ECHO Diabetes
Introduction to NAFLD & Diabetes

May 13,2021

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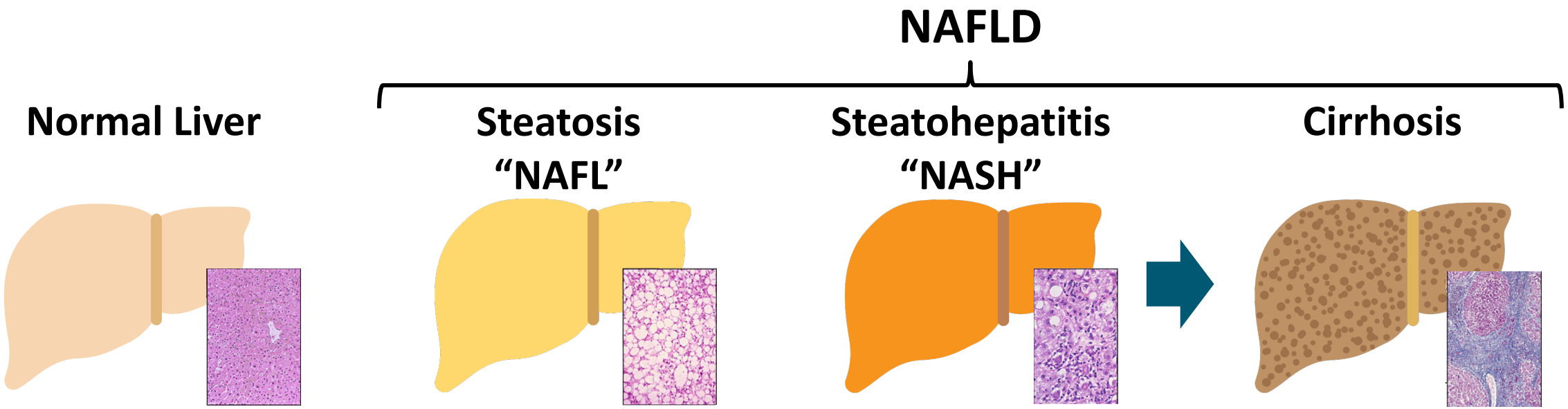
NAFLD and Diabetes

- What is NAFLD (Non-alcoholic Fatty Liver Disease)
- Why is it important
- What to do about it

What is NAFLD?

- Nonalcoholic fatty liver disease (NAFLD) is the build up of extra fat in liver cells that is not caused by alcohol.
  - It is normal for the liver to contain some fat. However, if **more than 5% – 10% percent** of the **liver's weight is fat**, then it is called a **fatty liver (steatosis).**
  - The ***more severe form*** of NAFLD is called **nonalcoholic steatohepatitis (NASH).** NASH causes the liver to swell and become damaged.
- NAFLD is one of the most common causes of liver disease in the United States(30 to 40% of adults, 10% of children) (25% of the world population – highest in Middle East Countries)
  - Most people with NAFLD have simple fatty liver.
  - ~20 -30% of people with NAFLD have NASH (~3 to 12% of adults in the United States have NASH).
  - In ***people with T2DM*** - estimated **76% prevalence of NAFLD** and **56% of NASH**
    - NAFLD is the most common cause of elevated liver enzymes in adults in the United States in patients with type 2 diabetes
- Research has found that **fat in the liver** can lead to **chronic inflammation that activates fibrosis**
- NAFLD is a ***silent*** (asymptomatic) condition until cirrhosis

The NAFLD Continuum



Worldwide prevalence:	25%[1]	3% to 5%[1]	1% to 2% at risk*

*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis[2]

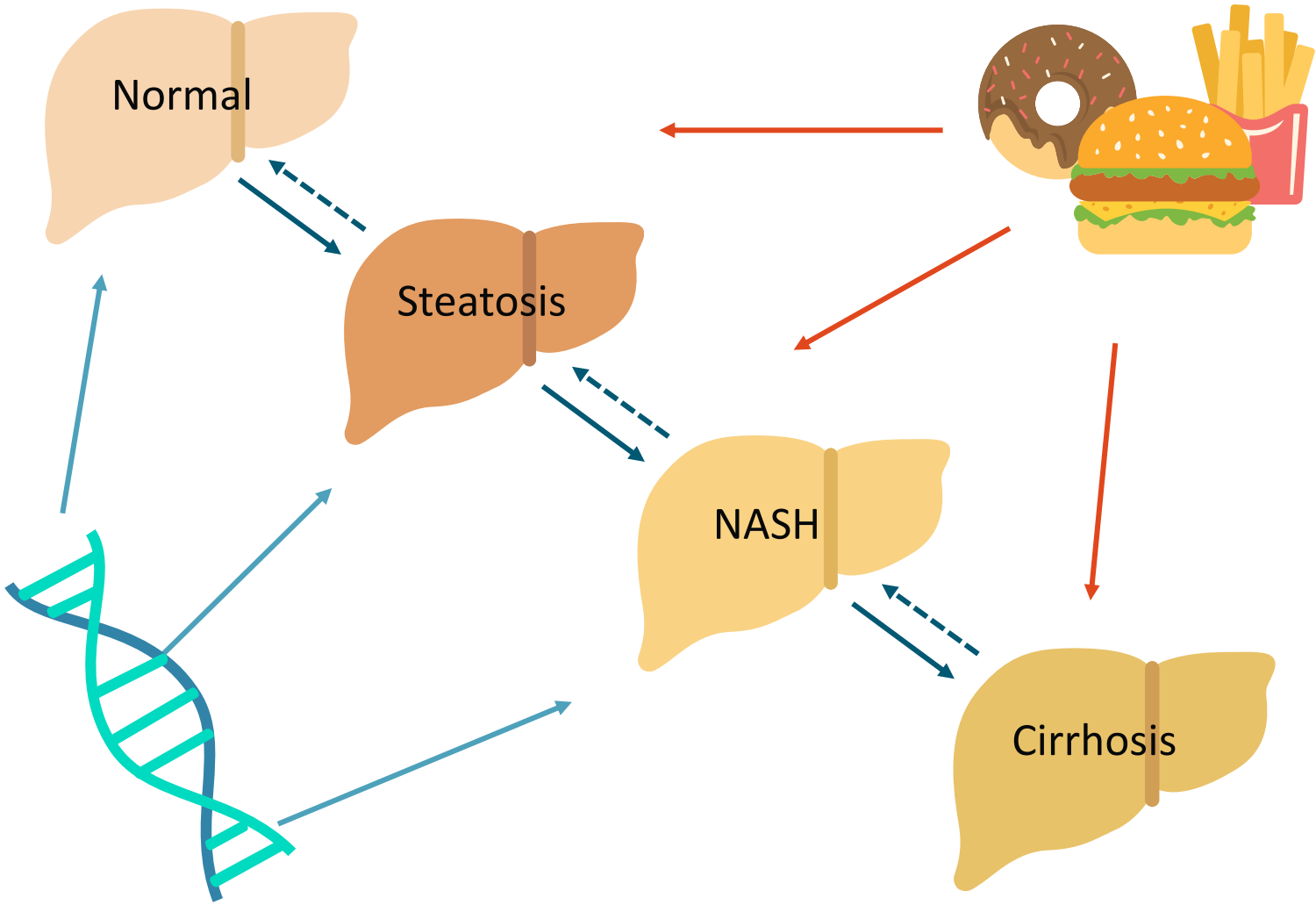
1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

Slide credit: clinicaloptions.com

Etiology

- The prevailing hypothesis for development of NAFLD includes development of a ***lipotoxic environment in the liver*** that poses survival challenges for hepatocytes at the cellular level
- Lipotoxicity may involve nutritional challenge with an ***overabundance of lipids and calories***;
  - specific caloric sources (for example, *high-fructose corn syrup*) may also play a role→NAFLD Dietary Characteristics
    - Higher in saturated fat/cholesterol and lower in polyunsaturated fat, fiber and antioxidant vitamins C and E
    - Higher intake of soft drinks and meat; less omega -3 fatty acids
    - Overall energy intake significantly higher
    - High fructose diets

NAFLD as a Complex Disease Trait: Genetic and Environmental Modifiers



Genes
PNPLA3
TM6SF2
GCKR
SOD2
MBOAT7

Environment
Sedentary lifestyle
Snacking, fast food
Saturated fats
Trans fats
Processed red meat

Epigenetics
Gut microbiome

Cotter. Gastroenterology. 2020;158:1851. Krawczyk. Gastroenterology. 2020;158:1865.

Slide credit: clinicaloptions.com

Why is it important?

- NASH can lead to complications, such as **cirrhosis and liver cancer (hepatocellular carcinoma)**
  - People with NASH have ***an increased chance of dying from liver-related causes.***
    - HCC reported increasingly in *non-cirrhotic* NAFLD
      - Obesity and diabetes → **increased rates of HCC** in NAFLD
    - If NASH leads to cirrhosis, and **cirrhosis** leads to **liver failure**, a liver transplant may be needed to survive.
- Studies also suggest that people with NAFLD have a greater chance of developing cardiovascular disease.
  - **Cardiovascular disease** is the ***most common cause of death in people who have either form of NAFLD.***
    - (statins are safe to use in NAFLD)

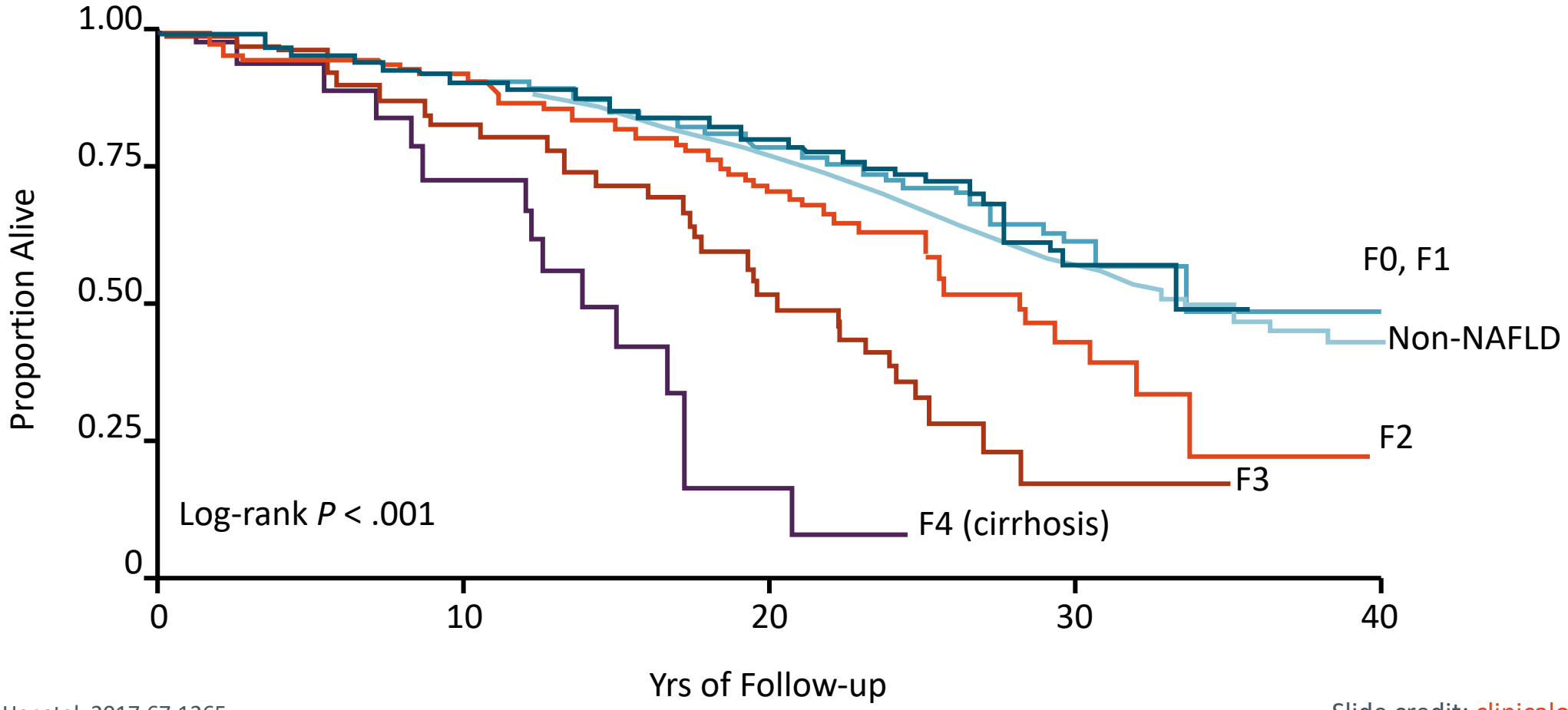
Liver fibrosis is the most important predictor of mortality in nonalcoholic fatty liver disease (NAFLD)

- NAFLD patients with obesity and type 2 diabetes are at high risk for inflammatory disease progression (non-alcoholic steatohepatitis, NASH).
- In such patients, the **stage of liver fibrosis** is the strongest predictor for overall survival and liver-related morbidity and mortality
  - Compared to NAFLD patients with no fibrosis (stage 0), NAFLD patients with fibrosis were at an increased risk for ***all-cause mortality***, and this risk increased with increases in the stage of fibrosis:
    - stage 1, MRR = 1.58 (95% CI 1.19-2.11)
    - stage 2, MRR = 2.52 (95% CI 1.85-3.42)
    - stage 3, MRR = 3.48 (95% CI 2.51-4.83)
    - stage 4, MRR = 6.40 (95% CI 4.11-9.95)
  - The results were more pronounced as the risk of ***liver-related mortality*** increased exponentially with each increase in the stage of fibrosis:
    - stage 1, MRR = 1.41 (95% CI 0.17-11.95)
    - stage 2, MRR = 9.57 (95% CI 1.67-54.93)
    - stage 3, MRR = 16.69 (95% CI 2.92-95.36)
    - stage 4, MRR = 42.30 (95% CI 3.51-510.34)

mortality rate ratios (MRRs)

Liver Fibrosis Is a Risk for Adverse Outcomes

- Retrospective survival analysis of 646 NAFLD patients and matched controls

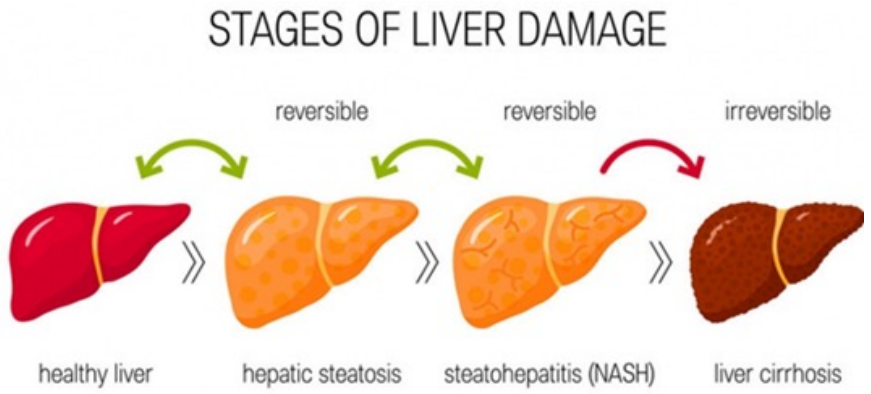


Hagström. J Hepatol. 2017;67:1265.

Slide credit: clinicaloptions.com

Patients have developed complications related to Cirrhosis who were not previously appreciated to have NAFLD.

- Many patients are only diagnosed once advanced fibrosis has already developed…
  - Many primary care physicians only suspect NASH if plasma aminotransferases are elevated, despite ample evidence that a significant number of patients with NASH have “normal” plasma aminotransferase levels (i.e., <40 IU/L).
  - Patients with NAFLD may even have a negative liver ultrasound, as this technique cannot detect steatosis unless it is rather significant (>30%)
- To modify the natural history of the disease, an *early* diagnosis is essential in high-risk populations, such as those with T2DM – when still reversible with weight loss



Liver Enzymes reliability in diagnosis & prognosis of NAFLD

- Persistently **elevated ALT** can be associated with disease progression but does NOT predict progression (53% of patients w NAFL w/o NASH)
- People with ***normal* ALT** can also have progressive disease & 60% of those with advanced disease have normal ALT
  - a normal alanine aminotransferase (ALT) level would be ~**20** IU/L for women and **30** IU/L for men - Values above that may suggest liver injury and should prompt further workup or referral to hepatology
- Elevation of AST >30 is reliably seen in advanced fibrosis
  - in contrast with alcoholic fatty liver disease, the ALT level in a patient with NASH will be higher than the aspartate aminotransferase (AST) level
  - when the AST begins going up above 40 [IU/L], it indicates fibrosis is highly likely
    - For patients with diabetes, a lower AST cutoff of 38 IU/L might be better

Signs and Symptoms of NAFLD

Most cases are *asymptomatic*

- Symptoms can include right upper quadrant pain & fatigue
- Hepatomegaly
- Unexplained abnormality of serum aminotransferase (ALT)
- Incidental finding of fat in the liver on imaging done for another reason
  - On Ultrasound fat must be >30% to detect & can't distinguish fatty liver from early cirrhosis (normal fat accumulation <5%)
  - CT superior to US only if significant obesity; less accurate if <30% fat accumulation (higher radiation exposure)
  - MRI most accurate & sensitive – can detect fat accumulation down to 5%

Recognizing the disease boils down to recognizing risk factors

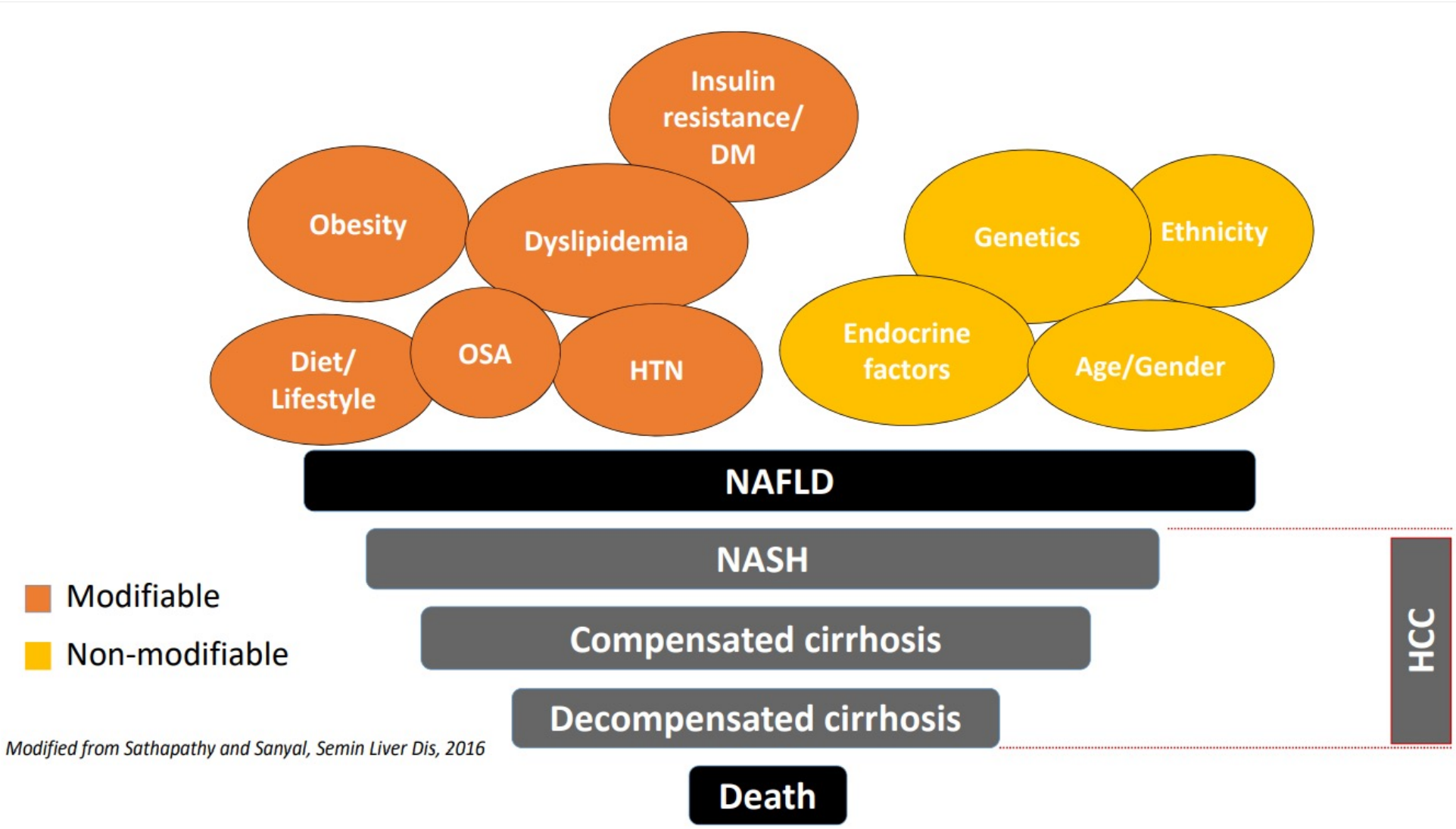
Nonalcoholic fatty liver disease (NAFLD) has no reliable symptoms—only risk factors

- The strongest risk factors for NAFLD
  - Obesity (particularly central obesity)
  - **Diabetes**
  - Hypertension
  - Age over 50 years
  - Obstructive sleep apnea
  - Metabolic dyslipidemia

Conversely, NAFLD increases the chance of developing Diabetes or Pre-diabetes

- Risk factors for progression to fibrosis & cirrhosis
  - Insulin resistance
  - **Diabetes**
  - Weight gain > 5 kg
  - Hypertension
  - Increasing alanine aminotransferase (ALT), aspartate aminotransferase (AST); or ratio AST:ALT > 1

Risk Factors for NAFLD



Modified from Sathapathy and Sanyal, Semin Liver Dis, 2016

Screening

- Routinely screening patients for NAFLD—even those at high risk—is ***not currently recommended*** by the American Association for the Study of Liver Diseases (AASLD) (since Rx is directed at risk factors not the condition per se)
- However, clinicians should have "a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes"
  - Patients with overweight/obesity & T2DM much more likely to have NAFLD in some form than not to have it (more reason to encourage healthy diet, exercise and weight loss)
    - Dr. Cusi and coauthors in their study in the February 2020 *Diabetes Care* found that about 15% of patients with type 2 diabetes had moderate or severe fibrosis or cirrhosis -
      - Degree of fibrosis can be complicated to determine (elevated AST/ALT ratio & US elastography (Fibroscan) can be suggestive)(many biomarker panels (such as Fibro-sure) are very expensive and not any more reliable than AST elevation – Diabetes Care Feb 2020) - may require liver biopsy
- There are other causes of fatty liver besides NAFLD and NAFLD can *co-exist* with other causes of hepatic dysfunction or damage (HCV, Alcohol, medications, etc.)

https://care.diabetesjournals.org/content/early/2020/12/15/dc20-1997
JAMA Dec 18, 2018, vol 320, No. 23 page 2474-2475
Annals 2018

What to do about it?

- No standard treatment exists. Instead, we need to treat the *underlying* conditions, such as obesity
- The first step in treatment is to identify all *modifiable* risk factors
  - that contribute to NAFLD,
    - such as obesity, metabolic syndrome, diabetes, dietary risk factors, quality of sleep (OSA), behavioral factors
  - that can contribute to fibrosis progression
    - including social habits (both smoking and alcohol consumption)
- The treatment of obesity/weight loss is the foundation of care
  - A little weight loss can make a big difference.
  - For those patients who have NASH, a 5% reduction in BMI translates into a 25% relative reduction in liver fat
  - Weight reduction of 4% to 10% consistently improves measures of liver fat and liver aminotransferase levels, according to a systematic review and meta-analysis of 23 randomized trials of patients with NAFLD

Six Strategies for People with NAFLD to Improve Liver Disease

- Just by losing 10% of your current body weight will be enough to reduce liver fat and lessen the harmful inflammation.
  - If you've tried diet and exercise but this approach hasn't been enough to help you get to that goal, consider discussing weight loss medications or even weight loss surgery.
  - Putting into place a plan to lower your body weight is highest on the list of healthy strategies needed to tackle fatty liver disease and overweight - ***losing at least 7% of [your starting] weight to reduce the inflammation***, ***and if there is fibrosis (scarring), meaning the NFALD has progressed, you probably need to lose closer to 10% of your initial weight***. - Kenneth Cusi, MD, FACE, FACP, chief of the division of endocrinology, diabetes and metabolism at the University of Florida, Gainesville
- Adjust your meals to more closely reflect the Mediterranean diet, an approach to eating that is features mostly unprocessed (Fresh or frozen) vegetables and fruits, and limits fats to olive oil and nuts.
- Avoiding foods and drinks high in fructose, such as artificially sweetened sodas, juices and desserts, might go a long way in lowering the level of liver fat.
  - Better yet, don't drink your calories.
- Exercising is strongly recommended—Build up to at least 150 minutes a week—or aim for 10,000 to 15,000 steps a day, based on your doctor's advice.
- Limiting alcohol (at most 1 drink daily for women and 2 for men) is suggested. Ask your doctor what limit is best for you.
- To further protect the liver, ask your doctor about your need for hepatitis A and B vaccinations, if you are not already immune.

Approach in the clinic

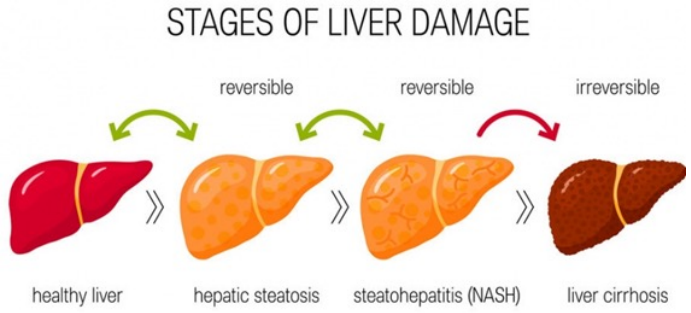
- Another reason to emphasize weight loss/ diet changes
- If *elevated ALT* or *fatty liver on imaging* or *hepatomegaly on exam* →
- Exclude XS alcohol use or other liver disease (Hx & labs (viral hepatitis panels, iron studies (hemochromatosis), ANA, IGG, TSH, A1c, lipids) →
- Noninvasive risk stratification (AST/ALT ratio; FIB 4; NAFLD score)
  - Low risk – weight loss/ Rx Metabolic Sn → annual reassessment
  - Intermediate or high risk → GI referral and/or VCTE
    - VCTE result >7.5 suggests advanced fibrosis
    - In general: [**age >50, obesity, diabetes**] suggests high risk (of NASH & progression to fibrosis, cirrhosis/HCC)
      - Note the platelet level (low with cirrhosis)

Links to Non-invasive fibrosis risk calculators

- Fibrosis-4 (FIB-4) Calculator - Clinical Calculators - Hepatitis C Online (uw.edu)
  - (age, AST, ALT, platelets)
- NAFLD fibrosis score calculator (nafldscore.com)
  - (age, BMI, albumin, platelets, AST, ALT, +/-diabetes)
- Ast Alt Ratio Calculator (omnicalculator.com)

Summary

- NAFLD is common in people with type 2 diabetes
  - It can be “silent” – aside from liver biopsy, no non-invasive gold standard screening, diagnostic or monitoring tests
- NAFLD increases the incidence of type 2 diabetes
- NAFLD is associated with higher risk of CVD
  - & possibly microvascular complications
- Diabetes aggravates NAFLD to more severe forms of steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma
  - Degree of fibrosis determines outcomes
  - “The challenge for the physician is to figure out who has plain old fatty liver disease and who has NASH”
- Weight loss can improve (possibly reverse) all stages of NAFLD except the final stage (cirrhosis) –
  - Diabetes meds that help weight loss have been shown to help reduce NAFLD
    - GLP-1 RA and SGLT2i



Metabolic Associated Fatty Liver Disease (MAFLD)

Proposed Definition[1]

- Diagnosis based on presence of **hepatic steatosis** plus at least 1 of:
  - **Obesity, T2D, metabolic disease**
- Not a diagnosis of exclusion
- Acknowledges metabolic basis of disease

Considerations[2]

- Ambiguity about definition of "metabolic disease"
- Better nomenclature will be based on **specific underlying causes,** not associations
- Consensus needed among *all* stakeholders:
  - Academic, pharma, regulatory, patient advocacy groups, payers, policy makers

1. Eslam. J Hepatol. 2020;73:202. 2. Younossi. Hepatology. 2020;[Epub].

Slide credit: clinicaloptions.com

Extra Slides

Some additional risk factors and causes for Fatty Liver

- obesity
- insulin resistance
- diabetes mellitus type 2
- metabolic syndrome

For non-obese patients

- elevated triglyceride levels
- increased waist circumference
- insulin resistance

Medication-induced

- amiodarone
- diltiazem
- tamoxifen
- methotrexate
- steroids
- highly active antiretroviral therapy

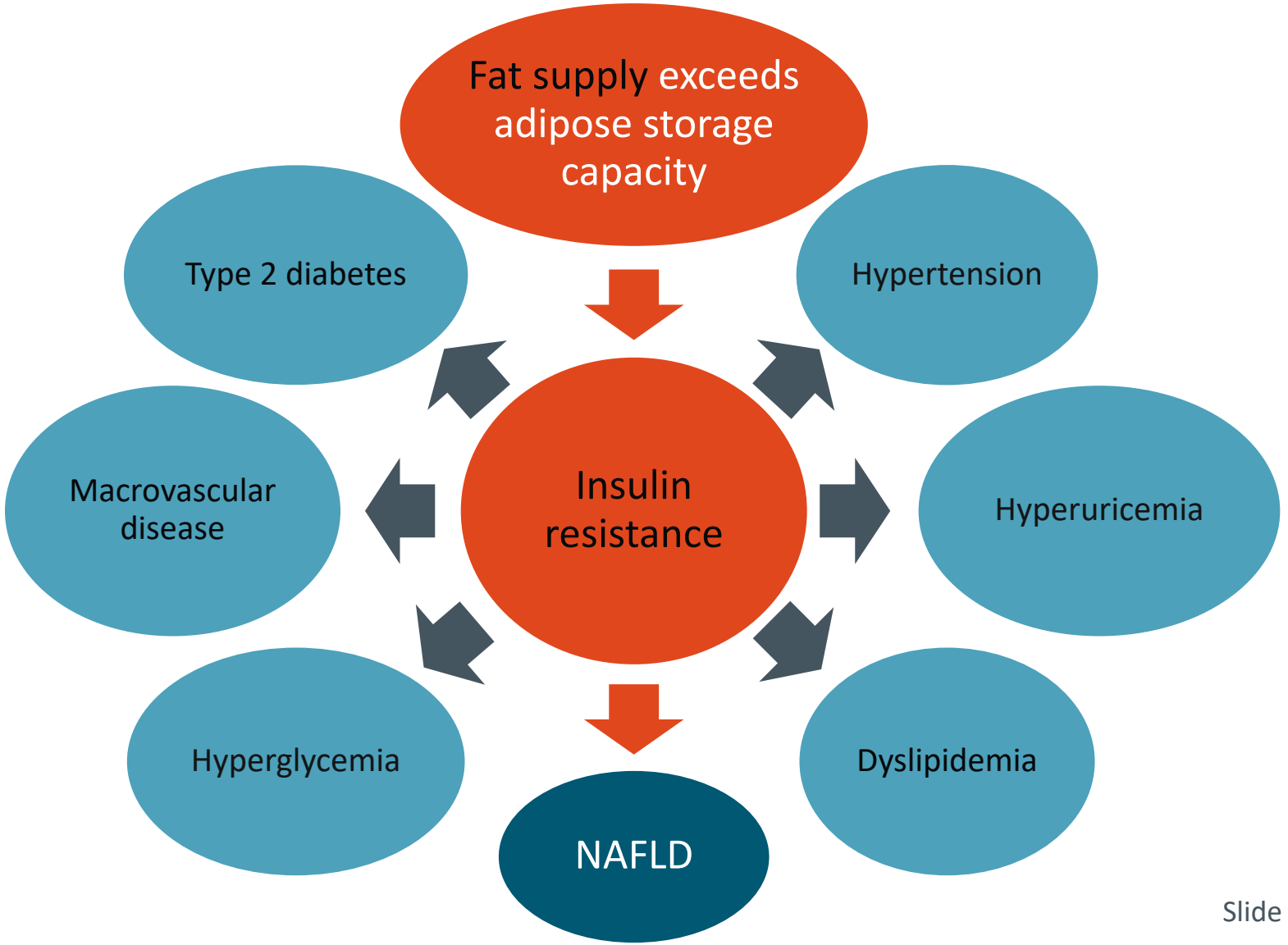
Toxic exposure (e.g., organic solvents, dimethylformamide)

Alcoholic Liver Disease

Secondary causes of hepatic fat accumulation

- severe weight loss
- jejunoileal bypass
- gastric bypass (less common than jejunoileal bypass)
- severe starvation
- Refeeding Syndrome

Obesity and Insulin Resistance as Pathogenic Drivers



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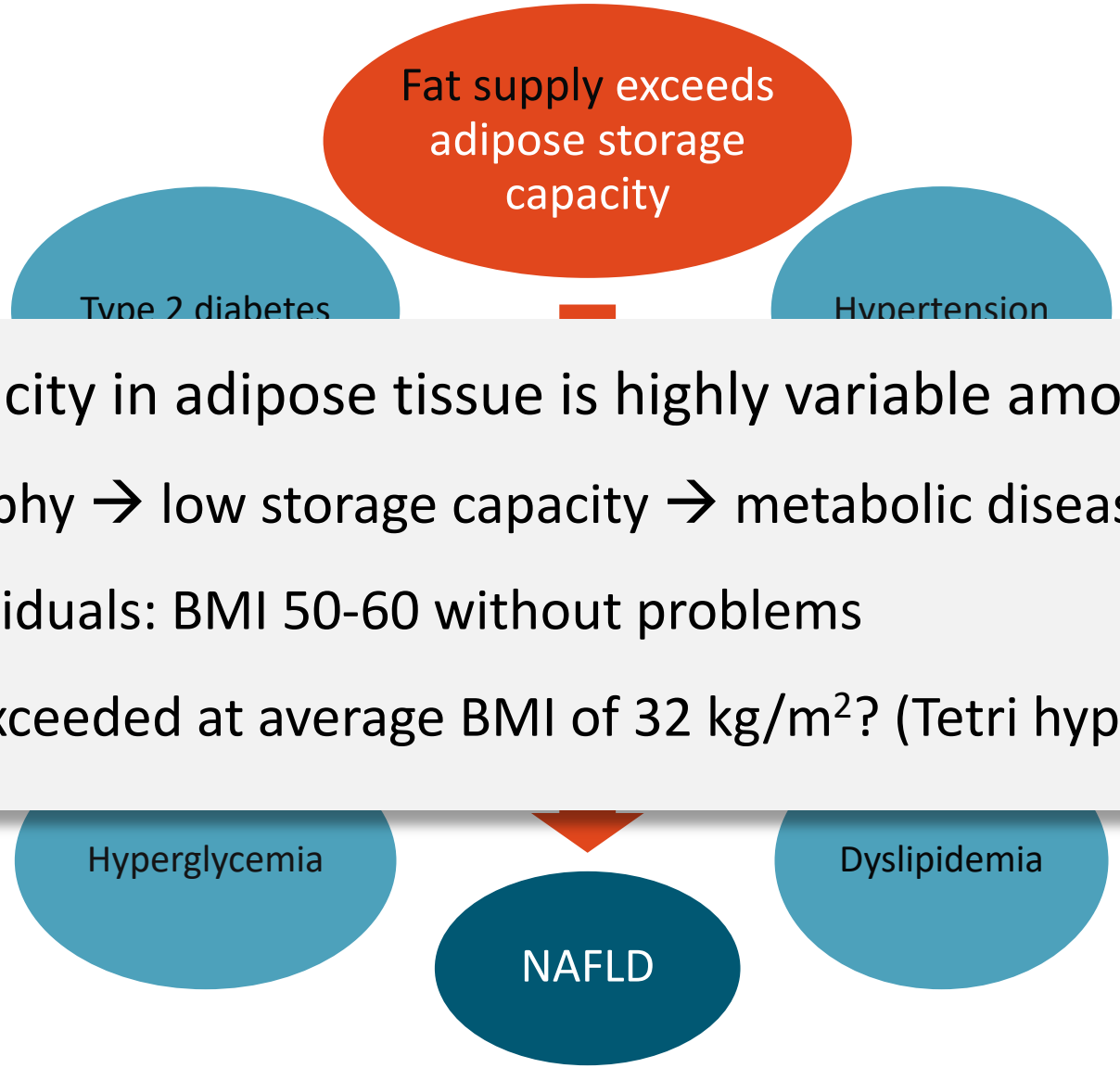
Obesity and Insulin Resistance as Pathogenic Drivers



Storage capacity in adipose tissue is highly variable among individuals

- Lipodystrophy → low storage capacity → metabolic disease with normal BMI
- Some individuals: BMI 50-60 without problems
- Capacity exceeded at average BMI of 32 kg/m^2? (Tetri hypothesis)

Slide credit: clinicaloptions.com

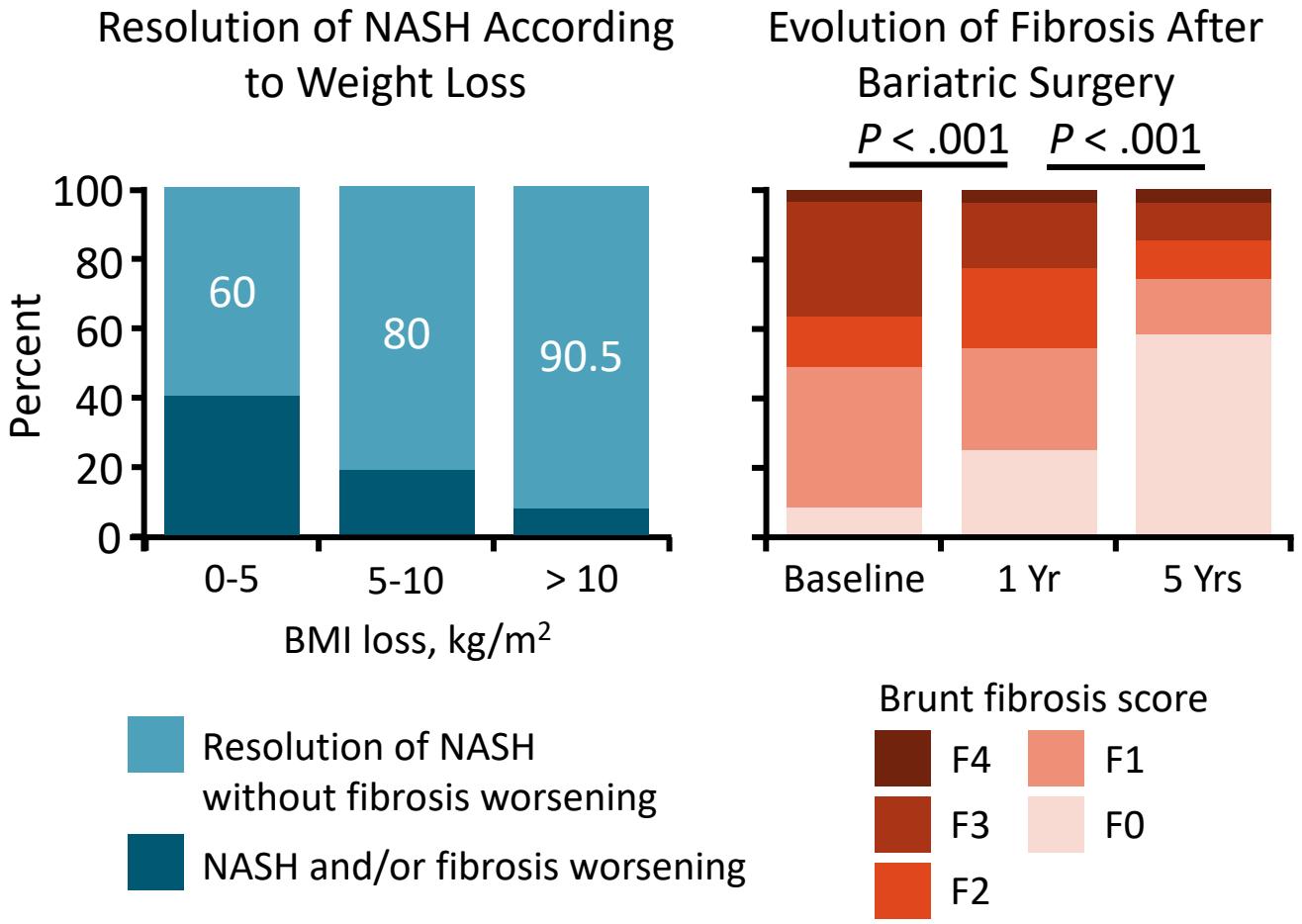
Published in Diabetes Journal Scan / Research · December 15, 2020

- To evaluate the relationship between weight loss and nonalcoholic fatty liver disease (NAFLD), the authors conducted a meta-analysis of weight loss interventions, which included 43 studies with 2809 participants. Median follow-up was 6 months. For every 1 kg of weight loss, there was a 0.83-unit reduction in alanine aminotransferase, a 0.56-unit reduction in aspartate transaminase, and a 0.77% drop in steatosis assessed by histology or radiology. A dose–response relationship was identified with regard to liver inflammation, ballooning, and resolution of NAFLD or nonalcoholic steatohepatitis; there was limited evidence of a dose–response relationship with NAFLD activity score or fibrosis.
- Even modest weight loss can effect clinically significant improvements in NAFLD, but greater weight loss is associated with greater improvements. Treatment of NAFLD could be enhanced by integrating support for formal weight loss programs.
- BACKGROUND: Trials show that weight loss interventions improve biomarkers of non-alcoholic fatty liver disease (NAFLD), but it is unclear if a dose-response relationship exists.
- OBJECTIVE: We aimed to quantify the dose-response relationship between the magnitude of weight loss and improvements in NAFLD.
- METHODS: Nine databases and trial registries were searched until October 2020. Single-arm, non-randomized comparative, or randomized trials of weight loss interventions (behavioral weight loss programs [BWLPs], pharmacotherapy, or bariatric surgery) in people with NAFLD were eligible for inclusion if they reported an association between changes in weight and changes in blood, radiological, or histological biomarkers of liver disease. The review followed Cochrane methods and the risk of bias was assessed using the Newcastle-Ottawa scale. Pooled unstandardized b coefficients were calculated using random-effect meta-analyses.
- RESULTS: Forty-three studies (BWMPs: 26, pharmacotherapy: 9, surgery: 8) with 2809 participants were included. The median follow-up was 6 (interquartile range: 6) months. The direction of effect was generally consistent but the estimates imprecise. Every 1 kg of weight lost was associated with 0.83-unit (95% CI: 0.53 to 1.14, $p < 0.0001$, $I2 = 92\%$, $n = 18$) reduction in alanine aminotransferase (U/L), 0.56-unit (95% CI: 0.32 to 0.79, $p < 0.0001$, $I2 = 68\%$, $n = 11$) reduction in aspartate transaminase (U/L), and 0.77 percentage point (95% CI: 0.51 to 1.03, $p < 0.0001$, $I2 = 72\%$, $n = 11$) reduction in steatosis assessed by radiology or histology. There was evidence of a dose-response relationship with liver inflammation, ballooning, and resolution of NAFLD or NASH, but limited evidence of a dose-response relationship with fibrosis or NAFLD activity score. On average, the risk of bias for selection and outcome was medium and low, respectively.
- CONCLUSION
- **Clinically significant improvements in NAFLD are achieved even with modest weight loss, but greater weight loss is associated with greater improvements. Embedding support for formal weight loss programs as part of the care pathway for the treatment for NAFLD could reduce the burden of disease.**

- https://www.hepmag.com/article/semaglutide-promise-fatty-liver-disease

Is NASH Reversible?

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss



Lassailly. Gastroenterology. 2020;159:1290.

Slide credit: clinicaloptions.com

Obesity risk factors in American Indians and
Alaska Natives: a systematic review

A. Zamora-Kapoor a,c,*K. Sinclair a,d L. Nelson, H. Lee D. Buchwald

https://doi.org/10.1016/j.puhe.2019.05.021
Public Health 174 (219) 85-96

- Abstract
- Objectives: We systematically reviewed the literature on risk factors for obesity in American Indians (AIs) and Alaska Natives (ANs) of all ages.
- Study design: We searched titles and abstracts in PubMed with combinations of the following terms: obesity, body mass index (BMI), American Indian, Alaska Native, and Native American.
- Methods: We limited our review to articles that provided an empirically testable claim abouta variable associated with obesity, measured obesity as a dependent variable, and provided data specific to AI/ANs.
- Results: Our final sample included 31 articles; 20 examined AI/AN youth (<18 years), and 11 examined AI/AN adults (18 years). Risk factors for obesity varied by age. In infants, low birth weight, early termination of breastfeeding, and high maternal BMI, and maternal diabetes increased the risk of childhood obesity. In children and adolescents, parental obesity, sedentary behaviors, and limited access to fruits and vegetables were associated with obesity. In adulthood, sedentary behaviors, diets high in fats and carbohydrates, stress, verbal abuse in childhood, and the belief that health cannot be controlled were associated with obesity.