Fatty Liver Disease

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What is Fatty Liver or NASH?

NASH= Non-Alcoholic Steatohepatitis

- This is part of the spectrum of NAFLD (Non-Alcoholic Fatty Liver Disease)
- Characterized by accumulation fat within the liver cells, with / without inflammation of liver or liver cell injury or damage.
- Patients lack the significant history of alcohol drinking

NAFLD

- Fatty Liver (NAFLD) can be progressive
  1. Fat accumulation in liver (Steatosis)
  2. Fat + Inflammation and liver cell injury
     -Non-alcoholic steatohepatitis (NASH)
  3. Non-alcoholic steatohepatitis + Fibrosis (scar tissue in the liver)
  4. Cirrhosis (multiple nodules formation from scar tissue)
  5. Liver Cancer (Cancer from Liver Cells)

- Diehl et al., Gastroenterology 1988; 95: 1056-1062 Teli MR et al. Hepatology 1995; 22: 1714-1719

How common is NAFLD?

- The most common cause of abnormal liver function tests in the United States.
- Estimated 30.1 million with NAFLD and 8.6 million with NASH
- Affects 10-24% of the population
- 58-74% of the obese population
- Affects 2.6% of children
  - 23-53% of obese children

What Causes Fatty Liver?

- Certain Drugs, Starvation, Obesity, Alcohol, Diabetes, Hypertriglyeridemia
- Wilson's disease, alpha-1 anti-trypsin disease, TPN, autoimmune hepatitis, special inherited syndromes, hepatitis C

What Causes NASH?

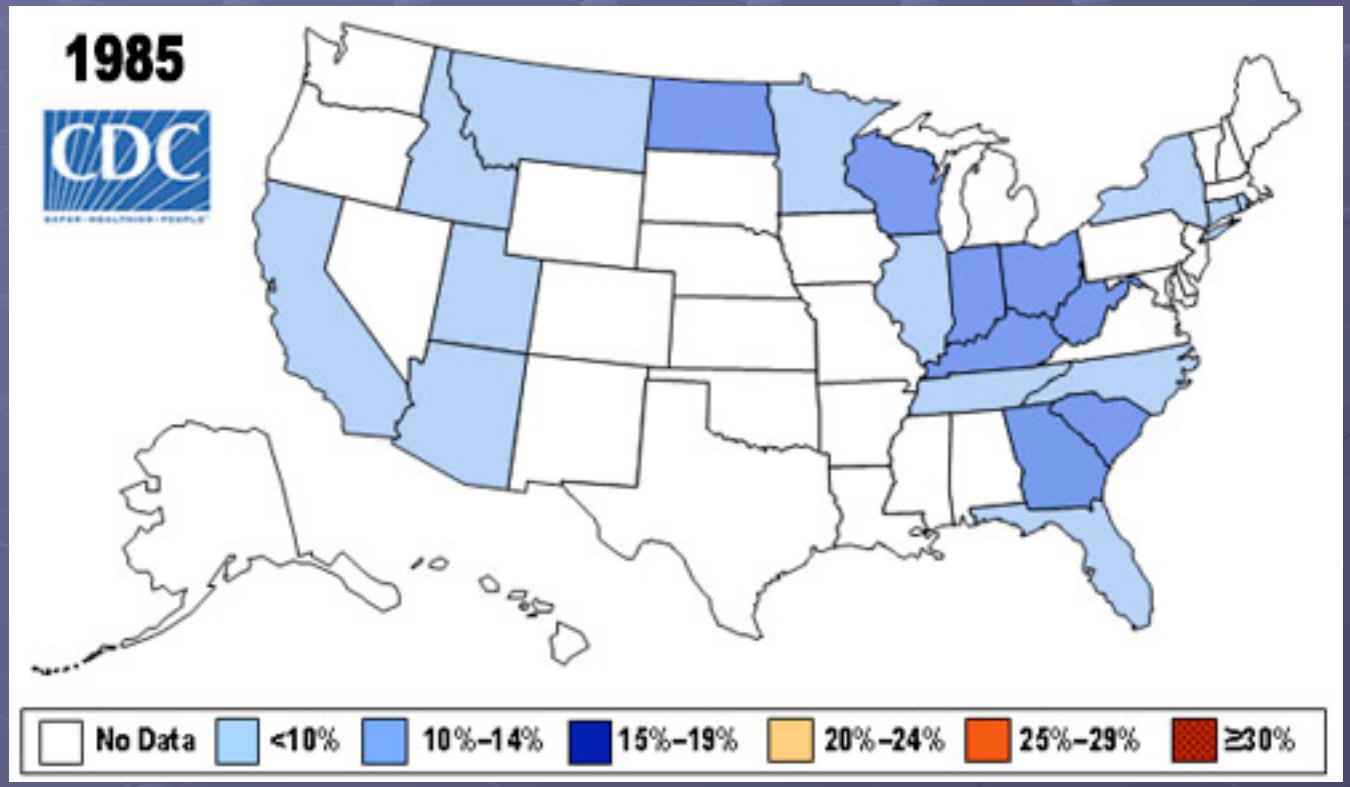
- Two Hit Hypothesis:
- 1st Hit:
  - Obesity
  - Insulin Resistance
- 2nd Hit:
  - Environment
  - Genetics
  - Oxidants
  - Some other form of liver disease (infection/ metabolic)

Who might develop NAFLD?

- Boys more than girls (2:1)
- Teenagers: most diagnosed 11.6-13.5 yrs
  - Now being seen commonly in pre-pubertal children
- Hispanics more than non-Hispanics
- Diabetics (Type 2)
- People with abnormal lipid profiles
- Obese children are at HIGH RISK
  - Obesity: weight >95 % for age and sex
  - Centripetal obesity is worse
  - 85% of children with NAFLD are obese
  - At least 50% of obese children have NAFLD

Obesity Trends* Among U.S. Adults

- Percentage BMI > 30



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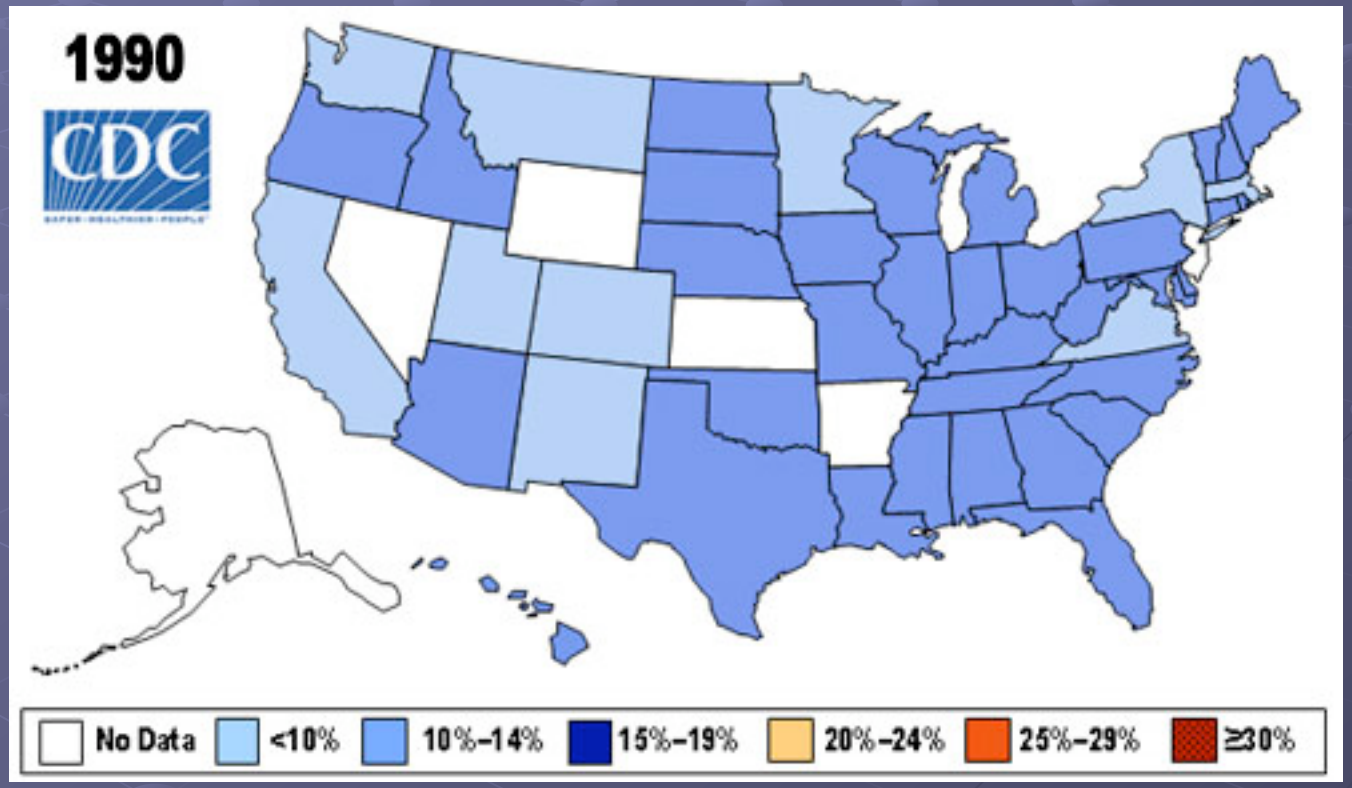

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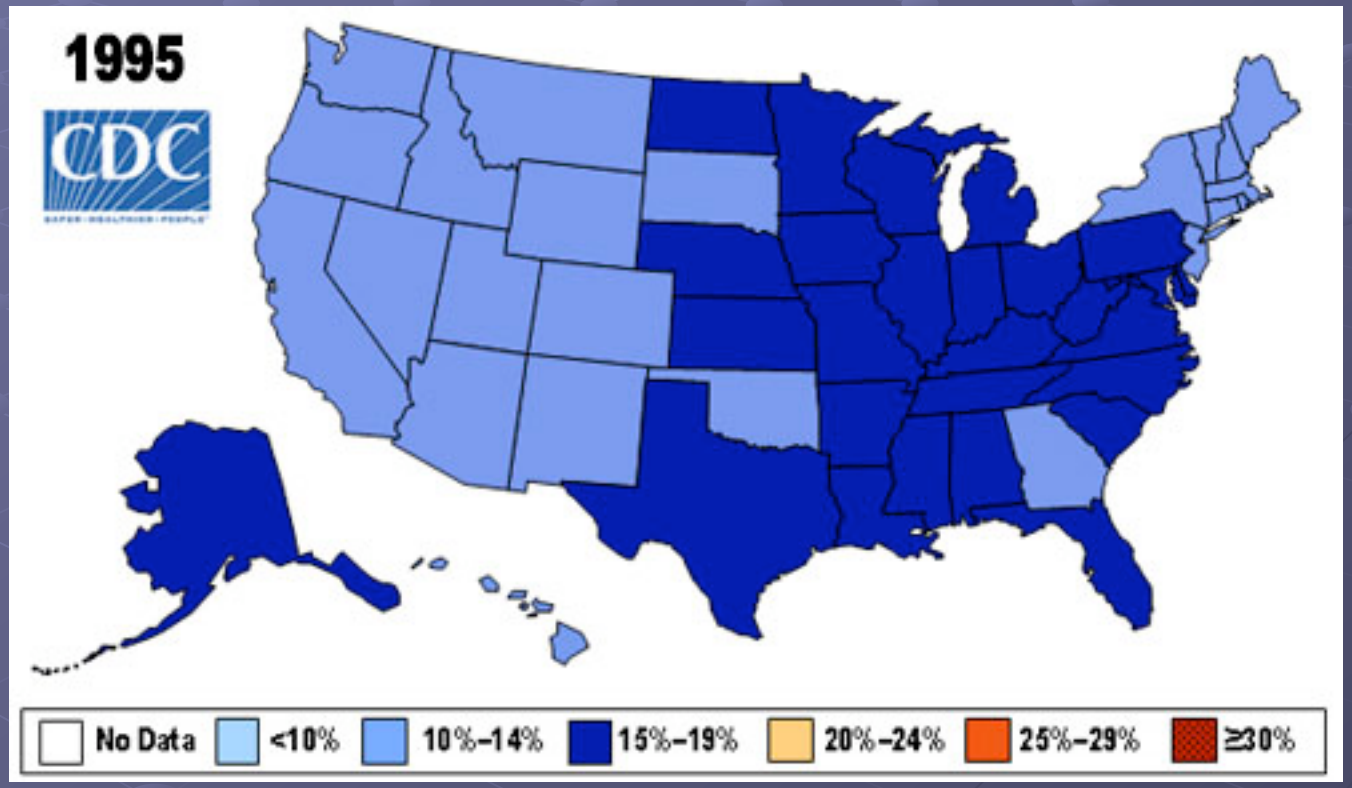

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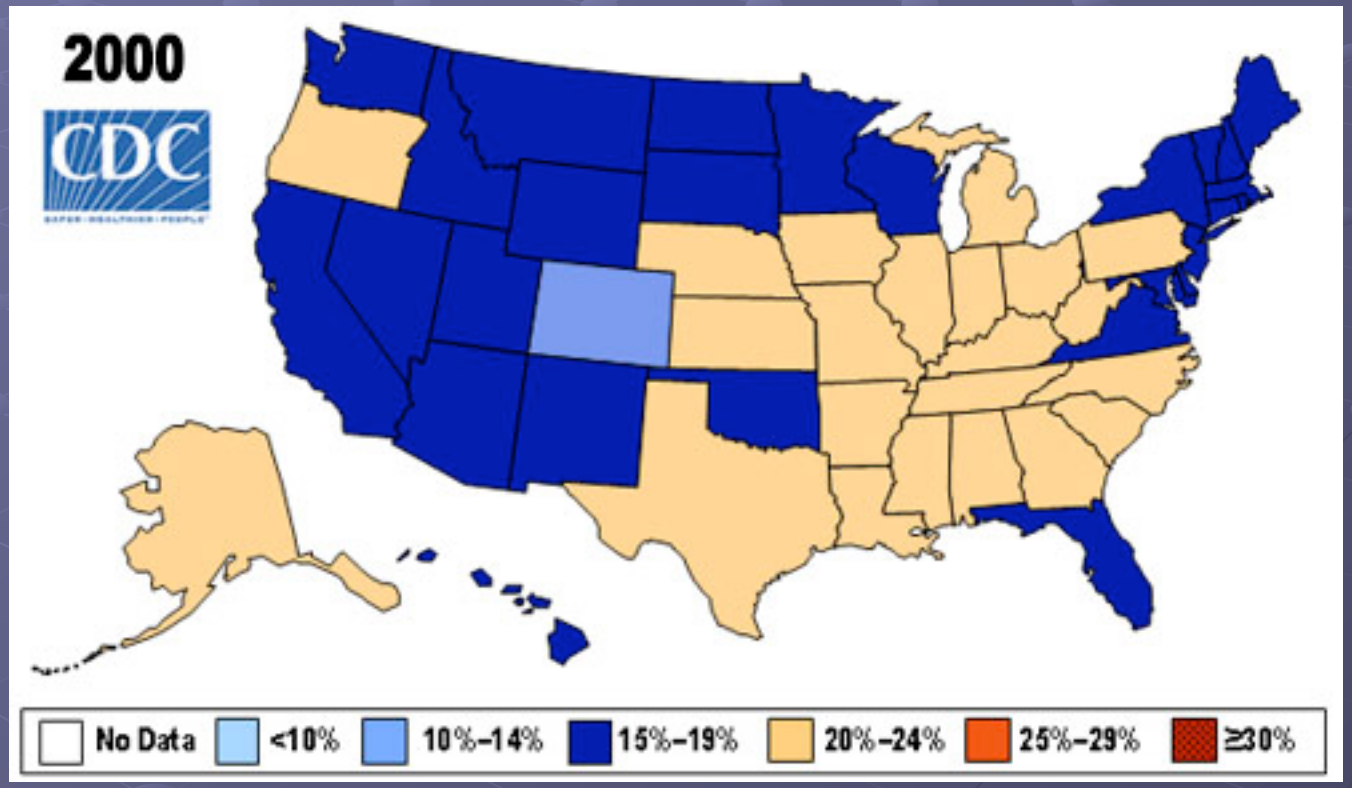

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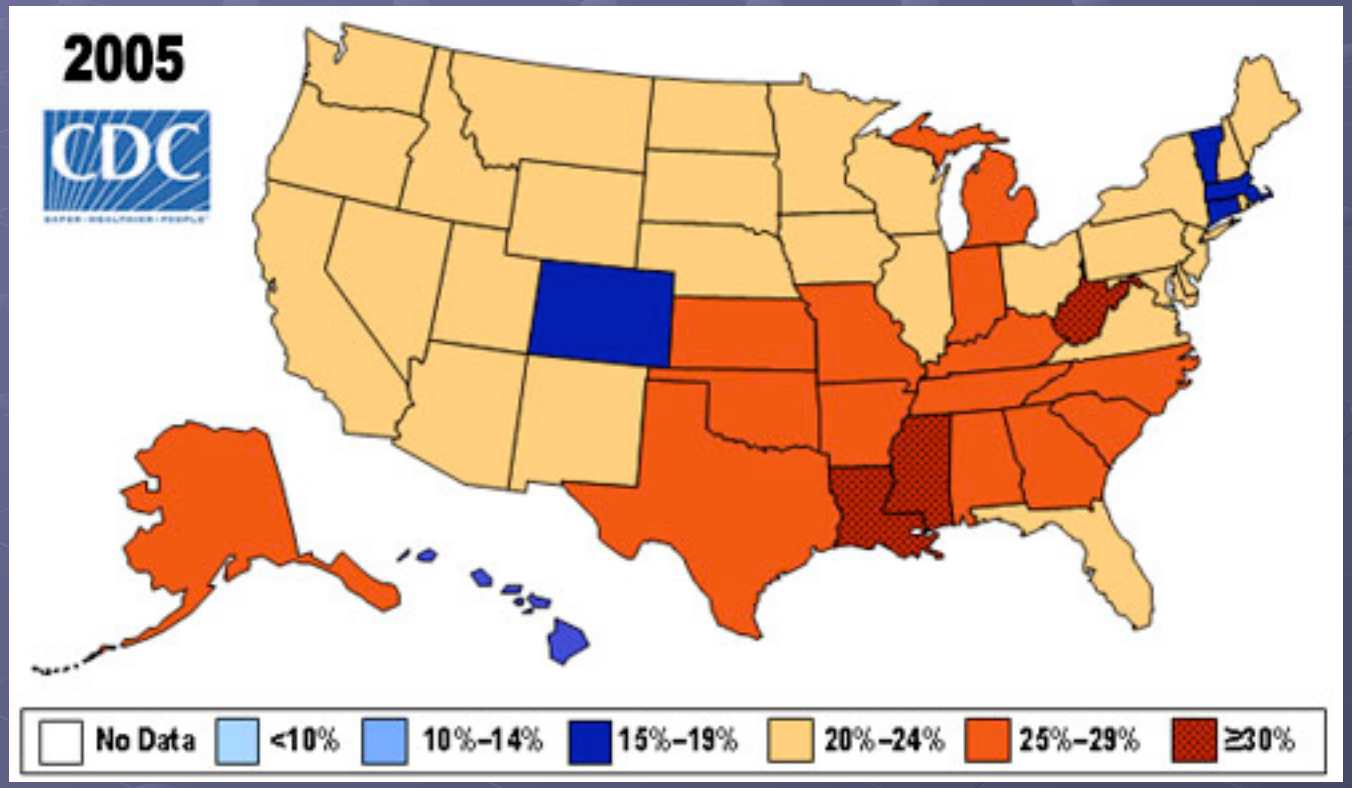

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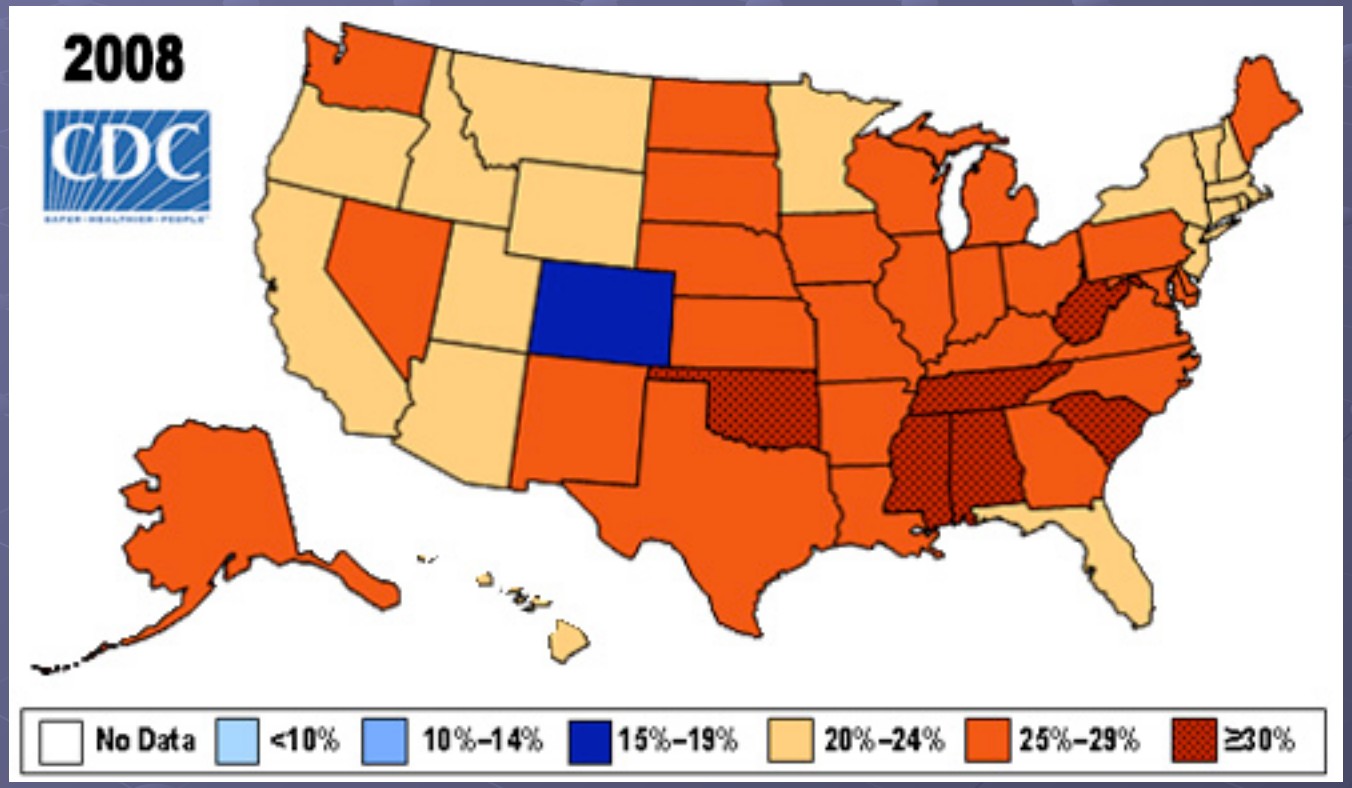

Obesity trends among US children

- Data from the National Health and Nutrition Examination Survey (NHANES) suggest a tripling of the prevalence of obesity among adolescents from 5% in 1960 to 15% in 2000

- Data from NHANES 2003-2004 show that this trend continues, with 17.1% of US children and adolescents obese on this most recent survey
- In conjunction with the alarming rise in obesity, population data indicate that 7% of US adolescents exhibit impaired glucose tolerance

Clinical Presentation

- Most are asymptomatic
  - Routine exam and blood work
    - Enlarged liver
    - Elevated liver function tests
      - 3% US adolescents had ALT elevation (NHANES III)
      - 6-23% Obese adolescents with ALT elevation in popluation based studies
- Symptomatic patients:
  - Right upper quadrant pain
  - Chronic periumbilical pain

Physical Exam

- >90% of patients will be obese
- 1/3-1/2 have an enlarged liver
- 1/3-1/2 will have acanthosis nigricans
  - Dark pigment around nape of neck and axilla
- Other co-morbid conditions
  - High blood pressure
  - Diabetes
  - High cholesterol and lipids
  - Snoring/obstructive sleep apnea

Acanthosis Nigricans

Diagnosis

- History of obesity
- History of other co-morbidities
- Physical Exam
- Blood work
  - Liver function tests, fasting glucose and lipid panel
  - Evaluation for other causes of chronic liver disease (must rule out)
- Radiology Tests: ultrasound or MRI
- Liver Biopsy

Blood work

- Elevated liver tests
  - Usually mild elevation of ALT/AST
  - Assure no evidence of liver failure (INR)
- Must rule out other causes of chronic liver disease (hepatitis, A1AT, Wilson's. . .)
- 30%-50% have Diabetes or Glucose intolerance
- 20%-80% have High cholesterol

Imaging

- U/S or MRI: Usually shows fatty infiltration in liver
  - Can not differentiate simple fat vs fat with scar tissue
  - Unable to recognize hepatic scar
  - Morbid obese individuals ultrasound image may be poor and unable to recognize liver fat

Role of Liver Biopsy

- Liver biopsy is gold standard for the diagnosis
- It can differentiate simple fat vs fat with inflammation and scar tissue
- Stages of scar and/or Cirrhosis
- 20% patients with increased liver tests may have alternate diagnosis on liver biopsy

Liver Biopsy- Does everyone need one?

- Liver biopsy should be individualized
  - Risk
  - Cost

Histopathologic Subtype Classification in NASH

- Type 1 NASH:
  - Steatosis, ballooning degeneration, and perisinusoidal fibrosis
  - Similar to Adult definition of NASH
- Type 2 NASH:
  - Steatosis, portal inflammation, and portal fibrosis
  - More common subtype in Children
    - Lavine and Schwimmer 2005

Histopathologic Subtype Classification in NASH

- 100 children from 1997-2003
  - Simple steatosis 16%
  - Advanced fibrosis 9%
- Type 1 NASH: 17%
  - Girls, Caucasian
- Type 2 NASH: 51%
  - Boys, Asian, Native American, Hispanic
  - Advanced fibrosis more common to be Type 2

What is the Natural History?

- Can fatty liver be progressive?
- What is the prognosis?
- Does fatty liver disease lead to liver cancer?

Can Fatty Liver be progressive?

- Generally, patients with simple fat in liver have non-progressive fatty liver
  - But one study has shown that simple fat liver may progress to progressive liver disease
- NASH may progress to cirrhosis (20%) and can lead to liver related death

- Matteoni CA et al.,Gastro 1999, Teli MR et al.,Hepatology 1995, Harrison SA et al., Am J Gastro 2003 and Ong JP et al., AM J Gastro 2003

How progressive can it be?

- Cirrhosis secondary to NASH has been reported in children as young as 10 years
- A recent case report described a young man dying of complications of liver failure secondary to NASH cirrhosis at the age of 34 years.
- The incidence rate of cirrhosis secondary to pediatric NASH is unknown at this time (no longitudinal pediatric studies)
- Predictors of advanced histology include severity of obesity and insulin resistance.

Treatment of Fatty Liver

- Currently, there is no proven effective therapy.
- Focus on modifying associated conditions
  - Metabolic Syndrome
  - Diabetes
  - Obesity
  - High Cholesterol

Treatment

- Weight loss (Diet and Lifestyle Change)
  - Wt. loss > 10 % leads improvement of liver enzymes and improvement of fat
  - Rapid weight loss may lead to increased inflammation and scar tissue in liver including liver failure
    - Gradual wt loss of 10 % of baseline wt is recommended
  - No significant data on liver scar tissue improvement

Treatment

- Management of high cholesterol
  - – Cholesterol lowering agents may be associated improvement of liver cell injury, inflammation and liver tests

Medications

- Few open label studies in pediatrics
  - Currently, weight loss is the only approved treatment option for NASH in children and adolescents
- Several large trials are currently underway

Insulin Sensitizing Agents

- Metformin
  - Pilot study (10 pts) showed improvement of LFTs and decreased fat on MRI at 6 months
- Rosiglitazone & Pioglitazone (diabetic drugs)
  - Liver test and liver inflammation/ scar tissue improvement
  - Potential liver toxicity
  - Lack of safety data in children
  - Marchesini et al. Lancet 2001 Neuschwander-Tetri et al., Hepatology 2003 Promrat K et al, Hepatology 2004

Vitamin E

- Vitamin E
  - Small pilot studies showed improvement of liver tests and liver inflammation / scar tissue in obese children and patients with fatty liver
  - 11 pediatric patients treated
  - Liver tests improved after 2-4 months
  - Results were temporary
  - Large Pediatric trial underway currently

- Lavine JE. J Pediatrics, 2000, Hasegawa et al., Aliment Pharmacol Ther 2001 Adelmalek MF et al. Am J Gastro 2001, Gulbahar et al. Gastro 2000 (Abstract)

Actigall (Ursodiol)

- A bile acid that serves as a cytoprotective agent, improves bile flow and has anti-inflammatory effects in the biliary tree
- Improved liver tests and liver biopsy results in small adult trials
- The only pediatric study showed no benefit but was flawed due to selection bias

Weight Loss Surgery

- In adults, good evidence that weight loss surgery can decrease the amount of steatosis/fat in liver
- Dixon et al. has demonstrated regression of fibrosis with weight loss surgery at 2 yrs

- Severe and progressive NAFLD may be an indication for early weight loss surgery in adolescents*

Conclusions

- Growing incidence of obesity in general population has made fatty liver disease and its complications a major public health issue.
- Fatty liver disease is associated with non-specific symptoms.
- Asymptomatic presentation does not imply benign course.
- Fatty Liver can be progressive and may lead to cirrhosis and liver cancer.

Conclusions

- There appears to be a histological dichotomy between pediatric- and adult-type histopathology in NAFLD that deserves further study.
- Currently, there is no proven effective treatment or therapy.
- Main stay of treatment is therapy for associated conditions such as metabolic syndrome, control of diabetes, high cholesterol and weight loss.

And the Final Conclusion

- There is still a lot of work to be done
  - Screening
  - Diagnosis
  - Genetics
  - Natural History
  - Management
    - Dietary/Lifestyle
    - Medications
    - Surgery