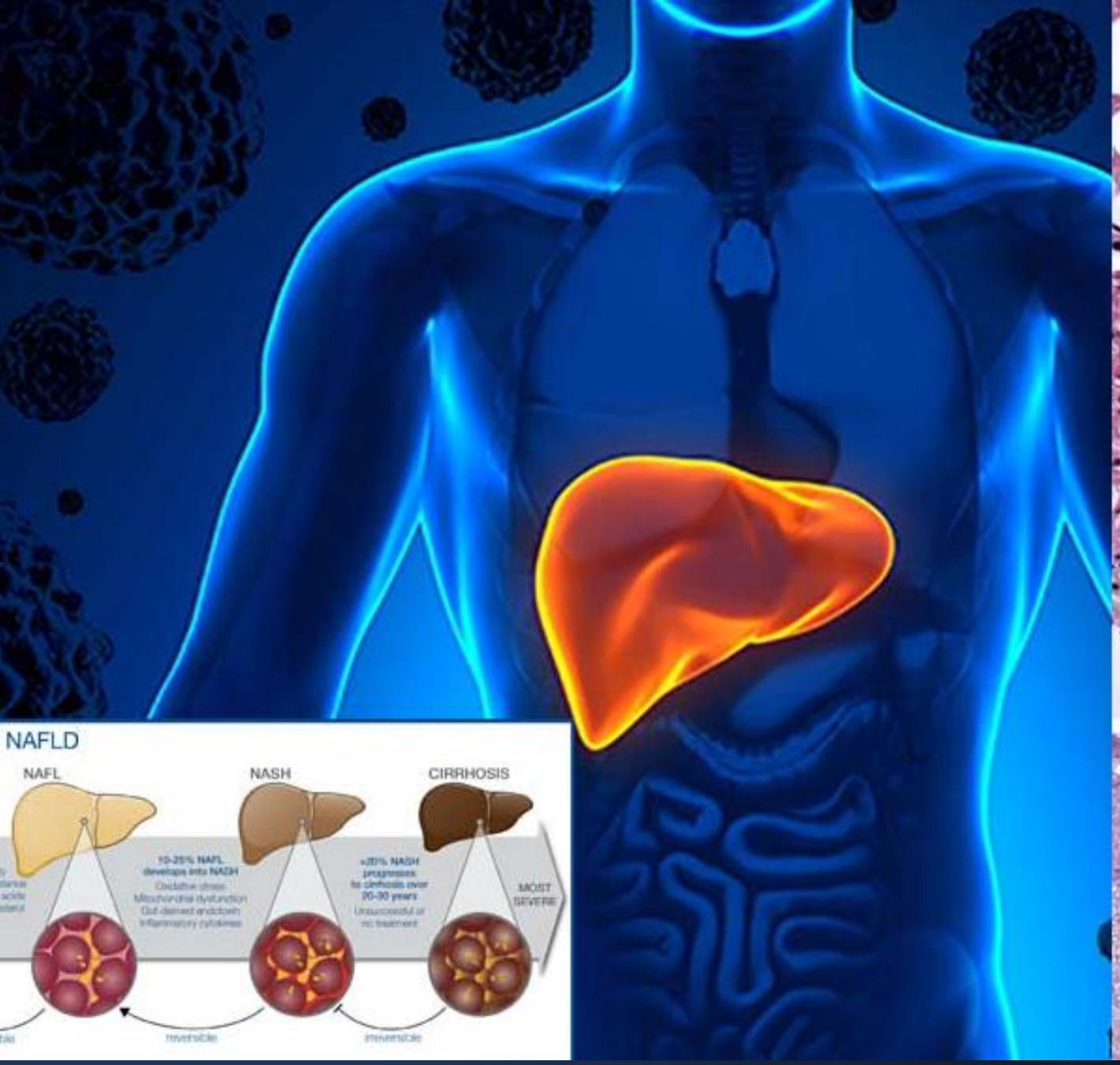
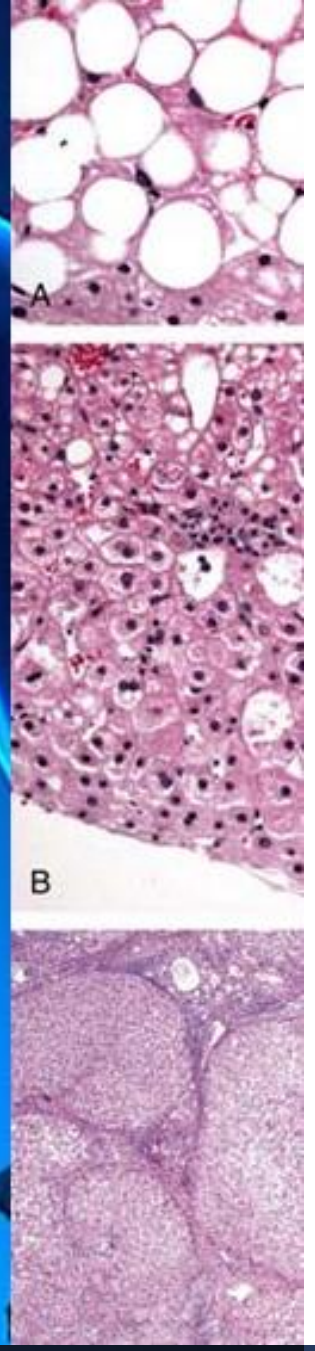



# ACOI 2021
# NASH: more than a fatty liver.
# A primer on NAFLD

Torfay Roman, MD

Advanced Hepatology and Transplant, AdventHealth Transplant Institute

Medical Director, AHMG Fatty Liver Disease Clinic at Winter Park

# DICLOSURES

- NONE

# Non-Alcoholic Fatty Liver Disease

- It is the **hepatic manifestation of metabolic syndrome** and, as obesity, diabetes and other lifestyle related diseases continue to rise, NAFLD will rise in parallel.

- NAFLD is now the most common driver of chronic liver disease in the US, being diagnosed in younger patients at rapidly increasing numbers.

# NAFLD/NASH

- NASH results in significant liver disease burden due to the development of cirrhosis and hepatocellular carcinoma (HCC) and, as such, the cost associated with the care of NAFLD is growing exponentially.

- NAFLD, which affects roughly 100 million Americans, costs **$32 billion annually to the U.S. healthcare system**, in the form of inpatient hospitalizations, ER visits, organ transplantation, mortality, medical procedures and medications (Gilroy et al, Intermountain Med Center).

- The prevalence of NAFLD is forecasted to increase to **101million in 2030 with 27million with NASH and 3.1million with cirrhosis.** The incidence of **decompensated cirrhosis will increase by 168%** to 105,430 cases by 2030, while incidence of **HCC will increase by 137%** to 12,240 cases (Estes et al, Hepatology 2018).

# NAFLD/NASH

- In 2013, NASH became the second leading disease among liver transplant waitlist registrants, after HCV.
- Definitive diagnosis relies on liver biopsy. Coupled with lack of symptoms, there is often delay in diagnosis with many patients diagnosed at advanced stage, with poor prognosis.
- NAFLD is predicted to be become the number one reason for liver transplant.
- Many patients with NASH cirrhosis may not qualify for liver transplant in the setting of significant comorbidities, including morbid obesity, significant cardiovascular disease, renal disease, decreased functional status, and others.
- As a result, many patients have progressive, irreversible chronic disease with little to no meaningful solutions.

# When to monitor fatty liver and when to refer

- NAFLD strongly associated with obesity, with prevalence increasing proportionally with increases in BMI, although can occur in those w/o overt metabolic risk factors, esp in Asian populations. *(Albhaisi et al, Ann Med 43, 617-649, 2011).*

- In majority of cases, NAFLD emerges in context of metabolic syndrome, with IR being the common mechanism.

- NAFLD shares bidirectional relationship with metabolic syndrome, IR, and DL.

# When to monitor fatty liver and when to refer

- Joint guidance by EASL, EASD, EASO recommends screening for NAFLD in pts with obesity, metabolic syndrome, in particular DMII. *(EASL-EASD-EASO Clin Pract Guidelines, J Hepatol, 64, 1388-1402, 2016)*
- ADA recommends screening for NASH and fibrosis in pts with elevated LFTS or hepatic steatosis on US. *(Lazarus et al, J Hepatol, 72, 14-24, 2020)*
- Management strategies for NAFLD tailored to disease stage.
- Risk factor modification cornerstone for all pts.
- For advanced disease, aggressive intervention/specialty care may be required.

# Possible approach

PCP: focus on controlling metabolic syndrome, weight loss, regular assessment for advanced fibrosis.

AST:ALT ratio >/= 0.8, send for fibroscan

US with steatosis and high risk, send for fibroscan

FIB-4 1.3-3.25, send for fibroscan. **>3.25 refer to hepatology.**

**Fibroscan: F2 (kPa 7.5-8) or greater, refer to hepatology.**

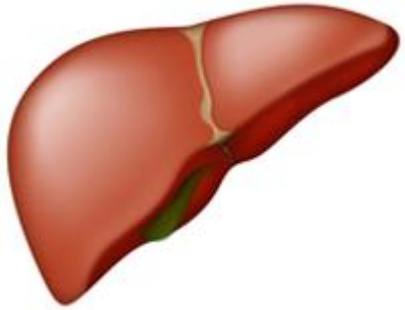
Fibroscan: F0-FI, continue surveillance in primary care. Aggressive risk factor optimization. Statins ok!

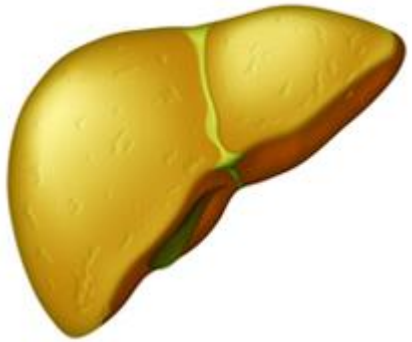
Multidisciplinary management with PCP, endocrinology, cardiology, hepatology, dietician, exercise physiotherapist.

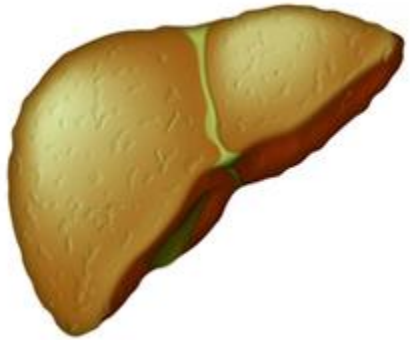
# NAFLD: therapeutics have been elusive

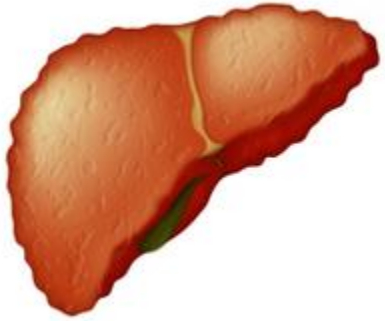
NAFLD is a complex disease with multiple pathways contributing to the pathogenesis of disease. Although patients are more clearly identified and diagnosed, the area of impactful interventions and therapeutics is sorely lacking.

NASH presents a major management challenge, and this is an area of active clinical research.

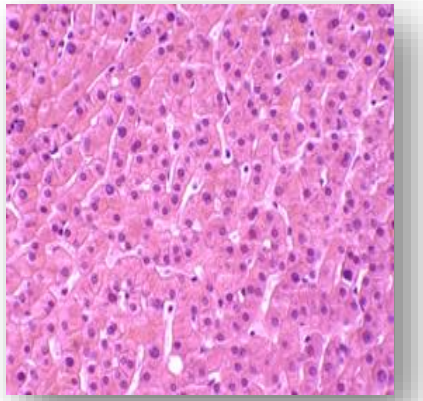




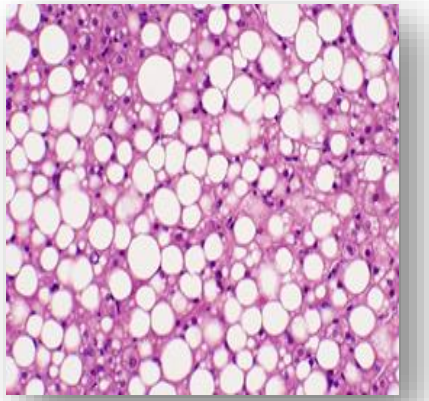




## Healthy liver

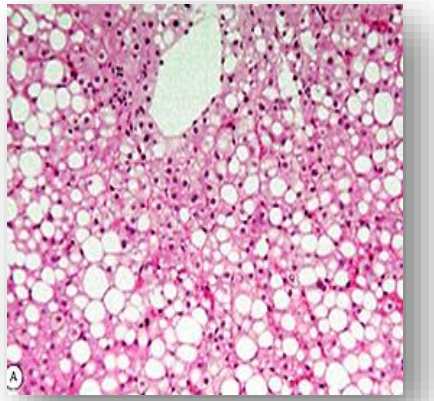


## Simple Steatosis



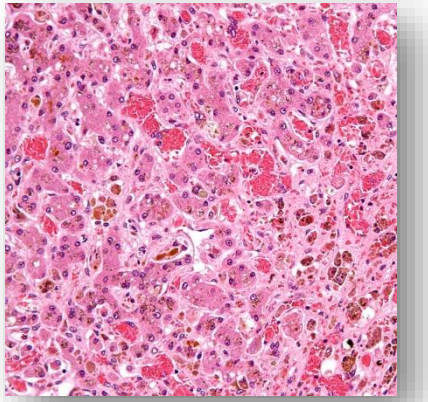
- Fat accumulation
- Oxidative stress

## NASH



- Fat accumulation
- Oxidative stress
- Apoptosis
- Inflammation
- Cytokine release
- +/- fibrosis
- Hepatocyte ballooning

## Cirrhosis



- Fibrosis
- HCC

# Who develops NASH?
# The multiple hit hypothesis

- Environmental factors:

- diet
- gut-liver axis
- comorbidities (those with IR/DMII at high risk)

- Genetic factors:

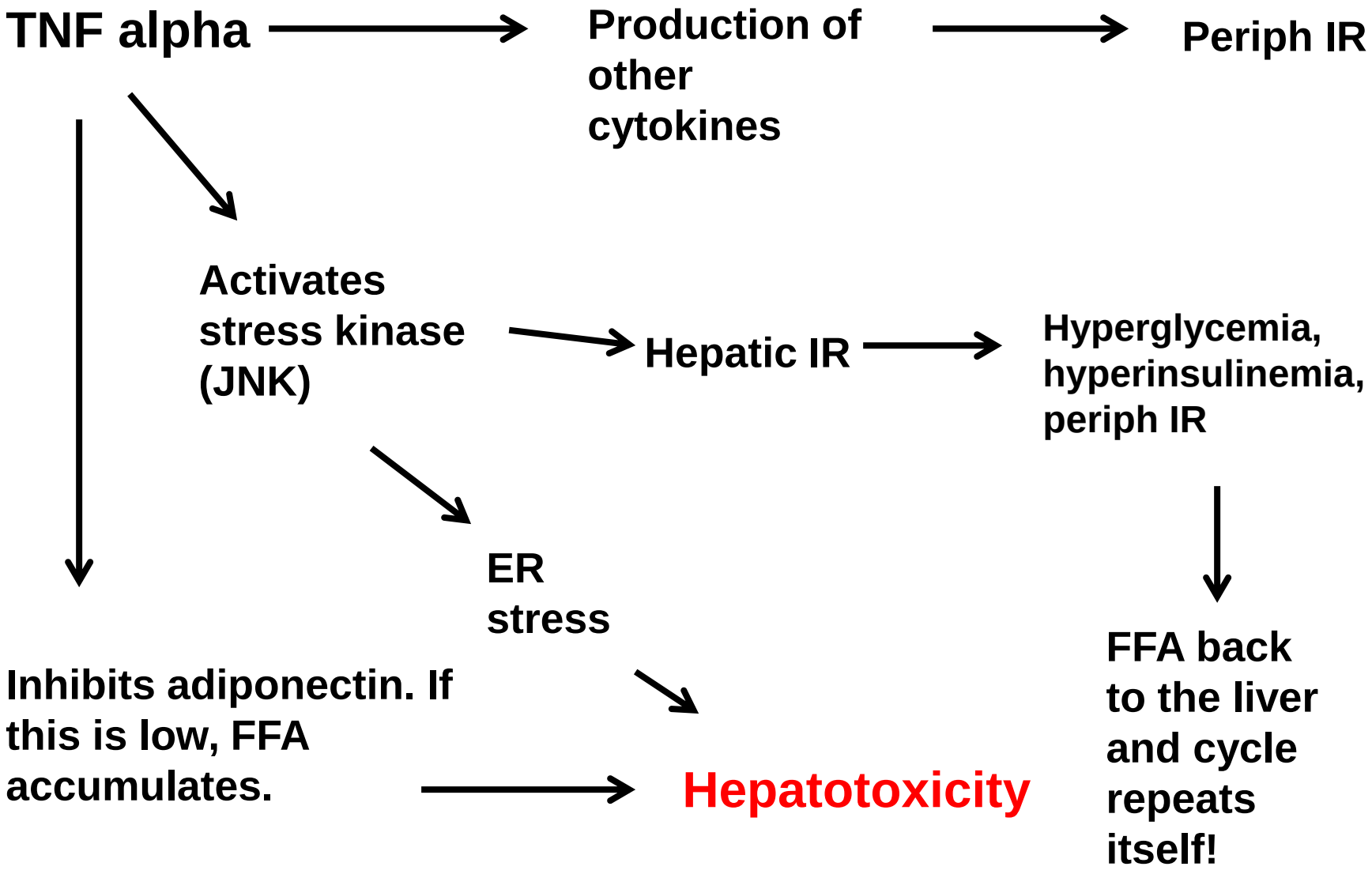
- PNPLA3
- poor repairers

# Free Fatty Acids are the true players in injury

- Injury by accumulation of invisible fats (FAs) tip NAFL to NASH and not absolute content of fat/TG *(Yamaguchi et al. Hepatology 2007*).

- FFAs cause injury: **potent signaling molecules, direct cytokines, promote cytokine synthesis** (ie. TNF alpha).

# TNF alpha induces signaling cascades that result in accumulation of FFAs and hepatotoxicity



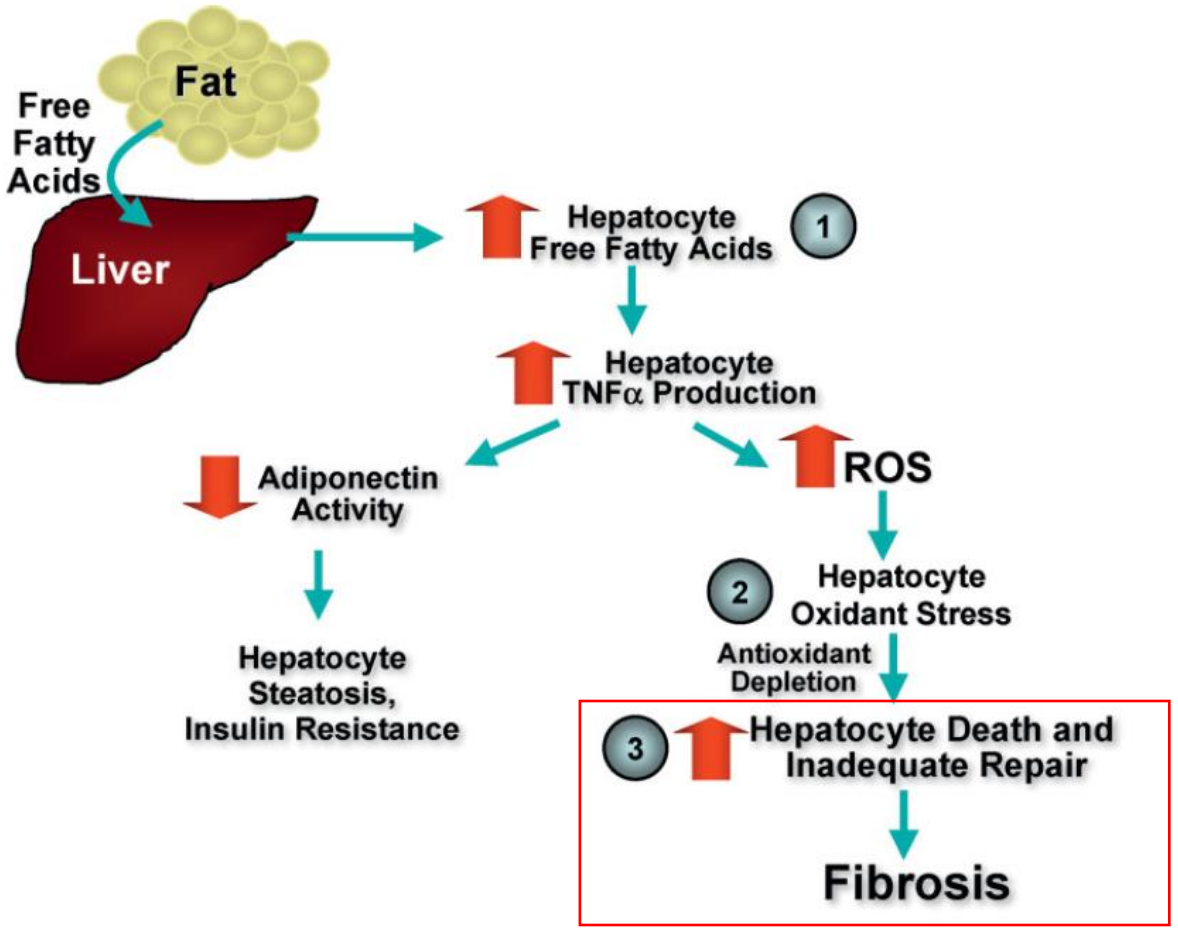

*(Adapted from Diehl, AASLD 2008)*

NAFL
30 million → NASH
10 million → Cirrhosis
3 million

NASH
(inflamm and
cell death) → Poor
repairers → ? Cirrhosis

↓

Good
repairers




- Cell death triggers repair responses to reconstitute tissue integrity.
- In healthy liver, mature hepatocytes proliferate to do this.
- In injured liver, hepatocytes can't proliferate because of oxidative stress.
- Perhaps, the inadequate ability to repair and replace dead cells leads to cirrhosis.

*Mechanisms of disease progression in NAFLD. Jou, Diehl et al. Sem in Liver Dz 2008.*

# The impact of chronic liver injury:

- Hepatic steatosis/TG accumulation is an expected outcome of obesity; cirrhosis and HCC are not.
- The risk of cirrhosis and HCC increase with liver injury.
- NASH is more likely when FA supply overwhelms TG synthesis, causing FA accumulation and the induction of alternative FA disposal.
- IR promotes NASH b/c it increases hepatic accumulation of FA.
- Improving IR reverses NASH when repair mechanisms are competent.
- Progressive liver damage ensues when injury is not repaired appropriately.

# Environmental or genetic? Both!

What are the susceptibility factors involved in NASH?

- Diet: several groups have found that increased fructose consumption correlates with NAFLD. *(Ouyang et al, J of Hepat 2008; Kohli et al Hepat 2010)*
- High fat diets: changes gut flora, increase in endotoxin release (LPS).

# Environmental or genetic? Both!

- There may be genetic factors involved as well.

1. First GWAS study done on FLD (Genetic variation in PNPLA3 confers susceptibility to NASH. Romeo et al. Nature Genetics 2008)

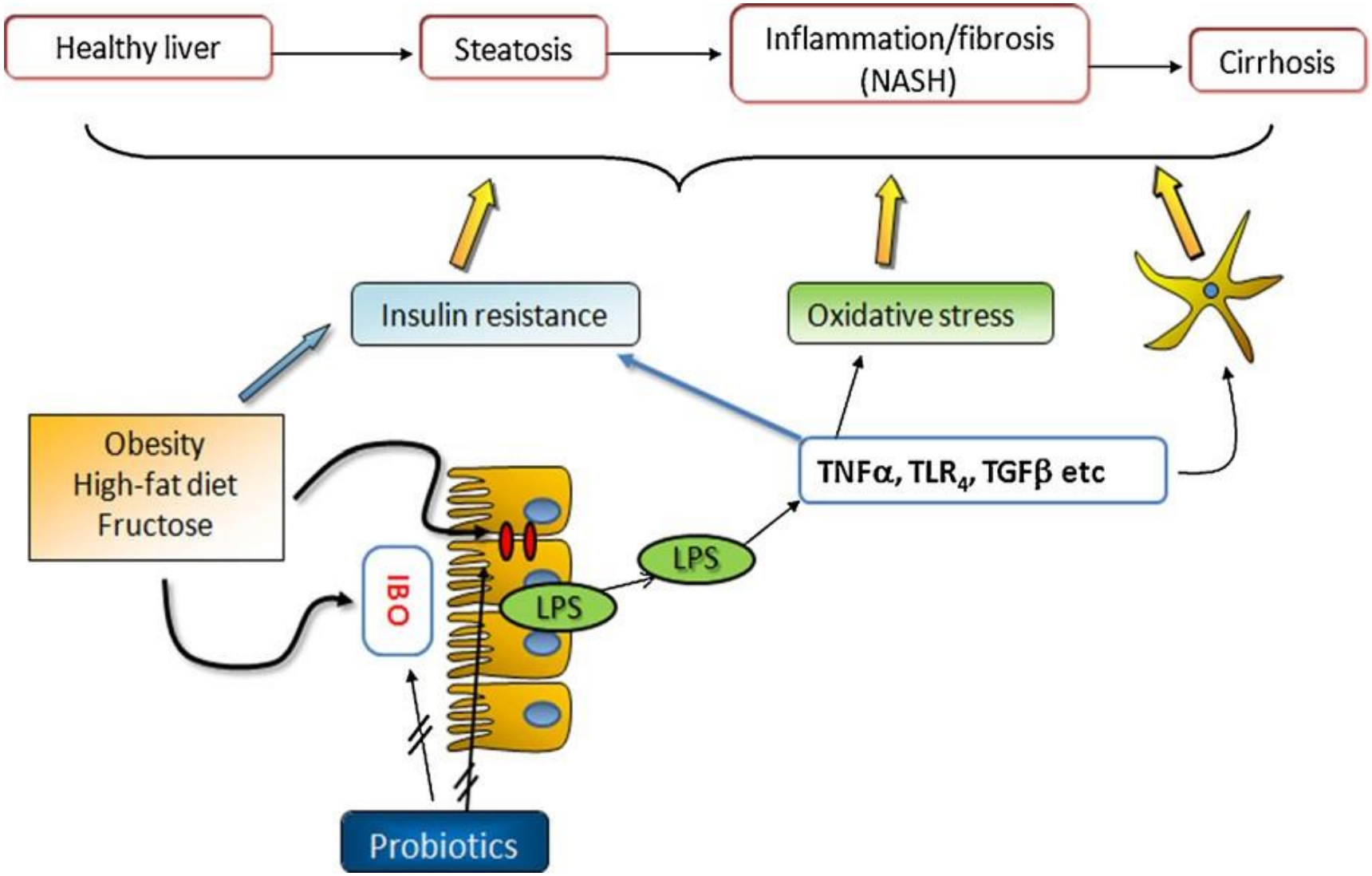
2. **PNPLA3 gene** polymorphism and NAFLD: 41 % of pts with NAFLD showed heterozygosity and 15% showed homozygosity for the **at-risk G allele**.

The **G allele was strongly associated:**
- with severity of **steatosis** (P< .0001)
- the presence of **NASH** (P< .0001)
- hepatocellular ballooning (P< .0001)
- lobular inflammation (P < .0001)
- presence of **fibrosis** P< .03), independent of cofounders.

**Pts carrying GG alleles almost always had severe steatosis and NASH; heterozygotes were at intermediate risk, and pts negative for G alleles had milder and often uncomplicated steatosis.**

(*I148M Patatin-Like Phospholipase Domain-Containing 3 (PNPLA3) Gene Variant and Severity of Pediatric NASH. Valenti et al. Hepat 2010.)*

# SB bacterial overgrowth: the liver-gut axis




*Cesaro et al. Dig and Liver Disease 2011*

# What to do?

- NAFLD: projected global prevalence 25-30% in general population. Reaches 70-90% in high risk populations, ie DMII, morbidly obese *(Fazel et al, Metabolism 2016).*

- Target obesity
- NASH specific therapeutics

# Obesity plays a central role in NASH

**Best treatment we have available at this point is weight loss**:

- Lifestyle modifications
- Medical weight loss (Qsymia, Contrave, Wegovy, Phentermine, Saxenda, Orlistat)
- Endo-bariatrics
- Bariatric surgery

- Weight loss of 4-5% of total body weight results in improved steatosis, and loss of 7-10% TBW has shown histological improvement in inflammation and fibrosis (Romero-Gomez et al, J Hepatology 2017).

- Intra-abdominal and intrahepatic fat preferentially lost with 10% TBW, leading to 52% liver TG reduction, which is well over the 30% steatosis reduction target currently used in NASH clinical trials.

- May not apply to LEAN NAFLD (7% of NAFLD pts).

Genetic predisposition or body fat distribution may be more important factors. Loss of visceral and ectopic fat may be more important than TBW but cutoffs unknown.

# Targeting those at risk of progression: Upcoming therapies in NASH

Pharmaceutical agents:

Clinical trials: accepted endpoints are resolution of NASH w/o worsening fibrosis and/or improvement of fibrosis w/o worsening NASH.

Many in the pipeline. Few available. None FDA approved (yet).

**Table 2**
Registered ongoing randomized controlled trials on pharmacological options in patients with NASH with histological and/or hard endpoint(s).

| Drug category (or categories) | Registration ID | Registration date | Title | Phase | Design | Intervention arm (dose) | Control arm (s) (dose, if active control) | Target of patients (n) | Duration (months) | Primary endpoint(s) | Primary responsible party |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GLP-1 RA | NCT02970942 | November 22, 2016 | Investigation of Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects With NASH | 2 | Multicenter, double blind, parallel group | Semaglutide (0.1 or 0.2 or 0.4) | Placebo | 320 | 18 | Resolution of NASH without worsening of fibrosis | Novo Nordisk A/S |
| SGLT2 inhibitors | NCT03723252 | October 29, 2018 | Efficacy and Safety of Dapagliflozin in NASH: a Multicentre, Randomized, Placebo-controlled Trial (DEAN) | 3 | Single center, quadruple blind, parallel group | Dapagliflozin (10 mg) | Placebo | 100 | 12 | Improvement in scored liver histological improvement | Nanfang Hospital of Southern Medical University |
| FXR agonists | JPRN-JapicCTI-121993 | October 25, 2012 | A Randomized, Double-blind, Parallel-group, Placebo-controlled, Exploratory Study of DSP-1747 in Patients with NASH | 2 | Multicenter, double blind, parallel group | OCA (NA mg) | Placebo | 200 | NA | Histological improvement | Sumitomo Dainippon Pharma |
| FXR agonists | NCT02548351 & EUCTR2015-002560-16 | September 14, 2015 | Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment (REGENERATE) | 3 | Multicenter, double blind, parallel group | OCA (10 or 25 mg) | Placebo | 2370 | 18 (for endpoint #1); 84 (for endpoint #2) | 1) Improvement in fibrosis by at least 1 stage without worsening of NASH OR resolution of NASH without worsening of fibrosis; 2) All-cause mortality and liver-related clinical outcomes | Intercept Pharmaceuticals |
| FXR agonists | NCT03439254 & EUCTR2017-000474-11 | April 16, 2018 | Study Evaluating the Efficacy and Safety of OCA in Subjects With Compensated Cirrhosis Due to NASH (REVERSE) | 3 | Multicenter, double blind, parallel group | OCA (10 or 25 mg) | Placebo | 900 | 12 | Improvement in fibrosis by at least 1 stage without worsening of NASH | Intercept Pharmaceuticals |
| FXR agonists; ACC inhibitor; ASK1 inhibitors | NCT03449446 | February 28, 2018 | Safety and Efficacy of Selonsertib, Firsocostat, Cilofexor, and Combinations in Participants With Bridging Fibrosis or Compensated Cirrhosis Due to NASH (ATLAS) | 2 | Multicenter, double blind, parallel group | Cilofexor (30 mg) | Firsocostat (20 mg) vs. Selonsertib (18 mg) vs. Placebo vs. their combinations | 395 | 12 | Improvement in fibrosis by at least 1 stage without worsening of NASH | Gilead Sciences |
| FXR agonists; CCR2/5 antagonists | CTRI/2019/01/017014 | January 9, 2019 | A Randomized, Double-blind, Multicenter Study to Assess the Safety, Tolerability, and Efficacy of a Combination Treatment of Tropifexor (LJN452) and Cenicriviroc (CVC) in Adult Patients With NASH and Liver Fibrosis | 2 | Multicenter, double blind, parallel group | Tropifexor (140 μg) | Cenicriviroc (150 mg) vs. their combination | 200 | 12 | Improvement in fibrosis by at least 1 stage without worsening of NASH | Novartis Pharmaceuticals |
| FXR agonists; SGLT2 inhibitors | NCT04065841 | August 22, 2019 | A Randomized, Double-blind, Parallel-group, Multicenter Study to Assess Efficacy, Safety, and Tolerability of Oral Tropifexor (LJN452) & Licogliflozin (LIK066) Combination Therapy, Compared to Each Monotherapy, for Treatment of Adult Patients With NASH and Liver Fibrosis (ELIVATE) | 2 | Multicenter, double blind, parallel group | Tropifexor (NA mg) | Licogliflozin (NA mg) vs. their combination | 210 | 12 | Resolution of NASH without worsening of fibrosis | Novartis Pharmaceuticals |
| PPAR-α/δ agonists | NCT02704403 & EUCTR2015-005385-38 | March 10, 2016 | Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With NASH (RESOLVE-IT) | 3 | Multicenter, double blind, parallel group | Elafibranor (120 mg) | Placebo | 2000 | 18 (for endpoint #1); 48 (for endpoint #2) | 1) Resolution of NASH without worsening of fibrosis; 2) Composite outcome of all-cause mortality, cirrhosis and liver-related clinical events | Genfit |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PPAR-α/γ agonists | NCT03863574 | March 5, 2019 | Saroglitazar Magnesium in the Treatment of NASH (EVIDENCE IV) | 2 | Multicenter, double blind, parallel group | Saroglitazar (2 or 4 mg) | Placebo | 15 | 6 | Improvement in NAS without worsening of fibrosis | Zydus Discovery DMCC |
| PPAR-α/γ/δ agonists | NCT03008070 | January 2, 2017 | A Randomized, Double-blind, Placebo-controlled, Multicenter, Dose-range, Proof-of-concept, 24-week Treatment Study of IVA337 in Adult Subjects With NASH (NATIVE) | 2 | Multicenter, double blind, parallel group | Lanifibranor (800 or 1200 mg) | Placebo | 247 | 6 | Improvement in SAF score by at least 2 points without worsening of fibrosis | Inventiva Pharma |
| PPAR-γ sparing modulators | NCT03970031 | May 31, 2019 | A Study of MSDC-0602 K to Assess Glycemic Control, Resolution of NASH, and Outcomes in Patients With Diabetes and NASH (MMONARCh) | 3 | Multicenter, double blind, parallel group | MSDC-0602 K (NA mg) | Placebo | 3600 | 12 | Resolution of NASH without worsening of fibrosis | Cirius Therapeutics |
| CCR2/5 antagonists | NCT03028740 | January 23, 2017 | A Phase 3 Study to Evaluate the Efficacy and Safety of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects With NASH (AURORA) | 3 | Multicenter, double blind, parallel group | Cenicriviroc (150 mg) | Placebo | 2000 | 12 (for endpoint #1); 60 (for endpoint #2) | 1) Improvement in fibrosis by at least 1 stage without worsening of NASH; 2) Composite outcome of all-cause mortality, cirrhosis and liver-related clinical events | Tobira Therapeutics |
| ASK1 inhibitors | NCT03053050 | February 14, 2017 | Safety and Efficacy of Selonsertib in Adults With NASH and Bridging (F3) Fibrosis (STELLAR 3) | 3 | Multicenter, double blind, parallel group | Selonsertib (6 or 18 mg) | Placebo | 808 | 12 (for endpoint #1); 60 (for endpoint #2) | 1) Improvement in fibrosis by at least 1 stage without worsening of NASH; 2) Event-Free Survival as assessed by time to the first clinical event | Gilead Sciences |
| ASK1 inhibitors | NCT03053063 | February 14, 2017 | Safety and Efficacy of Selonsertib in Adults With Compensated Cirrhosis Due to NASH (STELLAR 4) | 3 | Multicenter, double blind, parallel group | Selonsertib (6 or 18 mg) | Placebo | 883 | 12 (for endpoint #1); 60 (for endpoint #2) | 1) Improvement in fibrosis by at least 1 stage without worsening of NASH; 2) Event-Free Survival as assessed by time to the first clinical event | Gilead Sciences |
| FGF21 analogues | NCT03486899 | April 3, 2018 | A Phase 2B Randomized Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of BMS-986036 (PEG-FGF21) in Adults With NASH and Stage 3 Liver Fibrosis (FALCON 1) | 2 | Multicenter, quadruple blind, parallel group | Pegbelfermin (NA mg) | Placebo | 160 | 6 | Improvement in fibrosis by at least 1 stage without worsening of NASH OR NASH improvement without worsening of fibrosis | Bristol-Myers Squibb |
| FGF21 analogues | NCT03486912 | April 3, 2018 | A Phase 2B Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of BMS-986036 (PEG-FGF21) in Adults With NASH and Compensated Liver Cirrhosis (FALCON 2) | 2 | Multicenter, quadruple blind, parallel group | Pegbelfermin (NA mg) | Placebo | 100 | 12 | Improvement in fibrosis by at least 1 stage without worsening of NASH | Bristol-Myers Squibb |
| β-selective THR agonists | NCT03900429 | April 3, 2019 | A Phase 3 Study to Evaluate the Efficacy and Safety of MGL-3196 (Resmetirom) in Patients With NASH and Fibrosis (MAESTRO-NASH) | 3 | Multicenter, quadruple blind, parallel group | Resmetirom (80 or 100 mg) | Placebo | 2000 | 12 (for endpoint #1); 54 (for endpoint #2) | 1) Resolution of NASH; 2) Composite outcome of all-cause mortality, cirrhosis and liver-related clinical events | Madrigal Pharmaceuticals, Inc. |
| Caspase inhibitors | NCT03205345 | July 2, 2017 | Emricasan, a Caspase Inhibitor, for Treatment of Subjects With Decompensated NASH Cirrhosis (ENCORE-LF) | 2 | Multicenter, triple blind, parallel group | Emricasan (5 or 25 mg) | Placebo | 210 | 30 | Improvement in event-free survival based on a composite clinical endpoint | Conatus Pharmaceuticals |

Abbreviations: ACC, acetyl-CoA carboxylase; ALT, alanine aminotransferase; ASK, apoptosis signal-regulating kinase; CCR, C–C chemokine receptor; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP, glucagon-like peptide; HCC, hepatocellular carcinoma; NA, not available; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PPAR, peroxisome proliferator activated receptor; RA, receptor agonists; SAF, steatosis activity and fibrosis; SGLT, sodium-glucose cotransporter; THR, thyroid hormone receptor.
†: hard endpoints are regarded cirrhosis decompensation, HCC, transplantation and death [13].

*S.A. Polyzos, E.S Kang, C. Boutari et al. Current and emerging pharmacological options for the treatment of NASH, Metabolism Clinical and Experimental. 2020.*

**Table 1**
Potential effects of current and emerging medications on ALT, NAS, hepatic steatosis, inflammation and fibrosis in patients with NASH (data derived from clinical studies).

| Category/Medication | ALT | NAS | Hepatic steatosis | Hepatic inflammation | Hepatic Fibrosis |
|---|---|---|---|---|---|
| Current medications | | | | | |
| Vitamin E | Decrease | Decrease | Decrease | Decrease | No change |
| TZDs | Decrease | Decrease | Decrease | Decrease | Inconclusive |
| GLP-1 RA | Decrease | No change | Decrease | No change | Inconclusive |
| DPP-4 inhibitors | Inconclusive | Inconclusive | Inconclusive | Inconclusive | No change |
| SGLT-2 inhibitors | Decrease | NA | Decrease | NA | NA |
| Statins | Decrease | Inconclusive | Decrease | Inconclusive | No change |
| Omega-3 polyunsaturated fatty acids | Inconclusive | No change | Inconclusive | No change | No change |
| Orlistat | Decrease | NA | Decrease | Possibly decrease | No change |
| Ursodeoxycholic acid | Decrease | NA | Decrease | Inconclusive | Inconclusive |
| MRA | No change | NA | Possible decrease | NA | NA |
| Emerging medications | | | | | |
| FXR agonists; OCA | Decrease | Decrease | Decrease | Decrease | Decrease |
| PPAR-α/δ agonists; elafibranor | Decrease | Decrease[a] | Possible decrease[a] | Possible decrease[a] | Possible decrease[a] |
| PPAR-α/γ agonists; saroglitazar | Decrease | NA | NA | NA | NA |
| PPAR-γ sparing modulators; MSDC-0602 K | Decrease | Decrease | Decrease[b] | No change | No change |
| CCR2/5 antagonist; cenicriviroc | No change | Decrease[a] | No change | Decrease[a] | Decrease |
| ASK1 inhibitors; selonsertib | No change | No change | Possibly decrease | No change | Decrease |
| FGF-21 analogues; pegbelfermin | Decrease | NA | Decrease | NA | NA |
| ACC inhibitors; firsocostat | No change | NA | Decrease | NA | Possibly no change |
| LOXL-2 inhibitors; simtuzumab | No change | No change | No change | No change | No change |
| Gallectin-3 inhibitors | No change | NA | No change | No change | No change |
| β-selective THR agonists; resmetirom | Decrease | Decrease | Decrease | Decrease | No change |
| Caspase inhibitors; emricasan | Decrease | Increase | Decrease | Increase | No change |
| Selective MRA | NA | NA | NA | NA | NA |
| Adipokines; Leptin | Decrease[c] | NA | Decrease[c] | NA | NA |

Abbreviations: ACC, acetyl-CoA carboxylase; ALT, alanine transaminase; ASK, apoptosis signal-regulating kinase; CCR, C-C chemokine receptor; DPP, dipeptidyl peptidase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP, glucagon-like peptide; LOXL, lysyl oxidase like; MRA, mineralocorticoid receptor antagonist; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator activated receptor; RA, receptor agonist; SGLT, sodium-glucose cotransporter; THR, thyroid hormone receptor; TZDs, thiazolidinediones.

[a] Decreased only in the subgroup with severe NASH.
[b] Decreased only in the group of high dose.
[c] Data derived from NASH patients with lipodystrophy.

*S.A. Polyzos, E.S Kang, C. Boutari et al. Current and emerging pharmacological options for the treatment of NASH, Metabolism Clinical and Experimental. 2020.*

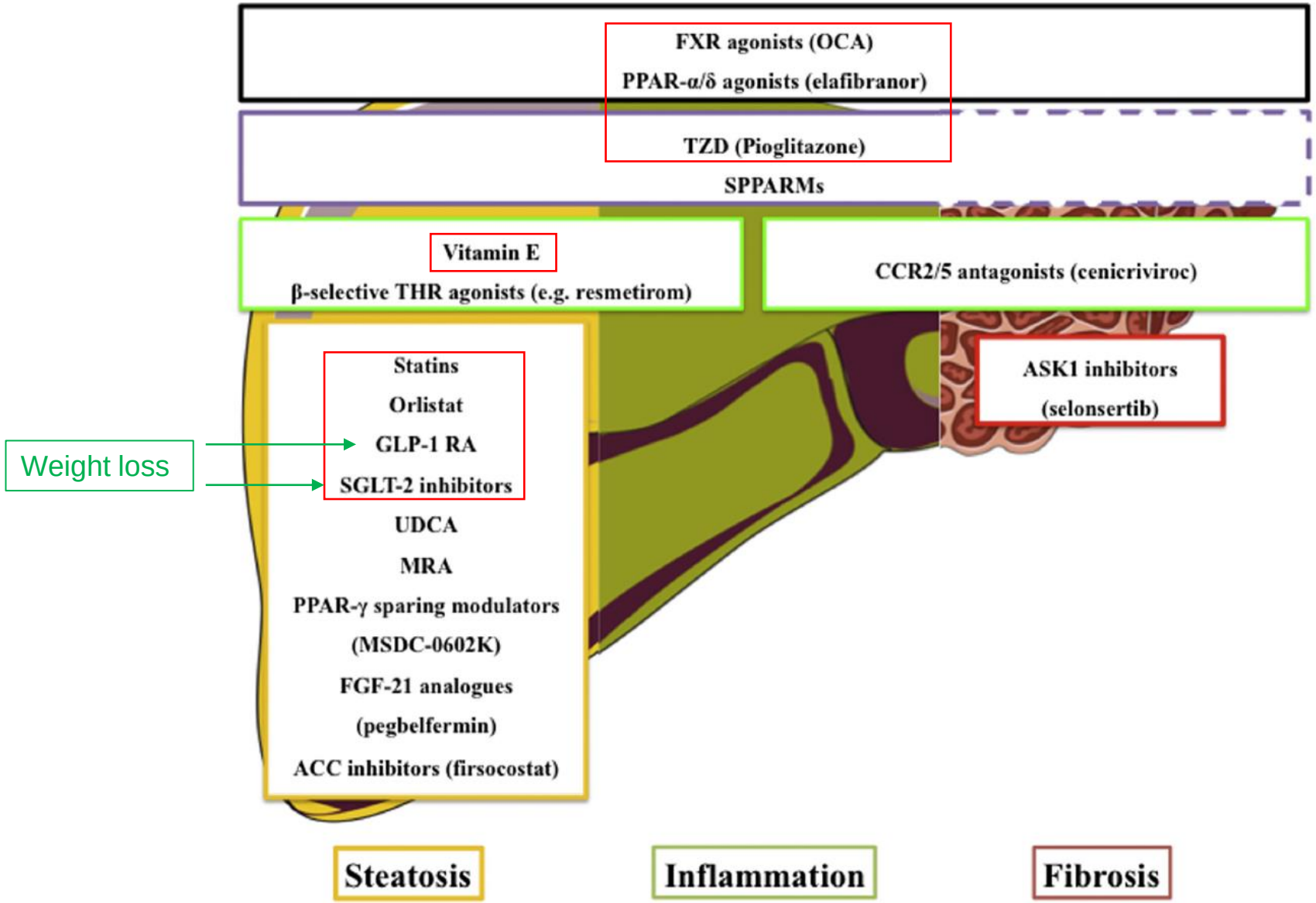



**Fig. 1.** Medications investigated or being under investigation for NASH and their effects on specific hepatic lesions based on current data of clinical trials. Some medications have shown so far a beneficial effect only on hepatic steatosis (e.g., statins, orlistat) or on fibrosis (e.g., selonsertib). Other medications have shown beneficial effect on both steatosis and inflammation (e.g., vitamin E), or on both inflammation and fibrosis (cenicriviroc). Finally, some medications have shown beneficial effect on all lesions (steatosis, inflammation and fibrosis: OCA, elafibranor), whereas others (e.g. TZD, SPPARMSs) have shown beneficial effects on steatosis and inflammation, as well as a marginal effect on fibrosis). Abbreviations: ACC, acetyl-CoA carboxylase; ASK, apoptosis signal-regulating kinase; CCR, C-C chemokine receptor; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MRA, mineralocorticoid receptor antagonist; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PPAR, peroxisome proliferator activated receptor; SGLT-2, sodium-glucose cotransporter-2; SPPARMs, selective PPAR modulators; THR, thyroid hormone receptor; TZDs, thiazolidinediones; UDCA, ursodeoxycholic acid.

*S.A. Polyzos, E.S Kang, C. Boutari et al. Current and emerging pharmacological options for the treatment of NASH, Metabolism Clinical and Experimental. 2020.*

# NAFLD Medications

- 5 drugs have entered phase 3 development for treatment of NASH:
- Pioglitazone
- Vitamin E
- GLP 1 agonists
- Obeticholic acid
- Elafibranor
- >10% TBW loss can lead to resolution of NASH in majority and improvement in liver fibrosis in almost half of patients.
- Pharmacologic treatment should be reserved for patients at risk of liver related complications.

# Insulin sensitizers: glitazones

- ***Rosiglitazone for NASH: one-year results of the randomized placebo-controlled fatty liver improvement with rosiglitazone therapy (FLIRT) trial. Ratziu et al. Gastro 2008.***
- Significant **improvement in steatosis, ALT and IR** and increase in adiponectin. **However, no improvement in fibrosis and NASH activity score (or necroinflammation)**

- Pts in the intervention arm had a mean weight gain of 1.5kg (vs -1kg in the placebo group)

- ***Long-term efficacy of rosiglitazone in NASH: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. Ratziu et al. Hepatology 2010.***

- 2-year extension.

- Despite good effect on steatosis, IR and ALT levels, rosiglitazone had **no effect on what we really care about: liver injury.** So, improving insulin sensitivity may not be sufficient in NASH.

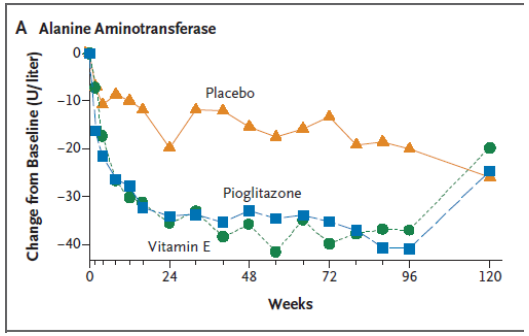
# *Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with NASH. Aithal et al. Gastro 2008.*

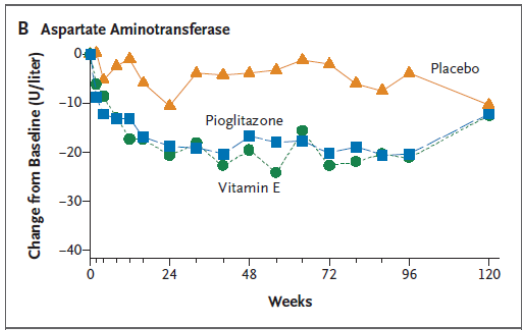
- Randomized 74 non-diabetic pts with NASH to 12 months of pioglitazone (30mg/d) vs placebo. 61 pts got liver bxs before and after
- They found a reduction in glu, HbA1C, insulin C peptide, ALT and ferritin in the pioglitazone group
- Notably, they also found **reduced steatosis, hepatocelluar injury, lobular inflammation, Mallory-Denk bodies (inclusion body found in the cytoplasm of liver cells) AND fibrosis**
- The pioglitazone group did have a mean weight gain of about 3kg compared to controls
- Drug of choice?

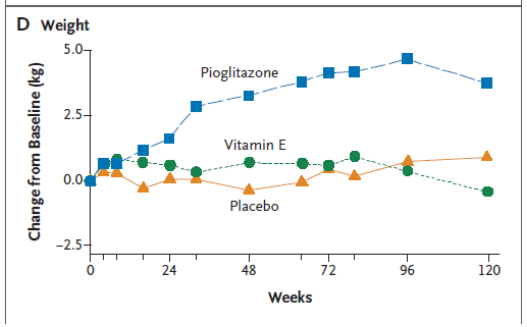
# *Pioglitazone, Vit E, or Placebo for NASH. Sanyal et al. NEJM 2010. PIVENS*

**Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.**

| Variable | Placebo | Vitamin E | Pioglitazone | P Value* | |
|---|---|---|---|---|---|
| | | | | Vitamin E vs. Placebo | Pioglitazone vs. Placebo |
| **Primary outcome†** | | | | | |
| No. of subjects randomly assigned | 83 | 84 | 80 | | |
| Subjects with improvement (%) | 19 | 43 | 34 | 0.001 | 0.04 |
| **Changes from baseline in histologic features** | | | | | |
| No. of subjects with biopsy specimens at baseline and 96 wk | 72 | 80 | 70 | | |
| Steatosis | | | | | |
| Subjects with improvement (%) | 31 | 54 | 69 | 0.005 | <0.001 |
| Mean change in score | −0.1 | −0.7 | −0.8 | <0.001 | <0.001 |
| Lobular inflammation | | | | | |
| Subjects with improvement (%) | 35 | 54 | 60 | 0.02 | 0.004 |
| Mean change in score | −0.2 | −0.6 | −0.7 | 0.008 | <0.001 |
| Hepatocellular ballooning | | | | | |
| Subjects with improvement (%) | 29 | 50 | 44 | 0.01 | 0.08 |
| Mean change in score | −0.2 | −0.5 | −0.4 | 0.03 | 0.01 |
| Total NAFLD activity score (mean change) | −0.5 | −1.9 | −1.9 | <0.001 | <0.001 |
| Fibrosis‡ | | | | | |
| Subjects with improvement (%) | 31 | 41 | 44 | 0.24 | 0.12 |
| Mean change in score | −0.1 | −0.3 | −0.4 | 0.19 | 0.10 |
| Resolution of definite nonalcoholic steatohepatitis (% of subjects) | 21 | 36 | 47 | 0.05 | 0.001 |




**Primary outcome: improvement in histologic features of NASH. Defined p 0.025 as significant.**
**Conclusion: Vit E superior to placebo for treatment of NASH in nondiabetics. No benefit of pioglit over placebo for primary outcome.**

# Pioglitazone

- PPARy agonist. Targets insulin resistance.
- PIVENS trial. Improvement in NAS >/= 2 w/o fibrosis worsening.
- Bx proven NASH.
- AE: increased edema, weight gain, increased risk of osteoporosis, increased risk of bladder ca in some, not all studies.

# Vitamin E

- Targets oxidative stress.
- Oxidative stress thought to play important role in progression to NASH and advanced fibrosis.
- Strong relationship between severity of NAFLD and degree of oxidative stress *(Hardwick et al, Drug Metab Dispos 2010).*
- **Vitamin E well known antioxidant.**
- Well known RCT in pts with bx proven NASH, vitamin E associated with significant improvement in NASH histology, although no change in fibrosis compared with placebo *(Sanyal et al, NEJM 2010).*
- **Led to AASLD guidelines recommending Vit E in patients with bx confirmed NASH <u>who do not have DMII or cirrhosis.</u>**
- AE: increase in all cause mortality risk at >400IU/d. Increased hemorrhagic stroke risk, also showed decreased ischemic stroke risk. Increased risk of prostate ca risk (p=0.06).

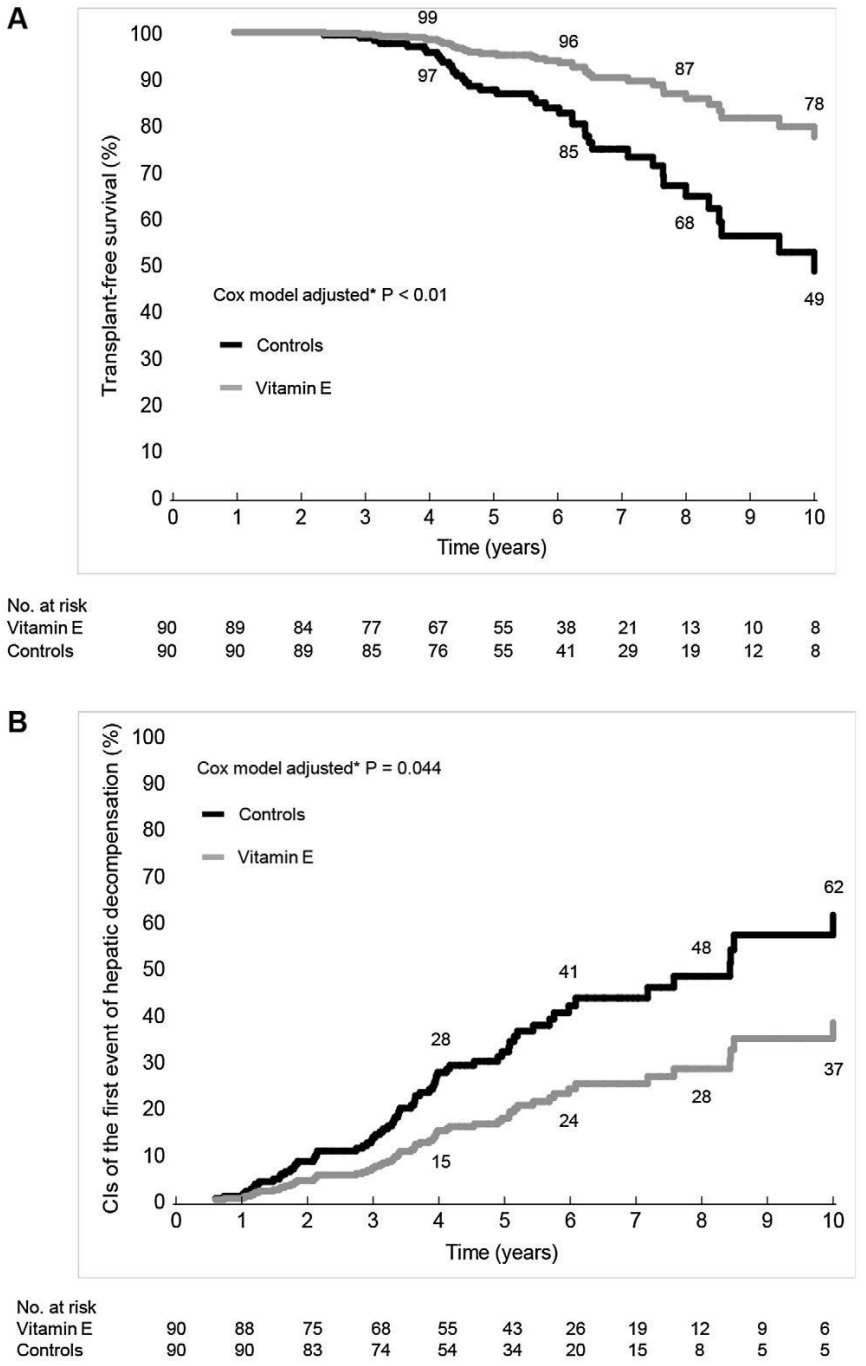
# *Vitamin E improves transplant free survival and hepatic decompensation among patients with NASH and advanced fibrosis. (Vilar-Gomez et al Hepatology 2020)*

- Retrospective study.
- Evaluated whether vit E improved clinical outcome of NASH pts with **bridging fibrosis or cirrhosis**.
- 236 pts with bx proven NASH and bridging fibrosis and cirrhosis, 2004-2016.
- Excluded: decompensated cirrhosis, MELD>/=15, HIV, h/o bariatric surgery, other concurrent liver disease.
- 90 pts took vit E 800 IU qd for >/= 2 yrs vs 90 matched controls. Included pts **with DMII**.
- Median f/u 5.6 yrs
- **Primary endpoint:** all cause mortality or liver transplantation
- Secondary endpoints: hepatic decompensation, vascular events, HCC, nonhepatic malignancies.

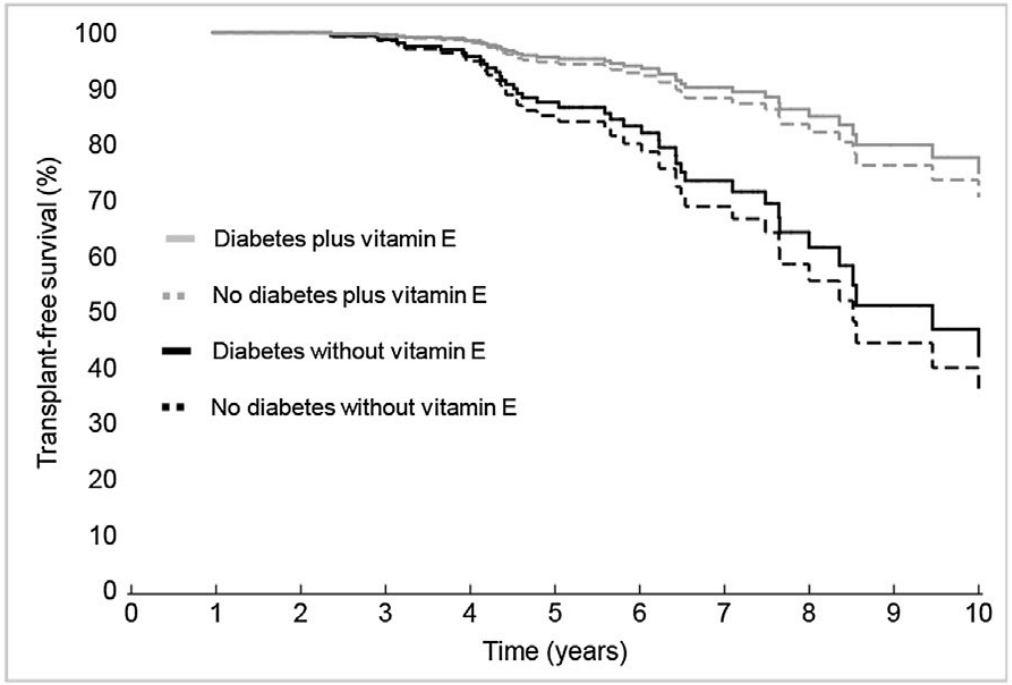
- Vit E users had higher transplant free survival (78 vs 49%); lower rates of hepatic decompensation (37 vs 62%)

- Vitamin E tx decreased risk of death or transplant by 70%; NNT 4.18 and 6.16.

- Vitamin E tx decreased hepatic decompensation by 35%; NNT 6.43.



- Benefits evident in both those with DMII and those w/o DMII.

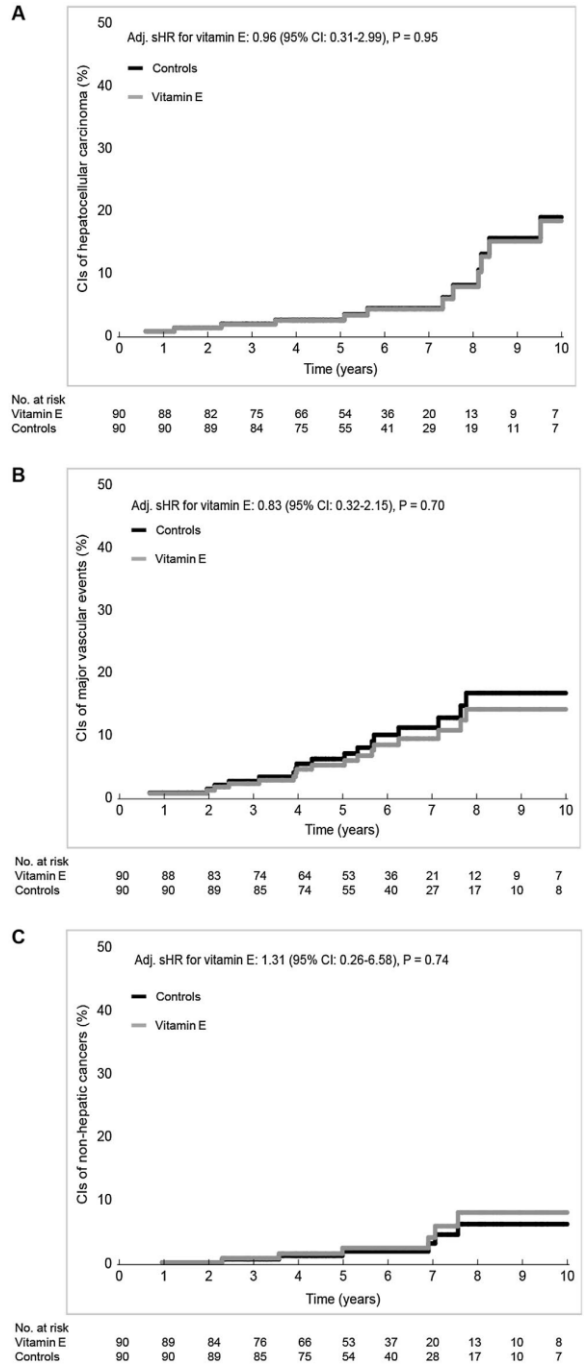



| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T2D + vit E | 56 | 55 | 50 | 49 | 43 | 34 | 23 | 10 | 6 | 5 | 3 |
| T2D + no vit E | 65 | 65 | 64 | 62 | 57 | 42 | 29 | 20 | 14 | 10 | 6 |
| No T2D + vit E | 34 | 34 | 34 | 28 | 24 | 21 | 15 | 11 | 7 | 5 | 5 |
| No T2D + no vit E | 25 | 25 | 25 | 23 | 19 | 13 | 12 | 9 | 5 | 2 | 2 |

- 10yr cumulative probabilities of HCC, vascular events, nonhepatic cancers not different.

- **Conclusion**: vit E associated with improved clinical outcomes in pts with NASH and bridging fibrosis or cirrhosis.

- Weaknesses: retrospective, nonrandomized. Association and not necessarily causal.



# Obeticholic acid

- Bile acids are steroid molecules produced by the liver to facilitate digestion and absorption of lipids from the gut.
- Bile acid receptors do more than controlling bile acid pool; they have actions on glucose and lipid metabolism.
- Obeticholic acid: potent synthetic FXR agonist.

# *REGENERATE: interim analysis from a multicenter, randomized, placebo-controlled phase 3 trial. (Younossi et al, Lancet 2019)*

- Bx proven NASH, NAS >/= 4, F2-F3 or F1 with at least one accompanying comorbidity (BMI >/= 30, DMII, elevated ALT).
- Obeticholic acid 10mg vs 25mg vs placebo
- Excluded: cirrhosis, increased etoh, other CLD
- 18mo with end of tx bx.
- 1968 randomized. Completed: 262 placebo, 263 10mg, 253 25mg
- Majority with F3, NAS at least 6/8.
- >50% with DMII.

- Met primary endpoint of improvement in fibrosis by >1 stage w/o worsening NASH. More pronounced in 25mg qd.

- Primary end of NASH resolution (no hepatocellular ballooning and no residual lobular inflammation) not met.

- BUT dose-dependent response observed in the ITT group, with more pts in 25mg group showing at least 1 point improvement in scores in key histological features of NASH vs placebo.

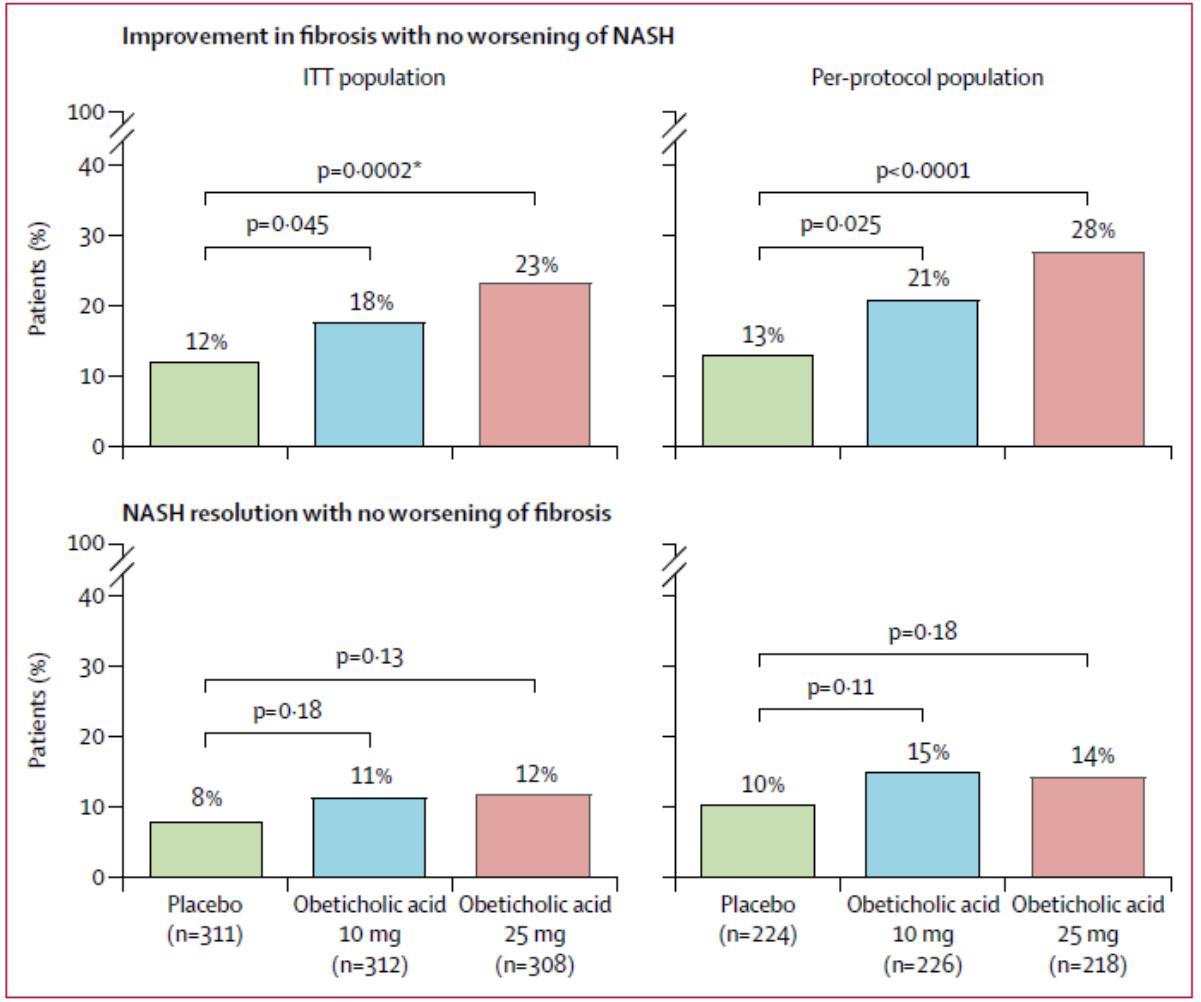



*Figure 2:* Primary endpoints in the ITT population

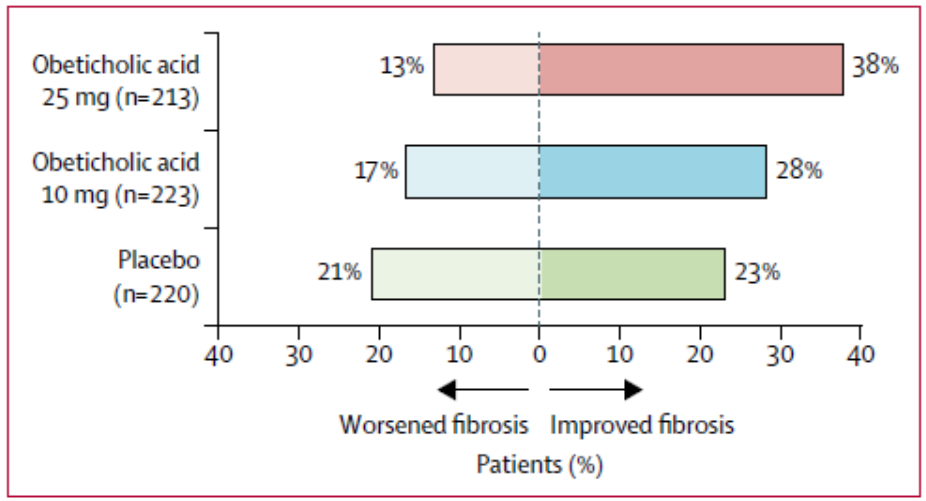



***Figure 3:*** **Regression or progression of fibrosis by at least one stage in the per-protocol population**

The proportion of patients with improved or worsened fibrosis by at least one stage is shown for the 656 patients in the per-protocol population with available fibrosis stage data at month 18 or end of treatment.

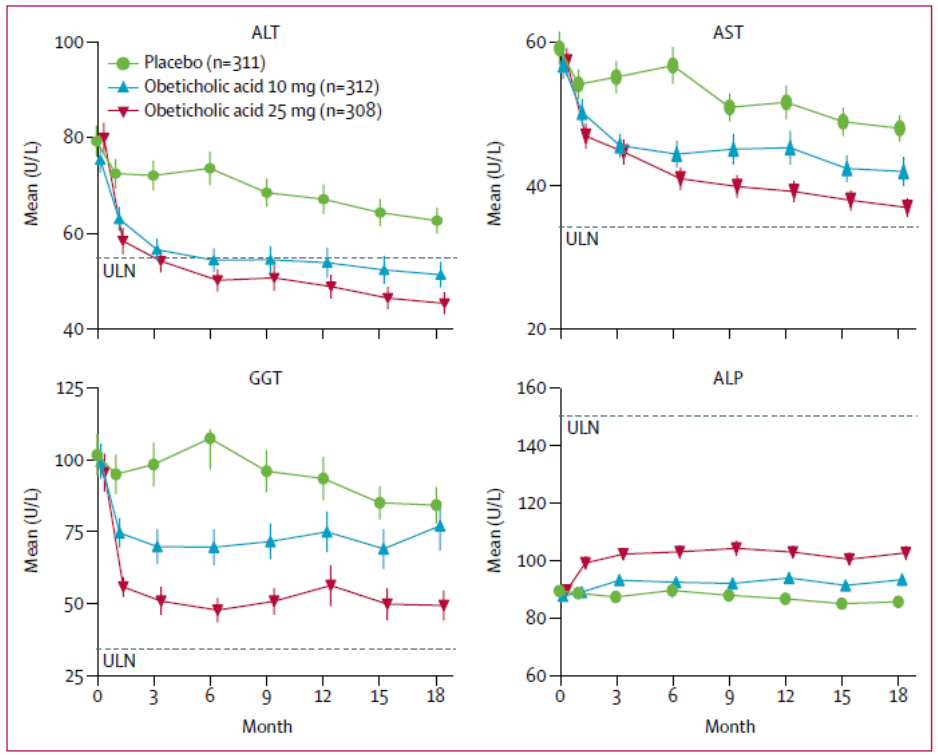



***Figure 4:*** **Changes in liver biochemistry over time in the ITT population**

Mean values of change from baseline up to month 18 are shown for patients from each treatment group in the ITT population, with vertical bars indicating SEs. ALP=alkaline phosphatase; ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyl transferase. ITT=intention to treat. ULN=upper limit of normal.

- AE: pruritus (dose dependent), increased LDL.

Incidence of CV adverse events and serious AE similar across groups.

Gallstone-related AE in <1% placebo, 1% 10mg, 3% 25mg

3 deaths: 2 in placebo (bone ca, cardiac arrest) , 1 in obeticholic 25mg (glioblastoma). None related to study treatment.

- Included DMII. F2-F3, 2% wgt loss. Cirrhotics excluded. Submitted for FDA approval. Currently, looking at cirrhotics; ongoing.

| | Placebo (n=657) | Obeticholic acid 10 mg (n=653) | Obeticholic acid 25 mg (n=658) |
|---|---|---|---|
| **Treatment-emergent and serious adverse events** | | | |
| At least one treatment-emergent adverse event | 548 (83%) | 579 (89%) | 601 (91%) |
| Severity* | | | |
| Mild | 160 (24%) | 163 (25%) | 130 (20%) |
| Moderate | 294 (45%) | 323 (49%) | 338 (51%) |
| Severe | 87 (13%) | 89 (14%) | 130 (20%) |
| Life-threatening | 5 (1%) | 4 (1%) | 2 (<1%) |
| Death | 2 (<1%) | 0 | 1 (<1%) |
| Leading to treatment discontinuation | 41 (6%) | 39 (6%) | 83 (13%) |
| Serious adverse events | 75 (11%) | 72 (11%) | 93 (14%) |
| **Adverse events occurring in ≥5% of patients in either obeticholic acid group** | | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | 123 (19%) | 183 (28%) | 336 (51%) |
| Grade 1 (mild or localised) | 90 (14%) | 113 (17%) | 148 (22%) |
| Grade 2 (intense or wide spread) | 30 (5%) | 67 (10%) | 152 (23%) |
| Grade 3 (intense or widespread and limit activities of daily living) | 3 (<1%) | 3 (<1%) | 36 (5%) |
| Gastrointestinal disorders | | | |
| Nausea | 77 (12%) | 72 (11%) | 83 (13%) |
| Constipation | 36 (5%) | 65 (10%) | 70 (11%) |
| Abdominal pain | 62 (9%) | 66 (10%) | 67 (10%) |
| Diarrhoea | 79 (12%) | 44 (7%) | 49 (7%) |
| Abdominal pain upper | 35 (5%) | 46 (7%) | 45 (7%) |
| Vomiting | 33 (5%) | 34 (5%) | 44 (7%) |
| Abdominal distension | 23 (4%) | 31 (5%) | 31 (5%) |
| Infections and infestations | | | |
| Urinary tract infection | 49 (7%) | 54 (8%) | 62 (9%) |
| Upper respiratory tract infection | 44 (7%) | 47 (7%) | 54 (8%) |
| Nasopharyngitis | 41 (6%) | 34 (5%) | 45 (7%) |
| Bronchitis | 28 (4%) | 34 (5%) | 35 (5%) |
| Sinusitis | 35 (5%) | 36 (6%) | 30 (5%) |

(Table 3 continues in next column)

| | Placebo (n=657) | Obeticholic acid 10 mg (n=653) | Obeticholic acid 25 mg (n=658) |
|---|---|---|---|
| (Continued from previous column) | | | |
| Investigations | | | |
| LDL cholesterol increased | 47 (7%) | 109 (17%) | 115 (17%) |
| Blood cholesterol increased | 12 (2%) | 30 (5%) | 38 (6%) |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | 55 (8%) | 50 (8%) | 50 (8%) |
| Back pain | 50 (8%) | 56 (9%) | 40 (6%) |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | 18 (3%) | 42 (6%) | 55 (8%) |
| Diabetes | 36 (5%) | 46 (7%) | 45 (7%) |
| Hypercholesterolaemia | 14 (2%) | 35 (5%) | 29 (4%) |
| General disorders and administration site conditions | | | |
| Fatigue | 88 (13%) | 78 (12%) | 71 (11%) |
| Nervous system disorders | | | |
| Headache | 51 (8%) | 42 (6%) | 34 (5%) |
| Dizziness | 28 (4%) | 32 (5%) | 25 (4%) |
| Respiratory, thoracic, and mediastinal disorders | | | |
| Cough | 27 (4%) | 29 (4%) | 38 (6%) |
| Vascular disorders | | | |
| Hypertension | 28 (4%) | 36 (6%) | 39 (6%) |

Table is arranged by descending order of incidence (system organ class and preferred term within system organ class) in the obeticholic acid 25 mg group, followed by descending order of incidence in the obeticholic acid 10 mg group.
*Patients reporting more than one adverse event are counted only once using the highest severity.

***Table 3:*** **Summary of treatment-emergent adverse events in the safety population**

# GLP1 receptor agonists: Liraglutide

- GLP1: gut derived incretin hormone. Induces wgt loss and insulin sensitivity.
- Native GLP1:

=> potent glu lowering action by inducing insulin secretion and reducing glucagon secretion in glu-dependent manner

=> Suppresses appetite

=> Delays gastric emptying

- Liraglutide: long-acting human GLP1 analogue
- => wgt loss
- => decrease A1c
- => improve beta-cell function
- => licensed for glycemic control in DMII
- Liraglutide for DMII and obesity may also improve NASH.

# *LEAN: multicenter, double-blind, randomized, placebo-controlled phase 2 study. (Armstrong et al. Lancet 2016)*

- Liraglutide in NASH. First randomized, placebo-controlled trial.
- Liraglutide 1.8mg qd vs placebo.
- Overweight, bx confirmed NASH +/- DMII, 52 pts randomized.
- NAS >/= 3, BMI >/= 25, A1c </= 9. Included **stage 3 fibrosis and cirrhosis**. Excluded CP B/C.
- Met primary endpoint of improvement in NASH w/o worsening fibrosis vs placebo at 48 weeks. Also benefit of wgt loss and A1c.
- AE: GI (N/V, diarrhea, abdominal pain).
- Effect likely 2/2 combination of direct hepatic effect and effect on wgt loss and glycemic control.
- In-vitro: GLP1 analogues improve ability of hepatocytes to handle excess FAs and lipid production by modulating lipid transport, beta-oxidation, de-novo lipogenesis. *(Mells et al AJP 2012; Ben-Shlomo et al J hepat 2011; Svegliati-Baroni et al Liver Int 2011)*

# Elafibranor

- PPAR nuclear receptors have numerous metabolic actions.
- Elafibranor is dual PPAR alpha/gamma agonist with beneficial effects on hepatic and insulin sensitivity.
- Acts on pathways involved in NASH: steatosis, inflammation, fibrosis.
- Improves lipids, glu homeostasis, peripheral and hepatic IR
- Reduces liver inflammatory markers.

# GOLDEN-505. Ratziu et al. Gastro 2016

- Randomized, international, double blind, placebo controlled.
- Phase II trial.
- Pts with NASH w/o cirrhosis randomized to 80mg, 120mg, placebo x 52 wks. N=276 randomized. 237 completed study.
- Included up to stage 3 fibrosis.
- Primary outcome: resolution of NASH w/o worsening fibrosis.
- 19% of 120mg Elafibranor grp met primary outcome vs 12% placebo.
- LFTS, lipids, glu profiles significantly reduced in 120mg grp.
- Patients with more severe NASH (NAS >/= 4) more significant effect with 120mg than those with mild disease compared to placebo.
- No wgt gain or cardiac events. AE: mild increase in cr that was reversible after treatment stopped.

As we wait for FDA approved therapies, what do we do in the meanwhile?

# Obesity, NASH, Cirrhosis and Liver Transplant

- Obesity is a world-wide epidemic.
- Prevalence of obesity, as defined by BMI >/= 30, in the US estimated to be 34.9%. *(Ogden et al. JAMA 2014)*
- Impact of  the obesity epidemic on incidence of liver disease is increasing, either as a primary (NAFLD) or secondary cause.
- Decompensated liver disease 2/2 NASH is the second most common indication for LT. *(Charlton et al, Gastroenterology 2011; Wong et al Gastroenterology 2015)*
- Predicted to be the number one reason for LT given the new HCV treatments and successful eradication of HCV.
- Multidisciplinary management of obese pts with liver disease before, during, after LT has become an important challenge.

# Before LT

- Obese patients have increased co-morbidities, higher risk for LTx.

- Obese pts less likely to:

- Be placed on the transplant list
- Less likely to undergo LT once on the list
- Exhibit higher waitlist mortality

*(Schlansky et al Transplantation 2016; Segev et al Ann Surg 2008)*

# After LT

- Metabolic and CV disease complications major cause of mortality post LT:
- Increased metabolic risk factors 2/2 IS; development of metabolic syndrome post LT
- Recurrent or de novo NASH in graft
- Worsening pre-existing risk factors (worsening obesity, DMII, atherosclerosis, HL)

*(Watt et al Am J Transplant 2010)*

# How do we improve outcomes?

- Await pharmaceutical options. Consider clinical trials.
- Aggressive risk factor modification: DL, DMII, HTN

Target obesity:

- Lifestyle modification: average 3-5% TBW.
- Medical weight loss with anti-obesity meds: BMI >/= 27 with wgt related comorbidity or BMI >/= 30.

7-10% TBW (up to 15% in some).

- Endobariatrics: BMI 27-35. Averages 30-40lb wgt loss.
- Bariatric surgery: BMI 40 or 35 with obesity related co-morbidity. Sustained weight loss, reversal of risk factors. Data has shown to be the most impactful with sustained improvement.

# Endobariatrics: an alternative or supplement to gastric bypass

1. Endoscopic sleeve gastrectomy
- OverStitch device (FDA approved)

2. Intragastric balloon
- Orbera (FDA approved 2015)
- Obalon (FDA approved 2016)
- Spatz3 (under trial)
- Elipse (under trial)

3. Aspiration therapy
- Aspire Assist System (FDA approved)

4. Gastroduodenal Implants
- TransPyloric Shuttle (FDA approved)

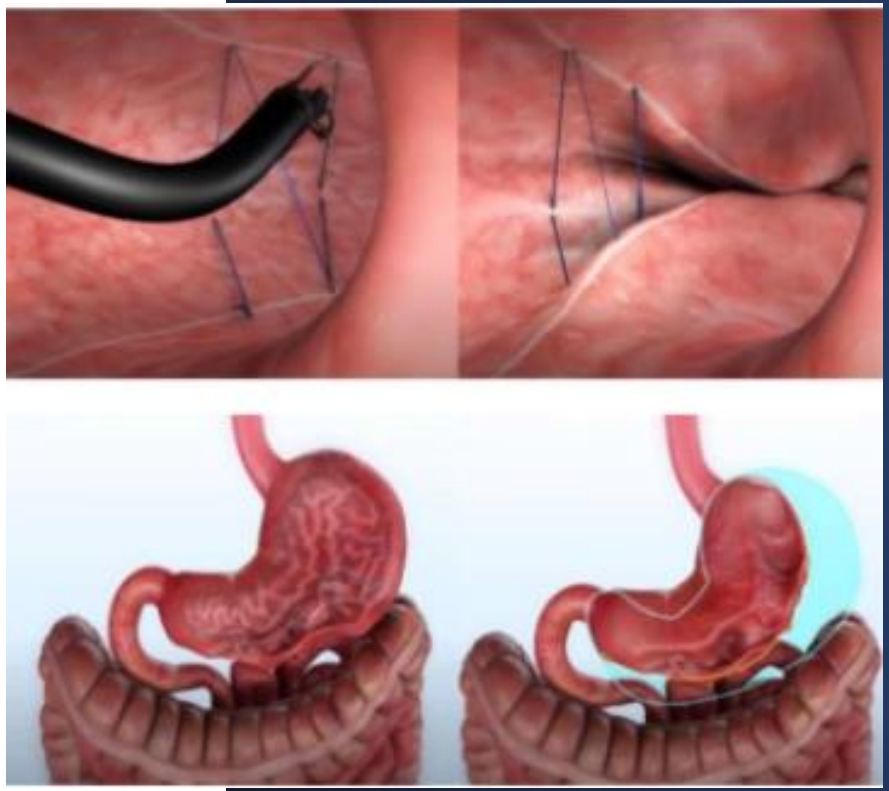
5. Malabsorptive Sleeves
- EndoBarrier-Duodenal-Jejunal Bypass Liner (in trial)
- ValenTx-Gastro-Duodeno-Jejunal Bypass (in trial)

6. Intestinal Alterations
- Revita Duodenal Mucosal Resurfacing (in trial)

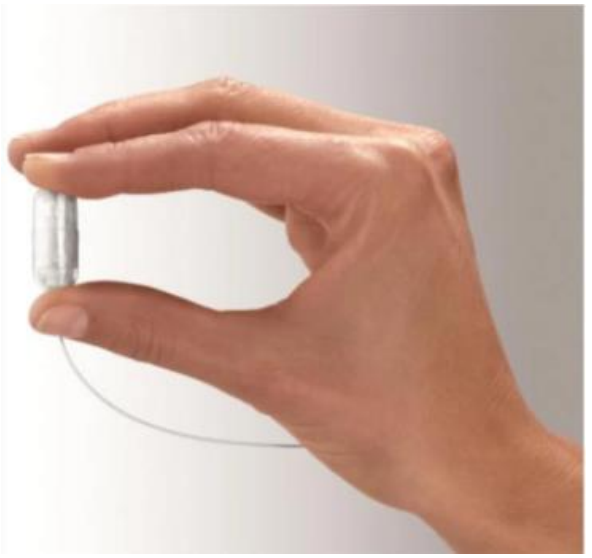
# Endoscopic Sleeve Gastroplasty: gastric plication

- OverStitch Device
- Restrictive procedure
- Delays gastric emptying
- Hormonal alteration
- Early satiety

- Full thickness sutures along greater curvature of stomach
- BMI 30- 40
- Reported AE: perigastric fluid collection, PE, PTX, abd pain, bleeding



# Intra-gastric balloon



- Diminished appetite
- Post prandial fullness
- Weight loss
- BMI 30-40
- Reported AE:

N/V, abd pain, pancreatitis, dehydration, bowel obstruction

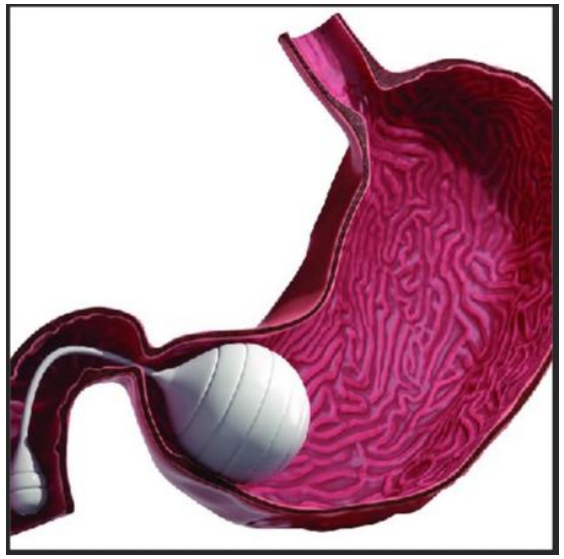
| | Orbera | Obalon | Spatz3 | Elipse |
|---|---|---|---|---|
| FDA approval status | Approved in 2015 | Approved in 2016 | Under trial | Under trial |
| Implantation | Endoscopy needed | Swallowed under fluoroscopic guidance | Endoscopy needed | Swallowed under fluoroscopic guidance |
| Removal | Endoscopy needed | Endoscopy needed | Endoscopy needed | Endoscopy not needed |
| Implantation period | Up to 6 months | Up to 6 months | Up to 12 months | 4 months |
| Capacity | 400–700 ml saline (1 balloon) | 250 ml gas (up to 3 balloons "750 ml") | 300–900 ml saline (1 balloon) | 550 ml saline (1 balloon) |
| Volume adjustability | Not adjustable | Not adjustable | Adjustable | Not adjustable |

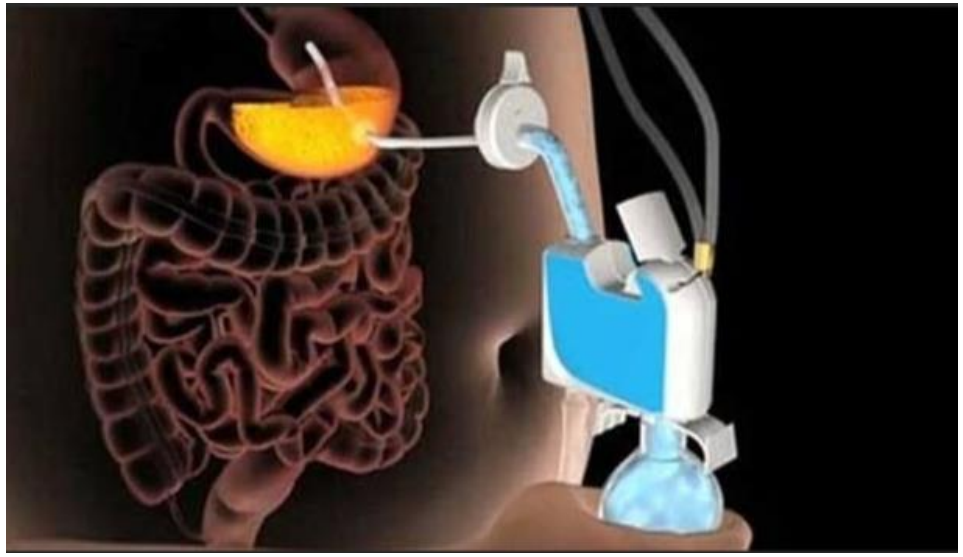
- Orbera: improvement in NAS in 18/20 pts; improvement in fibrosis by 1.5 stages in 10/20 pts. Improvement in fasting glu, A1C, lipids.

*(Bazerbachi et al. Intragastric balloon placement induces significant metabolic and histologic improvement in pts with NASH. Clin Gastro Hepatol 2020)*

*Farha et al. Endobariatrics and Metabolic Endoscopy: Can we solve the obesity epidemic with our scope? Current Gastro Reports 2020*

# Aspiration Therapy and Gastroduodenal Implants



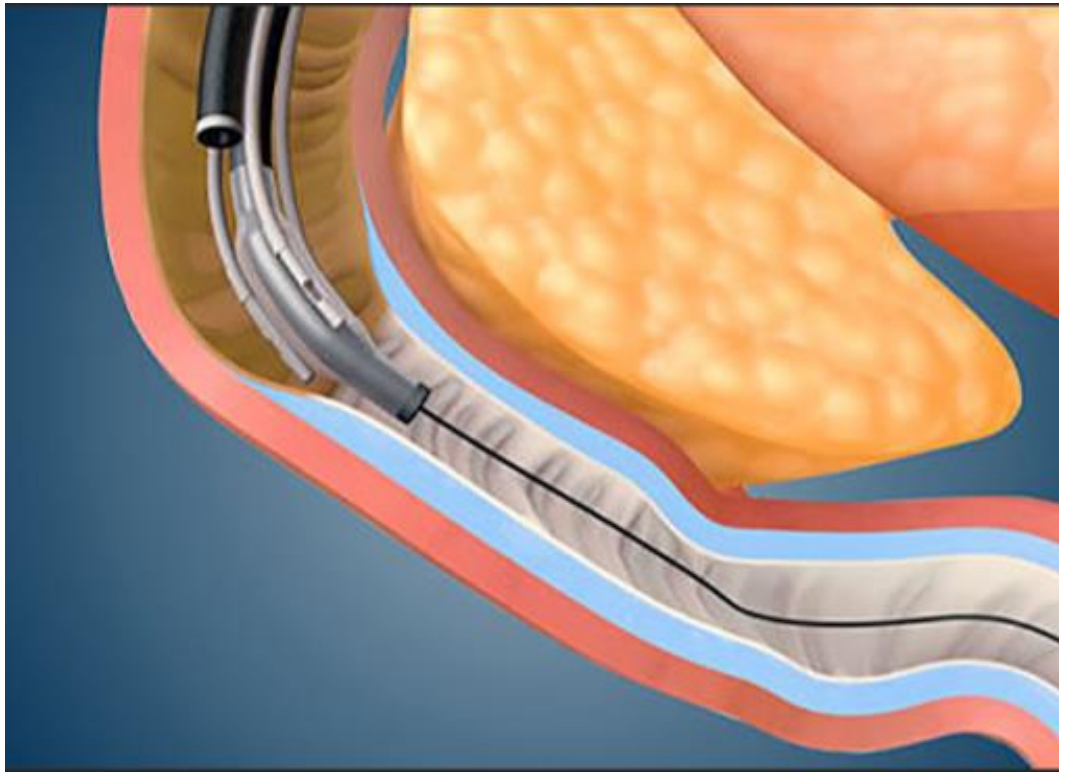


- Aspiration therapy: partial removal of 30% ingested calories via G tube.
- Gastroduodenal implants:

Device results in intermittent GOO, delayed gastric emptying, satiety.

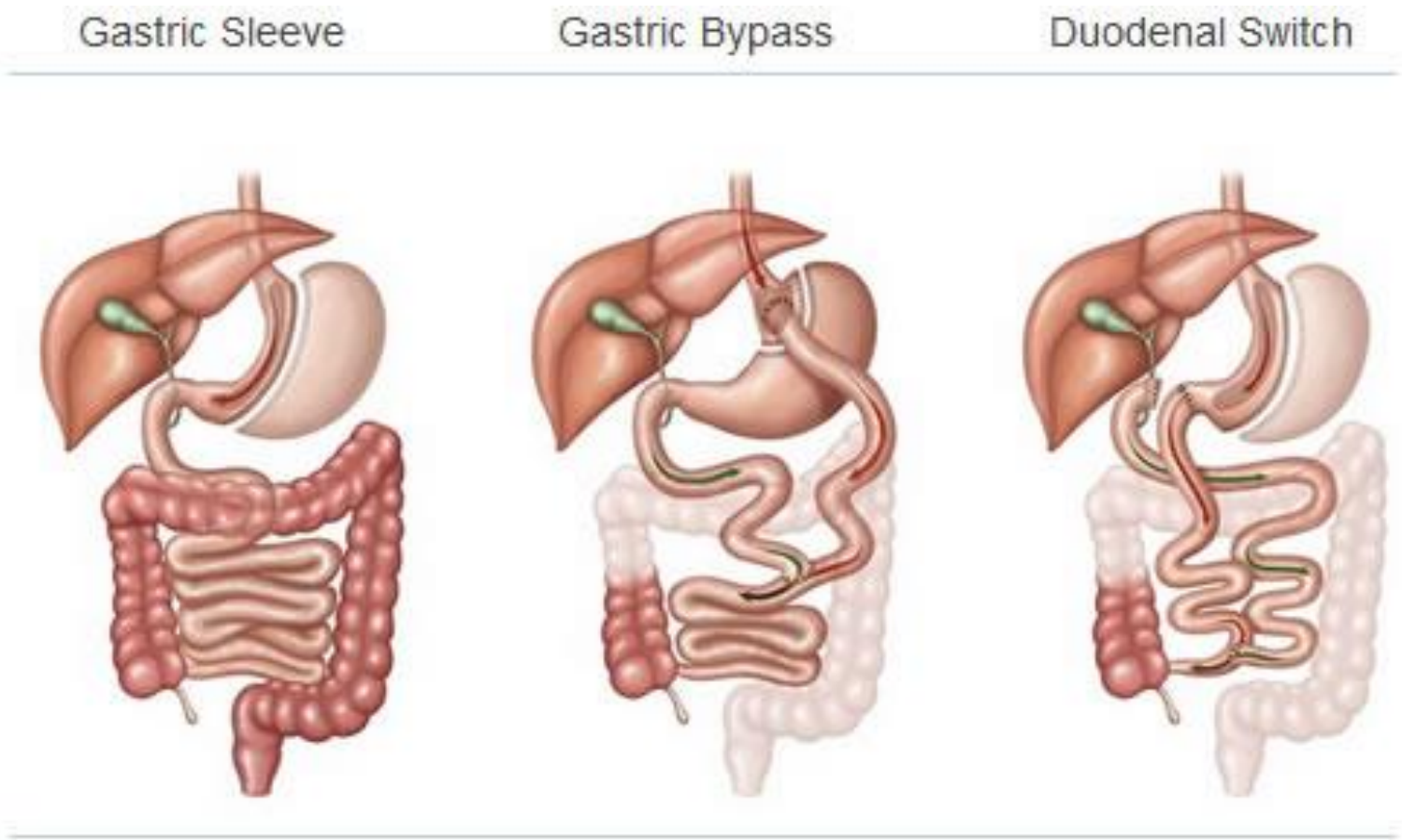
# Revita Duodenal Mucosal Resurfacing

- Hypothermal ablation of duodenal mucosa via balloon catheter.
- Assumed duodenum emanating abnormal signal to insulin sensitive tissues. Duodenal mucosal resurfacing allows mucosa to regenerate restoring normal signaling.
- Reduction in A1C seen in obese and non-obese. *(Cherrington et al. Hydrothermal duodenal mucosal resurfacing: role in the treatment of metabolic disease. Gastrointest Endosc Clin 2017)*



Gastric bypass in the setting of OLTx: is this an option??

Maybe…



## *Outcomes of Sleeve Gastrectomy in Obese Liver Transplant Candidates. Sharpton et al. Liver Transplantation 9/2018*

- Morbid obesity with BMI >/= 40 a relative contraindication to LT.
- 32 LT candidates with mean MELD 12 underwent SG.
- All with h/o decompensation but complications well controlled at time of SG. Median BMI 45.
- No perioperative deaths or liver related morbidity.
- 1 pt with perioperative morbidity secondary to gastric leak.
- Median wgt loss at 6 or 12mo after SG was 22kg and 31kg, respectively, corresponding to TBW loss of 33% and 52%.
- Within 6mo after SG, 88% pts deemed eligible for LT.

# *Long-term Outcomes of Patients Undergoing Simultaneous Liver Transplantation and Sleeve Gastrectomy. Zamora-Valdes et al. Hepatology 2018*

- Pts with BMI >/= 35 offered lifestyle modification intervention at listing. Those unable to achieve BMI <35 offered simultaneous LT and sleeve gastrectomy.
- Sleeve gastrectomy: restrictive procedure with resection of greater curvature of stomach with mechanical and hormonal effects.
- 49 pts with 3 yr follow up: 36 LT alone, 13 LT+SG. Largest series described.
- Mean BMI at LT 47
- NAFLD present in 48.9%, higher prevalence in LT+SG (LT cohort 44.4% vs LT + SG cohort 76.9%).
- Followed for >/= 3 yrs post LT

*Long-term Outcomes of Patients Undergoing Simultaneous Liver Transplantation and Sleeve Gastrectomy. Zamora-Valdes et al. Hepatology 2018*

Results:

-LT cohort had less severe obesity at enrollment (BMI 40 vs 46) and 83% achieved >10% TBW loss pre-LT

-3 yrs post LT, 29% of LT cohort maintained >10% TBW loss vs 100% of LT+SG.

-**LT+SG maintained higher percentage of TBW after 3 yrs of follow up.**

-**LT+SG: lower prevalence of HTN, IR, hepatic steatosis, required less HTN/lipid meds**

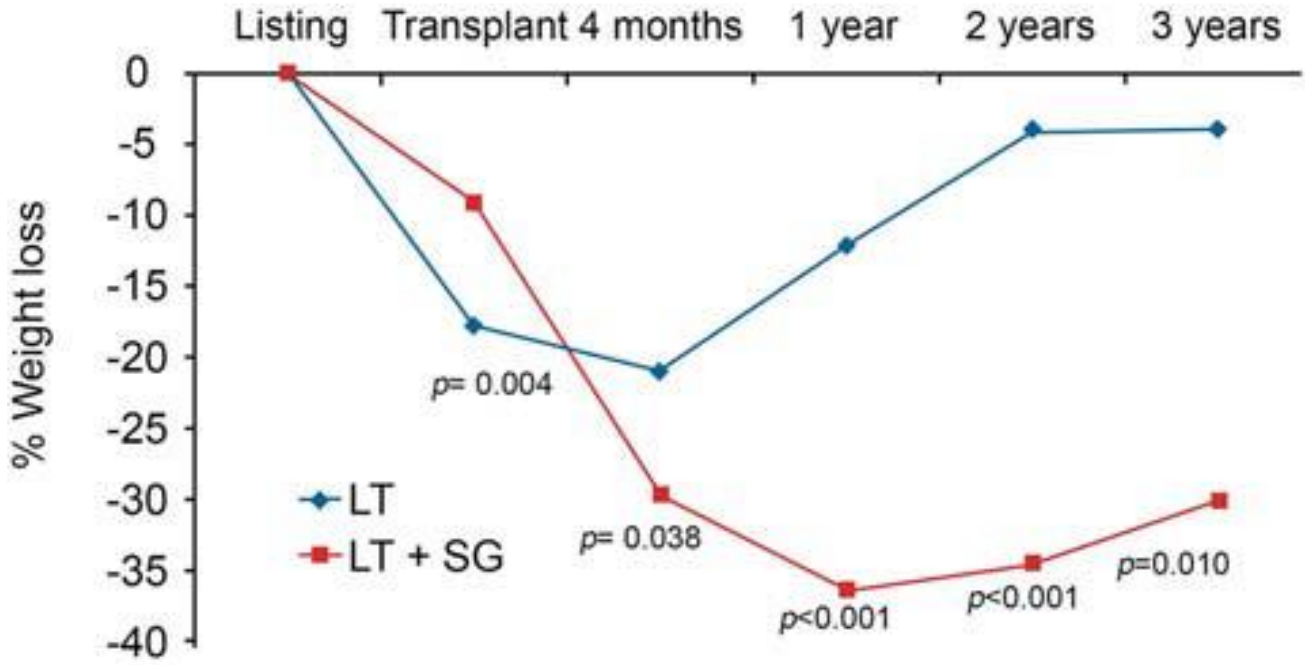



FIG. 1. Percentage of total body weight loss among patients who underwent medical therapy followed by LT (blue line) and those who underwent LT 1 SG (red line) at listing, transplant, 4 months, 1, 2, and 3 years.

# *Delayed Sleeve Gastrectomy following OLTx: a 5 yr experience. Morris et al. Liver Transplantation 8/2019*

- Retrospective. 15 patients. Underwent laparoscopic SG following LT. Median time from LT to LSG was 2.2 yrs with median f/u of 2.6yrs.
- All but 1 pt with dx NASH prior to LT.
- Median age 59, 86% Caucasian, 60% F.
- Median LOS 2 d after LSG.
- Mortality and ACR 0.
- Similar LOS, ICU stay, 30d complications between post-LT and non-LT undergoing LSG. Post-LT pts with longer f/u and higher blood loss.
- 1 post op complication: surgical site infection.
- Following LSG, BMI decreased from 43 to 36. At 1 yr f/u, 12 pts with TBW loss 21%.
- 60% d/ced insulin.
- **Post –LT pts had similar decrease in BMI and reduction in comorbidities at 1 yr compared with matched non-LT cohort.**

# LSG vs RYGB in post-LT

- LSG less risk of operative complications.
- Altered drug absorption (IS), hypovitaminosis associated with RYGB.
- Preserved access to biliary tree in LSG for potential need for ERCP of allograft liver.

# Summary

- Subset of patients with NAFL develop NASH, cirrhosis and HCC.
- Early identification of those at risk is key. Co-morbidities, FH. Screen those at high risk.
- Multi-hit pathways: environmental, genetic.
- Pharmaceutical agents: few available, lots in the pipeline. Stayed tuned!
- **Weight loss has been shown time and time again to work**. 5% TBW reverses steatosis, 7-10% reverses inflammation and fibrosis.
- Growing problem. Patients are younger and sicker.
- OLTx is not the definitive answer. Prevention is.
- Endo-bariatrics and gastric bypass: a good option in the right candidate.
- Patients need a multidisciplinary approach: primary care, hepatology, endocrine, medical weight loss, bariatrics, endo-bariatrics, nutrition, psychiatry.

# Thank You!