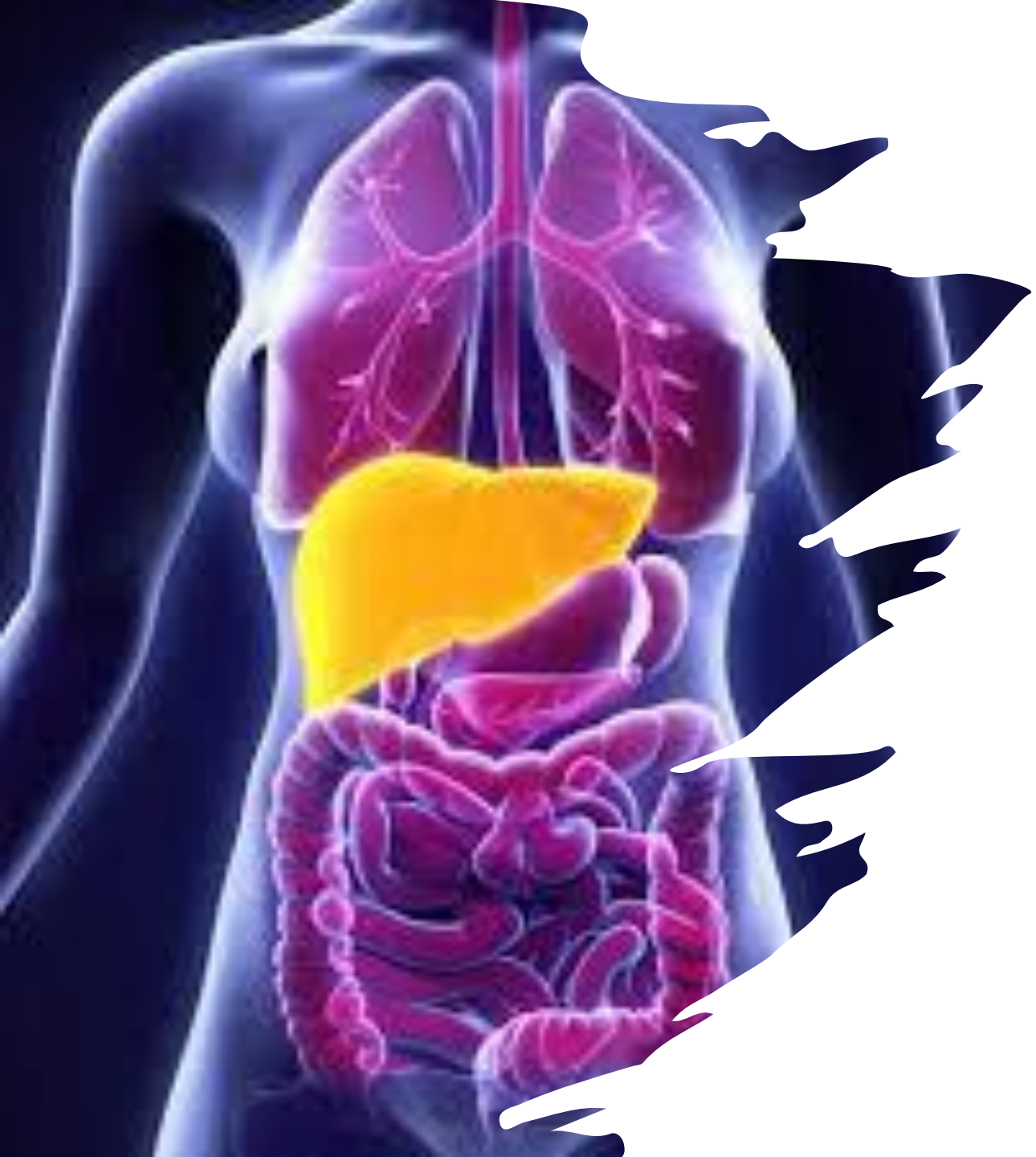
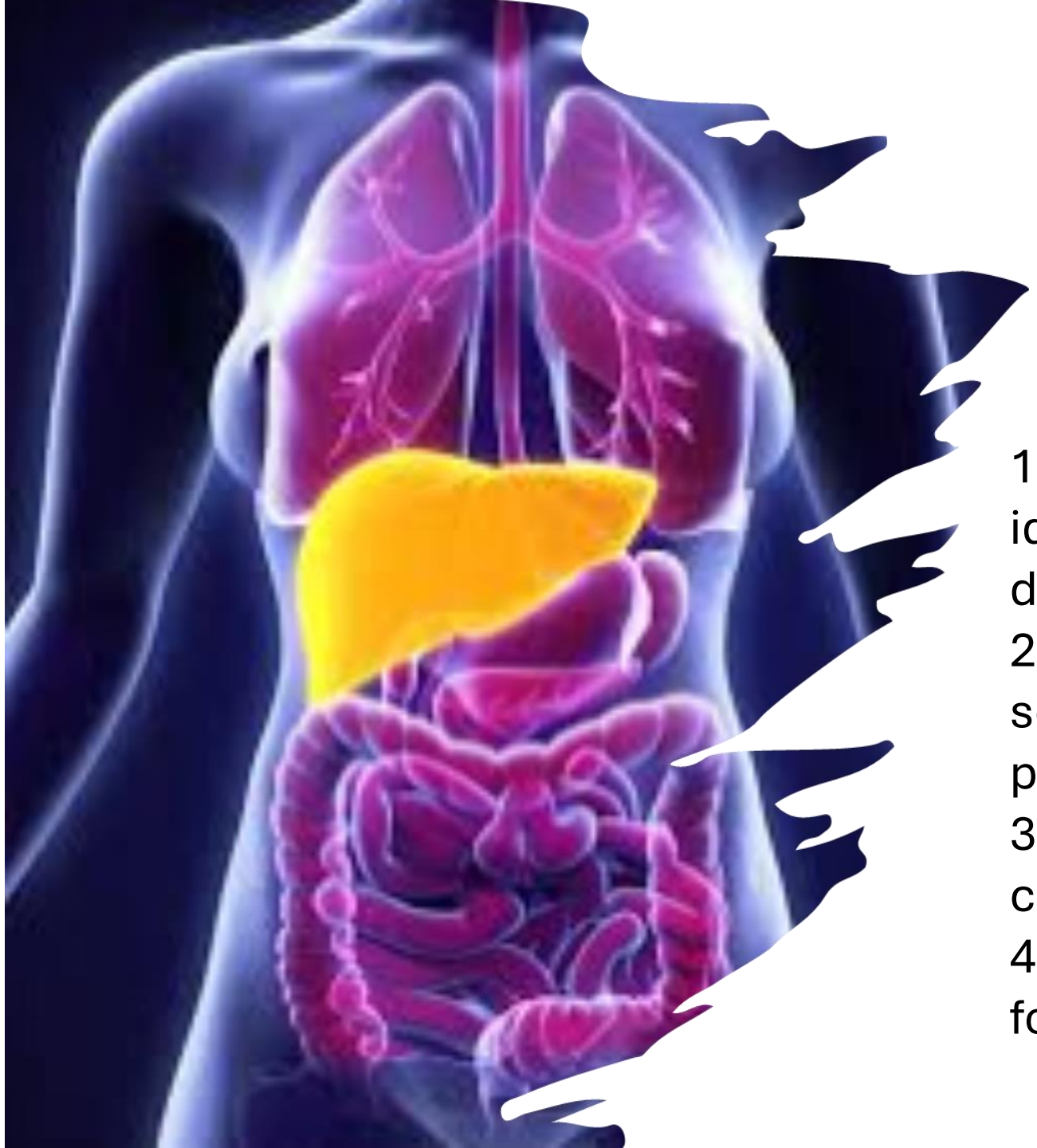


Nonalcoholic Fatty Liver Disease(NAFLD):

A Silent Epidemic

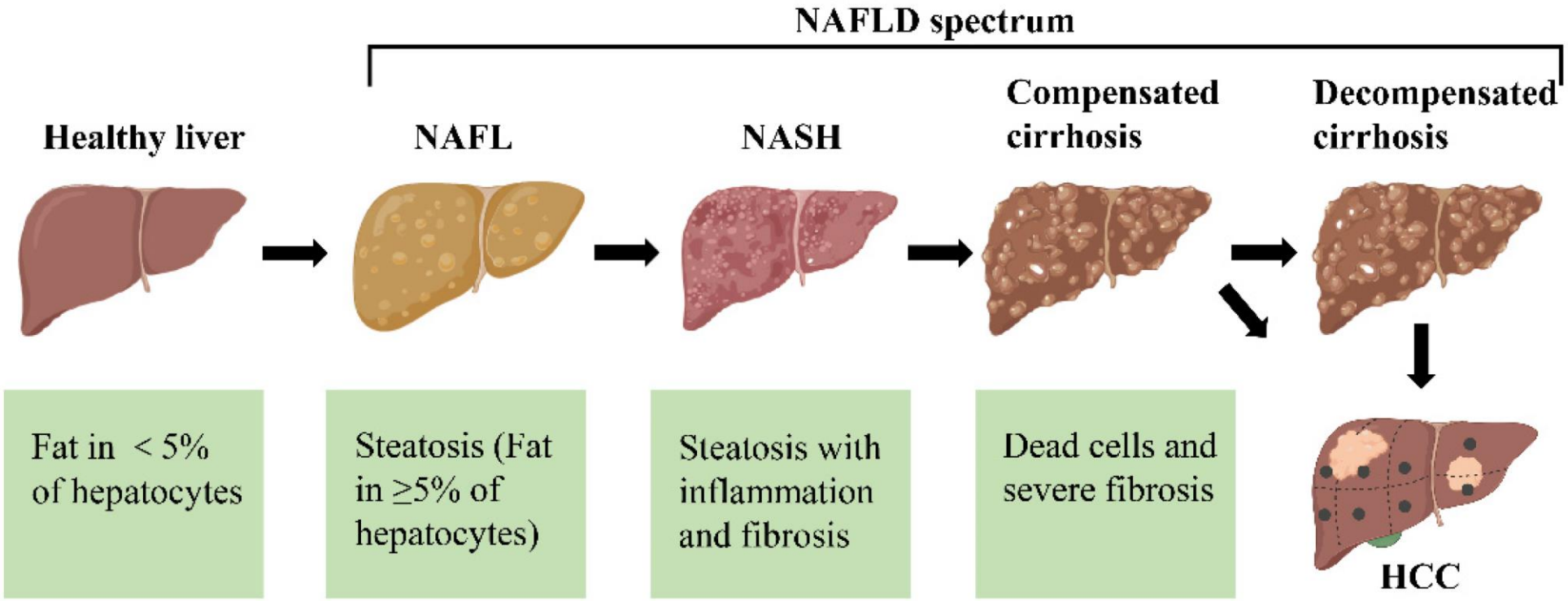
Dr. Linda “El” Summers, DMSc, PA-C
Physician Associate
Riverside Cardiology Specialists



Learning Objectives

1. Recognize the prevalence of NAFLD and identify risk factors that contribute to its development.
2. Describe the current recommendations for screening, diagnosing and assessing patients for NAFLD.
3. Examine the role of NAFLD in cardiovascular risk.
4. Determine the best management options for NAFLD.

What is Non-alcoholic Fatty Liver Disease (NAFLD)?



1. Guo X, Yin X, et al, International Journal of Molecular Sciences. 2022

Etiology of Nonalcoholic Fatty Liver Disease

It affects approximately 30% of the worldwide population

NASH was identified in 14% of asymptomatic patients undergoing colon cancer screening[4]

Hepatic decompensation, Hepatocellular Carcinoma, and death related to NASH cirrhosis are likewise expected to increase 2- to 3-fold by 2030

NAFLD is the most common liver disease worldwide[5]

There has been a 7.7 fold increase (from 2.1% to 16.2%) in the United States for NASH as the underlying etiology for hepatocellular carcinoma (HCC) in patients being listed for liver transplantation.[5]

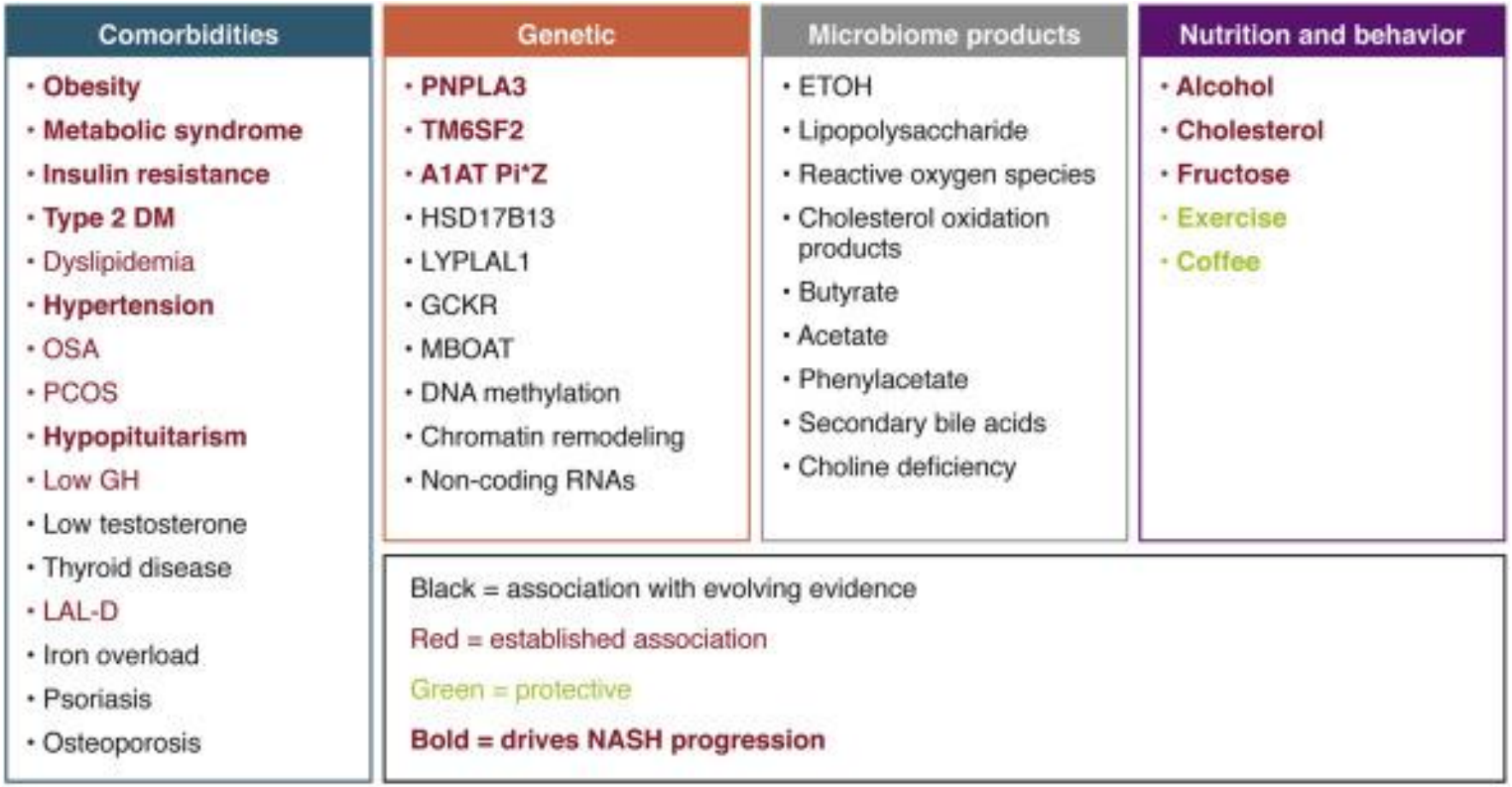
Rates of decompensated NASH cirrhosis are projected to increase by 168%, liver-related deaths by 178%, and incident HCC by 137% between 2015 and 2030.

NASH-related cirrhosis is already the leading indication for liver transplantation in women and those >65 years of age and is on par with alcohol as the leading indication overall.

The overall prevalence of NAFLD appears to be higher in men, however, the prevalence of NASH with more advanced stages of fibrosis is greater in women.

Cancer-related mortality is the second leading cause of death in NAFLD patients

Risk Factors for Nonalcoholic Fatty Liver Disease (NAFLD)



- Hispanic (origin is important due toPNPLA3 gene)[5]
- Although African Americans have high rates of metabolic syndrome, NAFLD is less common in African Americans compared with Caucasian and Hispanic populations (lower PNPLA3 and

5.Cotter T, Rinella M. Gastroenterology.2020

Nonalcoholic Fatty Liver Disease (NAFLD): Risk Factors

- Obesity, hypertension, dyslipidemia, diabetes or insulin resistance, hypothyroidism, polycystic ovary syndrome, and obstructive sleep apnea increase the risk of advanced disease and are associated with worse outcomes.[5]

- Obesity is ubiquitous among patients with NAFLD, as up to 75% of patients who are overweight and 90%–95% of patients with morbid obesity have NAFLD

- Visceral adipose tissue is independently associated with increased risks of NASH and advanced fibrosis. Systemic inflammation from dysfunctional adipose tissue, contributes to disease progression.

- Insulin resistance is a nearly universal feature of NASH; *liver-pancreas axis, diabetes and NAFLD*

- NAFLD is also associated with metabolic dyslipidemia; high triglycerides and low HDL

- NAFLD increases risk of hypertension: increased renal sodium reabsorption due to hyperinsulinemia, enhanced stimulation of the sympathetic nervous system, and impaired vasodilation secondary to insulin stimulation.

Screening for Nonalcoholic Fatty Liver Disease

Lean individuals in the general population should not undergo routine screening for NAFLD; however, screening should be considered for individuals older than 40 years with type 2 diabetes mellitus.[6]

High-risk individuals, such as those with T2DM, medically complicated obesity, family history of cirrhosis, or more than mild alcohol consumption, should be screened for advanced fibrosis[4]

Current evidence does not support genetic testing routine testing for NAFLD

Screening recommended[a]	Prevalence of advanced fibrosis, %
T2DM	6–19
Medically complicated obesity	4–33
NAFLD in context of moderate alcohol use	17
First-degree relative of a patient with cirrhosis due to NAFLD/NASH	18

Abbreviation: T2DM, type 2 diabetes mellitus.

4. Rinella M, Neuschwander-Tetri B, Siddiqui M, et al. Hepatology 2023

Assessing Comorbid Conditions Associated with NAFLD

NAFLD often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, central obesity, and hypertension). Metabolic abnormalities increases risk of histological progression of NASH and all-cause mortality.[4]

- Obesity
- Type II Diabetes Mellitus
- Hypertension
- Dyslipidemia
- Obstructive sleep apnea
- HIV
- Chronic kidney disease (CKD)
- Hypothyroidism
- Hypogonadism
- Menopause and sex hormones in NAFLD
- PCOS

Assessing Less Common Cause of Hepatic Steatosis

Condition	Clinical scenario	Diagnostic test	Treatment
Hypobetalipoproteinemia	Low LDL, low triglycerides, fat malabsorption	ApoB level, genetic testing (MTTP, PCSK-9)	Low-fat diet, fat-soluble vitamin supplementation
LAL deficiency	Markedly elevated LDL-C and low HDL-C, elevated triglycerides, xanthelasma, hypersplenism, advanced fibrosis in young age, predominately microvesicular steatosis on liver biopsy	Enzyme assay, genetic testing	LAL replacement
Nutrient deficiency (eg, carnitine, choline)	Anorexia, short bowel, bypass surgeries	Nutrient levels	Supplementation
Wilson disease	Younger age, neuropsychiatric symptoms, low alkaline phosphatase, low ceruloplasmin	24-h urine copper; quantitative copper on liver biopsy	Chelation
Celiac disease	Iron deficiency, abdominal pain, bloating, vitamin D deficiency, bone loss, diarrhea, dermatitis herpetiformis	Tissue transglutaminase IgA, duodenal biopsy	Gluten-free diet

4. Rinella M, Neuschwander-Tetri B, Siddiqui M, et al. Hepatology 2023

Medications That Increase Risk of NAFLD

Drug	Mechanism	Histological pattern
Amiodarone	Promotion of DNL, impairment of β-oxidation	Hepatic steatosis and steatohepatitis, phospholipidosis, cirrhosis
5-FU	Accumulation of 5-FU catabolites reduce hepatic capacity to metabolize lipids	Hepatic steatosis
Irinotecan	Induces mitochondrial dysfunction, impaired autophagy	Steatohepatitis
Tamoxifen	Estrogen receptor modulator, promotion of DNL, impairment of β-oxidation. *May or may not be independent of concomitant metabolic risk factors	Steatosis and steatohepatitis
Methotrexate	Mitochondrial injury (inhibits mitochondrial electron transport chain), injury to canals of Hering	Steatosis, steatohepatitis, cirrhosis
Corticosteroids	Exacerbation of metabolic comorbidities, impairment of β-oxidation, impairment of hepatic triglyceride secretion, lipid peroxidation	Steatosis

4. Rinella M, Neuschwander-Tetri B, Siddiqui M, et al. Hepatology 2023

Initial Evaluation for NAFLD

History	Weight history; medical comorbidities; recent and current medications; family history of T2DM, NAFLD, or cirrhosis; screening for OSA; alcohol use, including amount, pattern of use, and duration
Physical examination	Body fat distribution (eg, android vs. gynoid, lipodystrophic), features of insulin resistance (eg, dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (eg, firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomata, palmar erythema)
Laboratory tests	Hepatic panel, CBC with platelets, fasting plasma glucose and glycated hemoglobin (A1c), fasting lipid profile, creatinine and urine microalbumin or protein to creatinine ratio, hepatitis C if not previously screened. Consider as appropriate other causes of steatosis/steatohepatitis (). Additional evaluation if elevated liver chemistries present: autoimmune serologies, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin genotype, or phenotype

Diagnosis of Nonalcoholic Fatty Liver Disease (NAFLD)

- **Diagnosis of NAFLD:** requires evidence of hepatic steatosis, either by imaging or histology, and absence of secondary etiologies of hepatic fat accumulation, such as significant alcohol consumption, long-term use of a steatogenic medications (corticosteroids, methotrexate, amiodarone, and tamoxifen), hepatitis C virus infection, hereditary disorders, severe malnutrition, and Wilson disease.

- **NAFLD Fibrosis Score**: Reduce the need for liver biopsy by identifying patients with non-alcoholic fatty liver disease likely or unlikely to have advanced fibrosis
- NAFLD activity score (NAS) includes potentially reversible features of steatohepatitis, including steatosis (score 0 to 3), lobular inflammation (0 to 3), and hepatocyte ballooning (0 to 2). A total NAS of five or greater correlates with the diagnosis of steatohepatitis

- **Fibrosis-4** (available on MD Calc): liver fibrosis biomarker that is a potential alternative to liver biopsy for diagnosing and managing liver disease.
- A Fibrosis 4 Index score <1.3 is associated with strong negative predictive value for advanced hepatic fibrosis and may be useful for exclusion of advanced hepatic fibrosis in patients with NAFLD.[9]

- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4.

Diagnosis of Nonalcoholic Fatty Liver Disease (NAFLD)

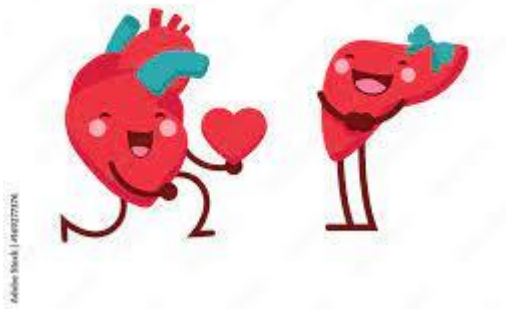
Ultrasound: first-line imaging exam used for the diagnosis of hepatic steatosis
computed tomography

Transient elastography (Fibroscan)

Magnetic Resonance Imaging (MRI): MRI has a better sensitivity for the evaluation of hepatic steatosis (with 92–100% sensitivity, 92–97% specificity) than US

Liver biopsy is required for NASH but not for NAFLD

Histologic evidence of NASH (stage 2 or higher) confers higher risk for adverse hepatic outcomes (hepatic decompensation, HCC, and liver-related mortality)



NAFLD and Cardiovascular Disease

The most common cause of death among NAFLD patients is cardiovascular disease

A strong association exists between NAFLD and atherosclerotic heart disease, heart failure, and arrhythmias, particularly atrial fibrillation.

Endothelial dysfunction developed during NAFLD progression is considered an independent risk factor for CAD[10]

NAFLD impairs endothelial nitric oxide synthase function due to insulin resistance

Several studies suggest that Fatty Liver Disease is an independent risk factor for coronary artery disease

Aggressively treating comorbid conditions such as hypertension, dyslipidemia, and hyperglycemia and promoting smoking cessation is recommended to decrease CVD in those at risk.

Management of Nonalcoholic Fatty Liver Disease

Weight loss has the strongest capacity to induce histological improvement in NASH.[7]

Lifestyle intervention, including exercise, diet modification, and avoidance of fructose- and sugar-sweetened drinks, to target a modest weight loss of 3%–5% is suggested.

Paleo Diet

Coffee

Exercise

Bariatric Surgery

Vitamin E: biopsy-proven NASH in patients without diabetes

Tirzepatide

Orlistat

Metformin

STATIN: moderate-intensity to high-intensity statins as first-line therapy based on lipid risk levels

Fenofibrate or icosapent ethyl (if triglycerides >500)

SGLT2 inhibitors

Pioglitazone

GLP-1: liraglutide

Management of Nonalcoholic Fatty Liver Disease

Fibrosis and the presence of steatohepatitis are the primary predictors of disease progression

Nonpharmacologic factors (frequent visits/monitoring, diet and lifestyle counseling) may reduce progression.

Moderate alcohol consumption decreases improvement in steatosis

Lean individuals with NAFLD should be evaluated routinely for comorbid conditions, such as type 2 diabetes mellitus, dyslipidemia, and hypertension.

Hepatocellular carcinoma surveillance with abdominal ultrasound with or without serum α-fetoprotein twice per year is suggested in patients with NAFLD and clinical markers compatible with liver cirrhosis.

Is NAFLD a Multi-Organ Systemic Disease that is Being Overlooked?

- **Cardiovascular Disease**: Independent Risk Factor
- **Gynecology:** Alterations in reproductive hormones are linked to the development and progression of NAFLD in women. Women with polycystic ovary syndrome and those with estrogen deficiency are at increased risk of NAFLD, with higher mortality rates in older women compared to men of similar ages
- **Psychology**: NAFLD more likely to suffer personality disorder.
- **Urology:** Increase risk of urolithiasis. Increase risk of BPH (regardless of metabolic syndrome)
- **Neurology:** NAFLD showed worse executive and frontal functions, and behavioral changes, such as depressive mood and anxiety, and apathy. Brain disorders may be extrahepatic manifestations of NAFLD, such as depression, changes to the cerebrovascular system, and worsening cognitive ability.
- **Oncology:** Increased cancer risk
- **Nephrology:** NAFLD increases risk of chronic kidney disease
- **Hematology**: Increased ferritin levels, hepatic iron deposits and iron overload are associated with NAFLD
- **Rheumatology:** NAFLD and inflammatory arthritis
- **Endocrinology:** hyperprolactinemia, hypercortisolemia, and polycystic ovary syndrome seem to worsen NAFLD's pathway. Hypothyroidism and low growth hormone levels also may contribute to NAFLD's progression

Take Home Points

Assessment of NAFLD

• Aminotransferase levels are frequently normal in patients with advanced liver disease
• ALT >30 U/L should be considered abnormal
• Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum
• CAP as a point-of-care technique may be used to identify steatosis. MRI can additionally quantify steatosis

Disease modifying interventions in patients with NAFLD

• Patients with NAFLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. When possible, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (Paleo, Mediterranean diet) should be encouraged due to their cardiovascular benefits
• Patients with NAFLD should increase their activity level.
• Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery as it effectively resolves NAFLD or NASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy

QUESTIONS?

Linda “El” Summers, DMSc, MS, PA-C
Physician Associate
Riverside Cardiology Specialists
Linda.summers@rivhs.com
214.335.1028

REFERENCES

1.Guo X, Yin X, Liu Z, Wang J. Non-Alcoholic Fatty Liver Disease (NAFLD) Pathogenesis and Natural Products for Prevention and Treatment. International Journal of Molecular Sciences. 2022; 23(24):15489. https://doi.org/10.3390/ijms232415489

2.Le MH, Yeo YH, Li X, et al. 2019 global NAFLD prevalence: A systematic review and meta-analysis. Clinical Gastroenterology and Hepatology. 2022;20(12):2809-2817.e28.https://www.sciencedirect.com/science/article/pii/S1542356521012805. doi: 10.1016/j.cgh.2021.12.002.

3.Wattacheril, Julia J. et al. AGA Clinical Practice Update on the Role of Noninvasive Biomarkers in the Evaluation and Management of Nonalcoholic Fatty Liver Disease: Expert Review. Gastroenterology, Volume 165, Issue 4, 1080 – 1088. August 04, 2023. DOI:https://doi.org/10.1053/j.gastro.2023.06.013

4.Rinella M, Neuschwander-Tetri B, Siddiqui M, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):p 1797-1835, May 2023. | DOI: 10.1097/HEP.0000000000000323

5.Cotter T, Rinella M. Nonalcoholic Fatty Liver Disease 2020: The State of the Disease. Gastroenterology, Volume 158, Issue 7, 1851 – 1864. February 12, 2020. DOI:https://doi.org/10.1053/j.gastro.2020.01.052

6.Long M, Noureddin M, Lim J. AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review. Gastroenterology, Volume 163, Issue 3, 764 - 774.e1. July 13, 2022DOI:https://doi.org/10.1053/j.gastro.2022.06.023

7.Godoy-Matos AF, Silva J, Valerio CM. NAFLD as a continuum: from obesity to metabolic syndrome and diabetes. Diabetol Metab Syndr 12, 60 (2020). https://doi.org/10.1186/s13098-020-00570-y

8.Byrne CD. Banting memorial lecture 2022: 'Type 2 diabetes and nonalcoholic fatty liver disease: Partners in crime'. Diabet Med. 2022;39(10):e14912. doi:10.1111/dme.14912

9.Wattacheril J, Abdelmalek M, Lim J, et al. AGA Clinical Practice Update on the Role of Noninvasive Biomarkers in the Evaluation and Management of Nonalcoholic Fatty Liver Disease: Expert Review. Gastroenterology, Volume 165, Issue 4, 1080 – 1088. August 04, 2023. DOI:https://doi.org/10.1053/j.gastro.2023.06.01

10.Cazac GD, Lăcătușu CM, Mihai C, Grigorescu ED, Onofriescu A, Mihai BM. New Insights into Non-Alcoholic Fatty Liver Disease and Coronary Artery Disease: The Liver-Heart Axis. Life (Basel). 2022;12(8):1189. Published 2022 Aug 4. doi:10.3390/life12081189