Non-alcoholic Fatty Liver Disease (NAFLD) in Children
Carisse Orsi, MD
Pediatric Endocrine Fellow
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Goals and Objectives
- Define NAFLD
- Discuss the theories behind the pathophysiology of the disease
- Know how to diagnose NAFLD
- Understand the disease progression
- Discuss current studies for the treatment of fatty liver

What is Non-Alcoholic Fatty Liver Disease (NAFLD)?
- A chronic liver condition characterized by:
  - Hepatic fat accumulation (in the absence of ethanol abuse & other identifiable causes)
  - Insulin resistance
  - Frequently associated with impaired glucose intolerance or type 2 diabetes

NAFLD
- Hepatic fat accumulation (steatosis) may range from simple steatosis
- Natural history poorly understood, no large long-term studies

Non-Alcoholic Steatohepatitis (NASH)
- NASH is fat accumulation plus
  - Necrosis
  - Inflammation
  - Fibrosis
- May progress to portal hypertension and cirrhosis

The Spectrum of NAFLD
- Fatty Liver
- NASH
- Cirrhosis
- Fat accumulates in the liver
- Fat plus inflammation and scarring
- Scar tissue replaces liver cells
Fatty Liver in Adults

- In adult patients with NAFLD, approximately 30-40% of patients eventually progress to NASH.
- A slightly smaller percentage (10-30%) of adult patients with NAFLD develop cirrhosis after 10 years.
- The most common cause of cirrhosis in adulthood and in childhood.
- Question of if/when patients will develop hepatocellular carcinoma.

Fatty Liver in Children

- First described in children in 1983.
- In children, the incidence of NAFLD and NASH is ~10% of the pediatric population.
- More common in obese children and those with type 2 diabetes.
- Long-term outcomes of this condition in children are not known, but are likely to be worse due to the anticipated lifespan of the typical adolescent.

Natural History of Pediatric NAFLD

- Not well understood.
- Case reports of rapid progression to cirrhosis.
- 106 NAFLD pts (mean 13.4 yrs)
  - All baseline liver biopsy.
  - 18 repeat liver biopsies, mean 28 months.
    - 8 pts no change fibrosis.
    - 7 pts worsening fibrosis.
    - 3 pts improved fibrosis BUT all lost weight.

Role of adipose tissue, insulin resistance, fatty acids and lipotoxicity

- Defects at multiple levels may tip the metabolic balance towards hepatic fat accumulation.
- Excessive substrate supply to the liver.
- Intrahepatic mismatch between lipid synthesis and oxidation.
- Inadequate export to peripheral tissues.
Proposed Pathophysiology

- An increase in suppressors of cytokine signaling-3 in the liver leads to:
  - persistent hyperinsulinemia
  - further exacerbates insulin resistance
  - Hyperinsulinemia stimulates the transcription factor sterol regulatory element-binding protein-1c, which leads to:
    - activation of lipogenic genes
    - a decrease in fatty oxidation

NAFLD in T2DM

- In T2DM, chronic hyperinsulinemia and hyperglycemia promote lipogenesis
  - Upregulating hepatic sterol regulatory element binding protein 1c (SREBP1c) and
  - Carbohydrate regulatory element binding protein (ChREBP) activity

Role of Leptin, Resistin, and Adiponectin

- Leptin is a peptide produced primarily in the adipose tissue
- Leptin deficient mice do not develop NASH
- Studies have not shown leptin levels are associated with specific liver fibrotic stages
**Resistin**
- An adipose-derived protein
- Overexpression of resistin in mouse models led to glucose intolerance, hyperinsulinemia, and impaired suppression of free fatty acids levels
- High resistin levels have been associated with hepatic steatosis

**Adiponectin**
- Hormone secreted exclusively by adipose tissue
- Produces beneficial effects on lipid metabolism, enhancing lipid clearance from plasma and beta-oxidation of fatty acids in muscle
- Direct anti-inflammatory effects, suppressing TNF-alpha production in the liver
- Appears to be protective against NASH

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**Proposed Progression from Adipose tissue to NASH**
- **Step 1:** Adipose tissue insulin resistance, provides lipotoxic environment that supplies liver with FFA and compensatory hyperinsulinemia that stimulates lipogenesis
- **Step 2:** Development of hepatic steatosis and of a lipid pool from where lipid-derived toxic metabolites may activate inflammatory pathways
- **Step 3:** Progression from simple steatosis to active necroinflammation depends on the ability of the liver to adapt to longstanding triglyceride accumulation
  - Failure leads to FFA-induced lipotoxicity with mitochondrial dysfunction, endoplasmic reticulum stress, reactive oxygen species (ROS) formation, and chronic necroinflammation
- **Step 4:** Fibrosis, chronic activation of hepatic stellate cells in a poorly understood cross-talk of Kupffer cells with hepatocytes

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**Who gets NAFLD?**
- Obese
- Metabolic syndrome
- T2DM
- Acanthosis nigricans
- Males > females
- Hispanics > Caucasians > AA

**San Diego Study**
- The largest study that has been undertaken on adolescents and NASH in a retrospective autopsy-based evaluation
  - Performed on 742 children between 2 to 19 years of age
  - Died traumatically (motor vehicle accidents, accidents, homicide or suicide)
  - Individuals were excluded if they had any factors that would potentially influence liver histology (i.e. recent inpatient hospital stay or a positive alcohol or drug toxicology screen)

San Diego Study

- In this unique group of previously healthy children, 9.6% had evidence of fatty infiltration of the liver as assessed by liver histology.
- Fatty liver disease was more prevalent among those who were older, overweight, and known associations with insulin resistance.
- Fatty liver was also more common in males (10.5% versus 7.4% in females) and Hispanics (11.8% versus 1.5% in Blacks and 8.6% in non-Hispanic whites).

San Diego Study

- Actual liver inflammation (steatohepatitis, NASH) was found in 23% of children with fatty liver and 3% of the total autopsies.
- This data is consistent with 3 smaller studies and also confirmed that Hispanics are more likely to develop advanced liver fibrosis.

Prevalence of Fatty Liver by Age, Gender, Race, and Ethnicity

<table>
<thead>
<tr>
<th>Category</th>
<th>Age</th>
<th>Gender</th>
<th>Race/Ethnicity</th>
<th>Percent Prevalence</th>
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<td>Hispanic</td>
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Prevalence of Pediatric NAFLD

<table>
<thead>
<tr>
<th>Country</th>
<th># of Subjects</th>
<th>Ages (years)</th>
<th>Fatty Liver %</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>USA</td>
<td>2450</td>
<td>12-18</td>
<td>3%</td>
<td>ALT</td>
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<tr>
<td>USA</td>
<td>742</td>
<td>2-19</td>
<td>9.6%</td>
<td>Biopsy</td>
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<tr>
<td>Korea</td>
<td>1594</td>
<td>10-19</td>
<td>3.2%</td>
<td>ALT</td>
</tr>
<tr>
<td>Japan</td>
<td>810</td>
<td>4-12</td>
<td>2.6%</td>
<td>Ultrasound</td>
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</tbody>
</table>

NASH & Cardiovascular Disease

Cardiovascular Risk Factors and the Metabolic Syndrome in Pediatric Nonalcoholic Fatty Liver Disease

- Aim: To determine the association between NAFLD and the presence of metabolic syndrome in overweight and obese children.
- Case-control study 5-17 yr old patients
  - 150 overweight children with biopsy-proven NAFLD
  - 150 overweight children without NAFLD

Cases and Controls

- **Study patients**
  - Biopsy proven NAFLD based on liver biopsy with > or = 5% hepatocytes containing microvesicular fat
  - Exclusion of other causes

- **Controls**
  - Overweight/obese children evaluated for weight management defined at Negative NAFLD = negative liver enzymes with ALT < 30 U/L and no hepatomegaly

Risk factors of Pediatric NAFLD

- Groups similar except NAFLD groups had higher numbers of Asians and Hispanics
- Children with NAFLD had higher glucose, insulin, systolic/diastolic BP, total cholesterol, LDL, TG, and lower HDL
- Adjusting for age, sex, race, ethnicity, BMI, insulin: Children with Metabolic syndrome had 5x rate of NAFLD


Diagnosis of NAFLD/NASH

- **Exam**
- **Laboratory analysis**
- **Imaging**
- **Liver biopsy**

Diagnosis of NAFLD

- **Laboratory: Elevated ALT**
  - May be associated with elevated liver aminotransferases (ALT>AST)
  - May NOT be associated with an elevation in ALT/AST
  - Using this tool, in the National Health and Nutrition Examination Survey (NHANES) III, 6% of overweight adolescents and 10% of obese adolescents had elevated levels of ALT

Diagnosis NAFLD & NASH

- **Clinical findings:**
  - Few clinical symptoms (i.e. right upper quadrant discomfort in about 42-59%)
  - Acanthosis Nigricans
  - Hepatomegaly

CATCH Trial

- Small cohort of 127 12th grade students (BMI ≥ 30kg/m²) taking part in the Child and Adolescent Trial for Cardiovascular Health (CATCH), 23% had an elevated ALT
  - Elevated ALT was seen in 36% of Hispanics, 22% of non-Hispanic whites, and 14% of black children
- Other studies have shown that 2/3 of pts with NAFLD diagnosis by more definitive and specific tests such as biopsy or imaging have normal liver function tests (LFTs).

Metabolic syndrome Criteria

5/5 required

- Abdominal obesity (>102 cm boys, >88 cm girls)
- High triglycerides (≥150)
- Low HDL (<40 for boys, <50 for girls)
- Elevated BP (sys ≥ 135, dia ≥ 85)
- Impaired fasting glucose (≥100)
Because NAFLD is a diagnosis of exclusion, we must rule out other etiologies of chronic liver disease and inflammation.

### Etiology of Chronically Elevated Aminotransaminases

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Risk Factors</th>
<th>Screening</th>
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<tbody>
<tr>
<td>NAFLD</td>
<td>Metabolic Syndrome</td>
<td>Imaging, Biopsy</td>
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<tr>
<td>Alcohol (1:130)</td>
<td>Family history</td>
<td>History, AST/ALT &gt;1, GGT</td>
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<tr>
<td>Hepatitis C (1:150)</td>
<td>IVDU, blood transfusions</td>
<td>Hep C Antibody</td>
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<tr>
<td>Medications</td>
<td>Exposure history</td>
<td>Estrogen, tylenol, propylthiouracil</td>
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<td>Hepatitis B (1:350)</td>
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<td>Hep B surface antigen</td>
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<td>Hemochromatosis</td>
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<td>Transferrin saturation, ferritin</td>
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<tr>
<td>α-1 Antitrypsin Ab (1:2500)</td>
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<td>α-1 Antitrypsin level and genotype</td>
</tr>
<tr>
<td>Autoimmune hepatitis (1:15,000)</td>
<td>Family history</td>
<td>Anti-nuclear Ab, anti-smooth muscle Ab, Immunoglobulins</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Family history</td>
<td>Ceruloplasmin</td>
</tr>
</tbody>
</table>


### Associated disorders of pediatric NAFLD

- Hypothalamic disorders
  - Prader-Willi syndrome
- Genetic disorders
  - Bardet-Biedl
  - Alstrom syndrome
  - Lipodystrophy syndromes
  - Dorfman-Chanarin syndrome
  - Cantu syndrome
  - Polycystic ovary syndrome

Roberts E. J Hepatol. 2007;46:1133-42

### Pediatric Endocrine NAFLD

#### Work-up

- α-1 antitrypsin
- Iron
- Total Iron Binding Capacity
- Antinuclear Antibody (ANA)
- Anti-smooth muscle antibody
- Anti-LKM-1 antibody
- Hepatitis C, B profile
- Ceruloplasmin

If many patients with fatty liver have normal liver enzymes, how should we diagnose them?
Imaging NAFLD/NASH

- Ultrasound
- Computed Tomography (CT)
- MRI and spectroscopy

Diagnosis by Ultrasound

- In adults, ultrasound of the liver is 60-94% sensitive and 73-95% specific for the diagnosis of liver fat when compared to liver histology
- With >30% fatty infiltration, sensitivity of ultrasound is 80%
- With 10-19% fatty infiltration, sensitivity of ultrasound is 55%
- Sensitivity and specificity of ultrasound decrease due to the presence of morbid obesity to 49% and 75%, respectively

Diagnosis by CT

- Computed tomography of the liver is 43-95% sensitive and 90% specific for detecting fatty liver
- These values are decreased if the fatty liver content is below 30%

Magnetic Resonance Imaging and Spectroscopy (MRS)

- New gold standard for imaging diagnosis of NAFLD
- The Dallas Heart Study was the first large-scale study to use MRS to measure fatty liver

Dallas Heart Study

- Evaluated 345 subjects with no other identifiable cause of fatty liver
- Fatty liver of 5.5% or greater corresponded to the 95% area of distribution
- Showed 33.6% of the adult population had hepatic steatosis
- Reproducibility r=0.99 p<0.001

Distribution of HTG in the Dallas Heart Study

Dallas Heart Study

- Prevalence was higher in obese, MS, T2DM, Hispanics and males
- Elevated ALT correlated with an increase in liver fat
- 2/3 of pts with fatty liver have normal liver enzymes

Graph illustrates the MR imaging spectrum of a fatty human liver

Experimental set-up for measurements of hepatic triglyceride (HTG) content by proton magnetic resonance spectroscopy (1H MRS)

Liver Biopsy

- Liver biopsy is the only way to differentiate between NASH and hepatic steatosis
- Imaging unable to stage the degree of fibrosis
- There are several definitions for the staging of NASH
- Sampling error may lead to variation by one fibrosis stage in 24-37% of biopsies
Pediatric NASH

- Portal inflammation (70%) and portal fibrosis (60%) was present in biopsies
- Typical adult pattern termed **Type 1**
- **Type 2**: Steatosis with portal inflammation and/or fibrosis
  - Without perisinusoidal fibrosis or evidence of ballooning degeneration

**Staging of NASH**

- Pediatric NASH is often histopathologically different than adult NASH in the degree of and location of fat, inflammation and fibrosis
- Typical adult pattern of NASH includes macrovesicular steatosis, lobular inflammation and ballooning degeneration

**Type 1 and Type 2 NASH**

- Distinct clinical and demographic differences between children with type 1 and type 2 histology
- This is suggestive of important pathophysiological differences between adult and pediatric NASH
- Children with type 2 are
  - younger
  - greater severity of obesity
  - male > female

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Pediatric NAFLD Algorithm

1. Elevated LFTs
   - Rule out other causes of fatty liver
   - Consider Liver Biopsy
   - Consider Imaging
2. Recheck liver enzymes
   - After 3 months
3. Consider: NAFLD
   - NASH
   - Reduce daily caloric intake
   - Exercise

Risk factors for Fatty Liver:
- Insulin resistance
- Obesity
- Diabetes

Pediatric NAFLD Algorithm

What are the treatments options for pediatric patients with NAFLD?

Pediatric NAFLD Ongoing Research

- 132 studies for “fatty liver treatment”
- 7 studies ongoing for “pediatric fatty liver”
  - Drugs under investigation
    - Acarbose (pilot study)
    - Xenical
    - Metformin
  - Other trials
    - Low glycemic diet vs low fat diet

Treatment Options

- In a 12-month double-blinded placebo study on 90 children with NAFLD
  - Subjects were placed on a balanced caloric diet
  - Physical exercise
  - Either placebo or Vitamin E 600 IU/day and Vitamin C 500 mg/day.
  - Diet and exercise alone was better than antioxidant therapy

Trial of Lifestyle Modification & Antioxidant Therapy for Pediatric NAFLD

- 53 patients followed for 24 months
- Diet & increased physical activity counseling plus placebo OR Vit E 600 IU/day & Vit C 500 mg/day

<table>
<thead>
<tr>
<th>Placebo Baseline</th>
<th>Placebo 1 year</th>
<th>p</th>
<th>VE + C Baseline</th>
<th>VE + C 1 year</th>
<th>p</th>
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<td>BMI</td>
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P = intergroup p, NAS = NAFLD activity score on liver biopsy

Antioxidants for Pediatric NAFLD

• Vit E (plus Vit C) plus Diet/Exercise or Placebo plus Diet/Exercise 1-2
• No added improvement with Vitamin E & C
• Key to improvement in AST/ALT, insulin resistance, steatosis (US) & NAS score (biopsy) was a 10-20% wt loss

A1 Weight losers (placebo)
A2 Weight not losers (placebo)
B1 Weight loser (Vit E/C)
B2 Weight not loser (Vit E/C)

1 Nobili V et al. Alim Pharmacol Ther 2006;24:1553-61

Effect of Weight Loss on Liver Free Fatty Acid Uptake and Hepatic Insulin Resistance

■ Results:
   ■ Subjects lost weight (11.2 ± 2.9 kg; P < 0.0001).
   ■ Liver volume decreased by 11% (P < 0.002), which was partly explained by decreased liver fat content (P < 0.0001).
   ■ Liver free fatty acid uptake was 26% lower after weight loss (P < 0.003) and correlated with the decrease in liver fat content (r = 0.54; P < 0.03).
   ■ Hepatic glucose uptake during insulin stimulation was unchanged, but the endogenous glucose production decreased by 40% (P < 0.04), and hepatic insulin resistance by 40% (P < 0.05).


Effects of Weight Loss on Liver Metabolism

Pharmacological Interventions in NASH

■ Weight-loss agents (orlistat)
■ Vitamin C and E
■ Hepatoprotective agents (ursodeoxycholic acid)
■ Lipid-lowering agents
   ■ Statins
   ■ Fibrates
■ Insulin-sensitizing Agents
   ■ Metformin
   ■ TZDs
   ■ Exenatide? Vitamin D?
## Mechanism of Metformin
- **Biguanide**
- Reduces hepatic glucose production
- Increases insulin sensitivity in patients with T2DM
- Proven to be safe in children and adolescents
- Used in children with T2DM and PCOS

## Metformin: Pediatric Trials
- Open-label phase 2 clinical trial in non-diabetic children and adolescents with biopsy proven NASH
  - 10 obese children with mean BMI 30.4 kg/m² treated with metformin 500 mg BID for 24 weeks
  - ALT improved from 184 to 98 U/L, p<0.01
  - Liver fat by MRS improved 30 to 23% p<0.01


## Metformin in Pediatric NAFLD
- Open label 24 month observational pilot study 500 mg MET TID compared to control group (lifestyle modification)
- 57 subjects 9-18 yr olds with biopsy proven NAFLD
- Metformin not more effective than lifestyle modification alone (both groups improved)


## Metformin in Pediatric NAFLD
- 50 adolescents, 6 months
  - lifestyle modification plus placebo
  - lifestyle modification plus metformin 850mg BID
  - ALT, GGT, fasting insulin improved in both groups
  - Metformin group superior:
    - Fatty liver prevalence & severity (US only),
    - Fasting insulin


## Mechanism of Thiazolidinediones
- Increase insulin sensitivity = increase lipid storage
- Decrease lipolysis and FFA output
- Increase number of metabolically active adipocytes
- Increase adiponectin
- Decrease leptin, TNF-alpha secretion, and other cytokines

![](Mechanism_of_metformin.png)

**UTHSCSA study on TZD**

- 55 adult pts randomly assigned to hypocaloric diet with/without pioglitazone
- Performed biopsy, MRS, OGTT
  - Improved glycemic control
  - Improved ALT
  - Decreased hepatic content
  - No change in fibrosis
- Safety of TZDs in children not established
- Ongoing trial of rosiglitazone in the T2DM TODAY trial


**Must Weigh Risks and Benefits**

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<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<tbody>
<tr>
<td>Adiponectin</td>
<td>Cardiovascular risk</td>
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<tr>
<td>Hepatic insulin sensitivity</td>
<td>Triglycerides w/saxenda</td>
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<tr>
<td>Steatosis</td>
<td>Bone Loss/Fracture</td>
</tr>
<tr>
<td>Necro-inflammation</td>
<td>Weight gain, peripheral fat</td>
</tr>
<tr>
<td></td>
<td>Worsening of CHF</td>
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**Incretins and Fatty Liver**

- Incretins are gastrointestinal hormones that enhance the postprandial insulin response.
- A synthetic form of exendin-4, exenatide, has been developed and undergone extensive clinical trials
- Exenatide is currently FDA approved for adults and children older than age 16 for treatment of T2DM in combination with sulfonylureas, metformin and/or thiglitazones

**Incretins and Fatty Liver**

- Exenatide mechanism of action includes:
  - Stimulates glucose-dependent pancreatic insulin secretion
  - Restores the first-phase insulin response (often lost in T2DM)
  - Suppresses glucagon secretion during periods of hyperglycemia
  - Decreases gastric emptying
  - Increases satiety
  - These effects lead to overall decreased insulin resistance and often weight loss

**Incretins and Fatty Liver**

- Recent published outcome data in adults with type 2 diabetes has shown an improvement of ALT while on exenatide
- Current study on adults with T2DM and NAFLD
  - Treated for 6 months with intensive insulin therapy
  - Followed with 6 months of exenatide plus long-acting insulin

**Detemir + Exenatide vs. Detemir + Aspart: Effect on Body Weight**

- Statistical significance: p<0.001
- n = 19
## Detemir + Exenatide vs. Detemir + Aspart: Mixed Meal Results

- **Glucose**
  - Detemir + Aspart
  - Detemir + EXE

- **Insulin**
  - Detemir + Aspart
  - Detemir + EXE

### Mean 1st & 2nd Phase Insulin Secretion: Hyperglycemic Clamp

- **Time**
  - 6am to 12pm

### Vitamin D and Fatty Liver

- Vitamin D is found in dietary sources such as fish, eggs, and fortified milk and is increased by sunlight exposure.
- Frequently found to be deficient in teens who have had suboptimal diets despite sun exposure.
- Its actions are well-recognized in their role in mineral homeostasis by regulation of calcium absorption from the gut and reabsorption in the kidney.
- More recently, Vitamin D is associated with autoimmune diseases, cancer, and Type 1 and Type 2 Diabetes.

### Effects of combined calcium and vitamin D supplementation:

(A) FPG & (B) HOMA-IR

- From the NHANES III data, cross-sectional analysis was performed on data of 6,228 participants.
- 2,766 non-Hispanic Whites, 1,736 non-Hispanic blacks, and 1,726 Mexican Americans.
- Homeostasis model assessment (HOMA) of IR was inversely associated with serum 25-hydroxyvitamin D (25OHD) in Mexican Americans (p=0.0024) and non-Hispanic Whites (p=0.058), but not with non-Hispanic Blacks (p=0.93).
- BMI was inversely related to 25 OHD levels.
- Non-Hispanic Whites in the highest quartile of 25 OHD levels had a four-fold lower odds of developing T2DM.


Vitamin D and Fatty Liver

- Cross-sectional analysis of 3577 adolescents from 2001-2004 NHANES
- Mean 25 (OH)D level 24.8 ng/mL
- W > MA > AA
- Associated with weight and abdominal obesity
- Adjusting for age, gender, race, and BMI
- 25 (OH)D inversely associated with plasma glucose concentration


Vitamin D and Fatty Liver

- In the cross-sectional analysis of 60 biopsy-proven NAFLD and 60 healthy control patients with comparable age, sex and BMI
  - NAFLD patients had lower serum 25 (OH)D (51.0 ± 22 vs. 74.5 ± 15 nmol/L, p=0.001) when compared to healthy controls
  - An inverse relationship exists between decreasing 25 (OH)D with increasing degree of liver histology (p <0.001)
  - This linear association may suggest a dose-effect relationship

- Ongoing trial here at our CHART center to observe if Vitamin D supplementation to physiologic levels has any effect on NAFLD in obese children between the ages of 10 and 17 who present with vitamin D deficiency


Summary

- NAFLD is a comorbidity of obesity and diabetes
- We do not know the progression of the disease but we do know in adults it can lead to cirrhosis and liver failure
- We need to find ways to prevent or stall fatty liver

References