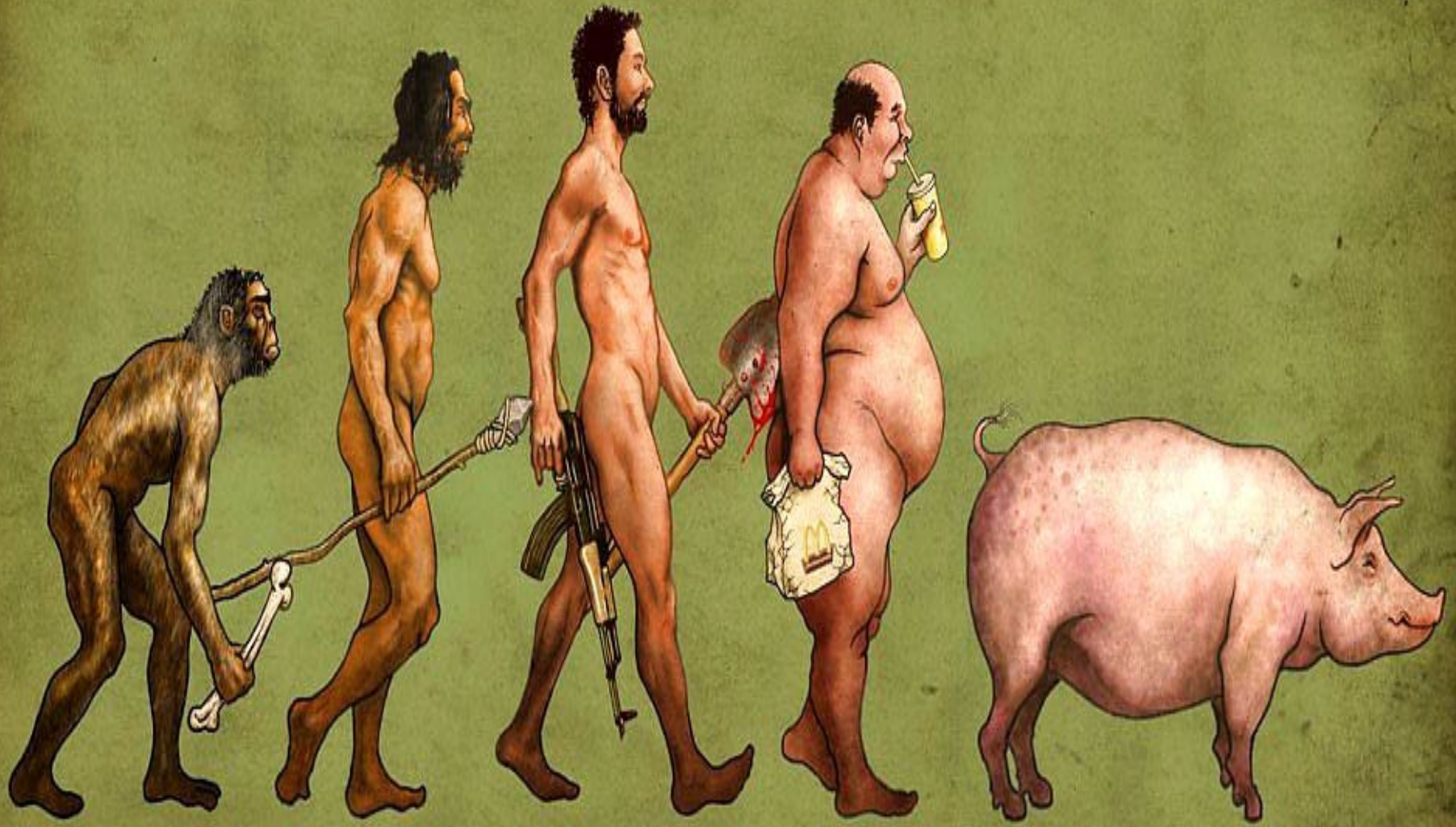
Fatty Liver- What the Primary Care Provider Needs to Know

Lucy Mathew, NP, MSN
Cedars-Sinai Medical Center

* 1. presentation
* 2. work up to establish the diagnosis
* 3. risk factors
* 4. assessment of fibrosis
* 5. referral and treatment



Updates in Nomenclature

Non-alcoholic fatty liver disease (NAFLD)

↓

Metabolic dysfunction-associated steatotic liver disease (**MASLD**)

Non-alcoholic steatohepatitis (NASH)

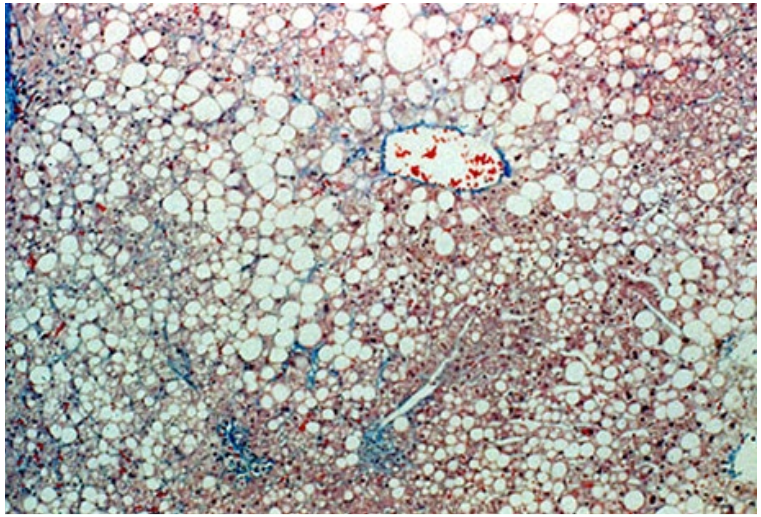
↓

Metabolic dysfunction-associated steatohepatitis (**MASH**)

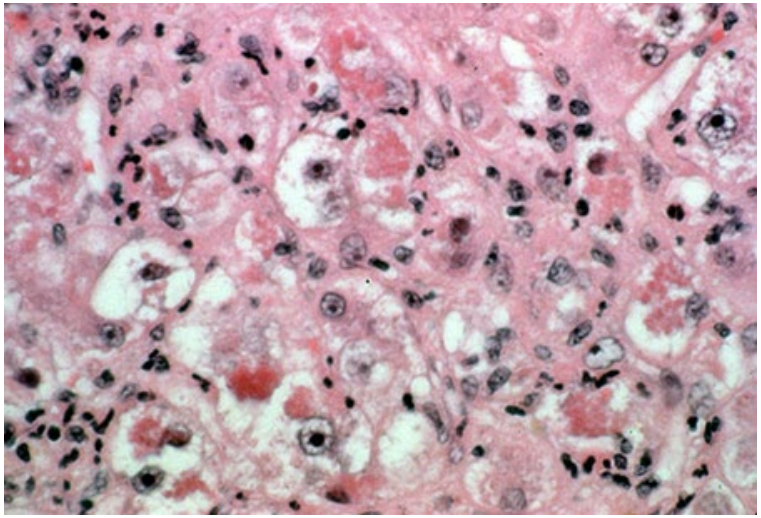
*In the absence of cardiometabolic risk factors, rule out other etiologies of non-alcoholic steatotic liver disease (drug-induced, lysosomal acid lipase deficiency, Wilson disease, celiac disease, malnutrition, inborn errors of metabolism, hypobetalipoproteinemia, environmental exposure, HIV, etc.)

Rinella et al., Hepatol. 2023; 79: 1542-1556

MASLD vs. MASH

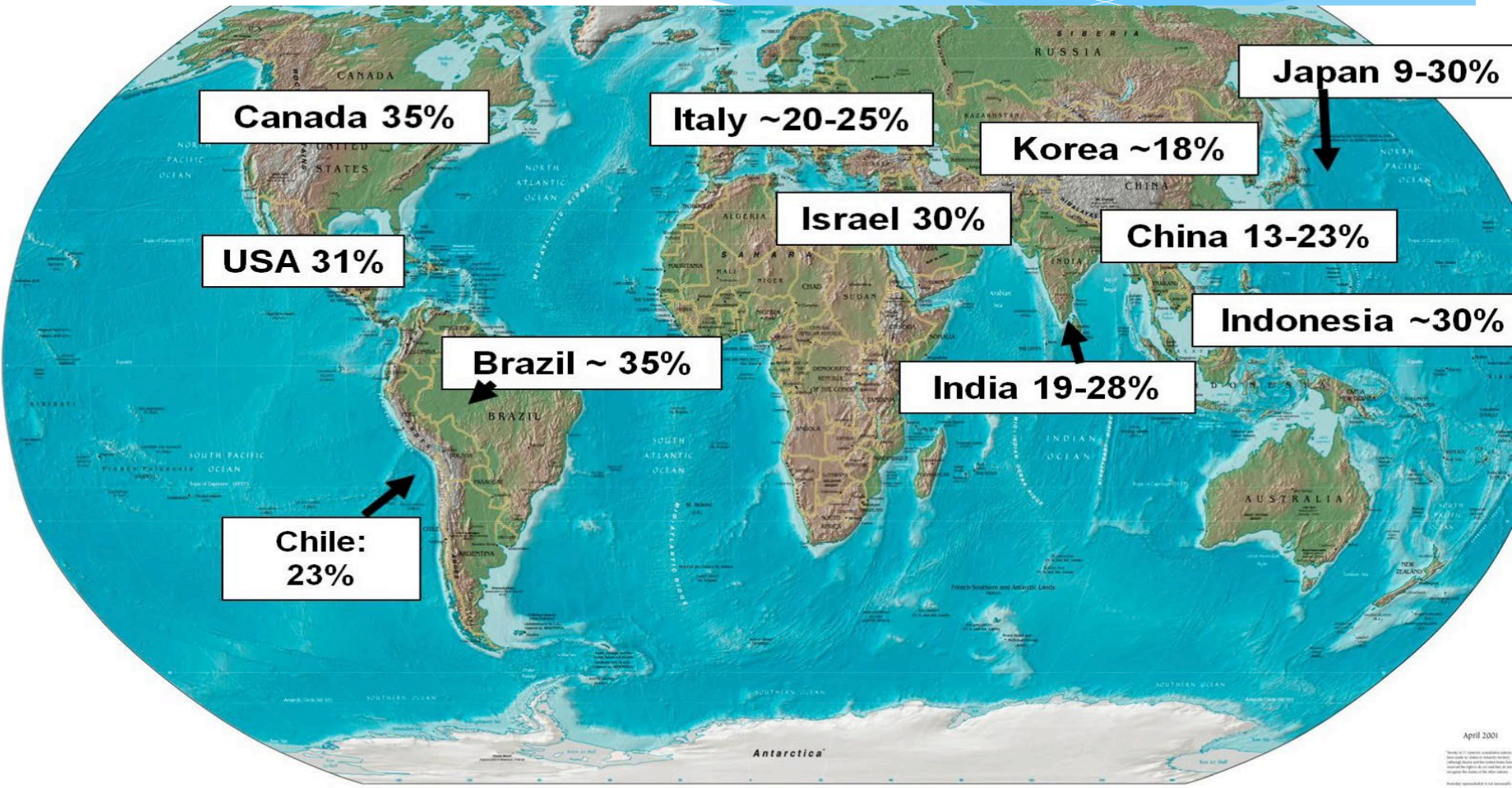


Steatosis



Steatohepatitis

NAFLD: A Global Epidemic



Fatty Liver- why is it important?

* Fatty liver can progress to cirrhosis, liver Cancer and liver failure
* MASH is the most common reason for chronic liver disease and cirrhosis in the US
* MASLD is related to cardiovascular disease and death
* #1 reason for liver transplant among women in the US

Hepatology 77(5):p 1797-1835, May 2023

MASLD Prevalence in US

Prevalence of MASLD

- General U.S. population: 30-46%
- DM2: 58%
- Morbidly obese: 90%
- Lean: 7-30% (higher among Asians)

Hepatology 77(5):p 1797-1835, May 2023

CEDARS-SINAI

Initial presentation

Abnormal Liver enzyme in blood test

OR

Fatty liver on US, CT or MRI done for non liver reason

Initial Evaluation- Abnormal liver test

- Look for all causes
- Hepatitis B – HBV surface antigen
- Hepatitis C – HCV antibody
- Autoimmune hepatitis – ANA, Anti-smooth muscle antibody
- Iron overload – ferritin, iron, % saturation
- Liver Imaging – yields diagnosis of MASLD
  - Ultrasound: 70% sensitivity
  - CT/MRI: 90% sensitivity

Hepatology 77(5):p 1797-1835, May 2023

Alternate Causes of MASLD

Alcohol (>21 drinks/wk in men, >14 drinks/wk in women;)

Hepatitis C (genotype 3)

Wilson's disease

Medications:

Amiodarone, methotrexate, prednisone, tamoxifen, valproic acid, HAART therapy

Celiac disease

Parenteral Nutrition

Discovered fatty liver on Imaging

Patient found to have Fatty liver incidentally on abdominal imaging

Test liver biochemistries:

- If normal consider testing for metabolic syndrome risk factors, but no further workup
- If abnormal liver test, perform liver injury evaluation

When to refer for biopsy?

- Confirm or aid in determining diagnosis

- Provide information which will lead to change in management or treatment

Lysosomal Acid Lipase Deficiency (LALD)

Wolman's disease (infants) ; cholesterol ester storage disease (adults))

- A rare systemic disease characterized by decreased LAL enzyme activity
- Results in intracellular accumulation of lipids
- Micro vesicular steatosis on biopsy, very high cholesterol level, not always obese.
- Reported in children most often but ranges up to age 68 in adults
- Effectively treated now with an FDA-approved compound : Kanuma IV

Hepatology 77(5):p 1797-1835, May 2023

LAL D (continued)

- Look for in non-obese patients with unexplained persistently elevated liver tests or unexplained hepatomegaly or any patient with cryptogenic cirrhosis or microvesicular steatosis on liver bx
- Usually with LDL> 160 mg/dl and HDL < 40 mg/dl (or <50 mg/dl in females)
- Diagnose with an enzymatic blood test that is commercially available (Lab Corps, Seattle Children's or Mayo Labs)

Staging Fibrosis

- Fibrosis is the best predictor of fibrosis
- Determine prognosis
- HCC screening (all patients with cirrhosis need q6 month ultrasound)
- Screening for varices
- Mortality risk for surgery

Noninvasive Fibrosis Staging

- Standard imaging:
  - Specificity high, though insensitive
- Platelet count <150
- NAFLD fibrosis score, FIB-4,
- Fibroscan
- MR Elastography

Labs

* Albumin, Total bili, INR
* Platelet <150
* Cirrhosis results in portal congestion- splenomegaly- platelet sequestration- low platelet
* Decreased thrombopoietin production- low platelet

Fibrosis-4 (FIB-4) Calculator

Share

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}} =$$

Interpretation:

Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Transient Elastography

Fibroscan/ Mindray

- Non-invasive estimate of liver fibrosis by measuring shear wave velocity which is then converted liver stiffness
- Duration of test 10 minutes
- Patient needs to fast 4-6 hours prior to exam
- 85% sensitivity and specificity compared to gold standard (biopsy)

CEDARS-SINAI

MR Elastography

* MRI without contrast
* Measures fat and fibrosis
* Only available in certain centers
* Expensive test- insurance
* Accuracy better than fibroscan

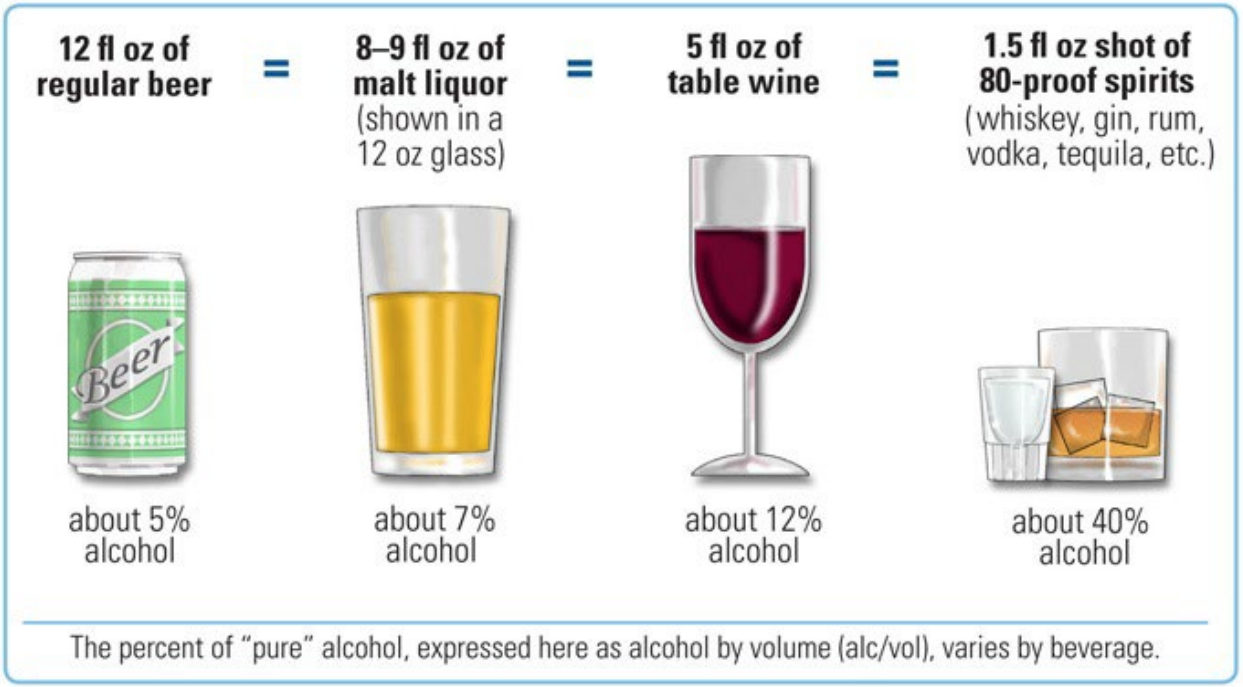
MASLD

* Diagnosis confirmed?
* Elevated liver enzyme?
* Fibrosis?
* Metabolic syndrome?
* Contributing factors?

Treatment

- Weight loss/lifestyle modification
- Anti-diabetic medications
- Lipid lowering agents
- Antioxidants
- The future is now!!!

One Drink!


12 fl oz of regular beer
=
8–9 fl oz of malt liquor (shown in a 12 oz glass)
=
5 fl oz of table wine
=
1.5 fl oz shot of 80-proof spirits (whiskey, gin, rum, vodka, tequila, etc.)
Beer
about 5% alcohol
about 7% alcohol
about 12% alcohol
about 40% alcohol
The percent of "pure" alcohol, expressed here as alcohol by volume (alc/vol), varies by beverage.

Weight loss

- First line treatment in all patients with MASLD/MASH
- Goal is loss of 7-10% body fat
- Weight loss should not be rapid, but paced at 1-2 pounds per week
  - Rapid weight loss through crash diet can worsen fatty liver.
- Body mass index not ideal target
  - Does not measure visceral adipose tissue
  - Does not account for percentage of muscle tissue

Dietary Modification

- No specific diet found to be superior; goal is overall weight loss of 7-10% body fat
- Patients should have deficit of 400-500 calories/day to yield 1 pound weight loss/week
- High amounts of fructose containing foods (sodas, fruit-juices) can worsen liver fibrosis
  - Analysis of 427 MASH patients demonstrated greater than 7 servings of fructose/week increases fibrosis
- Greater than 10% of saturated fats in diet may worsen insulin resistance and liver steatosis

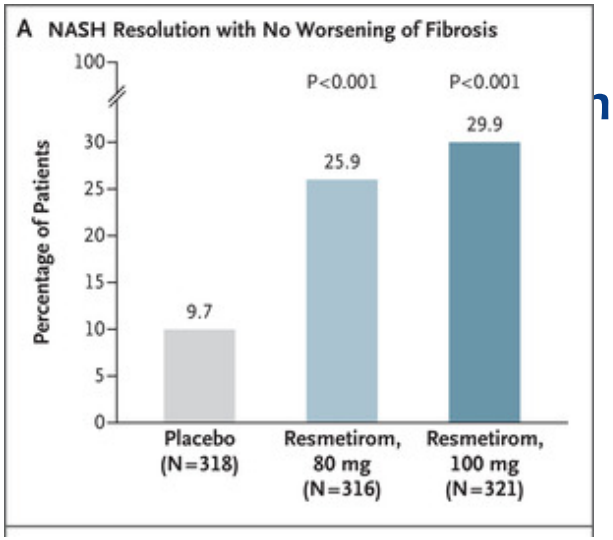
Coffee

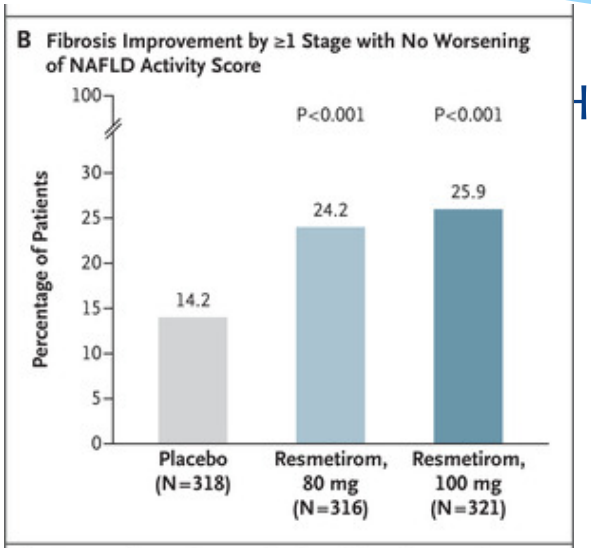
- Molloy et al: reduced hepatic fibrosis in MASH patients when drinking 1-2 cups of caffeinated coffee a day
- Additional study comparing coffee to espresso did not show same benefits in espresso drinkers
  - It's not the caffeine specifically which is beneficial
  - May be helpful in decreasing HCC risk
- If no other contraindications, recommend 2-3 cups of black coffee daily

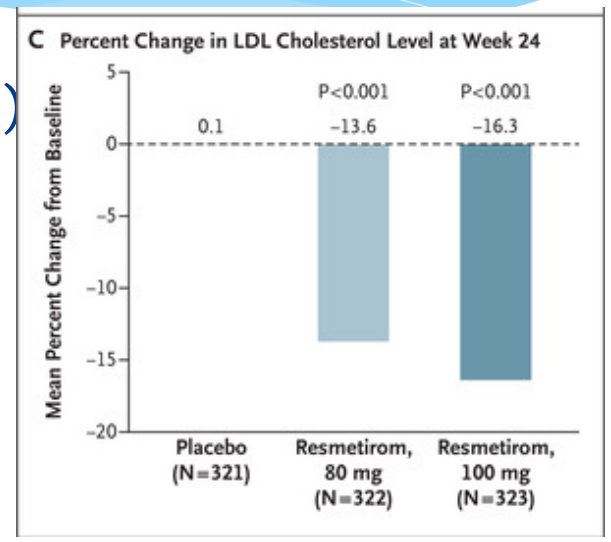
Exercise

- Study of 1267 patients with biopsy proven MASH found 54% were sedentary
- Exercise can reduce hepatic steatosis even without diet modification or weight loss
- Exercise associated with a reduction in hepatic fat even in the **absence** of weight loss
- Studies recommend 3 hours/week of moderate to vigorous exercise, incorporating aerobic and resistance training
- Exercise should be done in 45 minute intervals 3-4x/week (150 min/week)

Thyroid Receptor-β Agonist

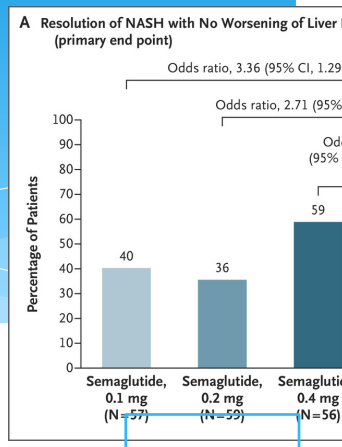






Adverse effects: GI side effects – diarrhea and nausea at treatment initiation

GLP-1 Receptor Agonist



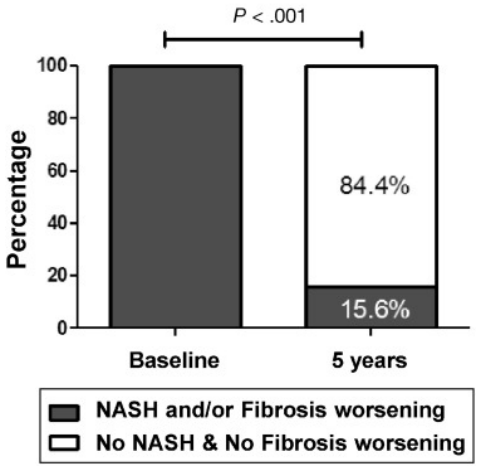
- **Semaglutide** (phase 2b): dose-dependent MASH resolution (59% vs 17%)
  - Fibrosis improvement but not statistically significant
  - Improved insulin sensitivity, weight loss (12.5%), stroke risk, CV/renal outcomes
  - Dose: 0.4 mg SC daily, 0.25 – 2.4 mg SC weekly
  - Consider in MASH without cirrhosis- not FDA approved
- **Tirzepatide** (phase 2: SYNERGY-NASH): improves steatosis (8%) and insulin sensitivity, promotes weight loss (20% vs 3 %)
  - Consider in T2DM or obesity with MASLD
- **Liraglutide** (phase 2: LEAN): improves steatosis and insulin sensitivity, resolves MASH, reduces fibrosis progression
  - Dose: 1.8 mg SC daily (T2DM), 0.6-3 mg SC daily (obesity)
  - Consider in MASH without cirrhosis- not FDA approved

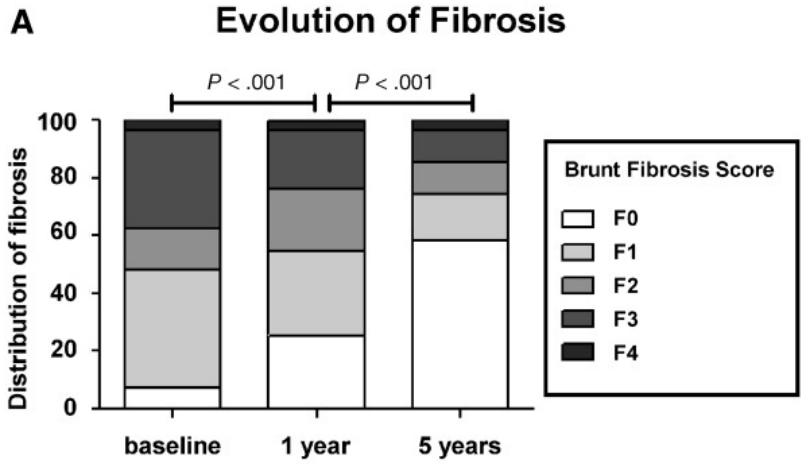
Adverse effects: GI side effects, gallstones (related to weight loss), pancreatitis

Newsome et al., N Engl J Med. 2021 Mar 25;384(12):1113-1124
Armstrong et al., Lancet. 2016;387:679–90
Gastaldelli et al., Lancet Diabetes Endocrinol. 2022;10:393–406

Bariatric Surgery

- Bariatric surgery can resolve MASH, improve hepatic fibrosis, induce sustained weight loss of up to 30%, cure diabetes, and decrease all-cause morbidity and mortality
- 1 year post-bariatric surgery, 80% of patients had resolution of MASH without worsening fibrosis
  - Maintained at 5 years





Subichin et al., Surg Obes Relat Dis. 2015; 11: 137-141
Fakhry et al., Surg Obes Relat Dis. 2019 Mar;15(3):502-511
Jirapinyo et al., Clin Gastroenterol Hepatol. 2022 Mar;20(3):511-524.e1

Vitamin E

- Sanyal et al, NEJM 2010
  - 247 patients with biopsy proven MASH randomized to vitamin E 800 units daily, Actos 30mg daily or placebo
  - Both Actos and Vitamin E improved liver inflammation and hepatic steatosis, but Vitamin E superior
- Concerns
  - Possible risk for cardiovascular disease and prostate cancer
  - Study did not enroll diabetic or cirrhotic patients
- For patients with MASH on biopsy and without diabetes and without cirrhosis, recommendation is vitamin E 800 units daily
- Remember, it is a supplement and NOT alternative to weight loss

Lipid Lowering Agents

- Statins:
  - In MASH, studies limited to pilot trials showing minimal benefits
  - However, many patients with fatty liver have risk factors for CV disease and should be on a statin if appropriate
  - Statins are SAFE in liver disease
    - Study demonstrated that 2% of drug induced liver injury from statins
- Omega-3 fatty acid supplementation (fish oil)
  - In animal models, shown to improve insulin resistance and reduce liver steatosis
  - Small RCT's have shown improvement in steatosis, ALT and serum triglyceride levels
  - Evidence is lacking to recommend for all patients, but appears to be beneficial

Medicines/ supplements

* Avoid supplements and herbs in general
* Liver tox website is recommended
* https://www.ncbi.nlm.nih.gov/books/NBK547852/
* When in doubt, check liver enzyme one month, 3 months and 6 months after starting a new medicine.
* Limit Acetaminophen to less than 2000 mg /day
* Safe to take occasional Tylenol even in patients with cirrhosis.

Take-Home Points

- MASH cirrhosis is a real epidemic which can be stopped
- Requires screening in high-risk patients (diabetics, obese, metabolic syndrome) and counseling regarding seriousness of disease
- Lifestyle changes are the foundation of any treatment plan:
  - Weight loss ≥ 3% to 10% associated with histologic improvement in MASLD
  - Minimize fructose containing foods
  - Consider Mediterranean diet and 2-3 cups of coffee daily

CEDARS-SINAI

Take-Home Points

- Interventions beyond weight loss:
  - GLP-1 receptor Agonist
  - Thyroid Receptor Beta Agonist
  - Vitamin E
  - Coffee
  - Control of metabolic syndrome
- More Investigational therapies on the way, but refer for clinical trial if moderate fibrosis

CEDARS-SINAI