Nonalcoholic Fatty Liver Disease (NAFLD), Atherosclerosis and Niacin emerging evidence

The Virtual 12th Annual Orange County Symposium for Cardiovascular Disease Prevention:
Crossroads in Cardiovascular Disease Prevention

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Disclosure

In past 12 months, Moti Kashyap, MD was executive director, and co-chair of publications, NIH sponsored AIM HIGH Trial, is co-founder of Aasta Pharmaceuticals, and co-inventor of a US patent: New Treatment for the Prevention and Reversal of Non-Alcoholic Fatty Liver Disease (NAFLD).
Nonalcoholic Fatty Liver Disease (NAFLD) is common worldwide. In USA, it is estimated to affect a stunning 75 million adults. The disease is characterized by fat accumulation in the liver (Steatosis). Associated with obesity, metabolic syndrome, type 2 diabetes mellitus and atherosclerotic cardiovascular disease (ASCVD). Recently, more appropriately called Metabolic Associated Fatty Liver Disease (MAFLD). In approximately 25-30% of NAFLD patients, it progresses to Nonalcoholic Steatohepatitis (NASH) characterized by inflammation and Fibrosis resulting in cirrhosis, portal hypertension, variceal hemorrhage, liver failure, transplantation, cancer and death.
NAFLD Progression to Fibrogenesis

Normal Liver\textsuperscript{[1,2]}

- Risk factors (metabolic syndrome, genetic factors)
- Hepatocytes are less responsive to insulin

Steatosis (NAFL)\textsuperscript{[1,2]}

- Increased fat storage
- Decreased fatty acid oxidation
- Fat droplets in cells
- Steatosis

Steatohepatitis (NASH)\textsuperscript{[1,2]}

- Oxidative and ER stress
- Mitochondrial dysfunction
- Lipotoxicity
- Inflammation, apoptosis

Cirrhosis\textsuperscript{[1,2]}

- Hepatic stellate cells produce extracellular matrix deposits

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Slide credit: clinicaloptions.com
There is an urgent need not only for treatment but for prevention of this silent and serious disease which is increasing worldwide and is a major public health problem.
Talk Outline

1. NAFLD and Atherosclerotic Cardiovascular Disease (ASCVD)

2. Niacin for NAFLD: new use of an old drug?
NAFLD and Atherosclerotic Cardiovascular Disease (ASCVD): risk factors and diagnosis

• NAFLD/NASH and ASCVD often occur together with other risk factors, especially Metabolic Syndrome (obesity, dyslipidemia, insulin resistance, hypertension, prediabetes) and T2 diabetes mellitus.

• NAFLD is often not diagnosed because of lack of readily available testing. Liver biopsy is needed for confirmation.

• Suspect it in patients with Metabolic Syndrome/Diabetes, especially those with elevated liver enzymes.

• Workup may include: Liver function tests, imaging (ultrasound, CT scan, Liver stiffness)

• Important for Lipidologists, Cardiologists, PCPs, and other practitioners to be aware of this condition in their patients.
Does NAFLD predict ASCVD?

In 3 metanalyses comprising 225,000 patients with NAFLD

- Relative Risk (RR) for Major Atherosclerotic Cardiovascular Events = 1.64 - 1.77
- Prevalent CVD: RR = 1.81
- Myocardial Infarction: RR = 1.51 (NASH patients)*

Other studies have shown increased association with:

- High risk plaque
- Increased coronary artery calcium and carotid thickness
- Atrial and ventricular arrhythmias


*Ghoneim S, Dhore A, Shah A, et al. Patients with non-alcoholic steatohepatitis (NASH) have a higher prevalence of myocardial infarction [DDW abstract234]. Gastroenterology. 2020;158(6 suppl 1).
NAFLD and ASCVD: common pathology features

- Fat accumulation
- Inflammation
- Fibrosis

NAFLD and ASCVD: common pathophysiologic mechanisms

- Caloric excess
- Atherogenic dyslipidemia
- Oxidative stress and inflammation
- Endothelial dysfunction
- Hepatic insulin resistance
- Genetic
- Others

Current Therapeutic Approaches for NAFLD

• Weight loss (caloric restriction, consider bariatric surgery in very obese patients at high risk)
• Exercise
• Healthy diet
• Aggressively treat associated risk factors: Dyslipidemia (statins, etc), Hypertension (ARBs etc), Prediabetes and T2 DM, and smoking cessation.
• Specific Medication for NAFLD: None recommended by the American Association for Study of Liver Disease (AASLD)
  
  Vitamin E, Pioglitazone can be considered but have other adverse effects
The Road for a Successful Drug for NAFLD

• Very steep challenge.

• Like atherosclerosis, NAFLD is a slow disease that takes decades to progress from steatosis, steatohepatitis, fibrosis and finally manifesting clinically as decompensated cirrhosis and its lethal complications.

• Regulatory authorities (e.g. FDA) have allowed the use of surrogate endpoints such as biopsy proven reduction in fibrosis score or resolution of NASH for initial approval for clinical use.

• The real test is successful clinical benefit of reduction in events: fatal and non-fatal endpoints (e.g. variceal hemorrhage, encephalopathy, transplantation, cancer).

• No drug or drug combinations are anywhere close to showing clinical benefit for NAFLD

• NAFLD is apparently at a stage where Lipidology was fifty years ago in terms of pharmacologic treatment for ASCVD.

• Then, Niacin was the only available proven drug for lowering cholesterol and CV events.
Disappointment of Recent Clinical Trials for NASH

- There are at least 40+ drugs in development for NAFLD.
- Most discouraging are 4 recent phase 3 trials in which 2 failed completely (Elafibranor and Selonsertib)
- Two drugs (Cenicriviroc and Obeticholic Acid) showed at least 1 stage reduction in fibrosis but no resolution of NASH. No data yet on clinical event endpoints
- Obeticholic Acid raised LDL-Cholesterol and caused itching as a nuisance side effect.
- Currently, the FDA has not yet approved any drug for clinical use for NASH/NAFLD.
- Other drugs have been suspended from further development including seladelpar, emricasan, selonsertib.

Niacin for NAFLD: current evidence

• After almost half a century of the demonstration that Niacin prevents heart attacks and stroke (The Coronary Drug Project Research Group. *JAMA*. 1975;231:360),

• This presentation will focus on the recent emerging evidence that Niacin may also prevent and reverse NAFLD.

• We believe that certain NASH patients with atherogenic dyslipidemia may get dual benefit (CVD and NAFLD) from niacin-based therapy, especially those with high triglycerides.

• Represents a new and repurposed use of niacin for NAFLD.
Preclinical Evidence: Niacin treats all 3 major stages of NAFLD.

Niacin for NAFLD: current evidence for steatosis, steatohepatitis and fibrosis

A. Preclinical:

In Vivo Animal Models

In Vitro: Human Hepatocytes

Human Stellate Cells

B. Clinical Trial in Patients with Steatosis
Niacin Prevents Hepatic Steatosis in Rats Fed High-Fat (HF) Diet

Expt. Protocol:
- Rats fed HF or HF + niacin (0.5% and 1%) diet for 4 wks.
- Liver sections stained with Haematoxylin & Eosin (H&E)

Niacin Reverses Hepatic Steatosis in Rats Fed High-Fat (HF) Diet

Expt. Protocol:
- Rats were first fed HF diet for 6 weeks to induce hepatic steatosis.
- Rats were then fed 0.5% niacin diet while continuing on HF diet for 6 weeks.
- Liver sections were stained with Haematoxylin & Eosin (H&E)

Niacin Inhibits Liver Oxidative Stress and Inflammation (NASH)

- Decreases Reactive Oxygen Species production in human hepatocytes.
- IL-8, an inflammatory mediator involved in NAFLD/NASH
- Neutrophil Myeloperoxidase (MPO), an additional inflammatory mediator associated with NAFLD/NASH

Ganji SH, et. al. Metabolism 64:982-90, 2015
Niacin Prevents Fibrosis: rat model

A: Control (no Niacin)
B: Rats treated with Thioacetamide x 8 weeks (collagen seen as gray tissue)
C and D: Rats treated with Niacin and Thioacetamide

Niacin Inhibits Fibrosis in Human Stellate Cells


VEH = Vehicle control
NIA = Niacin (0.5 mM)

* = p < 0.05 compared to control
+ = p < 0.05 compared to TGF-β or H₂O₂ treatments.
Unique Mechanisms of Action of Niacin on NASH-NAFLD: overview of current evidence


Mechanism of Action of Niacin on NASH-NAFLD

NIACIN

↓ Hepatic DGAT2

↓ TG (↓ Steatosis)

↓ ROS (↓ NADPH Oxidase)

↓ IL-8 → Inflammation

Hepatocytes

↓ NASH

Stellate cells

↓ FIBROSIS

DGAT2: Diacylglycerol Acyltransferase 2
ROS: Reactive Oxygen Species
TG: Triglyceride
NASH: Non-alcoholic Steatohepatitis
Clinical Trial Evidence:
Niacin decreases fatty liver and improves liver enzymes


Study Design/Methods:
• Hypertriglyceridemic patients (n=39, baseline liver fat content 12.8±7.6% were treated with Extended-Release Niacin [2g/day], generic for Niaspan) for 23 weeks
• Liver fat content before and after niacin treatment was measured by Proton MR spectroscopy.

Results:

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<tr>
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<th>Before</th>
<th>After Treatment</th>
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<tr>
<td>Liver fat content (%)</td>
<td>12.8 ± 7.6</td>
<td>6.7 ± 6.1 (-47.2%, p&lt;0.001)</td>
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<td>Fatty liver (liver fat &gt;5%)</td>
<td>31 pts.(79.5%)</td>
<td>19 pts.(48.7%), p&lt;0.01</td>
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<td>ALT (IU/l)</td>
<td>67.2 ± 15.7</td>
<td>63.0 ± 16.0 (p&lt;0.026)</td>
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<td>Alkaline phosphatase (U/l)</td>
<td>33.0 ± 12.5</td>
<td>28.5 ± 11.6 (p&lt;0.003)</td>
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<td>Gamma-glutamyltransferase (U/l)</td>
<td>41.6 ± 18.2</td>
<td>37.1 ± 26.6 (p&lt;0.019)</td>
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<td>hsCRP (mg/l)</td>
<td>0.32 ± 0.32</td>
<td>0.25 ± 0.27 (p&lt;0.043)</td>
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Combination Therapy Using Drugs in Development: rationale

- Because niacin appears to benefit all 3 major stages of NAFLD, a combination (e.g. Niacin+Drug X) would theoretically result in a wider and enhanced efficacy.

- For example drug (drug X) acting on fibrosis may not have efficacy on steatosis or inflammation. Combining niacin and drug X will theoretically result in a more powerful product with wider efficacy.

- Expected Result: Very Effective Broad Spectrum Compound for NASH-NAFLD.
Conclusions

- Emerging evidence indicates that NAFLD is a risk factor for ASCVD and often associated with Metabolic Syndrome. Often not diagnosed till cirrhosis manifestations emerge.
- NAFLD is a risk factor for ASCVD
- Early diagnosis includes assessment of risk factors, blood tests and imaging.
- Liver biopsy is needed for definitive diagnosis.
- Treatment is lifestyle changes. No drug approved for NAFLD yet.
- Emerging evidence that Niacin (not as a vitamin, but as a drug), is a potential repurposed therapeutic agent for the treatment of nonalcoholic fatty liver disease and its complications of steatosis, steatohepatitis, and fibrosis.
- Randomized clinical trials are needed. **Niacin is not recommended in absence of these trials.**
- Hopefully, exciting emerging data on a potentially new therapy for an important disease will contribute to a cost-saving therapy for NAFLD.
Thank you