



South Carolina  
Gastroenterology  
Association  
FOUNDATION

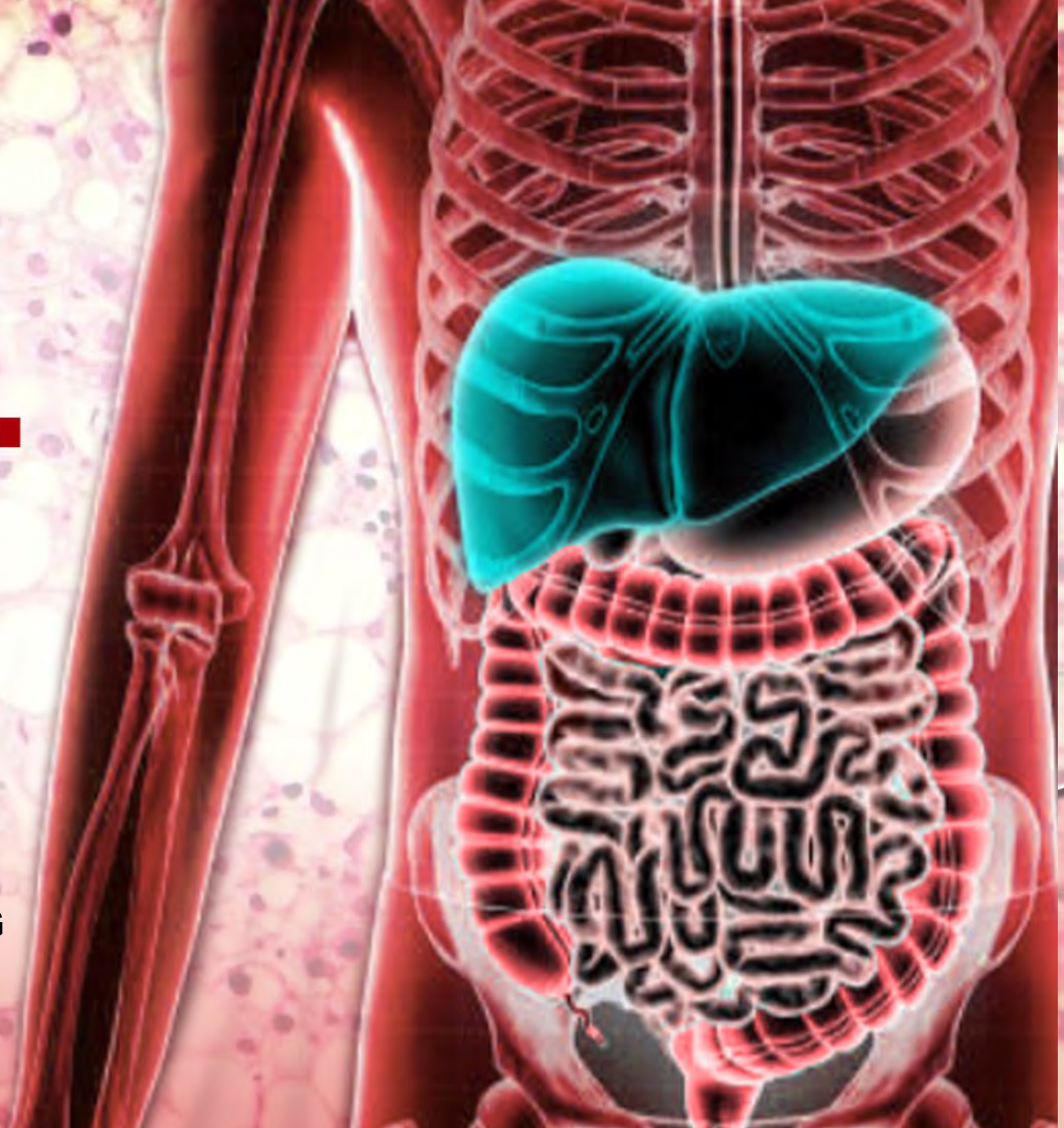
**HOT TOPIC...**

**FATTY LIVER  
DISEASE**

**BRYAN GREEN MD**

**SC MEDICAL ASSOCIATION ANNUAL MEETING**

**APRIL 25, 2024**



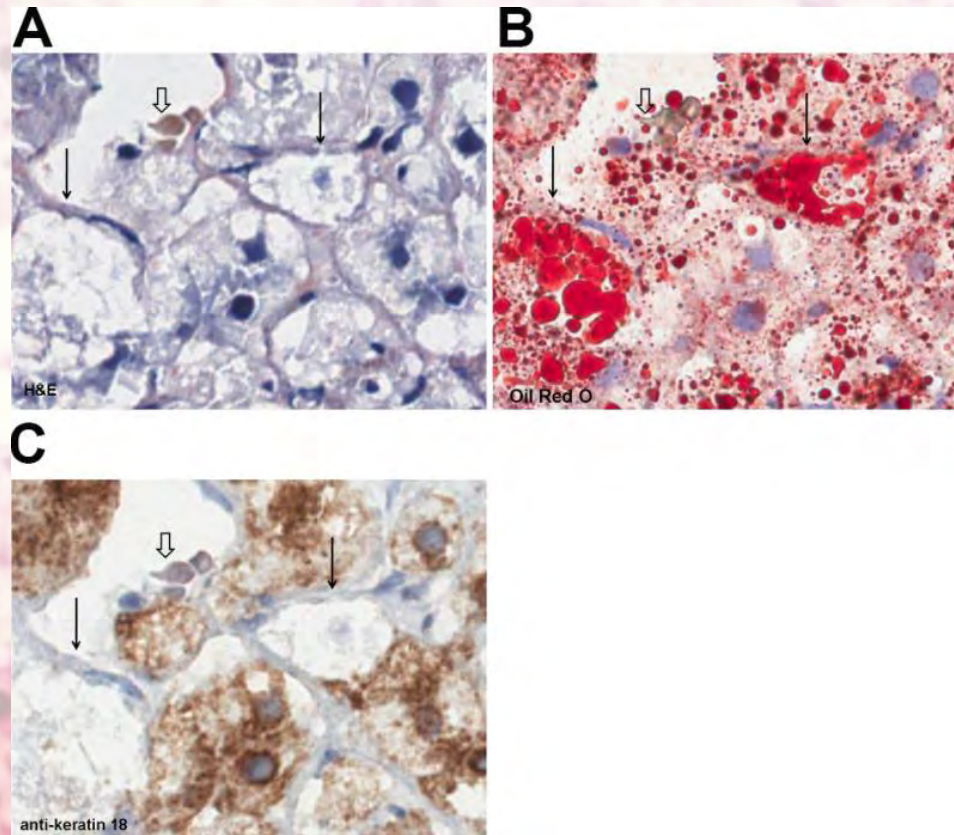


# TERMINOLOGY

- **NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)**
  - **>5% HEPATOCYTES MACROVESICULAR STEATOSIS IN ABSENCE OF ALTERNATIVE CAUSES IN PATIENTS WITH LITTLE ETOH INTAKE (<20 G/D WOMEN ,30 G/D MEN)**
- **NONALCOHOLIC STEATOHEPATITIS (NASH)**
  - **INFLAMMATION WITH CELLULAR INJURY (BALLOONING) WITH/WITHOUT FIBROSIS**



# BALLOONING HEPATOCYTES









# **NEW TERMINOLOGY**

- **METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)**
  - **PREVIOUSLY- NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)**
- **METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)**
  - **PREVIOUSLY – NONALCOHOLIC STEATOHEPATITIS (NASH)**



**(MASH) (NASH)- NOT MASHED POTATOES**





# PREVALENCE

- **INCREASING WORLDWIDE ALONG WITH DM, OBESITY, METABOLIC DYSFUNCTION**
- **NAFLD- 25-30% GENERAL POPULATION**
  - **SOUTH CAROLINA- 35% OBESE 15% DM**
- **NASH- 14% GENERAL POPULATION**
- **EXPECT 2-3 FOLD INCREASE BY 2030**
- **NASH CIRRHOSIS #1 INDICATION LIVER TRANSPLANT**



# NATURAL HISTORY

- **STEATOHEPATITIS AND FIBROSIS PRIMARY PREDICTORS OF PROGRESSION**
  - **STAGE 2 FIBROSIS “AT RISK” NASH - HIGHER RATE LIVER RELATED MORBIDITY AND MORTALITY**
  - **NAFLD- PROGRESSION OF ONE STAGE IN 14 YEARS**
  - **NASH PROGRESSION OF ONE STAGE IN 7 YEARS**
- **SINGH AJ CLIN GASTROENTEROL HEPATOL. 2015;13:643-54**



# SEVERITY OF DISEASE

- **GOLD STANDARD LIVER BIOPSY**
- **GRADE- DEGREE OF INFLAMMATION PRESENT**
  - **1- MILD**
  - **2-MODERATE**
  - **3- SEVERE**
- **STAGE- AMOUNT OF FIBROSIS (SCARRING)**
  - **1- MILD- , 2-MODERATE, 3- SEVERE**

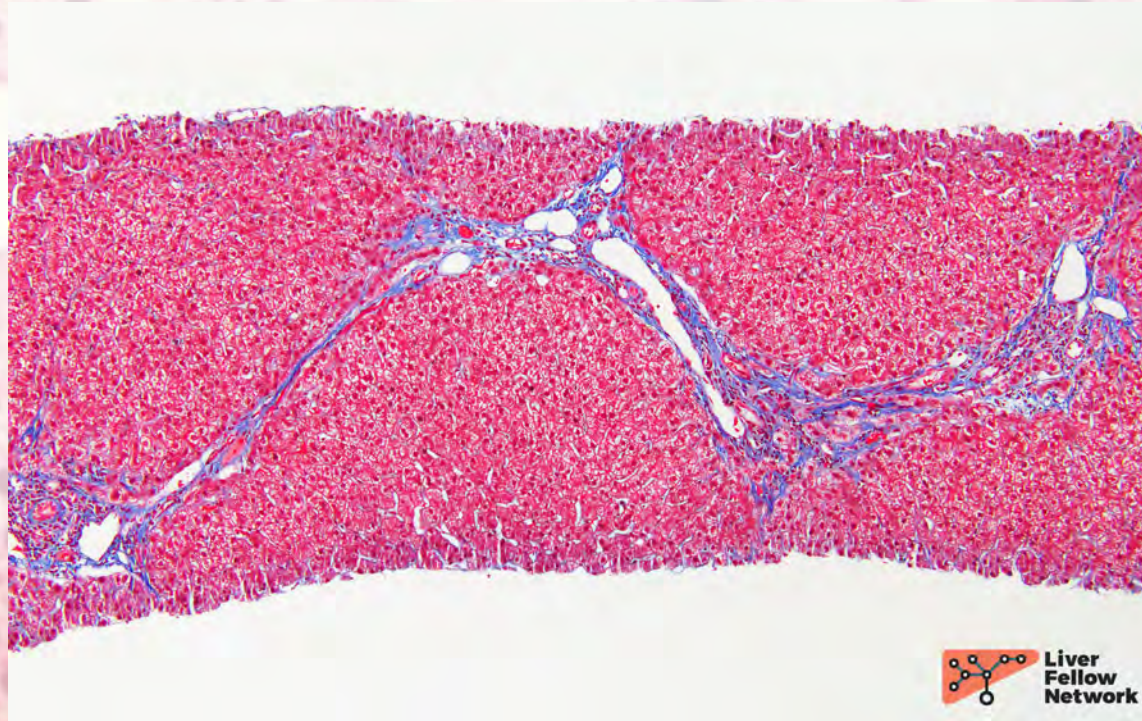


# SEVERITY OF DISEASE

- **STAGE- AMOUNT OF FIBROSIS (SCARRING)**
  - **1- MILD- PERICELLULAR FIBROSIS**
  - **2-MODERATE- PERICELLULAR FIBROSIS AND PERIPORTAL FIBROSIS**
  - **3- SEVERE- PERICELLULAR FIBROSIS AND PERIPORTAL FIBROSIS AND BRIDGING FIBROSIS**
  - **4 –CIRRHOSIS**



# NASH STAGE 3- BRIDGING FIBROSIS







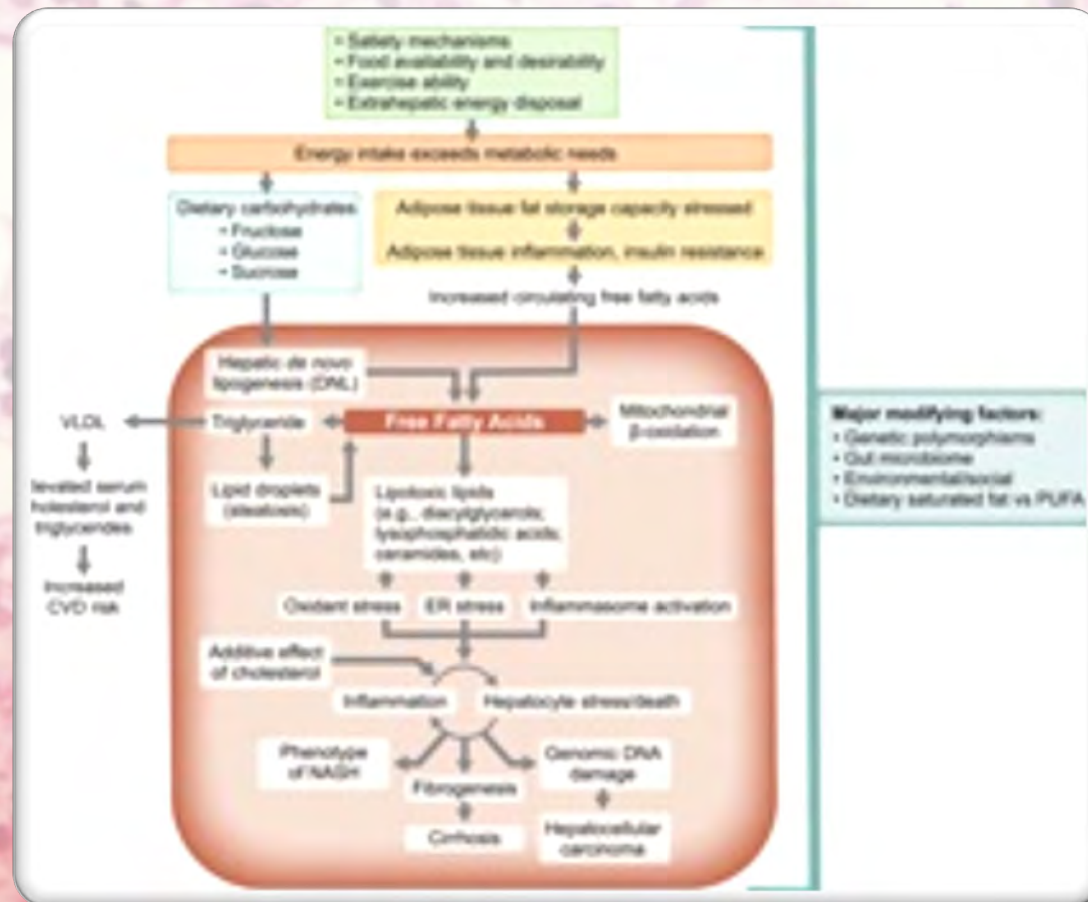


# NATURAL HISTORY

- **MOST COMMON CAUSES OF DEATH**
  - **NAFLD AND NASH WITH UP TO F1 FIBROSIS**
    - **CARDIOVASCULAR DISEASE AND NON HEPATIC MALIGNANCIES**
- **“AT RISK “ NASH STAGES 2-4**
  - **LIVER DISEASE**



# CELLULAR AND MOLECULAR PATHOGENESIS





# **COMORBID CONDITIONS NAFLD**

- **OBESITY-**
  - **ANDROID FAT DISTRIBUTION- TRUNCAL OBESITY AND VISCERAL FAT- WORSE**
  - **GYNOID FAT DISTRIBUTION- HIPS, BUTTOCKS, SUBCUTANEOUS FAT- PROTECTIVE**
- **TYPE 2 DIABETES MELLITUS (T2DM)**
  - **PREVALENCE OF 30% TO 70%**
  - **PREVALENCE OF FIBROSIS INCREASE WITH DURATION OF DIABETES**
  - **SHOULD BE SCREENED FOR ADVANCED FIBROSIS**
- **HYPERTENSION**



# **COMORBID CONDITIONS NAFLD**

- **DYSLIPIDEMIA**
  - **TWICE AS LIKELY THAN GENERAL POPULATION**
  - **STATINS (MODERATE TO HIGH INTENSITY)**
    - **SAFE EVEN WITH ADVANCED FIBROSIS, COMPENSATED CIRRHOSIS**
    - **REDUCE CARDIOVASCULAR MORTALITY**
    - **UNDERUTILIZED**
    - **MAY EVEN REDUCE PROGRESSION OF FIBROSIS (ATORVASTATIN)**
  - **FIBRATES AND OMEGA-3 FATTY ACIDS FOR HIGH TRIGLYCERIDES**



# **COMORBID CONDITIONS NAFLD**

- **HYPERTENSION**
  - **INCREASE IN FIBROSIS PROGRESSION**
- **CARDIOVASCULAR DISEASE (CVD)**
  - **MOST COMMON CAUSE OF DEATH IN PATIENTS WITH NAFLD**
  - **STRONG ASSOCIATION BUT UNCERTAIN IF NAFLD DRIVES CVD**



# **PRESENTATION**

- **INCIDENTAL HEPATIC STEATOSIS ON IMAGING**
- **ELEVATED LIVER CHEMISTRIES**



# **INITIAL EVALUATION AND DIAGNOSIS**

- **SCREEN FOR METABOLIC COMORBIDITIES**
- **AMOUNT OF ALCOHOL INTAKE**
- **IF CLINICAL PROFILE IS ATYPICAL (NOT ASSOCIATED WITH METABOLIC COMORBIDITIES)**
  - **CONSIDER OTHER CAUSES AND/OR REFER TO GI**
- **CONVENTIONAL ULTRASOUND LESS SENSITIVE FOR MILD STEATOSIS IN OBESE**
  - **ELASTOGRAPHY BETTER**



# **ROLE OF ALCOHOL CONSUMPTION**

- **MILD CONSUMPTION (UP TO 20 G WOMEN AND UP TO 30 G MEN PER DAY)**
  - **MAY BE PROTECTIVE**
- **MODERATE CONSUMPTION (21-39 G WOMEN AND 31-59 G MEN PER DAY)**
  - **INCREASES THE RATE OF ADVANCED FIBROSIS ( $\geq$ STAGE 2)**
  - **SYNERGISTIC WITH OBESITY AND DM 2**
- **PATIENTS WITH ADVANCED FIBROSIS ( $\geq$ STAGE 2)**
  - **ABSTAIN COMPLETELY**



# **LEAN NASH (BMI<25)**

- **PREVALENCE IN LEAN INDIVIDUALS 4%**
- **HIGHER IN ASIAN AND HISPANIC**
- **GENETIC FACTORS LIKELY**
- **TREATMENT- DIET ADJUSTMENT AND EXERCISE**



# **INITIAL EVALUATION WHO TO SCREEN FOR FIBROSIS**

- **IDENTIFY THOSE WITH SIGNIFICANT FIBROSIS (STAGE  $\geq 2$ )**
  - **T2DM**
  - **OBESITY WITH METABOLIC COMPLICATIONS**
  - **FAMILY HISTORY OF CIRRHOSIS**
    - **1 DEGREE RELATIVES PROBANDS WITH NASH CIRRHOSIS 12X HIGHER RISK FIBROSIS**
  - **MODERATE TO HIGH AMOUNTS ALCOHOL USE**



# **FIBROSIS SCREENING MODALITIES**

- **LIVER BIOPSY GOLD STANDARD**
  - **NOT CONSISTENTLY PERFORMED- RESERVE FOR SPECIFIC SCENARIOS**
- **NONINVASIVE BIOMARKERS-**
  - **FIB-4 ALGORITHM- AGE, ALT, AST, PLATELET COUNT**
  - **NAFLD FIBROSIS SCORE- CALCULATOR**
  - **AST PLATELET RATIO INDEX**



# **FIBROSIS SCREENING – BLOOD TESTS**

- **NONINVASIVE BIOMARKERS**
  - **ELF (ENHANCED LIVER FIBROSIS)-**
    - **PROPRIETARY BLOOD TEST- 3 BIOMARKERS**
  - **FIBROSURE- NASH**
    - **PROPRIETARY BLOOD TEST- 6 SERUM MARKERS AGE AND SEX**



# **FIBROSIS SCREENING - ELASTOGRAPHY**

- **LIVER STIFFNESS- INCREASES WITH FIBROSIS SEVERITY**
- **FIBROSCAN**
  - **POINT OF CARE**
  - **WIDELY VALIDATED AND PREDICTIVE**
- **ULTRASOUND BASED ELASTOGRAPHY**
  - **LESS WELL VALIDATED**
- **MAGNETIC RESONANCE ELASTOGRAPHY (MRE)**
  - **MOST SENSITIVE, ACCURATE AND MOST EXPENSIVE**



# TREATMENT

- **WEIGHT LOSS**
- **HEALTHY DIET AND EXERCISE**
- **OPTIMIZATION OF COMORBID METABOLIC CONDITIONS**
- **MEDICATIONS**



# WEIGHT LOSS

- **REQUIRES  $\geq 10\%$  TO IMPROVE FIBROSIS**
- **$< 10\%$  PATIENTS CAN ACHIEVE DESPITE STRUCTURED PROGRAMS AT 1 YEAR**
- **$< 5\%$  PATIENTS CAN MAINTAIN THAT WEIGHT LOSS AT 5 YEARS**



# DIET

- **EXCESS CALORIES PARTICULARLY**
  - **SATURATED FATS**
  - **REFINED CARBS**
  - **SUGAR SWEETENED BEVERAGES**
- **EXCESS FRUCTOSE CONSUMPTION**
  - **INCREASE RISK OF ADVANCED FIBROSIS INDEPENDENT OF CALORIE INTAKE**



# DIETS

- **LOW CARB VS LOW FAT DIETS**
- **SATURATED VS UNSATURATED FAT DIETS**
- **INTERMITTENT FASTING**
- **MEDITERRANEAN DIET**
- **DIFFERENT INTENSITIES OF CALORIE RESTRICTION**
  
- **ALL COMPARABLE IN EFFECTIVENESS**



# COFFEE

- **3 OR MORE CUPS**
  - **REDUCED RISK OF NAFLD AND FIBROSIS IN EPIDEMIOLOGICAL STUDIES AND META-ANALYSES**





# COFFEE





# EXERCISE

- **INDEPENDENT OF WEIGHT LOSS HAS HEPATIC AND CARDIOMETABOLIC BENEFITS**
- **MODERATE EXERCISE**
  - **5X WEEK FOR 30 MINUTES**
  - **TOTAL OF 150 MINUTES**
  - **OR INCREASE OF 60 MINUTES PER WEEK**



# **BARIATRIC SURGERY**

- **VAST MAJORITY OF BARIATRIC PATIENTS HAVE NAFLD**
- **NASH RESOLVES IN UP TO 80% OF PATIENTS 1 YEAR POST OP**
- **MALABSORPTIVE PROCEDURES BETTER THAN RESTRICTIVE**
- **ROLE IN WELL COMPENSATED NASH CIRRHOSIS?**
- **NO ROLE IN DECOMPENSATED NASH CIRRHOSIS**



# **MEDICATIONS- NOT FDA APPROVED**

- **VITAMIN E 800 IU DAILY**
  - **REDUCES ALT**
  - **IMPROVES HISTOLOGY-**
    - **LESS STEATOSIS, INFLAMMATION, BALLOONING**
  - **CONFIRMED IN META-ANALYSIS**
  - **UNCERTAIN IF REDUCES FIBROSIS**
  - **DOES LOWER RATE OF DECOMPENSATION**
  - **RISKS OF BLEEDING?**



# **MEDICATIONS**

- **PIOGLITAZONE (THIAZOLIDINEDIONES)**
  - **ONLY FOR PATIENTS WITH DIABETES**
  - **IMPROVES HISTOLOGY AND INSULIN RESISTANCE**
  - **NASH RESOLUTION IN UP TO 40%**
  - **META-ANALYSIS SOME FIBROSIS IMPROVEMENT**
  - **POTENTIAL SIDE EFFECTS- WEIGHT GAIN, HEART FAILURE AND FRACTURES**



# MEDICATIONS

- **GLP-1RAS**
- **LIRAGLUTIDE-**
  - **SMALL STUDY- RESOLVED NASH (40% VS 9%) AND REDUCED FIBROSIS PROGRESSION (9% VS 36%)**
- **SEMAGLUTIDE**
  - **DOSE DEPENDENT (0.4 MG DAILY)**
  - **LARGE STUDY- RESOLVED NASH (59% VS 17%) NO AFFECT ON FIBROSIS**
  - **MORES STUDIES UNDERWAY**



# UNCERTAIN BENEFIT

- **ATORVASTATIN**
  - **SMALL STUDY- AFTER 3 YEARS NAFLD ON IMAGING RESOLVED (66% VS 30%)**
- **OMEGA 3 FATTY ACIDS**
  - **SOME IMPROVEMENT IN STEATOSIS AND TRANSAMINASES**
- **ASPIRIN**
  - **DAILY USERS LESS LIKELY TO HAVE NASH AT BASELINE AND LESS LIKELY TO PROGRESS**



# FDA APPROVED MEDICATION





# **FDA APPROVED MEDICATION**

- **RESMETIROM (MADRIGAL PHARMACEUTICALS)**
  - **REZDIFFRA**
- **MAESTRO-NASH TRIAL (N ENGL J MED 2024; 390:497-509)**
- **ORAL THYROID HORMONE RECEPTOR BETA SELECTIVE AGONIST**
- **996 PATIENTS RANDOMIZED TO 80MG, 100MG, OR PLACEBO**



# **RESMETIROM (REZDIFFRA)**

- **NASH RESOLUTION WITH NO WORSENING OF FIBROSIS**
  - **25.9%- 60 MG**
  - **29.9%- 80 MG**
  - **9.7% PLACEBO**
- **FIBROSIS IMPROVEMENT BY AT LEAST ONE STAGE**
  - **24.2%- 60 MG**
  - **25.9%- 80 MG**
  - **14.2% PLACEBO**







# **SUMMARY PREVALENCE AND BURDEN**

- **NAFLD- 25-30% NASH- 14% GENERAL POPULATION**
  - **SOUTH CAROLINA- 35% OBESE 15% DM**
- **EXPECT 2-3 FOLD INCREASE BY 2030**
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# **SUMMARY**

## **RECOGNITION AND DIAGNOSIS**

- **RISK FACTORS- OBESITY, DM, METABOLIC SYNDROME**
- **STEATOSIS ON IMAGING AND/OR ABNORMAL TRANSAMINASES**
- **SCREEN FOR FIBROSIS**
  - **T2DM**
  - **OBESITY WITH METABOLIC COMPLICATIONS**
  - **FAMILY HISTORY OF CIRRHOSIS**
  - **MODERATE TO HIGH AMOUNTS ALCOHOL USE**



# **SUMMARY**

## **FIBROSIS SCREENING**

- **FIB-4 ALGORITHM**
- **NAFLD FIBROSIS SCORE – CALCULATOR**
- **ELF (ENHANCED LIVER FIBROSIS) - BLOOD TEST**
- **FIBROSURE - BLOOD TEST**
- **ULTRASOUND BASED ELASTOGRAPHY**
- **FIBROSCAN**



# **SUMMARY TREATMENT**

- **WEIGHT LOSS ( $\geq 10\%$  TO REVERSE FIBROSIS)**
- **DIET(S)- WHICHEVER GETS THE WEIGHT OFF**
- **EXERCISE- 5X WEEK FOR 30 MINUTES (150 MINUTES)**
- **COFFEE**
- **VITAMIN E**
- **LIRAGLUTIDE AND SEMAGLUTIDE OBESITY DOSE**
- **RESMETIROM (REZDIFFRA)**





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# HOT TOPIC...

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