Steatohepatitis

AASLD 2008 Wrap-Up

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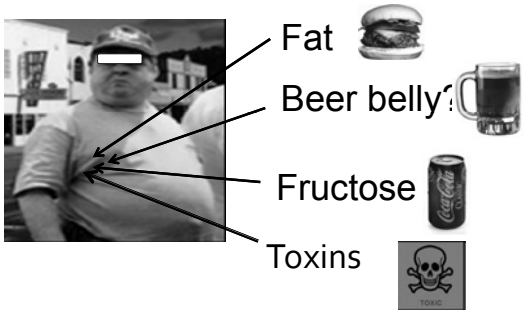
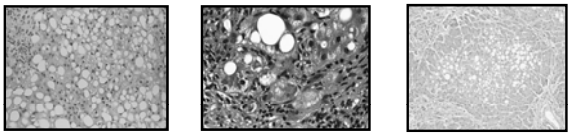
Overview

- Steatohepatitis overview.
- New information from the AASLD.

One Destination: Many Roads



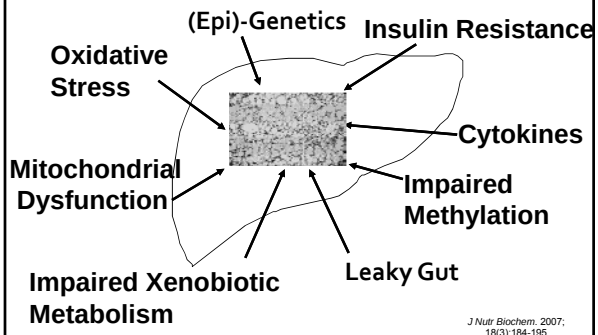
Pathologic Definitions



Steatosis | Steatohepatitis | Cirrhosis

Although the development of steatosis may be the expected result of over-nutrition or alcohol abuse, the development of steatohepatitis, cirrhosis, and hepatocellular cancer can not be considered normal.

Pathogenesis: 2 Hits

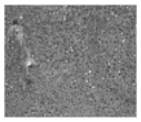


J Nutr Biochem. 2007; 18(3):184-195

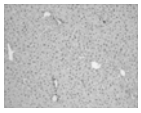
Impaired Xenobiotic Metabolism

Glutathione S-Transferase Expression	Fold Down-regulation
GST Mu 1	1.77
GST Theta 3	2.01
GST Mu 3	3.73
GST Alpha 2	8.01
GST Alpha 4	3.44

Acrolein Adducts – High Fat



Acrolein Adducts – Control Diet



Prevalence

- ALD: 2 Million in the U.S. (Ann Hepatol 2008;7:5-15)
- NAFLD: Unexplained abnl ALT (NHANES 2003).

Sex: Men	28%
Women	40%
Race: Hispanic	42%
White	34%
Black	26%
Weight: Normal	23%
Overweight	35%
Obese	>42%

Treatment

- Remove offending agent (alcohol, obesity).
- Still no FDA approved medication for any stage of ALD or NAFLD.
- Treat complications, Transplantation.
- Investigational Agents:

ALD: Pentoxifylline, Steroids, SAMe.

NAFLD: Antioxidants, Insulin Sensitizers.

Overview - Summary

- Steatohepatitis is the most common form of liver disease and has many convergent etiologies.
- Significant progress has been made in the pathogenesis of steatohepatitis.
- Despite this, there is still no FDA approved therapy.
- What's new from the AASLD?

NAFLD Prevalence

- #1133: **50% by ultrasound in a Texas primary care clinic.** N=170, 63% white, age 56, **BMI 29**. Hispanics had the highest prevalence (65%) and African Americans the lowest (42%).
- #1129: **66% by ultrasound in a group of 140 Italian psoriasis patients** (**BMI 27**). Both the prevalence of fatty liver and the metabolic syndrome rose with psoriasis severity. NAFLD occurred in all patients regardless of psoriasis treatment (MTX).

Biomarkers

- #477: **Fibrotest NAFLD**: A score of .94 had a 63% sensitivity and 90% specificity for cirrhosis (65% PPV and 87% NPV).
- #741: **Fibrotest ALD**: A severe fibrosis score (0.59-1.0) over a 10 year follow up was associated with a 23 fold increased risk of death (greater risk than fibrosis on biopsy – 1.5X).
- Methionine (#479) and octanoate (#1146) **breath tests** continue to evolve.

Biomarkers – Response to Therapy

- #1114: CK-18 (M30) is elevated in NASH vs. simple steatosis (407 vs. 171 U/L), and is reduced by therapy, correlating with histolgical improvement on liver biopsy (NAS score).
- #1122: A biochemical response to therapy defined as AST<= 33 or ALT <=37 U/L accurately identifies > 80% of biopsy proven treatment responders.

Pathogenesis: Diet

- #1150 (human): **Fructose** was associated with oxidative stress in pediatric NAFLD.
- #1112 (human): High **strearic and arachadonic acid** content on liver biopsy was associated with progression of fibrosis.
- #1186 (animal): **Trans-fats + fructose** (ALIOS) was associated with NASH with fibrosis and hepatocellular carcinoma at 1 year.

Pathogenesis - Toxins

- #441: **Chlorpyrifos** (pesticide) was associated with elevated CK-18, but patholgic confirmation was lacking (human data).
- #1118: **Vinyl Chloride** (human data).
- #1184/1358: **Particulate matter** (2.5 micron) when inhaled was associated with progression to NASH in mice fed a high fat diet. When injected IV into mice or in a cell culture model, it was associated with macrophage activation via TLR4 (animal data).

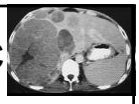
Pathogenesis – clinically relevant

- #1162 (cell culture): **CRP** enhances lipoapoptosis by PTEN mediated AKT down-regulation.
- #1124 (human): **OSA.** NASH (vs. simple steatosis) was associated with lower SaO2 and longer durations of SaO2<90%. CPAP decreased ALT.
- Hy Zimmerman Lecture (Ron Evans, PhD) & # 13: Stellate cells store **vitamin D**, and vitamin D suppressed HSC proliferation and collagen expression but increased MMP expression.

Pathogenesis – Basic Mechanisms

- #138 (mice): **MiRNA** XBP1 ↑UPR/NASH.
- #198 (cell culture): ETOH/acetate ↑histone acetylation/cytokines **(epigenetics)**.
- #152 (mice): TLR4 dependent IRF3 signalling is critical in ALD **(interferon signalling)**
- #1605/1190 (mice): KC **LMW-Fe primes** in ASH and generates ROS to alter lipids in NASH.
- #1123 (human): Racial Δ in **GSTs** in NAFLD.
- #1169/1170 (mice): **Hedgehog pathway** is active in diet-induced NAFLD.

Pathogenesis - HCC



- #1134/#1479: HCC recurrence is high (88%) in NASH patients following curative treatment and visceral fat is a risk factor for recurrence.
- #1451: There is a 2x increased risk of metabolic syndrome in patients undergoing LT for HCC vs. cirrhosis without HCC.
- #1454/#1481/#1514 : In HCV cirrhosis, leptin is associated with HCC, and insulin is a risk factor for recurrence. Adiponectin

Treatment – Lifestyle modification

- #1111: 48 wk RCT of diet & exercise in 31 subjects with NASH. Weight loss (9% vs .2%) was associated with histological improvement (NAS 4.3 to 2.0).
- #1132: 48 week RCT of diet & exercise in 103 diabetic subjects was associated with weight loss (8.2% vs. -.1%) and reduction of hepatic fat by MRI (-3% vs. -1.4%).
- #1119: Exercise training (aerobics, weights) for 45 min, 3x weekly was associated with a 2.5% reduction of hepatic fat independent of BMI Δ.

Treatment - Insulin Sensitizers

- #1113: 3 year RCT of **rosiglitazone**. Although Rosi was associated with improvement in steatosis at year 1, there was no incremental improvement with additional length of therapy, and no improvement in fibrosis.
- #LB6/#167/#168: Neither **metformin / pioglitazone** improved SVR in HCV with obesity or insulin resistance despite improvements in steatosis and phase 1

Treatment – Antioxidants

- #489: Open-label, uncontrolled, 5 year trial of vitamin C&E (600 mg each) in 54 Japanese patients was associated with improved steatosis and inflammation with unchanged fibrosis.
- #488: Open-label, uncontrolled, 1 year trial of probucol (500 mg daily) in 26 Japanese patients was associated with improved steatohepatitis (4.3 vs. 3.3), fibrosis, and HOMA score (3.7 vs. 2.1).

Treatment (pre-clinical): ACE / ARB

- #736: Angiotensin II type 1 receptor polymorphisms are more common in Japanese subjects with NASH.
- #1180: In a rat model, valsartan attenuated steatosis and protected mitochondrial function.
- #1194: In a mouse model, telmisartan improved adiponectin, steatosis, and fibrosis.
- #1354: PAI-1 KO mice are protected

Treatment (pre-clinical): PDE

- #1384 (cell culture): Methylxanthines inhibited TGFB stimulated connective tissue growth factor expression.
- #1395 (rat): Pentoxifylline reduced extablished fibrosis after bile duct ligation.
- #1397 (rats): Rolipram (PDE4 inhibitor) pre-treatment reduced injury and fibrosis in bile duct ligation.

Treatment (pre-clinical): SAMe

- #1423 (rats): SAMe reduced fibrosis in BDL.
- #LB5 (human): 5/7 HCV non-responders had had < 2 log drop at week 12 when treated with SAMe and 3/7 were undetectable.
- #1144 (human): Betaine was ineffective for NASH with advanced fibrosis and normal serum homocysteine levels.

Summary - AASLD

- Fructose, saturated fats, trans-fats and environmental toxins are emerging mediators.
- Lifestyle modification remains the cornerstone of therapy and antioxidants are re-emerging.
- The value of insulin sensitizers (metformin/TZDs) in inflammation / fibrosis is questionable.
- ACEi/ARB and phosphodiesterase inhibitors are emerging therapeutic targets.
- The development of cannabinoid antagonists has been halted due to side effects.

Conclusion