



FATTY LIVER

WHAT YOU NEED TO KNOW AND WHEN TO WORRY

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GASTROENTEROLOGY

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CONFLICT OF INTEREST AND DISCLOSURES

Financial Interest or Affiliation	Commercial Enterprise(s)
Financial Disclosure	
Advisory Board or similar committee	AbbVie, Janssen, Lupin, Gilead, Ferring
Clinical trials or studies	
Honoraria or other fees (e.g., travel support)	AbbVie, Allergan, Shire,
Research grants	
Other (specify)	

OBJECTIVES

- REVIEW EPIDEMIOLOGY AND NATURAL HISTORY OF FATTY LIVER
- DISCUSS LIFESTYLE MODIFICATIONS AND ROLE THEY PLAY IN TREATING FATTY LIVER
- HIGHLIGHT RED FLAGS IN HISTORY AND WORK UP WHICH CAN BE SEEN IN ADVANCED DISEASE
- THERAPEUTIC OPTIONS IN THE TREATMENT OF FATTY LIVER

CASE- DONALD

- 50 YEAR OLD MALE WITH RIGHT UPPER QUADRANT/FLANK PAIN IN ER
- BMI 34
- HISTORY OF TYPE 2 DIABETES, AND DYSLIPIDEMIA
 - CURRENTLY ON METFORMIN AND A STATIN
- RECENTLY PASSED A KIDNEY STONE
- RECENT BW ALT- 80 IU/L AND AST 90 IU/L. T BILI 12 AND ALK PHOS 108
- CBC- HBG 148, PLATELETS 190
- U/S – KIDNEY STONES AND MODERATE FATTY LIVER



CASE- DONALD

- DONALD ASKS WHETHER HIS R FLANK PAIN MAY BE DUE TO HIS FATTY LIVER
- HE HAS MANY QUESTIONS IN REGARD TO FATTY LIVER

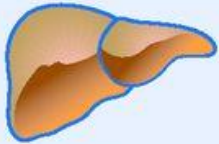
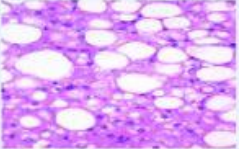

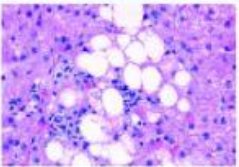
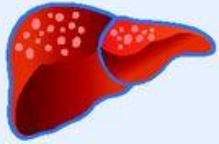
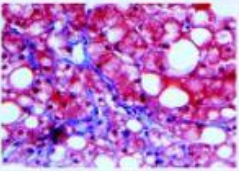

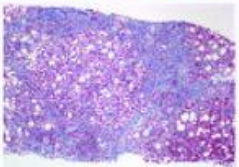
- IS HIS LIVER FAILING?
- WHAT CAN BE DONE FOR FATTY LIVER?
- DOES HE NEED TO SEE A SPECIALIST?
- WHAT EXACTLY IS FATTY LIVER AND WHAT DO I NEED TO DO ABOUT IT?

WHAT IS FATTY LIVER

- NAFLD IS CHARACTERIZED BY EXCESSIVE HEPATIC FAT ACCUMULATION, ASSOCIATED WITH INSULIN RESISTANCE (IR), AND DEFINED BY THE PRESENCE OF STEATOSIS IN $>5\%$ OF HEPATOCYTES
- NAFLD- NON-ALCOHOLIC FATTY LIVER
- NASH- NON-ALCOHOLIC STEATOHEPATITIS



NAFLD: Spectrum of disease

	Image	Histopathology	Pathophysiology
Non-alcoholic fatty liver (hepatic steatosis)			Accumulation of fat in liver (when excessive alcohol consumption is ruled out).*
Non-alcoholic steatohepatitis (NASH)			Accumulation of fat in liver is combined with inflammation and cell damage.
Fibrosis			Scarring (excess fibrous tissue) in an inflamed liver. Categorised into stages 0 to 4 (or mild, moderate and advanced) based on extent and distribution of scarring.
Cirrhosis			Late stage of chronic liver disease marked by nodules of damaged liver cells surrounded by scarring.

Non-alcoholic fatty liver without NASH or fibrosis takes on average 57 years to progress to cirrhosis.**

*The prevalence in the general population for different stages of non-alcoholic fatty liver disease is uncertain.

**The evidence for progression does not take into account the effect of interventions explored in the guideline that may modify progression such as lifestyle changes or pharmacological therapy.

PREVALENCE AND NATURAL HISTORY

- MOST COMMON LIVER DISORDER IN WESTERN COUNTRIES
- RANGING FROM 17-46% OF POPULATION
- HIGH RISK POPULATIONS CAN BE UP TO 90%
 - SEVERE OBESITY UP TO 90% WITH 5% PRESENTING WITH CIRRHOSIS
 - 70% OF TYPE 2 DIABETES

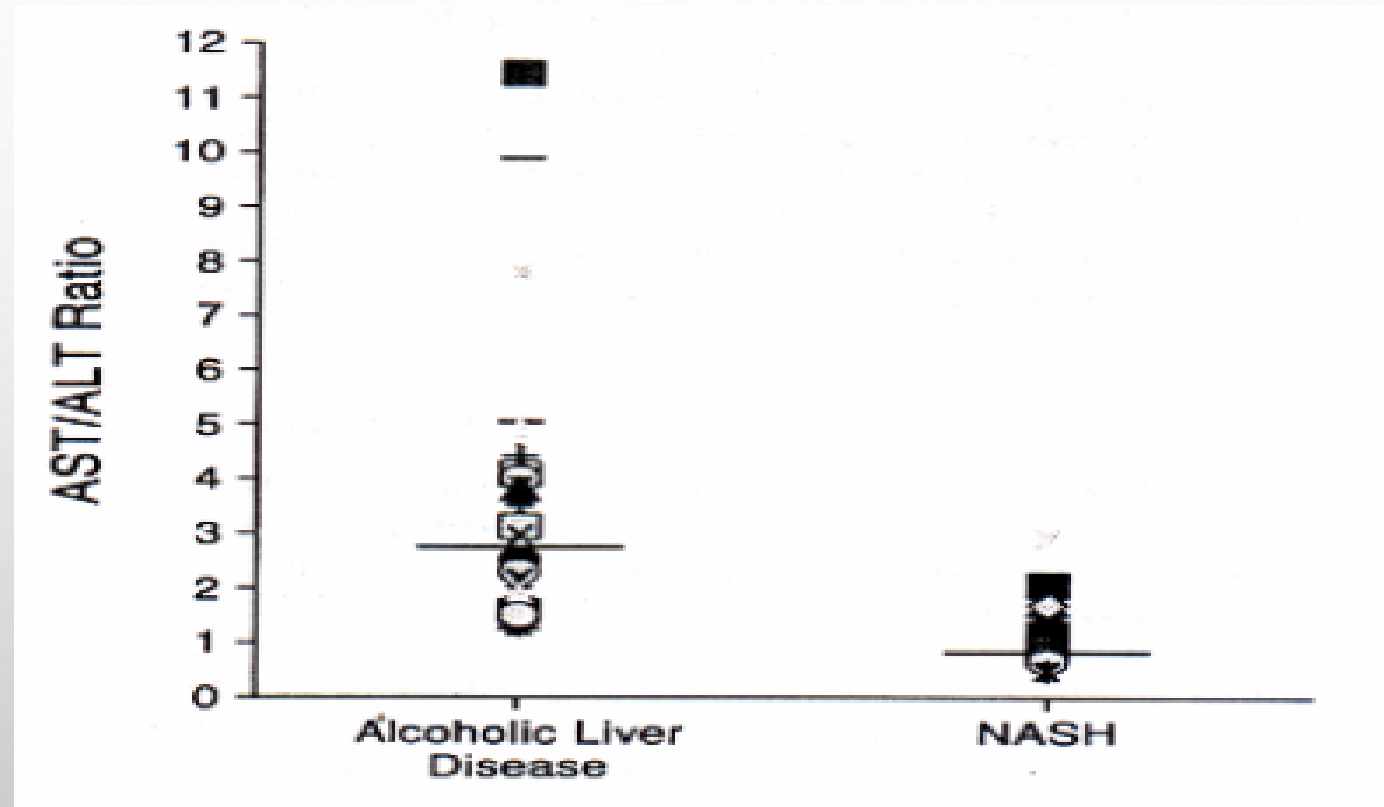
PREVALENCE AND NATURAL HISTORY

- ROUGHLY 20-30% OF PATIENTS WITH NAFLD WILL DEVELOP NASH
- 15-25% OF NASH PATIENTS WITH PROGRESS TO CIRRHOSIS
- 30-40 % OF CIRRHOTIC PATIENTS WITH DIE DUE TO LIVER RELATED COMPLICATIONS
 - 20 MILLION ADULTS IN CANADA* 7 MILLION WITH NAFLD
 - 1.4 MILLION WILL DEVELOP NASH AND 210,000 WILL DEVELOP CIRRHOSIS
- MOST COMMON CAUSE OF DEATH IN PATIENTS WITH NAFLD IS CARDIOVASCULAR, FOLLOWED BY EXTRAHEPATIC CANCERS WITH 3RD BEING LIVER RELATED
- 2.5 FOLD INCREASE NASH CIRRHOSIS AND ADVANCED FIBROSIS OVER PAST DECADE

EVALUATION

- TYPICALLY MODEST ELEVATION IN ALT AND AST
 - 2-5 TIMES UPPER LIMIT OF NORMAL
- CBC HELPFUL AS LOW PLATELETS SEEN IN MORE ADVANCED DISEASE
- ALK PHOS CAN BE ELEVATED YET BILIRUBIN, ALBUMIN AND INR ARE TYPICALLY NORMAL
- FERRITIN COMMONLY ELEVATED
 - HEMOCHROMATOSIS 1/300, VS NALFD 1/2
- POSITIVE SERUM AUTOANTIBODIES, DEFINED AS ANA > 1:160 OR ASMA >1:40 WERE PRESENT IN 21% OF PATIENTS WITH NALFD AND WERE NOT ASSOCIATED WITH MORE ADVANCED HISTOLOGIC FEATURES

EVALUATION



EVALUATION

- TO DIAGNOSE FATTY LIVER YOU NEED HEPATIC STEATOSIS BY IMAGING OR HISTOLOGY
- NO SIGNIFICANT ALCOHOL CONSUMPTION
- THERE ARE NO COMPETING ETIOLOGIES FOR HEPATIC STEATOSIS
- THERE ARE NO CO-EXISTING CAUSES FOR CHRONIC LIVER DISEASE

DIFFERENTIAL DIAGNOSIS

- COMMON SECONDARY CAUSES OF FATTY LIVER
 - >21 DRINKS FOR MEN AND >14 DRINKS FOR WOMEN PER WEEK
- HEPATITIS C- GENOTYPE 3
- WILSONS DISEASE
- MEDICATIONS
 - CORTICOSTEROIDS, METHOTREXATE, TAMOXIFEN, RETROVIRAL, AMIODARONE
- PREGNANCY
- TPN

CASE- DONALD

- REVIEW DONALD'S BLOODWORK.
- 10 YEARS AGO- ALT 28, AST 26
- YOU ORDER ASMA, AMA, ANA, ALPHA 1 ANTITRYPSIN, HEP B/C, IMMUNOGLOBULIN, CELIAC SCREEN, IRON STUDIES, TSH
- DRINKS 1-3 BEER ON WEEKEND AND NEVER A HEAVY DRINKER
- OVER PAST 7 YEARS HAS GAINED ROUGHLY 50-60 LBS AND ATTRIBUTES TO SORE KNEES FROM HOCKEY
- SAME TIME HE DEVELOPED DIABETES, HTN AND DYSLIPIDEMIA
- DONALD ASKS.....WHY ME?

RISK FACTORS

- OBESITY
 - BMI AND WAIST CIRCUMFERENCE RELATED TO PRESENCE OF NAFLD AND CAN PREDICT ADVANCED DISEASE
 - ETHNICITY AND GENETICS PLAY ROLE
- DIABETES IS CLOSELY ASSOCIATED WITH SEVERITY, PROGRESSION OF DISEASE AND DEVELOPMENT OF HCC
 - PATIENTS WITH INCIDENTAL FINDING OF NAFLD HAVE 2-5 FOLD INCREASED RISK OF DMT2
- INSULIN TREATMENT INCREASES BODY FAT, BUT IT DOES NOT APPEAR TO PROMOTE OR WORSEN NAFLD IN DIABETES
- MAJORITY OF PATIENTS WITH “CRYPTOGENIC CIRRHOSIS” LIKELY HAVE BURNT OUT NASH CIRRHOSIS

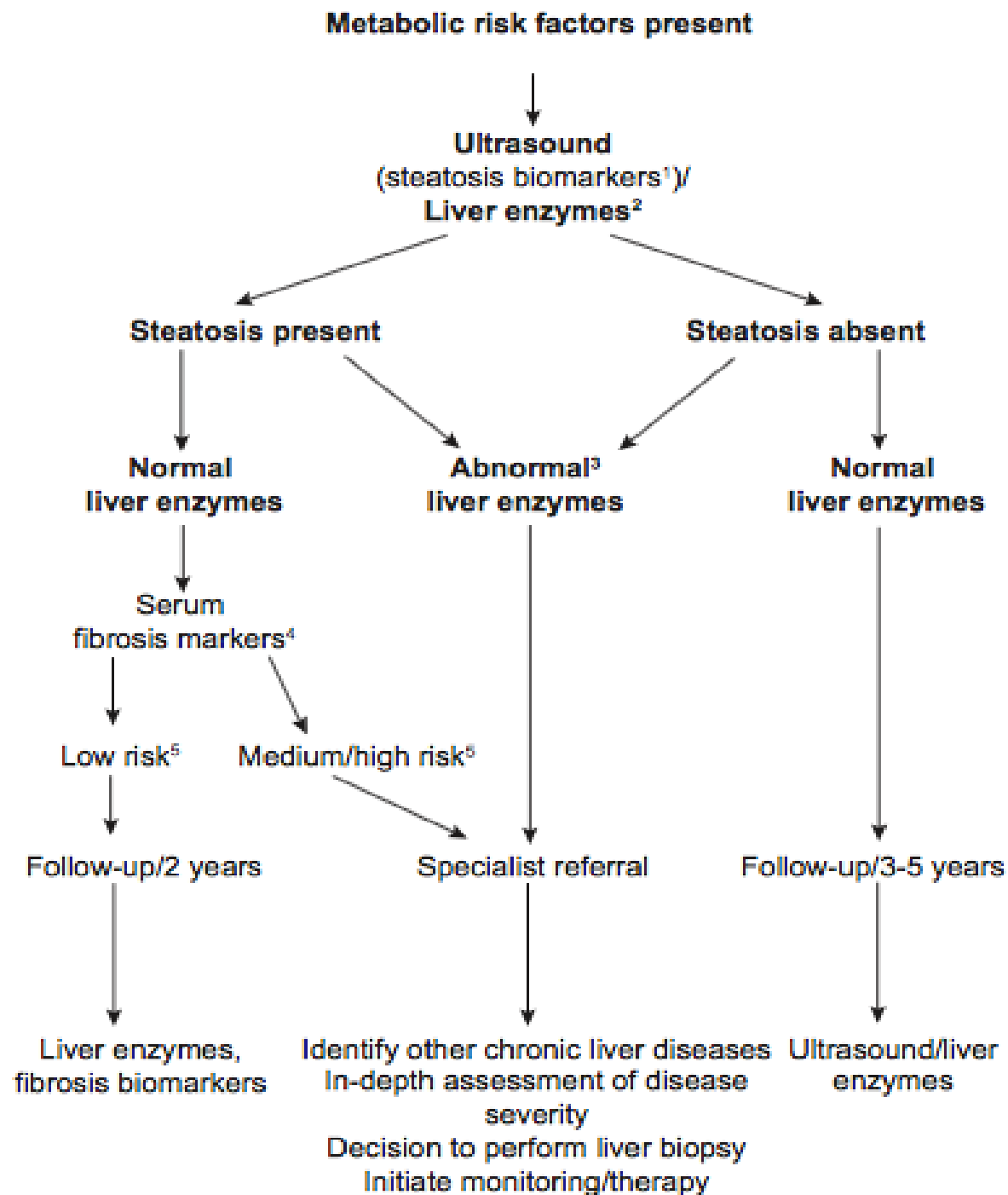
RISK FACTORS

- POLYCYSTIC OVARY SYNDROME
- HYPOTHYROIDISM
- OBSTRUCTIVE SLEEP APNEA
- HYPOPITUITARISM
- HYPOGONADISM



DO WE NEED TO WORRY ABOUT DONALD?

- NAFLD RELATIVELY BENIGN BUT NASH IS NOT
- THE DIAGNOSIS OF NASH PROVIDES IMPORTANT PROGNOSTIC
 - FIBROSIS IS THE MOST IMPORTANT PROGNOSTIC FACTOR IN FATTY LIVER
- BEST WAY TO DISTINGUISH IS WITH BIOPSY YET EXPENSIVE, INVASIVE AND SAMPLING ERROR
- SURROGATE MARKERS OF FIBROSIS HELPFUL AND CAN BE DONE IN CLINIC
 - NAFLD FIBROSIS SCORE, FIB-4
- IF ELEVATED THEN SHOULD GO ON TO HAVE FIBROSCAN THEN POSSIBLY BIOPSY



DO WE NEED TO WORRY ABOUT DONALD?

- FIBROSIS 0-4-- 4 BEING CIRRHOSIS
- TYPICALLY DEVELOPS SLOWLY, BUT CAN DEVELOP QUICKLY IN ROUGHLY 20%
- THE RATE OF PROGRESSION CORRESPONDS TO 1 FIBROSIS STAGE EVERY 14 YEARS IN NAFL AND EVERY 7 YEARS IN NASH, AND IS DOUBLED BY ARTERIAL HYPERTENSION
- NASH RELATED CIRRHOSIS HAS BEEN REPORTED AS EARLY AS 8 YEARS OLD

CASE- DONALD

- DONALD IS NOT OVERLY CONCERNED BUT HIS WIFE HAS BEEN ON INTERNET AND COMES BACK WITH QUESTIONS
- SHE HAS QUESTIONS REGARDING DIET, EXERCISE, MEDICATIONS AND HAS BOUGHT MULTIPLE HERBAL/NATURAL PRODUCTS
- SHE WANTS TO KNOW HOW MUCH WEIGHT AND WHAT DIET DONALD NEEDS
- CAN HE BE REFERRED FOR BARIATRIC SURGERY?
- SHE READ ABOUT SOME NEWER TREATMENTS. CAN HE BE STARTED ON THEM?

EXERCISE AND WEIGHT LOSS

- CALORIE RESTRICTION DRIVES WEIGHT LOSS AND THE REDUCTION OF LIVER FAT, INDEPENDENT OF THE MACRONUTRIENT COMPOSITION OF THE DIET
- A 12-MONTH INTENSIVE LIFESTYLE INTERVENTION WITH AN AVERAGE 8% WEIGHT LOSS LEADS TO SIGNIFICANT REDUCTION OF HEPATIC STEATOSIS
- 150-200 MIN/WEEK OF MODERATE INTENSITY AEROBIC PHYSICAL ACTIVITIES IN 3-5 SESSIONS ARE GENERALLY PREFERRED (BRISK WALKING, STATIONERY CYCLING)
- RESISTANCE TRAINING IS ALSO EFFECTIVE AND PROMOTES MUSCULOSKELETAL FITNESS, WITH EFFECTS ON METABOLIC RISK FACTORS
- ANY PHYSICAL ACTIVITY BETTER THAN INACTIVITY!

DIET

- LIMIT SATURATED FATS TO 7-10% AND INCREASE MONO-POLY UNSATURATED FATS
- LIMIT OR AVOID FRUCTOSE CONTAINING FOOD
 - 2-3 FOLD INCREASE IN HEPATIC STEATOSIS
- CARBOHYDRATES TO 40-50% OF DAILY CALORIC INTAKE
- FATS LESS THAN 30% AND PROTEIN 15-20%
- AVOID MSG
 - INCREASED RISK OF FATTY LIVER AND INFLAMMATION WITHIN THE HEPATOCYTES
- DATA FOR HIGH PROTEIN DIETS



DIET

- MEDITERRANEAN DIET HAS SHOWN BENEFIT
- STUDY COMPARING MEDITERRANEAN-LIKE DIET WITH TYPICAL DIET FOR TWO YEARS SHOWED SIGNIFICANTLY LOWER INSULIN RESISTANCE IN THE MEDITERRANEAN-STYLE DIET GROUP
- A SIGNIFICANT NEGATIVE CORRELATION BETWEEN ADHERENCE TO MEDITERRANEAN DIET AND ALT, INSULIN LEVELS, STAGE OF FIBROSIS, SEVERITY OF STEATOSIS, AND THE LIKELIHOOD OF HAVING NASH

DIET

- COFFEE- PROTECTIVE IN NAFLD, AS IN LIVER DISEASE OF OTHER ETIOLOGIES, REDUCING HISTOLOGICAL SEVERITY AND LIVER-RELATED OUTCOMES
- IN A RECENT META-ANALYSIS OF 16 STUDIES COMPRISING 31 53 CASES OF HEPATOCELLULAR CARCINOMA, THE RISK OF HCC WAS FOUND TO BE REDUCED BY 40% WITH COFFEE INTAKE COMPARED TO NO COFFEE
- NOT ONLY RELATED TO CAFFEINE, RATHER LIKELY ANTIOXIDANT AND BIOACTIVE PHYTOCHEMICALS IN COFFEE ITSELF
- THE BENEFICIAL EFFECTS OF COFFEE ARE REPORTED FOR >2 CUPS/DAY

DIET

- CAN BE DIFFICULT AND FOREIGN TO MANY PATIENTS
- LOW HANGING FRUIT
- QUICKLY GO THROUGH MEALS
- JUICE AND POP
- CREAM AND SUGAR IN COFFEE
 - MEDIUM DOUBLE DOUBLE- 212 CALORIES VS 4 CALORIES
- SNACKS
- CONDIMENTS AND SAUCES



THERAPEUTICS

- DM- METFORMIN WEAK EVIDENCE FOR IMPROVEMENT IN NASH
 - THIAZOLIDINEDIONES IMPROVE INSULIN RESISTANCE, BIOMARKERS, STEATOSIS, AND INFLAMMATION
- STATINS ARE SAFE TO USE IN NAFLD/NASH
 - DECREASE TRANSAMINASES, POSSIBLE ROLE IN DELAYING PROGRESSION FROM NAFL TO NASH
 - RECOMMENDED IN PATIENTS WITH NAFLD/NASH AND DYSLIPIDEMIA
- VITAMIN E
 - VITAMIN E (800 IU/DAY) IMPROVED STEATOSIS, INFLAMMATION AND BALLOONING AND INDUCED RESOLUTION OF NASH IN 36% OF PATIENTS (21% IN THE PLACEBO ARM)
 - CAN BE USED IN NON CIRRHOTIC, NON DIABETIC BIOPSY PROVEN NASH
 - INCREASE IN ALL CAUSE MORTALITY, STROKE AND PROSTATE CANCER

THERAPEUTICS

- RAAS BLOCKADE
 - ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS MAY BE USEFUL IN TREATING NAFL/NASH AS THEY MAY LEAD TO DECREASED FIBROSIS
- 54 PATIENTS WITH HYPERTENSION AND NASH WERE RANDOMLY ASSIGNED TO EITHER TELMISARTAN OR VALSARTAN; BOTH GROUPS SHOWED IMPROVEMENT IN TRANSAMINASES AND INSULIN RESISTANCE, WHILE TELMISARTAN WAS ALSO SHOWN TO IMPROVE NASH AND FIBROSIS
- RECENT CROSS-SECTIONAL STUDY OF 290 HYPERTENSIVE PATIENTS WITH BIOPSY PROVEN NAFLD, LIVER HISTOLOGY WAS COMPARED IN PATIENTS WITH AND WITHOUT RAS BLOCKER; THERE WAS SIGNIFICANTLY LESS BALLOONING AND LOWER FIBROSIS STAGE IN PATIENTS ON RAAS BLOCKERS

THERAPEUTICS

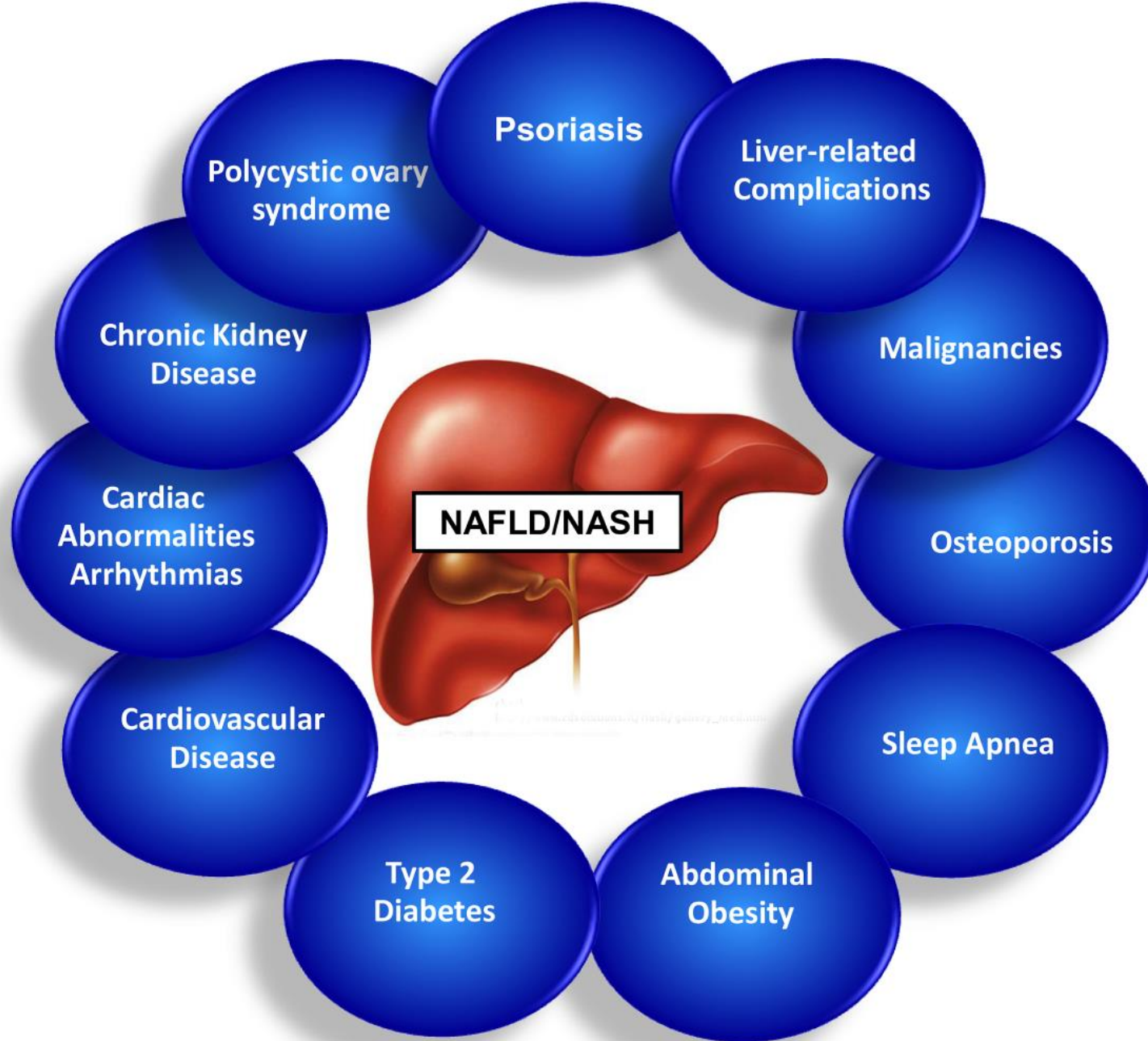
- MILK THISTLE HAS BEEN SHOWN IN SEVERAL STUDIES TO HAVE BENEFIT MAINLY AS COMBINATION THERAPY
 - RECENT RCT SHOWED PROMISE AND WAS SAFE YET FAILED PRIMARY ENDPOINT
- OBETICHOLIC ACID (OCA) IS AN FXR AGONIST WHICH HAS BEEN TESTED AS A TREATMENT OPTION FOR NAFLD.
 - SHOWN BENEFIT IN EARLY TRIALS AND CURRENTLY INTERNATIONAL PHASE 3 TRIALS ONGOING
- OTHER MOLECULES AND TREATMENTS BEING STUDIED

BARIATRIC SURGERY

- PATIENT CAN'T LOSE WEIGHT?
- RECENT COHORT STUDY WITH 1-YEAR FOLLOW-UP CONFIRMED THAT BARIATRIC SURGERY-ASSOCIATED WEIGHT LOSS CLEARED NASH IN 85% OF PATIENTS AND IMPROVED FIBROSIS IN 34%
- LONG WAIT LIST
- SOME STUDIES HAVE SHOWN WORSENING FIBROSIS
- COMPLICATIONS FROM SURGERY

TREATMENT APPROACH

- PATIENT WITH ELEVATED LIVER ENZYMES AND/OR EVIDENCE OF FATTY LIVER
- R/O OTHER POSSIBLE CAUSES
- TREAT METABOLIC RISK FACTORS
- REVIEW LIFESTYLE MODIFICATIONS AND REFER TO DIETICIAN/ EXERCISE AS NEEDED
- F/U IN 9 MONTHS WITH REVIEW AND REPEAT BLOODWORK
- IF STILL ELEVATED REFER FOR EVALUATION AND LIKELY FIBROSCAN AND POSSIBLE BIOPSY
- FATTY LIVER 2-3 YEARS, FIBROSIS YEARLY AND CIRRHOSIS 6 MONTHS
- WILL LIKELY HAVE TARGETTED THERAPEUTIC OPTIONS SOON
- IMPORTANT TO CONTINUE MONITOR OF METABOLIC RISKS ON GOING



SUMMARY

- FATTY LIVER IS COMMON AND IN ITSELF RELATIVELY BENIGN YET CAN PROGRESS TO CIRRHOSIS IN MINORITY
- MAJORITY OF PATIENTS WITH FATTY LIVER DIE FROM CARDIOVASCULAR OR EXTRA-HEPATIC MALIGNANCIES
- IMPORTANT TO SCREEN AND TREAT RISK FACTORS FOR METABOLIC SYNDROME
- LIFESTYLE MODIFICATION IS CURRENT MAINSTAY OF TREATMENT
- TREATMENT OF METABOLIC SYNDROME HELPS FATTY LIVER
- NEW TREATMENT OPTIONS WILL SOON BE AVAILABLE

QUESTIONS?

