Targeting Metabolism in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): The Emerging Role of GLP-1 Receptor Agonists

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The recent evolution from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD) reflects more than a change in nomenclature [1]. It acknowledges that MASLD is a multisystemic metabolic disorder that extends far beyond the liver. While progressive liver disease, cirrhosis, and hepatocellular carcinoma (HCC) remain critical concerns, epidemiological data consistently show that these patients are more likely to succumb to cardiovascular disease and non-HCC malignancies than to hepatic complications [2]. Consequently, therapeutic strategies cannot focus exclusively on reducing hepatic steatosis or improving histology; they must simultaneously address the broader cardiometabolic risk profile that ultimately dictates patient survival.

Indeed, MASLD is increasingly recognized as the hepatic manifestation of systemic metabolic dysfunction. Ectopic lipid accumulation in the liver is not an isolated event but rather the downstream consequence of a complex, pathological interplay among obesity, insulin resistance, adipose tissue dysfunction, and chronic low-grade inflammation [3]. Consequently, therapeutic approaches targeting solely liver-specific pathways risk failing to address the upstream metabolic drivers that fuel disease progression and ultimately determine morbidity and mortality.

This paradigm shift has profound implications for drug development. Historically, clinical trial endpoints have focused strictly on hepatic histology, specifically steatohepatitis resolution and fibrosis regression. While these outcomes remain clinically relevant, an ideal therapy for MASLD should also improve obesity, insulin sensitivity, dyslipidemia, type 2 diabetes mellitus (T2DM) and chronic kidney disease. In other words, treatments that target the metabolic roots of the disease may offer greater overall benefit than therapies acting primarily within the liver [3].

Among emerging options, GLP-1 receptor agonists (GLP-1RAs) have attracted considerable attention. Originally developed for the management of T2DM and later for obesity, these agents exert multiple beneficial effects across several organ systems [4]. By inducing substantial weight loss, improving insulin sensitivity, and reducing systemic inflammation, GLP-1RAs target key pathogenic mechanisms driving MASLD [4]. Because human hepatocytes lack functional GLP-1 receptors [5], these benefits are achieved indirectly, mediated through the reversal of lipotoxicity, visceral adiposity, and systemic inflammatory stress [5]. The resulting reduction in hepatic steatosis highlights how targeting extrahepatic, upstream pathways can yield profound downstream liver benefits.

The transition of these agents into the MASLD therapeutic armamentarium was a logical step considering

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that obesity and T2DM are the principal drivers of disease progression and adverse outcomes [6]. This approach achieved its definitive validation in the phase 3 ESSENCE trial, where semaglutide 2.4 mg demonstrated highly significant rates of steatohepatitis resolution without worsening of fibrosis, alongside a moderate anti-fibrotic effect [7]. These findings ultimately led to accelerated FDA approval of semaglutide 2.4 mg for metabolic dysfunction-associated steatohepatitis (MASH) in August 2025, marking a historic milestone.

Nevertheless, while GLP-1RA monotherapy consistently resolves steatohepatitis, its capacity to improve liver fibrosis has been comparatively modest [6]. This limitation has fueled the rapid development of the next generation of metabolic therapies: dual and triple incretin agonists. Multi-agonists combining GLP-1 with glucose-dependent insulinotropic polypeptide (GIP) and glucagon (GCG) receptors have achieved unprecedented weight loss and metabolic control [6]. Those incorporating glucagon agonism are particularly compelling; unlike GLP-1, glucagon acts directly on the liver to enhance lipid oxidation and energy expenditure. Emerging phase 2 data suggest that dual and triple agonists may achieve greater fibrosis improvement than first-generation GLP-1RAs, raising the possibility that metabolic therapies capable of inducing profound weight loss and directly modulating hepatic metabolism may ultimately overcome one of the principal limitations of current incretin-based treatment [8].

Most importantly, the clinical value of GLP-1RAs extends beyond the liver. Large-scale cardiovascular outcome trials in patients with obesity and T2DM have consistently demonstrated reductions in major adverse cardiovascular events (MACE), while recent studies have also documented slower chronic kidney disease progression [9, 10]. This holistic protection highlights a significant contrast with purely liver-directed therapies, such as the thyroid hormone receptor-β agonist resmetirom, the only other approved pharmacotherapy for MASH. While resmetirom effectively improves liver outcomes by directly targeting downstream intrahepatic pathways, its cardiorenal effects remain uncertain and appear largely neutral [11].

Therefore, clinicians are moving toward a personalized, risk-stratified treatment model. Many experts currently favor GLP-1RAs for patients with MASLD who have obesity, T2DM, or high cardiometabolic risk [12]. Conversely, resmetirom may be preferred in patients without obesity or diabetes, or in those for whom a more liver-focused therapeutic approach is appropriate [12]. Looking forward, the ultimate solution for MASLD management likely lies in combination therapy. Given the multifactorial nature of the disease, it is unlikely that a single agent will optimally address steatosis, inflammation, fibrosis, obesity, and cardiometabolic risk simultaneously in all patients. Combination regimens that pair metabolism-targeting therapies such as GLP-1 receptor agonists with liver-directed agents such as resmetirom may offer complementary benefits [12]. Ongoing and future studies will determine whether such combinations can achieve additive or even synergistic effects on both hepatic and extrahepatic outcomes.

Despite their promise, GLP-1RAs are not without limitations. Real-world data indicate that approximately 40% of patients discontinue treatment within the first year, primarily due to gastrointestinal intolerance [13]. Furthermore, rapid weight loss introduces the risk of lean muscle mass depletion, a serious concern for sarcopenia in older patients or those with cirrhosis [14]. Most importantly, discontinuation of therapy is frequently followed by substantial weight regain and metabolic relapse [15]. These observations highlight that MASLD, like obesity, is a chronic disease that requires long-term management to sustain clinical benefits.

To conclude, the emergence of GLP-1 receptor agonists has fundamentally altered the therapeutic landscape of MASLD. By treating the metabolic disease rather than the organ in isolation, these agents address the metabolic dysfunction that lies at the core of disease pathogenesis. While important questions remain regarding their mechanisms of action, long-term safety, antifibrotic efficacy, and optimal combination with liver-directed treatments, the overarching message is clear: effective management of MASLD requires targeting metabolism. Future therapies should be judged by their efficacy to reduce cardiovascular events, prevent kidney disease progression, improve quality of life, and ultimately reduce overall mortality.

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