

Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
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**Nonalcoholic Fatty Liver Disease
(NAFLD) Turns 38-What Have We
Learned?**

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This is to acknowledge that Jay D. Horton, M.D. has disclosed financial interests or relationships with commercial concerns directly or indirectly related to this program. Dr. Horton will be discussing off-label uses in his presentation.

Presenter: Jay D. Horton, M.D.

Rank: Professor

Division: Digestive and Liver Diseases

Purpose & Overview:

To discuss and explain the underlying mechanisms responsible for the development of nonalcoholic fatty liver disease as well as the mechanism of action for new drugs under development for the treatment of nonalcoholic fatty liver disease.

Objectives:

1. Understand the underlying changes in fatty acid metabolism that result in fat accumulation in liver.
2. Understand the genetic contributions to NAFLD.
3. Understand the risk factors associated with the development of NAFLD.

Biosketch:

Dr. Jay D. Horton is the Director of the Center for Human Nutrition and Professor of Internal Medicine and Molecular Genetics. He obtained his B.S. and M.D. degrees from the University of Iowa and completed his Internal Medicine residency, gastroenterology fellowship, and Howard Hughes post-doctoral fellowship at UT Southwestern. Dr. Horton's research interests are in determining how regulators of fat metabolism contribute to the development of fatty liver and delineating the function of PCSK9, a protein secreted into the blood that regulates LDL receptors in liver.

Facts Regarding NAFLD

- Approximately **83 million** people in the U.S. have NAFLD-projected to increase to **101 million** by 2030 (1).
- Global prevalence of NAFLD is ~25% (2).
- Insulin resistance is the key underlying metabolic abnormality present in the majority of individuals who develop of NAFLD and NAFLD could be considered a component of the metabolic syndrome (3, 4).
- Patients with NAFLD are twice as likely to die of cardiovascular disease than from liver disease (5).
- The clinical disease progression of NAFLD is highly variable but those with NASH progress to fibrosis ~ 2X faster than those with only steatosis on initial biopsy (1).
- NAFLD can lead to the development of hepatocellular carcinoma (HCC) even in the absence of cirrhosis and NAFLD-associated HCC represents 18% of those listed for transplant (1, 6).
- Current treatment options for NASH per 2018 AASLD Practice Guidelines (7):

1) **Weight loss**

At least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH. Foregut bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH. It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.

2) **Vitamin E**

Daily dose of 800 IU/day improves liver histology in *nondiabetic* adults with *biopsy-proven* NASH and therefore may be considered for this patient population. Vitamin E is **not** recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

3) **Pioglitazone**

Dose of 30 mg/day improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy. Should **not** be used to treat NAFLD without biopsy-proven NASH.

References

1. Friedman SL, Neuschwander-Tetri BA, Rinella M, and Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. 2018;24(7):908-22. doi: 10.1038/s41591-018-0104-9. Epub 2018 Jul 2.
2. Younossi Z, Tacke F, Arrese M, Sharma BC, Mostafa I, Bugianesi E, et al. Global Perspectives on Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis. *Hepatology*. 2018;4(10):30251.
3. Browning JD, and Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest*. 2004;114(2):147-52.
4. Cohen JC, Horton JD, and Hobbs HH. Human fatty liver disease: old questions and new insights. *Science*. 2011;332(6037):1519-23.
5. Lindenmeyer CC, and McCullough AJ. The Natural History of Nonalcoholic Fatty Liver Disease-An Evolving View. *Clin Liver Dis*. 2018;22(1):11-21.
6. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates. *Clin Gastroenterol Hepatol*. 2018;Jun 14. pii: S1542-3565(18)30611-6. doi: 10.1016/j.cgh.2018.05.057. [Epub ahead of print].
7. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1):328-57.

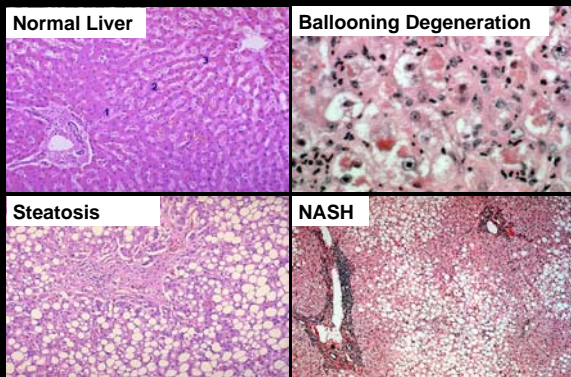
Case Presentation

- 49 y/o Hispanic female with Type 2 DM and HTN presents for evaluation of abnormal LFTs found in health screen
- PE significant for BMI of 42
- Labs: ALT 80, AST 40, Plts 300, INR 0.5
- Hep. serologies neg, ANA, AMA, AMSA, Ferritin, α -1 antitrypsin all NL
- Abdominal Sono: Increased echogenicity

Definitions

- **Nonalcoholic Fatty Liver Disease (NAFLD)**
 - Clinicopathologic syndrome that ranges from fatty liver alone to fatty liver plus inflammation/fibrosis
- **Hepatic Steatosis**
 - Excessive lipid accumulation in hepatocytes
- **Nonalcoholic Steatohepatitis (NASH)**
 - Severe form of NAFLD
 - Includes hepatic steatosis plus hepatitis

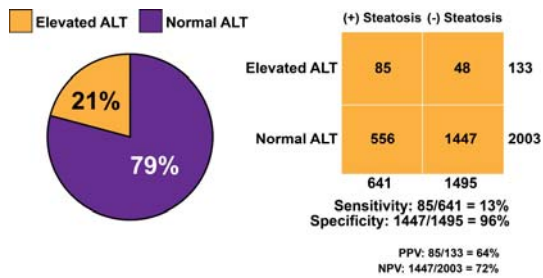
Liver Histology of NAFLD



Diagnosis of NAFLD

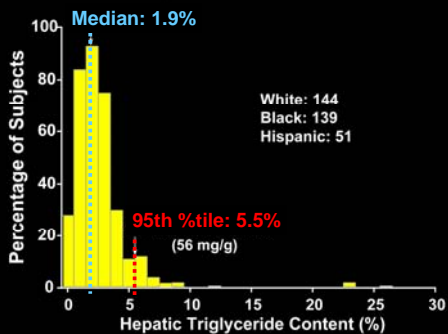
- Exclude other causes:
 - serologic tests for viral hepatitis
 - iron studies
 - ceruloplasmin
 - α -1 antitrypsin
 - anti-mitochondrial & antinuclear Ab
- Mild-moderate (2-5 X) increase in ALT/AST
- Radiologic studies very suggestive
 - Ultrasound, Unenhanced CT, MRI, MRS
- Liver biopsy

Abnormal ALT in Hepatic Steatosis



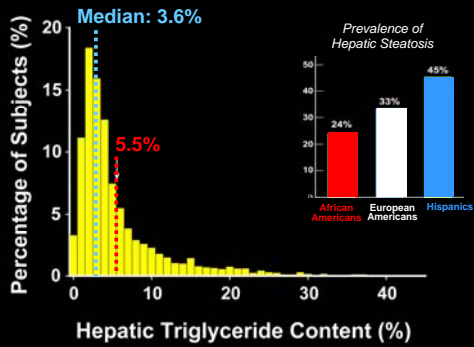
Browning et al. Hepatology 2004; 40:1387.

Hepatic Triglyceride Content (HTGC) in Subjects with No Risk Factors



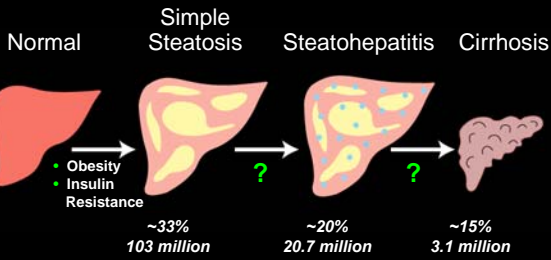
Szczepaniak et al. 2005. Am. J. Physiol. Endocrinol. Metab. 288:462-468.

Distribution of Hepatic Fat in DHS

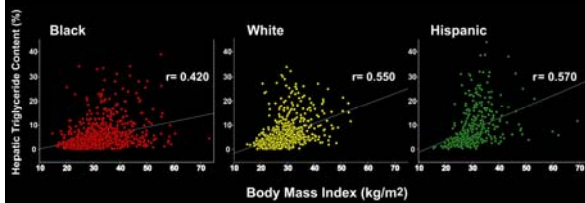


Browning et al. 2004. *Hepatology*. 40:1387-1395.

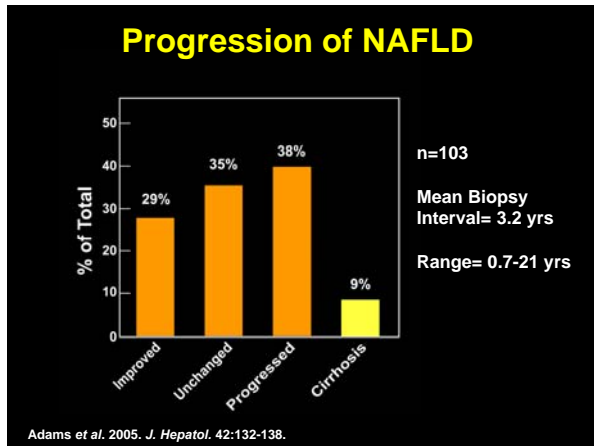
Estimated Prevalence of NAFLD in the U.S.

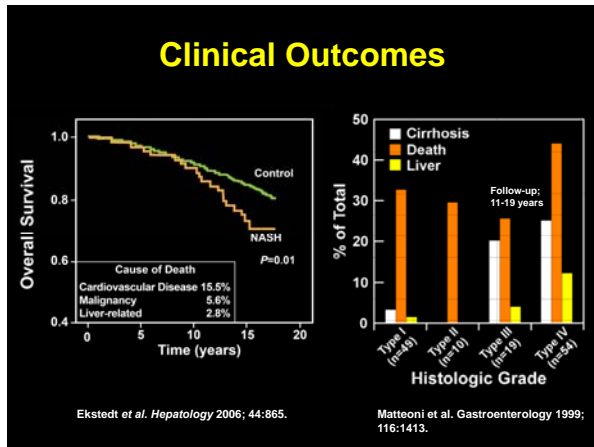


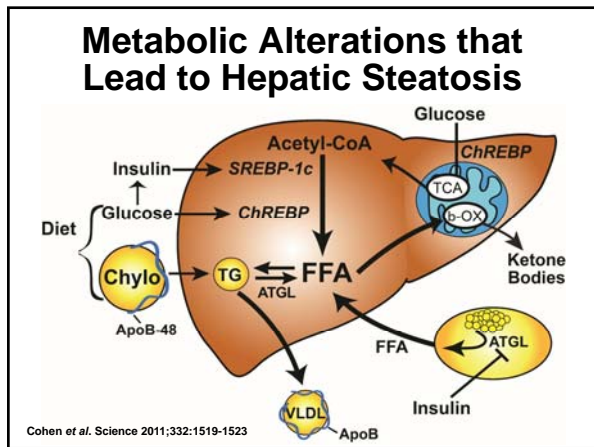
BMI and Insulin Resistance is Correlated with Hepatic Steatosis in the DHS



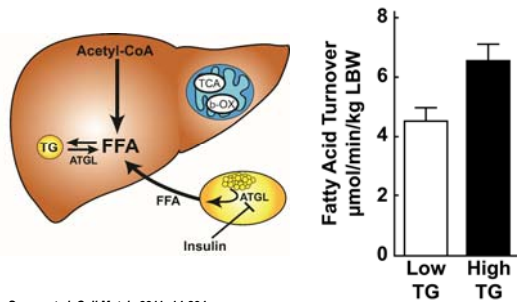
Browning et al. 2004. *Hepatology*. 40:1387-1395.





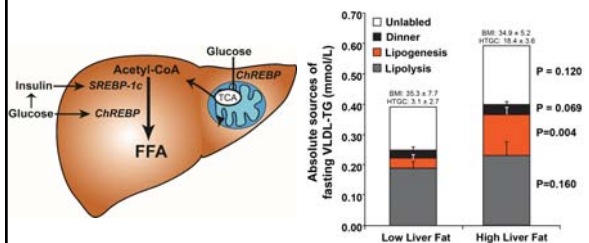


Adipose Fatty Acid Release: Increased FFA from Adipose (~60%)



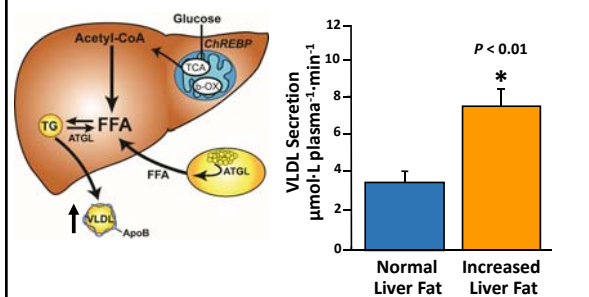
Sunny et al. *Cell Metab.* 2011; 14:804.

Fatty Acid Synthesis: Increased in NAFLD (~25%)



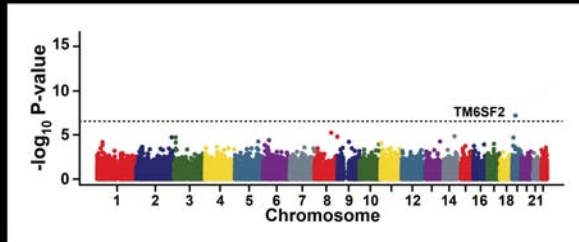
Lambert et al. *Gastroenterology* 2014; 146:726.

VLDL-TG Secretion: Increased in Most NAFLD Subjects



Fabbrini et al. *Gastroenterology* 2008; 134:424.

Exomewide Scan for SNPs Associated with Liver Fat in DHS

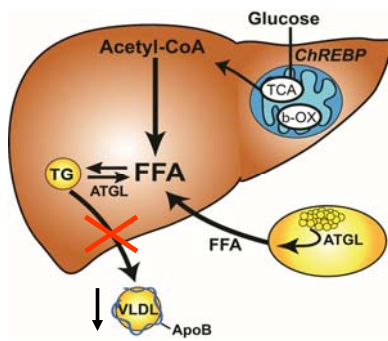


Kozlitina et al. 2014. Nat. Genet. 46:352-356.

TM6SF2 Variant Associated with NAFLD

- Frequency of *TM6SF2* p.Glu167Lys: 7.2% in Europeans, 3.4% in African Americans, and 4.7% in Hispanics
- Carriers of *TM6SF2* variant had elevated mean and median liver TGs, higher ALTs, lower plasma TGs & LDL

Metabolic Alterations that Lead to Hepatic Steatosis: Reduced Secretion (4-7%) with TM6SF2 SNP

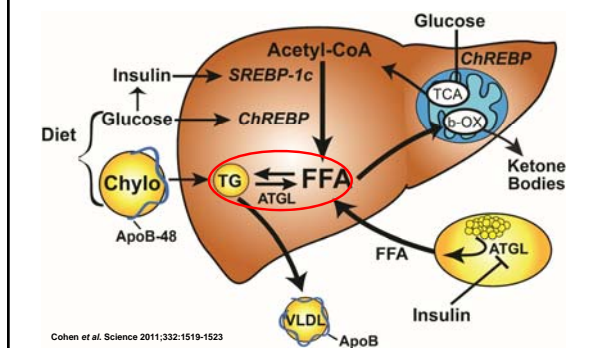


Hepatic β -oxidation: Increased in NAFLD



Sunny et al. *Cell Metab.* 2011; 14:804.

Metabolic Alterations that Lead to Hepatic Steatosis



Cohen et al. *Science* 2011; 332:1519-1523

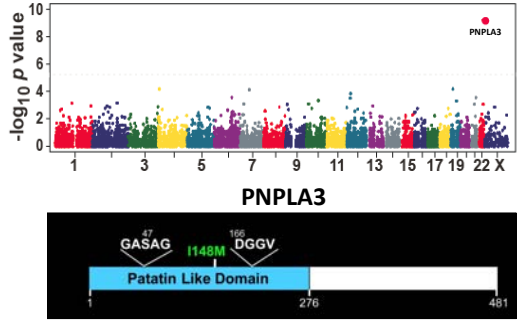
Genetic Variants Associated with NAFLD

Gene	Steatosis			NASH	OR	Cirrhosis
	DHS*	Consortium [§]	Liver Biopsy Cohort [¶]			
<i>PNPLA3</i>	+	+	+	+	3.26	+
<i>TM6SF2</i>	+	+	+	+	1.65	+
<i>MBOAT7</i>	+	+	+	+	1.30	+
<i>GCKR</i> Glucokinase regulatory protein	+	-	?	?	1.45	?
<i>HSD17β13[§]</i>			+	+		+

*Browning et al. *Hepatology* 2004, [§]Speliotes et al. *Plos Genetics*, 2011;
[¶]Rosellina et al. *Gastroenterology*, 2016; [§]Abul-Husn et al. *NEJM* 2018.

GWAS of Hepatic TG Content in DHS

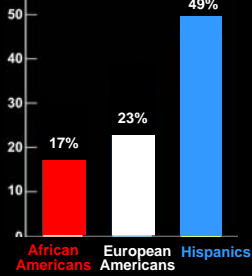
Nonsynonymous DNA Variations (n = 9,229)



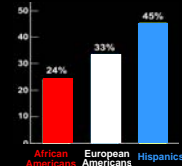
Romeo et al. 2008. Nat. Genet. (40) 1461-1465.

PNPLA3:I148M – Ethnic-specific Allele Frequencies in Dallas Heart Study

PNPLA3: I148M Allele Frequency

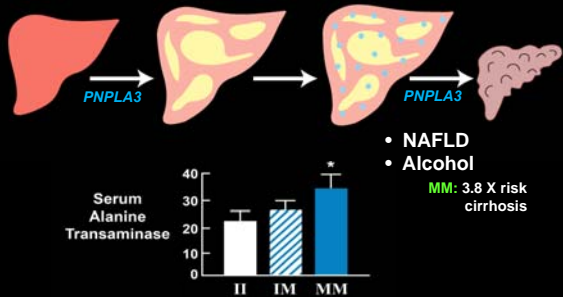


Prevalence of Hepatic Steatosis



Romeo et al. 2008. Nat. Genet. (40) 1461-1465.

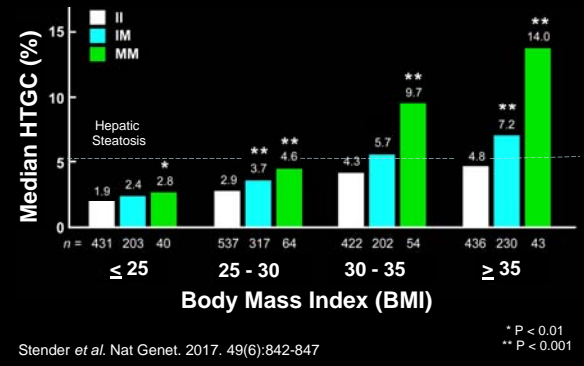
PNPLA3 I148M is Associated with Disease Progression



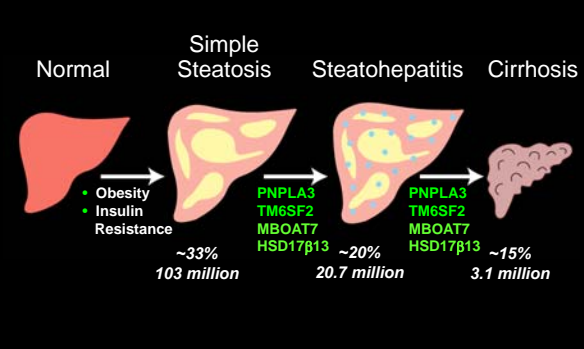
Yuan X et al. Am J Hum Genet. 2008 | LFTs
Sookoian et al. J Lipid Res 2009 Pathology

Tian C, et al. Nat Genet. 2010
Muller et al. J. Hepatol. 2011
Trepo et al. J Hepatol. 2011

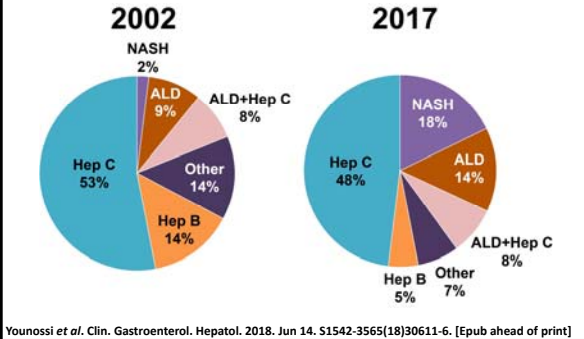
PNPLA3 Polymorphism Exacerbates Effect of Obesity on Hepatic TG Content



Estimated Prevalence of NAFLD in the U.S.



Cause of HCC for Waitlisted Transplant Candidates



Diagnosis and Management of NAFLD

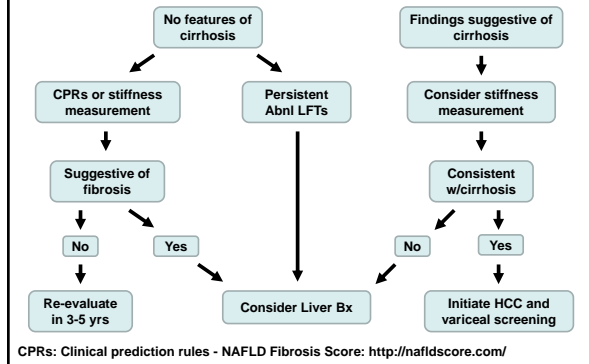
• ETOH

- Ongoing or recent ETOH of >21 drinks/wk in male and >14 drinks/wk in females considered significant (Strength 2, Quality C)

• Screening in Primary Care of High Risk Groups and Family Members

- Not recommended due to lack of treatment options and lack of evidence of long-term benefits and cost effectiveness (Strength 1, Evidence B)

Steatosis on Imaging



Therapeutic Trials for NAFLD

• Weight Loss (Strength 1, Evidence A)

- 8 RCTs (n=373)
- >3-5% weight loss improved NAS
- Improved HOMA, glucose tolerance, and plasma lipids

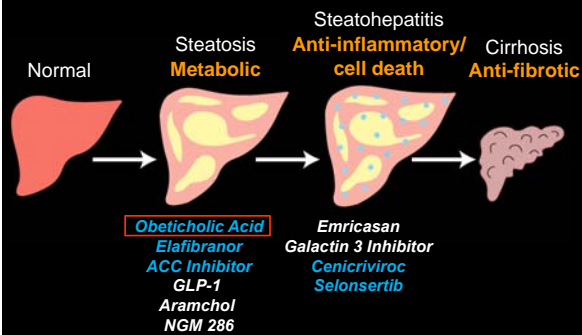
Therapeutic Trials for NAFLD

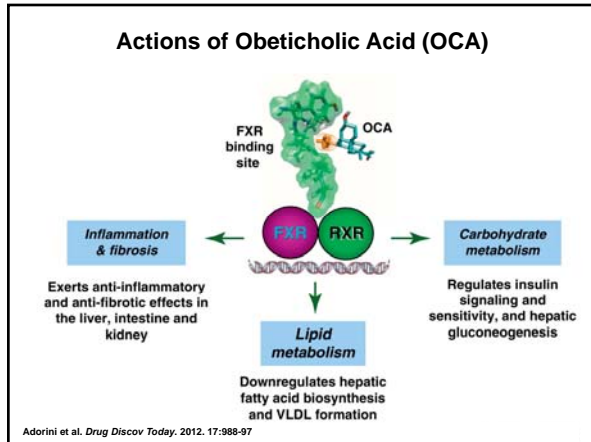
- **Vitamin E (Strength-1, Quality-B)**
 - 5 RCTs (n=685)
 - Improvement in steatosis and inflammation no progression of fibrosis
 - Should be considered first-line therapy (800 IU/d) in non-diabetics *with biopsy-proven NASH*
 - **Not** recommended in diabetics, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

Therapeutic Trials for NAFLD

- **TZDs (Strength-1, Evidence-B)**
 - 11 RCTs (n=862)
 - Improved steatosis, ballooning and inflammation but *not* fibrosis
 - Improved HOMA, A1c, HDL, TGs but weight gain
 - Pioglitazone (30 mg/d) can be used for biopsy proven NASH (most Pts nondiabetic and no long-term safety data)
- **Metformin (Strength-1, Evidence-A)**
 - 11 RCTs (n=671)
 - No improvement in histology

Drugs in Clinical Trials for NAFLD with Published Data

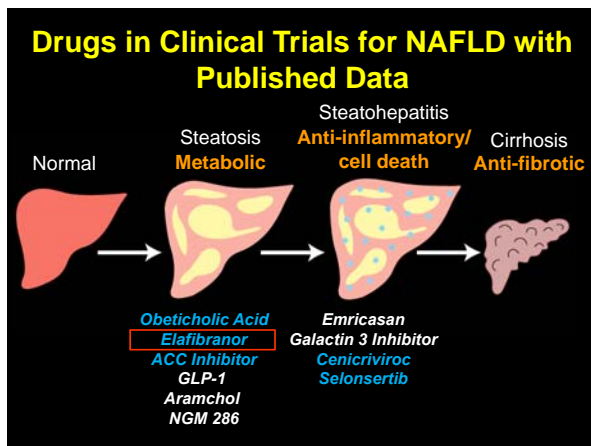




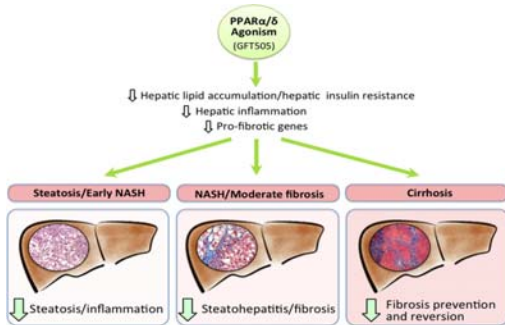
Therapeutic Trials for NAFLD

- **Obeticholic Acid**
 - RCT Phase II (n=283) “FLINT “
 - Improved steatosis, inflammation, and cellular injury, and fibrosis after 72 weeks
 - Pruritis (23%), weight loss, increased LDL major AEs

Neuschwander-Tetri et al. 2015. *Lancet*. 385:956-65.



Potential Therapeutic of Actions of Peroxisome Proliferator-activated Receptor α/δ agonist



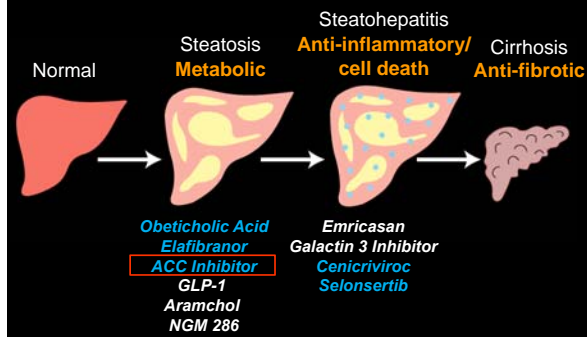
Quinter and Arrese. 2013. Hepatology. 58:1881-84.

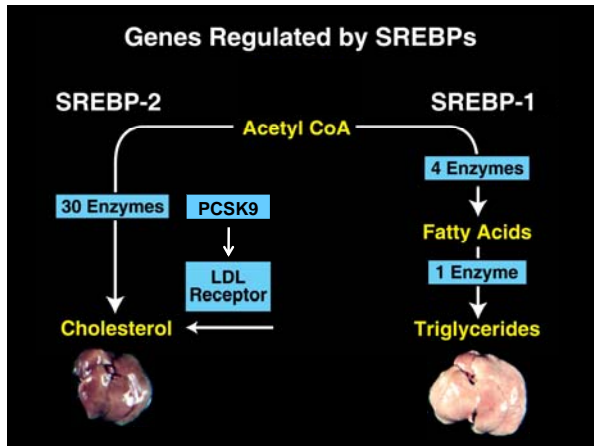
Therapeutic Trials for NAFLD

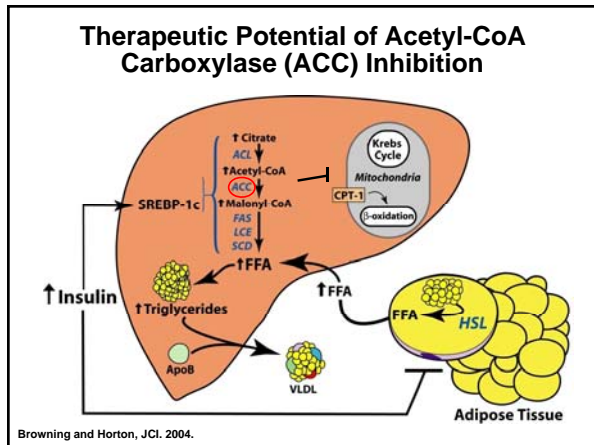
- **Elafibranor (PPAR α/δ dual agonist)**
 - RCT Phase II (n=276)
 - Improved inflammation and cellular injury only in those with NAS >4
 - No improvement in steatosis or fibrosis at 52 weeks
 - Mild increase in creatinine in 7.1%

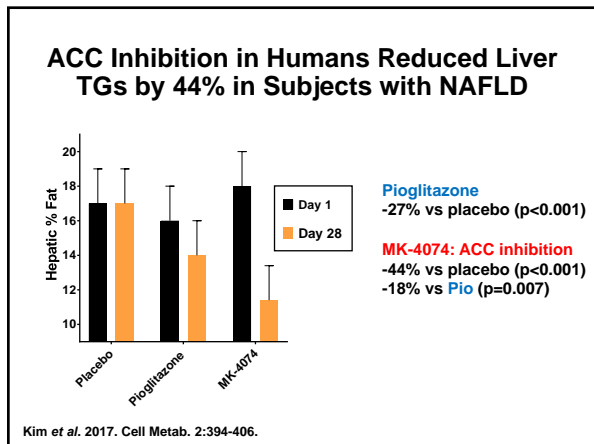
Gawrieh et al. 2018. Clin Liver Dis. 22:189-99.

Drugs in Clinical Trials for NAFLD with Published Data

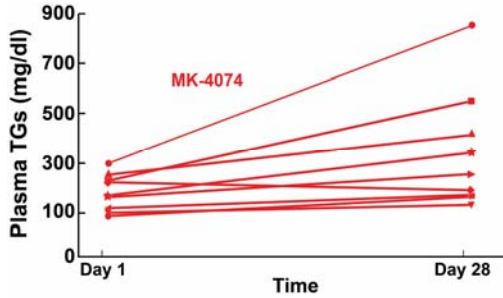






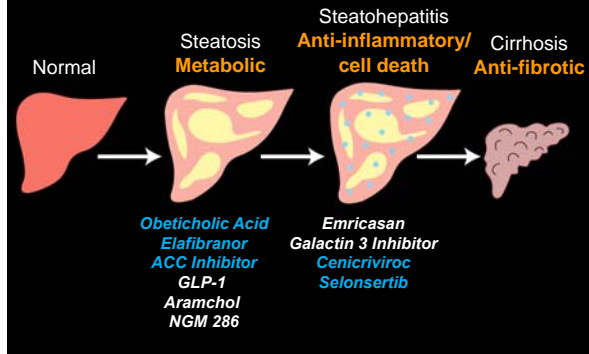


MK-4074 Increased Plasma TGs ~2-fold



Kim et al. 2017. Cell Metab. 2:394-406.

Drugs in Clinical Trials for NAFLD with Published Data



Case Presentation- ? Therapy

- 49 y/o Hispanic female presents for evaluation of abnormal LFTs found in health screen.
- Abdominal Sono: Increased echogenicity
- Dietary restriction for weight loss
- Bariatric surgery
