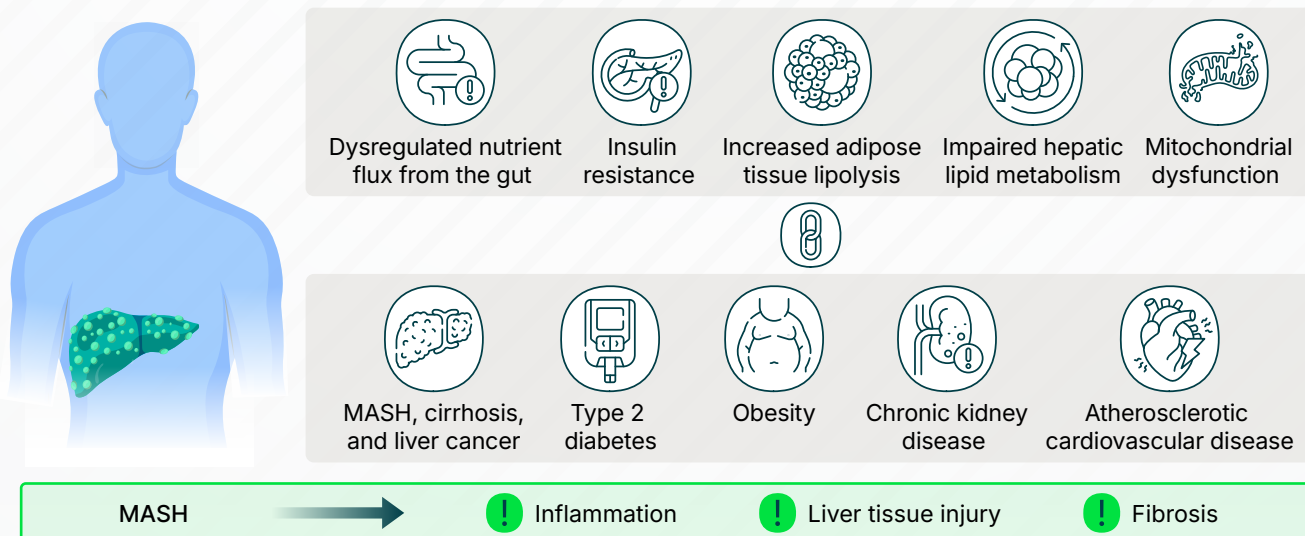


Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis: Pathophysiology and Therapeutic Approaches

This infographic is intended for researchers and healthcare professionals, and reflects the content of the following article:

Tsakiridis, E. E., and Steinberg, G. R. (2026). Incretin and glucagon signalling in MASLD and MASH: Integrating metabolic pathways with disease progression. *Diabetes, Obesity and Metabolism*. <https://doi.org/10.1111/dom.70624>

MASLD is a multisystem disorder driven by disrupted communication between different organs



Physiological Mechanisms Dysregulated in MASLD



Gut-liver axis

- Increased delivery of nutrients and microbial metabolites, such as acetate and ethanol, leading to liver inflammation



Adipose tissue-liver crosstalk

- Insulin-resistant adipose tissue
- Elevated non-esterified fatty acid concentrations
- Increased hepatic lipid uptake
- Hepatic insulin resistance



Liver inflammation

- Release of proinflammatory cytokines from Kupffer cells and B cells
- Heightened immune responses
- Increased hepatocyte apoptosis and necrosis
- Stellate cell activation driving steatohepatitis and fibrosis



Hepatic lipid metabolism

- Increased *de novo* lipogenesis
- Reduced fatty acid oxidation with advanced disease
- Activation of hepatic stellate cells and inflammation



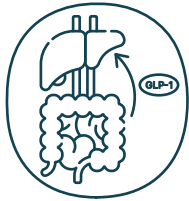
Mitochondrial function

- Impaired mitochondrial function
- Increased oxidative stress
- Accumulation of lipotoxic metabolites, promoting inflammation and fibrosis

MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis

Visit [10.1111/dom.70624](https://doi.org/10.1111/dom.70624) for additional resources

Hormone peptides act via distinct but complementary mechanisms, influencing the dysregulated gut–liver and adipose–liver axes and inflammatory pathways that drive MASLD



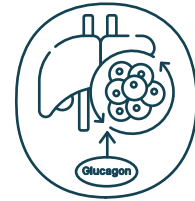
GLP-1 → targets the gut–liver axis

Lowers food intake, slows gastric emptying, and reduces inflammation



GIP → targets the adipose–liver axis

Improves lipid uptake in adipose tissue and insulin sensitivity, reduces lipid spillover, and decreases inflammatory signalling



Glucagon → targets hepatic lipid metabolism

Promotes fatty acid oxidation, enhances mitochondrial function, and suppresses *de novo* lipogenesis



Incretin (GLP-1)-based therapeutics have demonstrated clinical success in the treatment of diabetes and obesity

GLP-1: glucagon-like peptide-1; GIP: glucose-dependent insulintropic polypeptide

Therapeutic Targeting of Metabolic Pathways in MASH

GLP-1 receptor agonists [semaglutide (Phase 3)]



Weight-independent reductions in liver inflammation



Modest fibrosis reduction primarily in those without advanced disease



Greater reductions in markers of liver damage in individuals with the *PNPLA3* mutation

Dual GLP-1/GIP receptor agonists [tirzepatide (Phase 2 MASH)]



MASH resolution



Liver fat reduction

Dual GLP-1/glucagon receptor agonists [survodutide, cotadutide, efinopegdutide, and pemvidutide (Phase 2 MASH)]



Reductions in liver fat



MASH resolution with survodutide

Triple GLP-1/GIP/glucagon receptor agonists [retatrutide (Phase 2 MASH)]



Significant weight loss



Reduction in liver fat

Key message

- ✔ Treatment response in MASLD/MASH varies by disease stage, genotype, and comorbidities, underscoring the need for a personalised treatment approach

Reference:

Tsakiridis, E. E., & Steinberg, G. R. (2026). Incretin and Glucagon Signalling in MASLD and MASH: Integrating Metabolic Pathways with Disease Progression. *Diabetes, Obesity and Metabolism*.

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