

# Επιδημιολογία της μη αλκοολικής λιπώδους νόσου του ήπατος στο σακχαρώδη διαβήτη



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# Defining NAFLD...

Clinico-pathologic syndrome encompassing a **wide range of fatty liver disease** in the absence of significant alcohol intake (2 drinks or fewer daily) and other common causes of steatosis.

# NAFLD - Spectrum of Disease

Steatosis

Steatohepatitis (NASH)

NASH with Fibrosis

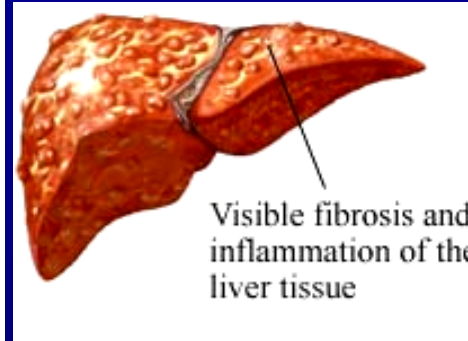
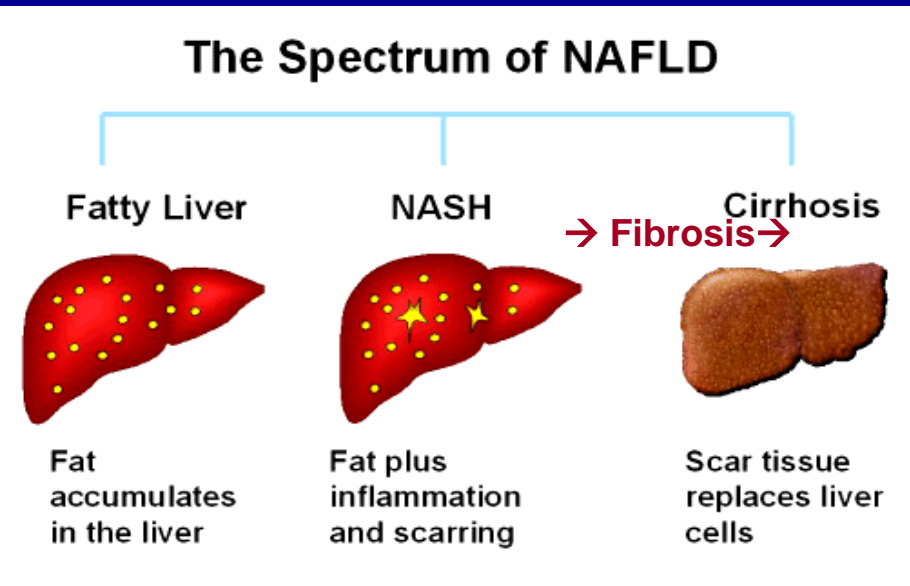
Cirrhosis

**NAFLD**



# Non-Alcoholic Liver Disease as a model

for the study of the secondary complications of obesity



Increased risk of hepatocellular carcinoma

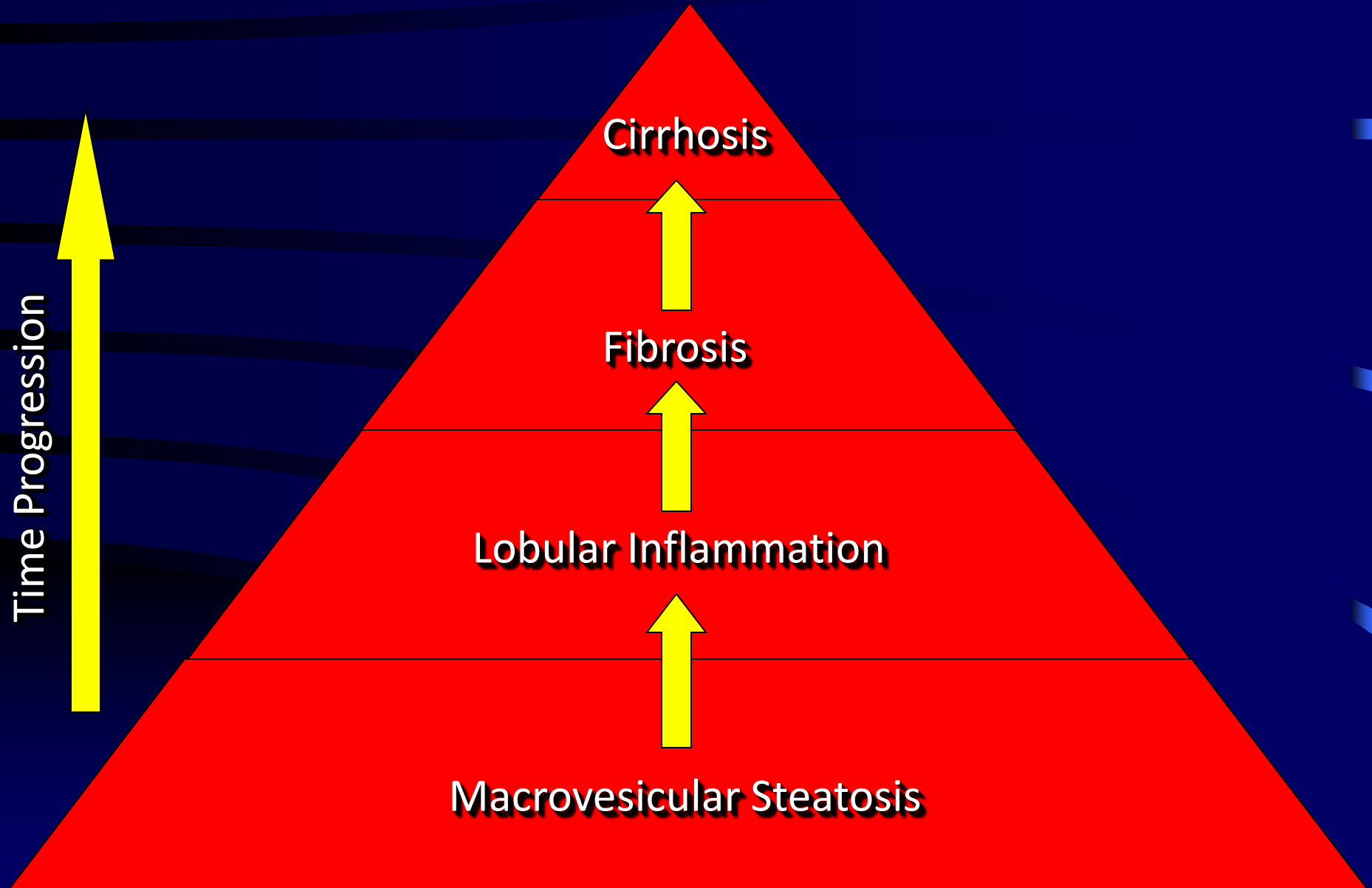
From: Ariel E. Feldstein and Marsha H. Kay, ACG website

**NAFLD** affects about 25 % of adults and nearly 5 % of children.

**NASH** → 2-5 % of adult Americans; up to 20 % of obese subjects.

The majority of individuals with NAFLD have no symptoms and a normal examination

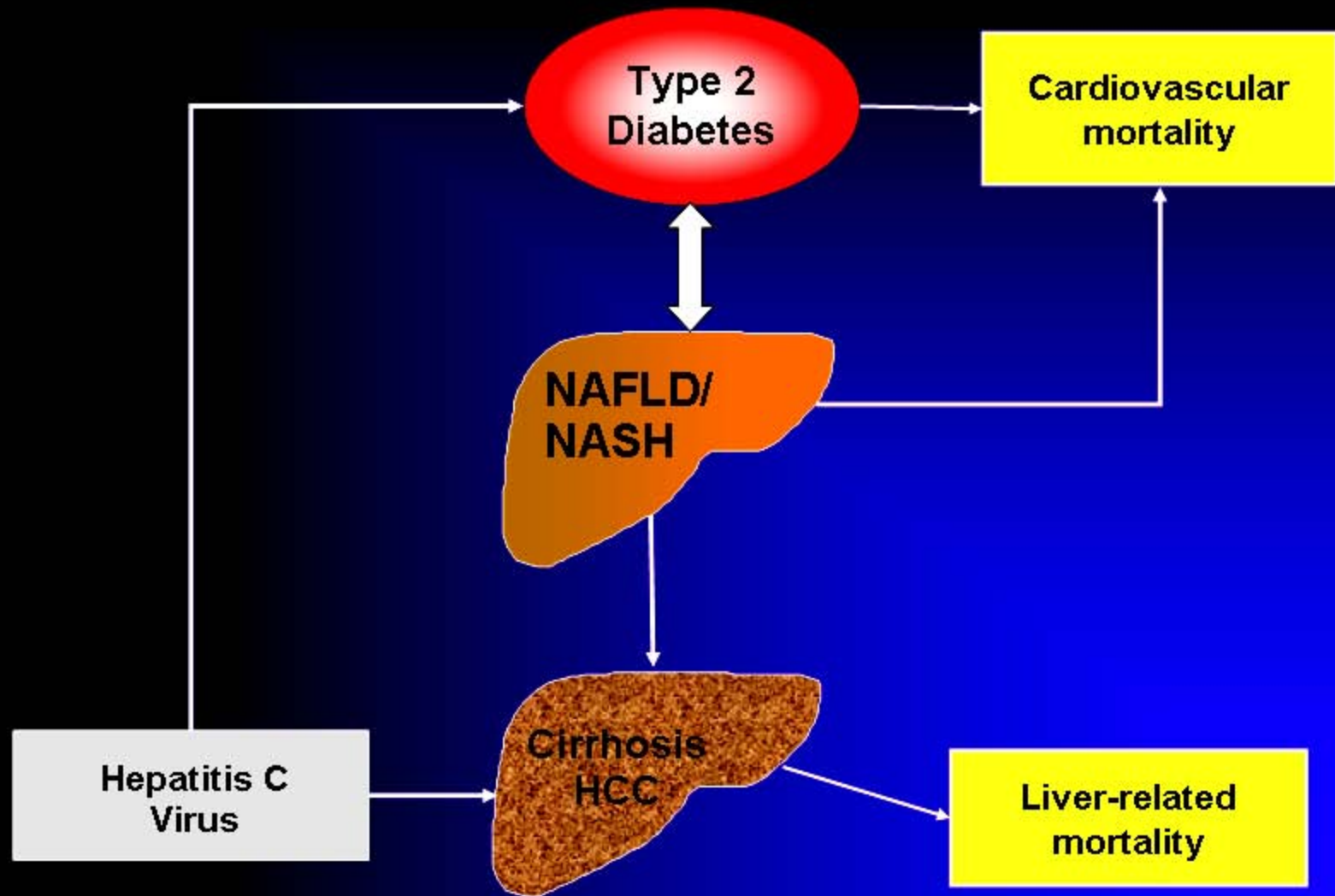
# NAFLD - Histological Spectrum



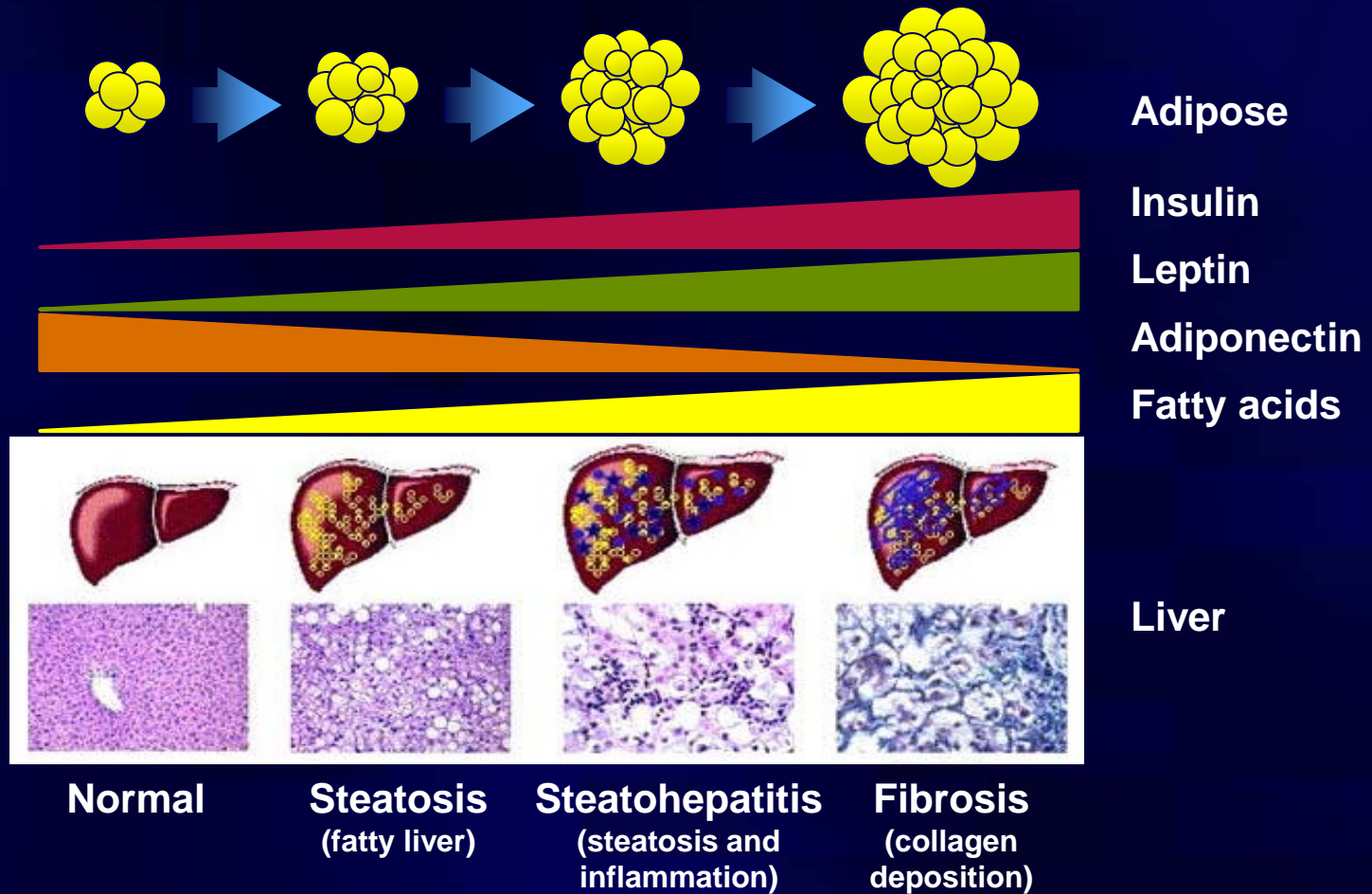
# NAFLD - Background

- **1958:** Zelman reported association of obesity with **fatty liver**
- **1980:** Ludwig coined “**non-alcoholic steatohepatitis**”
- **2010:** 400 million subjects **with NAFLD** and 100 million with **NASH**

# Liver Disease in T2DM

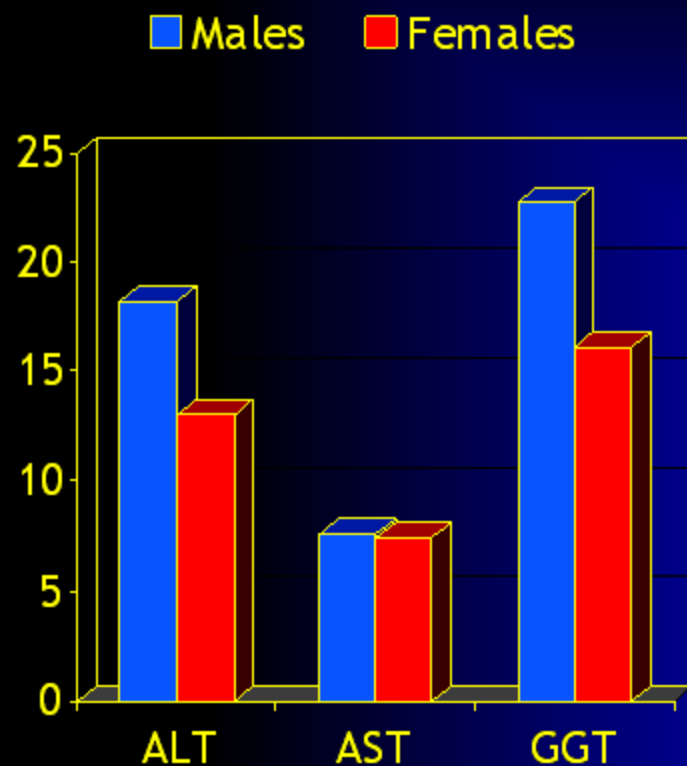


# DM - Adiposity in the development of NASH





# Elevated Liver Enzyme Levels in T2DM



- 9,632 consecutive T2DM patients in 8 Italian centers
- 21% normalweight, 41% overweight, 38% obese; median age, 53yrs
- Prevalence of high ALT higher in OB (19.7%), vs. 14.4% (NW) and 13.3% (OW)( $P < 0.0001$ ).
- The prevalence of high ALT is associated with poor metabolic control and obesity grade
- The presence of the MS highly predictive of raised ALT, even after exclusion of hepatitis B and C

# Epidemiologic Features- Prevalence

- NAFLD affects **10% to 33 %** of the general population in various countries. The prevalence increases to **57 % to 74 % in obese persons.**
- NAFLD affects **2.6 % of children** and **22 % to 53 % of obese children.**

# Epidemiologic Features- Prevalence

- **Steatosis is found in over 66% of the obese population**, regardless of diabetic status, and in more than 90 % of morbidly obese persons (BMI>40 or > 35 kg/m<sup>2</sup> with comorbidities).
- **Steatohepatitis affects about 3 % of the lean population), 29 % of the obese population (BMI>30 kg/m<sup>2</sup>), and 50% of morbidly obese people.**
- On the basis of U.S. population in year 2010, **40 million adults may have steatosis**, and **12 million may have steatohepatitis.**

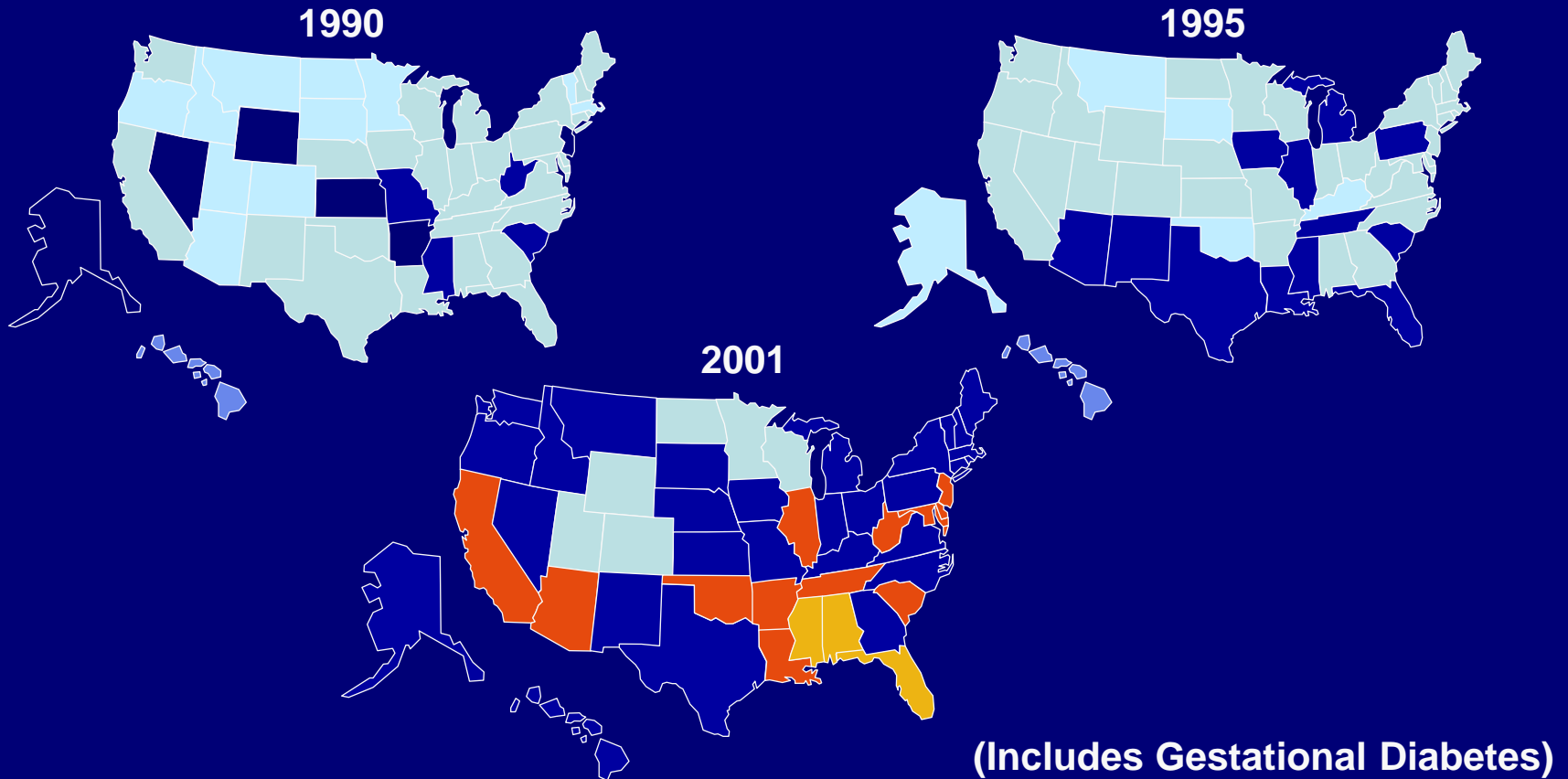
# Epidemiologic Features- Risk Factors

- **Obesity, type 2 DM, and hyperlipidemia** are coexisting conditions frequently associated with NAFLD.
- The reported prevalence of in NAFLD varied **obesity** between **30 and 100 %**, the prevalence of **type 2 DM** between **10 and 75 %**, and the prevalence of **hyperlipid.** between **20 and 92 %**.
- Some children with NAFLD have **type 1 DM**.

## Epidemiologic Features- Prevalence

- **DM affects 8 %** of the U.S. adult population, whereas about **50 % DM (8 million people)** have **clinical obvious NAFLD**.
- Among severely obese patients with DM, **100 % had at least mild steatosis**, **50 % had steatohepatitis**, and **19 % had cirrhosis**.

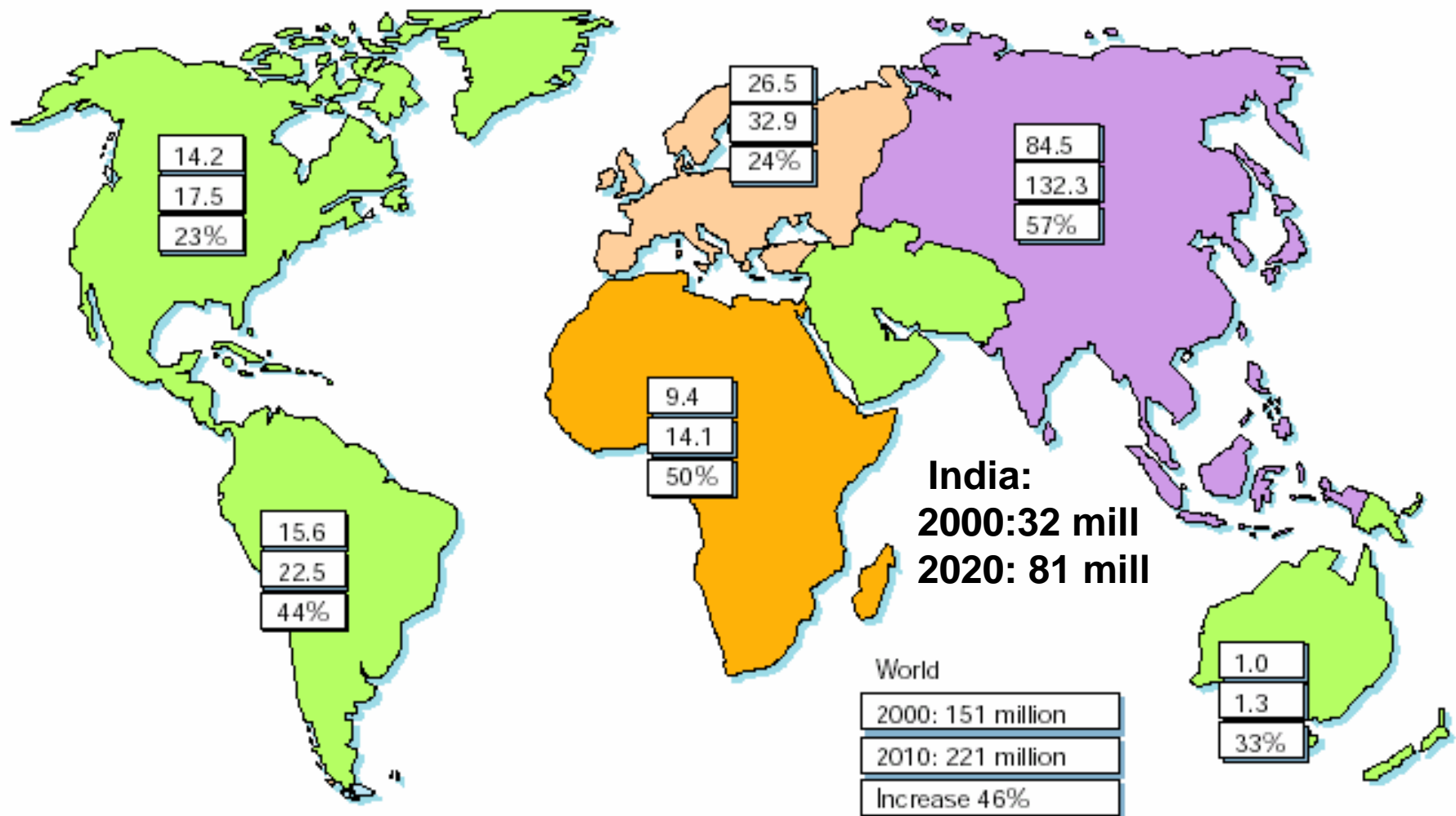
# Prevalence of Diabetes Is Escalating



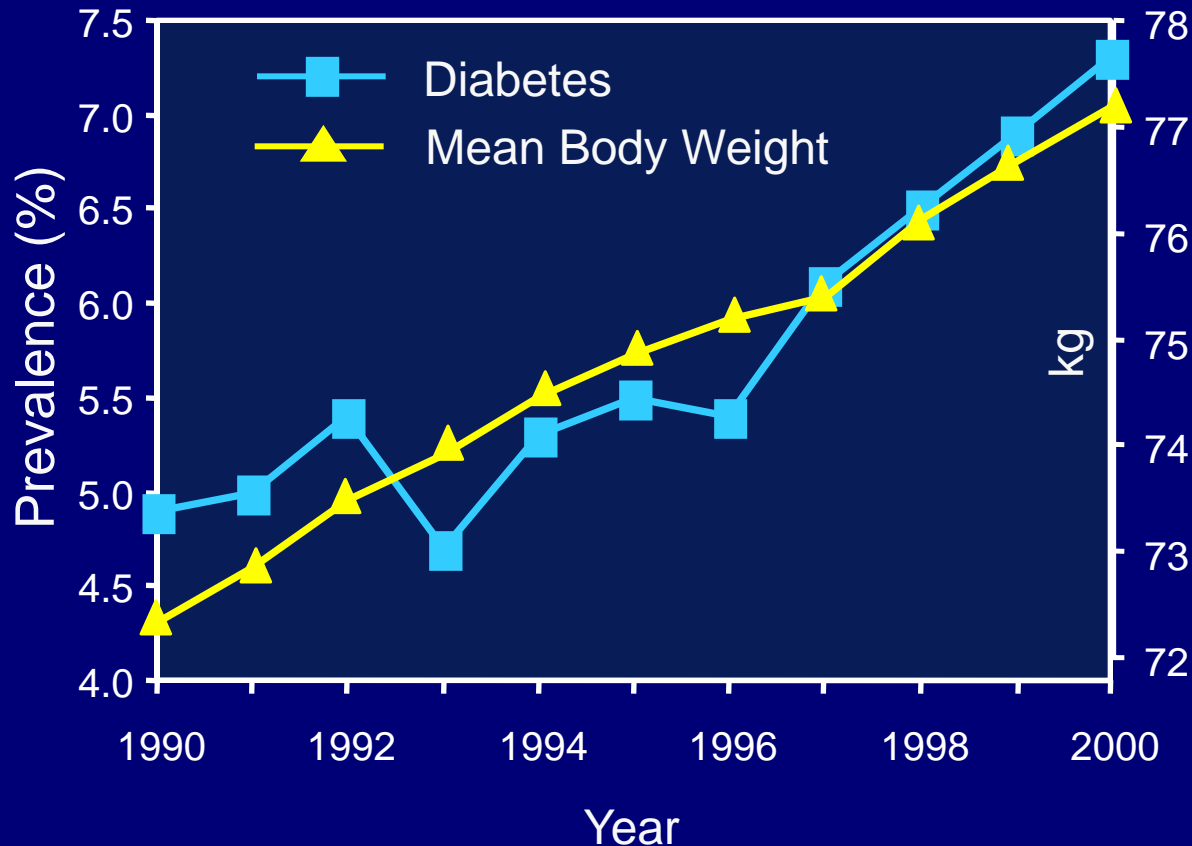
Legend: No Data, < 4%, 4%-6%, 6%-8%, 8%-10%, > 10%

Source: Mokdad A, et al. *Diabetes Care*. 2000;23:1278-1283; Mokdad A, et al. *J Am Med Assoc*. 2001;286:10; Mokdad A, et al. *JAMA*. 2003;289:76-79.

# DM: World wide epidemic



# Diabetes and Obesity: The Continuing Epidemic



- Prevalence of obesity increased by 61% since 1991
- More than 50% of US adults are overweight
- Only 43% of obese persons advised to lose weight during checkups
- BMI and weight gain major risk factors for diabetes

**BMI = body mass index.**

Mokdad AH et al. Diabetes Care. 2000;23:1278-1283; Mokdad AH et al. JAMA. 1999;282:1519-1522; Mokdad AH et al. JAMA. 2001;286:1195-1200.

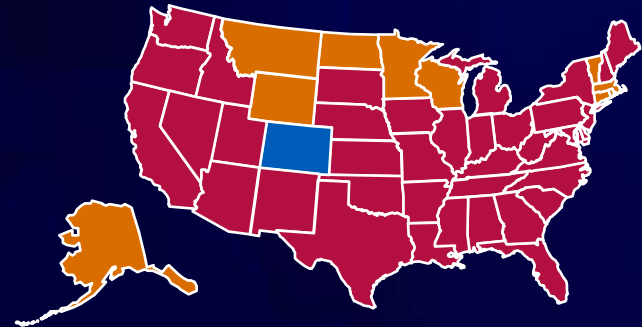
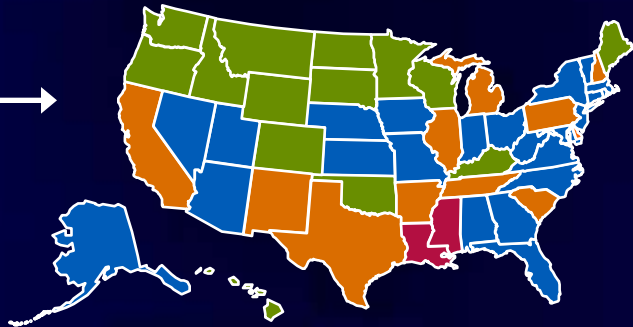


# Parallel epidemics of diabetes and obesity

1994

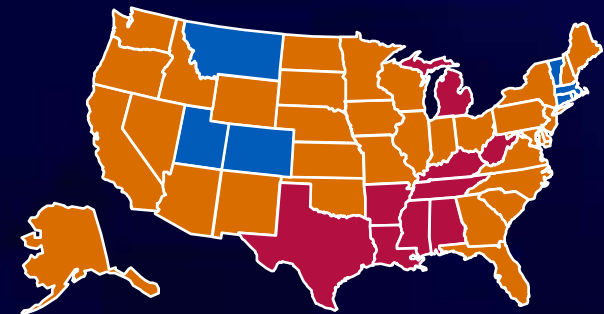
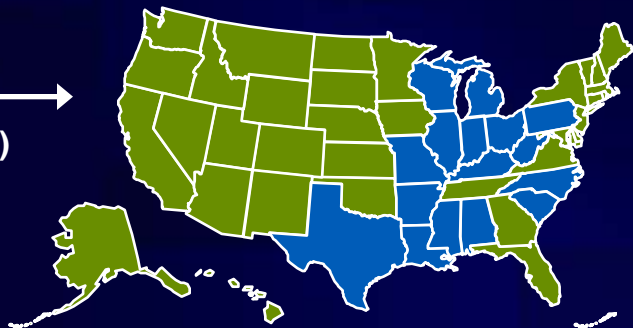
2004

Diabetes →



■ <4%   ■ 4%-4.9%   ■ 5%-5.9%   ■ ≥6%

Obesity →  
(BMI ≥30 kg/m<sup>2</sup>)



■ 10%-14%   ■ 15%-19%   ■ 20%-24%   ■ ≥25%

# NAFLD - Risk Factors

Acquired Metabolic Disorders	Obesity
	Diabetes Mellitus
	Hypertriglyceridemia
Surgery	Total Parenteral Nutrition
	Jejunioileal Bypass
	Extensive Small Bowel Loss
Medications	Corticosteroids; Estrogens
	Amiodarone
	Methotrexate; Tamoxifen
	Diltiazem; Nifedipine
Occupational Exposures	Organic Solvents

# NAFLD - Pathogenesis

**First Hit**

Insulin resistance

↑ Fatty acids



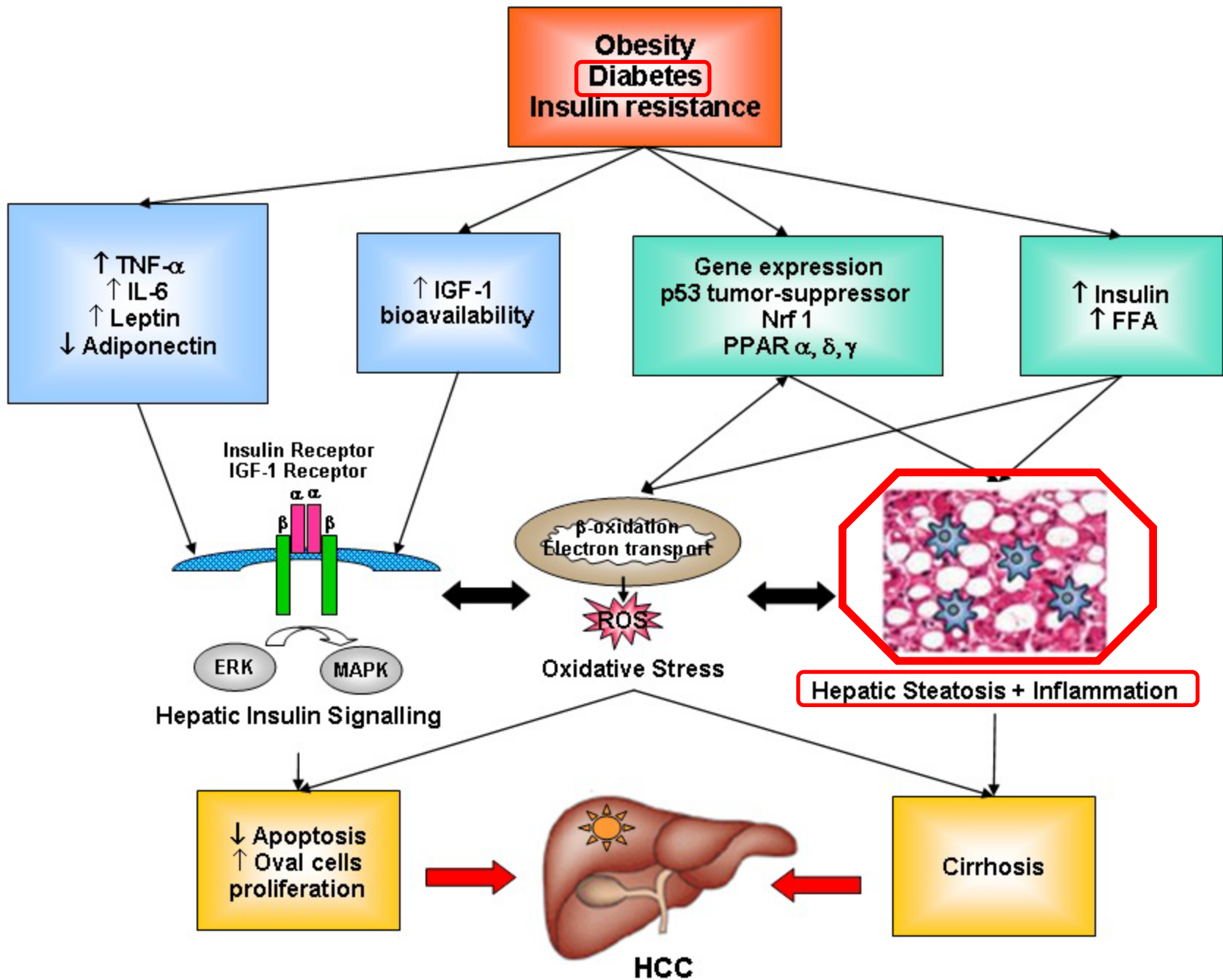
**Steatosis**

**Second Hit**



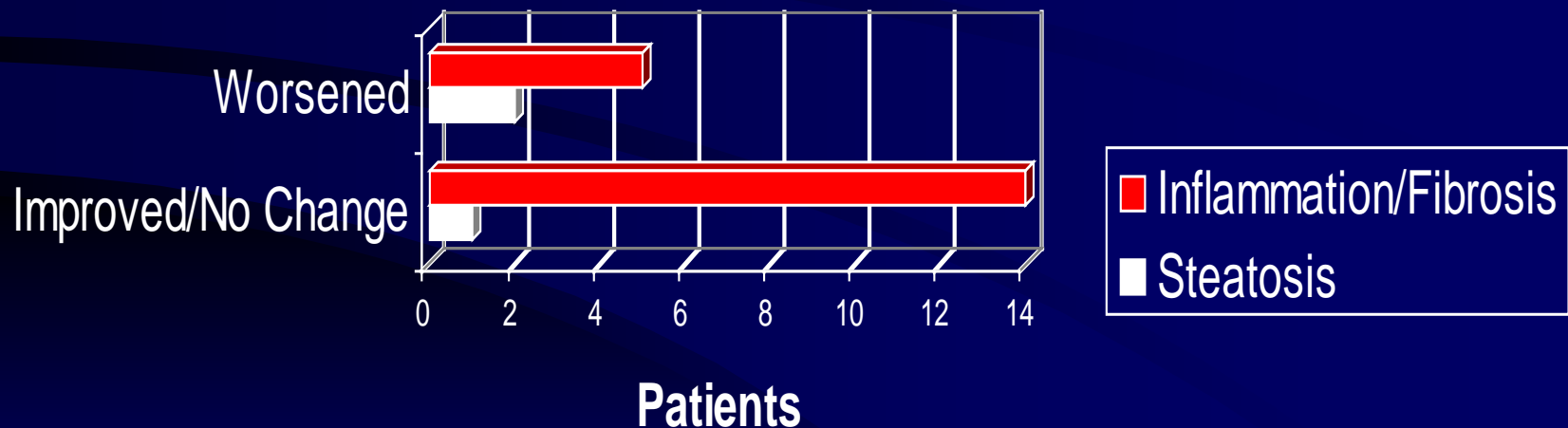
Lipid  
peroxidation

**NASH**



# NAFLD - Natural History

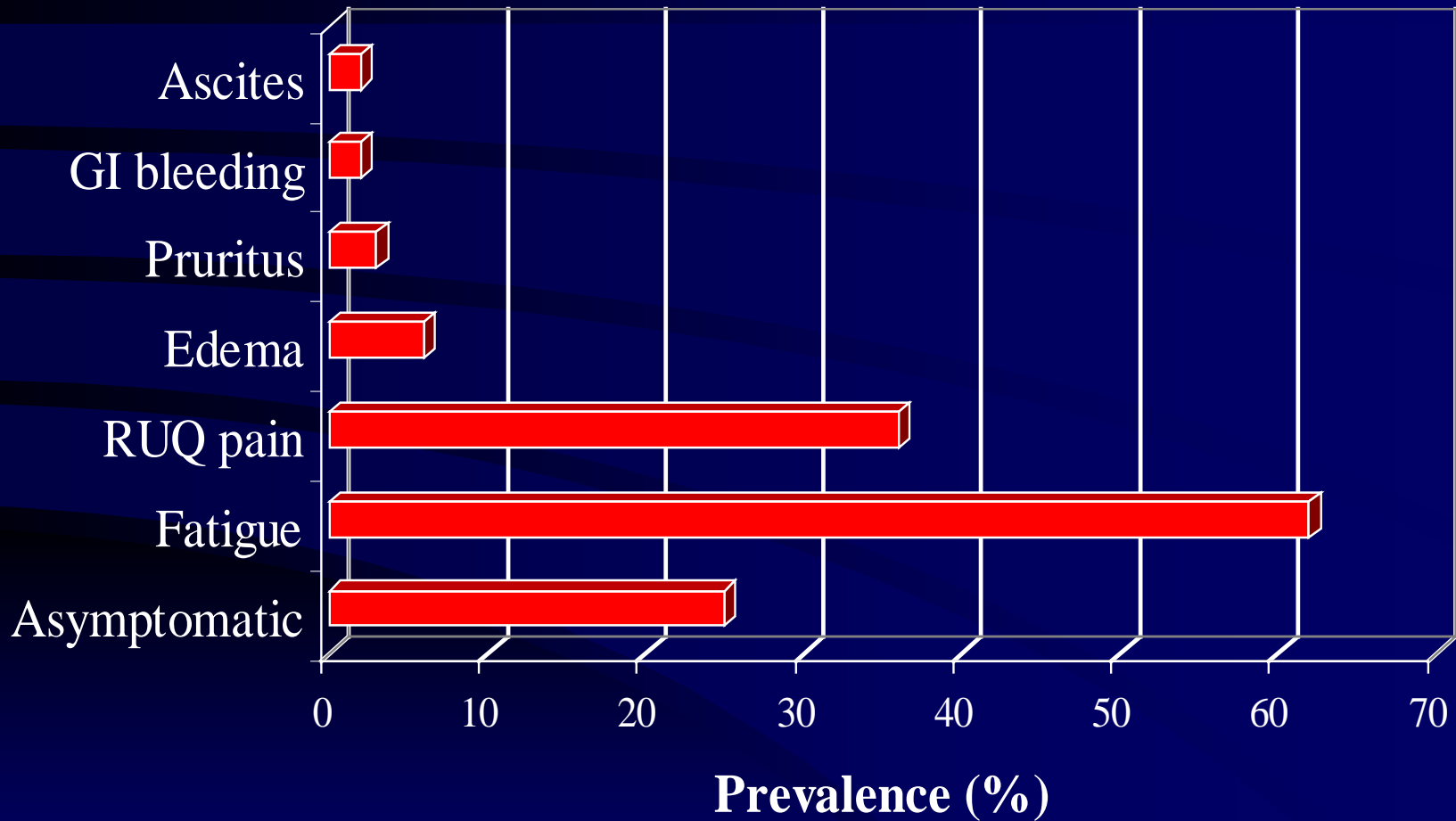
- Steatosis generally follows a benign course
- NASH with fibrosis has increased liver-related morbidity and mortality
- Steatosis can progress to NASH  $\pm$  fibrosis



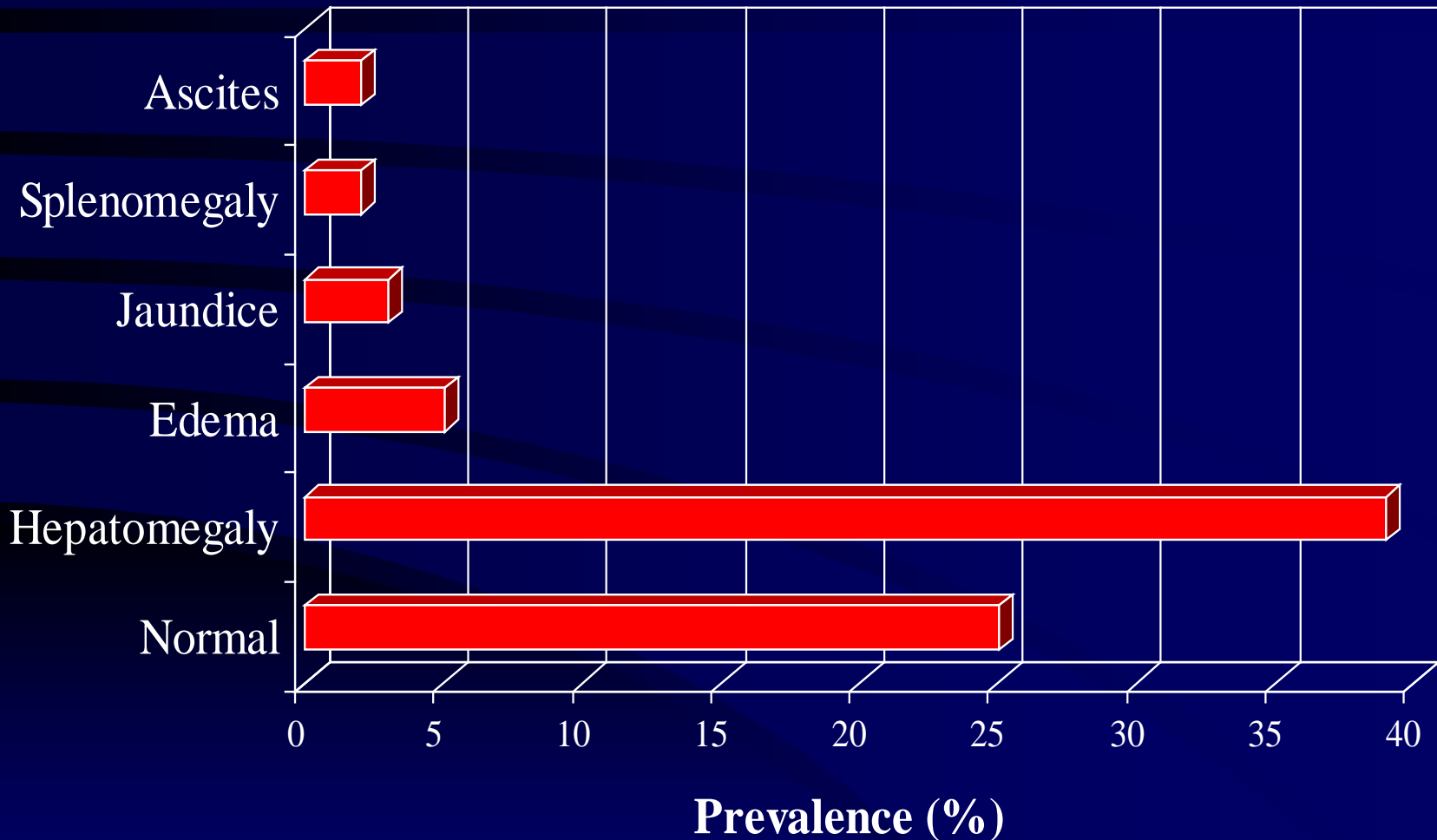
1. Harrison et al. The Natural History of NAFLD: A Clinical Histopathological Study. *Am J Gastro* 2003; 98:9; 2042-7

2. Matteoni et al. NAFLD: A Spectrum of Clinical and Pathological Severity. *Gastroenterology* 1999; 116; 1413-19

# NAFLD - Symptoms



# NAFLD - Exam Findings



# NAFLD - Laboratory Findings

- Mild elevation of ALT most common
- Elevated fasting glucose, triglycerides and depressed HDL with insulin resistance
- Elevated PT and low albumin with cirrhosis

**Normal labs do not rule out NAFLD**



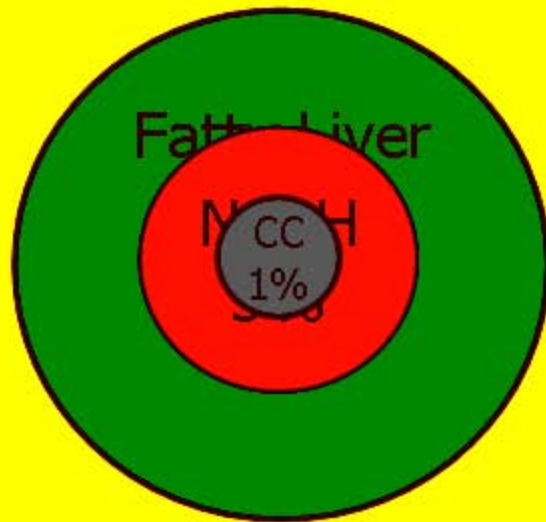
# NAFLD - Imaging

- **Ultrasound**
- **Computed Tomography**
- **Magnetic Resonance Imaging**

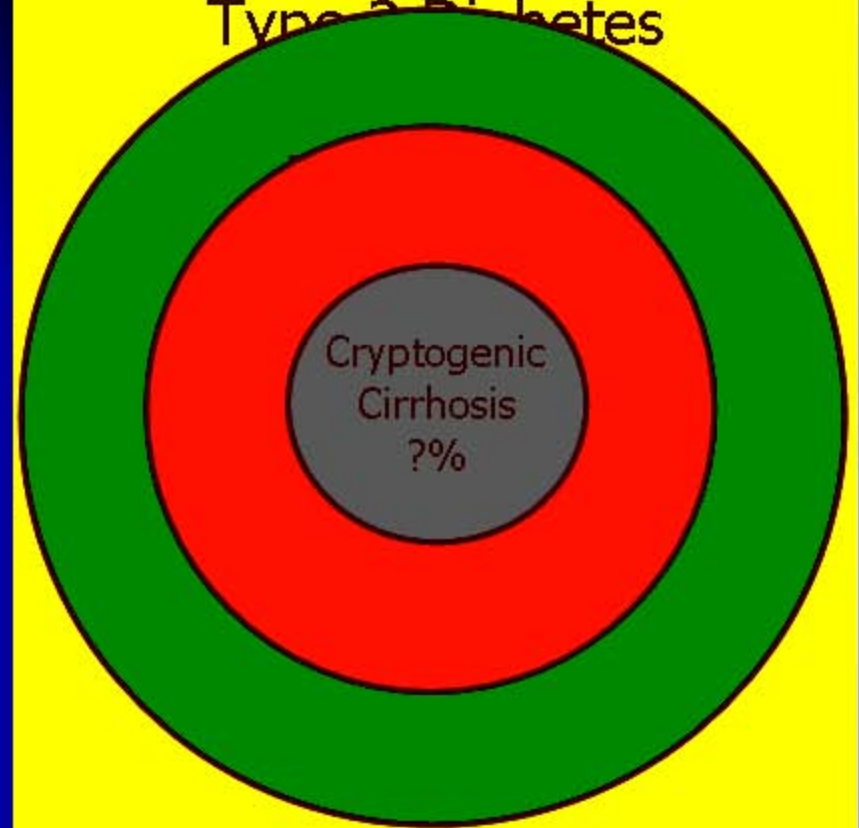
Fibroscan a non-invasive modality is able to detect NASH with fibrosis

# NAFLD/NASH in T2DM

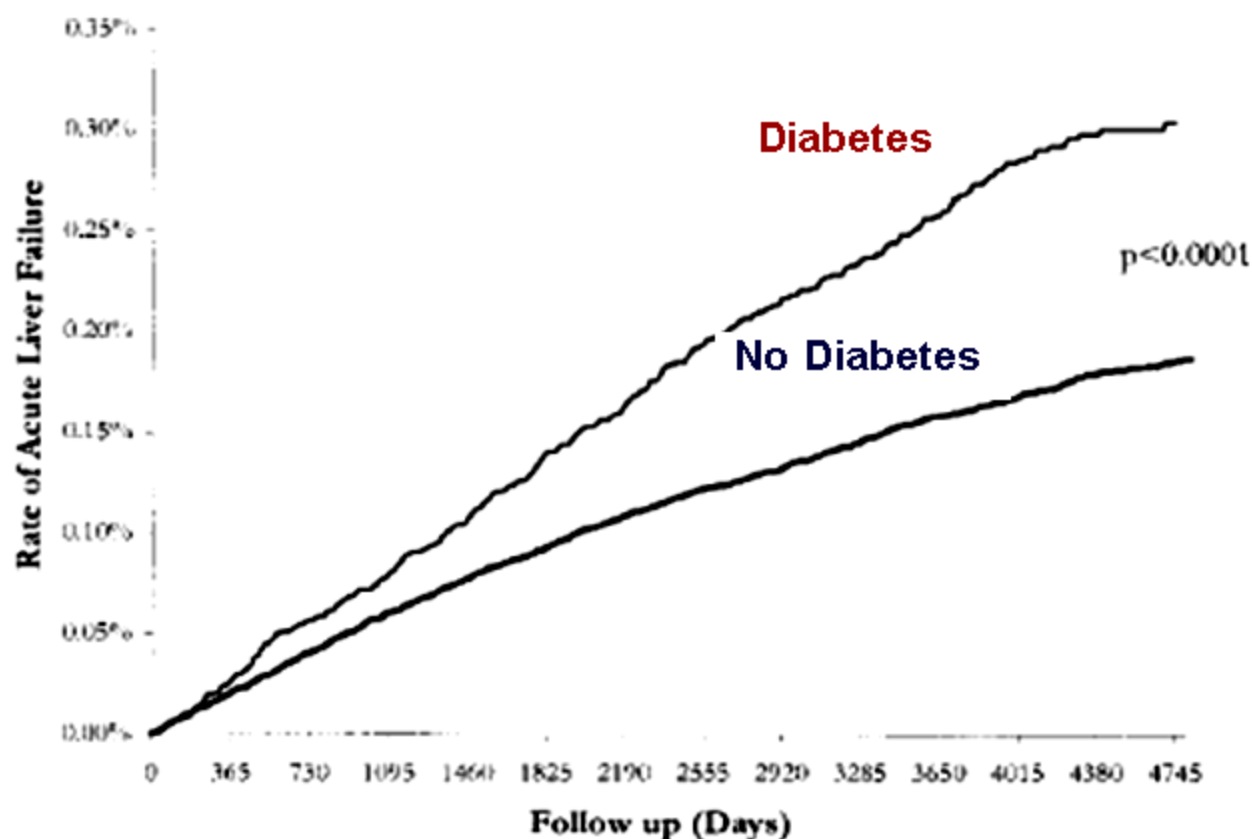
General population



Type 2 Diabetes

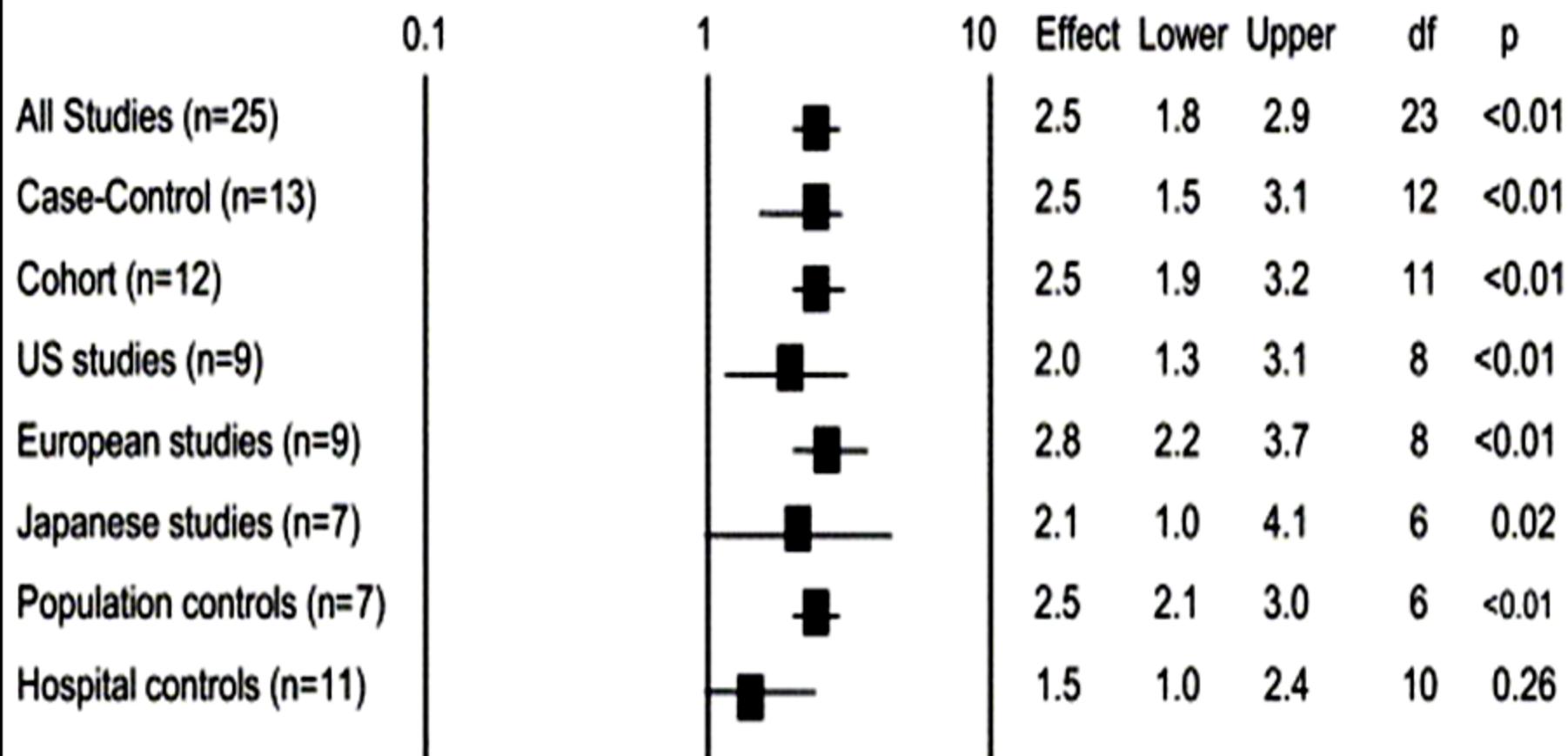


## The cumulative risk of acute liver failure among veteran patients with and without Type 2 Diabetes

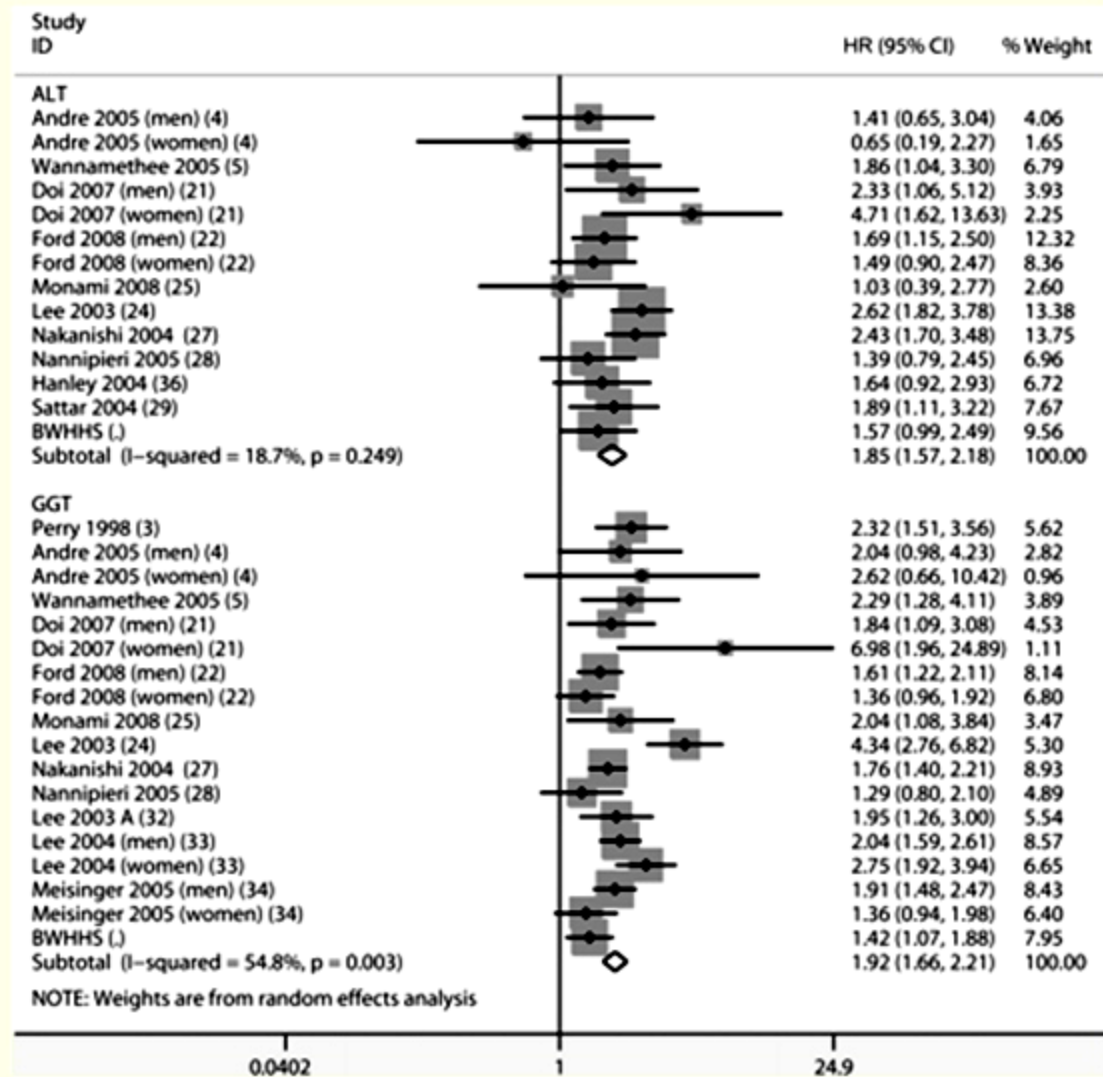


Analysis restricted up to 1997  
(before the introduction of troglitazone).

# Epidemiological evidence of the association bw T2DM and HCC

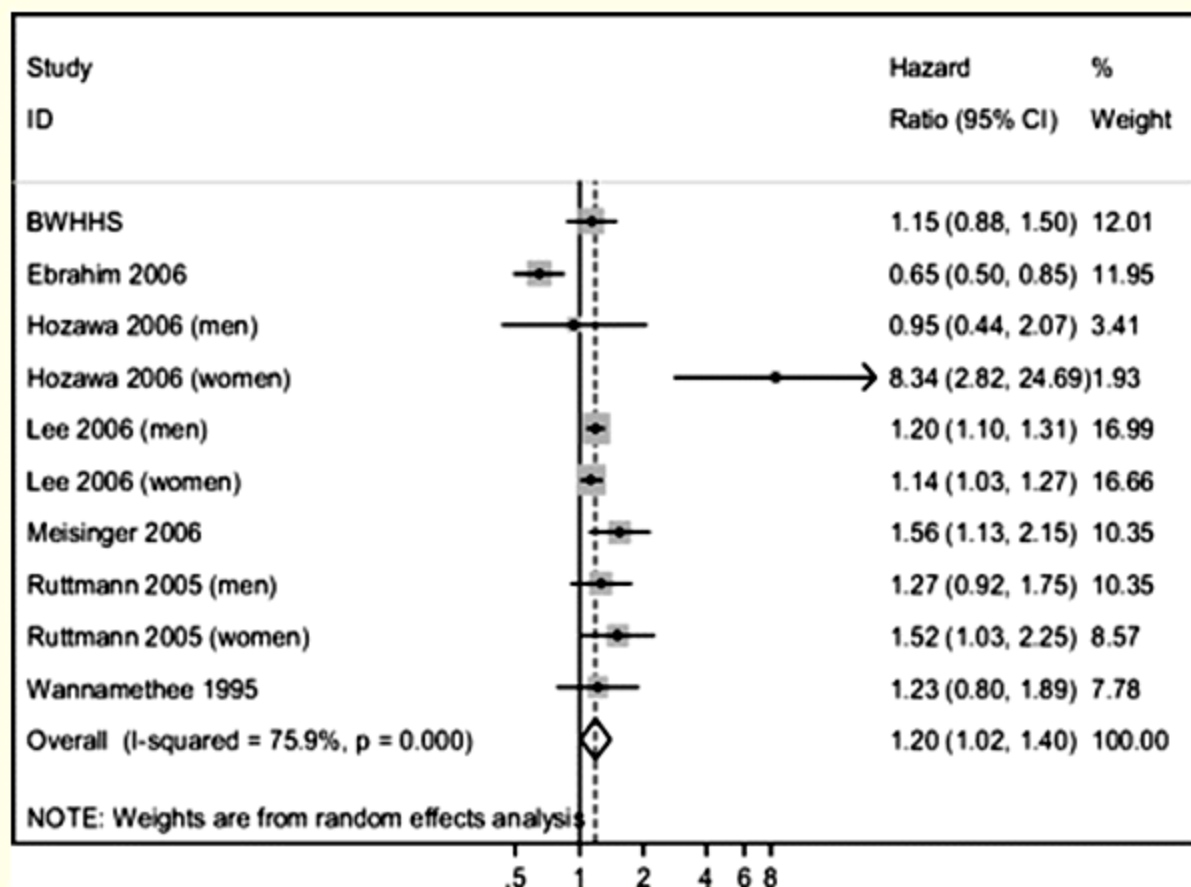


# Meta-analysis of fully adjusted associations of ALT and GGT with incident T2DM from prospective studies

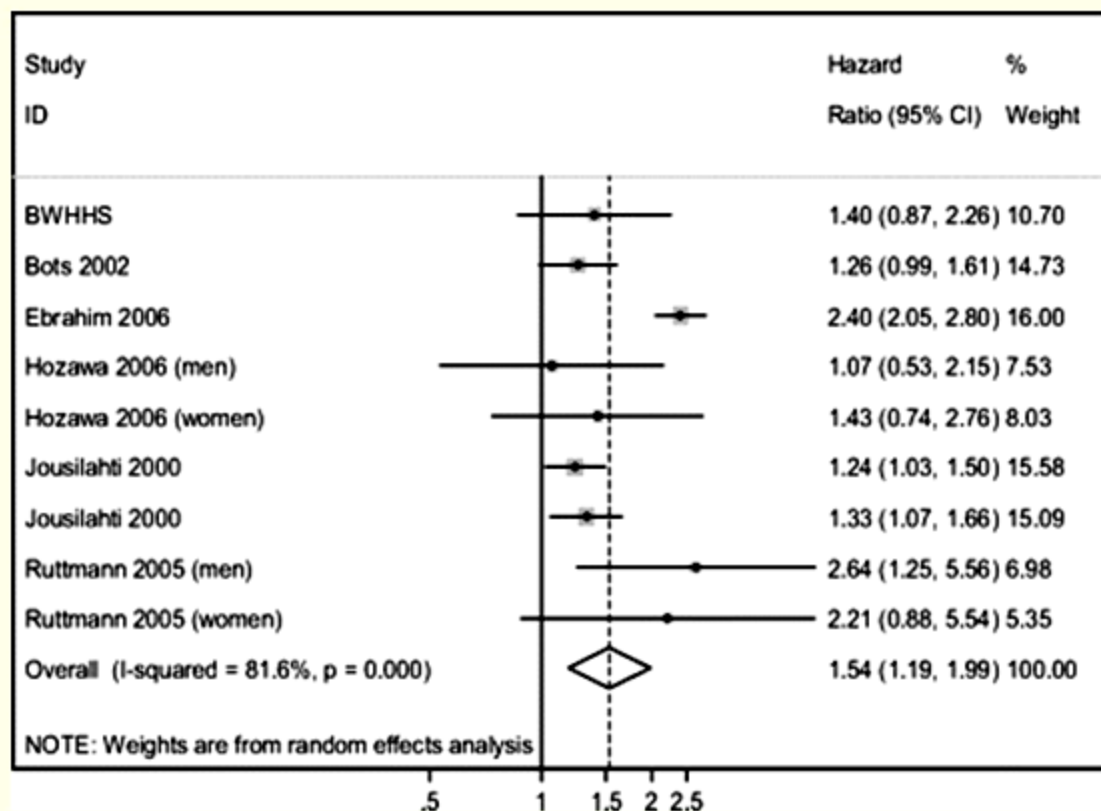


Fraser A, et al.  
Diabetes Care 2009

# Meta-analysis of fully adjusted associations of GGT with incident CHD from prospective studies



# Meta-analysis of fully adjusted associations of GGT with incident stroke from prospective studies





# NAFLD - Clinical Predictors

**Patients at risk to develop NASH with fibrosis:**

**A. Age > 45**

**B. Obesity (BMI > 30)**

**C. Diabetes**



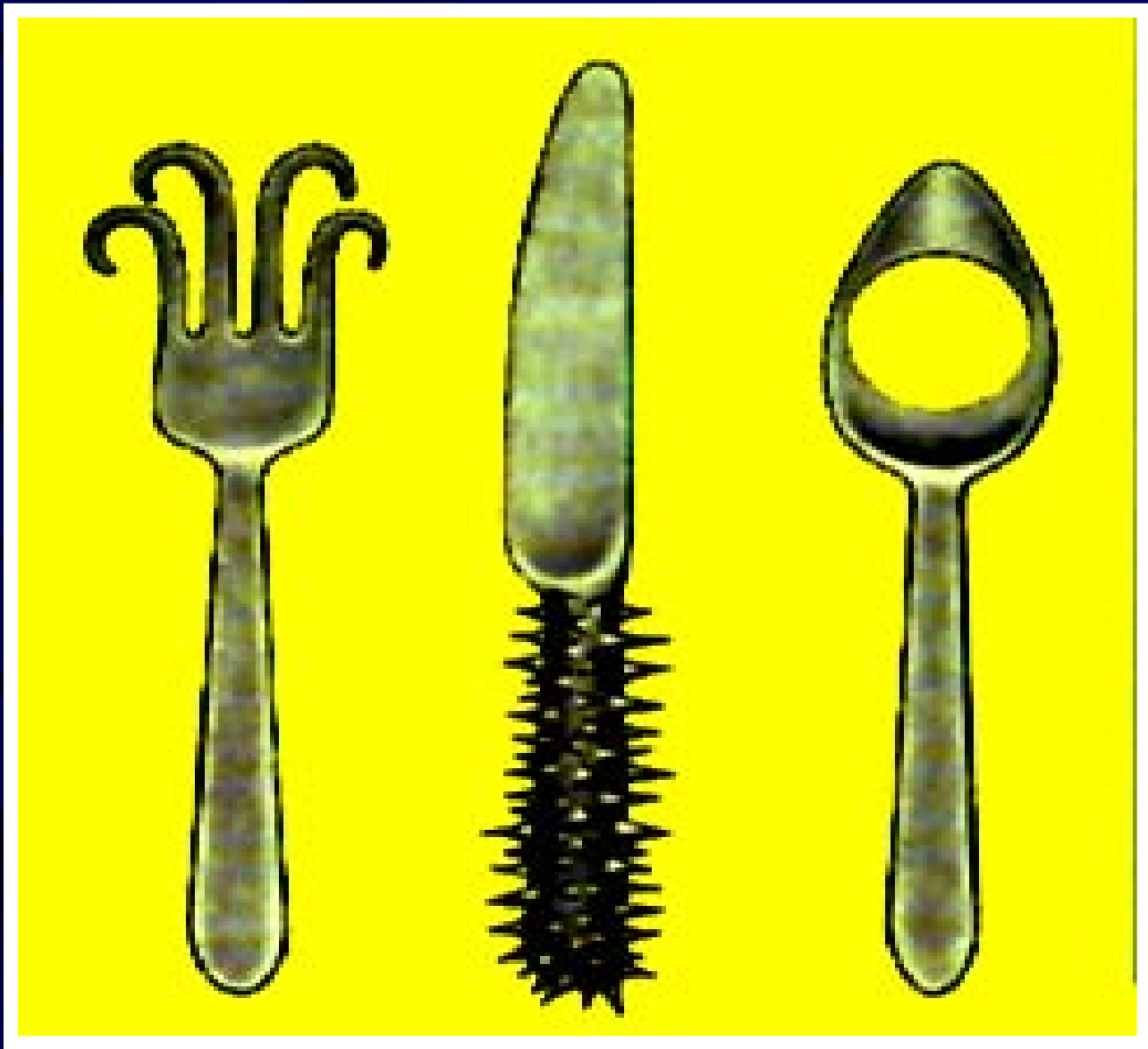
# NAFLD - Weight Loss/Exercise

## **Palmer et al. Gastroenterology 1990**

- 39 obese patients, no primary liver disease**
- Retrospective analysis after weight loss**
- Lower ALT seen in patients with >10% weight loss**

## **Anderson et al. Journal Hepatology 1991**

- 41 obese patients with biopsy-proven NAFLD**
- Low calorie diet (~400 kcal/d) x 8 months then re-biopsied**
- Most improved, but 24% with worse fibrosis/inflammation**
- Histological worsening associated with rapid weight loss**



**Silverware for dieting**

# NAFLD - Insulin Sensitizers

## Metformin

**Marchesini et al. Lancet 2001**

- 20 patients, biopsy-proven NASH**
- 14 metformin (500 tid) x 4 months; 6 controls**
- ALT & OGTT improved in metformin**

**Nair et al. Gastroenterology (in press)**

- 22 patients, biopsy-proven NASH**
- Received metformin 20 mg/kg/d x 12 months**
- Improvement in ALT & insulin sensitivity**
- No improvement in liver histology**

# NAFLD - Cytoprotectants

## **Ursodeoxycholic Acid**

**Laurin et al. Hepatology (1996)**

- 24 patients with biopsy-proven NASH**
- Treated with UDCA 13-15 mg/kg/d x 12 months**
- 63% had improved ALT and steatosis**
- No significant improvement in inflammation/fibrosis**

**Lindor et al. Gastroenterology (1999)**

- Randomized controlled double-blind study**
- 168 patients with biopsy-proven NASH**
- 82 received UDCA and 86 no treatment x 12 months**
- No significant improvement in ALT or histology**

# NAFLD - Antihyperlipidemics

**Laurin et al. Hepatology 1996**

- 16 patients biopsy-proven NASH**
- Received clofibrate 2 g/d x 12 months**
- No significant improvement in ALT or histology**

**Basaranoglu et al. Journal Hepatology 1999**

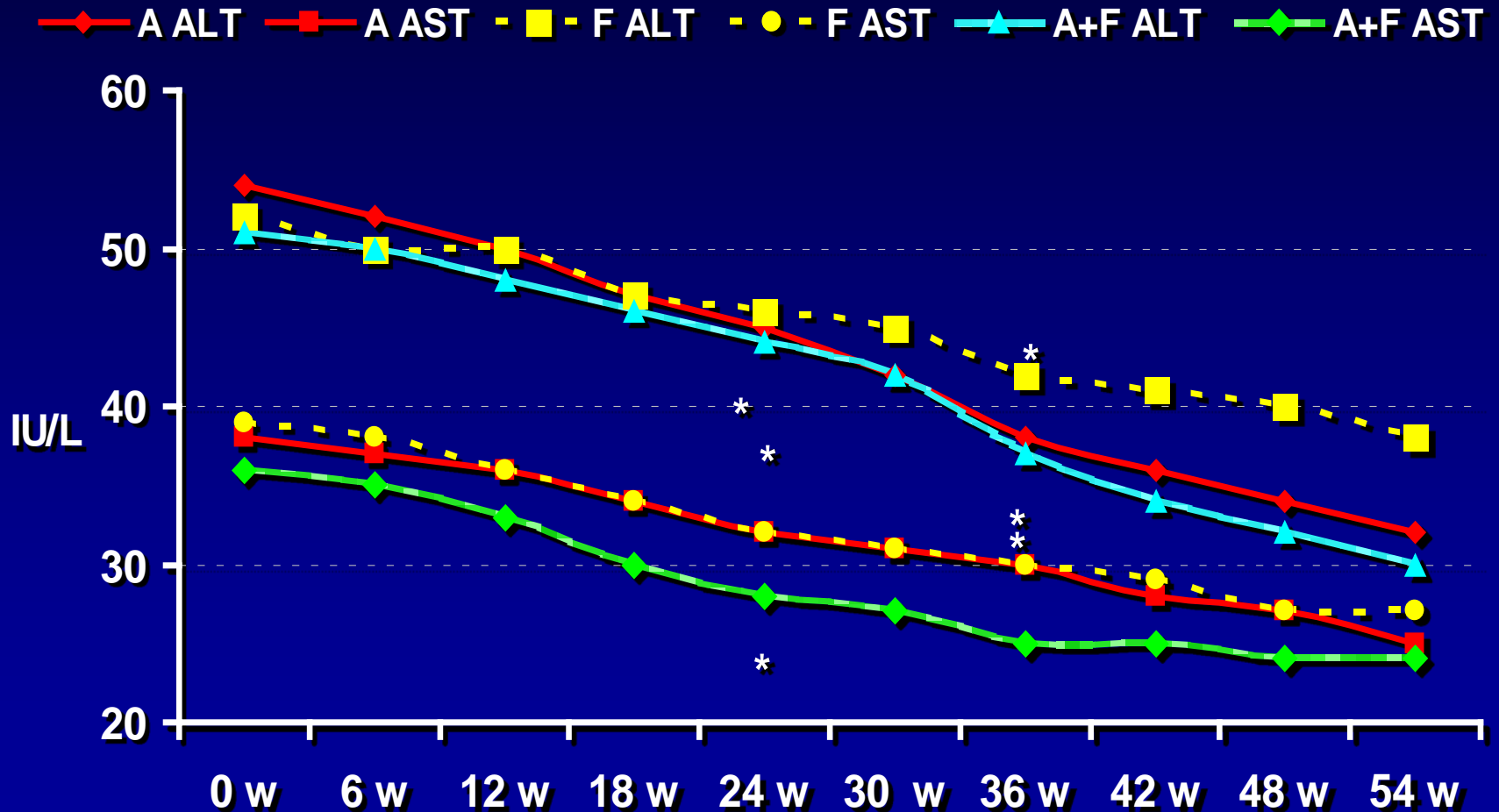
- 46 patients biopsy-proven NASH followed 4 months**
- 23 received gemfibrozil, 23 no treatment**
- 74% patients in gemfibrozil group had lower ALT**
- 30% patients no treatment group had lower ALT**

## TARGETS

Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome: a randomised study

# TARGETS

Χρονοδιάγραμμα μεταβολής των τρανσαμινασών σε ασθενείς με METS και λιπώδες ήπαρ μετά από χορήγηση ατορβαστατίνης, φαινοφιμπράτης και του συνδυασμού τους





ELSEVIER

# METABOLISM

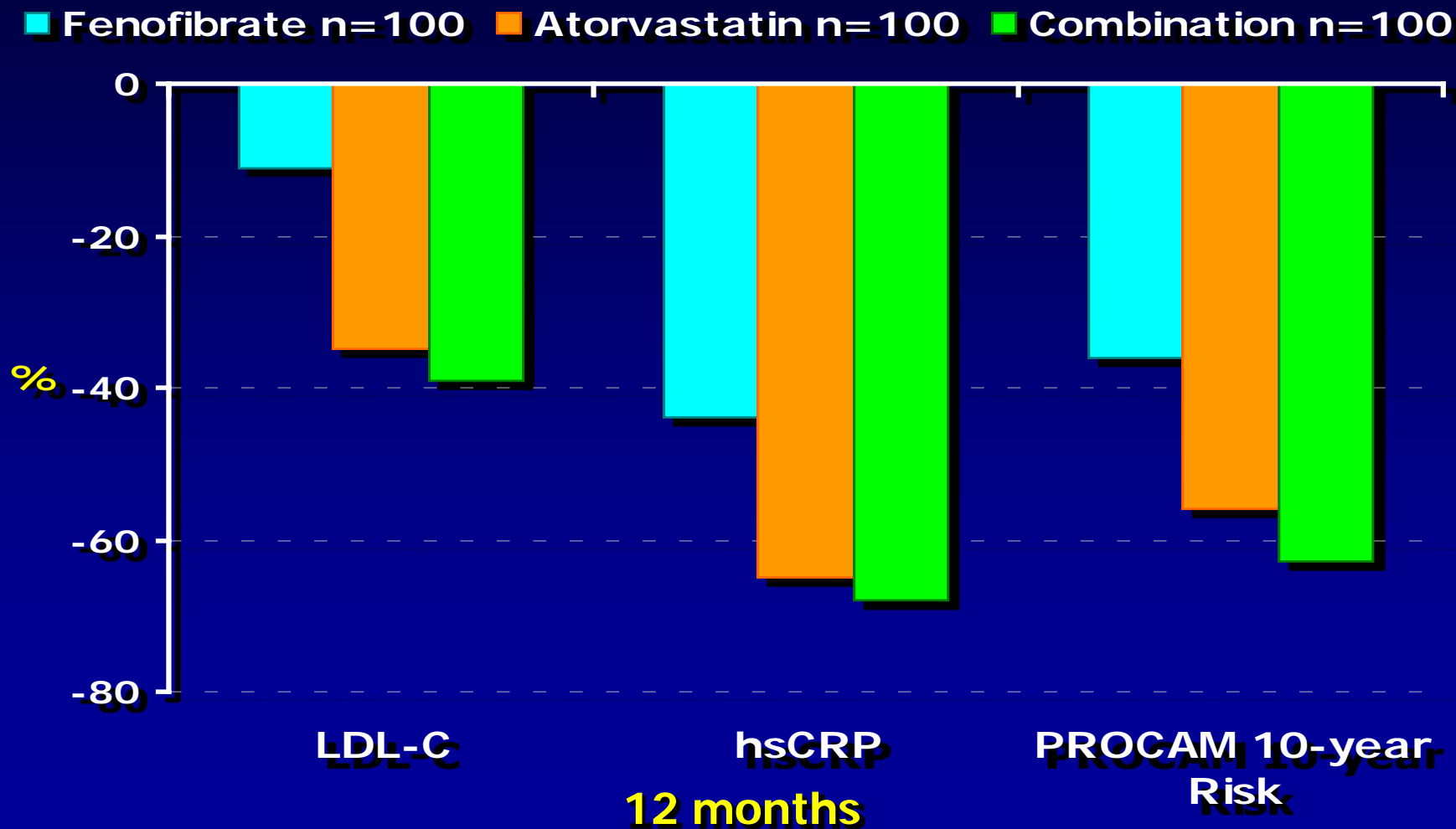
Clinical and Experimental

## Targeting vascular risk in patients with metabolic syndrome





# Targeting Cardiovascular Risk in Patients with Metabolic Syndrome without Diabetes



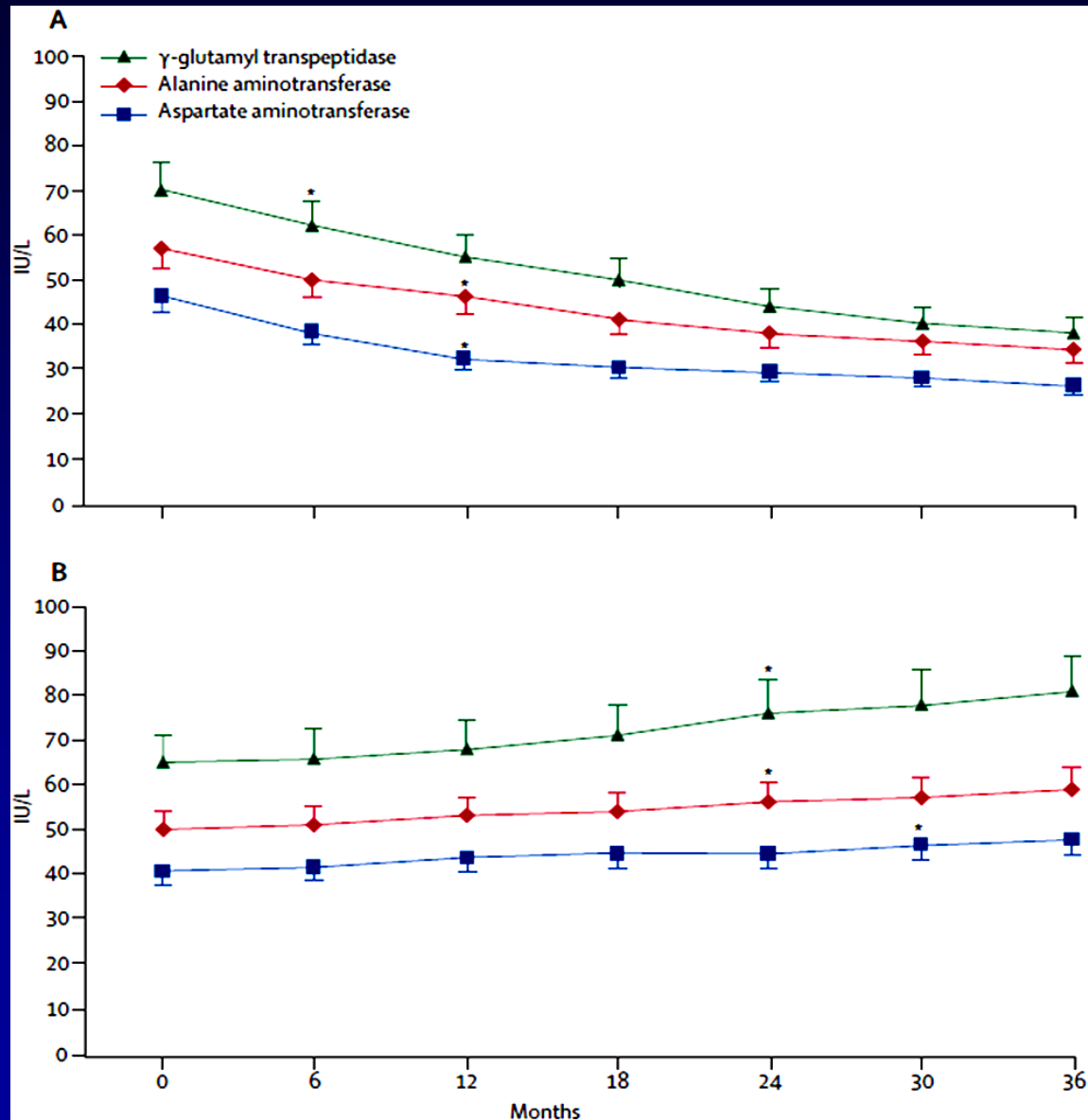
**THE LANCET**

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**Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis**

**Athyros V.G, et al. Lancet 2010, November 24; DOI:10.1016/S0140-6736(10)61272-X.**

# Enzyme activity during 3-year follow-up in GREACE patients with raised liver enzymes



# Cardiovascular events during the 3-year follow-up in GREACE patients with or without raised liver enzymes

	Participants on statins				Participants not on statins			
	Baseline (n=227)	End of study (n=227)	Percentage change	p value	Baseline (n=210)	End of study (n=210)	Percentage change	p value
Total cholesterol (mmol/L)	6.36 (0.70)	4.16 (0.21)*	-35%	<0.0001	6.41 (0.75)	6.21 (0.83)	-3%	0.8
LDL cholesterol (mmol/L)	4.37 (0.47)	2.46 (0.16)*	-44%	<0.0001	4.45 (0.72)	4.24 (0.83)	-5%	0.8
HDL cholesterol (mmol/L)	0.96 (0.18)	1.03 (0.18)*	8%	0.02	0.98 (0.26)	0.96 (0.23)	3%	0.9
Triglycerides (mmol/L)	2.20 (0.63)	1.49 (0.26)*	-32%	<0.0001	2.13 (0.58)	1.98 (0.62)	-7%	0.8
Alanine aminotransferase (IU/L)	57 (8)	37 (6)*	-35%	<0.0001	56 (9)	63 (7)	12%	0.003
Aspartate aminotransferase (IU/L)	49 (7)	26 (4)*	-47%	<0.0001	49 (7)	55 (8)	12%	0.01
γ-glutamyl transpeptidase (IU/L)	70 (10)	38 (6)*	-46%	<0.0001	68 (10)	79 (12)	16%	0.001
EGFR (mL/min per 1.73 m <sup>2</sup> )	59 (17)	70 (10)*	19%	<0.0001	68 (19)	64 (18)	-6%	0.8
Cardiovascular events	..	22 (9.7%)	..	..	..	63 (30.0%)	..	..
Cardiovascular events per 100 patient-years	..	3.2	..	..	..	10.0	..	..

Data are mean (SD) or n (%) unless otherwise stated. EGFR=estimated glomerular filtration rate. ..=not applicable. \*p<0.05 versus end of study in participants with abnormal liver function tests who were not on statins.

# NAFLD - Conclusions

- **NAFLD affects about 25% of the US population**
- Steatosis is relatively benign, but **NASH has significant morbidity/mortality risk**
- **Insulin resistance and cellular damage** are the key pathogenetic mechanisms
- Sustained **gradual weight loss and exercise** are hallmark therapies
- Insulin sensitizers, cytoprotectants, and antioxidants may play role for those who fail conservative therapy. **Statins are safe and beneficial for patients with dyslipidemia, CHD, MetS, and T2DM.**