TERMINOLOGY

- NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)
  - >5% HEPATOCYTES MACOVESICULAR 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 (>STAGE 2)
  • SYNERGISTIC WITH OBESITY AND DM 2

• PATIENTS WITH ADVANCED FIBROSIS (>STAGE 2)
  • ABSTAIN COMPLETELY
LEAN NASH (BMI<25)

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

WHO TO SCREEN FOR FIBROSIS

• IDENTIFY THOSE WITH SIGNIFICANT FIBROSIS (STAGE ≥2)
  • T2DM
  • OBESITY WITH METABOLIC COMPLICATIONS
  • FAMILY HISTORY OF CIRRHOSIS
    • 1DEGREE 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 ≥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
• NASH CIRRHOSIS #1 INDICATION LIVER TRANSPLANT
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 (>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)
HOT TOPIC...

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