IOSR Journal of Nursing and Health Science (IOSR-JNHS)
e-ISSN: 2320–1959.p- ISSN: 2320–1940 Volume 14, Issue 5 Ser. 3 (Sept. – Oct. 2025), PP 38-40
www.iosrjournals.org

Effect Of Combined Therapy With SGLT2 Inhibitors And GLP-1 Receptor Agonists In Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Systematic Review

Rehab Alshamrani,Hassan Alrizqi

Abstract
Metabolic dysfunction-related steatotic liver disease (MASLD), or non-alcoholic fatty liver disease (NAFLD), is becoming a significant complication of obesity and type 2 diabetes mellitus. The antidiabetic agents that have demonstrated positive outcomes in metabolic health and have demonstrated potential in MASLD are sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA). This is a systematic review and synthesis of the existing evidence on endocrinology of combined SGLT2i and GLP-1RA treatment in MASLD. Review of the literature was carried out in PubMed, MEDLINE, and ClinicalTrials.gov until September 2025. The results indicate that the use of GLP-1RAs has a significant effect in enhancing the liver fat content, weight loss, and histological outcomes in non-alcoholic steatohepatitis, whereas the use of SGLT2is alleviates steatosis of the liver and liver enzyme profiles. New observational studies indicate that they are additively effective in terms of hepatic and metabolic effects, but large randomized controlled trials with histological outcomes are not available. Combined therapy is thus a promising approach that endocrinologists can adopt to treat MASLD, but more trials are required to prove conclusively.

Date of Submission: 19-09-2025 Date of Acceptance: 29-09-2025

I. Introduction

MASLD has now been referred to as the primary cause of chronic liver disease in the world in that up to one third of the adult population is affected. The condition involves a continuum of simple steatosis to steatohepatitis metabolic dysfunction-related (MASH), fibrosis, cirrhosis, and hepatocellular carcinoma. The strong relationship that exists between MASLD, obesity and type 2 diabetes mellitus places the endocrinologists at the centre stage in managing it. The initial strategies are lifestyle change and loss of weight, which is complicated to maintain over time and requires pharmacologic treatment. Medications that have metabolic and hepatic advantages have thus been of interest, specifically GLP-1 receptor agonists and SGLT2 inhibitors.

GLP-1RAs, such as semaglutide, liraglutide, and the dual GIP/GLP-1 agonist tirzepatide, are famously known to cause a significant loss in weight, improve glycemic control, and reduce cardiovascular risk. Later on, large randomized controlled trials have shown that they also have the ability to induce steatohepatitis resolution and decrease liver fat content. Empagliflozin and dapagliflozin are the SGLT2 inhibitors that lower plasma glucose through glucosuria, lead to a slight weight loss, and improve cardiovascular and renal outcomes. Multiple studies have demonstrated that SGLT2i reduce hepatic fat as well as liver enzymes, indicating possible use in MASLD. A combination regimen can potentially help to improve metabolic and hepatic outcomes because these mechanisms are unique and complementary. This is a systematic review of the evidence on the endocrinologic mechanisms, clinical outcomes, and safety of combined therapy with SGLT2i and GLP-1RA in MASLD.

II. Methods

The systematic search was done in PubMed, MEDLINE and ClinicalTrials.gov up to September 15, 2025. The search terms were SGLT2 inhibitor, GLP-1 receptor agonist, combination therapy, MASLD, NAFLD and NASH. The criteria that were used to select eligible studies were randomized controlled trials, meta-analyses, or observational cohorts that reported hepatic outcomes which included liver histology, hepatic fat measured by MRI or ultrasound, hepatic enzymes, or fibrosis scores in adults with MASLD. Children, animal model and case reports were excluded. Full-text articles were reviewed after screening titles and abstracts and data extracted in order to synthesize the evidence narratively.

III. Results

GLP-1RA monotherapy has strong evidence. Semaglutide was found to induce histologic NASH improvements in almost 60% versus 17% of participants in a phase 2 randomized controlled trial compared to placebo. This was greatly correlated to the extent of weight loss and enhanced insulin sensitivity. On the same note, tirzepatide has been shown to significantly decrease hepatic fat on MRI and show signs of histological improvement, which are in line with its strong weight loss and metabolic effects. Liraglutide and dulaglutide had also shown improvements on liver enzymes and hepatic fat but their responses were less significant than new agents.

The evidence of the SGLT2 inhibitors is less but consistent. Several randomized studies, such as those that tested dapagliflozin and empagliflozin, showed a significant decrease in hepatic steatosis using MRI-PDFF and an increase in ALT and AST. These results are supported by meta-analyses which indicate decreased non-invasive fibrosis scores also. Nevertheless, not many studies have investigated histological outcomes directly, and it is not clear to what extent fibrosis can be improved due to SGLT2i.

The combination therapy is not well proven yet has some hope. Observational studies and retrospective studies have demonstrated that dual therapy using SGLT2i and GLP-1RA is linked to more significant liver enzyme, hepatic fat fraction, and metabolic health markers than either of the two monotherapy. The additive declines in hepatic steatosis by imaging in a Japanese real-world cohort were reported and in a European retrospective study, it was shown that combination therapy decreased cardiovascular and renal events and had exploratory advantages over liver enzymes. By 2025, there are however no large randomized controlled trials that have been conducted to directly test histological endpoints when using the combination, although several such studies are underway.

IV. Discussion

SGLT2i and GLP-1RA are a good rationale in the endocrinology of MASLD. The two agents act in different yet complementary pathways that cause hepatic steatosis and inflammation. The main mode of action in GLP-1RAs is appetite suppression, delayed gastric emptying, and weight loss, which decreases adipose tissue lipolysis and hepatic fat inflammation. They also increase the insulin sensitivity and have a direct effect of lowering hepatic lipogenesis. In comparison, SGLT2 inhibitors stimulate glucosuria, decrease glucotoxicity and alter the energy metabolism to greater lipid oxidation. They also increase glucagon levels, albeit humbly, which could stimulate hepatic fatty acid oxidation, which might be additive to the effect of GLP-1RA. The two classes have anti-inflammatory effects and enhance adipokine profiles, which lower the progression of hepatocellular injury and fibrosis.

These mechanisms are reflected in the clinical data. GLP-1RAs are uniformly effective in the resolution of steatosis and steatohepatitis, and some fibrosis improvement. SGLT2is consistently decrease liver fats and enhance enzymes, but have not yet shown histological effectiveness in large studies. Combined, initial real-life research indicates that there are additive effects on liver fat and biomarkers. The clinical implication, as far as endocrinologists are concerned, is that combination therapy would treat the underlying metabolic dysfunction of MASLD in addition to offering cardiovascular and renal protection.

Nevertheless, there are a number of limitations that are to be taken into account. The most significant gap is the lack of randomized histological support of combination therapy. Majority of the studies have limited follow-up periods and employ surrogate outcomes instead of biopsy-proven outcomes. The problem of weight loss still poses a significant confounding factor because liver improvement can be to a large extent due to decreased adiposity as opposed to liver-specific activity. Practical barriers to routine clinical endocrinology practice are also involved with cost and access, particularly not in high-income countries.

V. Conclusion

SGLT2 inhibitors and GLP-1 receptor agonist used in combination therapy are complementary to each other mechanistically and promising in the treatment of MASLD. Monotherapy trials have proven that there is considerable hepatic effect with GLP-1RAs and a steady reduction in hepatic fat with SGLT2is. Combination therapy is emerging with encouraging observational data indicating that the therapy has a combination of additive metabolic and hepatic effects, but there is an urgent necessity of large randomized trials that have histological endpoints. The combined regimen is a reasonable treatment option that must be discussed as a part of shared decision-making by endocrinologists treating patients with MASLD, particularly those with type 2 diabetes.

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