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LETTER TO THE EDITOR

Exploring the therapeutic potential of glucagon-like peptide 1 agonists in metabolic disorders

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Abstract

This article comments on the work by Soresi and Giannitrapani. The authors have stated that one of the most novel and promising treatments for metabolic dysfunction-associated steatotic liver disease (MASLD) is the use of glucagon-like peptide 1 receptor agonists, especially when used in combination therapy. However, despite their notable efficacy, these drugs were not initially designed to target MASLD directly. In a groundbreaking development, the Food and Drug Administration has recently approved resmetirom, the first treatment specifically aimed at reducing liver fibrosis in metabolic-associated steatohepatitis. Resmetirom, an orally administered, liver-directed thyroid hormone beta-selective agonist, acts directly on intrahepatic pathways, enhancing its therapeutic potential and marking the beginning of a new era in the treatment of MASLD. Furthermore, the integration of lifestyle modifications into liver disease management is an essential component that should be considered and reinforced. By incorporating dietary changes and regular physical exercise into treatment, patients may achieve improved outcomes, reducing the need for pharmacological interventions and/or improving treatment efficacy. As a complement to medical therapies, lifestyle factors should not be overlooked in the broader strategy for managing MASLD.

Key Words: Glucagon-like peptide 1 agonists; Liver diseases; Metabolic dysfunction-associated steatotic liver disease; Metabolic health; Pharmacotherapy; Diet; Gut microbiome; Physical exercise; Lifestyle; Non-alcoholic fatty liver disease

Core Tip: This article comments on the work by Soresi and Giannitrapani concerning glucagon-like peptide 1 agonists as potentially useful drugs to treat metabolic dysfunction-associated steatotic liver disease. The integration of dietary changes and regular physical exercise into treatment may improve patient outcomes. These lifestyle adjustments may reduce the reliance on pharmacological interventions and/or increase the effectiveness of existing treatments. Therefore, lifestyle factors should not be overlooked in the broader strategy to manage metabolic dysfunction-associated steatotic liver disease, since they complement medical therapies.

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TO THE EDITOR

Glucagon-like peptide 1 (GLP-1) is a biomarker that has been extensively studied and linked to metabolic disorders, such as type 2 diabetes (T2D), obesity[1-5], and liver diseases[6,7]. In response to food intake, intestinal L-cells release GLP-1, acting as an incretin hormone[3]. In the intestine, GLP-1 is synthesized through posttranslational processing of proglucagon. L-cells, predominantly found in the ileum and colon, are epithelial cells that interact directly with nutrients in the intestinal lumen[8]. Moreover, L-cells are located close to both neurons and the intestine microvasculature[9,10], making them susceptible to both neural and hormonal signals. In the context of normal gut physiology, the development of peptide multi-agonists for GLP-1 is a logical approach, as most peptide-secreting enteroendocrine cells are plurihormonal[11,12], and numerous peptide hormones exert insulin-like glucoregulatory or anti-anorexic effects[13]. The plurihormonal nature of gut biology is exemplified by L-cells, which express the proglucagon gene, often in conjunction with neurotensin, cholecystokinin, and peptide YY[2]. The proglucagon-derived peptides include GLP-1, glucagon, and oxyntomodulin, all with unique metabolic activities that make them suitable to treat T2D and obesity[14].

Several preclinical studies, emerging clinical data, and the results of bariatric surgery, which has been associated with sustained increases in multiple gut hormones[15,16], support the premise that combinatorial peptide therapy has great therapeutic potential. As highlighted by Yin *et al*[17], GLP-1 receptor agonists have demonstrated promising potential in the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease[18]. However, it is evident that monotherapy with GLP-1 receptor agonists alone is insufficient to manage this complex metabolic condition. While these agonists positively influence metabolism upstream of the liver, they do not adequately address fibrotic liver injury within the tested treatment durations. This aligns with the conclusions of Soresi and Giannitrapani[19], suggesting that combination therapy may be the most promising approach to comprehensively tackle all aspects of the disease.

Diet and the gut microbiome in liver disease

The portal vein, biliary tract, and systemic circulation communicate between the gut and liver. In this relationship, diet, genetics, and environmental factors play a key role in reciprocal cellular and molecular interactions[20]. The term microbiome refers to the collective genome of all the microbes residing in an environment. Microbiome regulation is influenced by a wide range of factors, including host characteristics, dietary patterns, and environmental and microbial factors[21]. Physiological processes such as inflammation and immunity are influenced by a dynamic equilibrium between the microbiome and the host. Gut microbes can produce metabolites that protect the host from pathogens, but they can also produce harmful molecules if the relationship between the host and gut microbes is disturbed (known as dysbiosis)[21,22]. Many studies have demonstrated that the gut microbiome plays a dual role, both in maintaining the host's health and in the development of diseases, such as liver disease[21,22].

Certain foods, such as soft drinks and red and/or processed meat, have been linked to an increased risk of MASLD, with relative risks ranging from 1.47 to 2.61 for soft drinks, and 2.68 for red and processed meat[23]. In contrast, a higher intake of vegetables has been associated with a reduced incidence of MASLD[23]. Additionally, coffee and white meat consumption have been inversely related to hepatocellular carcinoma risk, with relative risks ranging from 0.10 to 0.73 when comparing those who drink more than 3 cups/day of coffee to non-drinkers. Foods with higher anti-inflammatory properties are also associated with a reduced risk of MASLD and hepatocellular carcinoma, which suggests that diet-induced inflammation may influence MASLD progression toward hepatocellular carcinoma[23]. Several dietary approaches, such as hypocaloric low-carbohydrate and low-fat diets, have been shown to effectively improve MASLD through the reduction of liver fat and related biomarkers. The Mediterranean diet offers additional benefits, not only in reducing liver fat, but also in enhancing cardiometabolic health, while being more sustainable in the long term. Clinical practice guidelines recommend that patients with MASLD improve their diet quality by adopting a Mediterranean-style diet, avoiding the intake of sugar-sweetened beverages, and minimizing the consumption of ultra-processed foods rich in saturated fats and sugars[24].

During gut dysbiosis, intestinal inflammation contributes to gastrointestinal barrier dysfunction and the translocation of micro-organism-associated molecular patterns, such as lipopolysaccharides, to the liver and systemic circulation[25]. The pathophysiology of metabolic-associated steatohepatitis (MASH), previously known as non-alcoholic steatohepatitis

(NASH)[18], has been demonstrated in a high-fat diet mouse model, which showed dysbiosis and increased vascular and epithelial permeability, suggesting a potential mechanism for the disease[26]. In addition, serum levels of lipopolysaccharides have been positively correlated with liver injury in mouse models of diet-induced MASH[27]. MASH patients with increased intestinal permeability account for approximately one half of all cases[28].

In clinical terms, the gut microbiome is intimately linked to the pathogenesis of excessive portal pressures and every aspect of cirrhosis. For example, ascites can result in spontaneous bacterial peritonitis, a condition caused by gut bacteria translocation into the sterile peritoneum, leading to significant morbidity and mortality. In patients with cirrhosis who develop variceal bleeding, prophylactic antibiotics are the standard of care, as 30%-48% of patients without antibiotic treatment develop bacterial infections[29,30]. The systemic circulation in patients with cirrhosis may also accumulate nitrogenous waste products, such as ammonia, which may result in hepatic encephalopathy. Hepatic encephalopathy therapy is primarily based on the use of lactulose, a disaccharide that acts as a laxative and stimulates the growth of beneficial gut microorganisms that reduce ammonia production and acidify the colonic contents to enable hepatic encephalopathy to be treated. Additionally, rifaximin, a non-absorbable broad-spectrum antibiotic, is used to treat hepatic encephalopathy[31]. In summary, diet and the gut microbiome are important factors in the development and progression of liver diseases such as MASLD and NASH. Disruptions in the gut microbiome, often due to diet, can worsen liver conditions. Therefore, incorporating dietary changes and microbiome-focused approaches alongside pharmacological treatments is essential for effective management and improved patient outcomes.

Physical exercise in the background of liver disease

Regular physical exercise is widely recognized for its myriad health benefits, ranging from improved cardiovascular fitness and muscle strength to enhanced mental health and longevity. This contributes to better sleep quality, reduced stress levels, and increased life satisfaction[32]. Exercise is a proven effective strategy for preventing and treating liver diseases such as MASLD, liver cancer, cirrhosis, *etc.* Exercise effectively reduces hepatic steatosis with an absolute reduction ranging from -2.4% to -5.1%[33]. Meta-analyses comparing patients with non-alcoholic fatty liver disease who followed exercise interventions with those receiving standard care, or examining differences in exercise duration, have shown that exercise, either alone or combined with dietary interventions, significantly ($P < 0.05$) improves histology and serum liver enzyme levels, indicating a reduction in liver damage, and reduces liver fat and intrahepatic lipid levels[34-36]. Physical exercise is largely effective due to its positive impact on fat metabolism. This promotes liver fat reduction and enhances peripheral insulin sensitivity, as described by Stine *et al*[36] in a meta-analysis, which showed that exercise training led to a ≥ 30% relative reduction in magnetic resonance imaging-measured liver fat (odds ratio = 3.51; 95% confidence interval: 1.49-8.23; $P = 0.004$) compared to the control group. These changes lead to decreased adipocyte lipolysis, a reduced influx of free fatty acids into the liver, and a decrease in *de novo* lipogenesis. Beyond regulating lipid homeostasis, exercise also modulates liver disease progression by influencing the hepatic inflammatory response through the modulation of key cytokines and signaling pathways, thus providing strong anti-inflammatory benefits that can mitigate the chronic inflammation commonly associated with liver diseases[37].

Lifestyle modifications are the first line of therapy to combat most liver diseases and remains the most effective preventive measure. However, once patients begin medication, these strategies should continue to be promoted, as their effects can be additive or synergistic. For instance, the combined use of GLP-1 agonists and exercise in treating obesity has shown enhanced glucose tolerance. This combination has reported positive effects on body composition, energy expenditure, and overall metabolic health, all of which are critical to obesity pathophysiology[38]. This combined approach is very promising for liver diseases such as MASLD and should be explored further. Healthcare systems must encourage exercise integration as a complementary therapy, rather than relying exclusively on pharmacological treatments. It is imperative to ensure that physical exercise programs developed as interventions are designed to individual fitness levels. To achieve this, physicians should work closely with physical therapists or exercise physiologists to design, implement, and evaluate these programs. This collaboration ensures that the programs are effective, engaging, and considerate of each patient's physical fitness, capabilities, preferences, stage of liver disease, and any other comorbid conditions. This enhances adherence and prevents patient demotivation. According to current recommendations for GLP-1 receptor agonists in exercise regimens and dietary recommendations, 150 minutes of moderate-intensity aerobic physical exercise per week, or 75 minutes of vigorous-intensity aerobic physical exercise per week, or an equivalent combination of both is recommended[39], as well as an adequate intake of protein to maintain muscle mass and function, and essential vitamins and minerals to maintain overall health[40].

Clinical implications of GLP-1 agonists and emerging therapies in liver diseases

In a groundbreaking development, the Food and Drug Administration recently approved resmetirom[41]. This is the first treatment specifically aimed at improving liver fibrosis in MASH and combating the disease. This authorization marks a new era in MASLD treatment. The approval is based on the clinical trial led by Harrison *et al*[42], who are conducting a phase 3 multicenter, placebo-controlled, randomized, double-blind trial (MAESTRO-NASH trial, NCT03900429) with a planned duration of 54 months[42]. Preliminary results from 966 patients with biopsy-confirmed NASH and various stages of fibrosis (from moderate to advanced), who received different doses of resmetirom (80 mg or 100 mg) or a placebo over 52 weeks, indicate notable improvements in fibrosis without worsening MASH activity scores, and significant resolution of NASH[42]. These results were much more favorable than those observed in the placebo group.

Resmetirom is an orally administered, liver-directed thyroid hormone receptor beta (THRβ)-selective agonist that acts directly through intrahepatic pathways, enhancing its therapeutic potential. THRβ is a nuclear hormone receptor predominantly expressed in the liver, which plays an important role in regulating metabolic pathways within the organ. While the exact mechanisms through which THRβ activation improves NASH are still being elucidated, it influences fat synthesis, modulates cholesterol metabolism and fatty acid oxidation, mitigates inflammation and fibrosis, and enhances

mitochondrial function[43]. This mechanism of action differs from GLP-1 agonists, which primarily target metabolic pathways upstream of the liver and are traditionally employed in managing T2D and obesity. This difference in the mechanism of action underscores the need to explore the complementary potential of these two therapeutic approaches to combating MASH. Due to the overlap of MASH with obesity and T2D, GLP-1 agonists are promising adjuncts to resmetirom. Clinically, patients with moderate to advanced fibrosis, who are at the highest risk of disease progression and may not respond adequately to therapies that only target metabolic dysfunction, stand to benefit most from resmetirom. Its anti-fibrotic properties could address the limitations of GLP-1 agonists in treating liver fibrosis. Moreover, in these patients, the improvements observed in key biomarkers, such as liver enzymes and lipid profiles, could be further enhanced by combining resmetirom with GLP-1 agonists. In addition, GLP-1 agonists would support cardiometabolic health by improving insulin resistance and regulating glycemia, effectively controlling risk factors associated with metabolic syndrome, and contributing to a more comprehensive therapeutic approach. However, while these drugs offer benefits, they can also cause side effects. GLP-1 receptor agonists, such as semaglutide and liraglutide, can affect the gastrointestinal tract, leading to nausea, vomiting, constipation, and diarrhea. According to a recent study, GLP-1 receptor agonists are associated with a nine-fold higher risk of pancreatitis compared to other drugs[44]. Additionally, patients receiving this therapy experienced four times more intestinal obstructions and three times more gastroparesis. Despite this, the absolute risks associated with these complications were less than 1% per year of use[44]. Resmetirom has also been associated with gastrointestinal symptoms such as diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness (reported in at least 5% of patients and at higher rates than placebo)[45]. In addition, cases of liver toxicity have been reported with resmetirom, and when it is taken concomitantly with atorvastatin, pravastatin, rosuvastatin, and simvastatin, it increases the risk of adverse reactions to these medications[45]. Since GLP-1 receptor agonists and resmetirom act through changes in key metabolic pathways, *e.g.*, metabolic pathways upstream of the liver, cholesterol metabolism, and fatty acid oxidation, which are linked to physical exercise and diet, the treatment of metabolic disorders must combine the therapeutic effects of these drugs with weight loss through physical exercise and dietary changes.

As previously discussed, lifestyle changes should be considered and reinforced as an essential component of treating liver diseases. With the introduction of resmetirom, it is crucial to evaluate whether regular exercise and healthy diets can enhance its pharmacological effects. Given the well-documented metabolic benefits of exercise and healthy dietary patterns, it is likely that a combination of resmetirom with these lifestyle interventions will have a positive impact. Together, these interventions provide a more effective strategy to manage liver disease than either approach alone. By improving patient outcomes and potentially reducing the reliance on pharmacological interventions, lifestyle factors are key complements to medical treatments and should not be overlooked in the broader MASLD management strategy.

Studies that evaluated resmetirom followed the practice guidelines provided by the American Association for the Study of Liver Diseases[46], which recommend physical exercise and dietary recommendations concomitantly. Patients who maintain physical exercise for over 150 minutes/week or increase their level of exercise by more than 60 minutes/week experience a pronounced decrease in serum aminotransferases that is independent of weight loss. Adhering to a calorie-restricted diet over an extended period is associated with a reduction in cardiovascular risk and the mobilization of liver fat. The macronutrient composition of a diet over a period of months or years is less important than the result of sustained weight loss[46].

Another relevant aspect of this combined approach is its significant economic implications. The costs associated with the progression and management of liver diseases and their complications, *e.g.*, liver transplantation, expensive therapies for hepatocellular carcinoma, *etc.*, could be reduced through early and effective interventions, which would alleviate the burden on healthcare systems. While targeted pharmacotherapies, such as GLP-1 agonists and resmetirom, may be financially challenging in resource-constrained regions, lifestyle interventions offer a cost-effective alternative, promoting healthy habits that help prevent disease progression and decrease the reliance on expensive treatments. Preventing the progression of MASLD through this dual approach could generate long-term savings in healthcare costs, making it a sustainable and economically viable option, even in regions with limited resources.

CONCLUSION

The use of GLP-1 agonists and resmetirom improves metabolic health. By combining physical exercise, diet, and gut microbiome in a holistic manner with liver disease and metabolic disorders therapeutics, long-term success may be enhanced. Further research is necessary to investigate the possibility of long-term use of combined therapies, as well as to analyze the potential adverse reactions in more detail.

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FOOTNOTES

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