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Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis

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REVIEW ARTICLE

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Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis

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FATTY LIVER DISEASE IS THE MOST COMMON LIVER DISEASE IN THE WORLD. About 25% of adults in the United States have fatty livers in the absence of excessive alcohol consumption, a condition termed nonalcoholic fatty liver disease. More than a quarter of adults with nonalcoholic fatty liver disease are presumed to have nonalcoholic steatohepatitis on the basis of elevated serum aminotransferase levels and an absence of other identifiable causes of liver injury.[1] A definitive diagnosis of nonalcoholic steatohepatitis is currently based on histologic evidence not only of fat accumulation (steatosis) in hepatocytes but also of liver-cell injury and death and accumulation of inflammatory cells (Fig. 1A and 1B). Because livers with nonalcoholic steatohepatitis are more damaged than livers with isolated steatosis, nonalcoholic steatohepatitis is more likely than isolated steatosis to lead to progressive liver fibrosis and eventual liver-related illness and death[2-6] (Fig. 1C). This review focuses on our understanding of the epidemiology and pathogenesis of nonalcoholic steatohepatitis, which underpins practice guidelines and drug development for this life-threatening liver disease.

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Fatty liver: Terminology

- **ALD: Alcoholic Liver Disease**
Significant alcohol consumption

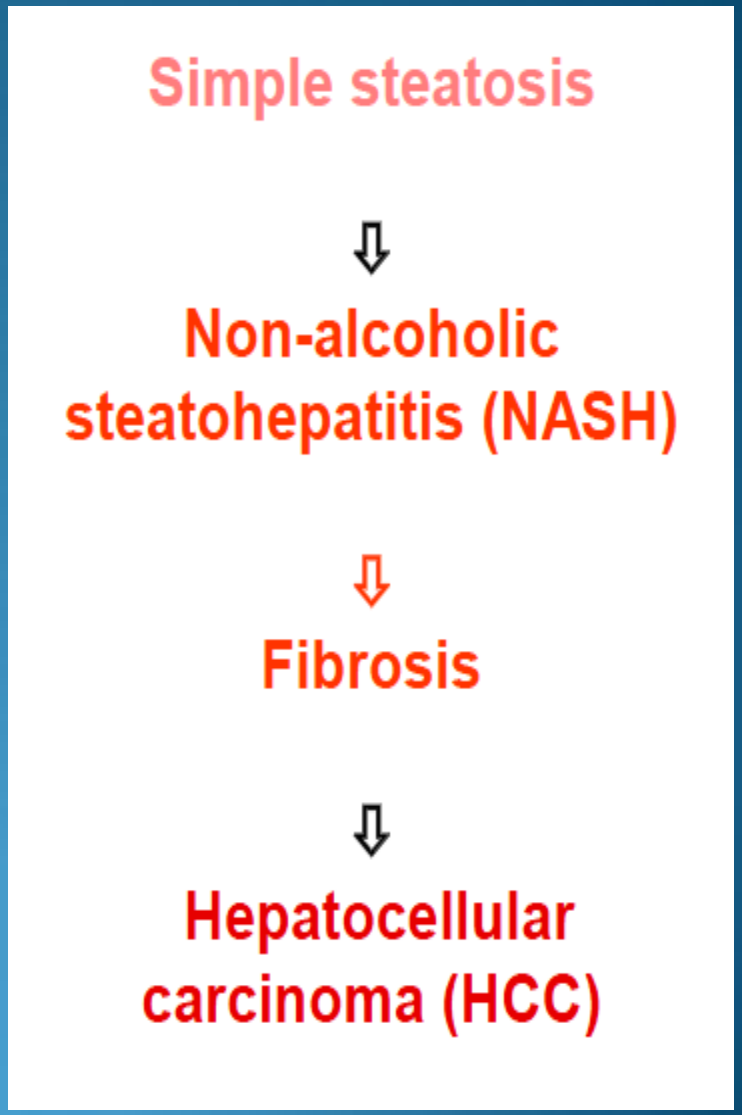
- **NAFLD: Non-Alcoholic Fatty Liver Disease**
steatosis without hepatocyte injury

- **NASH: Non-Alcoholic Steatohepatitis**
steatosis with inflammation,
hepatocyte injury with or without fibrosis

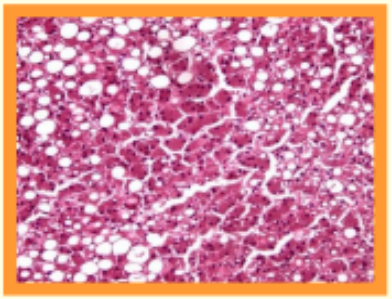
Fatty liver disease is the most common liver disease in the world.

About ٢٥% of adults in the United States have fatty livers in the absence of excessive alcohol consumption, a condition termed nonalcoholic fatty liver disease.

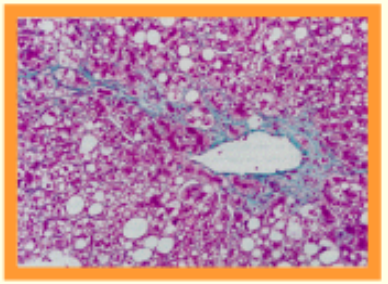
More than a quarter of adults with nonalcoholic fatty liver disease are presumed to have **nonalcoholic steatohepatitis** on the basis of elevated serum aminotransferase levels and an absence of other identifiable causes of liver injury.



Non-alcoholic fatty liver disease: Basic definitions



All pts with fatty liver



Liver biopsy

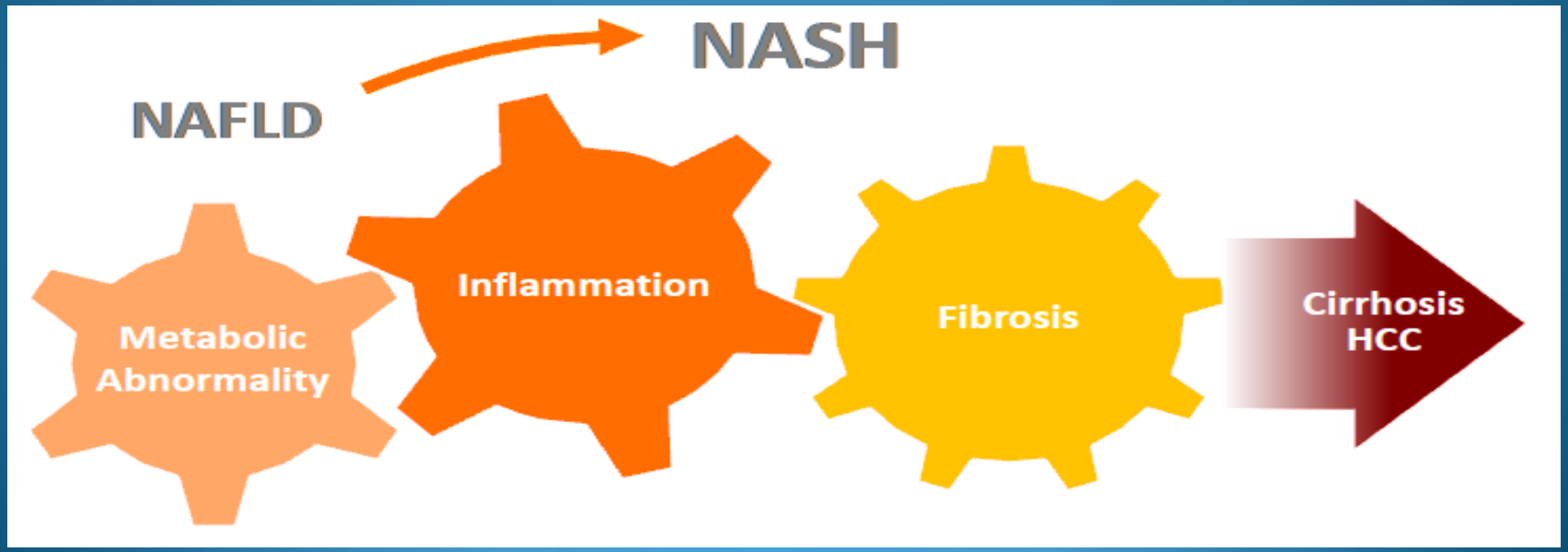
Isolated fatty liver

Non-alcoholic steatohepatitis (NASH): fat + inflammation +/- fibrosis

**Alcoholic steatohepatitis (ASH) cannot be differentiated from NASH on biopsy, history is critical

Increased risk: Cirrhosis & Liver cancer

A definitive diagnosis of nonalcoholic steatohepatitis is currently based on histologic evidence not only of fat accumulation (steatosis) in hepatocytes but also of liver-cell injury and death and accumulation of inflammatory cells.



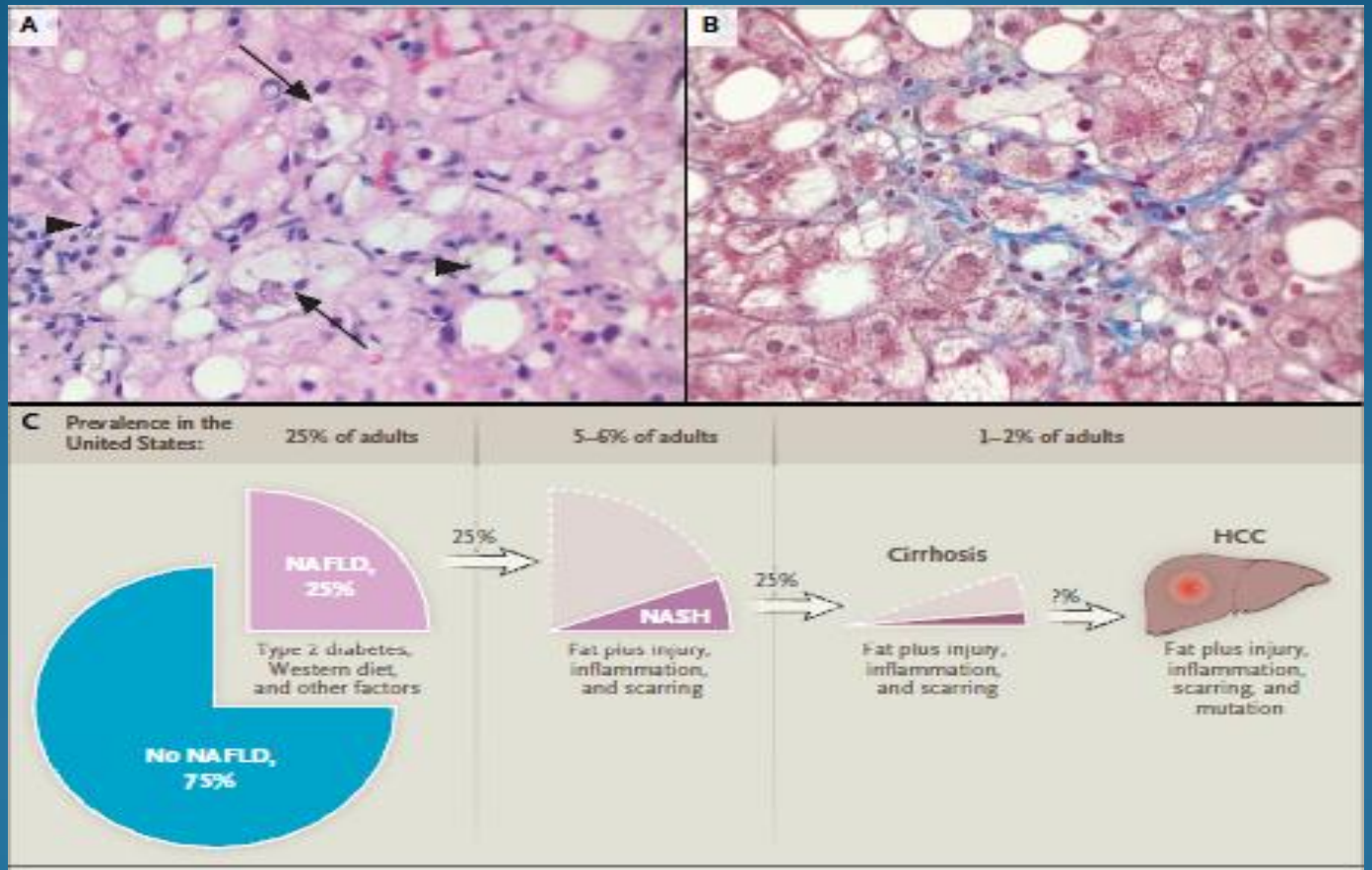


Figure 1. Histologic Features and Prevalence of Nonalcoholic Steatohepatitis (NASH).

NASH is a potentially progressive type of nonalcoholic fatty liver disease (NAFLD). Panels A and B show characteristic histologic features of NASH in liver-biopsy specimens: ballooned hepatocytes (arrows), inflammatory infiltrate (arrowheads), and fibrosis. Panel C shows the relative distribution of NASH, cirrhosis, and primary liver cancer in the U.S. adult population. Data in Panel C are from Williams et al.[2] and Adams et al.[3] HCC denotes hepatocellular carcinoma.

Epidemiologic Features

Nonalcoholic steatohepatitis is strongly associated with

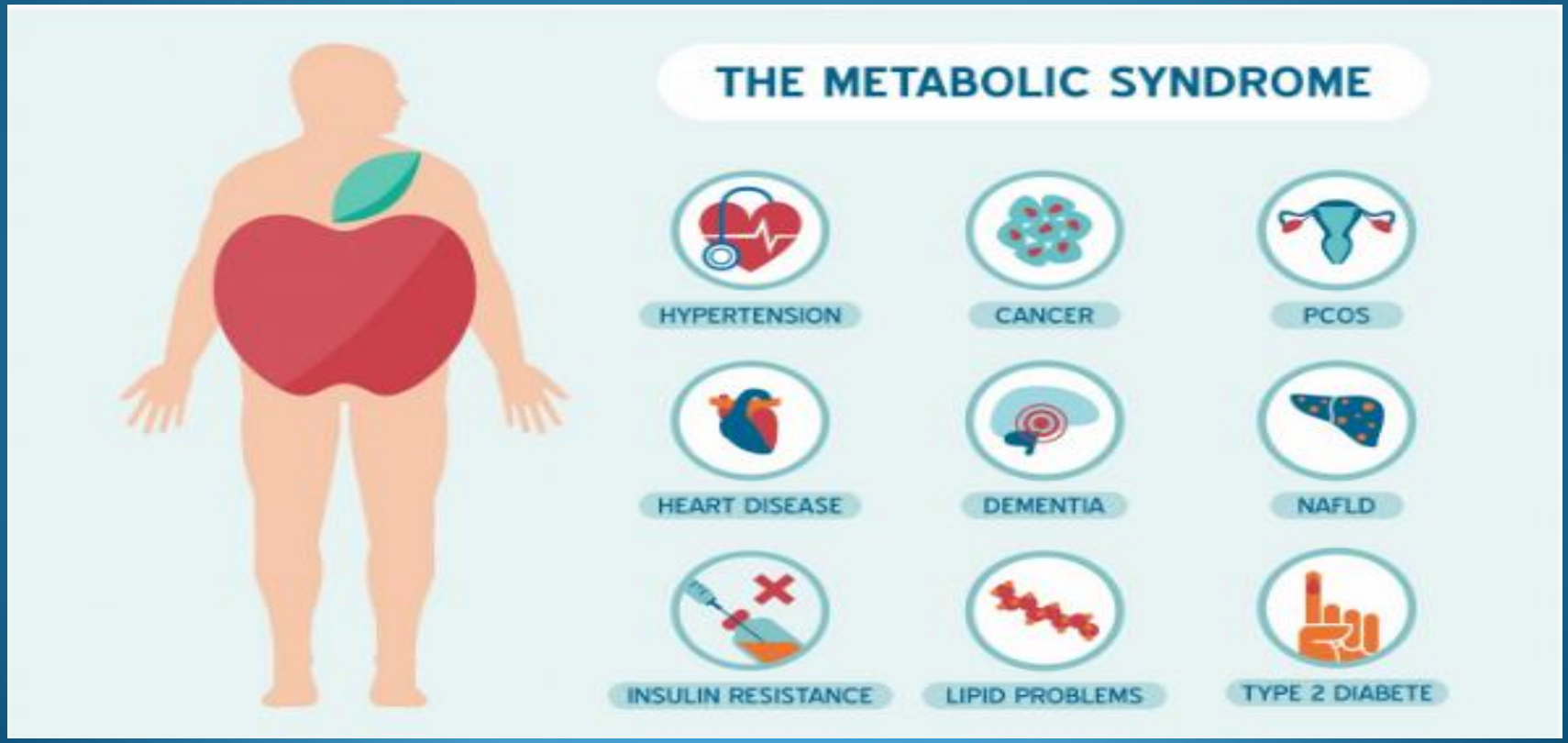
Overweight or obesity

Metabolic syndrome

٨٠% overweight or obese
٧٢% have dyslipidemia
٤٤% have received a diagnosis of type ٢ diabetes mellitus.

- Obesity
- Type 2 DM
- Dyslipidemia
- Metabolic syndrome

This information supports the concept that nonalcoholic steatohepatitis is the hepatic correlate of the **metabolic syndrome.**



Nonalcoholic steatohepatitis is strongly associated with **liver fibrosis** (scarring), according to liver biopsy series.

Comparative Scoring Systems for Histologic Stage (Fibrosis)			
Score	**IASL**	**Batts-Ludwig**	**Metavir**
0	No Fibrosis	No Fibrosis	No Fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion
2	Moderate fibrosis	Rare bridges or septae	Periportal septae (> 1 septum)
3	Severe fibrosis	Numerous bridges or septae	Portal-central septae
4	Cirrhosis	Cirrhosis	Cirrhosis

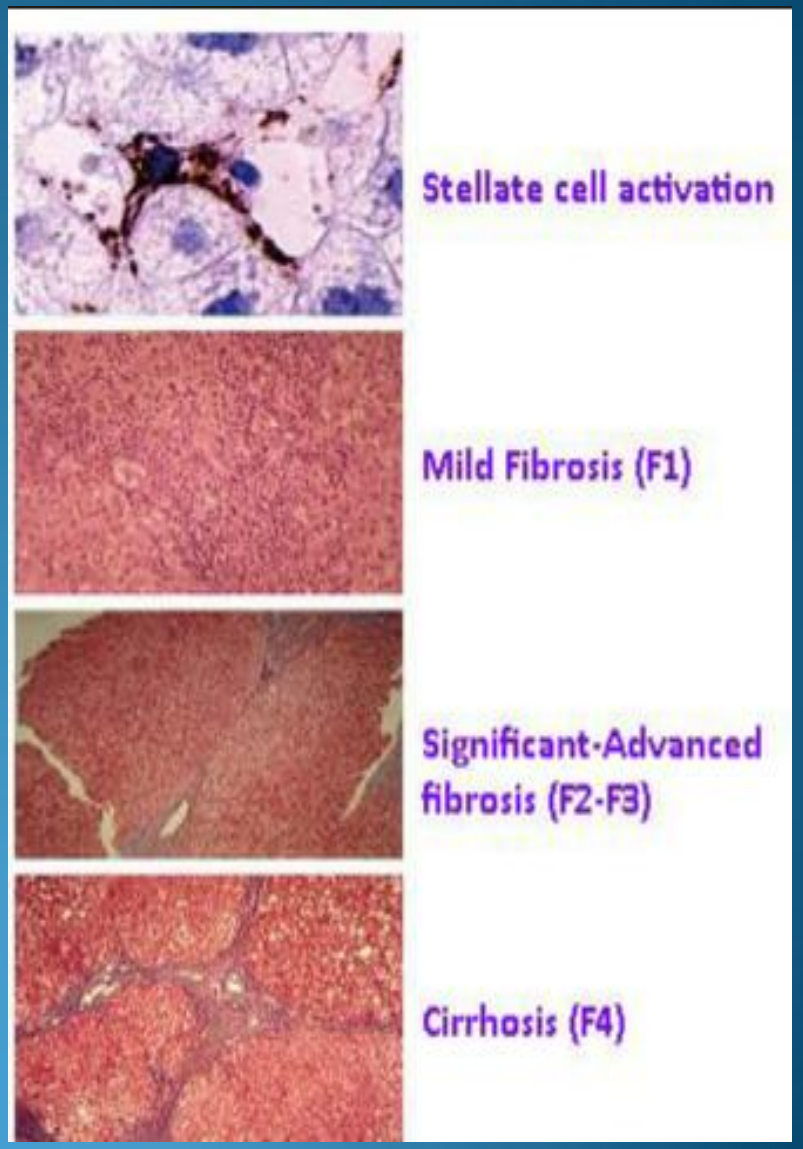
No fibrosis [F٠],

Portal fibrosis without septa [F١],

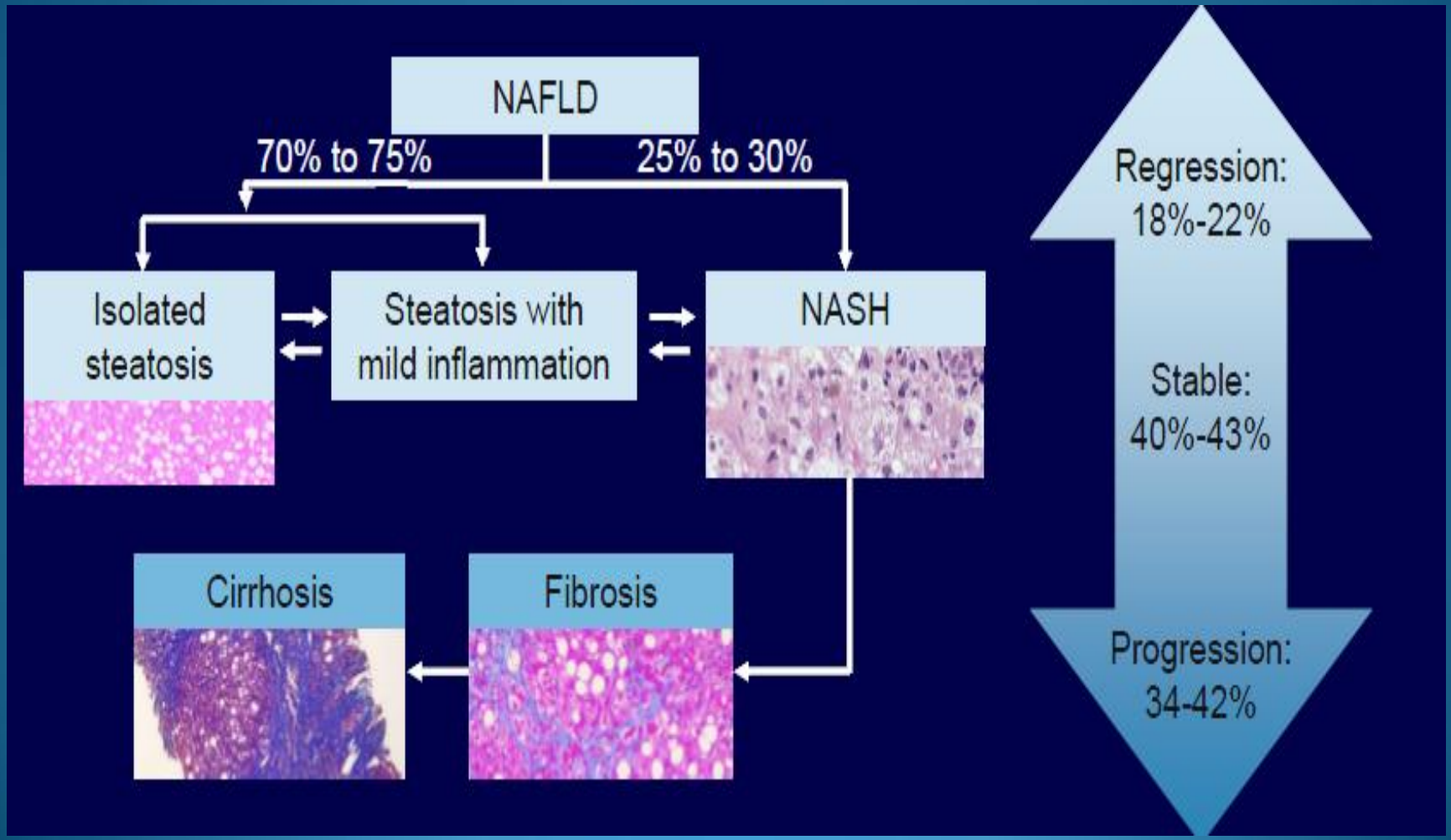
Portal fibrosis with few septa[F٢],

Bridging septa between central and Portal veins [F٣],

Cirrhosis [F٤]



Nonalcoholic steatohepatitis is a dynamic condition

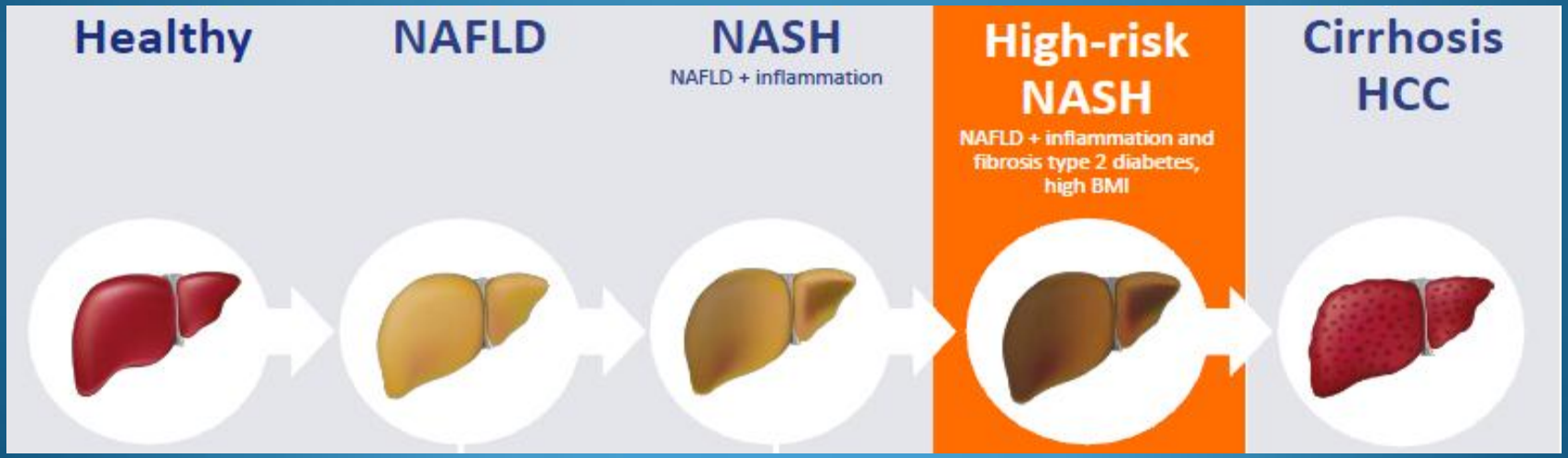


Severity of liver fibrosis is the only histologic measure that independently predicts

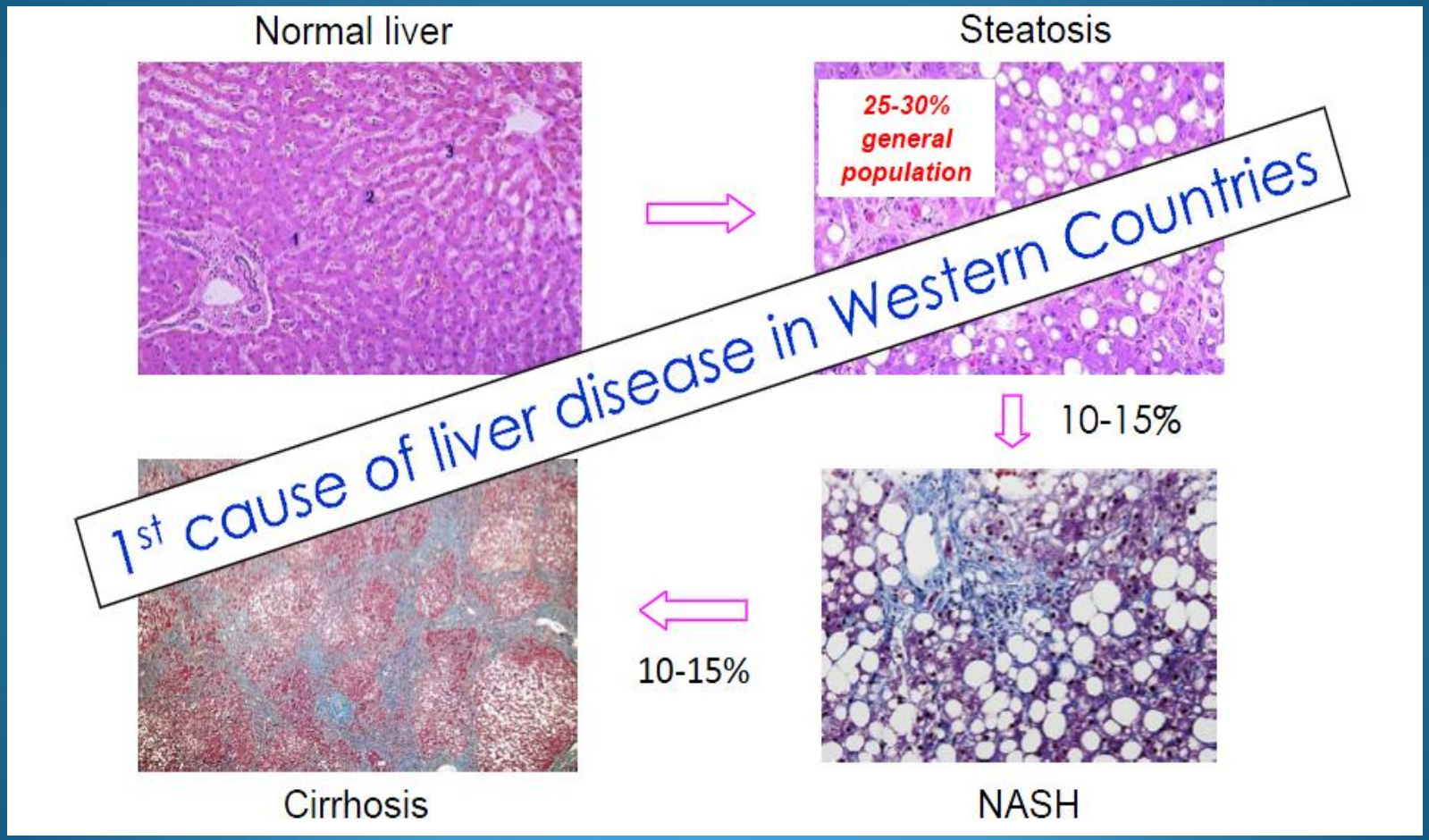
- **liver-related illness,**
- **liver transplantation,**
- **liver-related death**

in patients with nonalcoholic fatty liver disease.

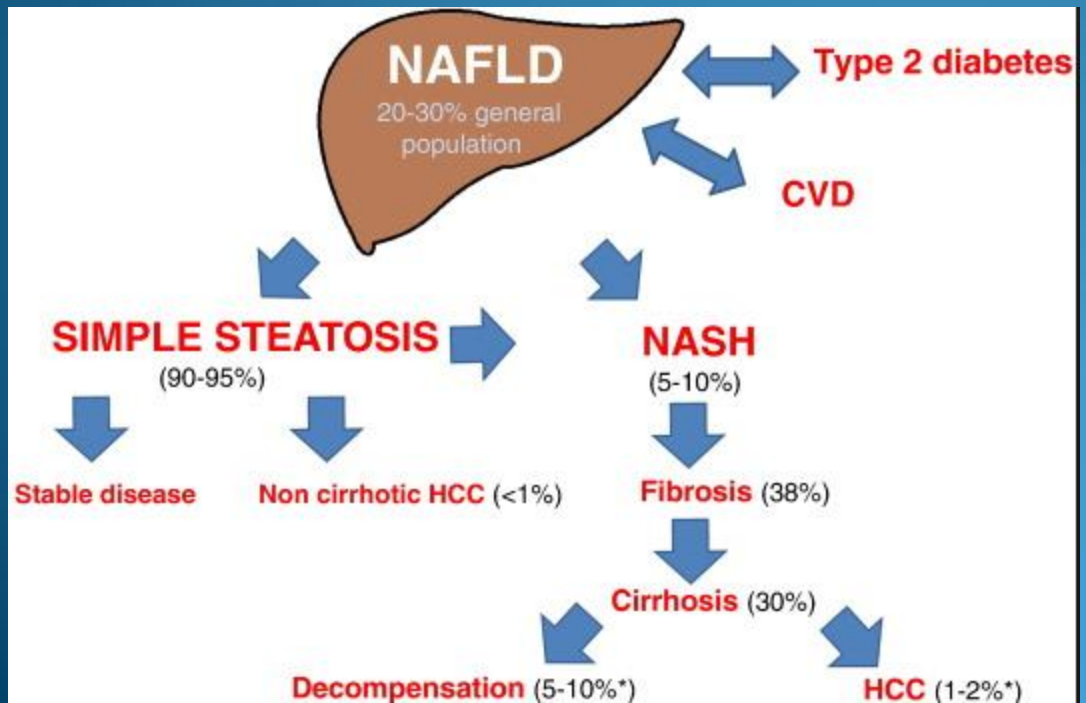
Analyses of sequential liver-biopsy specimens in patient cohorts indicate that **liver fibrosis progresses** at a rate of approximately **one stage per decade**, suggesting that F۲ fibrosis will progress to cirrhosis within ۲۰ years.



Nonalcoholic steatohepatitis will most likely be the top reason for liver transplantation in the United States by ٢٠٢٠.



The incidence of hepatocellular carcinoma is at least ١ to ٢% per year among **patients with cirrhosis** related to nonalcoholic steatohepatitis; **primary liver cancers** can also develop in patients with noncirrhotic nonalcoholic steatohepatitis.



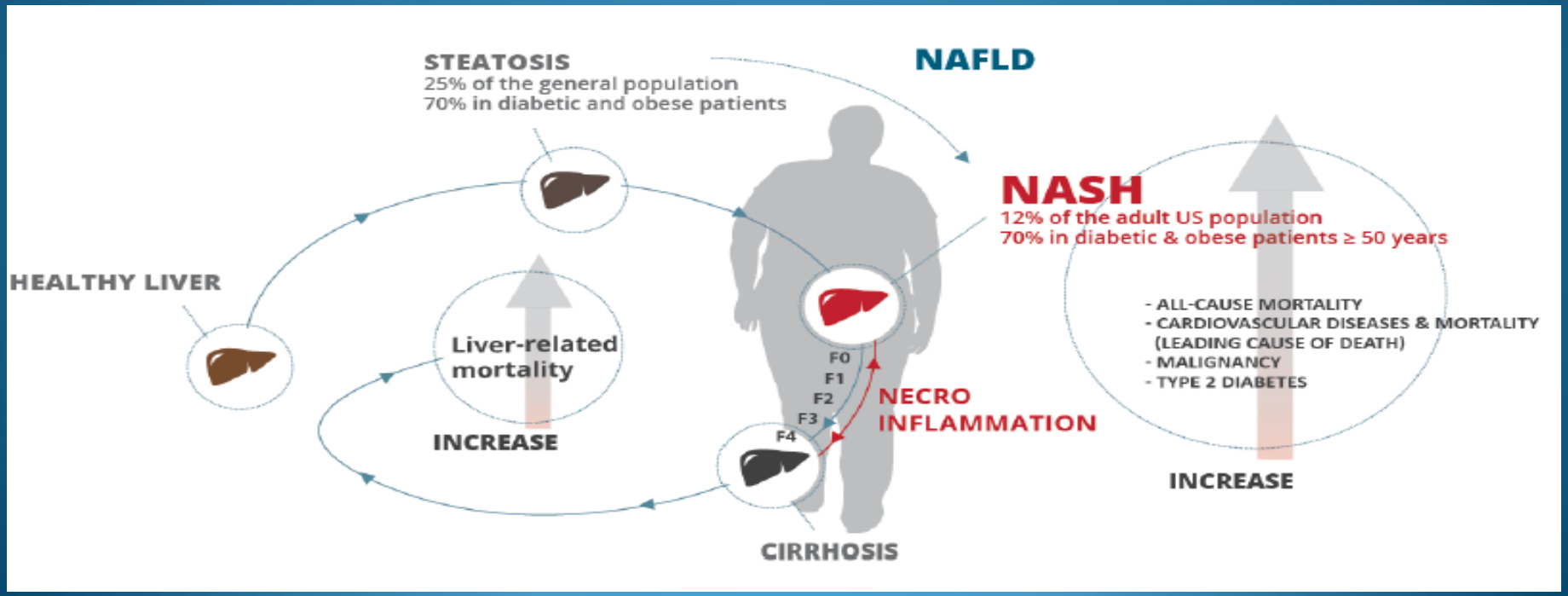
As with adults, nonalcoholic steatohepatitis in children is strongly associated with obesity.

Childhood obesity increased the risk of hepatocellular carcinoma in adulthood.

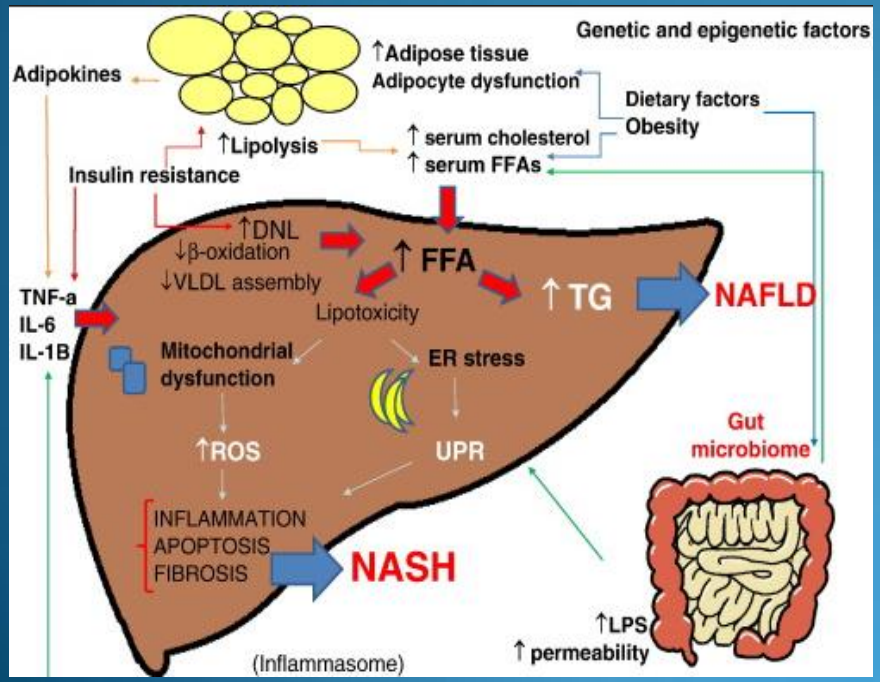
More than $١٠٠ billion in annual

Pathogenesis

Nonalcoholic steatohepatitis always develops in the context of hepatic steatosis, but isolated steatosis is three or four times as prevalent as nonalcoholic steatohepatitis.



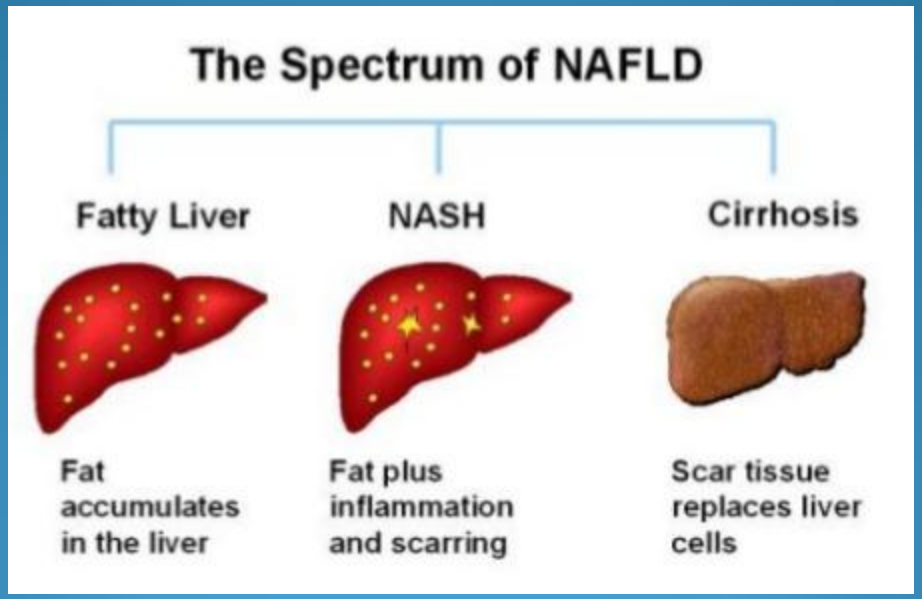
Hepatocyte injury is inflicted by toxic triglyceride precursors or products of triglyceride metabolism.



Hepatocyte injury and death

Nonalcoholic steatohepatitis

Isolated steatosis.



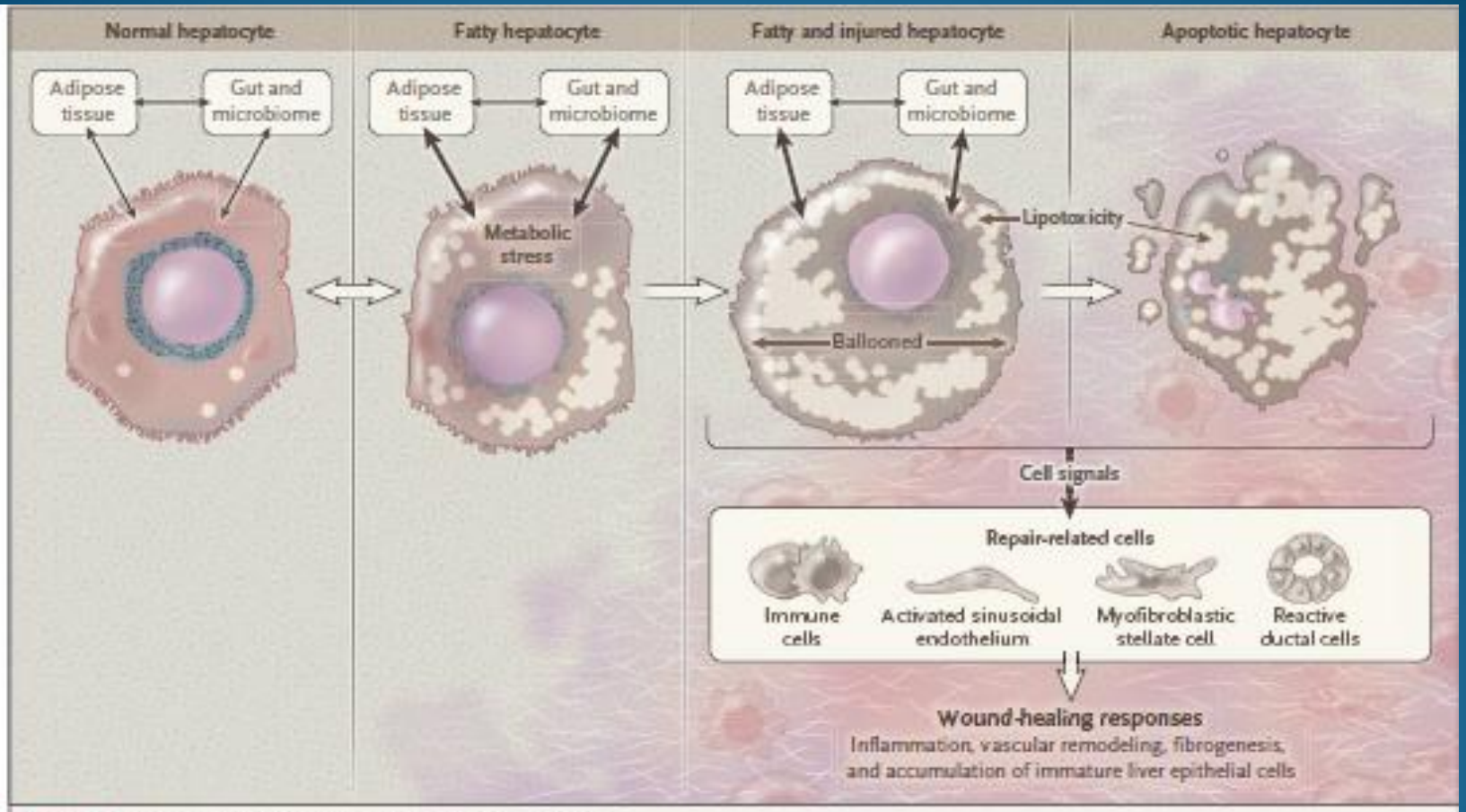


Figure 2. Pathogenesis of Nonalcoholic Steatohepatitis.

Various factors, including inflammation, hyperinsulinemia or insulin resistance, and altered lipid homeostasis, can induce metabolic stress, oxidative stress, and endoplasmic reticulum–related stress to develop in fatty hepatocytes (i.e., lipotoxicity). Changes from normal signaling patterns are indicated by thick double-headed arrows. When mechanisms to cope with these stresses become overwhelmed, hepatocytes die. Dying and dead hepatocytes release signals to cells that are necessary for the repair of liver damage, such as immune cells, sinusoidal endothelial cells, hepatic stellate cells, and ductal-type cells. The hepatocyte-derived, damage-associated signals cause the repair-related cells to accumulate and launch wound-healing responses, which include inflammation, vascular remodeling, fibrogenesis, and hepatic accumulation of immature liver epithelial cells. Nonalcoholic steatohepatitis is the sum of injury and repair responses triggered by lipotoxicity.

Pathogenic factors

- **Inherited factors**
- **Environmental factors**

Genetic Factors

Phospholipase domain–containing ۳ (PNPLA۳)

Transmembrane ۶ superfamily, member۲(TM۶SF۲)

The I١٤٨M polymorphism

Alcohol-induced fatty liver disease
Chronic hepatitis C,
Infection that promotes hepatic steatosis.

Ethnics

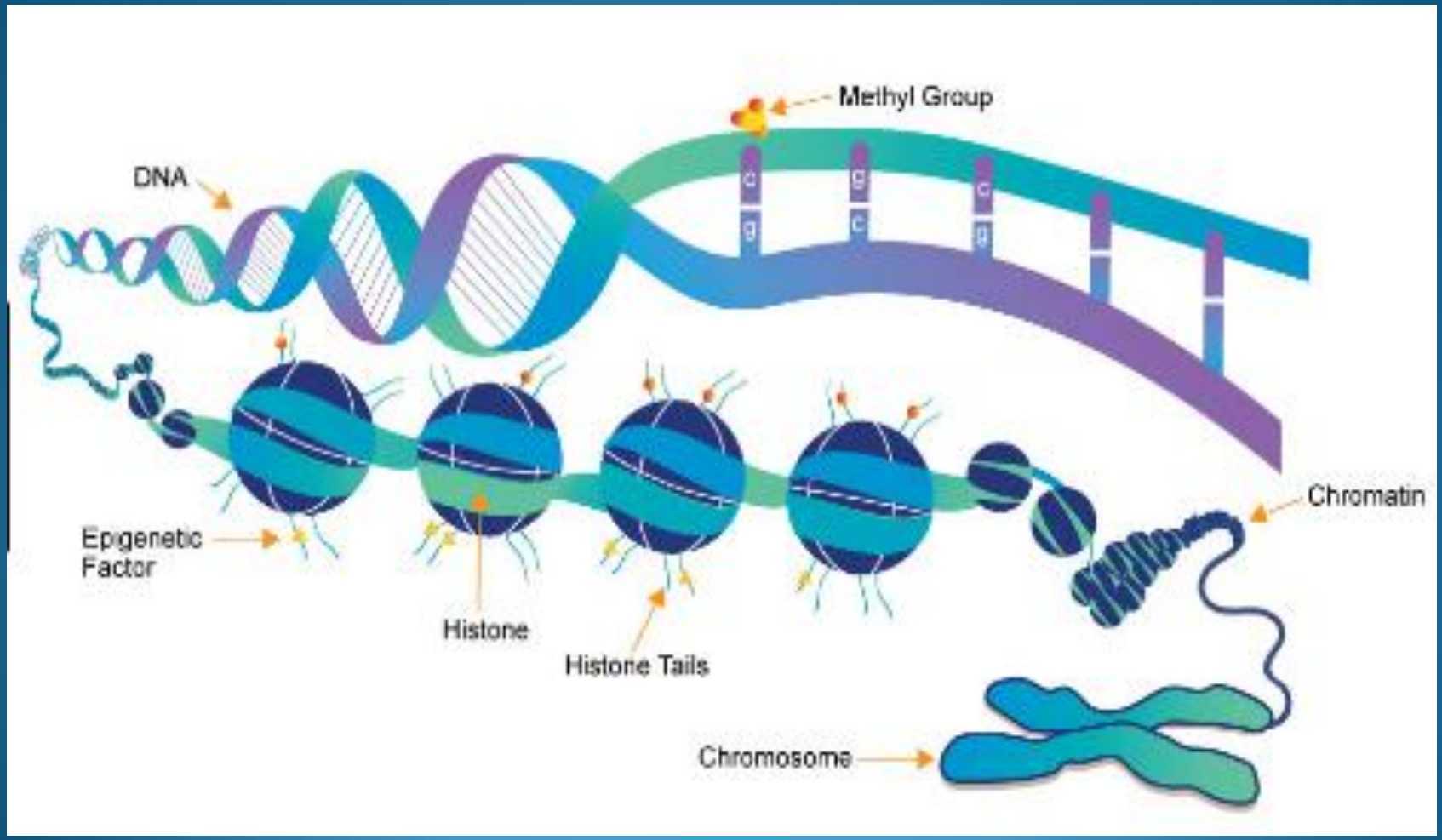
pathologic *PNPLA ۳ polymorphisms*

Asian and native American populations.

Whites of Northern Europe.

Blacks.

Epigenetic Factors

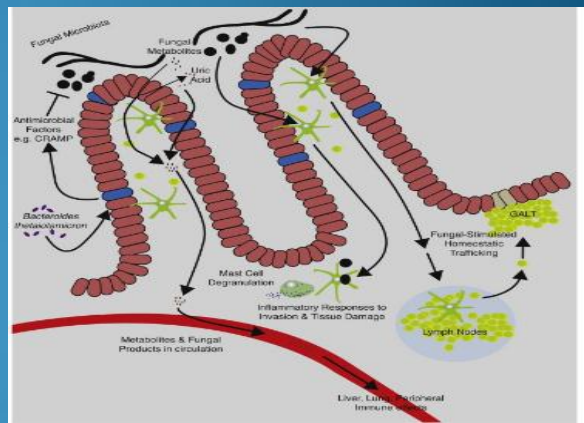


Environmental Factors

Modifiable risk factors

Shift work

Alterations in commensal microbiota



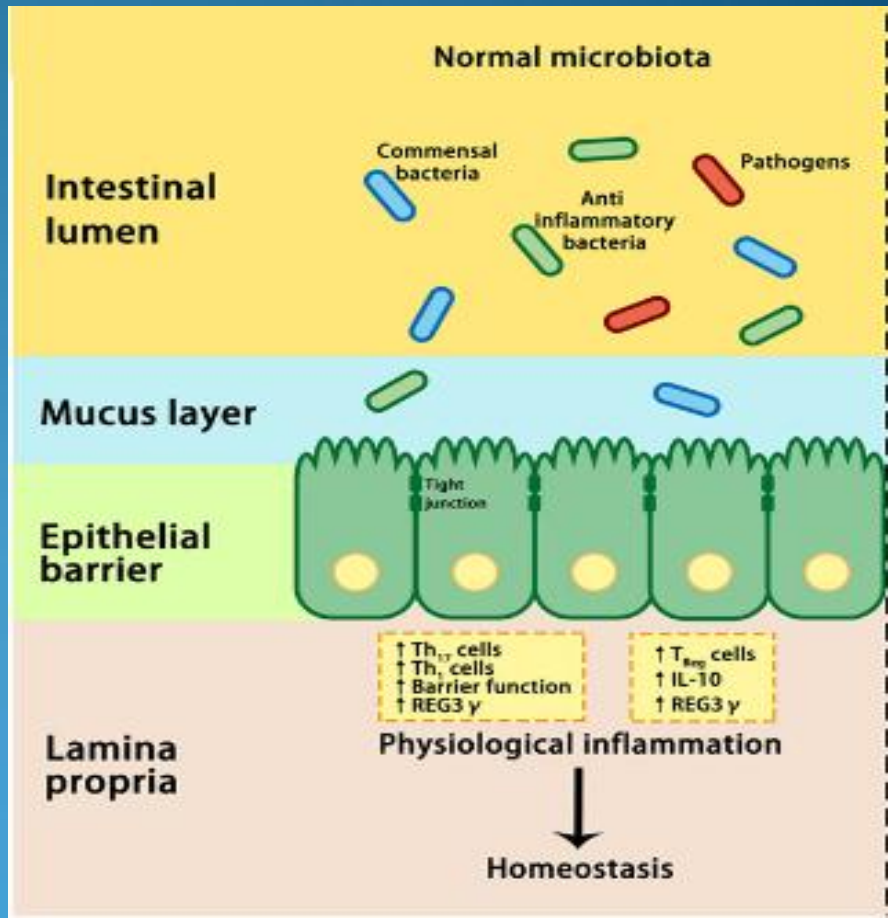
Environmental Factors

The intestinal microbiota influence host susceptibility to

- **Obesity,**
- **Hepatic steatosis,**
- **Nonalcoholic steatohepatitis,**
- **Liver fibrosis,**
- **Primary liver cancer.**

Host factors influence the intestina microbiota:

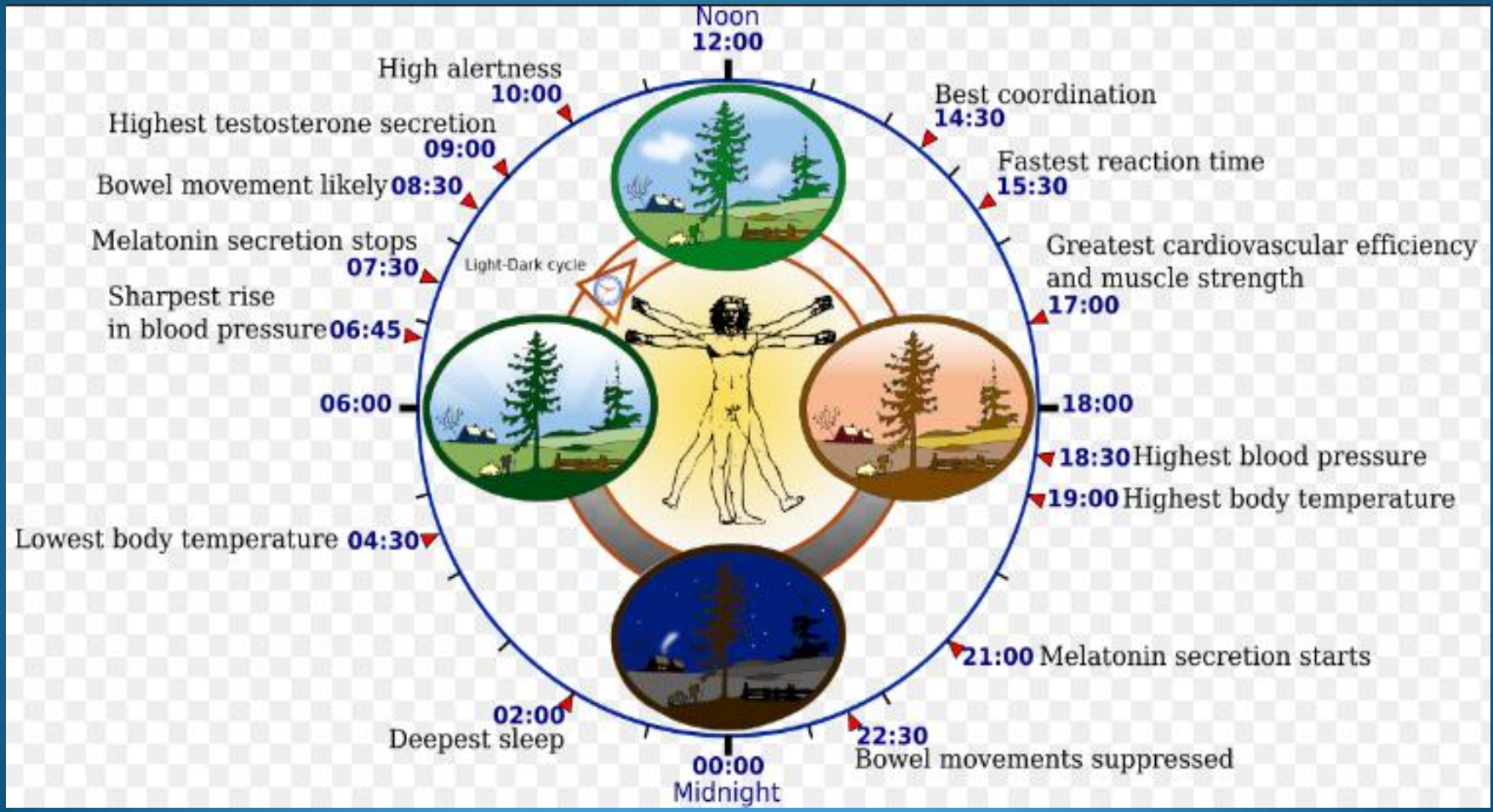
- Diet composition,
- Adiposity,
- Feeding frequency,
- Sleep–wake cycles.



Shift work and travel that perturb normal feeding and sleep–wake cycles promote

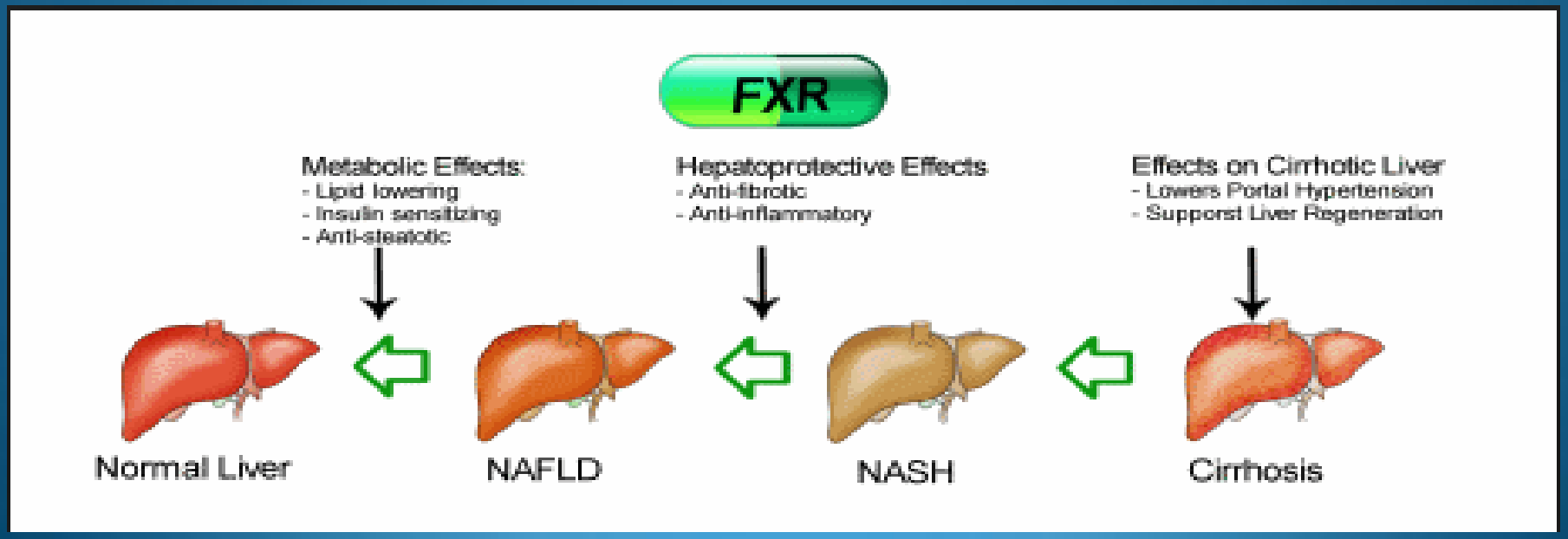
- **Adiposity,**
- **The metabolic syndrome,**
- **Nonalcoholic fatty liver disease.**

Normal circadian rhythms



Farnesoid X receptor (FXR)

Constitutive androstane receptor (CAR)

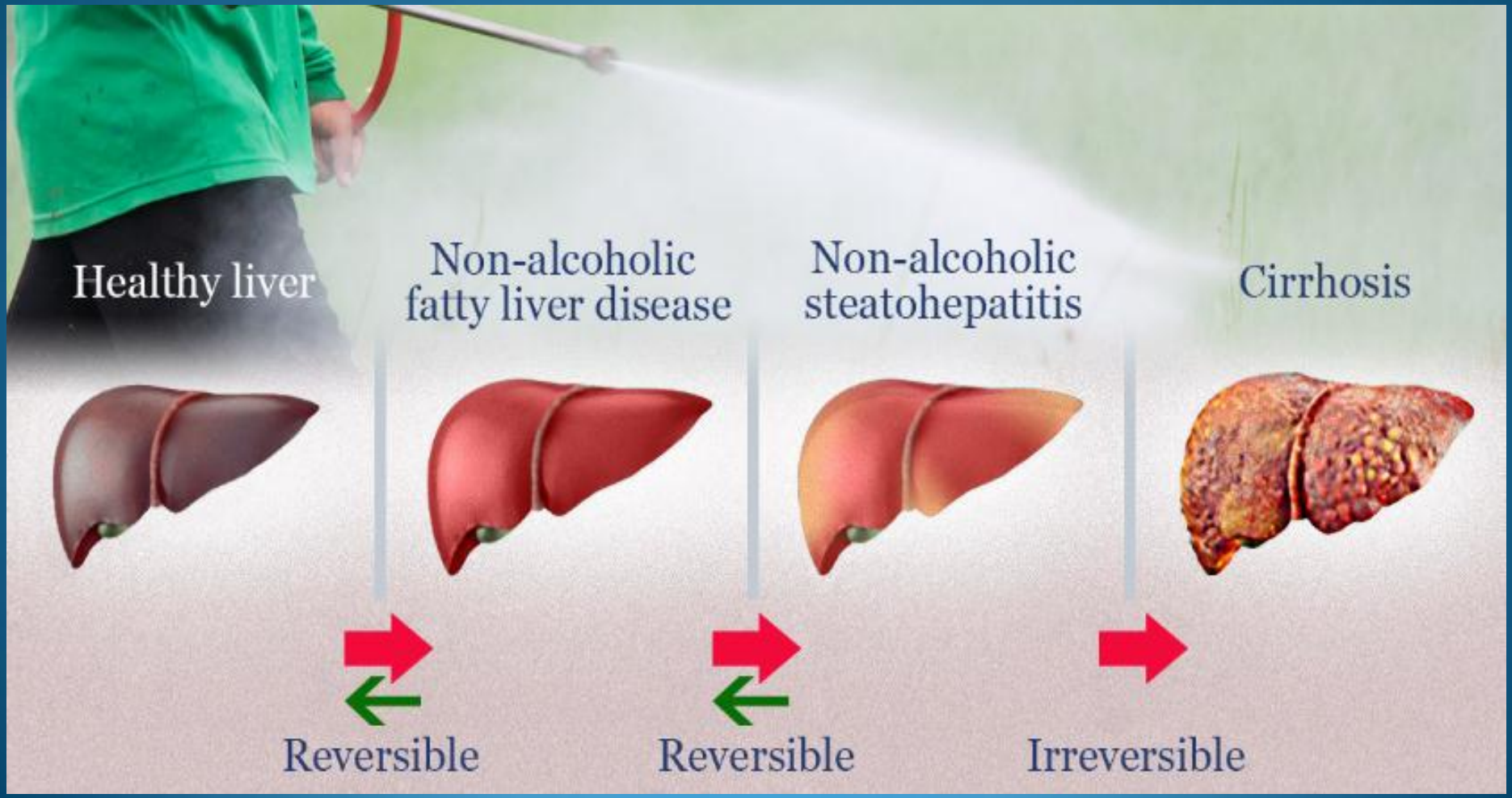


FXR agonists and certain **FXR-regulated factors** (e.g., fibroblast growth factors ١٩ and ٢١) are being evaluated as treatments for human nonalcoholic steatohepatitis.

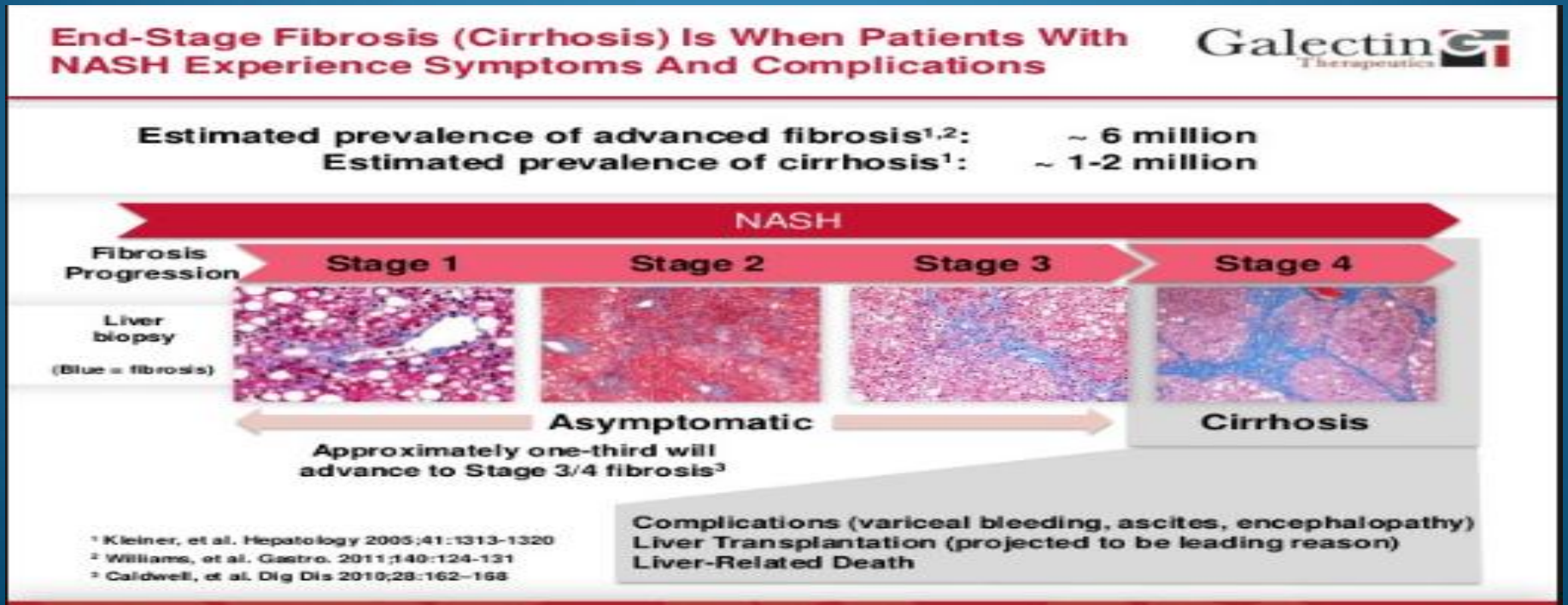
Inhibiting CAR might be beneficial in patients with nonalcoholic steatohepatitis.

losartan, an adrenergic antagonist, mitigates nonalcoholic steatohepatitis and fibrosis in humans.

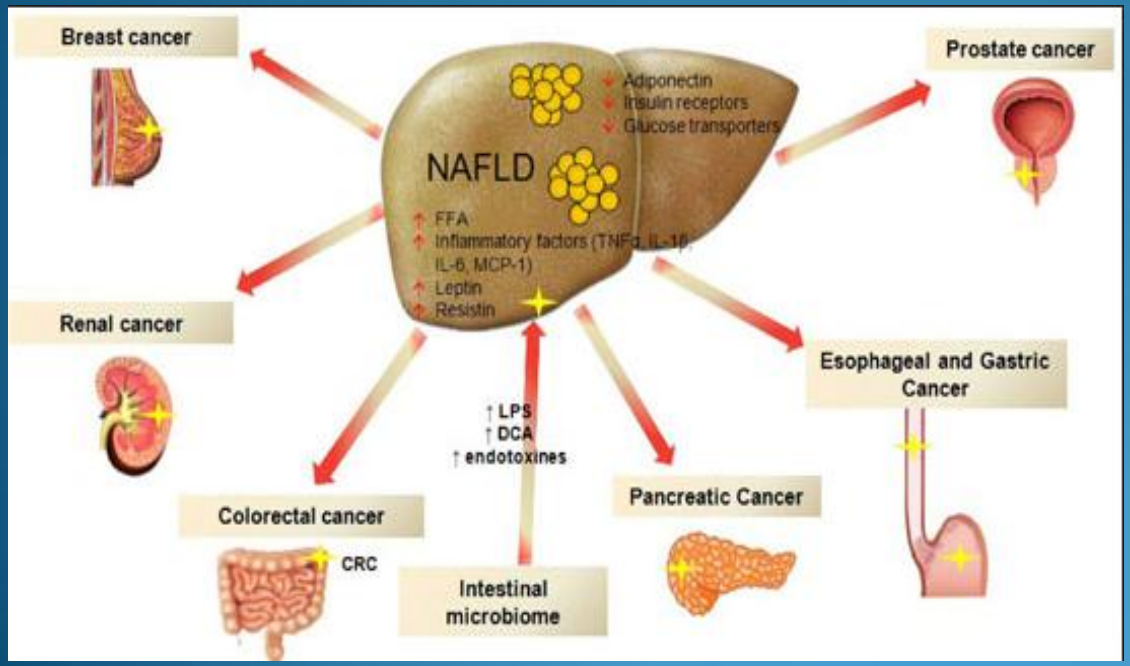
Diagnostic and Therapeutic Implications



The risk of death from liver disease increases by a factor of ٥٠ to ٨٠ for patients with nonalcoholic steatohepatitis who have F٣ or F٤ fibrosis, as compared with those who have nonalcoholic steatohepatitis with little or no fibrosis.



Isolated hepatic steatosis is not entirely benign.

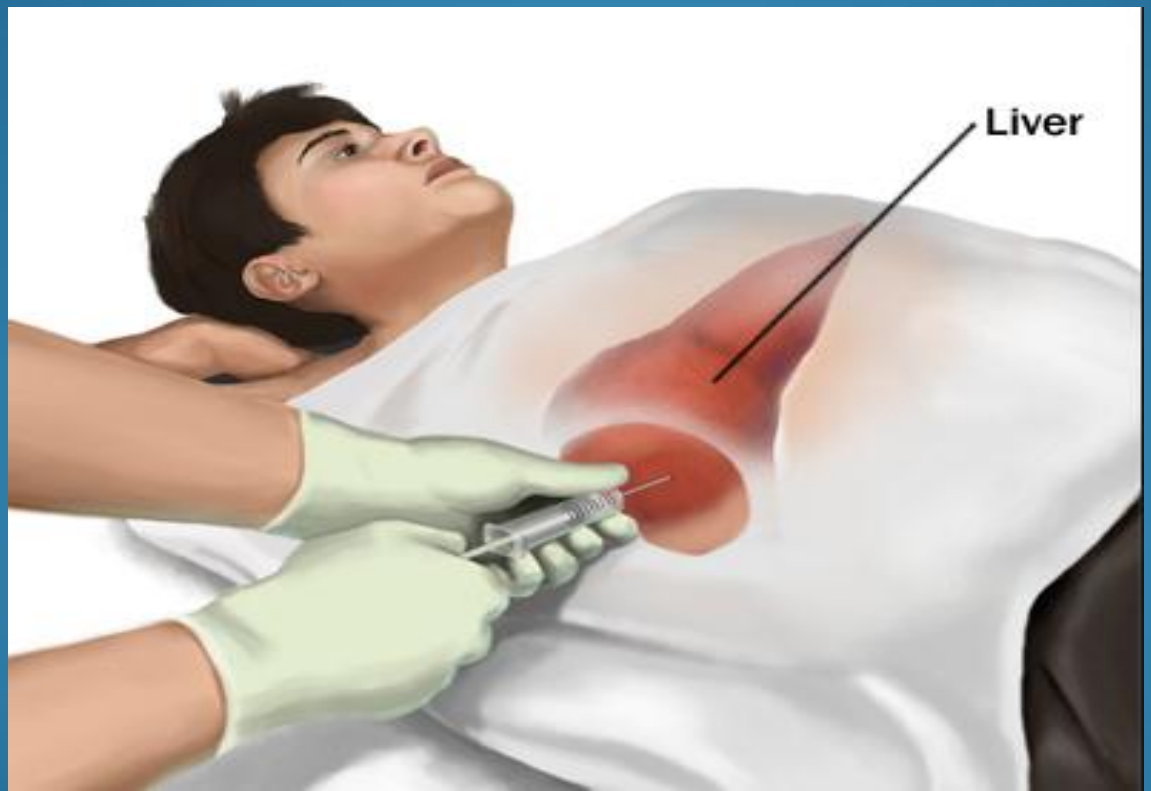


- Obesity,
- Insulin resistance,
- Hepatic steatosis.

Overweight or obese persons with the metabolic syndrome, elevated serum aminotransferase levels, and a negative noninvasive workup for other causes of liver disease are likely to have nonalcoholic steatohepatitis.

Those who are ۴۵ years of age or older and who have type ۲ diabetes are particularly likely to have advanced fibrosis and an increased risk of bad liver outcomes.

Liver biopsy is currently the most widely accepted approach for diagnosing nonalcoholic steatohepatitis and staging liver fibrosis.



- Serum biomarkers,
- New imaging tests that can quantify liver fibrosis,
- Dynamic tests of liver function,
- Genetic screening for polymorphisms.

Lifestyle modifications are the main intervention for nonalcoholic steatohepatitis without fibrosis.

Table 1. Lifestyle Modifications to Mitigate Nonalcoholic Steatohepatitis.*
Lose 7% of body weight if overweight or obese
Limit consumption of fructose-enriched beverages
Limit consumption of alcohol (≤1 drink/day for women and ≤2 drinks/day for men)
Drink two or more cups of caffeinated coffee daily

* Fructose increases the odds of the development of nonalcoholic fatty liver in high-risk patients and of nonalcoholic steatohepatitis and more advanced liver fibrosis in patients who already have nonalcoholic fatty liver disease. Caffeinated coffee reduces the risk of liver fibrosis in several liver diseases, including non-alcoholic fatty liver disease.

Adjunctive treatment with vitamin E or Pioglitazone might also be considered.

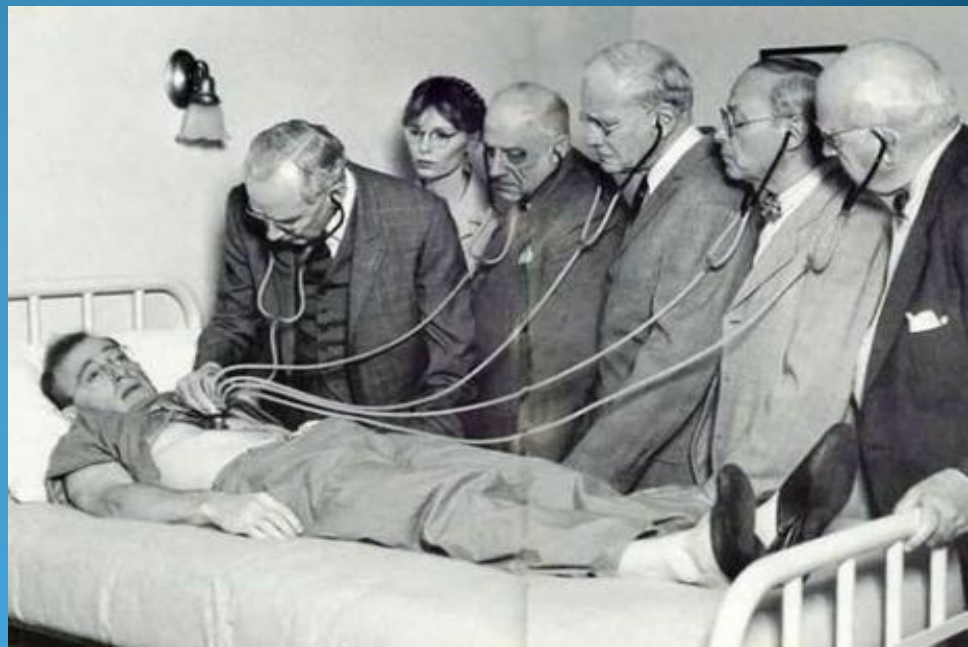
Pioglitazone

Mechanism of action

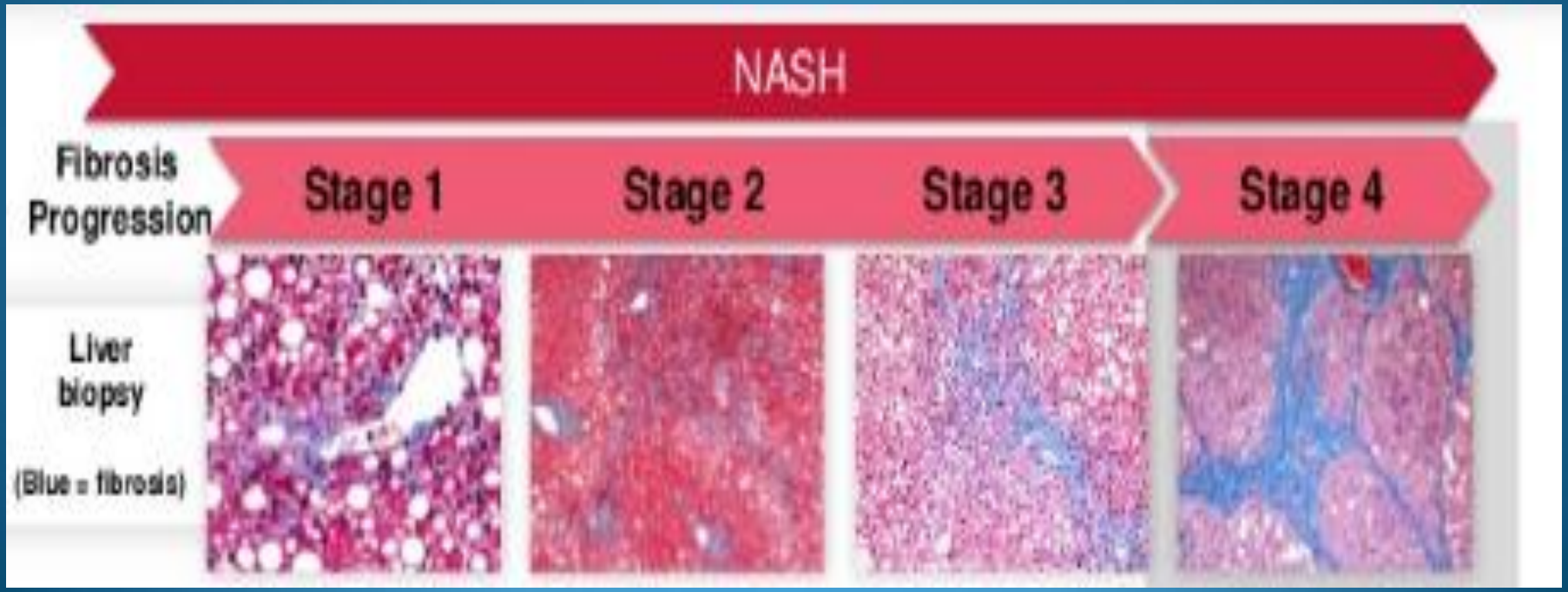
Increase sensitivity of target tissues to insulin.

Increase glucose uptake and utilization in muscle and adipose tissue.

Persons with nonalcoholic steatohepatitis and F۰ or F۱ fibrosis are evaluated annually for liver disease progression by means of blood tests and physical examinations.



For patients who have more advanced fibrosis (F٢ or higher) when nonalcoholic steatohepatitis is diagnosed, management is tailored according to the severity of the fibrosis.



Efforts have focused on ameliorating the three general processes that drive the pathogenesis and progression of nonalcoholic steatohepatitis:

- **Metabolic stress,**
- **Inflammation,**
- **Fibrosis.**

Table 2. Pharmacotherapies for Nonalcoholic Steatohepatitis Evaluated in Phase 2 or 3 Clinical Trials.*

Pharmacologic Agent	Therapeutic Target		
	Metabolic Stress	Inflammation	Fibrosis
Vitamin E†	Yes	Yes	No
Pioglitazone (PPAR-γ agonist)†	Yes	Yes	Yes
Obeticholic acid (FXR agonist)†	Yes	Yes	Yes
Chemokine receptor 2 and 5 antagonists	No	Yes	Yes
PPAR-α and PPAR-δ agonists	Yes	Yes	Yes
Lysyl oxidase–like 2 inhibitor	No	No	Yes
Galectin 3	No	Yes	Yes
Bovine milk colostrum	No	Yes	Yes
Stress-activated kinase 1 inhibitor	Yes	Yes	Yes
FGF-21	Yes	Yes	Yes
FGF-19–like agent	Yes	Yes	Yes

* FGF denotes fibroblast growth factor, FXR farnesoid X receptor, and PPAR peroxisome proliferator–activated receptor.
† This agent was superior to placebo in a randomized clinical trial.

Risky and expensive treatments merit consideration in patients with a high risk of bad liver-related outcomes but are not justified in patients at lower risk for disease progression.

Therapies that increase the risk of cardiovascular disease or cancer should not be used.

Aimed at eradicating nonalcoholic steatohepatitis and other metabolic syndrome–related diseases by encouraging healthful eating, facilitating exercise and fitness, limiting shift work, and minimizing exposure to environmental toxins.


Thank You
For Your Attention