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**Thyroid hormone receptor-beta agonists: new MASLD therapies**

Byrne CD, Targher G, Tilg H. [Thyroid hormone receptor-beta agonists: new MASLD therapies on the horizon](https://gut.bmj.com/content/73/4/573). Gut 2024; 73: 573-581. doi: 10.1136/gutjnl-2023-330596

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease worldwide. Primary hypothyroidism is associated with hypercholesterolaemia, decreased hepatic β-oxidation and increased insulin resistance. Patients with this condition have higher rates of MASLD. Hepatic thyroid hormone activity has emerged as a promising target for MASLD novel therapies. The active thyroid hormone triiodothyronine (T3) is the key regulator of metabolism and exerts its effects via binding to thyroid hormone receptors (THR). THR-β1 is expressed in the liver and appears to influence liver lipid metabolism. Individuals with mutations in the THR-β gene have loss of function of THR-β and demonstrate significant hepatic steatosis compared with their wild-type first-degree relatives.

Resmetirom is a liver-targeted THR-β agonist. In mouse models, reduction of steatosis, and hepatic and plasma cholesterol have been observed. It has been shown to suppress signalling pathways involved in inflammation such as nuclear factor kappa B (NF-kB) postulating its role in suppressing liver fibrosis in steatohepatitis (MASH).

The phase III MAESTRO clinical programme, has four ongoing phase III randomised clinical trials testing resmetirom for treatment of MASH and liver fibrosis. MAESTRO-NAFLD-1 evaluated the safety of resmetirom over 52 weeks in obese or overweight patients randomised to various dosing arms. It was well tolerated with no thyroid hormone axis changes. MAESTRO-NASH trial reported at least one stage fibrosis improvement of 14% in the placebo group vs 24% of the 80mg group. These findings posit THR-β agonists as promising new therapies for the treatment of MASLD.