo, MD[3], Renato Cutrera, MD[4], Ugo Giordano, MD[5], Cristiano De Stefanis, PhD[6], Anna Alisi, PhD[6], Ulrich Baumann, MD[7], Gianfranco Silecchia, MD, PhD[8], and Valerio Nobili, MD[2,6]

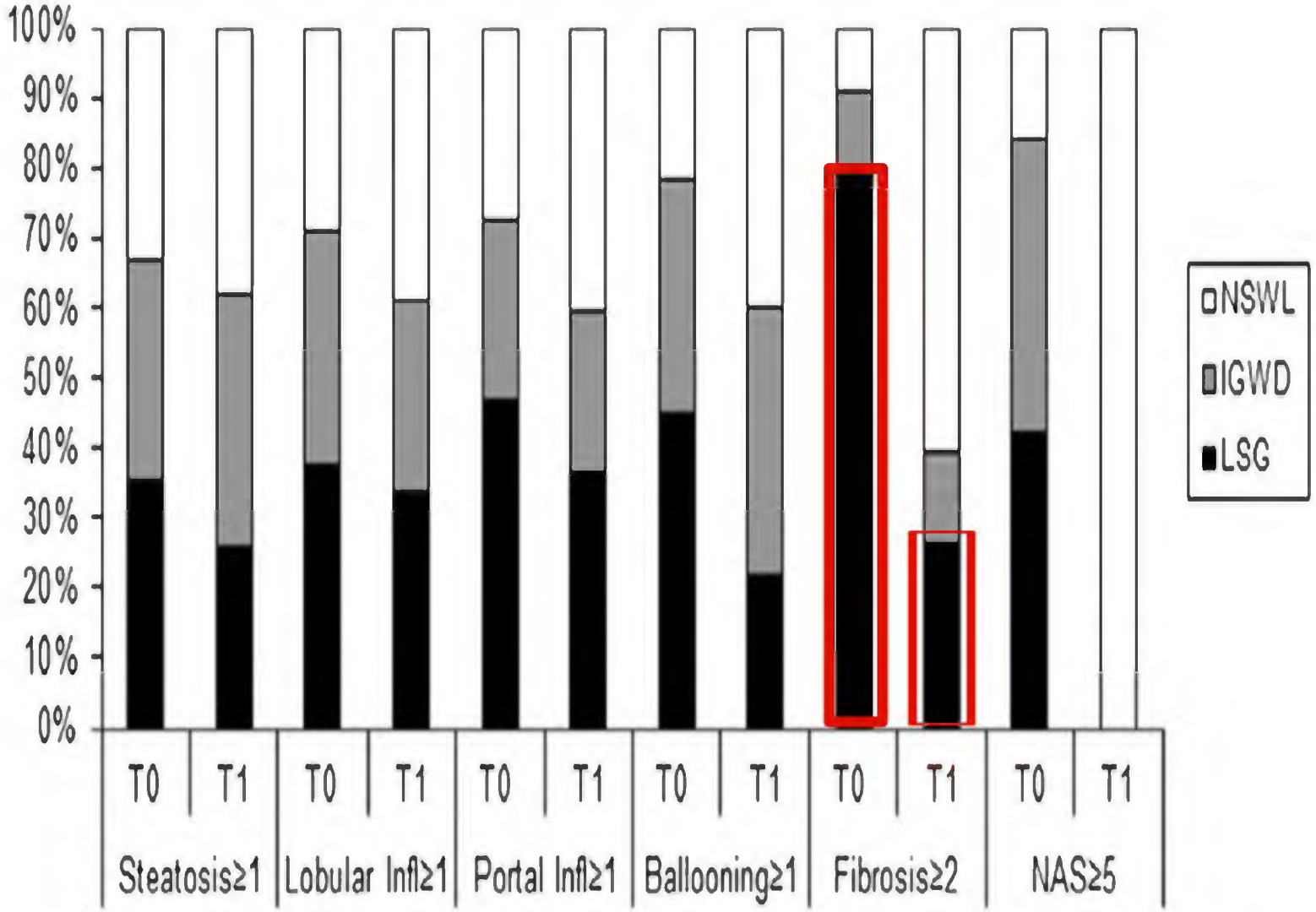

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
NSWL
IGWD
LSG
T0
T1
Steatosis≥1
Lobular Infl≥1
Portal Infl≥1
Ballooning≥1
Fibrosis≥2
NAS≥5

Table IV. The trend of comorbidities at T0 and T1 in 3 groups*

	Hypertension (%)				OSAS (%)				Dyslipidemia (%)				IGT (%)			
	T0	T1	IC 95%	*P*	T0	T1	IC 95%	*P*	T0	T1	IC 95%	*P*	T0	T1	IC 95%	*P*
LSG	60	0	28.24 to 60	**.005**	45	15	2.44 to 30	**.03**	60	5	23.66 to 55	**.001**	25	0	−1.09 to 25	**.05**
IGWLD	45	40	−4.75 to 5	.97	30	20	−6.84 to 10	0.5	40	25	−6.23 to 15	.45	20	10	−6.84 to 10	.5
NSWL	39.62	22.72	5.66 to 16.9	.25	22.64	27.27	−5.01 to −4.63	.98	41.5	36.3	−6.22 to 5.2	.5	15.09	13.63	−4.3 to 2.27	.98

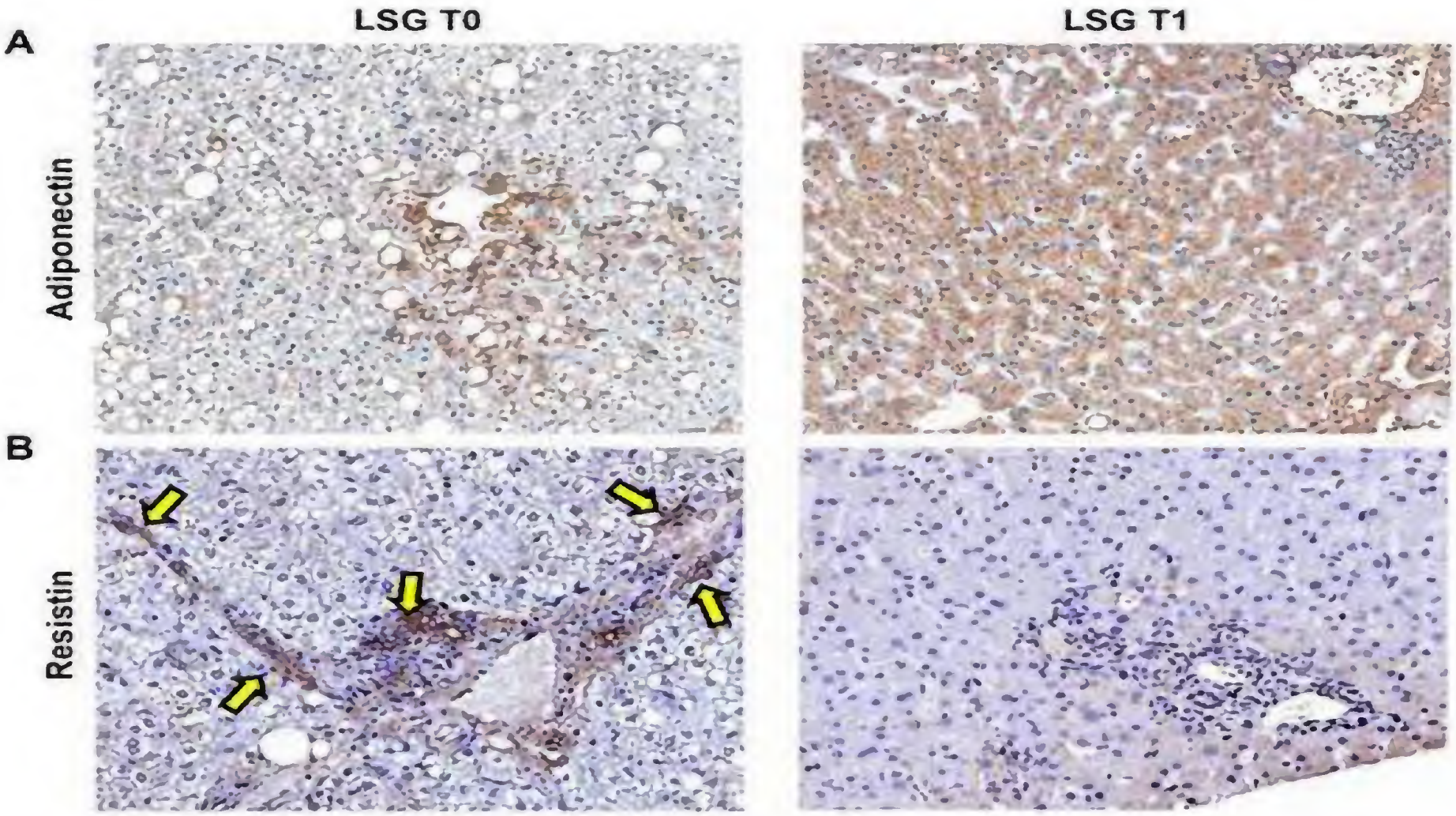
ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Laparoscopic Sleeve Gastrectomy Improves Nonalcoholic Fatty Liver Disease–Related Liver Damage in Adolescents by Reshaping Cellular Interactions and Hepatic Adipocytokine Production

Valerio Nobili, MD[1,2,*], Guido Carpino, MD, PhD[3,*], Francesco De Peppo, MD[4], Romina Caccamo, MD[4], Antonella Mosca, MD[1], Ilaria Romito, PhD[5], Diletta Overi, MD[6], Antonio Franchitto, MSc[6], Paolo Onori, MD[6], Anna Alisi, PhD[5], and Eugenio Gaudio, MD[6]

J Pediatr. 2018 Mar;194:100-108


LSG T0
LSG T1
A
Adiponectin
B
Resistin

Prevention Is Better Than Cure. Especially When Something Has

No Cure.

~ The Fresh Quotes ~

LA CAMPAGNA.

Medico amico test gratis dell'uricemia per prevenire infarti e ictus

GLICEMIA, creatinina, colesterolo, transaminasi, emocromo, Ves, sideremia, trigliceridi, urine esame completo: procedure di prevenzione firmate dal medico di famiglia. Ma manca qualcosa. Un test semplice e prezioso che va riabilitato: l'acido urico. E per questo il sindacato medici italiani (Snami) lancia la campagna "Medico Amico" dal prossimo 19 ottobre al 30 novembre negli studi con esame gratuito e il 25 ottobre in vari centri commerciali di 26 città italiane (info su www.medicoamicoday.it, sponsor Menarini).

Era una volta l'esame principe per individuare la gotta (diffusa forma di artrite infiammatoria, patologia cronica che provoca dolori e tumefazione e insorge quando l'organismo non riesce ad espellere l'acido urico) e su tale malattia ci si basa per determinare i valori medi (uomo tra 3,5 e 7,2 mg/dL e donna tra 2,6 e 6). Ma l'acido urico che si deposita sotto forma di cristalli di urato nei vasi sanguigni sarebbe una minaccia per il cuore. «Recenti ricerche lo segnalano come fattore di rischio cardiovascolare in 4 infarti su 10 soprattutto in chi ha colesterolo alto, ipertensione e iperglicemia», racconta Angelo Testa, presidente Snami, «le stime parlano di 13 milioni di italiani con uricemia "sballata" ma pochi lo sanno perché non si controlla nella routine». Afferma Claudio Borghi, Medicina Interna, ateneo di Bologna: «La soglia di rischio è fissata in 6 milligrammi per decilitro di sangue [illegible] che per ogni incremento di 1 milligrammo il rischio di complicanze cardiovascolari gravi cresce dal 9 al 26% e di oltre il 20% il pericolo di ictus». Ipertensione, danni renali, diabete altre minacce. L'incrocio del dato con gli altri valori rende ancor più personalizzata la diagnosi. Basta una goccia di sangue.

(m. pag.)

Sarebbero 13 milioni gli italiani con valori oltre la soglia Ma pochissimi fanno l'esame

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Mild Viral Infection May Trigger Celiac Disease Years Later

Rabies: What's an Exposure? Know When to Vaccinate

Pediatric Influe Deaths Concer in Unvaccinate

Kids, Food, and Fatty Livers: Fructose vs the Med Diet

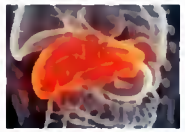
Antonella Mosca, MD; Andrea Vania, MD; Silvio Veraldi, MD; Valerio Nobili, MD

Disclosures | April 11, 2017

Comment Print Email

EDITORS' RECOMMENDATIONS

Fructose Tied to Advanced Liver Disease in Children and Teens


Liver Diseases in Children: Challenges and Opportunities

Pediatric Nonalcoholic Fatty Liver Disease

Diet and Fatty Liver Disease

Diet plays an important part in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). The roles of potentially noxious nutrients (eg, fructose), potentially protective foods (eg, omega-3 fatty acids), and eating styles (eg, Mediterranean diet) in NAFLD have been described in previous research.

Over the past decade, studies have suggested that fructose intake increases the serum concentration of uric acid, and that both are increased in persons with type 2 diabetes, cardiovascular disease,

May 2017

Research Article

CrossMark

EASL | JOURNAL OF HEPATOLOGY

Serum uric acid concentrations and fructose consumption are independently associated with NASH in children and adolescents

Antonella Mosca[1,†], Valerio Nobili[1,2,*,†], Rita De Vito[2], Annalisa Crudele[3], Eleonora Scorletti[4,5], Alberto Villani[6], Anna Alisi[3], Christopher D. Byrne[4,5]

VOLUME 66 No. 5 MAY 2017

ELSEVIER

JOURNAL OF HEPATOLOGY

The Home of Liver Research

Fructose

increases risk of NAFLD in children

Intrahepatic innate immunity in chronic HBV infection

A comprehensive view on NS5A resistance

Abnormal IFN signaling in cirrhosis PBMCs

EASL JOURNAL OF HEPATOLOGY

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EASL JOURNAL OF HEPATOLOGY

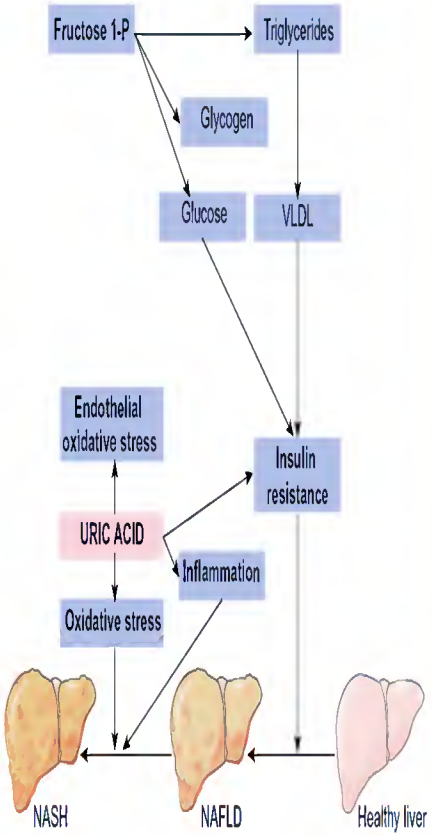
From the Editor's desk...

Richard Moreau*, Ramon Bataller, Thomas Berg, Jessica Zucmann-Rossi, Rajiv Jalan

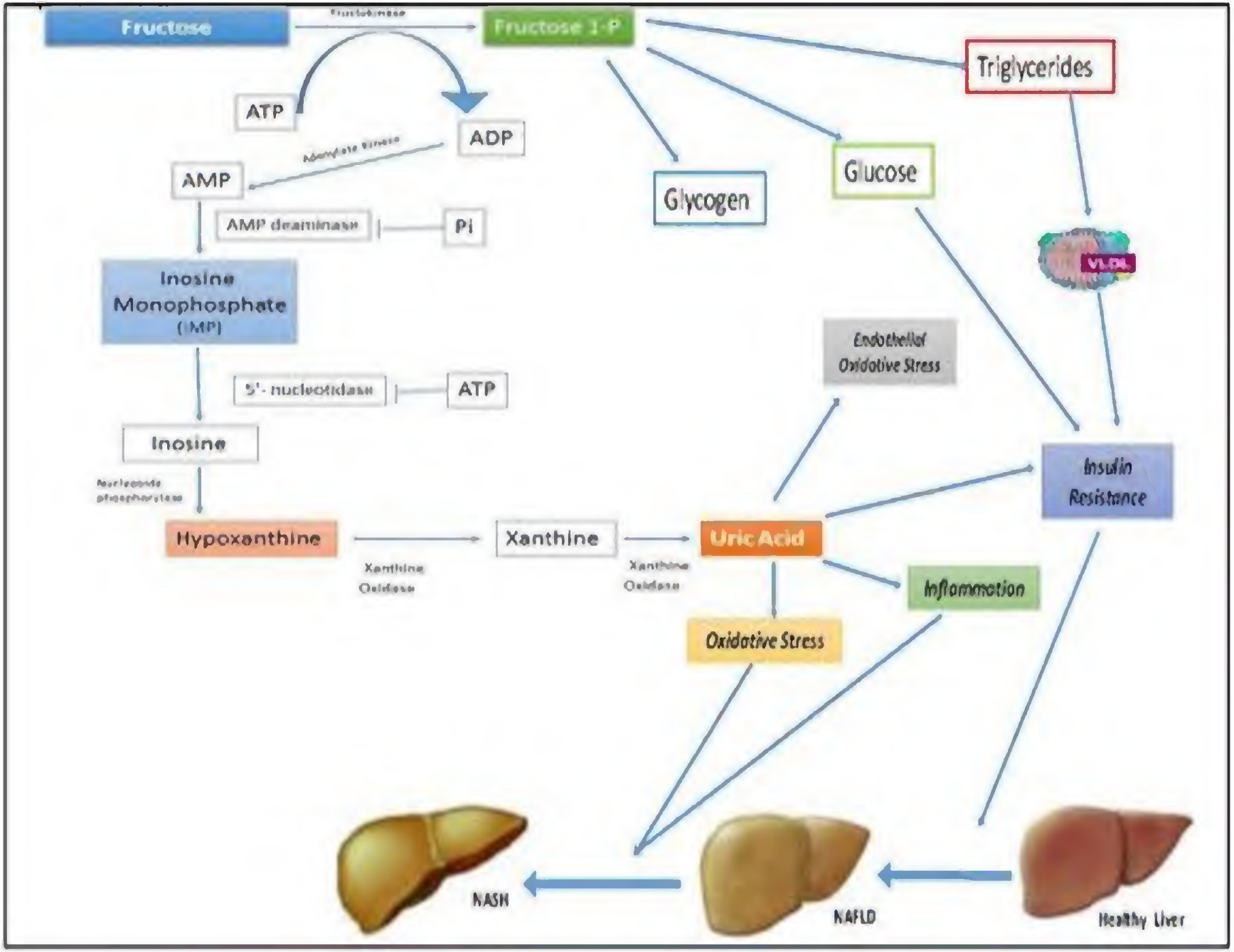
SELECTION OF THE MONTH

Fructose consumption and hyperuricemia in young population

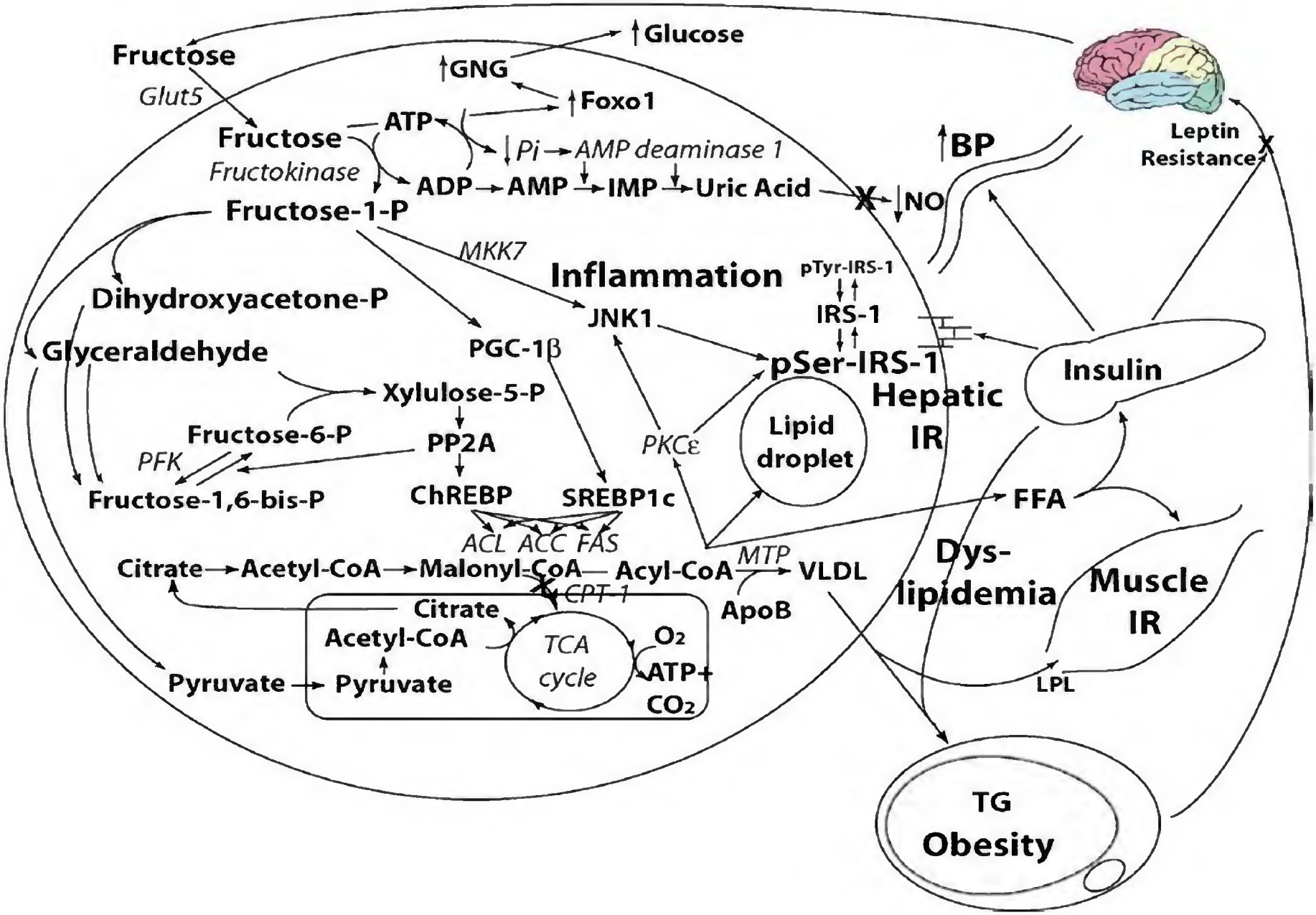
Excessive fructose intake is known to increase serum uric acid concentrations. In an important study by Mosca *et al.* a large cohort of children and adolescents with proven NAFLD (37% with NASH) were studied. Hyperuricemia was present in 47% of patients with NASH compared with 29% of non-NASH patients. Importantly, both **uric acid concentration and fructose consumption were independently associated with NASH**, after adjustment for multiple confounders. **Fructose consumption was the only factor independently associated with serum uric acid concentration.** This study suggests that excessive fructose consumption could lead to hyperuricemia and contribute to NASH development in young populations. Public health policies aimed at preventing excessive fructose-containing beverages among children are warranted.



Mosca *et al.* 2017


Fructose
Fructose 1-P
Triglycerides
ATP
ADP
AMP
Glycogen
Glucose
AMP deaminase
Pi
VLDL
Inosine Monophosphate (IMP)
Endothelial Oxidative Stress
5'- nucleotidase
ATP
Inosine
Insulin Resistance
Hypoxanthine
Xanthine
Uric Acid
Xanthine Oxidase
Xanthine Oxidase
Inflammation
Oxidative Stress
NASH
NAFLD
Healthy Liver

Metabolism of Fructose



AHA SCIENTIFIC STATEMENT

Added Sugars and Cardiovascular Disease Risk in Children

A Scientific Statement From the American Heart Association

BACKGROUND: Poor lifestyle behaviors are leading causes of preventable

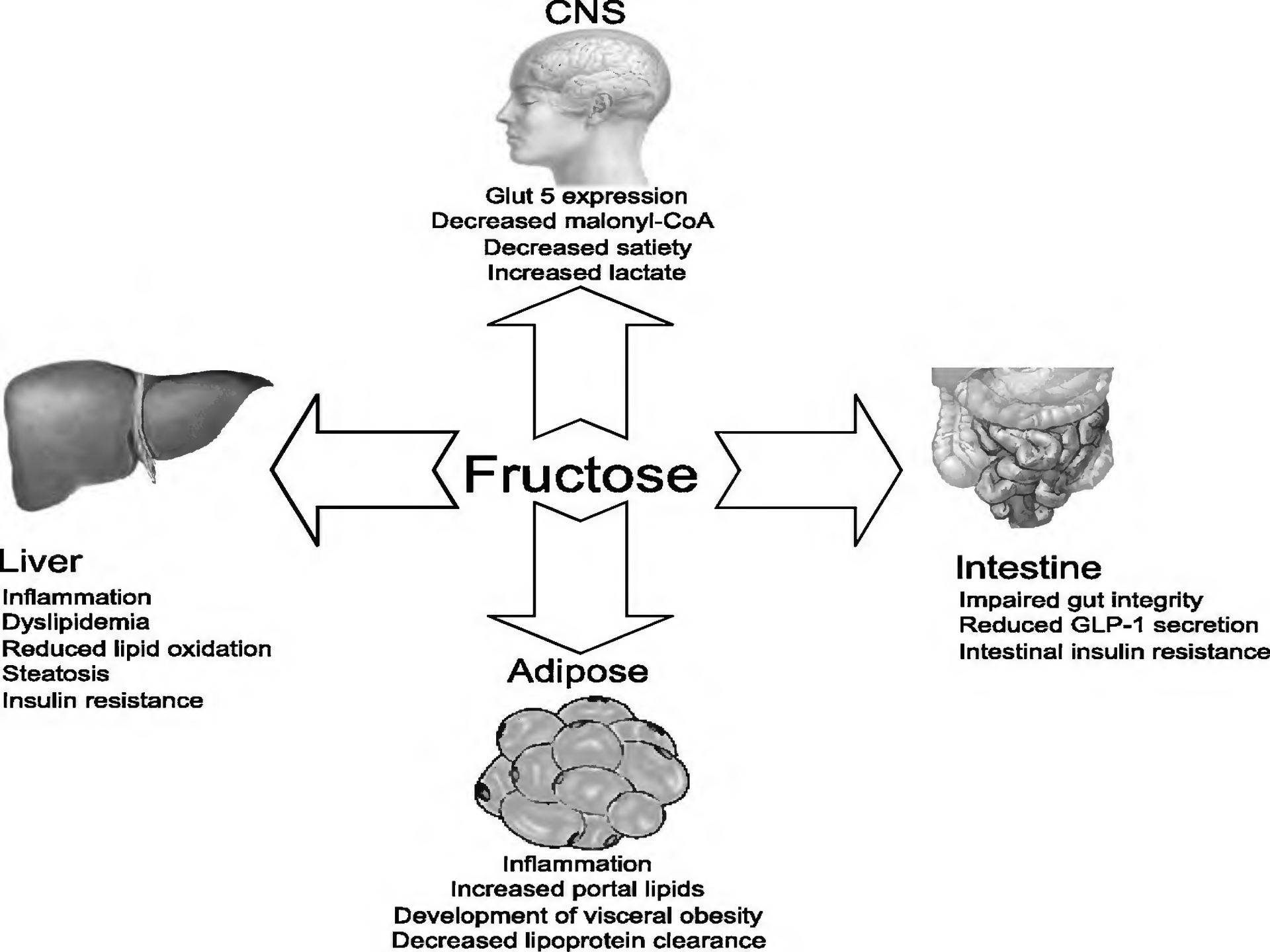
Miriam B. Vos, MD,

INTERNATIONAL CONFERENCE ON
FATTY LIVER
Seville, Spain, 1-3 June 2017

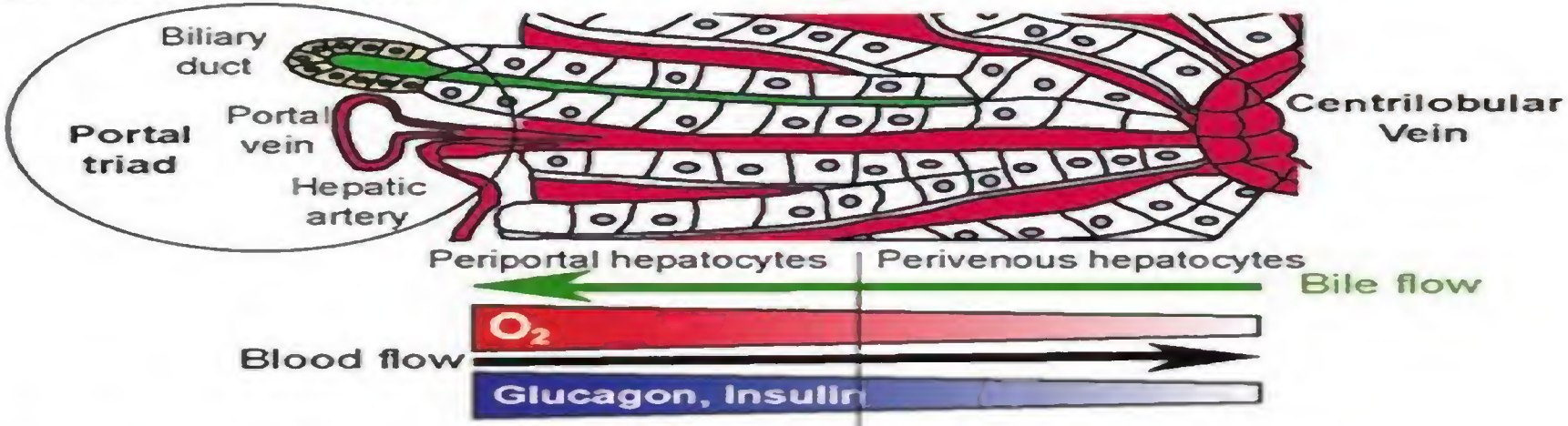
CONCLUSIONS: Associations between added sugars and increased cardiovascular disease risk factors among US children are present at levels far below current consumption levels. Strong evidence supports the association of added sugars with increased cardiovascular disease risk in children through increased energy intake, increased adiposity, and dyslipidemia. The committee found that it is reasonable to recommend that children consume ≤25 g (100 cal or ≈6 teaspoons) of added sugars per day and to avoid added sugars for children <2 years of age. Although added sugars most likely can be safely consumed in low amounts as part of a healthy diet, few children achieve such levels, making this an important public health target.

Table 1. Daily dietary consumption of fructose and carbohydrate and anthropometric and biochemical parameters in children and adolescents with NAFLD, stratified by NAFLD activity score (NAS).

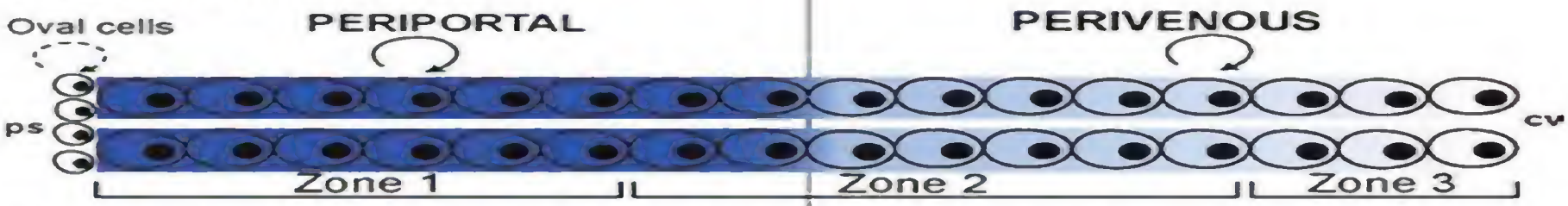
	NAS ⩾5 (n = 102)	NAS <5 (n = 169)	p value
Age (yr)[1]	11.4 (10.4–13.3)	11.6 (9.8–13)	0.68
Sex (F/M %)[3]	44/58 (43/57)	56/103 (33/67)	0.52
Weight (median; IQR)[1]	68 (50–75)	66 (49–71)	0.55
BMI, kg/mq (mean, SD)[2]	27.2 (4.3)	26.1 (5.1)	0.61
WC, cm (mean, SD)[2]	90.3 (9.1)	85.8 (11.6)	0.01*
z-BMI (mean, SD)[2]	2.8 (1.2)	2.2 (1.5)	0.66
AST, UI/L (median; IQR)[1]	55 (32–65)	42 (28–53)	0.001*
ALT, UI/L (median; IQR)[1]	65 (36–110)	58 (35–78)	0.02*
Uric acid, mg/dl (median; IQR)[1]	6.6 (4–7.2)	5.1 (4.2–6.5)	0.05*
Hyperuricemia, (uric acid >5.9 mg/dl) (%)[3]	47%	29.5%	0.003*
Total cholesterol, mg/dl (median; IQR)[1]	166 (149–195)	156 (131–176)	0.02*
LDL cholesterol, mg/dl (median; IQR)[1]	108 (76–113)	90 (70–108)	0.22
HDL cholesterol, mg/dl (median; IQR)[1]	43 (33–48)	46 (38–49)	0.81
Triglycerides, mg/dl (median; IQR)[1]	103 (78–146)	91 (70–110)	0.05*
Fasting plasma glucose, mg/dl (median; IQR)[1]	84 (75–92)	82 (76–87)	0.64
Fasting plasma gluc-120' (median; IQR)[1]	113 (100–130)	112 (101–127)	0.85
Fasting insulin, mU/L (median; IQR)[1]	16 (9–19)	14 (10–20)	0.61
Insulin -120 minute mU/L (median; IQR)[1]	104 (44–139)	93 (76–136)	0.09
HOMA-IR (mean, SD)[2]	2.99 (2.1)	2.7 (1.67)	0.81
SBP, mmHg (mean, SD)[2]	112 (11.9)	111.4 (10.3)	0.65
DBP, mmHg (mean, SD)[2]	69.5 (8.2)	67.2 (9.6)	0.32
Fructose, g/day (median; IQR)[1]	70.4 (53–85)	52.6 (38–73)	0.002*
Carbohydrates, g/day (median; IQR)[1]	234 (123–432)	227 (128–370)	0.62
TNF-α, (ng/ml) (median; IQR)[1]	59.8 (10–112)	43.4 (12–91)	0.04*
IL-6, (pg/ml) (median; IQR)[1]	29.3 (13–55)	26.2 (8–49)	0.22
IL-1β, (pg/ml) (median; IQR)[1]	14.3 (7–22)	13 (6–21)	0.76


CNS
Glut 5 expression
Decreased malonyl-CoA
Decreased satiety
Increased lactate
Fructose
Liver
Inflammation
Dyslipidemia
Reduced lipid oxidation
Steatosis
Insulin resistance
Intestine
Impaired gut integrity
Reduced GLP-1 secretion
Intestinal insulin resistance
Adipose
Inflammation
Increased portal lipids
Development of visceral obesity
Decreased lipoprotein clearance

b Liver Cell Plate



c Zonated functions



	Zone 1	Zone 2	Zone 3
Ammonia, Glutamine metabolism and transport			
	Urea formation		Glutamine synthesis
	Cps1, Arg1		Gs, Glt1, Oat, RhBg
Glucose/energy metabolism			
	Gluconeogenesis Pck1, *G6Pase*, FBPase		Glycolysis *Gk, Pk L*
	Oxidative phosphorylation Sdh		TCA cycle Idh3a, Dlat
Drug metabolism			
			Transcription factors Car, AhR
	Phase I: Monooxygenation Cyp2f2		Phase I: Monooxygenation Por, Cyp1a2, Cyp2e1
	Phase II: Conjugation Sult5a1		Phase II: Conjugation Gstm2,3,6

Marzo 2018

Liver zonation in children with non-alcoholic fatty liver disease: Associations with dietary fructose and uric acid concentrations

Valerio Nobili, Antonella Mosca, Rita De Vito, Massimiliano Raponi, Eleonora Scorletti, Christopher D. Byrne

Nutrition 39-40 (2017) 8–14

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Good adherence to the Mediterranean diet reduces the risk for NASH and diabetes in pediatric patients with obesity: The results of an Italian Study

Claudia Della Corte M.D. [a], Antonella Mosca M.D. [a], Andrea Vania M.D. [b], Arianna Alterio M.D. [a], Salvatore Iasevoli M.D. [c], Valerio Nobili M.D. [a,*]

[a] Hepatometabolic Department, Liver Research Unit, Children's Hospital, Rome, Italy
[b] Center of Dietetics and Nutrition, Sapienza University, Rome, Italy
[c] ASL Napoli 2 Nord, Naples, Italy

Table 1

KIDMED* score in four groups: NASH, not-NASH, FL+, and FL−

KIDMED score	NAFLD				*P*-value†
	NASH = 53 (%)	Not-NASH = 47	FL+ = 66 (%)	FL− = 77 (%)	
≤3	53 (100)	14 (29.79)	25 (37.88)	7 (9.10)	0.01
4–7	–	15 (31.92)	30 (45.45)	58 (75.32)	0.02
≥8	–	18 (38.29)	11 (16.67)	12 (15.58)	0.43

FL+, with fatty liver; FL−, without fatty liver; KIDMED, Mediterranean Diet Quality Index for children and adolescents; MD, Mediterranean diet; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis

Differences considered statistically significant at $P \leq 0.05$

* KIDMED score: ≤3: poor adherence to MD; 4–7: moderate adherence; ≥8: optimal adherence.

† Statistical significance with analysis of variance after Bonferroni correction.

Basta
bruciare
i grassi...
bruciamo i magri!
Destefano