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Review Article

Nutrient-stimulated Hormone-based Therapies: A New Frontier in the Prevention and Management of MASH-associated Hepatocellular Carcinoma

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most common chronic liver disease in the Western world, driven by obesity, insulin resistance, and systemic inflammation. Its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), can culminate in cirrhosis and hepatocellular carcinoma (HCC). While lifestyle modification remains central to MASLD management, there is growing interest in pharmacological interventions, particularly nutrient-stimulated hormone-based therapies (NuSHs), such as GLP-1 receptor agonists. NuSHs exert metabolic and anti-inflammatory effects primarily via weight loss and improved insulin sensitivity. Emerging clinical data support their efficacy in resolving MASH without worsening fibrosis. However, benefits in cirrhotic patients are less evident, suggesting greater utility in early intervention. Observational studies and clinical trials suggest a reduction in liver-related morbidity with GLP-1 receptor agonist use, though fibrosis regression remains inconsistent. Preclinical models indicate that NuSHs may also reduce MASH-related HCC incidence and tumor burden, likely through systemic metabolic improvements rather than direct antineoplastic action. Observational human data following bariatric surgery reinforce this link, suggesting that weight loss itself plays a key preventive role. Herein, we propose that NuSHs are promising candidates for MASH-related HCC prevention. We provide mechanistic suggestions for how this may occur. Furthermore, incorporating NuSHs into the post-locoregional treatment pathway for HCC may delay the need for systemic anti-cancer therapies, improve immunotherapy synergy and transplant eligibility, and even slow disease progression through reversal of carcinogenic drivers. Future studies are needed to target oncological endpoints and clarify immunometabolic mechanisms to guide the integration of NuSHs into MASLD treatment algorithms.

Keywords: Metabolic dysfunction-associated steatohepatitis; MASH; Hepatocellular carcinoma; HCC; MASH-HCC; Nutrient-stimulated hormone-based therapy; NuSH; Metabolic dysfunction-associated steatotic liver disease; MASLD; GLP-1 receptor agonist; GLP-1RA.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a complex spectrum of conditions influenced by both genetic predisposition and metabolic factors.[1] It is characterized by a steatotic liver with one or more cardiometabolic risk factors, in the absence of excessive alcohol consumption. MASLD includes steatosis, metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis, and MASH-related hepatocellular carcinoma (HCC). It is now the most prevalent chronic liver disease in the Western world.[2] Epidemiological work estimates that advanced liver disease in patients with MASH is set to rise by 160% by 2030, leading to 3.5 million cases of cirrhosis in the USA.[3]

The management of MASLD primarily focuses on non-pharmacological measures. These interventions include adopting healthy dietary patterns, such as the Mediterranean diet, minimizing processed foods and sugary drinks, engaging in regular physical activity, and avoiding smoking and excessive alcohol consumption.[2] Currently, there are no UK- or European-approved medications specifically for MASLD, and weight loss remains a cornerstone of management. In 2024, the U.S. Food and Drug Administration approved the selective thyroid hormone receptor βagonist, resmetirom, in the USA for the treatment of non-cirrhotic MASH with moderate-to-advanced fibrosis.[4] This occurred after a large-scale phase III randomized clinical trial (RCT) demonstrating increased rates of MASH resolution without fibrosis worsening (25.9% and 29.9%, respectively, versus 9.7% with placebo; $P < 0.001$) and fibrosis improvement by at least one stage (24.2% and 25.9% versus 14.2%; $P < 0.001$).[4]

Obesity, insulin resistance, metabolic disturbances such as dysglycaemia and dyslipidaemia, and chronic low-grade systemic inflammation are recognized as fundamental drivers of MASLD.[5] When unresolved, these chronic inflammatory components directly cause hepatic damage, overwhelm innate hepatic regeneration, and lead to fibrosis, cirrhosis, and

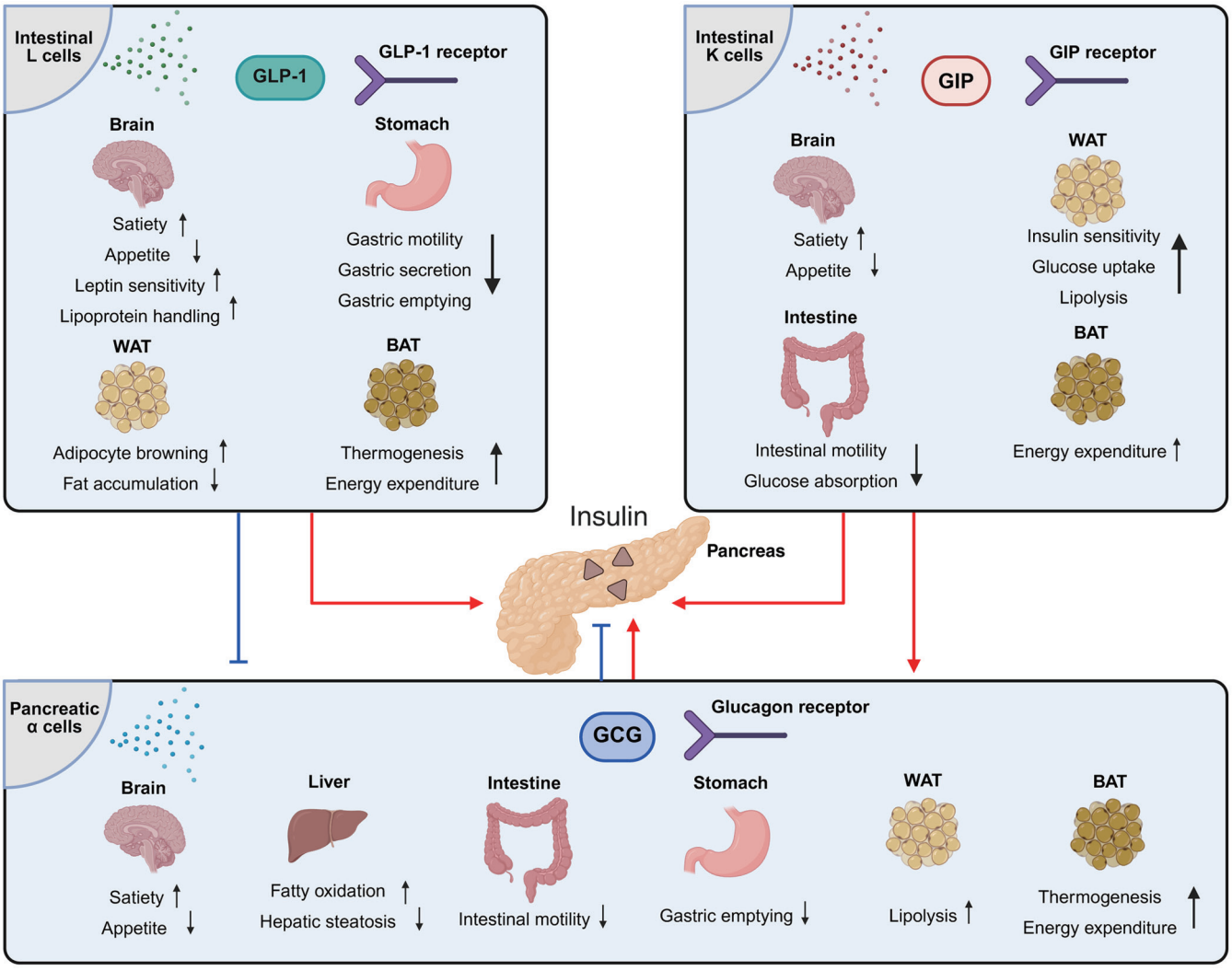

Fig. 1. Overview of the proposed routes of action of the incretin effect (e.g., GLP-1, GIP). Direct central effects on brain centers involved in the regulation of appetite and satiety. Improved lipoprotein handling via the porto-vagal axis. Increased energy expenditure through activation of thermogenesis in brown adipose tissue. Increased sensation of fullness via induced gastric emptying. Increased insulin release from the pancreas, with improved downstream glucose handling. Reduced glucagon release with improved hepatic glucose metabolism. Adapted with from Jiang *et al*. (2024).[8] Created with BioRender. BAT, brown adipose tissue; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; WAT, white adipose tissue; ↑, increase; ↓, decrease.

hepatocarcinogenesis.[6]

Emerging evidence highlights the role of extrahepatic signals, particularly from the gut, in modulating hepatic inflammation. A novel pipeline of nutrient-stimulated hormone-based therapies (NuSHs), which exploit gut-derived hormone effects, has demonstrated significant potential not only for weight loss management but also for liver- and inflammation-related benefits.[7] This family includes the established glucagon-like peptide-1 receptor agonists (GLP-1RAs), semaglutide and liraglutide. These drugs are already in clinical use for metabolic diseases (obesity and diabetes) and are being investigated for their potential roles in liver disease. More potent weight loss medications within this family include dual GLP-1/GIP agonists (tirzepatide), dual GLP-1/glucagon agonists (survodutide, mazdutide), and triple GLP-1/GIP/glucagon agonists (retatrutide). The physiological effects of the incretins that NuSHs mimic are demonstrated in Figure 1.[8] The impact of these medications on hepatic inflammation and fibrosis is believed to be largely indirect, acting through mechanisms such as weight loss, improved insulin signaling, and altered hepatocellular metabolism.[9,10]

Herein, we present the current clinical trial data that support the use of NuSHs in MASH, before discussing the evidence and proposed molecular mechanisms that support our hypothesis that NuSHs may play a future role in preventing MASH-HCC, or even serve as an adjunct to oncological treatment in patients with established MASH-HCC.

Established beneficial effects of NuSHs in MASH

GLP-1RAs

MASH is a complex liver disease driven by obesity, metabolic syndrome, and genetic factors. It progresses from simple steatosis to liver inflammation and fat accumulation in over 5% of hepatocytes.[11] Although fewer than 10% of steatosis cases progress to MASH, its molecular drivers can lead to cirrhosis and HCC (4–6% of cases). Notably, around 15% of

HCC cases arise from non-cirrhotic MASH, highlighting the disease's severity even in the absence of advanced fibrosis.[12] The prevalence of MASH and MASH-related HCC is rapidly increasing in the developed world due to the obesity pandemic.

The benefits of GLP-1RAs on hepatic function in MASH are well documented in systematic reviews and meta-analyses.[13] Moreover, improvements in cardiovascular risk factors, including fasting blood glucose, HbA1c levels, and lipid profiles, further support the use of GLP-1RAs in ameliorating the metabolic dysregulation associated with MASH.

Newsome *et al*. evaluated the efficacy of semaglutide in patients with MASH in a 72-week, randomized, double-blind phase II trial involving 320 patients, and semaglutide 0.4 mg daily led to MASH resolution without worsening fibrosis in 59% of patients, compared to 17% with placebo.[14] However, improvement in baseline fibrosis stage was not statistically significant. Notably, when semaglutide was tested in patients with MASH-related compensated cirrhosis in a phase II placebo-controlled trial, Loomba *et al.* demonstrated no significant improvement in fibrosis between groups.[15] This suggests the importance of introducing semaglutide at an earlier timepoint in the pathological time course.

The same group conducted a multicenter phase III RCT to assess the therapeutic potential of subcutaneous semaglutide 2.4 mg for improving liver histology in adults with biopsy-confirmed MASH and fibrosis stages F2 or F3.[16] The earliest interim efficacy results from the first 800 patients enrolled, released in April 2025,[17] showed that 534 patients received once-weekly subcutaneous semaglutide 2.4 mg and 266 received placebo. After 72 weeks, 62.9% of patients receiving semaglutide achieved steatohepatitis resolution without fibrosis worsening, compared to 34.3% with placebo (difference: 28.7 percentage points; 95% CI, 21.1–36.2; $P < 0.001$). Similarly, fibrosis improvement without worsening steatohepatitis occurred in 36.8% of semaglutide-treated patients versus 22.4% with placebo (difference: 14.4 percentage points; 95% CI, 7.5–21.3; $P < 0.001$). These interim results focus solely on histological endpoints; data on long-term outcomes such as progression to cirrhosis, decompensation, HCC, liver transplantation, and mortality are not yet available.

Dual and triple incretin RAs

Studies of dual and triple incretin RAs are more limited, but this emerging drug class may represent the next frontier in MASLD pharmacotherapy. Recent phase II trials have provided encouraging data, though outcomes are primarily histological. Tirzepatide, a dual GLP-1/GIP RA, significantly reduced liver fat content and fibrosis markers in patients with MASLD and T2DM.[18] Resolution of MASH without fibrosis worsening occurred in 10% of placebo patients, compared to 44%, 56%, and 62% of patients receiving 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, with all differences statistically significant ($P < 0.001$).

The liver is rich in glucagon receptors (GCGR), which promote fatty acid oxidation and reduce lipogenesis, making it a viable therapeutic target. Dual glucagon (GCGR)/GLP-1RAs, such as survodutide, have demonstrated potential in the treatment of MASH. In a phase II trial, survodutide significantly improved MASH resolution (up to 62%) and fibrosis (up to 36%) compared to placebo. Additionally, 57–67% of patients receiving survodutide experienced at least a 30% reduction in liver fat, versus 14% with placebo.[19]

Efinopegdutide and pemvidutide are other GCGR/GLP-1RAs under investigation for MASH treatment. In a phase II trial, efinopegdutide demonstrated a greater reduction in liver fat content (72.7%) compared to semaglutide (42.3%), alongside superior improvements in metabolic parameters.[20] Similarly, pemvidutide produced significant liver fat reductions at all tested doses versus placebo.[21] These promising results highlight the potential of these agents and warrant further evaluation in phase III studies.

Finally, the triple incretin retatrutide exhibits agonist activity at GIP, glucagon, and GLP-1 receptors. In a systematic review and meta-analysis of existing trials, Abouelmagd *et al*. highlighted the significant dose-dependent weight loss effects of retatrutide, as well as improvements in BMI, waist circumference, fasting plasma glucose, HbA1c, and blood pressure.[22] While retatrutide outperforms dual GLP-1/GIP RAs in weight loss, gastrointestinal side effects are more common. Studies specifically exploring triple incretins in MASH are not yet published. Although these data are encouraging, it is important to highlight the absence of long-term outcome data for these novel agents, particularly regarding the durability of response after treatment cessation. Furthermore, these trials make it difficult to disentangle the direct pleiotropic effects of NuSH targets (e.g., GLP-1R activation) from those attributable solely to weight reduction.

Future directions: A role for NuSHs in the treatment pathway of MASH-HCC

Current evidence

Evidence for the role of GLP-1RAs in MASH-related HCC is sparse. Mouse models with biopsy-confirmed MASH and advanced fibrosis have demonstrated that semaglutide can reduce the incidence of HCC (40% vs. 88%) and tumor burden.[23] Histological analysis revealed a reduction in Ki67-positive hepatocytes, suggestive of decreased cell proliferation, supported by a decrease in alpha-fetoprotein levels, a canonical biomarker of HCC. Notably, semaglutide did not induce any reversal in the fibrosis stage. These anti-tumor effects are likely mediated by systemic metabolic improvements rather than direct tumor targeting, given the expression patterns of GLP-1 receptor in tumor versus non-tumor tissues.

These results are consistent with earlier murine work by Kojima *et al.,*[24] in which liraglutide completely abolished hepatocarcinogenesis in mice with streptozotocin- and high-fat diet-induced diabetes and MASH, whereas all control mice developed HCC.

Observational data in patients undergoing bariatric surgery further support these findings.[25] Subsequent rates of both MASH and MASH-related HCC are significantly reduced, confirming the pivotal role of maintaining a healthy weight in preventing hepatocarcinogenesis. However, the paucity of clinical data on this phenomenon highlights an urgent need for clinical trials investigating the potential benefits of NuSHs in MASH and MASH-HCC by abolishing or reversing the oncogenic driver of this disease. If these agents were to find an adjunctive role in the oncological management of MASH-HCC, hard endpoints such as overall survival and progression-free survival would be warranted when comparing the addition of NuSHs against the current standard of care.

Proposed mechanism for the reversal of hepatocarcinogenesis

NuSHs represent particularly attractive candidates due to their multimodal effects on the metabolic derangements driving this disease continuum. By promoting weight loss, improving insulin sensitivity, and reducing systemic inflammation, these agents address key upstream drivers of oncogenesis in MASLD. Crucially, their ability to reduce hepatocyte stress and injury may create a microenvironment more conducive to immune surveillance and tumor suppression,

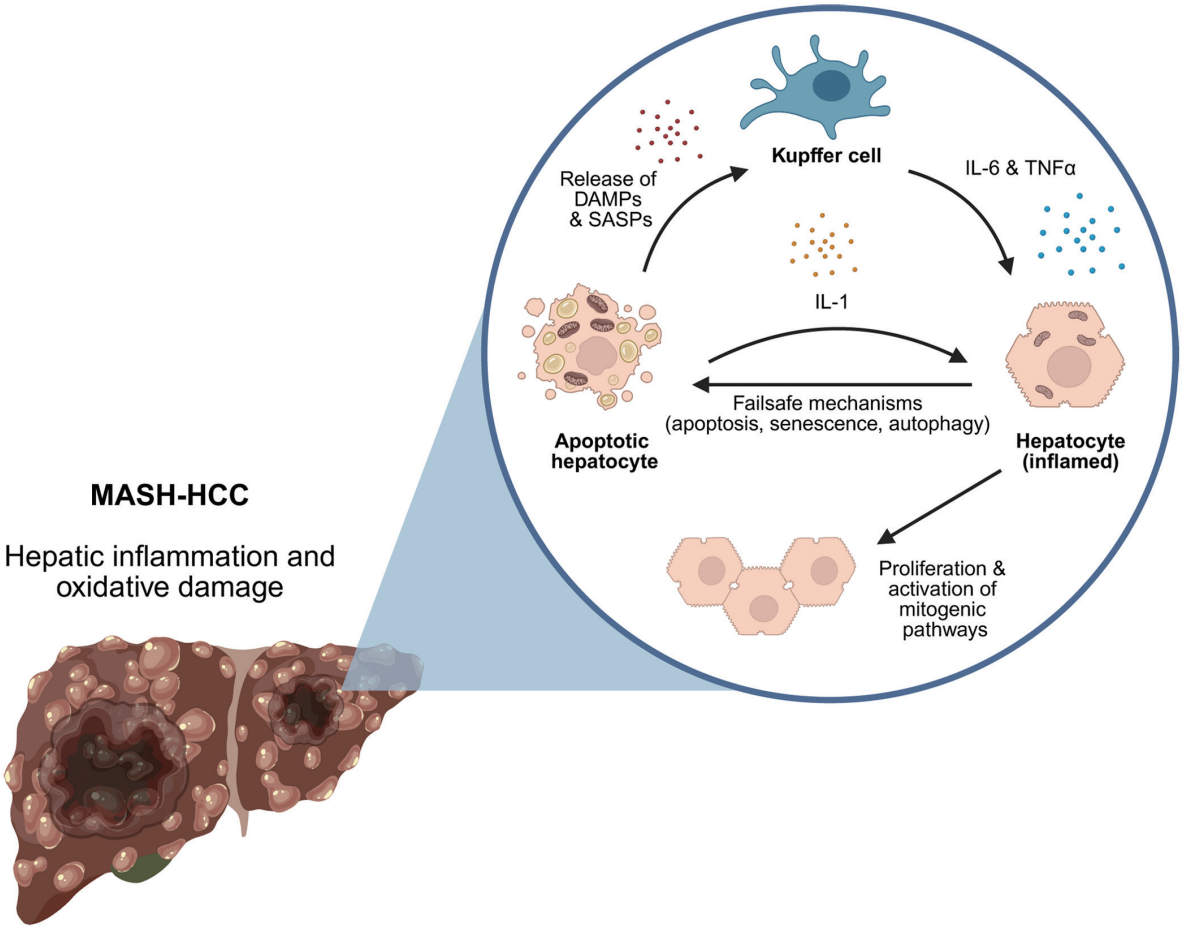

Fig. 2. Hepatic inflammation and oxidative damage at the cellular level. Cellular processes linking hepatic injury and inflammation to oncogenesis, highlighting DAMP/SASP signaling and cytokine-mediated mitogenic pathways. Created with BioRender. DAMPs, damage-associated molecular patterns; IL1, interleukin-1; IL6, interleukin-6; SASPs, senescence-associated secretory phenotypes; TNF-α, tumor necrosis factor-α; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma.

potentially enhancing endogenous mechanisms of cancer control.

MASLD progresses through a chronic cycle of immune-mediated injury, in which hepatic inflammation, oxidative damage, and compensatory regeneration establish a permissive environment for malignant transformation. Oxidative stress induces mutagenic damage, while the regenerative response to chronic hepatocellular injury activates mitogenic pathways.[26] Concurrently, immune tolerance to emerging neo-antigens establishes a tolerogenic microenvironment that allows transformed cells to escape immune surveillance. This immune–metabolic axis favors hepatocarcinogenesis.

However, intrinsic failsafe mechanisms are present to prevent malignant progression. Cell-intrinsic checkpoints (e.g., senescence, autophagy, apoptosis) are triggered in damaged hepatocytes. These processes release damage-associated molecular patterns (DAMPs) and senescence-associated secretory phenotypes (SASPs), recruiting and activating immune cells to clear damaged cells and reinforce tissue homeostasis.[6] However, immune activity contributes directly to hepatic oxidative stress through reactive oxygen species, leading to DNA damage and further damage-associated molecular pattern release. This persistent inflammatory state increases the risk of oncogenic escape via accumulated secondary mutations.

Among the mediators of this immunometabolic loop, cytokines IL-6 and TNF-α are key players. Both are elevated in cirrhosis and HCC, where they activate STAT3 and NF-κB, transcription factors that mediate oncogenic inflammation.[27] Kupffer cells, the liver's resident macrophages, are a major source of IL-6, promoting hepatocyte proliferation, a process further supported by interleukin release from apoptotic hepatocytes (Fig. 2).

Single-cell RNA sequencing (scRNA-seq) studies in HBV-HCC have identified specific enriched tumor-associated macrophage (TAM) subsets (CCL18+ M2 macrophages) associated with disease progression, suggesting they help sculpt a tumor-permissive microenvironment.[28] Terminally differentiated MMP9+ TAMs are also implicated.[29] Further studies are needed to assess the role of these macrophages in MASH-HCC.

The proposed mechanisms by which GLP-1RAs and other NuSHs may reverse hepatocarcinogenesis remain speculative, as direct hepatic mechanisms are unclear. Canonical GLP-1R expression has not been consistently detected in hepatocytes, Kupffer cells, or hepatic stellate cells.[30] This suggests that observed hepatic benefits may occur via indirect or extrahepatic mechanisms. Recent evidence indicates that GLP-1 may act via a gut-brain-immune axis, in which neuronal GLP-1Rs modulate systemic inflammation through

autonomic pathways. Immune cells themselves express minimal GLP-1Rs, pointing to central modulation as a key anti-inflammatory mechanism.[31]

The downstream effects of GLP-1RAs on hepatic immune cells are not fully delineated. However, GLP-1RAs have been demonstrated to inhibit hepatic stellate cell activation by downregulating TGF-β1/SMAD and p38 MAPK signaling, thereby reducing fibrosis.[32] Similarly, they can suppress NLRP3 inflammasome activation in Kupffer cells, leading to decreased IL-1β, IL-12, and TNF-α, and increased IL-10.[33] This suppression of a pro-inflammatory state may disrupt the chronic inflammation-regeneration cycle that drives hepatocarcinogenesis.

Additionally, the therapeutic potential of GLP-1RAs and other incretin-based NuSHs in reversing the drivers of hepatocarcinogenesis in MASLD may be grounded in their ability to restore hepatic insulin sensitivity and correct metabolic dysregulation. Insulin regulates hepatic glucose and lipid metabolism through both direct and indirect mechanisms. Canonically, direct hepatic insulin action activates the insulin receptor tyrosine kinase, triggering PDK1 and mTORC2 signaling and culminating in AKT2 phosphorylation.[34] This cascade promotes glucokinase translocation, glycogen synthase activation, and FOXO1 nuclear exclusion, thereby suppressing gluconeogenic gene expression. A refined model of insulin action further delineates that insulin also exerts indirect effects on gluconeogenesis via insulin receptor tyrosine kinase/AKT2 signaling in white adipose tissue, which suppresses lipolysis and reduces fatty acid and glycerol flux to the liver, thereby modulating gluconeogenesis through substrate availability and allosteric control.[35] In MASLD, insulin resistance in both liver and adipose tissue disrupts these pathways, exacerbating steatosis and inflammation. GLP-1RAs, by enhancing insulin secretion and sensitivity, may reduce adipose lipolysis, restore hepatic AKT2 signaling, and suppress hepatic glucose production. In doing so, they target upstream metabolic drivers of inflammation, fibrosis, and hepatocarcinogenesis.

We propose that the use of NuSHs at the intermediate stage of MASH-HCC, following locoregional treatments, such as transarterial chemoembolization or selective internal radiotherapy, may delay commencing systemic anti-cancer therapy or even slow disease progression by removing the carcinogenic driver. There is also potential for increasing the number of patients who convert from unresectable to surgically resectable.

Proposed immunotherapy synergy as a mechanism of action

In patients with established MASH-related HCC requiring systemic anti-cancer therapy, NuSHs may still confer benefit. While their direct antitumor effects remain speculative and mechanistically unclear, the indirect benefits are compelling. These may include delays in progression to cirrhosis and liver decompensation—events that frequently necessitate pauses or cessation of systemic anti-cancer therapies, such as first-line palliative atezolizumab with bevacizumab—and improvements in metabolic parameters that may enhance tolerability of oncological treatments, particularly PD-1/PD-L1 immune checkpoint blockade.

A distinct $CD8^+CXCR6^+$ T cell subset has been shown to be highly enriched in the livers of patients with severe MASLD, particularly within MASH-HCC lesions, expressing elevated levels of PD-1, indicative of chronic activation and exhaustion.[36] Strikingly, in preclinical MASLD models, PD-1/PD-L1 immune checkpoint blockade, while intended to restore antitumor immunity, paradoxically led to exacerbated liver injury, increased regenerative signaling, and a rise in tumor number and size, without meaningful tumor regression.[36] These findings suggest that lipotoxicity and chronic hepatic inflammation characteristic of MASLD create an immune contexture that converts an otherwise favorable "hot" tumor microenvironment into a maladaptive one, promoting tissue damage and carcinogenesis rather than immune-mediated tumor clearance.[37] This underscores the need for metabolic reprogramming alongside immunotherapy. GLP-1RAs and other incretin-based NuSHs, by ameliorating hepatic lipotoxicity, improving insulin sensitivity, and reducing inflammation, may help restore a more functional immune milieu. In this context, they hold promise not only for halting MASH progression but also for reconditioning the hepatic tumor microenvironment to enhance responsiveness to immunotherapies in MASH-HCC. However, both preclinical and patient-based assessments of their effects in this context are urgently needed.

Furthermore, improving metabolic status with NuSHs may reduce comorbidities such as diabetes, hypertension, and hypercholesterolaemia, as well as the risk of myocardial infarction and stroke. This could improve overall fitness, increasing the likelihood of eligibility for liver transplantation and thereby potentially curing patients of their MASH-HCC.

A summary of the established and potential roles of NuSHs in this setting is provided in Figure 3.

Safety considerations

Gastrointestinal adverse effects (AEs)

It is important to note that, while NuSHs are generally well tolerated, their side effect profiles are not negligible. Gastrointestinal AEs, such as nausea and vomiting, as well as diarrhea and constipation, are relatively more common with dual and triple incretins. Even so, these AEs are often transient and manageable, with tolerances built up through careful dose titration.[38] More notable gastrointestinal AEs include pancreatitis (including gallstone pancreatitis), gastroparesis, and bowel obstruction, although their incidences remain extremely low.[39] It is worth emphasizing that no clear causal relationship has been demonstrated between NuSHs and these effects in either the general population or MASLD-specific populations, limiting the conclusions that can be drawn.

Theoretical thyroid cancer risk

A further concern specific to GLP-1RAs is the reported risk of medullary (C-cell) thyroid cancer. Although a link was initially reported in murine studies, evidence from human cohort studies has been contradictory.[38,40,41] Due to these conflicting results, there is no clear consensus regarding this risk. Nonetheless, the U.S. Food and Drug Administration has issued a black-box warning recommending against use in individuals with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2.

Sarcopenia

It is important to acknowledge the potential impact of NuSHs on skeletal muscle mass. A recent systematic review and meta-analysis of 22 RCTs demonstrated an absolute reduction in lean mass with tirzepatide and semaglutide, but not liraglutide.[42] However, results from the SURMOUNT trial, a phase III RCT of tirzepatide, demonstrated that lean-mass reduction is approximately three times less than fat-mass reduction, contributing to an overall improvement in body composition. Furthermore, the ratio of fat-mass loss to lean-

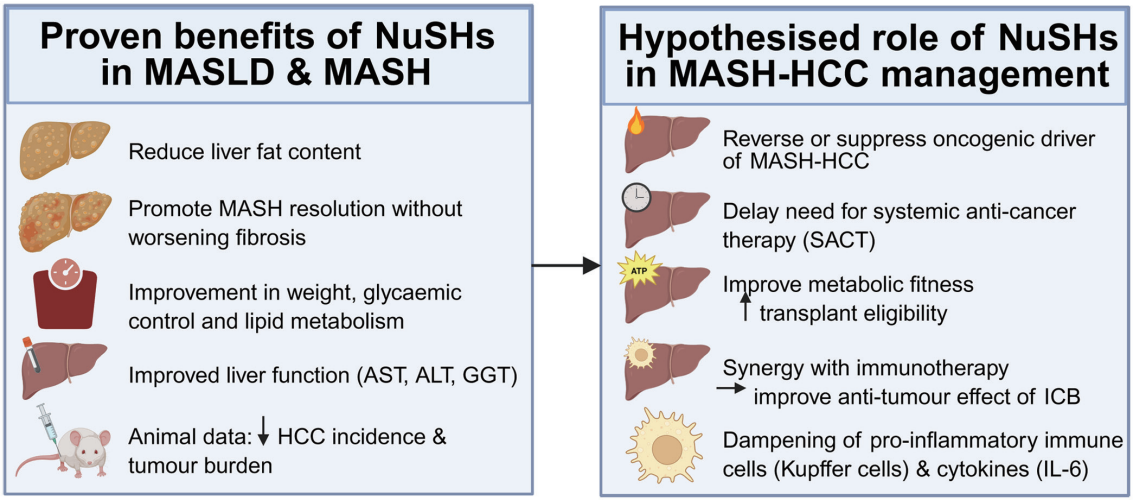

Fig. 3. Summary of the proven benefits of NuSHs in the management of MASLD and MASH (left panel) and hypothesized benefits of NuSHs in the context of MASH-HCC (right panel). Created with BioRender. ALT, alanine aminotransferase; AST, aspartate aminotransferase; MASH, metabolic dysfunction-associated steatohepatitis; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; GGT, gamma-glutamyl transferase; ↑, increase ↓, decrease.

mass loss is similar to that observed with lifestyle and surgical treatments for obesity.[43] This sarcopenic effect poses genuine concern in older adults and in individuals with low baseline muscle mass, such as the MASLD (+/- HCC) population. A large retrospective study assessing GLP-1RAs in older adults demonstrated a significant reduction in muscle mass in a dose-dependent manner, primarily attributed to the negative energy balance derived from appetite suppression.[44] Awareness of this potential side effect is critical for clinical use. High-protein diets and weight-bearing exercises should be incorporated into treatment plans for high-risk individuals, alongside careful dose titration.

Conclusions

Collating the latest trial evidence from the past two years, this review supports the rationale for further investigation of the efficacy of NuSHs, particularly GLP-1RAs, in MASH, as well as their potential as a chemopreventive strategy against MASH-related HCC. Prospective trials specifically designed to evaluate oncological endpoints in MASH-HCC populations are warranted. In parallel, translational studies should aim to delineate the precise immunometabolic mechanisms through which GLP-1RAs and other NuSHs exert protective effects in hepatic tissues. Given the relative affordability of GLP-1RAs compared to standard oncology treatments and their potential to alter the trajectory of MASH-associated HCC, there is a strong rationale for a publicly funded Health Technology Assessment trial to evaluate their efficacy. Such a study would clarify therapeutic value and assess long-term NHS impact and cost-effectiveness.

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Conflict of interest

SS: Servier, AstraZeneca, Pfizer, Pierre Fabre, Novartis (speaker/advisory board), BMS (salary and research funding), Genentech, Arcus, Amgen (institutional funding), holds a US patent for diagnostic technology in pancreatic cancer, Astron Health (shares). The other authors have no conflict of interests related to this publication.

Author contributions

Draft and critical revision of the manuscript (all authors). All authors approved the final version of the article, including the authorship list.

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