Fatty Liver Disease
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NAFLD

“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.”

“Nonalcoholic fatty liver disease (NAFLD) affects 25% of the global adult population and is the most common chronic liver disease worldwide.

Nonalcoholic steatohepatitis (NASH) is the active form of NAFLD, with hepatic necroinflammation and faster fibrosis progression. “

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)

BMJ. 2014; 349: g4596.
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 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
• NASH is 3rd most common indication for liver transplantation in the US
healthy liver  simple fat accumulation  non-alcoholic steatohepatitis  cirrhosis

reversible  reversible  irreversible
NAFLD Risk Factors

Obesity:

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

NAFLD Risk Factors

• Polycystic ovary syndrome (independent of obesity)
• Hypogonadism (testosterone deficiency)
• Hypothyroidism
• Sleep apnea
• Chronic hepatitis C
• Celiac disease

NAFLD Risk Factors

Rapid post-surgical weight loss

Pharmaceuticals:
- Corticoteroids
- HAART (Anti-retrovirals)
- Tamoxifen
- Methotrexate (cumulative dose effect)
- Amiodarone
NAFLD: Genetic Risk Factors


MTHFD1 (Methylene tetahydrofolate dehydrogenase 1) SNP — folate methylation  Curr Opin Gastroenterol. 2012 Mar; 28(2): 159–165


Leptin receptor (LEPR) SNPs

PNPLA3 (Patatin-like phospholipase domain-containing 3) gene variant
NAFLD:
Emerging perspectives

February 2018
Everyone accepts, and current guidelines recommend lifestyle intervention with diet modulation and physical activity as first line management for NAFLD/NASH.

Unfortunately, while large scale trials in cardiovascular and metabolic diseases demonstrate clear benefits, practicing physicians are either skeptical of its efficacy in clinical practice or are not sufficiently resourced to provide effective interventions.

Lipotoxicity and the gut-liver axis have come to the forefront both as drivers of disease, but also as targets for therapeutic intervention.
NAFLD Diagnosis

Gold standard: liver biopsy is impractical and costly

In parallel with drug development, there has been a push to develop non-invasive tools to stage and grade the severity of metabolic liver disease.

Of the tools available, imaging based technologies are perhaps the most advanced for day to day practice.

-MRI and MRE techniques have the best performance but given cost are used in clinical research

Blood-based biomarkers for staging and grading NAFLD are particularly attractive for population level disease screening, providing they have high sensitivity and specificity
NAFLD Biomarkers

In the clinical setting, biomarkers may discriminate between patients with NASH or advanced fibrosis, predict dynamic changes in NASH/fibrosis over time, and provide long-term prognostic information.

Biomarkers:

• NAFLD fibrosis score
• FIB-4 index
• BARD score

Direct measures of fibrosis (e.g. FibroTest®, ELF™ or Pro-C3 tests) are very expensive
NAFLD Treatment

“The outcome in the broadest possible terms, is a composite of gene × gene, environment × environment and gene × environment interactions.

Thus, our present understanding of NAFLD/NASH as a single conglomerate disease is perhaps overly simplistic.

There are likely multiple subtypes and drivers of various intensity that operate in any single individual leading to his or her final phenotype.

Single therapies … may have suboptimal effects compared to combination therapies. Moreover, a single agent may be most effective if it targets the predominant driver of the disease in a particular patient.”
Lipotoxicity

The role of lipotoxic free fatty acids such as palmitic acid, cholesterol, lysophosphatidylcholine and ceramides has recently emerged.

These lipotoxic agents affect the cell behavior via multiple mechanisms:
• activation of signalling cascades and death receptors
• endoplasmic reticulum stress
• modification of mitochondrial function, and oxidative stress.

These include modifications to the microbiota, which provide signals through the intestine and bacterial products, as well as hormones produced in the bowel that affect metabolism at different levels including the liver.
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

NAFLD and Insulin resistance

- Insulin resistance is both the cause and consequence of fatty liver disease
**NAFLD:**
Diet and Lifestyle Risk Factors

- Sedentary Lifestyle
- Caloric excess
- Refined carbohydrates Fructose / high fructose corn syrup
  

- Choline/phosphatidylcholine deficiency

- NAD deficiency (diet, aging)

Where does the fat come from?

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 key player in Fatty Liver Disease

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.

World J Gastroenterol. 2013 Feb 28;19(8):1166-72
Toxicant-associated Steatohepatitis (TASH)

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
• obesity

Matthew Cave, Toxicologic Pathology, 2013, Vol 41: 343-360,
Increased Intestinal Permeability and NAFLD

Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease
Hepatology. 2009 Jun;49(6):1877-87

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.
Intestinal Dysbiota

Intestinal Permeability
Increase LPS and other bacterial products reaching the liver

Energy Metabolism
Increase energy/free fatty acids reaching the liver

Choline Metabolism
Decrease choline and hence VLDL export from the liver

Bile acids Metabolism
Modulation of FXR response

Toxic Products
Generation of toxic substances such as ethanol and TMAO
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
NASH Treatment Pharmaceuticals

There are currently no approved therapies for NASH.

Preclinical models of non-alcoholic fatty liver disease
Santhekadur, Prasanna K. et al.
Journal of Hepatology, Volume 68, Issue 2, 230 - 237
NAFLD/NASH Pharmaceuticals used

- **Insulin sensitizers**: metformin (lowers glucose but no effect on liver histology), thiazolidinediones (TZD’s), incretin-based therapies (only used in clinical trials)

- **Lipid-lowering agents**: statins, fibrates, PUFA

- **Anti-TNF-α agents**: Pentoxifylline, monoclonal antibodies
The results of the largest study of metformin, the Treatment of nonalcoholic fatty liver disease in children (TONIC) trial, which evaluated metformin, vitamin E and placebo in a pediatric population, were recently published.

-Metformin failed to demonstrate superiority to placebo in attaining the primary outcome of sustained reduction in transaminase levels.

-Metformin was associated with improvement in hepatocellular ballooning, but not fibrosis, steatosis, inflammation or NAFLD activity score (NAS)
Overall, the results of trials of TZDs for NAFLD suggest some benefit from this class of drugs.

However, prolonged therapy is likely necessary to achieve sustained histological improvement, which may be limited by their side effect profile, and the fact that the safety and efficacy of their long-term use in patients with NAFLD is currently unknown.

Presently, TZDs should be reserved for second-line treatment in the majority of patients. One exception may be patients with DM2 and NAFLD, in whom TZD therapy may help both conditions.
Anti TNF-α agents

Inflammatory activation plays a significant role in NAFLD progression, with tumour necrosis factor-alpha (TNF-α) possibly playing a direct role in obesity and insulin resistance.

- Pentoxifylline
- Infliximab
- Adalimumab
- Certolizumab

Clinical studies are underway.
NAFLD/NASH
Diet & Lifestyle Approaches

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

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
NAFLD/NASH Dietary Supplements

- Probiotics
- Choline / Phosphatidylcholine
- Curcumin (phytosome)
- Berberine
- Vitamin E +/- vitamin C
- Pantethine
- Silybin (Milk Thistle)-phosphatidylcholine
- Omega-3 fatty acids (deep sea fish oil)
- Glutathione and glutathione enhancers: NAC, alpha lipoic acid
- Nicotinamide Riboside
- Vitamin D
- Melatonin
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.
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)
Curcumin

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-HDL cholesterol (P < 0.001)
• uric acid
Berberine


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.
Berberine

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 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
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.

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
Vitamin C + Vitamin E for NASH

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:

- Group 1- Vit E 600 IU/d + vit C 500 mg /d
- Group 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
Vitamin E and Alpha Lipoic Acid in NAFLD

Effect of vitamin E and alpha lipoic acid (ALA) in non-alcoholic fatty liver disease: a randomized 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 (B5) 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
Pantethine

The effects of pantethine on fatty liver and fat distribution J Atheroscler Thromb. 2000;7(1):55-8

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 (NAC)

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
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

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% of treatment group vs. 7% of controls
Significant regression of steatosis in 53% of tx group vs. 35% in controls

World J Gastroenterol 2008; 14(41): 6395-6400
Omega-3 Fatty Acids

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 Clin Nutr. 2016 Dec 23. pii: S0261-5614(16)31350-4

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

75% of metabolic syndrome cohort shown to be D deficient
Low vitamin 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

Melatonin & Tryptophan

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

- Group 1: 1 gram tryptophan
- Group 2: 10 mg melatonin
- Group 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)
- Vitamin D
NALFD: Summary of Natural 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 Natural 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
SUMMARY

• NAFLD is a global problem affecting over 1 billion people and now #1 cause of liver disease

• Associated with metabolic syndrome and insulin resistance

• No clear medication option

• Multi-factorial in cause and treatment

• Many natural supplements have been shown to improve