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Review

Glucagon-like peptide-1 receptor agonist (GLP-1-RAS) treatment in patients with cirrhosis: A scoping review

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Abstract

Cirrhosis is a chronic disease characterized by diffuse fibrosis and morphological changes in the hepatic parenchyma. It is estimated that one-third of patients with cirrhosis also have diabetes. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown significant benefits in managing liver diseases, such as nonalcoholic fatty liver disease. However, little is known about its utility in patients with cirrhosis. This study aimed to explore the existing literature on the use of GLP-1 analogs in patients with hepatic cirrhosis, examining their potential advantages and disadvantages and possible indications for their use. Scoping reviews that included PubMed, Scopus, the International Clinical Trials Registry Platform search portal and ClinicalTrials were used. Six publications were included: prospective cohort (n=1), retrospective cohort (n=3), and clinical trial (n=2). The use of GLP-1 RAs proved beneficial in cirrhosis, demonstrating a decrease in mortality and complications and a reduction in weight. Using them over other available antidiabetic agents in this patient population is preferable. However, GLP-1 analogs in advanced fibrosis stages do not appear to be effective in reversing this condition.

Keywords: cirrhosis, glucagon-like peptide-1 receptor agonists, diabetes.

Introduction

Cirrhosis is a chronic liver disease characterized by inflammation, diffuse fibrosis, and changes in hepatic morphology [1]. It is the 11th leading cause of death worldwide, with an estimated 1.16 million deaths annually [2]. Additionally, it significantly impacts the health and quality of life of those affected [3]. Of concern, obesity, overweight, diabetes, and metabolic syndrome are important risk factors that have been increasing in parallel with this condition [4, 5]. With geographically variable etiologies, hepatitis B infection (HBV) is the leading cause in Asian countries. In contrast, alcohol abuse and nonalcoholic fatty liver disease (NAFLD) are the most common causes in Western countries [2, 6].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a new class of antidiabetic drugs used for the past 20 years for type 2 diabetes mellitus and obesity [7]. These agents have been shown to reduce both glycated hemoglobin and body weight [7, 8]. Additionally, they have been observed to have beneficial effects on the liver, although the underlying mechanism is not fully understood. They have been used for the treatment of nonalcoholic fatty liver disease (NAFLD), presumably because of their ability to indirectly reduce inflammation [8, 9]. Preliminary evidence suggests that using GLP-1 RAs for some liver pathologies could be beneficial because they have multiple positive effects.

Although more research is needed, the results presented in nonalcoholic fatty liver disease are promising and could indicate the potential use of GLP-1 RAs in other liver diseases, such as cirrhosis, especially considering that one-third of cirrhotic patients also have diabetes [10]. However, there needs to be more scientific

information regarding the use of these agents under this condition [7]. Therefore, the aim of this review is to delve into the available literature on the use of GLP-1 analogs in patients with liver cirrhosis, evaluating their potential risks, benefits, and indications.

Material and methods

An exploratory systematic review was conducted in accordance with PRISMA-ScR [11], following the methods proposed by Arksey and O'Malley [12] and modified by Levac [13]: a) defining the research question; b) searching and identifying relevant studies; c) collecting data, and d) summarizing and reporting the results. This review addresses the following research question:

What is the current state of scientific evidence regarding the use of different GLP-1 analogs in patients with liver cirrhosis?

Eligibility criteria

Analytical or experimental studies and retrospective or prospective studies conducted in humans published between 2005 and 2023 were included in this study. Articles published in English were also included. Theoretical studies, such as clinical management guidelines, literature reviews, protocols, and articles without abstracts, were excluded.

Information sources and search

The search was conducted until December 2023 in the PubMed, Scopus, International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov databases. The search mainly used terms such as "Liver cirrhosis" and "Glucagon-Like Peptide 1". New updates were searched for monthly. Subsequently, the search was expanded to include the names of various GLP-1 analogs available on the market.

Study selection, data extraction, and synthesis

Two authors conducted the initial search, and subsequently, three authors independently reviewed the literature. Periodic meetings were held to determine eligible publications for the study and evaluate potential bias. The following data were extracted: authors, research type, publication date, objective, sample, and results (Table 1).

Results

Six publications were included, including prospective (n=1) and retrospective (n=2) cohorts, clinical trials (n=2), and observational studies (n=1) (Figure 1). The number of publications was mostly 2023 (n=3), followed by 2022 (n=1), 2020 (n=1), and 2010 (n=1).

Yen *et al.* [14] used the Taiwan National Health Insurance Research Database, which included 934 patients with cirrhosis and type 2 diabetes mellitus, dividing both groups equally into 467 patients, between users and non-users of GLP-1 receptor agonists (AR-GLP1), with a follow-up time of 3.28 and 3.06 years, respectively. The analysis revealed that AR-GLP1 users have a significantly lower risk of all-cause mortality (AHR, 0.47; 95% CI, 0.32–0.69), cirrhosis decompensation (aHR, 0.7; 95% CI, 0.49–0.99), hepatic encephalopathy (aHR, 0.59; 95% CI, 0.36–0.97), hepatic insufficiency (aHR, 0.54; 95% CI, 0.34–0.85), and major cardiovascular events (aHR, 0.6; 95% CI, 0.41–0.87), compared with non-users. There were no significant differences in the risk of esophageal varices with bleeding, ascites, jaundice, liver transplantation, or hepatocellular carcinoma.

A study from the United States estimated the risk of hepatic decompensation in patients with type 2 diabetes and cirrhosis using GLP-1 analogs and compared three different types of antidiabetic medications. With a median follow-up of 132 days, patients who started treatment with a GLP-1 analogue had a significantly lower risk than patients who started with a DPP-4 inhibitor or a sulfonylurea, in terms of general hepatic decompensation (HR 0.68; 95% CI, 0.53–0.88; HR 0.64; 95% CI, 0.48–0.84), ascites, bacterial peritonitis, hepatorenal syndrome (HR 0.66; 95% CI, 0.45–0.97; HR 0.66; 95% CI, 0.46–0.94), esophageal variceal bleeding (HR 0.62; 95% CI, 0.41–0.92; HR 0.59; 95% CI, 0.37–0.92), and hepatic encephalopathy (HR 0.76; 95% CI, 0.55–1.06; HR 0.60; 95% CI, 0.39–0.92). However, no significant differences in the risk of hepatic decompensation were found between patients who started treatment with a GLP-1 analog and patients who started treatment with an SGLT-2 inhibitor (HR 0.89; 95% CI, 0.62–1.28). The results were consistent in subgroups of patients with and without previously decompensated cirrhosis [15].

A phase 2 clinical trial [16] evaluated the use of semaglutide in patients with compensated nonalcoholic fatty liver disease (NAFLD)-related cirrhosis. The study included patients from Europe and the United States with biopsy-confirmed cirrhosis with or without type 2 diabetes. There were no significant differences between the groups in the proportion of patients with

Table 1: Features of publications.

Authors	Research type	Publication date	Objective	Sample	Results
Yen *et al.*	Population-based cohort study.	2023	To investigate whether GLP-1 receptor agonists (GLP-1 RAs) influence the risk of cirrhotic decompensation, hepatic encephalopathy, acute-on-chronic liver failure, and cardiovascular events in patients with type 2 diabetes and compensated cirrhosis.	A total of 934 patients from 467 matched pairs of GLP-1 RA users and non-users were included.	GLP-1 analog users exhibited a significantly lower risk of death, cardiovascular events, decompensated cirrhosis, hepatic encephalopathy, and liver failure.
Simon *et al.*	Retrospective cohort study.	2022	To compare the effectiveness of GLP-1 receptor agonists (GLP-1 RAs) with DPP-4is, sulfonylureas, or SGLT-2is in reducing decompensation events in patients with cirrhosis and type 2 diabetes.	There were three matched cohorts: the first (GLP-1 RAs *vs*. DDP-4is) with 6,621 participants, the second (GLP-1 RAs *vs*. sulfonylureas) with 10,385 participants, and the third (GLP-1 RAs and SGLT-2is) with 3,416 participants.	Among cirrhotic patients with type 2 diabetes, the rates of decompensation were lower for GLP-1RAs than for DPP-4is or sulfonylureas and were similar for SGLT-2is.
Loomba *et al.*	Randomized, double-masked, placebo-controlled phase 2 clinical trial.	2023	To investigate the efficacy and safety of semaglutide in patients with compensated nonalcoholic fatty liver disease-related cirrhosis with or without diabetes.	71 patients had nonalcoholic fatty liver disease-related cirrhosis and a body mass index of 27 kg/m^2 or more.	2.4 mg of semaglutide weekly did not significantly improve fibrosis or achieve nonalcoholic fatty liver resolution. However, it was well-tolerated, did not cause any new problems, and led to improved cardiometabolic parameters.

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Table 1: Continued.

Authors	Research type	Publication date	Objective	Sample	Results
Huynh *et al.*	A multicenter retrospective cohort study.	2023	To determine whether patients with diabetes and cirrhosis treated with metformin and a GLP-1 receptor agonist (AR-GLP1) experience a reduction in mortality, hepatic decompensation events, and hepatocellular carcinoma (HCC) compared with patients receiving metformin alone.	This study included 150,934 patients in total. Of these, 20,053 were randomized to receive monotherapy and 1,422 to receive dual therapy.	Dual therapy with metformin and GLP-1 analogs has lower mortality and morbidity rates in patients with cirrhosis and diabetes than those receiving metformin alone.
Flint *et al.*	Open-label parallel-group clinical trials.	2010	To compare the pharmacokinetics of a single dose of liraglutide in patients with hepatic impairment.	A total of 25 subjects were enrolled, of whom 24 were analyzed (14 males and 10 females).	There were no safety concerns regarding the use of liraglutide in patients with liver impairment.
Fakhreddine *et al.*	Retrospective study.	2020	To provide preliminary data on the safety and efficacy of pharmacological agents for weight loss in patients with advanced liver disease.	38 patients and 63 prescriptions	GLP-1 analogs are the second-most associated group with weight loss. In addition, pharmacological weight loss in patients with advanced liver fibrosis appears to be safe and effective.

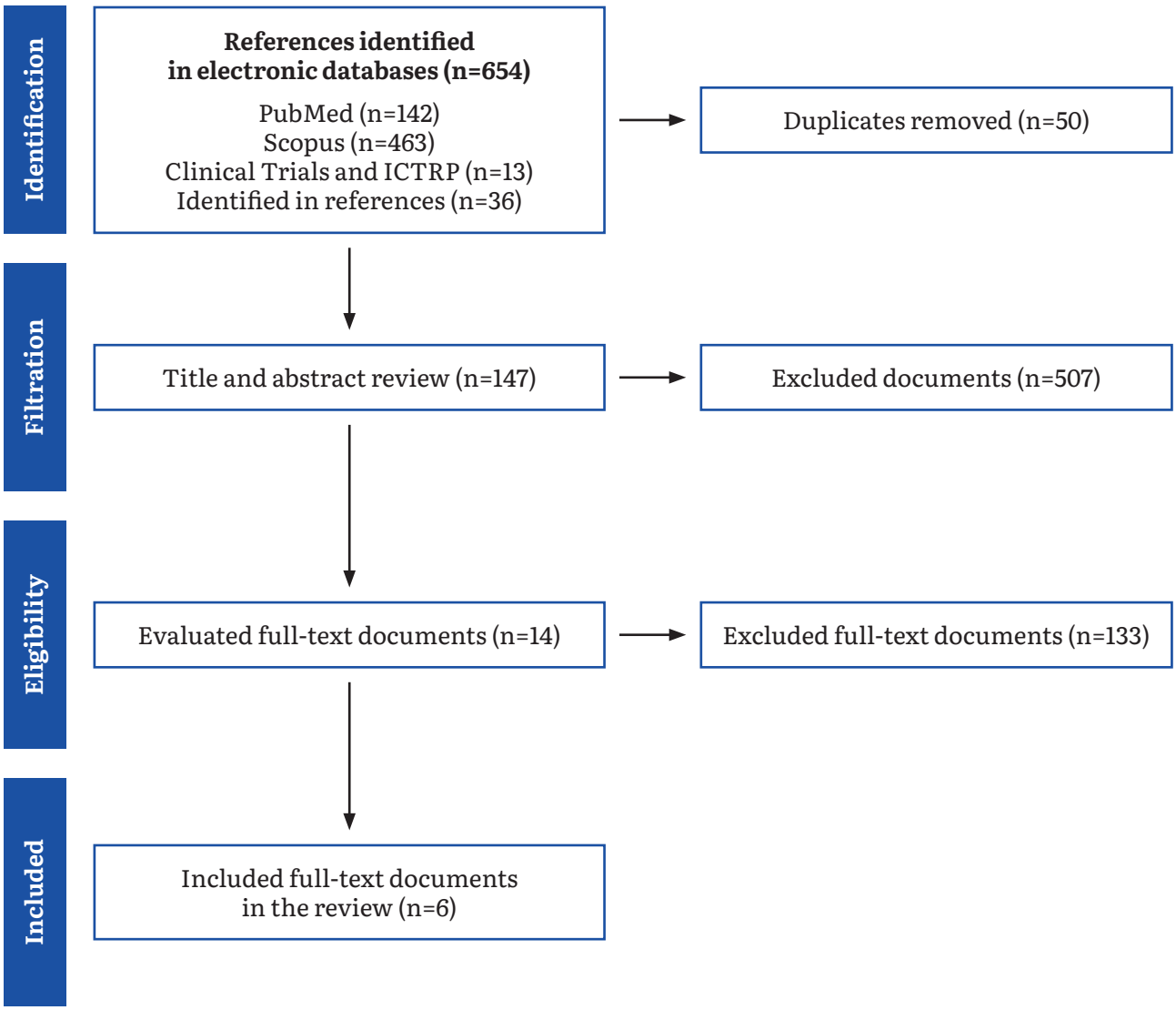

Figure 1: PRISMA flowchart.

improvement in liver fibrosis or resolution of NAFLD after 48 weeks (odds ratio [OR] 0.28 [95% confidence interval (CI) 0.06–1.24]; p=0.087). However, the improvement in hepatic steatosis from baseline was significantly greater in the semaglutide group than in the placebo group (effect size [ES] 0.67 [95% CI 0.51–0.88]; p=0.0042), as was body weight (ES -8.75 [95% CI -12.41, -5.09]; p<0.0001). Significant improvements were also observed in liver enzymes, triglycerides, VLDL cholesterol, and glycated hemoglobin levels. Gastrointestinal adverse events were the most common, but the liver function remained stable after semaglutide treatment and did not cause decompensation events.

Other authors, such as Huynh *et al.* [17], conducted a multicenter study to compare dual therapy with metformin and GLP-1 analogs with metformin monotherapy. Up to the 5-year follow-up, patients with type 2 diabetes mellitus and compensated cirrhosis were included to evaluate progression. The results showed that patients who received dual therapy had a lower risk of 5-year mortality (HR 0.61; 95% CI: 0.42–0.89; p=0.011), as well as developing decompensated cirrhosis (HR 0.65; 95% CI: 0.46–0.93; p=0.02) and hepatocellular carcinoma.

Flint *et al.* [18] conducted a clinical trial to evaluate the pharmacokinetics of liraglutide in patients with hepatic insufficiency. The participants were divided into two groups: a healthy group with normal function and a healthy group with mild, moderate, or severe hepatic insufficiency (according to the Child-Pugh classification). The results showed that patients with severe hepatic insufficiency had the lowest average liraglutide concentration throughout the study period. The bioavailability of the drug was also lower in these patients, with lower mean AUC (0–∞) values in patients with severe insufficiency. The free fraction of the drug was

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lower in these patients. There were no serious adverse events or episodes of hypoglycemia. The results of this study suggest that liraglutide can be safely administered to patients with hepatic insufficiency. (HR 0.44; 95% CI: 0.26–0.74; p=0.001).

Fakhreddine *et al.* [19] conducted a study to assess the safety and efficacy of pharmacological weight loss in patients with advanced liver fibrosis in the US population. Among the various drugs evaluated, GLP-1 analogs were the second group with the most associated weight loss (39%; n=15). The observed adverse events included decreased appetite and nausea. There was no overall significant effect on the laboratory model of end-stage liver disease or on the number of hospitalizations adjusted for the subjects. These results suggest that pharmacological weight loss is feasible in patients with advanced liver fibrosis.

Discussion

Our findings suggest that glucagon-like peptide-1 receptor agonists (GLP-1RAs) are safe and effective for treating type 2 diabetes mellitus and obesity in patients with cirrhosis. Additionally, GLP-1RAs are beneficial for managing decompensated cirrhosis, reducing mortality, and preventing cardiovascular events. Moreover, GLP-1RAs demonstrate greater benefits than other antidiabetics, such as DPP-4 inhibitors (DPP-4i), sulfonylureas, and metformin.

Glucagon-like peptide-1 (GLP-1) plays an important role in human health. It is an incretin hormone derived from the intestine that stimulates insulin secretion from pancreatic β-cells after food intake. It also affects gastrointestinal motility, appetite, glucagon release, and postprandial nutrient distribution. It has been shown that this hormone is significantly lower in cirrhotic patients [20], which could explain why the administration of GLP-1 receptor agonists could play an important role in these patients.

Translational studies have demonstrated that hepatic microvascular function significantly improves in patients receiving liraglutide, resulting in lower portal pressure, improved intrahepatic vascular resistance, and marked improvement in fibrosis [21]. This is consistent with our results, as using GLP-1 receptor agonists demonstrated a lower occurrence of portal hypertensive cirrhotic decompensation, such as ascites and esophageal varices. Although this was not achieved in all studies, it can be explained by the differences in the populations included [14, 15]. Additionally, with respect to advanced fibrosis, some of our results did not show improvements in the same advanced stages [16].

Pharmacokinetic studies have shown that GLP-1 receptor agonists are safe in patients with diabetes and cirrhosis [16–18]. This is because they are not metabolized by the liver but are excreted by the kidneys [22, 23]. In addition, it has been suggested that owing to their high plasma protein binding, they could be affected in patients with advanced cirrhosis and hypoalbuminemia. However, our research found that this is not a major safety concern in patients with advanced cirrhosis [18].

Other questions arose regarding the possible etiologies of cirrhosis in the study population [24]. In Asian countries, the leading cause is infection with hepatotropic viruses, whereas in the West, nonalcoholic fatty liver disease plays an important role [2, 6]. This could interfere with GLP-1 treatment. Given that most of the studies were conducted in European and American populations, this could influence the varying results of this review [16, 19].

With respect to complications, diabetes worsens and occurs more frequently in cirrhosis [25, 26]. Type 2 diabetes can accelerate the progression of chronic liver disease to liver cirrhosis, its complications, and even death [22]. Many of these studies have reported decreased mortality [14–17]. As demonstrated by these results, good glycemic control and the use of GLP-1 analogs reduce the occurrence of various complications and could become another possible indication for these drugs.

Another possible benefit is metabolic control, not only at the glycemic level but also with a decrease in triglycerides and VLDL cholesterol [16], as well as major cardiovascular events [14] and weight loss [19]. This could be explained by the fact that GLP1 agonists have demonstrated significant cardiovascular benefits, as recently shown by the 2024 updates of the American Diabetes Association [27], which widely recommend using GLP1 agonists in patients at cardiovascular risk.

Another question regarding cardiovascular benefits could arise with sodium-glucose cotransporter 2 inhibitors (SGLT2i), given that our results were not conclusive as to which is better in patients with cirrhosis and diabetes [15]. Several studies have already found that SGLT2i in patients with type 2 diabetes and nonalcoholic fatty liver disease (NAFLD) is associated with an improvement in liver steatosis and fibrosis markers, as well as circulating proinflammatory status and oxidative stress [28–30]. Nevertheless, GLP-1 receptor agonists have demonstrated superiority over DPP-4 inhibitors, sulfonylureas, and metformin in this patient class [15, 17].

Conclusion

The use of glucagon-like peptide-1 (GLP-1) receptor agonists is beneficial in cirrhosis, demonstrating a decrease in mortality and associated complications and a reduction in weight, glycated hemoglobin, and other metabolic and cardiovascular parameters. In addition, it is superior to other antidiabetic drugs available in the market for this type of patient. However, further research is needed, as cirrhosis is a multifactorial disease, and GLP-1 analogs in advanced stages of fibrosis do not seem to be effective in reversing this condition.

Conflict of interest

The authors declare no conflict of interest.

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