Non-alcoholic fatty liver disease (NAFLD):
The emerging pandemic

Why is it happening?
What can we do about it?

Robert Rountree, MD
Integrative Healthcare Symposium
February, 2017
“Non-alcoholic fatty liver disease (NAFLD) is now considered to be the most common liver disease in the Western world and has no approved pharmacological therapy.”

Non-alcoholic fatty liver disease (NAFLD)

- Asymptomatic accumulation of triglycerides and other fats in hepatocytes (steatosis)
- Fat content exceeds 5% of liver volume
- Similar condition occurs with regular consumption of alcohol (esp if >30 g ~ 2.5 drinks daily)

BMJ. 2014; 349: g4596.
Non-alcoholic fatty liver disease (NAFLD)

- Involves a spectrum of changes ranging from reversible steatosis to inflammatory hepatitis (NASH) and eventually to fibrosis & cirrhosis
- Diagnosed (often incidentally) with serologic testing (ALT, GGT)
- Confirmed with ultrasound, elastography, MRS, or biopsy

BMJ. 2014; 349: g4596.
Non-alcoholic Steatohepatitis (NASH)

- Affects 2-3% of patients with NAFLD
- Characterized by chronic inflammation, fibrosis, scarring, and necrosis
- Definitive diagnosis is difficult: requires biopsy, elastography, or cytokeratin-18 fragments (CK 18)
- Progression results from multiple intersecting factors
- 5-8% of NASH patients develop liver cirrhosis within 5 years
healthy liver

simple fat accumulation

non-alcoholic steatohepatitis

reversible

reversible

irreversible

cirrhosis
Dramatic Increases in NASH

“It is projected that 25 million Americans will develop NASH by 2025, with 20% progressing to cirrhosis, hepatocellular carcinoma, or both, that may require liver transplantation.”

NAFLD: Prevalence and Mortality

- NAFLD may be the most common form of chronic liver disease worldwide (more common than alcoholic liver disease)
- NHANES III determined 22% of the more than 10,000 patients surveyed had NAFLD
- Other studies estimate prevalence >30%


Children: at increased risk of NAFLD

- **May affect** 9.6% of the general pediatric population in U.S.

- **3–10%** of lean children from South and North America, Europe, Asia and Australia at risk for NAFLD

- NAFLD prevalence in obese children from industrialized countries: up to **80%**, with a **male-to-female ratio of 2 : 1**

- **23%** of overweight and **38%** of obese children in the U.S. with NAFLD have NASH (3% of population)

References:
World J Hepatol 2010; 2:275–288
Gut 2009; 58:1538–1544
NAFLD and Mortality

- Those with NAFLD had 70% higher overall mortality compared with controls and most deaths were due to cardiovascular events.
- NASH also increases risk of liver cancer
- The independent predictors of mortality in these patients were: male sex, older age, increased waist circumference, and low HDL levels.
Non-alcoholic fatty liver disease and progression of coronary artery calcium score: a retrospective cohort study


- 4731 Korean adults (men & women) with no Hx of CVD, diagnosed with or without NAFLD by US
- Followed for 9 years with intermittent EBCT scans (average 3.9 yr interval)
- NALFD was significantly associated with progression of coronary atherosclerosis based on coronary artery calcium scores (Agatston), including those with baseline CAC scores of zero
NAFLD: The metabolic consequence of overconsumption plus underactivity (but why?)
Foie Gras ("Fat Liver"): A 2500 yo technique
NAFLD and Insulin Resistance

- Non-alcoholic fatty liver disease is the hepatic manifestation of metabolic syndrome: it is tightly linked with overweight/obesity and insulin resistance

- Strong association with T2DM:
  - Up to 70% of type 2 diabetics have NAFLD
  - Up to 30% have NASH

Insulin resistance is a cause and consequence of fatty liver
NAFLD: Medical Risk Factors

- **Obesity:**
  - 40-90% of obese individuals (BMI >30) have NAFLD
  - but it *can also occur in lean people* -- especially with sarcopenia

- **Polycystic ovary syndrome**
  (independent of obesity)

NAFLD: Medical Risk Factors

- Hypogonadism (testosterone deficiency)
- Hypothyroidism
- Sleep apnea
- Chronic hepatitis C
- Celiac disease

NAFLD/NASH
Additional Risk Factors

- Rapid post-surgical weight loss
- Pharmaceuticals:
  - Corticosteroids
  - HAART (Anti-retrovirals)
  - Tamoxifen
  - Methotrexate (cumulative dose effect)
  - Amiodarone
NAFLD: Genetic Risk Factors

- MTHFR SNPs -- increases homocysteine

- MTHFD1 (Methylene tetahydrofolate dehydrogenase 1) SNP — folate methylation

- PEMT SNP -- increases choline requirement

- Leptin receptor (LEPR) SNPs

- PNPLA3 (Patatin-like phospholipase domain-containing 3) gene variant
NAFLD: Lifestyle/Dietary Risk Factors

- Sedentary Lifestyle
- Caloric excess
- Refined carbohydrates
- Fructose / high fructose corn syrup
- Choline/phosphatidylcholine deficiency
- NAD deficiency (diet, aging)
Sources of hepatic free fatty acids

- 59%: uptake of circulating free fatty acids derived from lipolysis of triglycerides in adipose tissue – regulated by insulin

- 29%: de novo hepatic lipogenesis (DNL)

- 15%: dietary

Fructose as a key player in the development of fatty liver disease
World J Gastroenterol. 2013 Feb 28;19(8):1166-72

- The fast food diet which includes fructose and fats produces a gene expression signature of increased hepatic fibrosis, inflammation, endoplasmic reticulum stress and lipoapoptosis.

- High fructose intake increases de novo lipogenesis (DNL) which contributes to fat accumulation in the liver and the development of NAFLD.
De novo lipogenesis (DNL) is a central abnormality in NAFLD (conversion of carbohydrate derived acetyl-CoA into triglycerides).

Dietary fructose increases levels of enzymes involved in DNL.

Fructose also leads to ATP depletion and suppression of mitochondrial fatty acid oxidation, resulting in increased production of reactive oxygen species.

Fructose promotes uric acid formation and endoplasmic reticulum stress, both of which contribute to DNL.
“High fructose corn syrup has a direct proportion to obesity in the U.S. and to fatty liver. They are rising exponentially in parallel.”

Douglas T. Dieterich, MD,
Professor of medicine, Division of liver diseases
Icahn School of Medicine at Mount Sinai, NYC
Healio Endocrine Today, March, 2016
Estimated intakes of total fructose (•), free fructose (▲), and high-fructose corn syrup (HFCS, ♦) in relation to trends in the prevalence of overweight (○) and obesity (☒) in the United States.
“We observed that regular sugar-sweetened beverage consumption was associated with greater risk of fatty liver disease, particularly in overweight and obese individuals, whereas diet soda intake was not associated with measures of fatty liver disease.”

Sugar-sweetened beverage, diet soda, and fatty liver disease in the Framingham Heart Study cohort
J Hepatol. 2015 August; 63(2): 462–469
Obesity and high fructose corn syrup

The number of Americans who are obese has quadrupled in recent years, a study shows. At the same time, high fructose corn syrup consumption has risen at parallel rates.

Pounds consumed: The graph traces average number of pounds of high fructose corn syrup consumed by Americans each year.

Obesity: Bars track the increased percentage of obese Americans age 20 years and older, for available years studied.
High fructose corn syrup found in processed foods and soda is currently the “biggest cause of NAFLD.”

Dina Halegoua-De Marzio, MD, Director, Jefferson Fatty Liver Center, Thomas Jefferson University Hospital, Philadelphia, PA
Healio Endocrine Today, March, 2016
NAFLD/NASH
Additional Risk Factors

- Environmental toxins
  - Persistent organic pollutants (organochlorines)
  - Atrazine
  - Glyphosate
  - Heavy metals (Mercury, lead)
- Iron overload (cause and effect of NAFLD)
- Intestinal dysfunction
  - Dysbiosis
  - Hyperpermeability (leaky gut) with endotoxemia
Toxicant-associated Steatohepatitis (TASH)
Matthew Cave, Toxicologic Pathology, 2013, Vol 41: 343-360,

- Similar pathology to alcoholic and non-alcoholic liver disease = elevated ALT, GGT; but without traditional risk factors (eg. obesity)

- An individual’s susceptibility to chemical-induced liver disease is determined by polymorphisms in the genes of xenobiotic metabolism, concomitant use of alcohol or prescription medications, nutritional factors, and obesity
Our results provide the first evidence that NAFLD in humans is associated with increased gut permeability and that this abnormality is related to the increased prevalence of SIBO in these patients.

The increased permeability appears to be caused by disruption of intercellular tight junctions in the intestine, and it may play an important role in the pathogenesis of hepatic fat deposition.
Diet, Microbiota, Obesity, and NAFLD: A Dangerous Quartet

NASH Etiology:
“First Hit” = NAFLD

- **Hepatic fat accumulation** resulting from chronic positive caloric balance coupled with sedentary lifestyle
- **Hyperinsulinemia**: inhibits beta-oxidation & increases hepatic accumulation of “bad” fats: free fatty acids, diacylglycerols, ceramides
- **Phosphatidylcholine deficiency** (PC is needed to package and export triglycerides out of liver in VDLD—deficiency causes TG accumulation)
- **Lipotoxicity** disrupts insulin signaling pathways, accelerating the problem
NASH Etiology: “Multiple Parallel Hits”

- Ongoing injury leads to progression of disease. Causes of injury include:
  - Endotoxemia from gut barrier dysfunction
  - Oxidative stress
  - Chronic inflammation
  - Environmental toxicants & metals
  - Mitochondrial dysfunction

- Result: necrosis & fibrosis from activation of hepatic stellate cells
NAFLD/NASH: Pharmaceutical Treatments

- Hypoglycemics
  - Metformin: lowers glucose, but no effect on liver histology
  - Thiazolidinediones ??
  - Incretins (GLP-1 agonists) ??
- Lipid lowering medication
  - Statins ??
  - Fibrates ?
- Appetite Suppressants
NAFLD/NASH: Diet and Lifestyle Approaches

- **Weight loss**
  - >3-5% of total body weight to reduce steatosis
  - >10% loss to improve necroinflammation

- **Dietary Strategies**
  - **Caloric restriction**
  - Elimination of refined carbohydrates, especially sucrose, fructose, & HFCS

- **Exercise: benefits independent of weight loss**
  - aerobic and resistance
  - minimum of 150 minutes per week
Weight Loss and Hepatic Fat

Hepatic lipid accumulation is a “robust” predictor of hepatic, muscle and adipose insulin sensitivity: better than intra-abdominal fat, body mass index (BMI), or other obesity measures.

Modest weight loss (about 8 kg) normalizes intrahepatic lipid in subjects with type 2 DM, in parallel with normalization of hepatic insulin sensitivity, even in the absence of changes in circulating adipocytokines.

NAFLD/NASH: Functional Medicine Approaches

- Supporting gut microbiome
  - Prebiotic fiber
  - Probiotics

- Repairing intestinal barrier function (leaky gut)
  - L-glutamine
  - Quercetin
  - Curcumin
  - Aloe vera
Diet
- PUFA and n-3 PUFA
- Non-digestible carbohydrates
- Vitamin E
- Cinnamon
- Protein
- Prebiotics
- Probiotics

Exercise
- Voluntary activity
- Structured running

Overall effects
- Reduced blood flow to GI tract
- Improved metabolic control
- Body weight
- Improved body composition
- Blood lactate
- Endotoxemia

Liver effects
- Hepatic lipids
- Lipogenesis
- Plasma triglycerides
- Cholesterol
- Bile acid synthesis

Gastrointestinal effects
- Gut motility
- SCFA production
- Epithelial integrity
- Inflammation
- Bile acid excretion
- Fat absorption
- Altered hormone release

Altered bacterial composition and increased diversity
Partially Hydrolyzed Guar Gum (PHGG) Attenuates Nonalcoholic Steatohepatitis (NASH) in Mice Through the Gut-Liver Axis

- C57BL/6J mice were fed for 8 weeks on CRF-1 (control) or NASH-inducing atherogenic (high in fat and cholesterol) diet with or without 5% PHGG (Sunfiber)

- Atherogenic diet induced fat accumulation in liver with increased inflammatory cytokines and fibrosis

- PHGG
  - attenuated hepatic fat accumulation and inflammation
  - increased Lactobacilli and intestinal butyrate levels

- “PHGG may be a candidate of treatment for NASH”

Gastroenterology, 2014, Vol 146(5), S1: S-477
Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis

World J Gastroenterol 2013 October 28; 19(40): 6911-6918

- Probiotics decrease levels of ethanol, phenol, indolesin and endotoxins in the liver and result in lowering of proinflammatory cytokines: TNF-α, IL-6, and IFN-γ via down-regulation of the NF-κB.

- Animal trials in NASH: histologic improvement in steatosis, hepatic fat content, reversed insulin resistance, some trials improved fibrosis but not steatosis

- Four randomized human trials showed improved ALT, AST, total-cholesterol, TNF-α and decreased insulin resistance in NAFLD patients.
Beneficial Effect of Synbiotic Supplementation on Hepatic Steatosis and Anthropometric Parameters, But Not on Gut Permeability in a Population with Nonalcoholic Steatohepatitis

Nutrients. 2016 Jun 28;8(7)

- RCT of 50 bx-proven NASH patients given either:
  - L. reuterii + guar gum & inulin
  - Nutritional counselling

- NASH patients presented high gut permeability, but low prevalence of SIBO.

- After 6 wks of the intervention, only the synbiotic group presented a reduction in steatosis, lost weight, diminished BMI and waist circumference measurement.
NAFLD/NASH
Dietary Supplements

- Choline / Phosphatidylcholine
- Curcumin (phytosome)
- Berberine
- Vitamin E +/- vitamin C
- Pantethine
- Silybin-phosphatidylcholine
- Omega-3 fatty acids (deep sea fish oil)
- Glutathione and glutathione enhancers: NAC, alpha lipoic acid
- Nicotinamide Riboside
- Vitamin D
- Melatonin
Choline metabolism provides novel insights into nonalcoholic fatty liver disease and its progression
Corbin, Zeisel, Curr Opin Gastroenterol. 2012 March; 28(2): 159–165

- Humans eating **low choline diets develop fatty liver and liver damage by multiple mechanisms**

- The spectrum of choline’s effect on the liver range from steatosis to development of hepatocarcinomas

- Several recent epidemiologic studies reported that 25% of Americans ate diets very low in choline

- Variations in **dietary requirements for choline are influenced by estrogen status and genetic variations (PEMT SNP)**
Figure 2
Summary of Choline Deficiency Mediated Mechanisms of Liver Dysfunction

The progression of NAFLD from simple steatosis to hepatocarcinoma is influenced by multiple cholinemediated mechanisms.

Choline Metabolism Provides Novel Insights into Non-alcoholic Fatty Liver Disease and its Progression
Curr Opin Gastroenterol. 2020;28(2):159-165.
Turmeric: *Curcuma Longa Linn*
Treatment of Non-alcoholic Fatty Liver Disease with Curcumin: A Randomized Placebo-controlled Trial
Phytother Res. 2016 Sep;30(9):1540-8

- 80 subjects with ultrasonically confirmed NAFLD, given 500 mg of curcumin phytosome or placebo for 8 weeks

- Compared to placebo, **curcumin** recipients had
  - 78.9% reduction in liver fat content (vs 27.5%)s
  - significant reductions in BMI, AST/ALT, Total cholesterol, LDL-C, Trig, FBG, and HgbA1c
Curcumin Lowers Serum Lipids and Uric Acid in Subjects With Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial


- 87 subjects with NALFD confirmed by US given curcumin, 500 mg bid (n = 44) or placebo (n = 43) for 8 weeks

- Compared to placebo, supplementation with curcumin was associated with a reduction in serum levels of
  - total cholesterol (P < 0.001)
  - LDL-C (P < 0.001)
  - triglycerides (P < 0.001)
  - non-high-density lipoprotein cholesterol (P < 0.001)
  - uric acid
Oregon Grape Root
*Mahonia aquifolium*
INDIAN BARBERRY
Berberis aristata
Berberine prevents progression from hepatic steatosis and fibrosis by reducing endoplasmic reticulum stress

- Db/db mice and methionine-choline-deficient mice were administered berberine via gavage

- We found that berberine treated mice were more resistant to hepatic steatosis than vehicle treated mice and berberine significantly reduced hepatic inflammation, fibrosis, and lipid peroxides

- The beneficial effect of berberine was associated with suppressing ER stress; additionally, berberine decreased FFA accumulation in primary hepatocytes
60 patients with T2DM & NAFLD divided into two groups: berberine or Xuezhikang (red yeast rice extract)

Patients receiving berberine showed significant improvement in hepatic ultrasound, decreased blood viscosity, lower transaminases, and increased HDL
The Effect of Berberis Vulgaris Extract on Transaminase Activities in Non-Alcoholic Fatty Liver Disease

Hepat Mon. 2015 Feb; 15(2): e25067

• 80 NAFLD patients with elevated transaminases and US-confirmed steatosis, including 32 males (40%) and 48 females (60%)

• Randomized to 750 mg of Berberis vulgaris aqueous extract or placebo for 3 months

• Relative to controls, case group experienced significant drop in body weight, AST, ALT, total cholesterol, LDL-C, and triglycerides
Vitamin E (tocopherols)

- American Association for Study of Liver Diseases (AASLD) guidelines recommend vitamin E intake of 800 IU per day as first-line therapy for non-diabetic adults with biopsy-proven NASH

- Benefits have also been reported in children.

Alpha-tocopherol vs Pioglitazone: PIVENS Trial

- **Vitamin E** therapy (800 IU QD X 96 wks), as compared with placebo, was associated with a significantly higher rate of improvement in NASH (43% vs. 19%, P = 0.001)

- Pioglitazone had positive effect on steatosis but no significant improvement in fibrosis score
Vit. E Interrupts Fibrosis

- **Plasma TGF- β1 (fibrosis marker):** measured in 10 NAFLD and 12 NASH patients at baseline, after completion of dietary intervention, and after one year on alpha-tocopherol.

- **Baseline TGF- β1 levels** significant higher in NASH group, compared to NAFLD patients or healthy controls (p<0.01),

- **TGF- β1 levels** were unchanged after dietary intervention, but **significantly decreased after taking alpha-tocopherol** for one year (p<0.01).

Vitamin C + Vitamin E for NASH

- 40 patients with biopsy-proven NASH
- 1000 mg vitamin C + 1000 IU of alpha tocopherol qd for 6 months
- Statistically significant improvement in biopsy fibrosis scores.

Am J Gastroenterol 2003;98(11):2485
Management of fatty liver disease with vitamin E and C compared to ursodeoxycholic acid treatment

- Patients with histologically proven NAFLD and chronically elevated transaminase levels who did not respond to a 3 month weight-loss diet

- Two groups, given one of the following x 6 mos:
  - (1) Vit E 600 IU/d + vit C 500 mg /d
  - (2) ursodeoxycholic acid

- Result: serum transaminase levels decreased significantly in both groups

- “Vitamin E plus C combination treatment is a safe, inexpensive and effective treatment option in patients with fatty liver disease, with results comparable to those obtained with ursodeoxycholic acid”

Turk J Gastroenterol. 2005 Sep;16(3):124-8
Effect of vitamin E and alfa lipoic acid (ALA) in non-alcoholic fatty liver disease: a randomised placebo control open label prospective clinical trial: V A I N trial
Gut 2012;61:A204

- n=155 with BMI >28% with NAFLD and NASH, randomized to 3 groups, placed on diet of 1600 kcal with modest exercise & supplemented x 6 months with
  - (A) placebo
  - (B) ALA, 300 mg
  - (C) Vitamin E 700 IU
  - (D) ALA + Vitamin D
- In patients receiving the antioxidants: inflammation and steatosis scores improved from baseline to 6 months, compared with placebo.
- Compared with placebo, combination therapy resulted in a 70% difference in change in tumor necrosis factor-alpha levels from baseline. (no change in fibrotic score)
Pantethine

- Derived from pantothenic acid by adding cysteamine
- Composed of two molecules of pantetheine linked by disulfide
- Precursor to Coenzyme A, critical factor for cellular energy production
- Well documented effects lowering LDL-C and triglycerides, while increasing HDL-C
The effects of pantethine on fatty liver and fat distribution


- 600 mg/day of pantethine was administered for >6 months to 16 outpatients with hypertriglyceridemia and fatty liver (based on abdominal CT)

- At end of study period 9 patients had complete resolution of fatty liver with significant decrease in visceral fat

- “Pantethine may transfer fat from the liver and viscera to the subcutaneous tissue.”
N-Acetylcysteine

- Raises hepatic glutathione (GSH) levels – neutralizes free radicals involved in NASH
- Human study: Hepatol Res. 2008;38(2):159-65
  - 27 consecutive patients with biopsy-proven NASH
  - NAC (1.2 g/day) + metformin (850-1000 mg/day) x 12 mos
  - Results: significant improvement in labs and steatosis/fibrosis (NASH activity score) on post-biopsy
Milk Thistle (Silybum marianum)
The effect of a silybin-vitamin e-phospholipid complex on nonalcoholic fatty liver disease: a pilot study

- 85 patients in 2 groups: (1) HCV+/NAFLD+  (2) HCV-/NAFLD+

- Vitamin E (360 IU/day) with silybin (376 mg/day), and phosphatidylcholine (776 mg/day) for 12 months resulted in improvements in both steatosis and fibrosis.

- Significant improvement in ALT/AST, hyperinsulinemia, fibrosis index and reduction of steatosis on ultrasound

- Significant correlation: fibrosis index, body mass index, insulinemia, plasma levels of, TGF-β, tumor necrosis factor-alpha, degree of steatosis, and GGT.

Dig Dis Sci. 2007 Sep;52(9):2387-95
Omega-3 Fatty Acids

- Omega-3 PUFAs may play a critical role in regulating the metabolic switch from anabolism (lipogenesis) to catabolism (fatty acid oxidation) by activating peroxisome proliferator-activated receptor alpha (PPARα), a positive regulator of fatty acid oxidation.

- Animal/human studies: improved insulin sensitivity, lowered markers of liver inflammation in animal models of NAFLD and clinical trials of NAFLD.

- No consensus on dosage (1 g qd to 2 g tid).

Omega-3 Fatty Acids

*World J Gastroenterol* 2008; 14(41): 6395-6400

- 140 patients with NAFLD/mixed lipidemia
- Randomized: control versus treatment group on dose of **2 grams tid for 24 wks**
- Improvement in triglycerides vs controls
- Complete regression of steatosis (by sonogram) in 20 percent of treatment group vs. 7% of controls
- Significant regression of steatosis in 53% of tx group vs. 35% in controls
Effectiveness of Omega-3 Polyunsaturated Fatty Acids in Non-Alcoholic Fatty Liver Disease: Meta-analysis of RCTs
PLoS ONE 11(10): e0162368

- Included seven RCTs involving 442 patients (227 for the experimental group and 215 for placebo group)

- Omega-3 PUFA treatment favored beneficial changes in alanine aminotransferase (ALT), total cholesterol, triglyceride, and HDL-C)

- Omega-3 PUFA also has a tendency toward a beneficial effect on AST, GGT and LDL-C.
Omega-3 fatty acids as a treatment for non-alcoholic fatty liver disease in children: A systematic review and meta-analysis of randomized controlled trials


- 4 studies with 263 subjects were identified.
- Omega-3 PUFA supplementation was associated with significantly improved hepatic steatosis grade on ultrasound.
- Omega-3 PUFA supplementation could decrease AST levels after 6 months, but could only reduce ALT levels after 12 months.
Vitamin D & NAFLD

- 75% of metabolic syndrome cohort shown to be D deficient

- Low vit. D levels in 60 NAFLD patients were closely associated with:
  - Severity of steatosis
  - Severity of inflammation and
  - Fibrosis independent of age, sex, BMI, creatinine, HOMA

Melatonin

- In animal models of NASH, given 10 mg/kg of melatonin
- reduced steatosis
- Increased hepatic antioxidant enzyme levels
- normalized ALT, AST, and decreased levels of oxidative stress in high-fat diet induced liver fibrosis

Effects OF Treatment with Melatonin & Tryptophan on Liver Enzymes, Parameters of Fat Metabolism & Plasma Levels of Cytokines in Patients with NAFLD

14 months Follow-Up


- 74 patients, NAFLD confirmed with biopsy, assigned to 3 groups; over 14 month period, all received a 900 mg phospholipid preparation, plus
  1. 1 gram tryptophan
  2. 10 mg melatonin
  3. No additional supplements

- After the 14-month treatment period, GGPT & levels of triglycerides and LDL-cholesterol were significantly reduced in group I and II (tryptophan & melatonin)

- Statistically significantly lower levels of IL-1, IL-6 and TNF-a were observed in group I & II compared with group III

- Complete resolution of NASH in groups I & II
NAFLD/NASH: “Natural” Treatment Options = Human Trials Showing Clinical Benefits

- Choline / phosphatidylcholine
- Curcumin (phytosome)
- Berberine
- Vitamin E (+ vitamin C) (+alpha lipoic acid)
- Pantethine
- Omega-3 fatty acids
- NAC
- Silybin phytosome (with vitamin E)
- Melatonin
NAFLD Potential Treatment Options (Benefits Seen in Animal Models)

- Nicotinamide Riboside
- Quercetin
- Honokiol (magnolia extract)
- Artemesia annua
- Traditional Chinese Medicine (multiple formulas)
- Vitamin D
NALFD: Summary of Therapeutic Options

- Choline: 500+ mg daily
- Curcumin (phytosome): 500 mg bid
- Berberine: 500 mg bid - tid
- Vitamin E: 500-1000 IU qd
- Silibin phytosome (+ vit E): 180 mg bid
- Pantethine: 500-750 mg qd
NALFD: Summary of Therapeutic Options

- Melatonin: 3-20 mg hs
- EPA-DHA: 2-4 caps qd
- NAC: 500 mg tid
- Alpha lipoic acid: 300-600 mg bid
- Vitamin D: 5000 IU qd
"You've been fooling around with alternative medicines, haven't you?"
With appreciation to:
Lyn Patrick, ND,
for opening my eyes to the epidemic