Non-Alcoholic Fatty Liver Disease (NAFLD): Emerging Concepts

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Clinical Associate Professor of Medicine, Baylor College of Medicine
Non Alcoholic Fatty Liver Disease (NAFLD) Emerging Concepts: Outline

- Definition
- Epidemiology
- Natural History & Prognosis
- Pathogenesis
- Evaluation & Management
- Approach to NAFLD in Ghana
- Summary
NAFLD

Definition
NAFLD- Definition

- NAFLD- Nonalcoholic Fatty Liver Disease
- Hepatic Steatosis by Imaging OR Histology

- WITHOUT other etiology for hepatic fat accumulation
- There is no significant alcohol consumption
- there are no competing etiologies for hepatic steatosis
- there are no co-existing causes for chronic liver disease
# Fatty Liver: Etiologies

## Table 1: Causes of Hepatic Steatosis

<table>
<thead>
<tr>
<th>Macrovesicular</th>
<th>Microvesicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>Reye’s syndrome</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>Hepatitis C, genotype 3</td>
<td>HELLP syndrome</td>
</tr>
<tr>
<td>Medications</td>
<td>Medications</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Antiretroviral medications</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Valproate</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Inherited metabolic disorders</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Lysosomal acid lipase deficiency</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Lecithin-cholesterol acyltransferase deficiency</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td></td>
</tr>
<tr>
<td>Starvation</td>
<td></td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td></td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td></td>
</tr>
<tr>
<td>Abetalipoproteinemia</td>
<td></td>
</tr>
</tbody>
</table>
Spectrum of Non-Alcoholic Fatty Liver Disease (NAFLD)

**Steatosis (NAFL)**
- Fat
- None or mild inflammation
- No cell injury
- No fibrosis

**Steatohepatitis (NASH)**
- Fat
- Inflammation
- Cell injury (ballooning)
- Risk of fibrosis/cirrhosis

**NASH Fibrosis/cirrhosis**
NAFLD Risk Factors: Established Association - Metabolic Syndrome (Syndrome X)

NAFLD - The Hepatic Manifestation of the Metabolic Syndrome

ATP III Criteria ≥ 3 of the following

- Diagnosed based 3 or more of the following features
  - Abdominal obesity (waist > 40”/102 cm for men and >34.5”/88 cm for women)
  - Triglyceride level > 150 mg/dL
  - HDL < 40 mg/dL for men and < 50 mg/dL for women
  - Fasting blood sugar ≥ 110 mg/dL/Type 2 DM: insulin resistance (IR)
  - Blood pressure ≥ 130/85 mm of Hg
NAFLD Risk Factors: Emerging Associations

- Polycystic ovary syndrome
- Hypothyroidism
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Pancreatic-duodenal resection
NAFLD

Epidemiology
Obesity is a Global Threat
Global Correlation of Obesity & NAFLD

Loomba and Sanyal Nature Rev Gastro 2013
Global Prevalence of NAFLD

**FIG 1** Prevalence of NAFLD in different regions of the world.

Younossi, ZM, Clinical Liver Disease April 2018
Energy availability per capita and NAFLD Prevalence

Added Sugar Consumption = refined beet, sugar cane sucrose & high-fructose corn syrup (HFCS). Currently 15% of overall energy intake in the average western diet – higher % in younger individuals & ethnic minorities (African American, Hispanic, Native American & Pacific Islanders).
Fructose : O.J. will kill you!

- High-Fructose Corn Syrup (HFCS = mixture of fructose & glucose monosaccharides; usual ratio 65:35)
- Table sugar/sucrose (disaccharide of fructose & glucose)
- Unique hepatic metabolism of fructose: leads to hepatic and extra-hepatic fat accumulation - a potent risk factor for NAFLD
- Fructose intake predicts development of NAFLD & MetS/Obesity

A unique aspect of fructose metabolism: transient depletion in intracellular phosphate & ATP: transient block in protein synthesis; induction of oxidative stress & uric acid production; Insulin Resistance & mitochondrial dysfunction → NAFLD. Mediated by Fructokinase C pathway in the liver.
A large percentage of the U.S. population is affected by NAFLD

NAFLD: 19-45% (24.7)
NASH: ≈ 5%
NASH cirrhosis: ≈ 1.25%

US population ≈ 320,000,000

NAFLD ≈ 96,000,000
NASH ≈ 16,000,000
NASH cirrhosis ≈ 3,200,000
Prevalence of NASH & Advanced Fibrosis in type 2 DM

**Fig. 1.** Prevalence of NASH and advanced fibrosis on liver histology in patients with type 2 diabetes (irrespective of serum aminotransferase concentrations). Data were derived from studies published by Kwok et al.\(^6\), Bazick et al.\(^6\), and Portillo-Sanchez et al.\(^6\) NASH, non-alcoholic steatohepatitis.

Lonardo A et al J of Hepatology 2018
Prevalence of NAFLD in Africa

The global NAFLD epidemic

Hepatologists only see the most severe cases (the tip of iceberg), and have a scarce idea of the global extent of disease.

Obesity
1 billion persons overweight or obese around the world

Type 2 Diabetes
> 380 million cases (550 in 2030)

NAFLD

Natural History
Natural History of Nonalcoholic Fatty Liver Disease

100 patients with NAFLD → 20+ yrs → 5 develop cirrhosis → 5-10 yrs → 2-3 decompensate → 1-5 yrs → 1-2 liver-related death or transplant

95 (F0-3) (Never develop cirrhosis or hepatic complications) + 2-3 Cirrhosis without hepatic complications → 97-98 Non-liver related death
NAFLD disease progression

Histological Subtypes\(^{[1,2]}\)

NAFLD

70-75%

25-30%

NAFL

70-75%

25-30%

Isolated steatosis

Steatosis with mild inflammation

NASH

Cirrhosis

Fibrosis

Change in Fibrosis\(^{[3,4]}\)

Regression:
18%-22%

Stable:
40%-43%

Progression:
34-42%

*N = 108 pts with NAFL/NASH and median 6.6 yrs follow-up (data from serial biopsies).

## Clinical Predictors of NASH in Patients With NAFLD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age*[^1]</td>
<td>Greater duration of disease</td>
</tr>
<tr>
<td>Sex[^2]</td>
<td>Men, Postmenopausal women ↑ disease</td>
</tr>
<tr>
<td>Race[^3]</td>
<td>↑ Prevalence, severity in Hispanic, Asian patients; ↓ Prevalence, severity in black patients</td>
</tr>
<tr>
<td>HTN,* central obesity, dyslipidemia (↑ TG, ↓ HDL), insulin resistance/diabetes*[^4]</td>
<td>Risk increases with metabolic syndrome, † 66% prevalence of bridging fibrosis if older than 50 yrs of age and obese or diabetic[^5,6]</td>
</tr>
<tr>
<td>AST/ALT ratio &gt; 1,[^7] low platelets[^8]</td>
<td>Indicators of NASH cirrhosis</td>
</tr>
<tr>
<td>Persistently elevated ALT[^9]</td>
<td>Can be associated with ↑ disease progression</td>
</tr>
</tbody>
</table>

*Strongest predictors of advanced disease, regardless of liver enzyme elevation.

†Based on ATP III criteria.

### Genetics
- PNPLA3 gene (Others include NCAN, GCKR, LYPLAL1)

### Other (HCV/HIV)
NAFLD - Prognosis

- Increased overall mortality compared to matched control populations.

- Commonest cause of death in patients with NAFLD, NAFL and NASH is **cardiovascular disease**.

- Increased liver-related mortality rate – increasingly common indication for liver transplantation (15-20%).

Fibrosis, not NASH, predicts survival

N=619 biopsy-proven NAFLD, FU 12.6 yrs

Survival free of liver transplantation

Causes of death: cardiovascular 38%, cancer 19%, cirrhosis 8%, HCC 1%

ANGULO et al, Gastroenterology 2015;149:389-97
NAFLD

Genes & Natural History
Genetic basis for NASH: Evidence

- Familial aggregation
- Twin studies
- Ethnic differences
- Genome-wide association studies

Genetic Susceptibility to NASH

PNPLA3

NAFLD: Genome-wide association studies (GWAS)

Fatty liver (MR spectroscopy)
N = 2,111

PNPLA3 mutation p.I148M


Hepatic TG Content (%)

PNPLA3 G-Allele Frequency Accounts for Ethnic Variation in NASH

**PNPLA3-NAFLD:**
Spectrum of liver phenotypes

**PNPLA3 risk variant**
\[ p.I148M \]
- 70% higher liver fat contents
- 3.5-fold increased risk of steatohepatitis (NASH)
- 2.0-fold increased cirrhosis risk
- 1.5-fold increased HCC risk
- 1.8-fold increased risk of alcoholic hepatitis (AH)

Krawczyk, Portincasa & Lammert *Semin Liver Dis* (2013)
More NAFLD Risk Genes

**PNPLA3, TM6SF2 & MBOAT7: NASH Triangle**

<table>
<thead>
<tr>
<th></th>
<th>Steatosis</th>
<th>NASH</th>
<th>Fibrosis F2-F4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PNPLA3</strong></td>
<td>23% (11-36)</td>
<td>19% (12-26)</td>
<td>18% (10-26)</td>
</tr>
<tr>
<td><strong>TM6SF2</strong></td>
<td>4% (0-14)</td>
<td>4% (1-8)</td>
<td>3% (0-7)</td>
</tr>
<tr>
<td><strong>MBOAT7</strong></td>
<td>15% (3-28)</td>
<td>7% (0-14)</td>
<td>11% (2-23)</td>
</tr>
</tbody>
</table>


"Population Attributable Fraction" (PAF):

![Mean Hepatic TG %](chart)

*P*-trend < .0001
NAFLD

Pathogenesis
NASH Pathogenesis—Multiple-Hit Hypothesis

1st Hit
- Increased lipolysis and increased delivery of FFA to liver
- Results in steatosis and accumulation of liver fat

2nd Hit
- Oxidative stress from mitochondrial ROS and CYP-450 enzymes
- Alternative 2nd hit: adipokines associated with obesity and factors associated with apoptotic pathway
- Results in inflammation and necrosis

Obesity
IR
Type 2 DM

Fibrosis and progression of disease

NASH

Abbreviations: DM, diabetes mellitus; FFA, free fatty acids; IR, insulin resistance; NASH, nonalcoholic steatohepatitis; ROS, reactive oxygen species.

Lipotoxicity

Endotoxin

Cholesterol tox

Hypoxia

Adipokines

Innate immunity

Hepatocyte free fatty acid flux

Lipotoxic intermediates:
- Phosphatidic acid
- Lysophosphatidic acid
- Lysophosphatidyl choline
- Ceramides
- Diacylglycerols
- Others

- ER stress
- Inflammation
- Apoptosis
- Necrosis

Lipotoxic Liver Injury “NASH”

Tetri, Hepatology 2010
High glycemic diet; high fat diet & high salt diet & *PNPLA3* gene polymorphism all exacerbate fructose-induced NAFLD. Fructose from sucrose & HFCS (High-fructose corn syrup) : O.J...
NAFLD

Evaluation of NAFLD
Evaluation of Suspected Fatty Liver

- Diagnosis requires:
  - Hepatic Steatosis by imaging or histology:
    - WITHOUT other etiology for hepatic fat accumulation
    - There is no significant alcohol consumption
    - there are no competing etiologies for hepatic steatosis
    - there are no co-existing causes for chronic liver disease
Evaluation of a Patient with NAFLD

Goal: to determine if advanced fibrosis/NASH is present?

- Liver Biopsy & Pathologic Protocols
- Clinical and Routine Labs - Not very Helpful
- Routine Radiologic Test (US, CT, MRI) - Only able to detect fat - Not Fibrosis or NASH

Diagnostic & Prognostic Biomarkers for NASH

- New Pathogenic Biomarkers
  - Fibrosis: Fibrotest, ELF, Fibrometer
  - NASH: CK-18, NAFLD Diagnostic Panel
- Clinical Predictive Panels - Based on routine tests
  - Fibrosis: APRI, Fib-4, Simple, BARD, BAA, Fibrotest, NAFLD Fibrosis Score
  - NASH: Hair, NASH test, NPI
- New Modalities
  - Fibroscan: Central Obesity - MR Elastography better
Non-invasive assessment of steatohepatitis and advanced fibrosis in NAFLD

- Clinical
- Blood/serologic Biomarkers
- Imaging
Clinical Assessment for possible NASH Fibrosis

Metabolic Syndrome – Poor man’s predictor of NASH

- Metabolic syndrome is associated with 2.5 fold higher risk for NASH – proportionality between the number of MS components and the likelihood of NASH

Assessment of Advanced Fibrosis in NASH: Serum Biomarkers & Scoring Systems

### Table 3: Statistical analysis of various scoring methods for non-alcoholic fatty liver disease

<table>
<thead>
<tr>
<th></th>
<th>NAFLD fibrosis score</th>
<th>Fibrotest</th>
<th>FIB-4</th>
<th>ELF</th>
<th>BARD</th>
<th>NICE</th>
<th>NASH test</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUROC</td>
<td>0.84</td>
<td>0.75-0.86</td>
<td>0.86</td>
<td>0.87</td>
<td>0.81</td>
<td>0.88</td>
<td>0.79</td>
</tr>
<tr>
<td>Sens (%)</td>
<td>82</td>
<td>77</td>
<td>85</td>
<td>89</td>
<td>84</td>
<td>84</td>
<td>33</td>
</tr>
<tr>
<td>Spec (%)</td>
<td>98</td>
<td>98</td>
<td>65</td>
<td>96</td>
<td>86</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>90</td>
<td>90</td>
<td>36</td>
<td>80</td>
<td>43</td>
<td>44</td>
<td>66</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>93</td>
<td>73</td>
<td>95</td>
<td>98</td>
<td>96</td>
<td>98</td>
<td>81</td>
</tr>
</tbody>
</table>

NAFLD: Nonalcoholic fatty liver disease; AUROC: Area under the receiver operating characteristic curve; ELF: European Liver Fibrosis Test; PPV: Positive predictive value; NPV: Negative predictive value; Sens: Sensitivity; Spec: Specificity; NASH: Nonalcoholic steatohepatitis.

Hassan, K et al WJG 2014
NAFLD fibrosis score
Online calculator

Angulo P, Hui JM, Marchesini G et al. The NAFLD fibrosis score
A noninvasive system that identifies liver fibrosis in patients with NAFLD

Age (years)  
BMI (kg/m²)  
IGF/diabetes  
AST  
ALT  
Platelets (x10⁹/l)  
Albumin (g/l)  

BMI: body mass index
IGF: impaired fasting glucose
NAFLD fibrosis score

• < -1.455: predictor of absence of significant fibrosis (F0-F2 fibrosis)

• ≤ -1.455 to ≤ 0.675: indeterminate score

• > 0.675: predictor of presence of significant fibrosis (F3-F4 fibrosis)

NAFLD Fibrosis Score
- Three values: No advanced fibrosis, Indeterminate, Advanced fibrosis
  - Good test for determining patients without advanced fibrosis ((NPV 88%)
# Imaging Modalities in NAFLD: Assessment of Fibrosis

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Used to Assess</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>Steatosis</td>
<td>Good for detection of moderate-to-severe steatosis, widely available, low cost, safe</td>
<td>Poor sensitivity and negative predictive value, unable to detect mild steatosis, not quantitative, fibrosis and steatosis have similar appearance, operator dependent, accuracy influenced by BMI</td>
</tr>
<tr>
<td>CT</td>
<td>Steatosis</td>
<td>Good for detection of moderate-to-severe steatosis, better specificity than ultrasound, provides additional anatomic information</td>
<td>Poor sensitivity, unable to detect mild steatosis, ionizing radiation exposure, limited by variable amounts of iron</td>
</tr>
<tr>
<td>MR imaging</td>
<td>Steatosis</td>
<td>Better sensitivity and specificity than ultrasound</td>
<td>Limited by high iron burden, limited clinical experience</td>
</tr>
<tr>
<td>CAP</td>
<td>Steatosis</td>
<td>Quantitative, more sensitive than conventional ultrasound</td>
<td>Limited availability, high cost</td>
</tr>
<tr>
<td>MR Spectroscopy</td>
<td>Steatosis</td>
<td>Quantitative, sensitive</td>
<td>Limited availability</td>
</tr>
</tbody>
</table>

**Transient elastography**
- Fibrosis
  - Correlates with stage of fibrosis
  - Point-of-care test
  - Less accurate with nonhomogeneous fat distribution, accuracy reduced in obesity, severe steatosis may lead to false positives, operator dependent, accuracy influenced by BMI, higher failure rates than TE, higher failure rates than TE, operator dependent, accuracy influenced by BMI, limited availability, high cost

**Acoustic radiation force impulse**
- Fibrosis
  - Similar sensitivity/specificity as TE

**MR elastography**
- Fibrosis
  - Most accurate test for determining fibrosis stage
  - Accuracy not affected by BMI, degree of steatosis
  - Limited availability, high cost

Adapted from Cleveland E et al Clinical Liver Disease, April 2018
FibroScan – Assessment of Fibrosis in NAFLD

- **FibroScan (Transient Elastography)**
  - Fast, painless, noninvasive, reproducible for advanced fibrosis
  - Increase sample size than liver biopsy
  - XL probe to try and diminish results in obese patients
  - 88% Sen and 95% Spec
  - 78-84% will have reliable liver stiffness measurement
  - Can not determine NASH

**Table 2. Recommended Cutoff Values for Different Stages of Fibrosis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Fibrosis Stage and Cutoff Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F0-F1, kPa</td>
</tr>
<tr>
<td>HBV infection</td>
<td>≤6</td>
</tr>
<tr>
<td>HCV infection</td>
<td>≤7</td>
</tr>
<tr>
<td>HIV/HCV coinfection</td>
<td></td>
</tr>
<tr>
<td>Cholestatic liver disease</td>
<td>≤7</td>
</tr>
<tr>
<td>NAFLD/NASH</td>
<td>≤7</td>
</tr>
</tbody>
</table>

HBV: hepatitis B virus; HCV: hepatitis C virus; kPa: kilopascals; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis

*Based on references 14, 15, 18, 19, and 21.*
Liver Stiffness Correlates with Fibrosis Stage

Liver Stiffness Correlates with Fibrosis Stage

Kruskal Wallis Dunnett’s Test
\( \alpha = 0.05 \)

Normal

Chronic Liver Disease

(Fibrosis Stage)

Yin et al. CGH 2007;5:1207-13
MR Elastography (MRE) of the Liver

PLastic Tube
Passive Driver

Active Driver

Gradient-Echo MRE

-70

0

+70

Amplitude (mm)

-90

0

+90

Amplitude (mm)

60 Hz
MRE Correlates with Fibrosis Stage and NASH

Stage 0

1.7 kPa

Loomba et al., *Hepatology* 60:1919–1927, 2014

AUC = 0.924
P<0.001

- **MR Elastography:**
  - Provides standard MR evaluation
  - Fat quantification
  - Fibrosis measurement
  - “whole liver” evaluation
  - Sen 85% Spec 93%
Composite Clinical Assessment for Advanced Fibrosis in NAFLD

High likelihood of NASH and fibrosis:
- Age >50, Hispanic, DM, obesity, HTN, FS kPa >8.5, AST >40, AST/ALT ratio ≥1, NFS >0.676, FIB-4 >2.67

Intermediate likelihood of NASH and fibrosis:
- Age >40, well-controlled DM, obesity, HTN, FS kPa >7.0, AST >20

Low likelihood of NASH and fibrosis:
- Age <40, non-DM, non-obese, FS kPa <7, AST <20, NFS < -1.455, FIB-4 < 1.30

AST, aspartate aminotransferase; ALT, alanine aminotransferase; DM, diabetes mellitus; FS, fibroscan; HTN, hypertension; NASH, non-alcoholic steatohepatitis; NFS, non-alcoholic fatty liver disease fibrosis score.

Konerman, MA et al J of Hepatology 2018
NAFLD Assessment of Fibrosis: What to do... in clinical practice?

Vilar-Gomez & Chalasani N
J of Hepatology 2018

Fig. 1. Algorithm to non-invasively assess patients with NAFLD and advanced fibrosis using prediction rules and blood-based biomarkers. "Estimated prevalence for low, intermediate and high risks groups. ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NPV, negative predictive value; PPV, positive predictive value; VCTE, vibration controlled transient elastography."
NAFLD

Management
Management of Patients with NAFLD

Figure 1  Management strategies in non-alcoholic fatty liver disease (NAFLD).

Dyson JK et al.  Frontline Gastroenterology 2014
Weight loss

-Options:
  - Diet
  - Surgery
  - Exercise
  - Pharmacotherapy
Diet

“I must be eating right. I’m narrow at the top and wide at the bottom, just like the Food Pyramid!”

Exercise

“Sometimes it’s good to change your walking routine. Try walking around the block instead of wandering around the kitchen.”
1) **Lifestyle changes – WEIGHT LOSS**

- Explain diagnosis and set realistic target weight
- Nutritional counselling – refer to dietician
- Exercise – 3-4 times per week, expend 400 kcal per session
- Promrat et al 2010: **Intensive lifestyle intervention** (diet, exercise, behaviour modification) vs structured education alone.
  - Weight loss 9.3% vs 0.2% ($p = 0.003$)
  - Decrease in NAS 72% vs 30% ($p=0.03$)

Diet

Exercise

Drugs
Source of Daily Food (1889-2009)

The Evolution of Diet
- Large food portions
- High energy-dense food
- Inappropriate mealtimes

Cartoon: "Too bad SparkPoints are not based on calories consumed."
Weight Loss Effectiveness of Three Different Diets

- Caloric restriction below metabolic requirements is key for weight loss (500-750 kcal/d)

- Mediterranean diet recommended
  - Improves metabolic profile
  - Improves outcomes (DM, CVD)

- Coffee beneficial

Nutritional Treatment Options in NAFLD

Fig. 1. A summary of the nutritional treatment options (based on clinical trials or observational studies) through the course of NAFLD. Remission of steatosis can occur with weight reduction achieved by several types of diet or with isocaloric Mediterranean diet (which induces metabolic and anti-inflammatory benefits), as indicated by clinical trials. For remission of NASH or fibrosis, there is no evidence from clinical trials for a benefit of merely improving dietary composition, while there is evidence that at least 7% weight reduction is needed. For prevention of progression to liver cancer, the evidence regarding certain foods and nutrients is derived only from large observational studies and needs further confirmation.
Dietary Intervention

Caloric restriction is the most important goal

Targeted Treatment works best:

- Diabetic pts.: low-carbohydrate diet
- Hyperlipidemia pts.: Low-fat diet

Clin Nutr 2013
Coffee: Protective Effect in NAFLD

Table 1. Summary of epidemiological studies testing the association between coffee or caffeine consumption and NAFLD.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of coffee</th>
<th>Sample size</th>
<th>Improvement in steatosis</th>
<th>Improvement in fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelber-Sagi 2015</td>
<td>All caffeinated coffee types</td>
<td>347</td>
<td>No</td>
<td>Yes (Fibrotest)</td>
</tr>
<tr>
<td>Bambha 2013</td>
<td>Caffeinated and decaffeinated</td>
<td>782</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Anty 2012</td>
<td>Regular coffee, not espresso</td>
<td>195</td>
<td>NE</td>
<td>Yes</td>
</tr>
<tr>
<td>Birerdinc 2012</td>
<td>Caffeine intake</td>
<td>41,658</td>
<td>Yes</td>
<td>NE</td>
</tr>
<tr>
<td>Molloy 2012</td>
<td>Regular coffee</td>
<td>306</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Catalano 2010</td>
<td>Only espresso coffee</td>
<td>245</td>
<td>Yes</td>
<td>NE</td>
</tr>
</tbody>
</table>

NE, not evaluated.
Coffee: Protective Effect in NASH, T2DM & Liver Cancer

- Protective effect in NASH (bx. proven) through a reduction in inflammation and fibrosis
- Reduces insulin levels and risk of Type II DM
- 40% Risk Reduction of HCC:
  - dose response: 1 to 2 cups = 20% reduction
  - 75% > 5 cups

Hepatology 2007
J Natl Cancer Inst 2005
Clin Gastroenterol 2013
Frequent Barriers to Dietary Weight Loss

- Socioeconomic limitations
- Work schedule
- Too strict
- Too impatient for results
- Cravings
- Social Pressure
- Emotions

"After I lost weight, I had a lot more energy! More energy for cooking, more energy for chewing, more energy for going out to dinner..."
Diet

Exercise

Drugs
Encourage Physical Activity
What About Energy Expenditure?

- Resting energy expenditure (depends on age, gender, body size)
- Physical activity expenditure

[Chart showing time taken to burn as much energy as a 30-minute run and participation in activity vs calories burned]

Tozer J, The Economist February/March 2017
Exercise Alone Has Little Impact on Weight Loss

Thom G, Gastroenterology 2017
Physical Activities Fail to Achieve Weight Loss

- Lack of time
- Physical limitations
- Not part of daily routine
- Overwhelming

“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”
Aerobic or Anaerobic Exercise?

- Aerobic exercise results in higher energy consumption (150-180 min per week)
- Cardiorespiratory fitness is needed for aerobic exercise
- Long-term adherence to aerobic exercise is poor

Physical Activity Recommendations, Exercise Intensity, and Histological Severity of Nonalcoholic Fatty Liver Disease

- **Moderate physical activity (min./wk)**
  - Minimum: $\geq 150$
  - Best: $\geq 300$

- **Vigorous physical activity (min/wk)**
  - Minimum $\geq 75$
  - Best $\geq 150$

AJG 2011
Weight Loss Pyramid


*Depending on degree of weight loss

Figure courtesy of S. Harrison
Exercise & NAFLD

Benefits of exercise in NALFD

Changes in the liver
1. Peripheral insulin sensitivity $\uparrow = de~novo~lipogenesis \downarrow$
2. Visceral fat $\downarrow = $ lipid supply to liver $\downarrow$
3. VLDL clearance $\uparrow = $ lipid storage $\downarrow$

Changes to cardiovascular system
1. Torsion $\downarrow = $ myocardial damage $\downarrow$
2. EDV $\uparrow = $ preload $\uparrow$
3. Ca$^{2+}$ handling $\uparrow = $ SV $\uparrow + $ EF $\uparrow$
4. FMD $\uparrow = $ O$^2$ supply $\uparrow$

Fig. 2. Benefits of exercise and physical activity in NAFLD: changes in the liver and changes to cardiovascular system. EDV, end diastolic volume; SV, stroke volume; EF, ejection fraction; FMD, flow-modulated dilatation; VLDL, very low density lipoprotein.
Weight Loss Can Reverse Comorbidities

- T2D prevention and control
  - Weight-related QoL
  - Improvements in CVD risk
  - HDL-C, cholesterol, triglycerides, BP

- Previous improvements + T2D remission
  - Improvements in sleep apnea
  - Reductions in intima-media thickness

- Previous improvements + Reductions in CVD events
  - Reductions in all-cause mortality
  - Reductions in cancer risks (only with bariatric surgery)

≥ 5%
≥ 10%
≥ 15%

Comprehensive Lifestyle Intervention Program

- Long-term (lifelong) program
- Multidisciplinary approach delivered by trained interventionists that set specific attainable goals
  - **Diet**
    - reduced caloric intake
  - **Exercise**
    - 200-300 min per week
  - **Behavior therapy**
    - Educate and engage the patient
    - Self-monitoring of food/caloric intake
    - recording of physical activity and weight

Jensen MD, J Am Coll Cardiol 2014; Perri MG, J Consult Psychol 1988; Wing RR, NEJM 2006; Bellentani S, Hepatology 2008
Weight Loss and Lifestyle Modification

• Only 15% achieve a weight loss of > 10% and most regain their weight

• Best average weight loss: 3-4 kg at 2 and 4 years

• **Functional Difficulty:** (multivariate analysis) Increased cognitive difficulty, fatigue, lower albumin, and bilirubin associated

Dig Dis 2010
Disabil Rehabil 2013
Metabolic Surgery

“Belly button enlargement is a popular alternative to other types of weight loss surgery.”
Bariatric Surgery Procedures

Roux-en-Y gastric bypass
Sleeve gastrectomy

Change in Weight (%)

Sjoestroem L, NEJM 2007
Long-term Effect of Bariatric Surgery on Weight Loss

Maciejewski ML, JAMA Surgery 2016
### Bariatric Surgery Improves Clinical Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Surgery</th>
<th>After 5 Yrs</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>94 (24.8)</td>
<td>24 (10.8)</td>
<td>.000001</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>185 (48.8)</td>
<td>85 (37.0)</td>
<td>.00005</td>
</tr>
<tr>
<td>Serum triglycerides, mean (g/L)</td>
<td>1.67</td>
<td>1.06</td>
<td>.00001</td>
</tr>
<tr>
<td>Fasting glucose, mean (g/L)</td>
<td>1.18</td>
<td>0.94</td>
<td>.00001</td>
</tr>
<tr>
<td>Insulin resistance index, mean</td>
<td>3.2</td>
<td>2.83</td>
<td>.00001</td>
</tr>
<tr>
<td>ALT, mean (IU/L)</td>
<td>30.1</td>
<td>22.8</td>
<td>.00003</td>
</tr>
<tr>
<td>GGT, mean (IU/L)</td>
<td>39.9</td>
<td>29.2</td>
<td>.00001</td>
</tr>
</tbody>
</table>

Bariatric Surgery Improves Long-term Survival

Improvement of obesity-related conditions:
- Diabetes mellitus
- Hypertension
- Dyslipidemia

Bariatric Surgery Improves Fibrosis in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)

Distribution of Fibrosis METAVIR Scores

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 1 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>27.5</td>
<td>43.75</td>
</tr>
<tr>
<td>F1</td>
<td>40</td>
<td>32.5</td>
</tr>
<tr>
<td>F2</td>
<td>13.75</td>
<td>7.5</td>
</tr>
<tr>
<td>F3</td>
<td>21.25</td>
<td>3.75</td>
</tr>
<tr>
<td>F4</td>
<td>7.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Wilcoxon signed-rank paired t test

*P* < .003

The Treatment Gap

Unmet need for a safe minimally-invasive treatment option

- Lifestyle
- Medication

Low Risk

Low Effectiveness

High Risk

High Effectiveness

Surgery
Metabolic Endoscopy

"Not that balloon you idiot ..."
Gastric Balloon Systems

- Balloon volume of at least 400ml needed for weight loss
  - Satiety
  - Gastric motility
  - Decreased CCK levels

- Improvements have been described for
  - Steatosis
  - ALT
  - Liver histology

- Weight loss maintained for 6 months in 66-90% and for 18 months in 50%

Endoscopic Sleeve Gastroplasty

- Using a full-thickness suturing system the stomach volume is reduced
- 60-90 min outpatient procedure performed under general anesthesia
- Low adverse event rate
- 21% weight loss after 2 years
- Metabolic profiling shows lowering of HbA1c, triglycerides, ALT and systolic BP

Sharaiha RZ, Clin Gastroenterol Hepatol 2017; Kumar N, Gastroenterology 2014
NAFLD

Pharmacotherapy

“What’s wrong with eating donuts to cure obesity? Don’t you believe in alternative medicine?”
Pharmacotherapy Guidance

- If possible, replace weight-favorable medications
- Use pharmacotherapy as adjunct to a comprehensive lifestyle intervention program
- Assess efficacy and safety monthly for the first 3 months and thereafter quarterly
- If weight loss after 3 months is >5% continue, otherwise seek alternative medication

An Endocrine Society Clinical Practice Guideline, J Clin Endocrinol Metab 2015
## Targeting Components of Metabolic Syndrome in NAFLD Patients with T2DM

### Table 2: Treatment of type 2 diabetes and the metabolic syndrome in NAFLD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary intervention</td>
<td>See table 1</td>
<td>Escalate treatment if HbA1c &gt; 7.5%</td>
</tr>
<tr>
<td>Metformin</td>
<td>First-line treatment of T2DM</td>
<td>Aids weight loss&lt;br&gt;Reduces risk of any diabetes-related endpoint, microvascular disease, myocardial infarction (large vessel disease) and all-cause mortality.&lt;sup&gt;52&lt;/sup&gt; &lt;sup&gt;53&lt;/sup&gt;&lt;br&gt;Reduced HCC risk&lt;sup&gt;57&lt;/sup&gt; &lt;sup&gt;58&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Second-line treatment of T2DM in NASH</td>
<td>Improve insulin sensitivity and reduces hepatic steatosis/steatohepatitis&lt;sup&gt;41&lt;/sup&gt;&lt;br&gt;18% reduction in death, myocardial infarction and stroke in T2DM&lt;sup&gt;45&lt;/sup&gt;&lt;br&gt;Consider risks of bladder cancer, increased bone loss&lt;sup&gt;44&lt;/sup&gt; and cardiac failure&lt;sup&gt;42&lt;/sup&gt;</td>
</tr>
<tr>
<td>GLP-1 analogue</td>
<td>Third-line treatment of T2DM in NASH</td>
<td>Reduce HbA1c by 1% and average 3 kg weight loss&lt;br&gt;Improve liver enzymes and reduce steatosis&lt;sup&gt;56&lt;/sup&gt;&lt;br&gt;Risk of pancreatitis&lt;sup&gt;55&lt;/sup&gt;</td>
</tr>
<tr>
<td>Insulin/sulfonylureas</td>
<td>Fourth-line treatment of T2DM in NASH</td>
<td>Lead to weight gain that can be detrimental in NAFLD</td>
</tr>
</tbody>
</table>

GLP-1, glucagon-like peptide-1; HbA1c, glycosylated haemoglobin; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.
# Targeting Components of Metabolic Syndrome in NAFLD Patients with HTN and Hyperlipidemia

## Table 3: Management of hypertension and dyslipidaemia in NAFLD

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Treatment/indication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>ACEI and ARBs first-line if BP &gt;140/90 mm Hg&lt;sup&gt;61&lt;/sup&gt; Escalate treatment according to NICE hypertension guidelines</td>
<td>Blocking RAS reduces hepatic fibrosis&lt;sup&gt;62, 63&lt;/sup&gt; ARBs improve transaminase levels and insulin sensitivity&lt;sup&gt;64&lt;/sup&gt; 20% reduction in new onset T2DM with ACEI or ARBs&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>Primary prevention with statin if ≥20% 10-year risk of developing cardiovascular disease&lt;sup&gt;66&lt;/sup&gt; If secondary prevention, aim total cholesterol &lt;4 mmol/L</td>
<td>Statins reduce 5-year incidence of all-cause mortality, major coronary events, coronary revascularisation and stroke by about 20% per mmol/L reduction in LDL cholesterol&lt;sup&gt;67&lt;/sup&gt; May reduce incidence of HCC&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; HCC, hepatocellular carcinoma; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; RAS, renin–angiotensin system.
## Use of Weight-Favorable Medications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Promote Weight Gain</th>
<th>Weight-Neutral</th>
<th>Promote Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Insulin*, Sulfonlureas, TZDs, Metiglinides</td>
<td>DPP-4 Inhibitors</td>
<td>Metformin, Pramlintide, GLP-1 Agonists, SGLT2 Inhibitors, Acarbose, Miglitol</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>β Blockers**, α Blockers</td>
<td>ACE Inhibitors, ARBs, CCBs</td>
<td>--</td>
</tr>
<tr>
<td>Depression</td>
<td>Paroxetine, Fluvoxamine, Amitriptyline, Doxepin, Imipramine, Nortriptyline, Trimipramine, Mirtazapine, Lithium</td>
<td>Fluoxetine*, Sertraline*</td>
<td>Bupropion</td>
</tr>
</tbody>
</table>
# Obesity Reduction Drugs for Obese NAFLD Patients

## FDA-Approved Medications For Long-term Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat (Xenical)</td>
<td>Pancreatic lipase inhibitor</td>
<td>Steatorrhea, flatulence, fecal urgency, fecal incontinence</td>
</tr>
<tr>
<td>Lorcaserin (Belviq®)</td>
<td>5HT2c receptor agonist</td>
<td>Headache, nausea, dry mouth, dizziness, fatigue, constipation</td>
</tr>
<tr>
<td>Phentermine/Topiramate ER (Qsymia®)</td>
<td>NE-releasing GABA receptor modulator</td>
<td>Insomnia, dry mouth, constipation, dysgeusia</td>
</tr>
<tr>
<td>Naltrexone/Bupropion (Contrave®)</td>
<td>Opioid antagonist/reuptake inhibitor of NE and dopa</td>
<td>Nausea, constipation, headache, vomiting, dizziness</td>
</tr>
<tr>
<td>Liraglutide (Saxenda®)</td>
<td>GLP-1 agonist</td>
<td>Nausea, vomiting, pancreatitis</td>
</tr>
</tbody>
</table>
Fig. 4. Mechanism of action of pharmacologic treatments for NAFLD and NASH. ACC, Acetyl-CoA Carboxylase; AOC, amine oxidase, copper containing; ASK, Apoptosis signal-regulating kinase; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FGF, fibroblast growth factor; FFA, free fatty acids; FXR, Farnesoid X receptor; IL, interleukin; LPS, lipopolysaccharide; ROS, reactive oxygen species; SIM, simtuzumab; SHP, small heterodimer partner; SREBP, Sterol regulatory element binding proteins; TGF, Transforming growth factor; TLR, toll like receptor; TNF, tumor necrosis factor; TR, thyroid receptor; UPR, unfolded protein response; Jun N-terminal kinases; VLDL, very low density lipoprotein.

Konerman MA et al J of Hepatology 2018
# Pipeline for NASH – 2018

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatment Paradigm</th>
<th>Treatment Regimens</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila/b</td>
<td>Cenicriviroc CCR2/CCR5 inh</td>
<td>100mg once daily PO, &gt;550 pts studied to date, CCR2/5 involved in macrophage recruitment, maturation and in stellate cell activation</td>
<td>FDA fast tracked</td>
</tr>
<tr>
<td>Ila</td>
<td>Emricasan, Caspase inhibitor</td>
<td>Up to 500mg daily PO, Conatus</td>
<td></td>
</tr>
<tr>
<td>Ila</td>
<td>ASK1 inhibitor</td>
<td>Inhibits inflammatory and ROS pathways</td>
<td></td>
</tr>
<tr>
<td>Ila</td>
<td>Cysteamine, antioxidant</td>
<td>300, 375, or 450 mg once daily PO 41% decr in AST, ns impr in adip, CK18 NVD in Huntington’s Chorea trial</td>
<td></td>
</tr>
<tr>
<td>Ila</td>
<td>Liraglutide, GLP-agonist</td>
<td>70mg once a day S/C for 24 months 6/27 pts “decreased” NAS score</td>
<td></td>
</tr>
</tbody>
</table>
### Pipeline for NASH - 2018

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatment Paradigm</th>
<th>Treatment Regimens</th>
<th>notes</th>
</tr>
</thead>
</table>
| IIb/III| FXR agonists. OCA, INT777, PX-102, WAY-362 | • 25mg once daily PO, for INT 747 (OCA) | • Endpoints met  
  • Elev alk phos, lipids and itching |
| IIb   | GFT-505 PPAR α/δ agonist | • 40-100mg daily PO, Genfit Pharma  
  • Also studied in dyslipidemia, (effective) and T2DM | • Benefits at 60mg and 30mg |
| IIb   | Galectin GR-MD-02 | • Binds to galectin 1 and 3,  
  • 26 IV infusion doses | • FDA fast tracked |
| IIb   | Simtuzumab LOXL2 mAb | • Multiple doses in development, cross link inhibitor | • Subcut admin |
| Ila/b | Aramchol, FA/bile acid conjugate | • 300mg once a day for 3 months  
  • Effective in ph 2a in decr easing liver fat by 12%, also decr ALT and incr adiponectin | • FDA fast tracked for 240 pt study |

**Earliest** launch dates Q4 2018?
Therapeutic Steps in NAFLD/NASH

- Simple steatosis
- NASH
- Cirrhosis
- HCC

- Lifestyle (Diet, exercise)
- Pharmacological
- Bariatric surgery (MO)
- Rx of complications, OLT
# Managing Complications of NASH Cirrhosis

## Table 4 Managing the complications of cirrhosis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular</td>
<td>Yearly cumulative incidence 2.6% per year(^5^0)</td>
<td>6 monthly abdominal USS± α-fetoprotein</td>
</tr>
<tr>
<td>carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varices</td>
<td>40%–44% if Child–Pugh grade A</td>
<td>Endoscopic surveillance and management according to BSG or AASLD guidelines(^9^4 \quad ^9^3)</td>
</tr>
<tr>
<td></td>
<td>75%–85% if Child–Pugh grade C(^9^2)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Cirrhotic patients are at increased risk of osteoporosis and fractures</td>
<td>Correction of vitamin D insufficiency with oral daily vitamin D(_3) and calcium(^9^5)</td>
</tr>
<tr>
<td></td>
<td>Larger studies assessing the effects of vitamin D supplementation on BMD are lacking</td>
<td>Dual x-ray absorptiometry scan to assess BMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Assess fracture risk using FRAX tool (<a href="http://www.shef.ac.uk/FRAX/tool">http://www.shef.ac.uk/FRAX/tool</a>)</td>
</tr>
</tbody>
</table>

AASLD, American Association for the Study of Liver Diseases; BMD, bone mineral density; BSG, British Society of Gastroenterology; USS, ultrasonography.

---

**Routine medical management of Portal HTN complications:**
- Ascites/SBP; variceal bleed; Hepatic encephalopathy
- Liver Transplantation evaluation for decompensated cirrhosis/MELD > 15

*Dyson JK et al. Frontline Gastroenterology 2014*
Approach to NAFLD in Ghana

- Increase awareness of NAFLD – community, MDs, local government partners
- Prevention and Rx of Metabolic Syndrome: Obesity and Diabetic Clinics- lifestyle modification a key component
- Early detection of NAFLD with appropriate risk assessment and prompt referral via non-invasive techniques: safe, low cost and reliable.
- Fatty Liver Referral Clinic: a multidisciplinary approach - hepatologists, diabetologists, radiologists, dieticians, psychologists, physical therapists/exercise physiotherapists - nurses

NAFLD- Summary

- NAFLD has tremendous clinical, economic burden to patients and to society and this burden is growing globally
- NASH is the progressive form of NAFLD
- Pathogenesis is complex & biomarkers based on pathogenetic pathways are evolving
- Histologic advanced fibrosis stage predicts liver related mortality- Noninvasive assessment is promising & facilitates screening
- Comprehensive lifestyle intervention with a calorie-restricted diet, exercise and behavior therapy: cornerstone of NAFLD Mx
- There are currently no FDA-approved Rx. Pharmacologic Rx currently targeted to control DM or hyperlipidemia
- Prevention –is crucial especially in developing countries