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

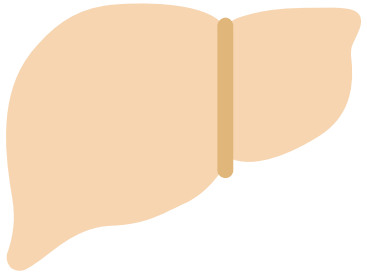
In past 12 months, Moti Kashyap, MD was executive director, and co-chair of publications, NIH sponsored AIM HIGH Trial, is co-founder of Aasta Pharmaceuticals, and co-inventor of a US patent : New Treatment for the Prevention and Reversal of Non-Alcoholic Fatty Liver Disease (NAFLD).

Introduction

- 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.

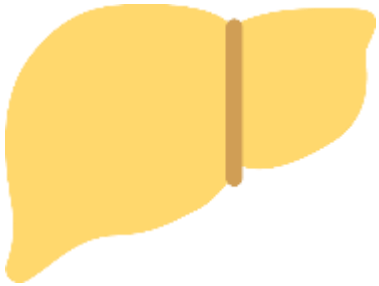
NAFLD Progression to Fibrogenesis

Normal Liver[1,2]



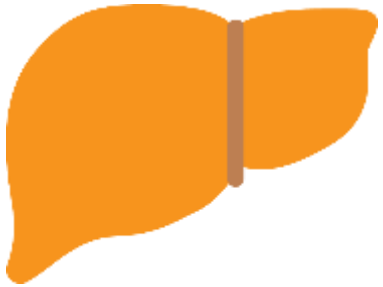
- Risk factors (metabolic syndrome, genetic factors)
- Hepatocytes are less responsive to insulin

Steatosis (NAFL)[1,2]



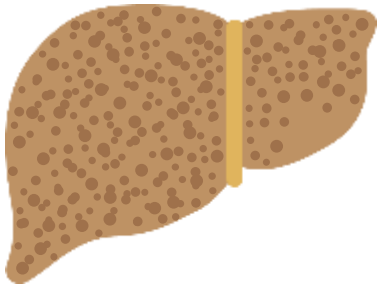
- Increased fat storage
- Decreased fatty acid oxidation
- Fat droplets in cells
- Steatosis

Steatohepatitis (NASH)[1,2]



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

Cirrhosis[1,2]



- Hepatic stellate cells produce extracellular matrix deposits

1. Machado. Gastroenterology. 2016;150:1769. 2. Schuppan. J Gastroenterol Hepatol. 2013;28:68.

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

Stahl EP, Dhindsa DS, Chalasani NP, Sperling LS. J Am Coll Cardiol 2019;73:948-63

***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**

Kashyap ML, Ganji S, and Kamanna VS, Pharmacologic Therapy with Niacin for Nonalcoholic Fatty Liver Disease (NAFLD): emerging evidence. Archives of Gastroenterology Research, In Press 2020

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NAFLD and ASCVD: common pathophysiologic mechanisms

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

Stahl EP et al. Nonalcoholic Fatty Liver Disease and the Heart. J Am Coll Cardiol 2019;73:948–63)

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.

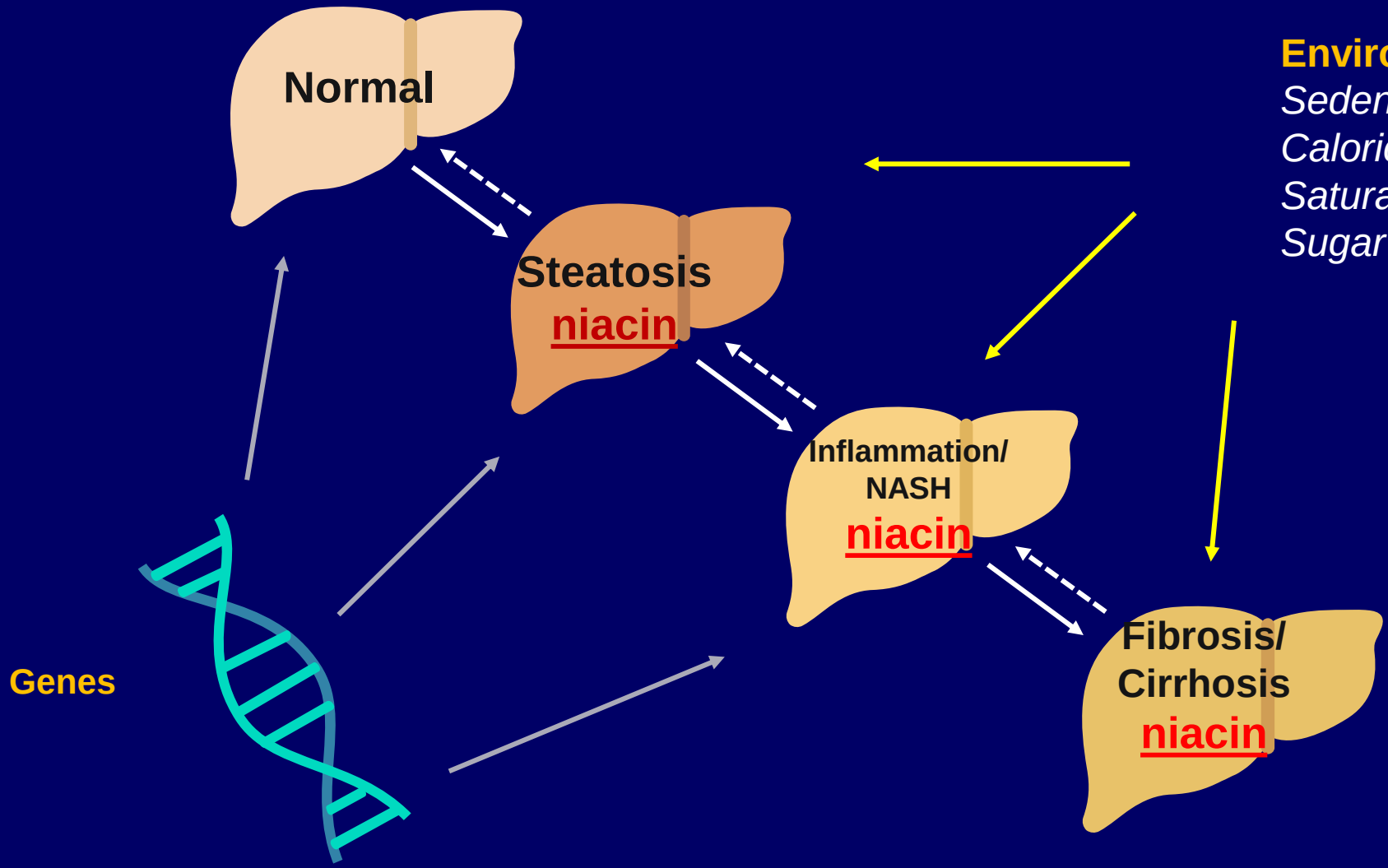
- *Kashyap ML, Ganji S, and Kamanna VS, Pharmacologic Therapy with Niacin for Nonalcoholic Fatty Liver Disease (NAFLD): emerging evidence. Archives of Gastroenterology Research, In Press 2020*

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.

Reviewed in: *Kashyap ML et al. Niacin for Treatment of Nonalcoholic Fatty Liver Disease* Journal of Clinical Lipidology (2019) 13, 873–879



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

A. **Preclinical:**

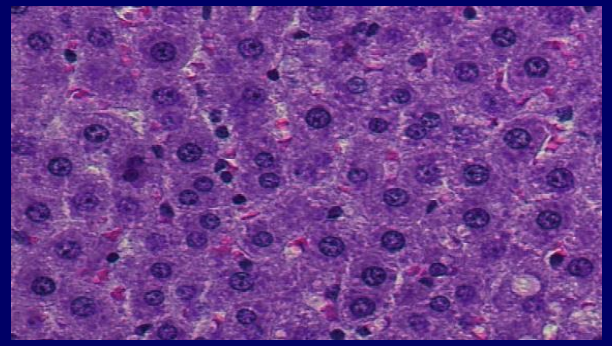
In Vivo Animal Models

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



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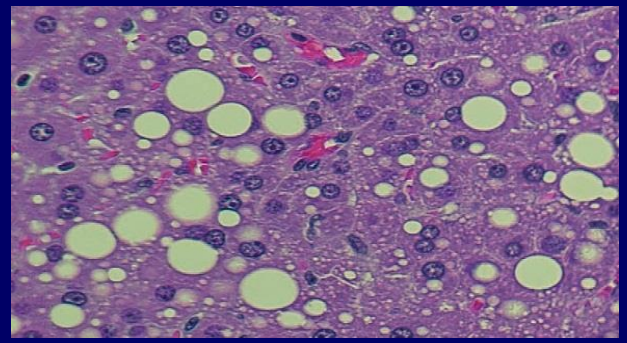
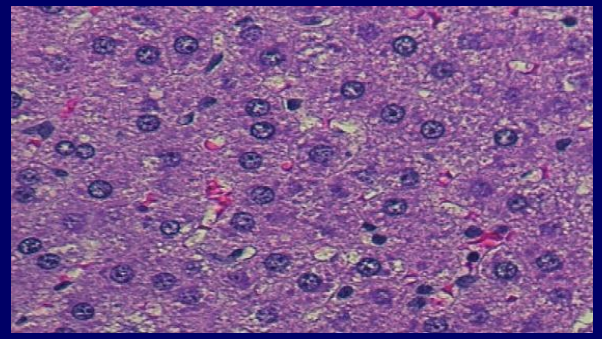
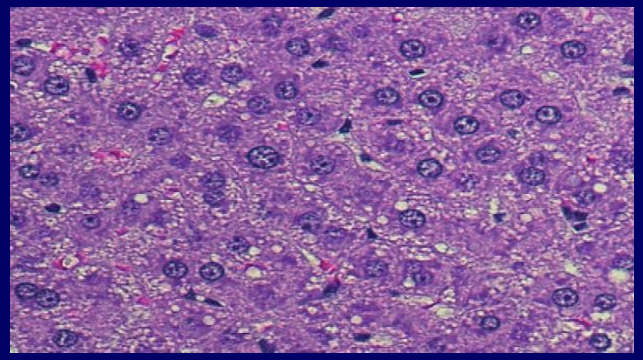


HF



HF + 0.5% Niacin



HF + 1% Niacin

Expt. Protocol:

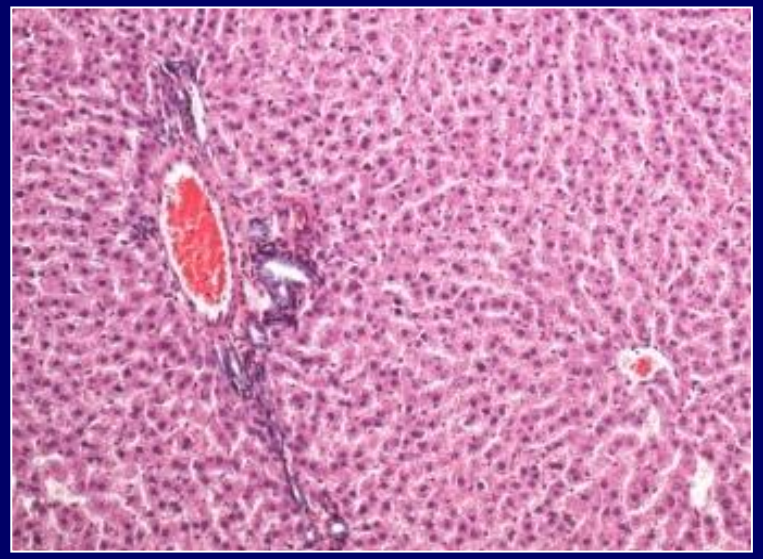
- Rats fed HF or HF + niacin (0.5% and 1%) diet for 4 wks.
- Liver sections stained with Haematoxylin & Eosin (H&E)

Ganji SH, et. al. Amer J Physiol Gastroenterol Liver Physiol 306:G320-7, 2014

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)



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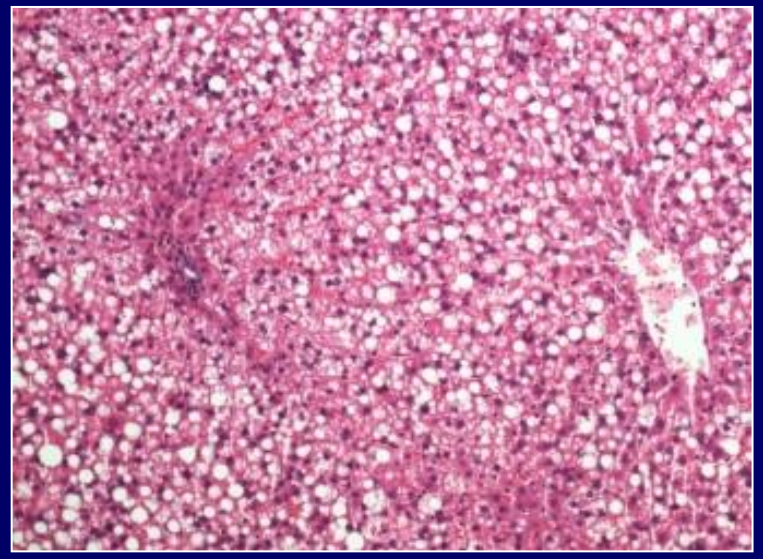

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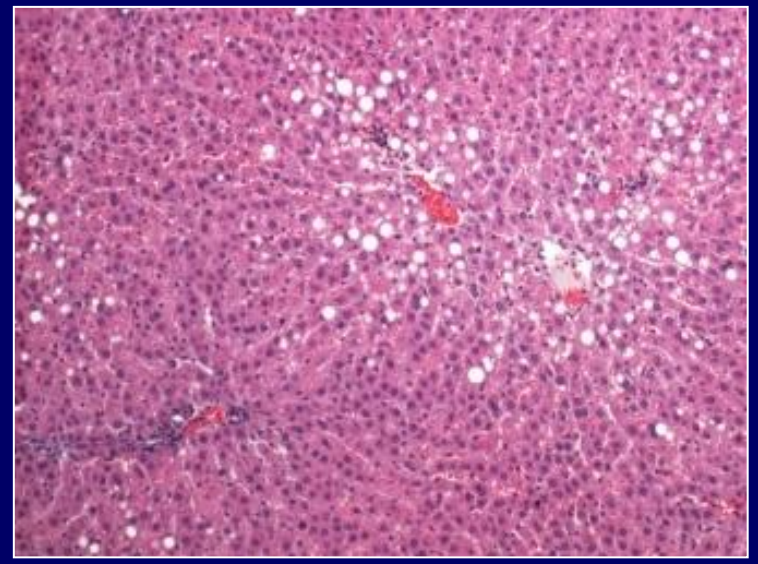


Niacin (0.5%)

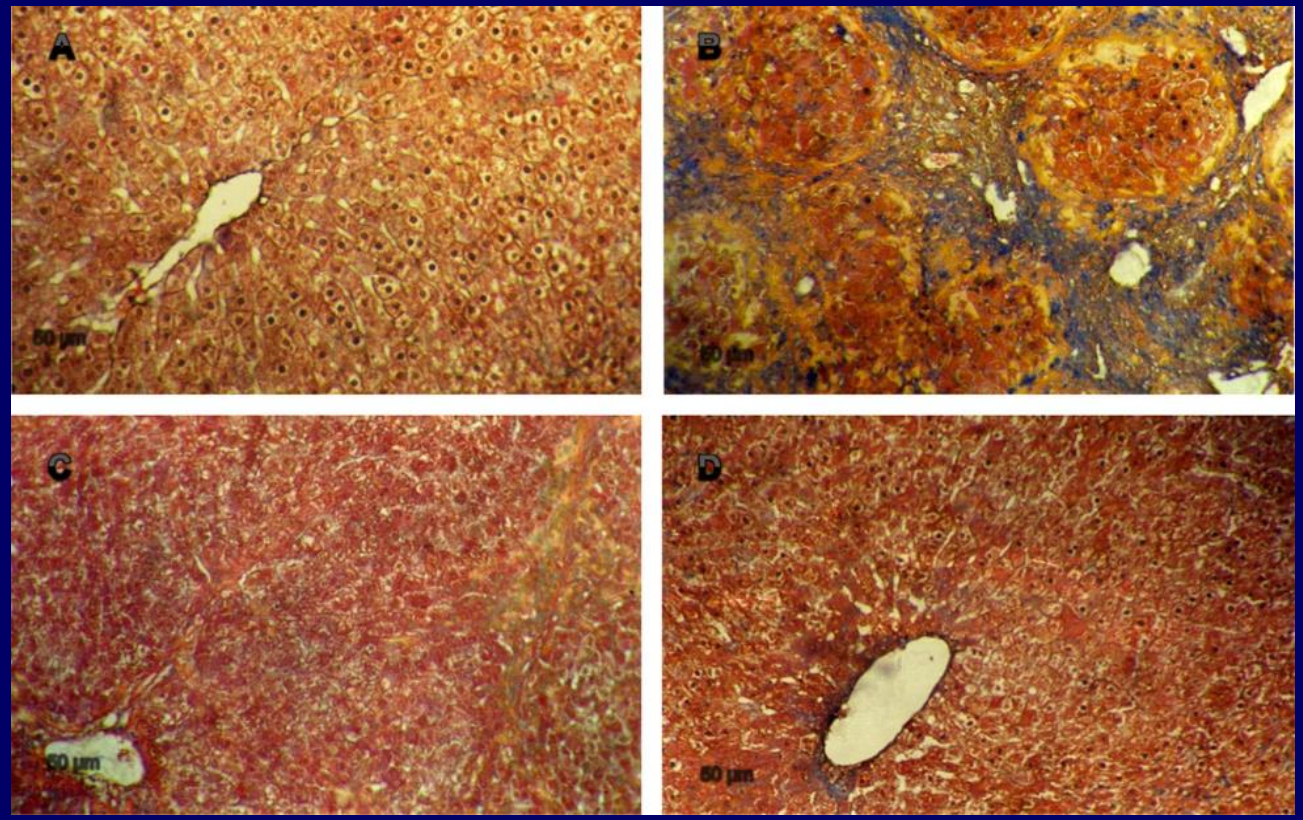
Ganji SH, et. al. Amer J Physiol Gastroenterol Liver Physiol 306:G320-7, 2014

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)

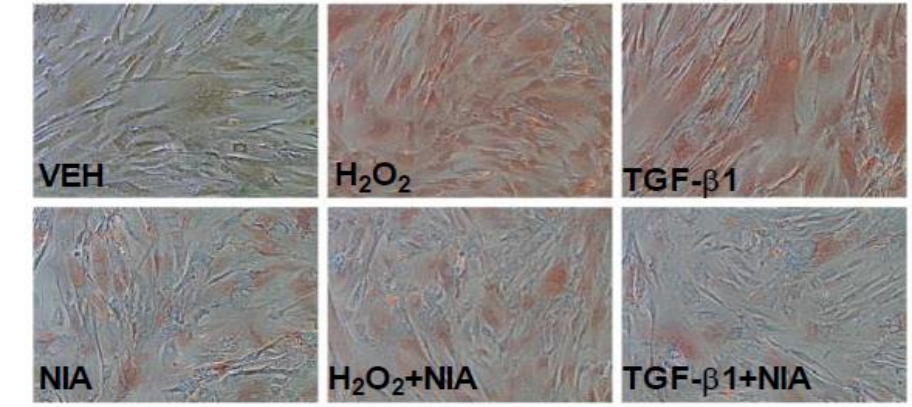
B: Rats treated with Thioacetamide x 8 weeks (collagen seen as gray tissue)

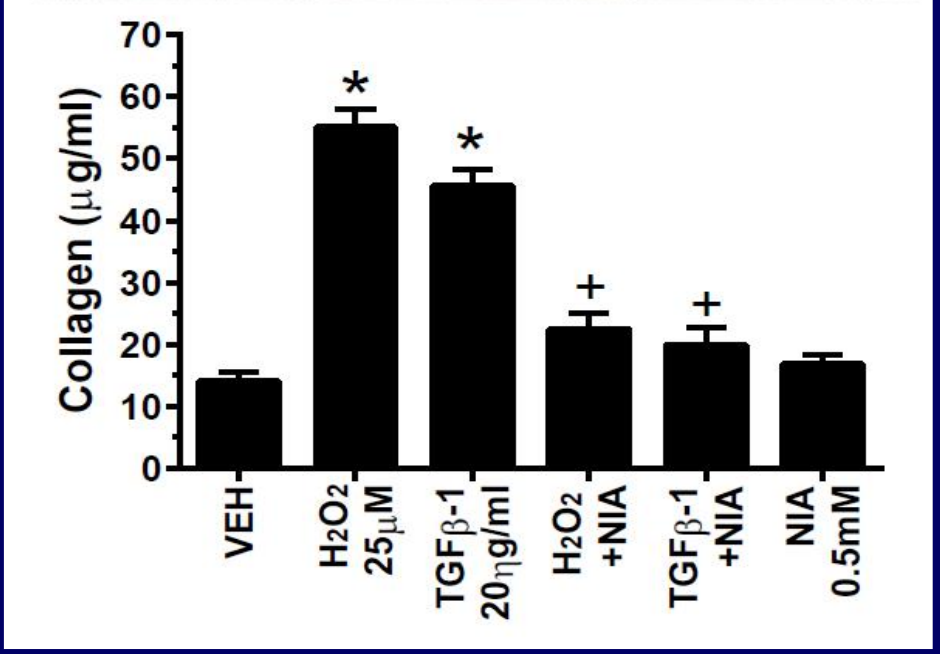
C and D: Rats treated with Niacin and Thioacetamide

Arauz J, et al. Nicotinic acid prevents experimental liver fibrosis by attenuating the prooxidant process. Internat. Immunopharmacol. 2015; 28:244-251.

Niacin Inhibits Fibrosis in Human Stellate Cells

Reviewed: ***Kashyap ML et al.*** *J. Clin. Lipidology (2019) 13, 873–879*





VEH = Vehicle control

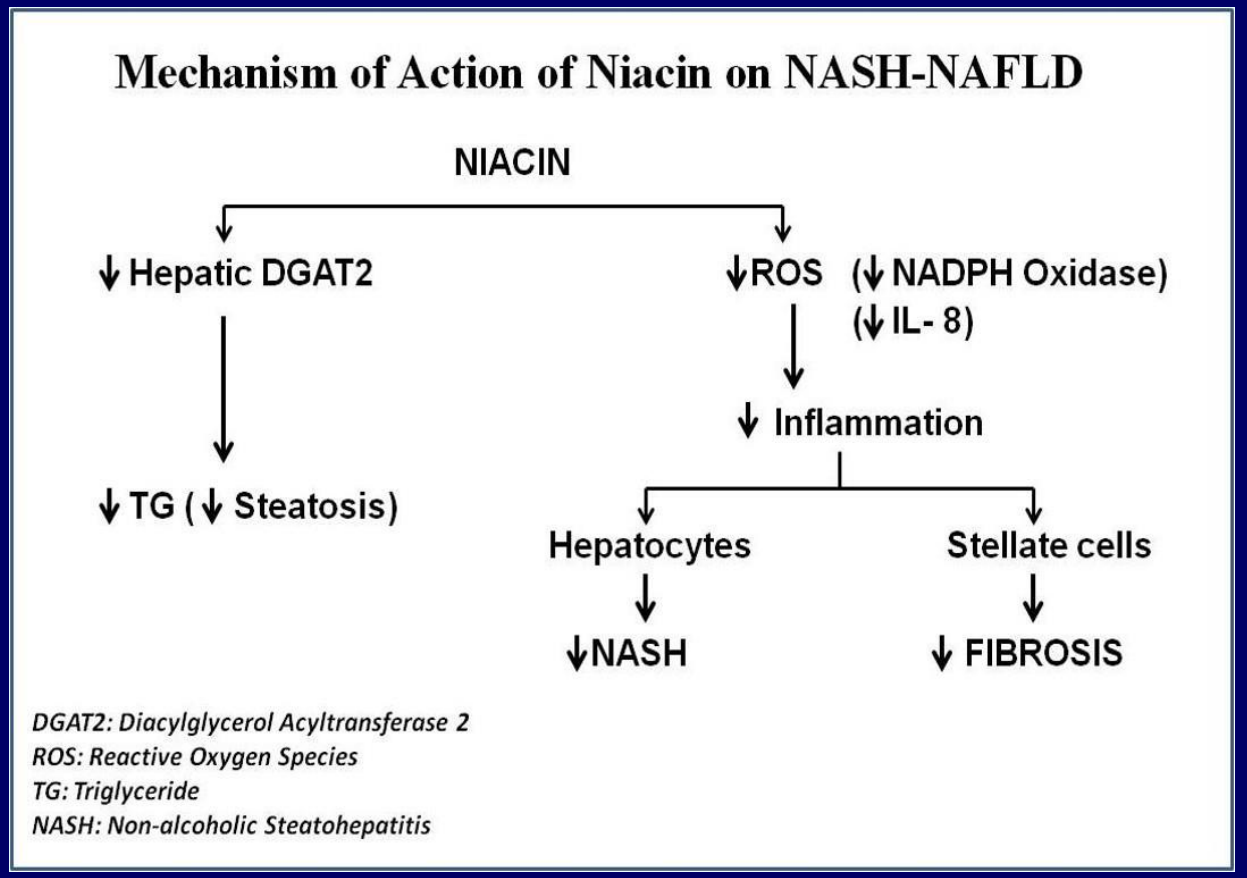
NIA = Niacin (0.5 mM)

* = $p < 0.05$ compared to control

+ = $p < 0.05$ compared to TGF - β or H_2O_2 treatments.

Unique Mechanisms of Action of Niacin on NASH-NAFLD: overview of current evidence

Kashyap ML et al. Niacin for Treatment of Nonalcoholic Fatty Liver Disease Journal of Clinical Lipidology (2019) 13, 873–879



Clinical Trial Evidence:
Niacin decreases fatty liver and improves liver enzymes

Hu M., et al. J Lipid Res. 53:802-809, 2012

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:

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

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