Annals of Case Reports & Reviews

Research Article

doi: 10.39127/2574-5747/ACRR:1000214
Konstantinou F, et al. Annal Cas Rep Rev: ACRR-214

The Place of GLP-1 Receptor Agonists in the Treatment of NAFLD: A Review

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Citation: Konstantinou F (2021) The Place of GLP-1 Receptor Agonists in the Treatment of NAFLD: A Review. Annal Cas Rep Rev: ACRR-214.

Received Date: 24 March 2021; **Accepted Date:** 29 March 2021; **Published Date:** 05 April 2021

Abstract

Background: *Non-alcoholic fatty liver disease (NAFLD) is prevalent today on a scale similar to an epidemic, and it further increases as the prevalence of obesity and type 2 diabetes are rising. Although in most patients it remains in a clinical stage with minor symptoms, the risk for fibrosis, cirrhosis and cancer development is high. Glucagon Like Peptide 1 (GLP-1) receptor agonists is a class of antidiabetic medication which offer great glycemic efficacy, cardiovascular and other metabolic advantages, with minor adverse events. A beneficial effect of the use of GLP-1 agonists has been reported in NAFLD, based on their pleotropic metabolic actions.*

Objective: *The aim of this study is to review the evidence of the benefit of GLP-1 receptor agonists on NAFLD and the underlying pathophysiologic mechanisms.*

Methods: *Online published literature was researched on the action of GLP-1 receptor agonists on NAFLD.*

Results: *Multiple evidence suggest the great benefit that GLP-1 receptor agonists can offer in NAFLD, in molecular and clinical level, sometimes achieving complete resolution. The European and American guidelines for the treatment of NAFLD, though, are still reluctant in recommending these agents.*

Conclusion: *Although more studies are required to establish a clear position of the GLP-1 receptor agonists in the treatment of NAFLD, their benefit is undeniable and future guidelines have to include them in the arsenal against this dangerous metabolic burden.*

Keywords: *GLP-1, NAFLD, NASH, steatosis, diabetes, metabolic syndrome.*

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations

- Alanine Aminotransferase (ALT)
- Dipeptidyl Peptidase-4 (DPP-4);
- Gamma Glutamyl Transferase (GGT)
- Glucagon Like Peptide 1 (GLP-1)
- Glucagon Receptor (GCGR)
- Glucose-Dependent Insulinotropic Polypeptide (GIP)
- Intercellular Adhesion Molecules (ICAM-1)
- Invariant Natural Killer T Cell (iNKT cell),
- Liraglutide Safety and Efficacy in Patients (LEAN)
- Magnetic Resonance Imaging (MRI)
- Non-Alcoholic Steatohepatitis (NASH)
- Non-Alcoholic Fatty Liver Disease (NAFLD)
- Peroxisome Proliferator-Activated Receptor α (PPARα)
- Peroxisome Proliferator-Activated Receptor γ (PPARγ)
- Reactive Oxygen Species (ROS)
- Aspartate Aminotransferase (AST)
- Signal Transducer and Activator Of Transcription 3 (STAT3)
- Sodium-Glucose Co-Transporters 2 (SGLT-2)
- Vascular Cell Adhesion Molecules (VCAM-1)
- Very Low-Density Lipoprotein (VLDL)

Introduction

Non Alcoholic Fatty Liver Disease (NAFLD) is characterized by fat accumulation in more than 5% of hepatocytes [1]. As the prevalence of obesity rises and considering the close association between obesity or metabolic syndrome with NAFLD [2], the latter is considered a modern epidemic, with an enormous economic burden, and with a prevalence of 25.24% [3]. Non Alcoholic Steatohepatitis (NASH) represents a later stage in NAFLD's natural progression, where inflammation also develops in an already fat-infiltrated liver parenchyma. Most importantly, even though NAFLD can often exist in a subclinical state, it can sometimes deteriorate to possibly serious illness, including cirrhosis. Severe complications include cardiovascular disease [4], while NAFLD is now the leading cause of hepatocellular cancer [5].

An overwhelming fat delivery towards the liver, together with de novo triglyceride synthesis in the liver and decreased beta-oxidation contribute to fat accumulation in the liver parenchyma [6]. The above procedures appear to be a result of insulin resistance, which is associated with increased peripheral lipolysis, enhanced triglyceride synthesis and increased hepatic uptake of fatty acids [7]. The release of oxygen free radicals, has a toxic effect on the liver parenchyma and promotes inflammation [8], while the stressed and injured hepatocytes produce a signaling cascade, which results in the activation and differentiation of hepatic stellate cells into myofibroblasts [9], leading to fibrosis and chirrosis.

Treatment strategies include changing unhealthy lifestyle habits [1]. Due to the close interaction between NAFLD and type 2 diabetes, in the context of a general metabolic dysfunction, common treatment agents for the two diseases have been developed [10]. Treatment targets include mechanisms which involve insulin sensitivity, weight-loss and improvement of dyslipidemia. Pioglitazone, a thiazolidinedione, was found to offer significant histological improvement in NAFLD, along with improvement in ALT [11], in both patients with diabetes [12] and without diabetes [13, 14]. Due to the various side effects of this class medications, individualized consideration of the risks and benefits is recommended before using it for NALFD [15].

Glucagon Like Peptide 1 (GLP-1) receptor agonists are a class of antidiabetic medication with very good results in terms of glycemic efficacy [16]. They also offer cardiovascular protection, renoprotection and have many other pleotropic actions that benefit the patient's metabolic profile [17]. Many studies, both in animal models and in human trials, indicate that GLP-1 receptor agonists can offer significant benefit in several stages in NAFLD. In fact, some of the evidence suggest total amelioration of NAFLD pathogenetic traces in histological samples of patients treated with GLP-1 receptor agonists. The large international associations for the study of NAFLD are still reluctant to recommend GLP-1 receptor agonists for the treatment of NAFLD, even for patients with type 2 diabetes [1, 15]. Some experimental studies have suggested that SGLT-2 inhibitors can show a benefit in NAFLD as well, but only few studies have evaluated this effect in clinical settings [18, 19, 20, 21].

The process of wondering on whether GLP-1 receptor agonists should be used for the treatment of NAFLD, has led to the following review. The purpose of this study is to find the evidence surrounding the use of GLP-1 receptor agonists in NAFLD, in animal and human subjects.

Methods

A search was done for every published article during the last 30 years (since 1990) available in the databases of PubMed and ResearchGate and through the references of the available articles. The terms NAFLD, NASH, and GLP-1 were used as search criteria. Each study was evaluated for relevance with the topic, using the following criteria; literature on NAFLD, NASH, fibrosis or cirrhosis derived from NAFLD, were included. Literature that describe the action of GLP-1 on non-NAFLD associated liver diseases or the action of other medication on NAFLD were excluded from the main part of the research. The remaining number of studies were analyzed to draw conclusions.

Results

The effect of GLP-1 activity on NAFLD or steatosis has been demonstrated in multiple studies and many different pathways are suspected to contribute in this procedure. The GLP-1 action on the liver is complex; the different ways of GLP-1 agonists effect on NAFLD are shown in 29 studies below and they include hormone regulation-mediated action on reducing hepatic lipid overload, regulation of the immune and nervous system, gut microbiome alteration and the secondary effects of other pleotropic actions, like weight-loss. 13 human trials evaluate the effect of GLP-1 agonists on NAFLD amelioration, either using laboratory, imaging or biopsy criteria.

1. Effectiveness in human trials

The use of liraglutide in diabetes and NAFLD patients was associated with reduction in AST, ALT and adiponectin levels in multiple studies [22, 23]; in these studies, the benefit on NAFLD was only assessed in terms of liver function tests, though.

Imaging criteria with abdominal computed tomography were used for NAFLD disease assessment in the study by Bouchi et al [24], where liver attenuation index and visceral fat area were reduced with the use of liraglutide plus insulin, compared to insulin alone in NAFLD and diabetes patients.

Liraglutide 1.8mg per day for 48 weeks offered histological resolution and attenuation of progression to fibrosis, compared to placebo, in patients with NASH, in the Liraglutide Safety and Efficacy in Patients (LEAN) [25]. In the LEAN study in Japan, in 19 patients with NASH who were treated with liraglutide for 24 weeks, additional to lifestyle modifications, decrease in visceral fat accumulation, body mass index and aminotransferases were observed [26]. In the same study, in 6 patients who continued treatment for 96 weeks, a decrease of histological inflammation in the liver, as determined by NASH activity score and stage by Brunt classification, was

observed. Reduction of intrahepatic fat content was also observed in a study by Feng et al [27], in patients with diabetes and NAFLD who were treated with liraglutide, metformin or gliclazide, with greater reductions in the liraglutide arm. Meanwhile, in a study by Petit et al [28], treatment with liraglutide 1.2mg per day after 6 months in patients with NAFLD and uncontrolled type 2 diabetes, compared to intensification of antidiabetic treatment with insulin, resulted in 31% reduction of liver fat content. According to the authors, though, this effect was attributed to the weight-loss effect of liraglutide. Using MRI-proton density fat fraction, Yan et al [29] found a greater reduction of intrahepatic lipid in patients treated with liraglutide compared to intensification of insulin treatment, but no significant difference when compared to sitagliptin. In similar studies that use exenatide, compared to intensification of insulin treatment in newly diagnosed diabetes patients and NAFLD, respective results were observed, with 93,3% reversal rate of fatty liver and significant decrease of AST, ALT and GGT in the exenatide group [30]. Treatment with either liraglutide or exenatide for 6 months, in 25 patients with type 2 diabetes and NAFLD, demonstrated a 42% reduction in intrahepatic lipid, with greater reductions in those with highest pre-treatment levels [31]. In another Japanese study by Seko et al [32], treatment of 13 patients with diabetes and NAFLD, using dulaglutide for 12 weeks, resulted in decreased transaminases activity, lower total body fat and decrease in liver stiffness. A recently published clinical trial showed resolution of NASH with the use of semaglutide compared with placebo [33].

On the other hand, Tang et al [34] failed to prove superiority of liraglutide compared to insulin glargine in patients with diabetes and NAFLD, either in terms of glycemia control or liver fat fraction. Similar disappointing results were shown in the study by Smits et al [35], where treatment with liraglutide, metformin or placebo, didn't show between-group differences in hepatic fibrosis scores. A study comparing liraglutide 3mg treatment with a structured lifestyle intervention program in obese Asian patients with diabetes and NAFLD, also failed to show any benefit of liraglutide, in terms of weight-loss, liver fat fraction, AST or ALT levels [36].

2. GLP-1 mechanisms of action on liver steatosis and NAFLD

a. Metabolic effects

Glucagon can stimulate hepatic glucose production and it can also increase lipolysis in adipose tissue [37]. Due to this action, it has been used in experimental studies for weight reduction. Its diabetogenic properties, though, required the combination with the GLP-1 receptor agonists, to balance out its effect on glycemia. The idea of using glucagon receptor and GLP-1 receptor co-agonists was used in many studies, with promising results in metabolic diseases and NAFLD as-well. The coagonist that was used by Patel et al [37] in mice with NAFLD prevented the accumulation of fat in liver, reduced the expression of inflammatory markers implicated in liver steatosis, such as IL-6, TNF-α, MCP-1, MMP-9 and TIMP-1 and reduced ballooning, steatosis and fibrosis in the liver parenchyma. In a study by Valdecantos et al [38], an oxymodulin analogue was used in mice with NASH, which acts as a double agonist on glucagon receptor (GCGR) and GLP-1 receptor. The experimental group showed improvement of NASH markers, in liver histology and a decrease in circulating triglycerides. The analogue's action was associated with reduced inflammation, steatosis, oxidative stress and apoptosis and increased mitochondrial biogenesis. Furthermore, it increased glucose uptake by the liver and increased glycogen synthesis, overall improving glucose homeostasis, while it improved liver regeneration in partial-hepatectomized mice. The authors were unable to distinguish which of the two separate actions as an agonist were responsible for the multiple homeostatic actions, though. The idea of agonist combination was taken one step further, with the use of a monomeric GLP-1/GIP/glucagon triagonist, in mice, which was associated with a decrease in body weight and body fat mass, while it improved dyslipidemia and reversed diet-induced steatohepatitis [39].

One of the possible mechanisms that one GLP-1 analogue, liraglutide, uses to reduce hepatic steatosis, is through autophagy enhancement. He et al [40] found that liraglutide enhances autophagy, by activating AMPK signaling and inhibiting mTOR pathways. The livers of mice with steatosis, treated with liraglutide were found to have increased autophagosomes and less fat vacuoles, which resulted in improvement of steatosis.

GLP-1 analogs CNTO3649 and exendin-4 reduced the overall Very Low Density Lipoprotein (VLDL) and triglyceride production and hepatic content of triglycerides, cholesterol and phospholipids. This was expressed through a GLP-1 analog action in down-regulation of expression of the genes Srebp-1c, Fasn, Dgat1, which are involved in de novo hepatic lipogenesis and Apob, which is responsible for apoB synthesis.

Hepatic steatosis was also attenuated with the use of Exendin-4, via inhibition of FATP4-related free fatty acid influx in the liver, restriction of SREBP-1c-related hepatic lipogenesis, and stimulation of ACOX1-induced β-oxidation [41].

Collectively, these data strongly suggest that GLP-1 receptor agonism primarily reduces hepatic lipogenesis, thereby causing a reduction in hepatic triglyceride content, with a compensatory reduction in fatty acid oxidation [42]. Taken together with the concomitantly reduced apoB production, lower hepatic availability of triglycerides results in a reduced production of VLDL particles.

In patients with NASH, the GLP-1 receptor in the liver is under-expressed, which could be one of the reasons for the observed hepatic insulin resistance in such patients, in contrast with the many times normal peripheral insulin sensitivity [43]. Furthermore, Svegliati-Baroni et al [44]

refer to a GLP-1 resistance state in NASH, and it has been demonstrated that in such NASH patients, the GLP-1 degradation enzyme Dipeptidyl Peptidase-4 (DPP-4) is increased [45]. In mice with NASH, apart from GLP-1 receptor, the expression of peroxisome proliferator-activated receptor γ (PPARγ) was also decreased and the activity of peroxisome proliferator-activated receptor α (PPARα) was reduced. The above two receptors act in lipid homeostasis and insulin sensitivity regulation and free fatty acid oxidation, respectively. In obese mice treated with exenatide, these defects were ameliorated, by activation of intracellular kinases such as PI3K and AMPK [44].

Exendin-4 treatment increases Sirt1 expression and enhances Sirt1 signaling pathway, which controls hepatic lipid and glucose metabolism and free fatty acid oxidation, resulting in attenuation of NAFLD [46]. The same study reported an increased hepatic expression of Lkb1 and Nampt mRNA, which are involved in the Sirt1 signaling cascade.

b. Gut microbiome

The gut microbiome is known to have a large effect on obesity, and there are also studies that support a connection with NAFLD. In fact, dysbiotic microbiome can be considered a risk factor for NAFLD development, with multiple implicating pathogenetic mechanisms; it is associated with the induction of obesity and the alteration of immune responses and gut hormonal production, which affect the bile acid profile and the endogenous production of ethanol [47]. Metagenomics analysis and phylogenetic identification on the bacteria extracted from fecal material of obese mice treated with liraglutide, showed alterations in microbiota diversity, which can be linked to reduced liver steatosis [48]. In detail, a reduction in the abundance of the Proteobacteria phylum and an increase in Akkermansia muciniphila was observed in liraglutide treated obese mice. Liraglutide, though, didn't inflict the same microbiota alterations in control mice, which creates the question, which exact microbiome alteration liraglutide causes to improve NASH. In the same study, liraglutide treatment was associated with a reduced inflammatory cell infiltration of the cecal mucosa, and an increased number of goblet cells. The inflammation in the mucosa can be a result of the disruption of the physical barrier of the intestinal epithelium by several identified putative bacterial targets and others that remain to be revealed.

c. Adipose tissue

As discussed above, the GLP-1 agonist activity in attenuating NAFLD is not limited in their action on the hepatocytes, but it utilizes multiple pathways, in the peripheral tissues as-well. GLP-1 analogues can reduce adipose tissue insulin resistance and the release of free fatty acids from adipose tissue [49]. They also enhance lipolysis and oxidation, which is also Sirt1-mediated, as discussed in their actions on lipid metabolism in the hepatocytes [45, 50]. GLP-1 supports differentiation of pre-adipocytes to mature adipocytes, which results in increased glucose disposal and increased adiponectin secretion [51]. This increases insulin sensitivity and inhibits ectopic lipid accumulation in the liver, heart or muscle.

d. Myocytes

The overall glucose lowering effect, increased free fatty acid oxidation and reduction of insulin resistance by GLP-1 analogues is also observed at the level of myocytes. Exendin-4 was able to increase energy expenditure in muscle, and this was mediated by upregulation of AMPK activation and increased expression of UCP1, farnesoid X receptor, PPARα and β3-adrenergic receptor genes [52].

e. Immune system regulation

M2 macrophages are a subtype of macrophages which present an anti-inflammatory effect, wound repair and angiogenesis, by secreting IL-10, TGF-β and IL-1 receptor antagonist. This is in contrast with the M1 macrophages subtype which promotes a pro-inflammatory state. GLP-1 induces the differentiation of macrophages towards the M2 phenotype, through activating the signal transducer and activator of transcription 3 (STAT3) signaling pathway [53]. They also promote the secretion of IL-10, CD163, and CD204, which are normally secreted by activated M2 macrophages. The same study, also, has shed light on the way GLP-1 promotes adiponectin secretion. Obesity is known to promote a subclinical pro-inflammatory state, that results in adipose tissue inflammation and insulin resistance. In the above study, GLP-1 action was revealed to inhibit the inflammatory effect that M1 macrophages inflict on adipose tissue, which eventually results in increased adiponectin secretion. Another study by Lee et al [54] revealed that GLP-1 causes a reduction in overall macrophage infiltration of the adipose tissue, reduction of the M1 subtype and reduced production of IL-6, TNF-α and monocyte chemoattractant protein-1.

The Kupfer cells play a major role on the inflammatory infiltration of the liver in NASH, as their increased numbers in liver is considered one of the primary steps in promoting inflammation. This is mediated through the release of reactive oxygen species (ROS) and pro-inflammatory cytokines, such as TNF-a and MCP-1, which in turn, promote further infiltration of the liver by macrophages. The macrophage infiltration is reflected by the number of F4/80 positive cells. Both F4/80 positive cells and TNF-a and MCP-1 mRNA levels were attenuated with the use of exendin-4, and the Kupfer cell activation was modulated [40, 55].

Long term liraglutide treatment was also associated with decreased levels of CRP, an acute reactant protein which is produced by the liver and reflects an inflammatory state [56].

Apart from the Kupfer cells and macrophages that respond to GLP-1, such receptors are also found on a human invariant natural killer T cell (iNKT cell), human monocytes and intestinal intraepithelial lymphocytes Tαβ and Tγδ. iNKT cells is a rare subset of innate T cells with

immunomodulatory function and GLP-1 act on these cells by suppressing cytokine secretion and promoting expression of anti-inflammatory genes, like IL-10 [57]. Exendin-4 was found to inhibit monocyte adhesion on the arterial wall, suppress the lipopolysaccharide-induced activation of macrophages and reduce the expression of CD11b [58]. The activation of the GLP-1 receptors on the intraepithelial lymphocytes by exendin suppresses the expression of inflammatory cytokines IL-2, IL-17a, interferon γ, and tumor necrosis factor-α, thus modulating enteric endocrine and immune responses [59].

f. Fibrosis

Hepatic stellate cells have a major role in the development of fibrosis, by excessive synthesis and deposition of extracellular matrix. The normal hepatic stellate cells are transdifferentiated, in response to liver injury, to an activated α-SMA-positive phenotype, which is characterized by unlimited proliferation; this results in excessive vasoconstriction and induce a pro-inflammatory state. In vitro studies showed that liraglutide can undo this effect, by either preventing the activation of hepatic stellate cells or de-activating them [60]. In vivo trials in rats that were administered liraglutide, validated the above results, showing decreased expression of α-SMA and reduction in extracellular matrix synthesis. In the same study when the hepatic microvascular phenotype was analyzed, a reversal in capillarization was seen, accompanied by increased porosity and nitric oxide bioavailability, proving that intrahepatic microcirculatory amelioration was achieved. Human precision-cut liver slices further validated the anti-fibrotic effects of liraglutide [60].

Similar studies on the effects of GLP-1 on endothelial cells outside the liver, either in aorta or the umbilical vein, show an increase in molecules, such as sirtuin 6 (SIRT6), associated with inflammation and endothelial regulation [61]. They also show an inhibition of the expression of vascular cell adhesion molecules (VCAM-1), intercellular adhesion molecules (ICAM-1), and E-selectin, overall promoting a vasodilatory state and better endothelial function [62].

g. Nervous system regulation

GLP-1 action in the central nervous system is the main mechanism for promoting satiety, which results in weight-loss, as discussed above [63]. Weight-loss is a significant factor that helps in amelioration of NAFLD. There is limited knowledge on the interaction of central nervous system GLP-1-driven stimulation and its interaction with the liver. There is evidence that shows increased production of glycogen in the liver, after intracerebroventricular infusion with exendin-4 [64]. Insulin-resistant mice were treated with continuous infusion of GLP-1 agonist to suppress the endogenous hepatic glucose production; glucose production was increased, after intracerebroventricular infusion of these mice with exentin-9, which is a GLP-1 inhibitor [65]. Hepatic glucose output is also decreased when the arcuate nucleus of the hypothalamus is stimulated by GLP-1 agonists [66].

Discussion

Metabolic diseases appear to have a common pathogenetic background, either involving genetic predisposition, or acquired characteristics, like unhealthy lifestyle. Furthermore, metabolic disease appears to cause multiple end-organ damages, starting from a subclinical stage and, later evolving into serious manifestations. NAFLD is one aspect of the metabolic burden a patient carries, and it is often accompanied by type 2 diabetes and metabolic syndrome. NAFLD is a serious condition that doesn't only affect the liver, but it carries a risk for several multisystemic defects, which can eventually lead to significant complications. Cirrhosis and hepatocellular cancer are the most dangerous complications, but cardiovascular disease, associated with NAFLD and the accompanying metabolic distress, has a high risk for death as-well. This raises the need for prompt management of NAFLD and its comorbidities, even though many NAFLD patients can live normally for a long period of time, without any significant clinical symptoms.

The triggering point for this metabolic defect to exist, is insulin resistance. Hyperinsulinemia, increased lipolysis in the peripheral adipose tissue, and increased fatty acid levels in circulation and accumulation in several tissues, like in the liver, are central in the pathophysiology of NAFLD [6]. Additionally, an inflammatory response also comes later to further deteriorate the liver distress, leading to worsening insulin resistance. This cascade of events reinforces and perpetuates the cycle of insulin resistance.

NAFLD management follows an etiologic approach and is based in targeting each of the metabolic defects that lead to its development. Even though new studies shed more light each day on the various mechanisms that this condition uses, distinct treatment targets are not clearly identified yet. The medications that are used, mostly offer a mild action in altering insulin sensitivity and oxidative stress. The results are encouraging though. One appealing treatment approach is to simultaneously target different metabolic defects in several levels, leading to an overall accumulative benefit.

Such ways of multiple targeting are used by the GLP-1 receptor agonists. Older publications provide with convincing evidence of the role of GLP-1 receptor agonists in the regulation of metabolic defects, which mainly stem from insulin and glucagon control, but from many different secondary mechanisms as well. The benefit of this class of medication in serious metabolic comorbidities, such as cardiovascular disease is now undoubted, while their minor adverse effects, make them easy to use.

This project has reviewed the studies, available in the literature, regarding the place of GLP-1 receptor agonists in the treatment of NAFLD. Several different molecular mechanisms have been described that GLP-1 receptor agonists can use, which result in NAFLD improvement. Large animal and human studies have also provided with evidence that this class of medication actually has a benefit, in disrupting NAFLD's natural progression. Most importantly, GLP-1 agonists can offer both clinical and histological improvement, sometimes leading to remission

of NAFLD. It is critical to say, that GLP-1 action in NAFLD is not confined in the liver, but it is multisystemic. Latent action on adipose and vascular tissue, the central nervous system, immune system and the gut microbioma, can result in hormone regulation, inflammation control and other secondary effects, that eventually lead to a benefit in liver disease.

The European and American guidelines for NAFLD [1, 15] have not yet included GLP-1 receptor agonists in the treatment of NAFLD. The evidence is overwhelming in favor of GLP-1 receptor agonists in NAFLD treatment and such studies are growing in numbers. Taking into account that GLP-1 agonists is a class of medication with multiple metabolic benefits and considering that a NAFLD patient usually suffers from several metabolic disorders, it is a matter of time that the GLP-1 receptor agonists are included in basic treatment strategies for NAFLD.

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