

# NASH in Children

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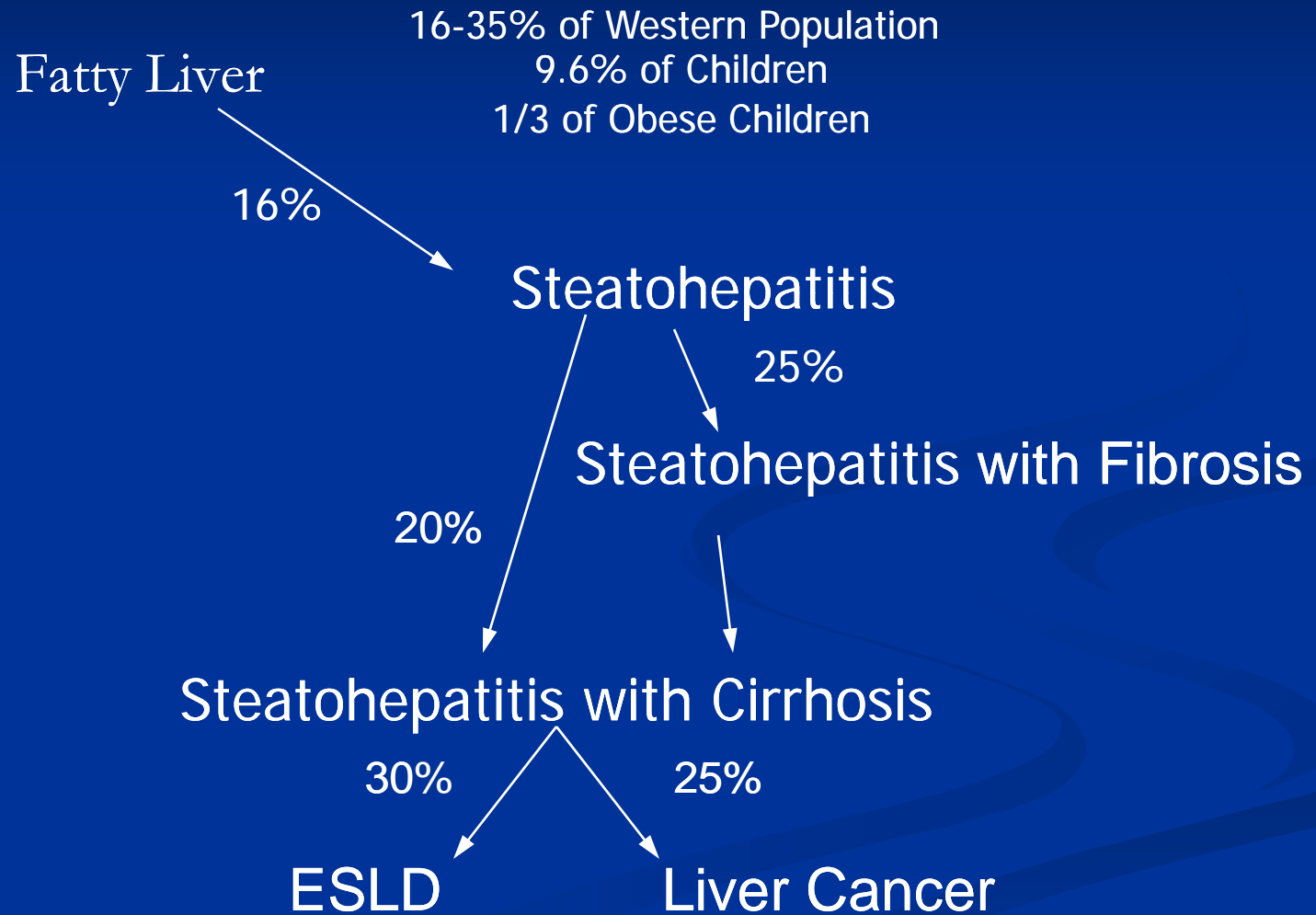
# History of NASH

- 1980- A pattern of liver injury resembling alcoholic hepatitis in patients with no history of drinking is described: non-alcoholic steatohepatitis, NASH (Ludwig)
- 1983- NASH is described in children (Moran)
- 1990- Cirrhosis in NASH is described
- 2002- NASH Clinical Research Network begins

# Definitions

- **NAFLD** Non-Alcoholic Fatty Liver Disease:
    - Simple steatosis: Fat, no inflammation
  - **NASH**: Fat, accompanied by inflammation and evidence of hepatocyte injury
  - **Cirrhosis**: Bridging fibrosis with regenerative nodules, possibly without fat
- \* No history of significant alcohol consumption
- < 2 drinks/day in women, < 3 drinks/day in men

# Stages of Fatty Liver Disorders



# Non-NASH Diseases that Can Cause Fatty Liver

- Wilson's Disease
- Metabolic Disorders including mitochondrial disease
- Hepatitis C
- Cystic Fibrosis
- Drugs: Steroids, tamoxifen, methotrexate, amiodarone
- TPN, starvation

# Conditions Associated with NAFLD

- Obesity
- Diabetes
- Metabolic syndrome
- Polycystic Ovary Syndrome
- Hyperlipidemia

# NAFLD: Adult Epidemiology

- Prevalence estimate 13-26%
- MRS prevalence 34%
- Ultrasound prevalence:
  - 16% of normal weight persons
  - 62% of diabetics
  - 76% patients with BMI >30
- Autopsy prevalence:
  - 2.7% of those with normal weight
  - 18.5% of obese persons
- Abnormal ALT 2.5-5.5% of adults in US

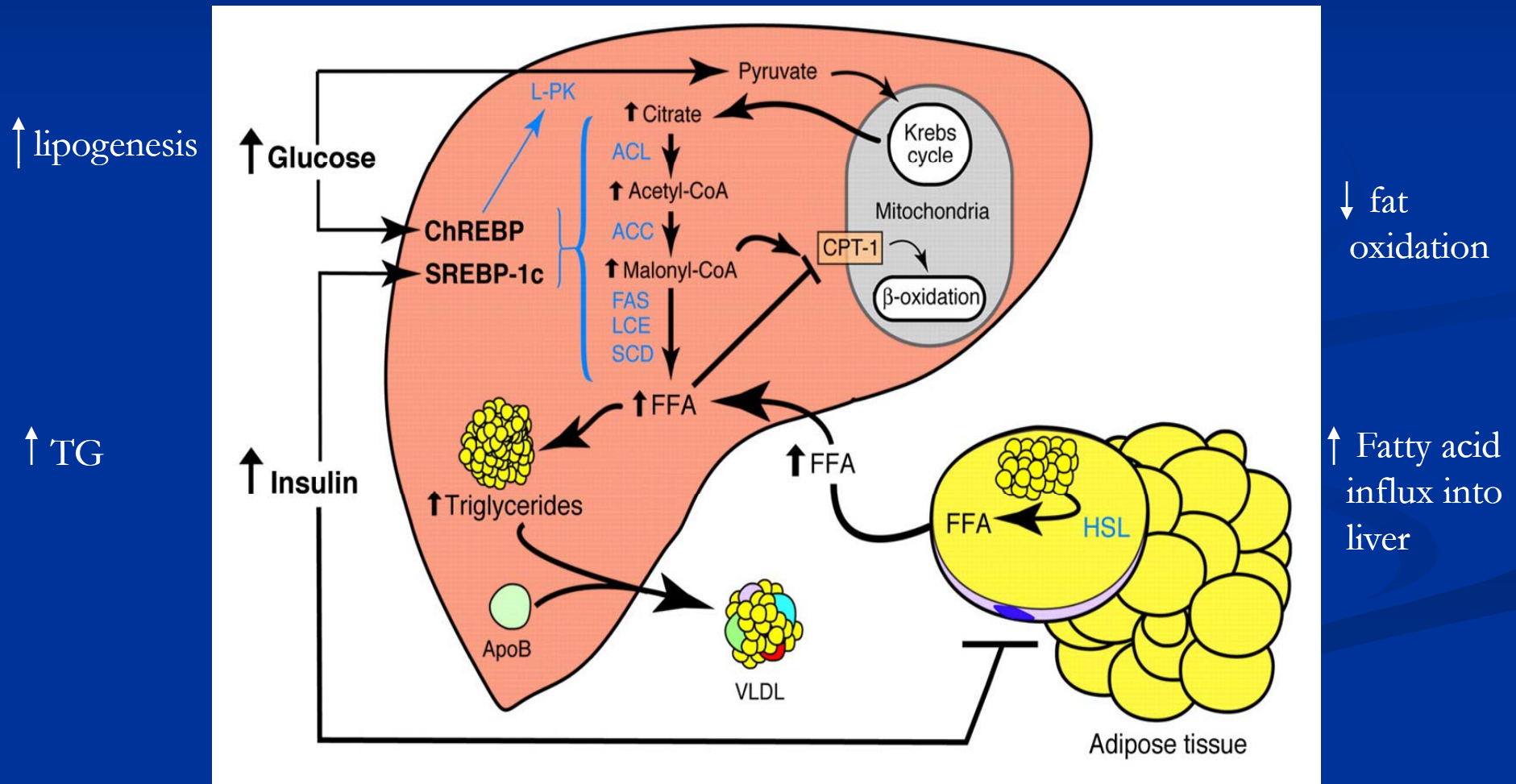
# Pediatric NASH Epidemiology

- Obesity (90%), Acanthosis nigricans, hepatomegaly
- Boys 40% > Girls
- Ages 2-17 years (avg 12 years)
- 25-30% abdominal pain
- Autopsy data:
  - Fatty liver in 9.6% of 742 pediatric autopsies
  - Fatty liver: Hispanic 12%, Asian 10.2%, White 8.6%, African-American 1.5%
  - Fatty liver in 38% of obese children
  - NASH in 3% (23% of the subjects with fatty liver)



# NASH Pathophysiology: “2-Hit Theory”

First hit: Hepatic steatosis due to **insulin resistance**



# NASH Pathophysiology: “2-Hit Theory”

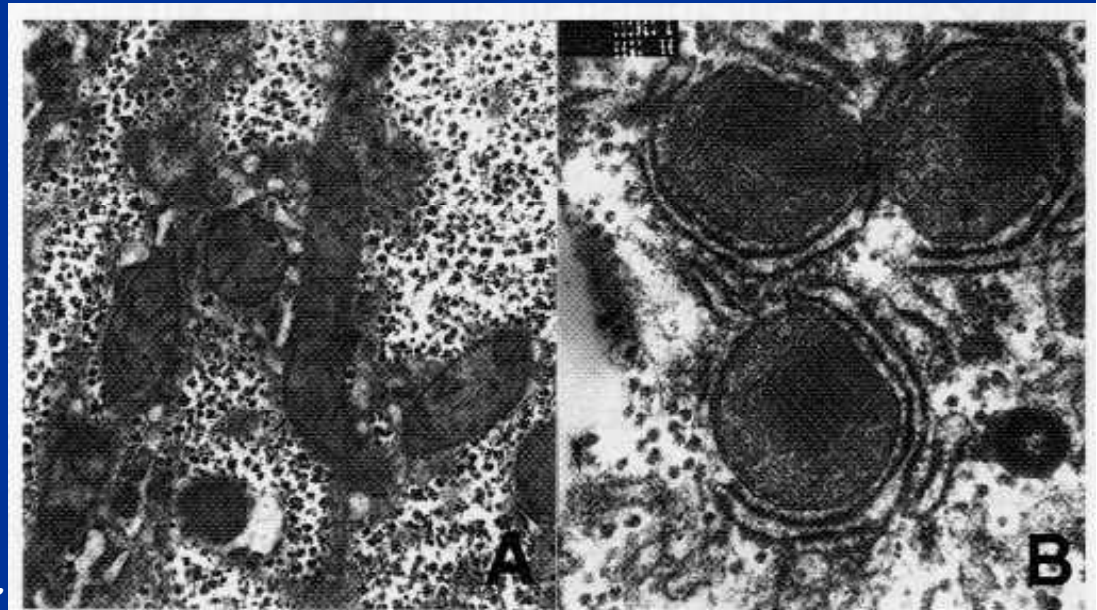
- **First hit: Hepatic steatosis is caused by insulin resistance:**
  - Leptin may stimulate inflammation, fat storage
  - Adiponectin is anti-inflammatory, anti-steatotic

# Recent Bench Data: Insulin Resistance Underlies NASH

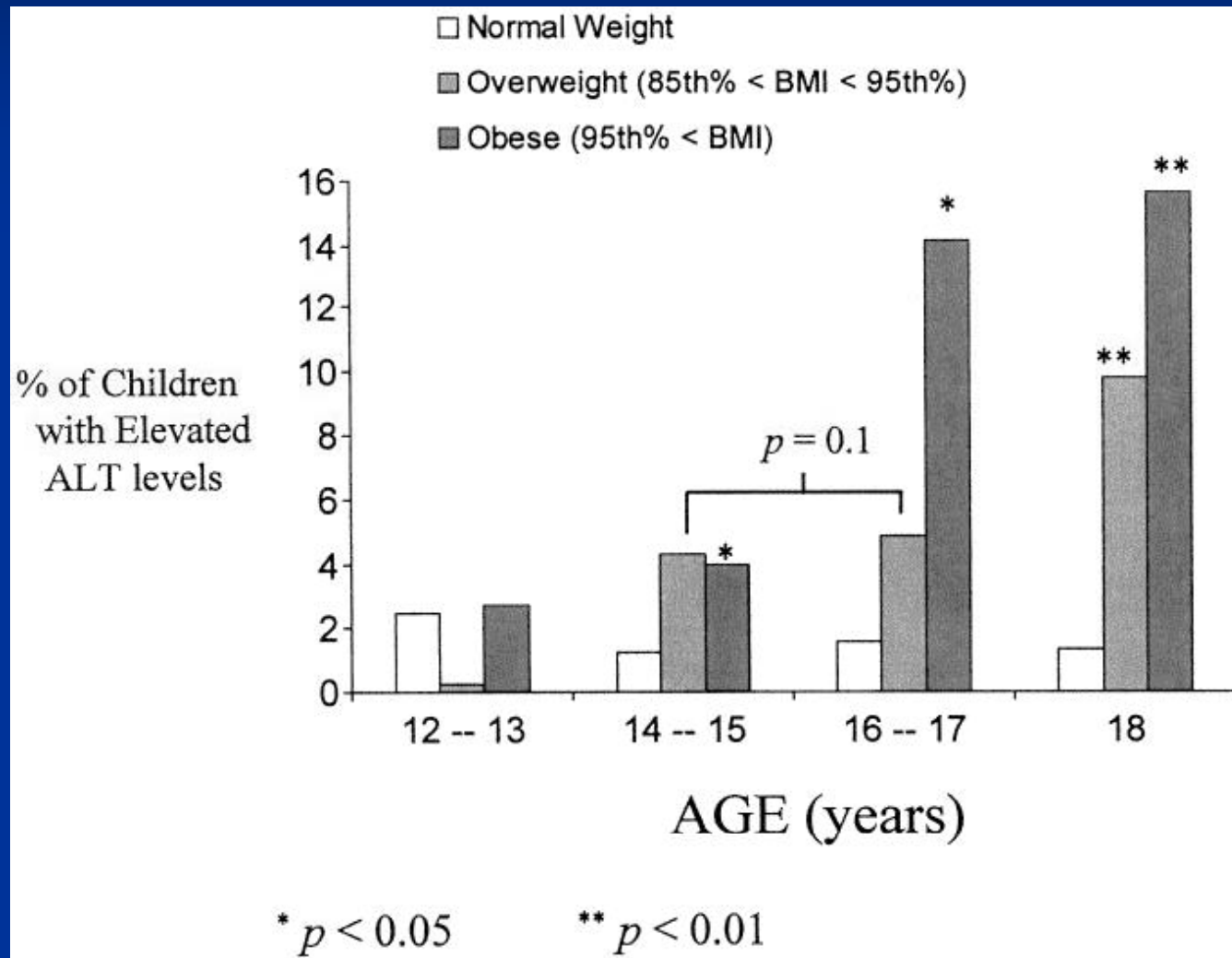
- 2 rat strains: One strain obese/insulin-resistant, one not
- NASH induced in rats via choline deficient diet
- Non insulin-resistant rats were resistant to NASH
- NASH improved only when obese/IR rats were treated with pioglitazone and increased adiponectin

# NASH Pathophysiology: 2<sup>nd</sup> Hit

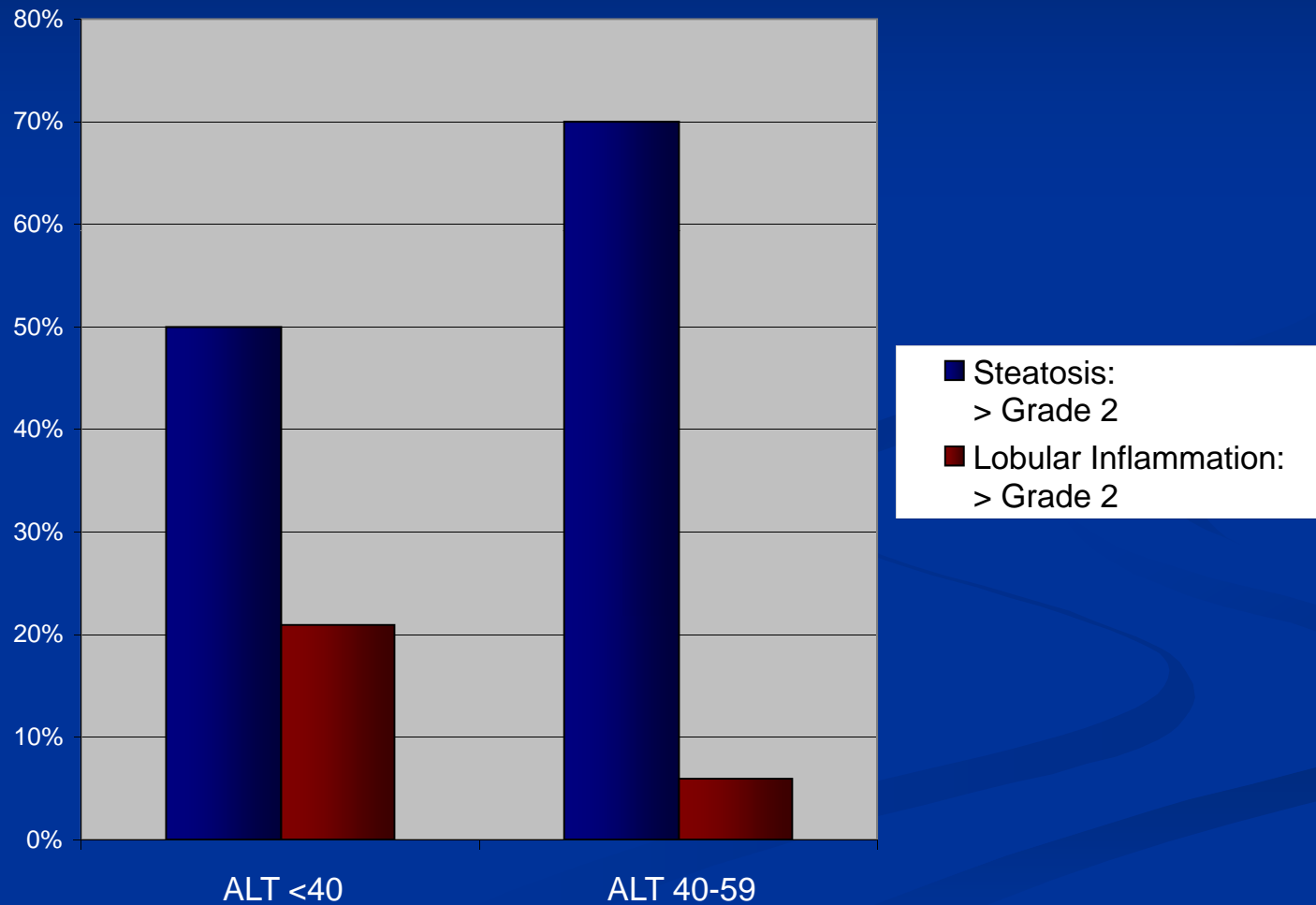
- Oxidative stress
- Inflammatory mediators/cytokines
- Lipotoxicity: Direct toxicity to hepatocytes (lipid peroxidation)
- Mitochondrial permeability
- Stellate cell activation/mediators of fibrosis
- Other factors



# Prevalence of Elevated ALT in Children: NHANES III

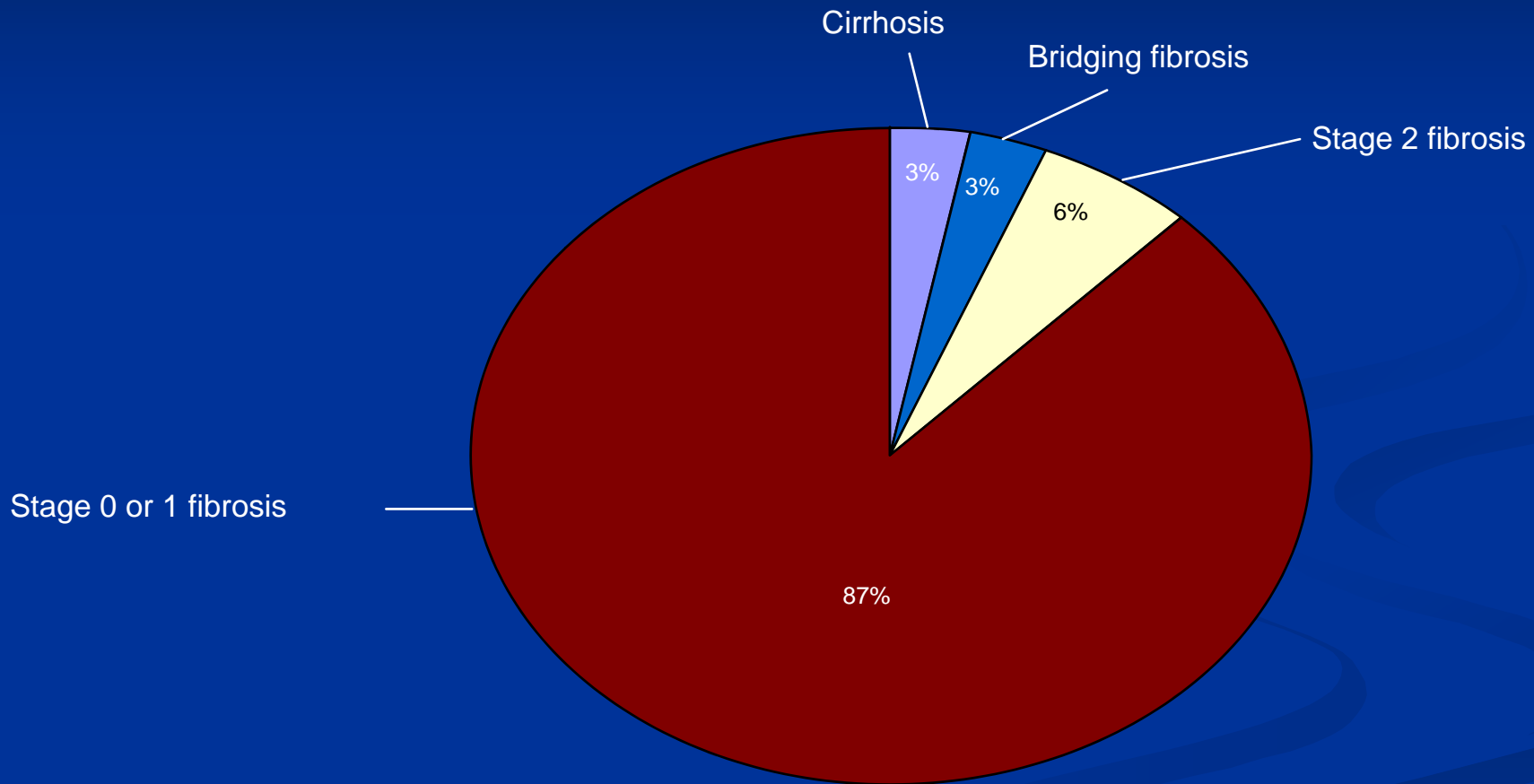


# Significant Histologic Abnormalities in Children with ALT < 60



Molleston: NASPGHAN Abstract 2008.

# Fibrosis in Children with NASH and ALT < 60



# Imaging of NAFLD

CT Fatty Liver



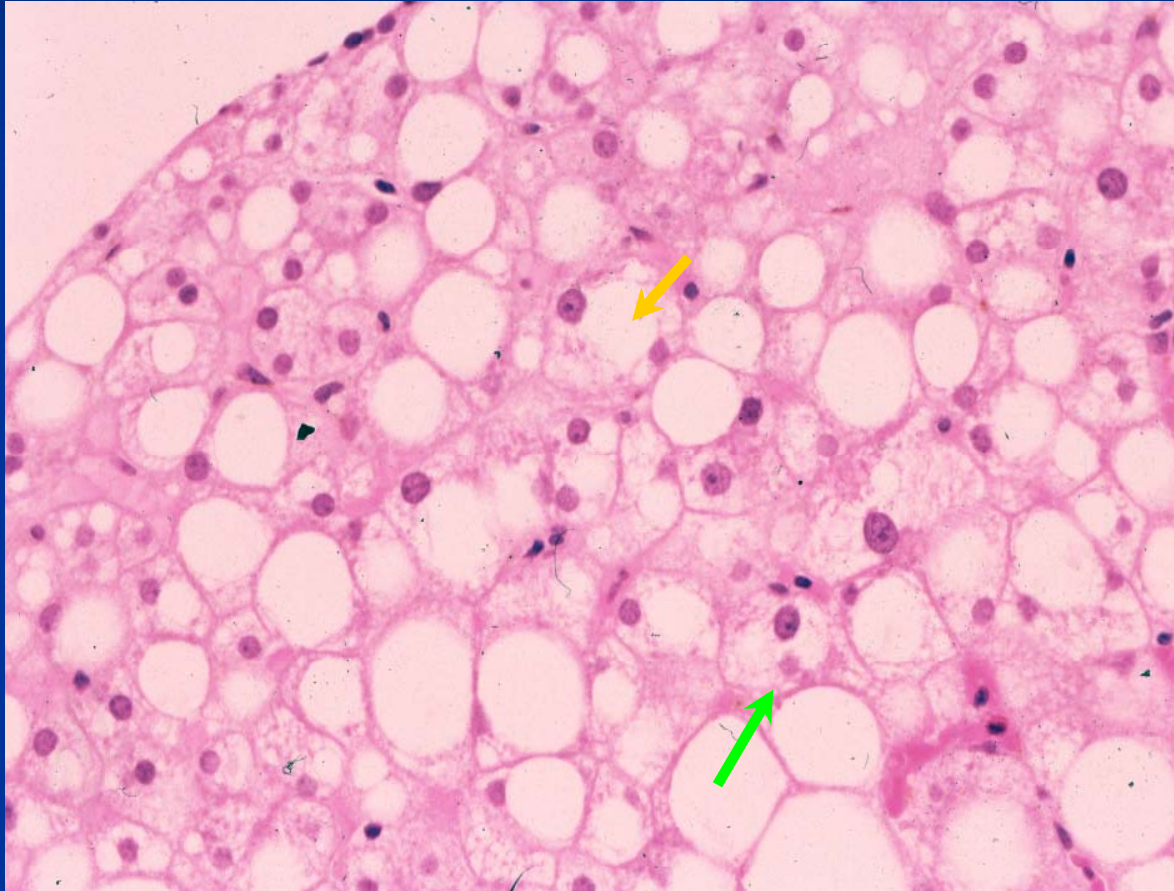
US Fatty Liver



Images from Medscape



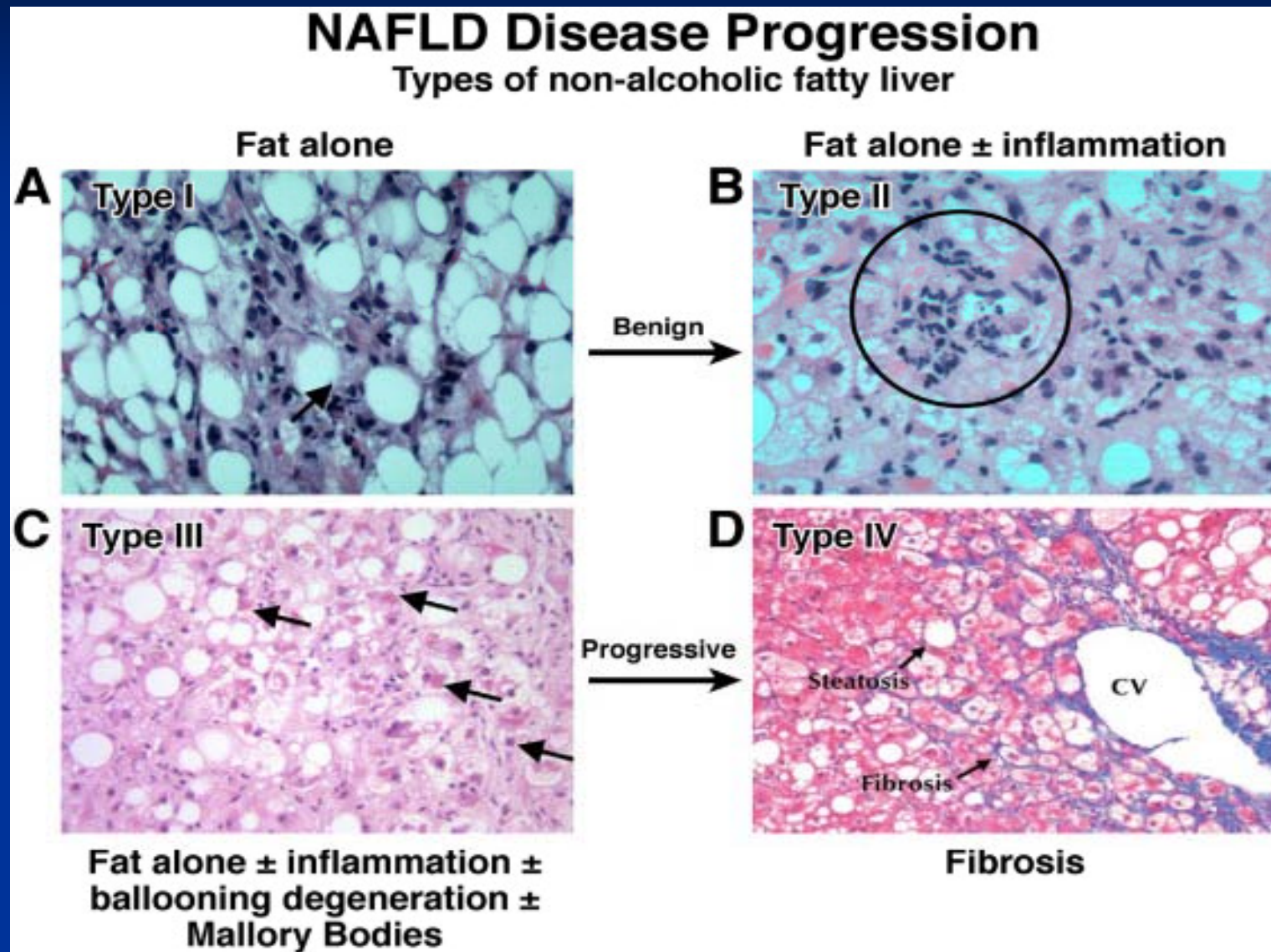
# Histology of NASH



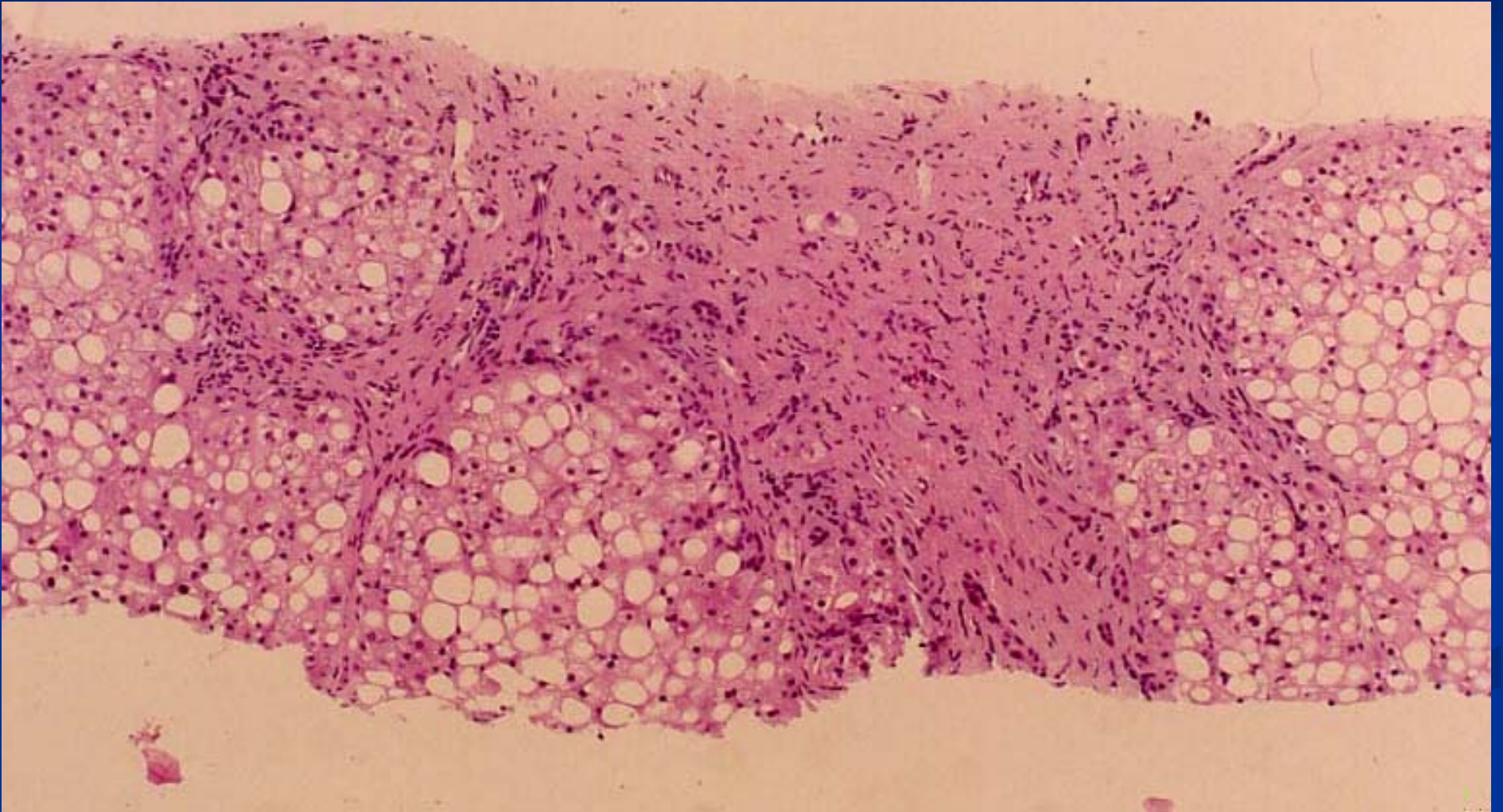
Ballooning  
degeneration

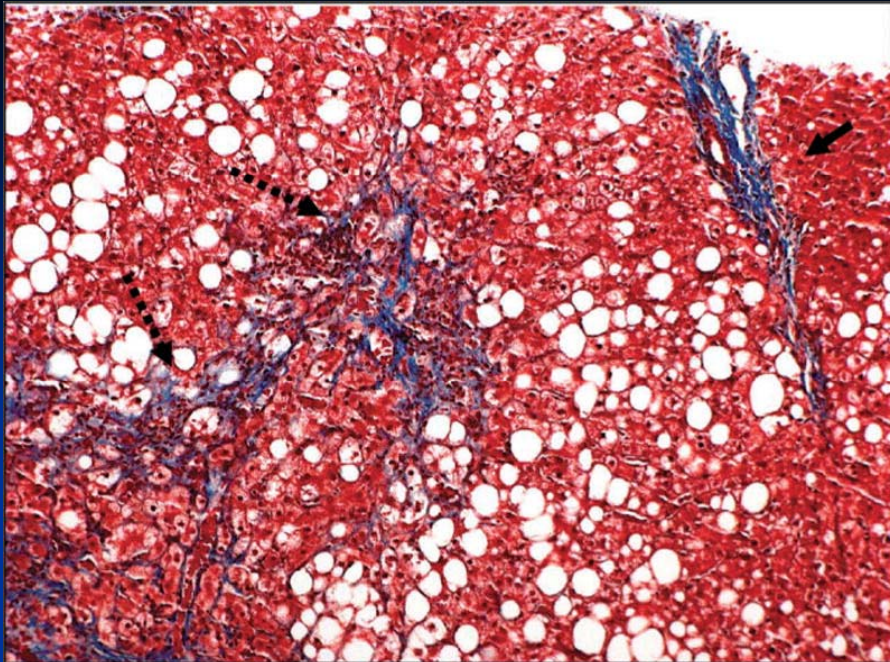
Mallory's  
hyalin

# Progressive Histology of NASH

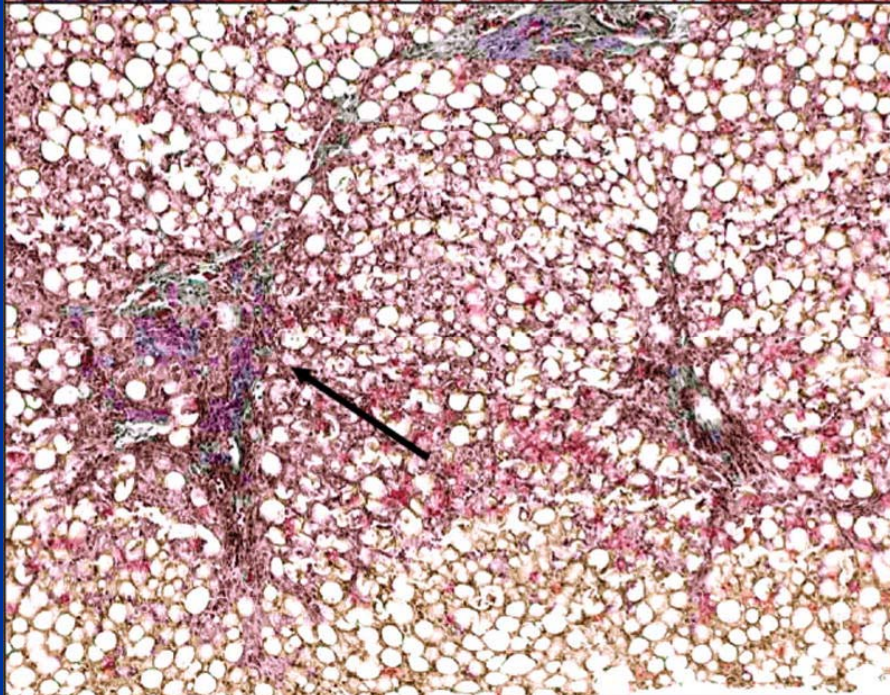


# NASH Cirrhosis





**Adult NASH:** Centrilobular steatosis, ballooning, Mallory bodies, sinusoidal fibrosis



**Pediatric NASH:** Severe diffuse steatosis, periportal inflammation and fibrosis

# Natural History of NAFLD

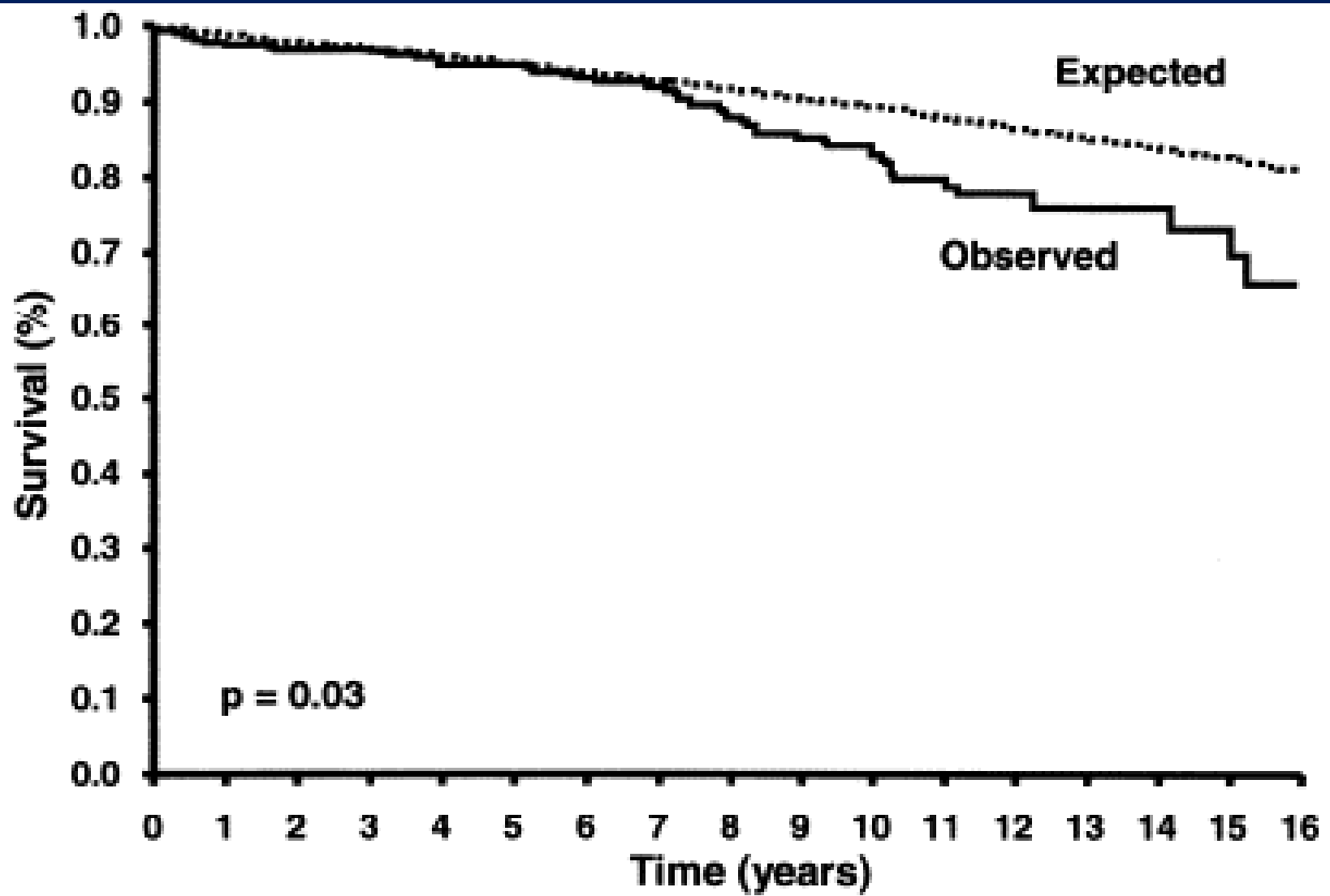
- 420 adults in USA diagnosed with NAFLD
- 7.6 (0.1 - 23.5) year follow-up
- 22% developed diabetes
- 5% with cirrhosis
- 3.1% with liver-related complications (including one transplant and 2 HCC)
- Among deaths, 13% due to liver disease, 25% due to CAD

*Gastroenterology* 2005;129:113

- RR of Liver Cancer in men BMI>35 is 4.52 (Prostate = 1.34; All cancers = 1.52)

*N Engl J Med* 2003;348:1625-1638

# ↑ Mortality in Adults with NASH



No. at risk 420 399 389 382 361 306 254 217 176 143 109 71 54 40 31 23 14

# Natural History of NASH in Children

- 66 Children followed for up to 20 years
- 4/66 (6%) developed diabetes in 4-11 years
- 4/5 children with multiple liver biopsies showed progression of fibrosis
- 2 children died
- 2 children were transplanted for decompensated cirrhosis (both had recurrent NASH in the graft)
- Standardized **mortality ratio 13.6**

# NASH Comorbidities

- Obstructive sleep apnea may correlate with ALT
- NASH is associated with increased risk of cardiovascular disease in adults
- NASH is associated with higher carotid artery intimal thickness in children
- NAFLD is associated with increased risk of metabolic syndrome in children



# Proposed NASH Causes and Treatments

## Cause

- Obesity
- Nutritional deficiencies
- Insulin resistance
- Oxidative stress
- Cytokines, adipokines
- Bacterial overgrowth
- Hyperlipidemia

## Treatment

- ★ Diet, exercise
  - Increase vitamins/fiber
- ★ Metformin, pioglitazone
- ★ Antioxidants
  - Anticytokine therapy
  - Probiotics/antibiotics
  - Antihyperlipidemics

# NASH Treatment

## Lifestyle/Weight Loss

- Studies in adults:
  - 4 studies (40 subjects) of calorie restriction
  - 10 studies (626 subjects) of diet + exercise
- Beneficial effects have been seen on ALT, insulin resistance, liver fat, and inflammation/fibrosis

# Treatment of Adult NASH

## Metformin

- RCT in 110 adults with NASH:
  - 55 treated with metformin 1g bid
  - 55 treated with either vitamin E or diet
- ALT improved in all groups, especially metformin
- In metformin patients, improvement in fat, inflammation, and fibrosis on biopsy

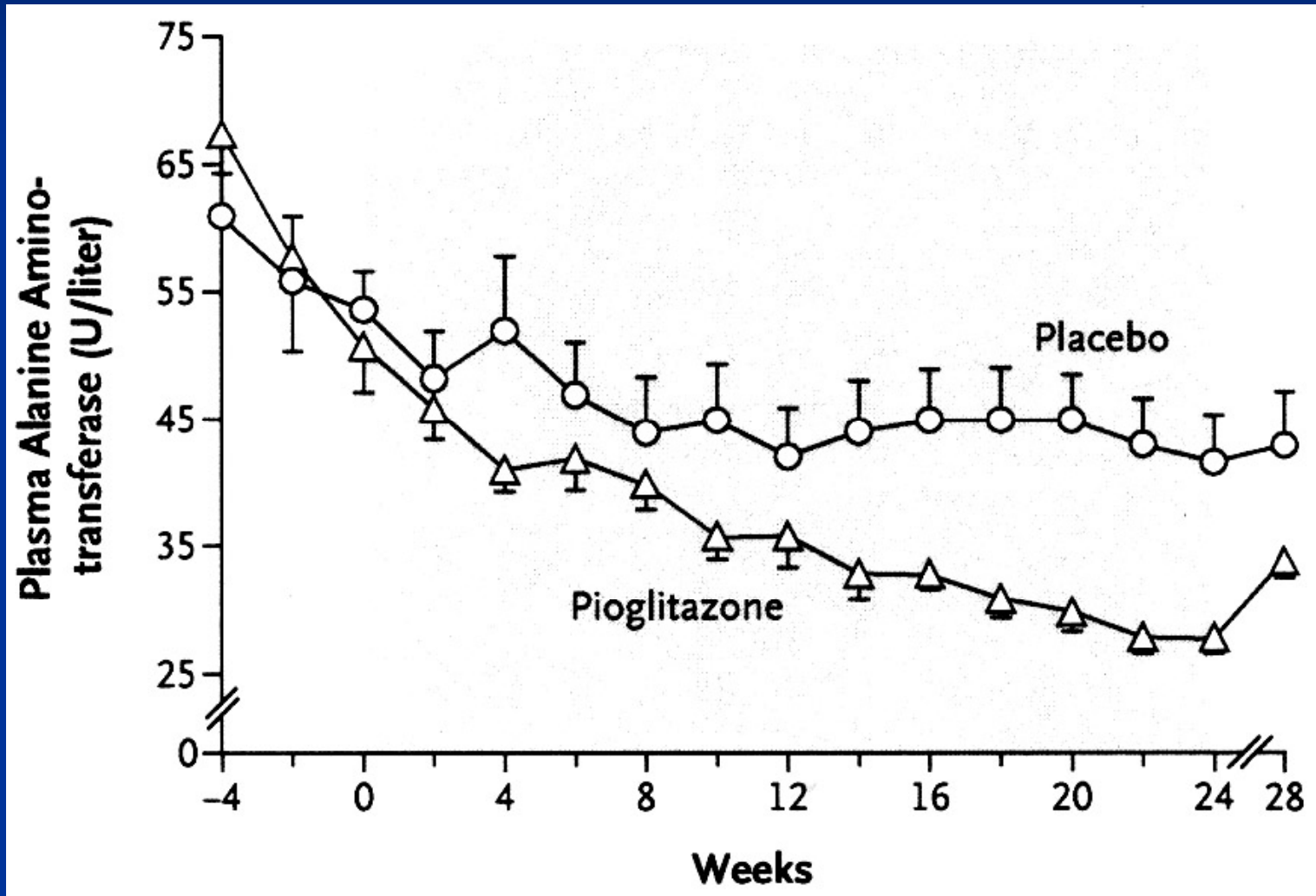
# Treatment of Adult NASH

## Pioglitazone

- 55 adults with insulin resistance and NASH
- RCT 6 months:
  - hypocaloric diet + pioglitazone
  - hypocaloric diet + placebo

	<u>Pioglitazone</u>	<u>Diet</u>
■ ↓ ALT:	58%	34%
■ ↓ liver fat:	54%	0%
■ Improved inflammation but not fibrosis		

# Improvement in ALT in Adult NASH on Pioglitazone



# Summary of Adult Clinical Studies Regarding TZDs and NASH

Author/Year	N	Design	Agent	Duration	Liver Biopsy	Amino-transferases	Histology
Caldwell, et al. 2001	10	Open label	Troglitazone	3-6 Months	5	Improved	Improved mild inflammation
Neuschwander-Tetri, et al. 2003	30	Open label	Rosiglitazone	48 Weeks	22	Improved	Improved steatosis and inflammation
Promrat, et al. 2004	18	Open label	Pioglitazone	48 Weeks	18	Improved	Improved steatosis, inflammation, and fibrosis
Sanyal, et al. 2004	21	RCT	Pioglitazone	6 Months	?	Improved	Improved steatosis, inflammation and fibrosis
Belfort, et al. 2006	55	RCT	Pioglitazone	6 Months	47	Improved	Improved steatosis and inflammation

# Adult NASH PIVENS Trial: Pioglitazone vs Vitamin E vs Placebo

- 247 Adult patients randomized to Pioglitazone or Vitamin E or placebo for 2 years in NASH CRN
- Histologic improvement endpoint reached by:
  - 43% of Vitamin E
  - 34% of Pioglitazone
  - 19% of placebo
- ↓ steatosis, inflammation, ALT in Pioglitazone and Vitamin E group
- Ave weight gain: Pioglitazone- 5 kg  
Vitamin E- 0.4 kg  
Placebo- 0.8 kg

# Effects of Bariatric Surgery on NASH: A Meta-analysis

- 15 Studies, 766 paired liver biopsies
- Reduction in BMI of 19% to 42%
- Steatosis improved 92%
- Steatohepatitis improved 81%
- Fibrosis improved 66%
- Complete resolution of NASH 70%



# NASH Treatment in Children: Metformin

- Open-label pilot study: 10 children NASH and elevated ALT; Treatment 6 months
  - Mean ALT 184 → 98
  - MRI Liver fat 30% → 23%
  - HRQOL improved
  - Weight decreased by 1kg, BMI by 1.6 (80% of subjects didn't lose weight)

# NASH Treatment in Children: Vitamin E

- Open-label Pilot study in 11 children with NASH
- Vitamin E 400-1200 IU, for 2-4 months
- All 11 normalized ALT, without weight loss

# Pediatric NASH TONIC Trial

## Metformin vs Vit E vs Placebo

- Inclusion criteria:
  - Ages 8-18 years
  - Liver biopsy showing NASH within last 6 months
  - ALT >60 IU/L
- Outcomes:
  - ALT
  - Biopsy
  - HRQOL, etc, etc

# Summary

- NASH is a potentially serious disease
- Diet and exercise resulting in slow steady weight loss should, for many reasons, be recommended and can improve NASH
- Vitamin E appears to be helpful for the treatment of NASH in adults
- Insulin sensitizers like metformin and pioglitazone may be helpful for treatment of NASH
- Monitor for co-morbidities