



Future perspective of GLP-1 receptor agonists across the spectrum of steatotic liver disease

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INTRODUCTION

Metabolic syndrome and harmful alcohol consumption represent the leading causes of chronic liver disease in Western countries^[1]. Together, obesity and alcohol use disorder (AUD) affect more than one billion people worldwide and are projected to substantially increase liver-related morbidity and mortality over the coming decades^[2,3]. The 2023 multi-society Delphi consensus nomenclature revision formalized this dual burden by introducing the umbrella term of steatotic liver disease (SLD), stratified according to the relative contribution of metabolic risk factors [Metabolic dysfunction-Associated Steatotic Liver Disease (MASLD)], significant alcohol intake [alcohol-related liver disease (ALD)], and a new entity named metabolic dysfunction-associated and alcohol liver disease (MetALD), where both drivers co-exist^[4]. Accordingly, SLD now represents the leading indication for liver transplantation in many Western countries, accounting for more than 60% of cases as viral hepatitis-related liver disease continues to decline^[5]. These trends underscore the urgent need for early identification and treatment across the full SLD spectrum before progression to advanced disease.

Despite their distinct clinical manifestations, obesity and AUD share several neurobiological mechanisms^[6]. Both are chronic relapsing disorders characterized by dysregulation of mesolimbic dopaminergic signaling, leading to compulsive consummatory behaviors mediated through reward circuits involving the nucleus accumbens, dorsal striatum, and orbitofrontal cortex. In parallel, stress-response pathways and appetite-regulating hormones, including ghrelin, contribute to both alcohol-seeking behavior and energy homeostasis^[6]. This shared neurobiological substrate suggests the potential for convergent pharmacological intervention. Nevertheless, treatment strategies for these conditions remain largely separated in clinical practice.



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GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1RA) BETWEEN METABOLIC SYNDROME AND AUD

Approved medications for AUD, such as naltrexone and acamprosate, remain markedly underutilized, being prescribed to fewer than 10% of eligible patients and to less than 15% of individuals with established ALD, reflecting persistent stigma and limited clinician awareness^[7,8]. In contrast, pharmacologic development in obesity and metabolic dysfunction-associated steatohepatitis (MASH) has advanced rapidly over recent years, largely driven by the emergence of incretin-based therapies. Among these therapies, Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs) have demonstrated substantial efficacy not only in weight reduction and metabolic improvement, but also in improving key histologic features of MASH, resolution of steatohepatitis, and improvement of fibrosis stage^[9]. In the phase 3 ESSENCE randomized controlled trial (RCT), treatment with subcutaneous semaglutide 2.4 mg once weekly for 72 weeks resulted in significantly higher rates of both primary histologic endpoints. Resolution of MASH without worsening of fibrosis was achieved in 62.9% of participants receiving semaglutide compared with 34.3% in the placebo group, while improvement in ≥ 1 fibrosis stage without worsening of steatohepatitis occurred in 37% and 22.4%, respectively^[10]. On the strength of these results, in August 2025, semaglutide (Wegovy®) received the US Food & Drug Administration's (FDA) accelerated approval for the treatment of MASH and F2-F3 fibrosis, while in January 2026 the European Medicines Agency (EMA) adopted a positive opinion recommending a conditional marketing authorization for Kayshild® (semaglutide 2.4 mg).

Originally developed for the treatment of type 2 diabetes mellitus (T2DM) and obesity, GLP-1RAs exert pleiotropic effects through activation of GLP-1 receptors in multiple organs, including the pancreas, gastrointestinal tract, and central nervous system. Their metabolic effects include glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and reduced appetite, leading to sustained weight loss and improved insulin sensitivity. Beyond these systemic effects, accumulating evidence suggests that GLP-1RAs may directly modulate key mechanisms involved in SLD, including hepatic lipid metabolism, inflammation, and fibrogenesis, through both weight-dependent and weight-independent pathways^[11]. Moreover, GLP-1RAs may also modulate central reward pathways involved in addictive behavior. Although they do not efficiently cross the blood-brain barrier, GLP-1 signaling reaches key reward circuits through vagal afferent pathways and circumventricular organs, attenuating the rewarding properties of food and alcohol via modulation of dopaminergic, GABAergic, and glutamatergic neurotransmission^[12]. Translating this rationale into clinical evidence, emerging data for GLP-1 in AUD have been progressively extrapolated from RCTs. The first RCT of exenatide in patients with AUD did not meet its primary endpoint (overall reduction in number of heavy drinking days), despite significant evidence being restricted to the subgroup of patients with obesity^[13]. Similarly, in a smoking cessation trial, dulaglutide demonstrated a significant reduction in alcohol intake independent of smoking outcomes^[14]. Clinical evidence supporting GLP-1RAs in AUD has recently strengthened with two semaglutide RCTs. In a phase 2 trial involving 48 adults with AUD, semaglutide (titrated to 1 mg/week over 9 weeks) significantly reduced alcohol self-administration, drinking days, and craving compared with placebo^[15]. Recently, a landmark study conducted in 108 treatment-seeking adults with moderate-to-severe AUD and obesity showed that semaglutide 2.4 mg/week significantly reduced heavy drinking days compared with placebo (41% vs. 26% reduction from baseline), while also improving multiple secondary alcohol-related outcomes^[16]. Population-level data add further support: in a Swedish nationwide cohort of 227,866 individuals with AUD, semaglutide and liraglutide were associated with significantly lower rates of AUD-related hospitalization than AUD medications^[17], and a large real-world study confirmed a significantly reduced risk of incident AUD with semaglutide^[18]. Similarly, observational studies in patients with ALD and T2DM reported lower rates of hepatic decompensation and adverse liver outcomes among GLP-1RA users^[19], with one study also demonstrating reduced all-cause mortality as compared to DPP-4 inhibitor users^[20]. These findings provided the rationale for dedicated RCTs of semaglutide, tirzepatide, and pemvidutide for either AUD or metALD^[21], supporting the potential role of GLP-1RAs as unified therapies across the SLD spectrum.

Table 1. Ongoing phase 2 and phase 3 trials of incretin-based therapies across SLD

NCT	Drug name	Sponsor	Mechanism of action	Target population	Phase of RCT	Duration of trial
NCT05877547	Efinopegdutide	Merck	GLP-1 and glucagon dual receptor agonist	MASH with F2 or F3 fibrosis	2b	52 weeks
NCT05292911	Pemvidutide	Altimmune	GLP-1 and glucagon dual receptor agonist	MASH with F2 or F3 fibrosis	2b	48 weeks
NCT06632444	Survodutide	Boehringer Ingelheim	GLP-1 and glucagon dual receptor agonist	MASH with F2 or F3 fibrosis	3	52 weeks
NCT04639414	Semaglutide and empagliflozin	German Diabetes Center	GLP-1 receptor agonist and SGLT-2 inhibitor	MASH with F1-F3 fibrosis and type 2 diabetes	4	48 weeks
NCT07165028	Tirzepatide and retatrutide	Eli Lilly	GLP-1/GIP dual agonist (tirzepatide) and GLP-1/GIP/glucagon triple agonist (retatrutide)	MASLD with high risk of MALO, defined by NITs	3	224 weeks
NCT05016882	NNC0194-0499 (FGF21 analog) and semaglutide	Novo Nordisk	FGF21 analogue and GLP-1 receptor agonist	MASH with F2-F4c fibrosis (compensated cirrhosis)	2	19 months
NCT07046819	Tirzepatide	NIAAA	GLP-1 and GIP receptor dual agonist	AUD and MetALD	2	12 weeks

AUD: Alcohol use disorder; FGF21: fibroblast growth factor 21; GIP: glucose-dependent insulintropic polypeptide; GLP-1: glucagon-like peptide-1; MALO: major adverse liver outcomes; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; MetALD: metabolic dysfunction-associated alcohol-related liver disease; NCT: National Clinical Trial (ClinicalTrials.gov registration identifier); NIAAA: National Institute on Alcohol Abuse and Alcoholism; NITs: non-invasive tests; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter-2.

The field is further evolving beyond single GLP-1RA toward next-generation incretin-based approaches designed to simultaneously target complementary metabolic pathways. Current development strategies increasingly include dual and triple-receptor agonists combining GLP-1 signaling with glucose-dependent insulintropic polypeptide (GIP) and/or glucagon receptor activation, as well as combination regimens pairing GLP-1RAs with agents acting through distinct mechanisms [Table 1].

FUTURE DIRECTION: IMPLEMENTATION OF NON-INVASIVE TESTS FOR PROGNOSTICATION AND DRUG ELIGIBILITY

A major challenge will be identifying patients at highest risk of progressive liver disease who are most likely to benefit from treatment using non-invasive tests (NITs) as alternatives to liver biopsy. While stepwise NIT-based algorithms are increasingly incorporated into MASLD referral pathways, evidence supporting similar strategies in MetALD and ALD remains limited, with important implications for both clinical risk stratification and trial design, where the absence of validated surrogate endpoints represents a major limitation.

Recent data suggest that active alcohol consumption remains the strongest determinant of fibrosis progression across the SLD spectrum and, therefore, a key target for risk modification. In patients with ongoing alcohol exposure, fibrosis progression appears more than 2-fold faster than in abstinent individuals, corresponding to progression of one fibrosis stage approximately every 3 years *vs.* 8 years^[22]. However, alcohol assessment in routine practice still relies largely on self-reported intake, which poorly captures the dynamic nature of alcohol exposure over time. As pharmacological therapies become increasingly available across the SLD spectrum, accurate characterization of alcohol consumption will become fundamental not only for disease classification but also for risk stratification, patient selection, and therapeutic

decision-making. In this context, validated screening tools such as the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)^[23], combined with objective biomarkers of alcohol intake, particularly phosphatidylethanol (PEth), may improve the identification of patients with ongoing harmful alcohol use, complement clinical assessment, and support longitudinal monitoring^[24]. Their integration with non-invasive fibrosis assessment may ultimately enable a more personalized approach to treatment allocation and prognostication^[25]. Nevertheless, although alcohol exposure remains a major determinant of disease progression, emerging evidence suggests that NITs retain prognostic value across different levels of alcohol consumption and may further refine risk stratification beyond alcohol exposure alone.

In particular, evidence from the MASLD population suggests a very low rate of liver-related outcomes for liver stiffness measurements by vibration-controlled transient elastography (VCTE) < 10 kPa^[26]. Moreover, in a recent study including 164 patients with MetALD and ALD undergoing paired liver biopsies, histological fibrosis stage and non-invasive biomarkers (VCTE, FIB-4, ELF, LiverPRO) showed comparable ability to predict adverse outcomes and mortality despite varying degrees of alcohol exposure over a 2-year follow-up period^[22].

In this evolving landscape, the challenge will not only be expanding access to GLP-1-based therapies but also identifying which patients across the SLD spectrum are most likely to benefit from specific therapeutic strategies through more personalized approaches integrating metabolic profiling, alcohol exposure assessment, behavioral phenotyping, and non-invasive risk stratification. At the same time, important unmet needs still include the long-term safety and tolerability of GLP-1-based therapies in patients with chronic liver disease. It also remains unclear whether the benefits observed on alcohol-related behaviors and obesity can be sustained over time and how these agents should be integrated with established addiction-focused interventions. Ultimately, addressing these challenges will be critical to defining the role of incretin-based therapies as disease-modifying strategies across the full spectrum of SLD.

In conclusion, GLP-1 receptor agonists have the potential to redefine the management of SLD by addressing metabolic dysfunction and harmful alcohol use through shared biological pathways. Their expanding therapeutic role, supported by rapidly evolving clinical evidence, may ultimately establish them as disease-modifying therapies across the spectrum of SLD. This Perspective highlights developments likely to shape the future management of these conditions, while several important aspects (including long-term efficacy and safety, patient selection and implementation in clinical practice) warrant further discussion beyond the scope of this article.

DECLARATIONS

Authors' contributions

Conceptualization: Gjini K, Calleri A, Armandi A

Writing, original draft: Gjini K, Calleri A, Armandi A

Critically reviewed and revised the manuscript for important intellectual content: Bugianesi E, Armandi A

All authors read and approved the final version of the manuscript.

Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI tool ChatGPT (version 5.6, released 2026-09-07) was used solely for grammar, spelling, and language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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