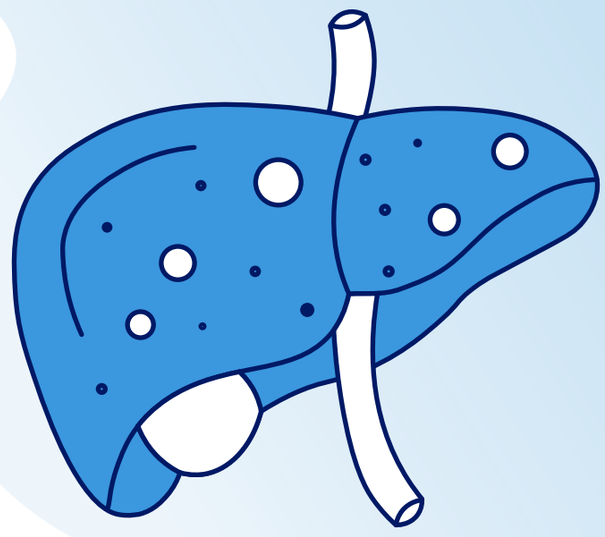
Science behind MASH

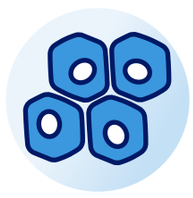
MASH is the progressive form of MASLD



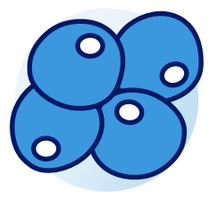
Metabolic dysfunction-associated steatotic liver disease (MASLD) is a spectrum of hepatic disease ranging from **steatosis to metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis** including progression to cirrhosis.[1]

MASLD is defined by the presence of hepatic steatosis (evident in ≥5% of hepatocytes) in patients with one or more cardiometabolic risk factors, including obesity, type 2 diabetes, hypertension and dyslipidemia (high triglycerides and/or low HDL).[1]

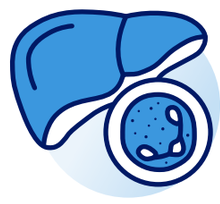
MASH is characterized histologically by 3 key hallmarks[2,3]:



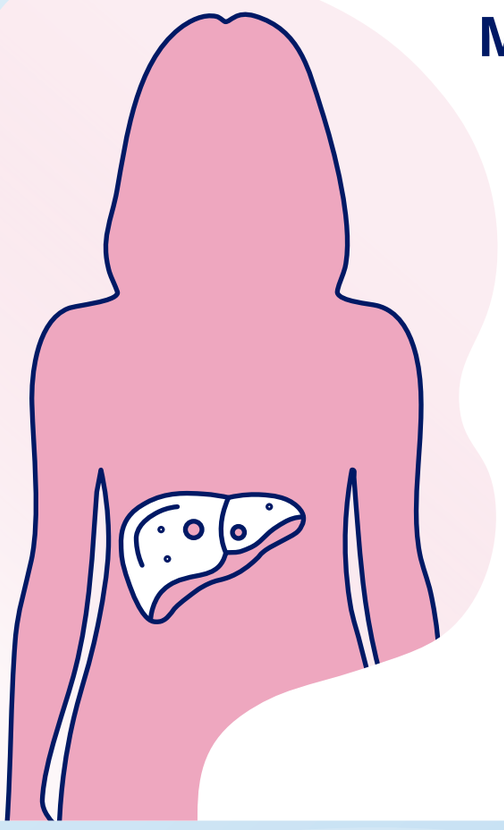
Steatosis



Ballooning



Inflammation



MASH pathogenesis begins with insulin resistance and metabolic stress, leading to free fatty acid accumulation in the liver[4,5]

Fatty acid build-up leads to **lipotoxicity**, which encompasses deleterious effects of accumulation of lipid intermediates in non-adipose tissue[6], as well as **mitochondrial and endoplasmic reticulum stress within hepatocytes**

Cell stress ultimately leads to **apoptosis** (cell death), which can cause local inflammation

Chronic inflammation leads to reactionary **hepatic collagen deposition and the development of fibrosis** with stiffening of the liver over time

Gradual or rapid progression of fibrosis can lead to cirrhosis and other liver-related complications, if untreated

Fibrosis staging ranges from F0 to F4, with F0 indicating no fibrosis and F4 indicating cirrhosis of the liver[7,8]:

No fibrosis: Healthy liver

Mild fibrosis: perisinusoidal fibrosis or portal/periportal fibrosis

Moderate fibrosis: perisinusoidal and portal/periportal fibrosis

Advanced fibrosis: bridging fibrosis

Cirrhosis: Extensive scarring in the liver

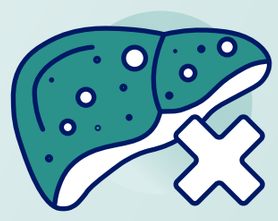
MASLD

Clinically significant MASH with fibrosis

Advanced fibrosis

Although MASH is often a slowly progressing disease, **1/5 patients** with MASH may progress rapidly to advanced fibrosis (F3-F4) from no fibrosis within 2 years[7]

Risk of major adverse liver-related outcomes, such as hepatic decompensation and death increases exponentially in patients with at-risk MASH (≥F2)[9]



Progression to decompensated cirrhosis can lead to **hepatocellular carcinoma (HCC), need for liver transplantation and liver-related death**[4]

The exact cause of MASLD/MASH is not fully understood, but several cardiometabolic risk factors are associated with its development. Early detection of MASH is critical to prevent progression to cirrhosis and reduce liver-related complications.

F, fibrosis stage; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease.

1. Rinella ME et al. Hepatology. 2023;77:1797-1835; 2. Pais R et al. J Hepatol. 2016;65(6):1245–1257; 3. Younossi ZM et al. Hepatology. 2016;64:73–84; 4. Marengo A et al. Clin Liver Dis. 2016;20:313–24; 5. Li Y et al. Lipids Health Dis. 2024;23:117; 6. Noureddin M et al. Hepatology. 2023;79:135-148; 7. Loomba R and Adams LA. Hepatology. 2019;70:1885–1888; 8. Huang, D.Q. et al. Nat Rev Dis Primers. 2025 11:14; 9. Dulai PS et al. Hepatology. 2017;65:1557–65.