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LETTER TO THE EDITOR

Interplay of gut microbiota, glucagon-like peptide receptor agonists, and nutrition: New frontiers in metabolic dysfunction-associated steatotic liver disease therapy

Merve Guney-Coskun, Metin Basaranoglu

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Abstract

The gut-liver axis plays a crucial role in the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Key metabolites, including lipopolysaccharides, short-chain fatty acids (SCFAs), bile acids, and beneficial gut bacteria such as Bifidobacterium and Lactobacillus, are pivotal in this process. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) show promise in managing MASLD by promoting weight loss, enhancing insulin secretion, and improving liver health. They restore gut-liver axis functionality, and their effects are amplified through dietary modifications and gut microbiome-targeted therapies. Emerging research highlights the interplay between GLP-1 RAs and gut microbiota, indicating that the gut microbiome significantly influences therapeutic outcomes. Metabolites produced by gut bacteria, can stimulate glucagon-like peptide-1 (GLP-1) secretion, further improving metabolic health. Integrating dietary interventions with GLP-1 RA treatment may enhance liver health by modulating the gut microbiota-SCFAs-GLP-1 pathway. Future research is needed to understand personalized effects, with prebiotics and probiotics offering treatment avenues for MASLD.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Glucagon-like peptide-1 receptor agonists; Gut microbiome; Gut-liver axis; Diet intervention

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Core Tip: The gut-liver axis is integral in the progression of various diseases, with key metabolites like lipopolysaccharides, short-chain fatty acids, bile acids, immune factors, inflammatory cytokines, and beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* playing pivotal roles. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) contribute to substantial weight loss, enhance insulin secretion, reduce appetite, and improve liver health by restoring gut-liver axis functionality. Dietary modifications can amplify these benefits, while gut microbiome-targeted therapies may offer additional advantages in treating metabolic dysfunction-associated steatotic liver disease. Future multi-omics research will underscore the importance of personalized GLP-1 RAs treatment considering gut microbiota effects, with prebiotics and probiotics potentially improving liver health *via* the gut microbiota.

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TO THE EDITOR

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease globally, affecting 25% of the adult population[1]. To reflect its complex nature, experts have suggested renaming NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD), providing a more comprehensive and inclusive framework for diagnosis, research, and clinical management, free of stigmatization[2]. Unmanaged MASLD can progress to serious liver complications, including advanced fibrosis, cirrhosis, and an increased risk of hepatocellular carcinoma[3,4]. The diagnosis of MASLD involves the presence of hepatic steatosis and at least one cardiometabolic risk factor (overweight, dysglycemia, hypertension, hypertriglyceridemia, or low high-density lipoprotein cholesterol, excluding significant alcohol consumption[5]. Currently, the primary treatment for MASLD focuses on sustained lifestyle changes, particularly adopting a healthy diet and engaging in physical activity to promote weight loss. Additionally, metabolic drugs that induce weight loss, especially glucagon-like peptide-1 receptor agonists (GLP-1 RAs), are valuable to achieve metabolic dysfunction-associated steatohepatitis (MASH) resolution, though evidence of fibrosis regression is still lacking[6]. Importantly, significant improvements in MASLD's histological components can be achieved without weight loss by using drugs that directly modulate adipose tissue function and hepatic lipid metabolism.

A recent comprehensive review by Rochoń *et al*[7] delves into the critical dynamics of the gut-liver axis, highlighting how dysbiosis and altered microbial interactions lead to significant disruptions. It emphasizes the role of GLP-1 RAs in addressing core metabolic dysfunctions, such as steatosis and impaired glycemic control, while also potentially restoring gut-liver axis functionality. Although the precise role of the gut microbiota in the effects of these peptide hormones remains unresolved, it has been speculated that host-gut microbiota crosstalk, facilitated by bacterial fermentation end-products like short-chain fatty acids (SCFAs), may influence intestinal chemo-sensing and modulate the release and activity of gut peptides[8,9]. This interplay presents a promising avenue to treat MASLD, underscoring the necessity of a multifaceted approach to manage this complex disease. We aimed to present our editorial article, which offers additional insights into this review by Rochoń *et al*[7], discussing the role of GLP-1 RAs and their interplay with the gut microbiome in the management of metabolic dysfunction-associated fatty liver disease.

GUT-LIVER AXIS AND MASLD

In recent years, the importance of the gut microbiota in human metabolism and health has become increasingly recognized. The gastrointestinal system harbors a diverse microbial community, with approximately 1014 bacterial cells predominantly found in the colon, which is ten times higher than the total number of somatic and germ cells in the human body[10]. The gut-liver axis is a term used to describe the complex interplay between the liver and the gut microbiota[11]. This axis plays a pivotal role in the pathogenesis of MASLD, with gut microbiota significantly influencing liver disease progression[12].

Recent human studies have compared the gut microbiota of patients with MASLD, MASH, and cirrhosis to those of individuals with healthy livers. These comparisons aim to identify specific microbiota signatures associated with these liver conditions[13]. While the role of the gut-liver axis in the pathogenesis of MASLD has been investigated in these studies, the relationship remains not fully understood. However, the identification of unique gut microbiome signatures in MASLD, MASLD fibrosis, and cirrhosis suggests their potential use as non-invasive diagnostic biomarkers for liver diseases[14]. Human studies have identified distinct microbiome signatures associated with MASLD, such as the enrichment of Proteobacteria in steatosis and MASH, and a reduction in beneficial bacteria like Faecalibacterium prausnitzii in cirrhosis and other metabolic diseases[14]. Dysbiosis and altered microbial interactions within this microbiota can lead to the translocation of harmful substances, such as lipopolysaccharides (LPS), to the liver, triggering hepatic inflammation and aggravating MASLD[15]. The gut microbiota is crucial to maintain intestinal barrier integrity by regulating mucus layer thickness, producing antimicrobial peptides, and maintaining tight junction proteins and immune cell activation. In individuals with MASLD, dysbiosis reduces mucus layer thickness, antimicrobial peptide

production, and tight junction proteins, while altering immune cell numbers in the lamina propria. This leads to increased intestinal permeability and disruption of gut-liver axis homeostasis[7].

The gut microbiota produces various metabolites, such as SCFA, secondary bile acids, and LPS, which regulate enteroendocrine cells and hormone secretion. These metabolites can be categorized into three types: (1) Those directly derived from food components, like SCFAs; (2) those modified by gut microbes, such as secondary bile acids; and (3) those synthesized by microbes, including LPS. The gut microbiome plays a pivotal role in the pathogenesis of MASLD, with specific metabolites such as lactate, ethanol, and trimethylamine N-oxide driving disease progression by affecting FXR signaling and reducing the bile acid pool, while LPS trigger hepatic inflammation. In contrast, SCFAs possess anti-inflammatory properties that can prevent MASLD progression. SCFAs and secondary bile acids stimulate glucagon-like peptide-1 (GLP-1) secretion, while metabolites like 2-oleoyl glycerol and indole directly activate GLP-1 release.

INTERRELATIONSHIP BETWEEN GLP-1 RECEPTOR AGONISTS AND GUT MICROBIOTA

GLP-1 is secreted by gut endocrine cells in response to food intake, and functions as an incretin hormone, enhancing glucose-dependent insulin secretion. Pharmacological activation of GLP-1 RAs reduces glucagon secretion and slows gastric emptying, which contributes to improved liver health. By activating GLP-1 receptors in the hypothalamus and brainstem, GLP-1 RAs promote satiety and decrease appetite, leading to reduced caloric intake and significant weight loss [16,17]. This weight loss is a primary mechanism through which GLP-1 RAs medicines, principally acylated peptides such as liraglutide and semaglutide, exert their beneficial effects on metabolic syndrome components, including steatohepatitis. Besides weight loss, GLP-1 RAs reduce de novo lipogenesis, stimulate fatty acid oxidation, and enhance insulin signaling pathways, collectively improving liver homeostasis and reducing hepatic inflammation[18-21].

GLP-1 RAs may also reduce hepatic inflammation through mechanisms that do not solely rely on weight reduction, such as improving insulin sensitivity, reducing oxidative stress, and modulating inflammatory pathways[19]. Clinical studies robustly demonstrate the efficacy of GLP-1 RAs in treating MASLD. A meta-analysis of 11 placebo- or active-controlled phase II randomized controlled trials (RCTs) involving nearly 950 participants showed that GLP-1 RA treatments, such as liraglutide, semaglutide, exenatide, and dulaglutide, significantly reduced liver fat content, improved serum liver enzyme levels, and achieved greater histological resolution of MASH without worsening fibrosis[22]. Specifically, liraglutide and semaglutide showed significant reductions in liver fat content and liver stiffness, along with improvements in glycated hemoglobin and lipid profiles[22]. A recent systematic review and meta-analysis encompassing eight studies with 2413 patients found that 24 weeks of semaglutide treatment significantly reduced serum alanine transaminase and aspartate transaminase levels, improved liver fat content and liver stiffness, and enhanced metabolic parameters in patients with MASLD/MASH[23]. Despite these benefits, the treatment was associated with an increased risk of gastrointestinal adverse events, such as nausea, vomiting, and gallbladder-related diseases, necessitating careful consideration in clinical practice[23].

Our clinical observations from the Gastroenterology and Hepatology Clinic at Bezmialem Vakif University indicate that five patients treated with GLP-1 receptor agonists demonstrated promising results. Patients experienced significant reductions in NAS scores and body weight, with common side effects including reduced appetite, nausea, and bloating. Despite some variability, including one patient gaining weight, improvements in liver fibrosis were observed, highlighting the potential efficacy of GLP-1 RAs in treating MASLD. Taken together, it is likely that, in the near future, GLP-1RA will play a greater role among clinicians to treat patients with MASLD[24]. Continuous long-term evaluation is essential to ensure their safety and effectiveness, with hopes for broader access as more real-world data emerge[25].

Research has also indicated that GLP-1 RAs impact the gut microbiota and intestinal environment by affecting both the central nervous system and local peripheral receptors. GLP-1 RAs are known to impact the intestinal immune system and alter gut microbiota[26,27]. They trigger norepinephrine release, activating the sympathetic nervous system and increasing *Escherichia coli* levels. Liraglutide decreases Bacteroidetes and increases Actinobacteria while reducing *Ruminococcus* spp. without affecting *Akkermansia* spp.[7]. Treatment with GLP-1 and dual GLP-1/GLP-2 receptor agonists in diet-induced obese mice resulted in significant weight loss, improved glucose tolerance, and gut microbiome alterations, suggesting these microbiome shifts may be linked to the metabolic benefits of GLP receptor signaling[9]. A study investigating semaglutide's effects on gut microbiota, cognitive function, and inflammation in obese mice found that it significantly increased beneficial bacteria such as Akkermansia, Muribaculaceae, Coriobacteriaceae _UCG_002, and Clostridia _UCG_014, while reducing Romboutsia, Dubosiella, and Enterorhabdus[28]. These changes suggest that semaglutide may help correct gut flora imbalances from a high-fat diet. Additionally, liraglutide, a GLP-1 receptor agonist, was found to improve dyslipidemia in high-fat diet-fed mice by significantly altering gut microbiota composition, notably increasing the abundance of beneficial bacteria like Akkermansia, which is associated with better lipid metabolism[29]. Additionally, studies show that varying gut microbiota compositions can influence responses to GLP-1 RA treatment. Patients may occasionally need to discontinue GLP-1 RA treatment due to reduced efficacy, a condition known as GLP-1 resistance[30]. This resistance may be linked to gut microbiota dysbiosis. The interaction between GLP-1 and gut microbiota significantly impacts host metabolism and health. However, the precise mechanisms linking gut microbiota, GLP-1 secretion, and host health remain unclear.

NUTRITIONAL INTERVENTIONS TARGETING THE GUT-LIVER AXIS TO PROMOTE GLP-1 SECRETION

Poor diet and limited physical activity are prevalent among individuals diagnosed with MASLD[31]. Both observational and interventional studies indicate that excess caloric intake, regardless of diet composition, is associated with MASLD [32,33]. Poor dietary choices, such as consuming fructose-rich soft drinks and high amounts of animal protein, are linked to an increased risk of MASLD[34]. Additionally, diets rich in saturated fats and refined sugars disrupt the gut microbiota, leading to dysbiosis. This imbalance promotes the translocation of harmful substances to the liver, triggering hepatic inflammation and exacerbating MASLD[13]. Conversely, healthy dietary modifications can reverse obesity, lipidemia, and gut microbiota dysbiosis, playing a crucial role in preventing and treating MASLD. Given that diet significantly influences MASLD and alters gut microbiota, there is a clear need for integrated research to explore how nutrients and microbial changes affect liver health and metabolism. Bacterial metabolites from amino acids and prebiotics play key roles in the gut-liver axis. Gut bacteria convert tryptophan, phenylalanine, and tyrosine into various metabolites, while SCFAs are produced from fermenting inulin-type fructans[35]. These metabolites can cross into the liver or influence intestinal permeability, stimulating the release of GLP-1 and GLP-2.

GLP-1 improves liver metabolism and insulin sensitivity, while GLP-2 enhances gut barrier function. Liver enzymes further process these metabolites, impacting inflammation and lipid accumulation. These findings, largely from mouse models, highlight how diet shapes gut microbiota, leading to the production of metabolites like SCFAs that influence metabolic processes[30,35]. Most of these findings are based on studies using mouse models of obesity or NAFLD.

Dietary intake influences gut microbiota composition, which in turn produces metabolites like SCFAs that can stimulate GLP-1 secretion. GLP-1 affects the brain, intestine, and pancreas to enhance metabolic processes. Emerging evidence underscores the potential of gut microbiome-targeted therapies, including probiotics, prebiotics, synbiotics, and specific receptor agonists, in managing MASLD[36]. Available data suggest that modulating gut microbiota with pre-, pro-, and synbiotics may reduce liver fat accumulation and lower serum hepatic enzyme levels[35].

Nutrients interact with gut microbiota and influence MASLD development by altering dietary energy absorption, bile acid metabolism, intestinal permeability, and ethanol production. Additionally, nutrients can mitigate MASLD by promoting a diverse gut microbiota, lowering the Firmicutes/Bacteroidetes (F/B) ratio, and increasing beneficial gut microbes[37]. Recent meta-analyses have shown that gut microbiome-targeted therapies significantly reduce liver enzyme levels, suggesting a promising avenue to prevent hepatocyte damage in MASLD patients[38]. However, further research is needed to determine the optimal bacterial strains, treatment duration, and dosages for effective therapy. A meta-umbrella review of 13 studies found that gut microbial modulation significantly improved homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin (FI) levels in MASLD, although it did not significantly affect fasting blood sugar levels[39]. Prebiotics had the strongest impact on HOMA-IR, while synbiotics were most effective for FI, indicating the potential of these therapies in managing glycemic indices in MASLD. The effects on HOMA-IR and FI were robust, with prebiotics showing the strongest impact on HOMA-IR, and synbiotics on FI.

Despite the promising results, there are concerns about the efficacy and safety of probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation. Studies investigating these microbiome-altering therapies have shown potential benefits, particularly for lean patients with limited treatment options, by counteracting gut dysbiosis[40]. However, large-scale studies are essential to confirm their effectiveness and address safety concerns before they can be widely recommended for MASLD treatment. Furthermore, identifying disease-specific bacterial markers and integrating gut microbiota manipulation into therapeutic strategies could enhance personalized treatments for MASLD patients[41]. Advanced methods that combine microbiome signatures with systemic metabolites hold promise for diagnosing liver alterations and monitoring therapeutic responses in routine clinical care. In conclusion, GLP-1 RAs hold significant promise in managing MASLD (Figure 1). Combining GLP-1 RAs with tailored dietary advice and gut microbiome-targeted therapies, RCTs have demonstrated that GLP-1 RAs, combined with a reduced-calorie diet and increased physical activity, significantly improve liver health and metabolic outcomes[25].

CONCLUSION AND FUTURE DIRECTIONS FOR RESEARCH AND CLINICAL IMPLICATIONS

Managing MASLD requires an integrated approach that combines lifestyle modifications, pharmacological interventions, and gut microbiota-targeted therapies. The current lack of clear guidelines and therapeutic interventions creates a significant gap in MASLD management. Additionally, some recent clinical practice updates still reference MASLD, complicating the clinical implementation of the latest terminological changes and potentially causing confusion as MASLD-specific therapies emerge. This inconsistency underscores the urgency for updated guidelines that reflect current research and terminology. To advance the field, multidisciplinary approaches involving hepatologists, endocrinologists, dietitians, and researchers are essential. These collaborations can foster comprehensive studies that address the multifactorial nature of MASLD, incorporating aspects of diet, microbiome, and pharmacological interventions. Future research should focus on large-scale, longitudinal studies to validate the efficacy and safety of emerging therapies, including microbiome-targeted treatments and GLP-1 RAs in diverse populations. Additionally, incorporating advanced technologies such as multi-omics and machine learning can enhance our understanding of disease mechanisms and lead to more personalized treatment strategies[42].

In conclusion, bridging the current gaps in research and updating clinical guidelines will be critical in improving the management and outcomes of MASLD. By integrating multidisciplinary efforts and leveraging innovative research methodologies, the field can move toward more effective and personalized therapeutic approaches for this complex disease.

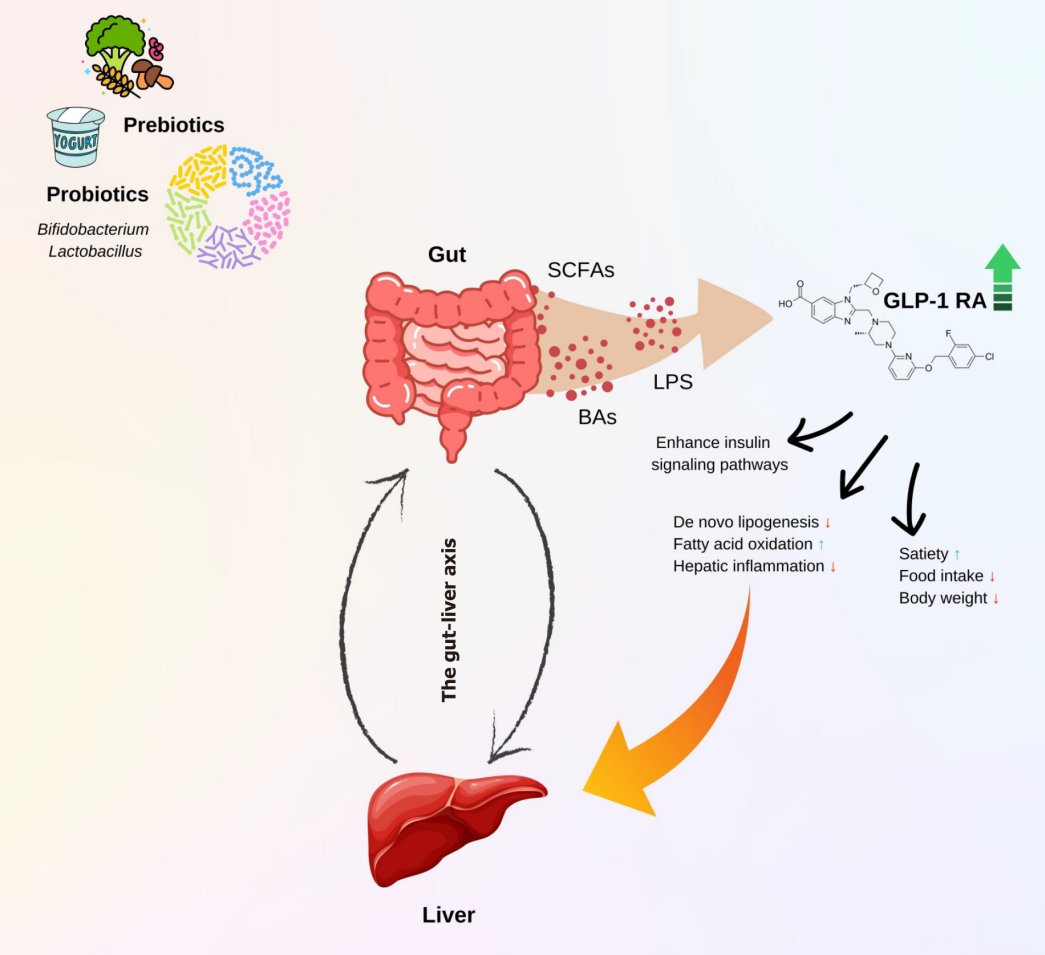

Figure 1 Interaction between the gut microbiota, glucagon-like peptide-1 receptor agonists, and dietary interventions in the management of metabolic associated steatotic liver disease. The intake of certain diets produces dietary fibers, and the consumption of probiotics may affect the function and composition of the gut microbiota. This process supports the production of beneficial metabolites, such as short-chain fatty acids (SCFAs), bile acids (BAs), and lipopolysaccharides (LPSs) by gut microbiota, which in turn promote glucagon-like peptide-1 (GLP-1) production. GLP-1 receptor agonists (RAs) play a role in enhancing insulin secretion, improving insulin signaling pathways, increasing satiety, promoting weight loss, reducing de novo lipogenesis, stimulating fatty acid oxidation, and reducing hepatic inflammation, collectively improving liver homeostasis. The figure highlights the integrated approach to managing metabolic dysfunction-associated steatotic liver disease (MASLD) through gut microbiome modulation and GLP-1 RA therapy.

FOOTNOTES

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