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Are GLP-1 Analogues a New Solution for the Treatment of NAFLD?

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ABSTRACT

Introduction and purpose:

There is currently a pandemic of overweight and obesity, which is closely associated with non-alcoholic fatty liver disease (NAFLD). It is the most common cause of chronic liver disease [1]. The global prevalence of this condition reaches 25% of the population and 65-70% of patients with type 2 diabetes [2]. There is no approved pharmacological treatment for NAFLD, and the current mainstay of NAFLD treatment is lifestyle modification and weight reduction, which is difficult to achieve and even more difficult to maintain. NAFLD represents a serious health and economic burden, which is why the search for an effective therapy is so important [1,2,3].
The purpose of this review was to assess the current knowledge of the efficacy of GLP-1 (Glucagon-like peptide-1) analogs in the treatment of NAFLD.

Material and methods:

Data bases such as Pubmed and GoogleScholar were used for research with the key words included: MAFLD, NAFLD, GLP-1 receptor agonists, GLP-1 analogues, incretin mimetics. The review included studies that evaluated the efficacy of GLP-1 receptor agonists in the adult population.

Description of the state of knowledge:

Glucagon-like peptide-1 (GLP-1) analogues are drugs approved for the treatment of type 2 diabetes and obesity with pleiotropic effects. They have a beneficial effect on the glycemic profile, reduce body weight and have an anti-inflammatory effect. They appear to be

a promising therapy for the treatment of NAFLD, as these patients are usually overweight/obese and have insulin resistance and/or diabetes [1,3].

Conclusions:

It is hoped that in the coming years the efficacy of these drugs in NAFLD will be confirmed and they will be approved for this indication [1].

Keywords: MAFLD, NAFLD, GLP-1 receptor agonists, GLP-1 analogues, incretin mimetics

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases. The incidence is steadily increasing which is associated with an increase in metabolic syndrome. It now affects as much as ¼ of the population [4]. In patients with type 2 diabetes, it reaches about 70%, some sources report that the frequency reaches up to 90% [2, 5, 6]. A bidirectional relationship between NAFLD and type 2 diabetes has been observed. NAFLD can be triggered by diabetes and can promote its onset [7].

It is the leading cause of end-stage liver failure, hepatocellular carcinoma (HCC) and liver transplantation in the world [8]. One-third of patients will either die from complications or require liver transplantation. It is estimated that by 2023, the number of advanced liver disease in patients with NASH (nonalcoholic steatohepatitis) will increase by 160% [6]. Which makes NAFLD an important public health problem [9].

Due to the close association of NAFLD with metabolic disorders, international consensus has decided to rename NAFLD as steatohepatitis associated with metabolic dysfunction (MAFLD) [10, 11]. In the following review, the acronym NAFLD will be used instead of MAFLD, because the works cited used diagnostic criteria for NAFLD when recruiting patients [10].

GLP-1s analogues are drugs that, by acting on the endogenous GLP receptor, reduce appetite and food intake. By increasing glucose-dependent insulin secretion, they improve glucose homeostasis, inhibit glucagon secretion and slow gastric emptying by additionally inhibiting pancreatic beta-cell apoptosis [1, 8]. When used in type 2 diabetes, they reduce body weight. GLP-1 analogs have been shown to reduce inflammation and liver fibrosis and regulate

the gut microbiota [1, 12]. This makes their effects ideal for patients with NAFLD who usually present with metabolic syndrome.

Aim of the study

The purpose of this review was to assess the current knowledge of the efficacy of GLP-1 analogs in the treatment of NAFLD.

Material and methods

Data bases such as Pubmed and GoogleScholar were used for research with the key words included: MAFLD, NAFLD, GLP-1 receptor agonists, GLP-1 analogues, incretin mimetics. The review included studies that evaluated the efficacy of GLP-1 receptor agonists in the adult population.

Description of the state of knowledge

NAFLD covers a wide spectrum of severity from local steatosis to non-alcoholic steatohepatitis (NASH) associated with fibrosis, cirrhosis and even the development of hepatocellular carcinoma [5, 8]. NASH occurs in 2-3% of patients with NAFLD. Up to 9-20% of patients with NASH develop cirrhosis [8]. Progressive liver failure and hepatocellular carcinoma as a result of the development of NAFLD have made it the second most common indication for liver transplantation, and the demand for transplantation will increase in the coming years. The co-occurrence of diabetes doubly accelerates this process [1].

NAFLD is defined as an accumulation of fat in the liver of more than 5% by weight and is not associated with alcohol consumption (>20g/day in women, >30g/day in men) [13]. It is also not associated with infections, viruses, autoimmune diseases, or toxic insults such as drugs [13]. The pathogenesis is not well understood. However, it is known that improper diet, insulin resistance, oxidative stress, inflammation, and abnormalities in lipid synthesis and transport underlie steatosis and NASH [8, 13]. The increase in proinflammatory and prothrombotic factors in NAFLD increases the risk of chronic diseases such as ischemic heart disease, chronic kidney disease, cardiomyopathy, and arrhythmias. As a result, cardiovascular disease is the leading cause of mortality in NAFLD [1].

Pathophysiologically, NAFLD is associated with lipid accumulation, lipotoxicity and inflammation [13]. There is an excessive accumulation of fat in the liver [14, 15]. It is closely associated with insulin resistance, so its incidence increases with comorbidities such as obesity, type 2 diabetes, hypercholesterolemia, hyperuricemia [4, 15]. It is considered to be a hepatic manifestation of the metabolic syndrome [7].

The increased insulin resistance in patients with NAFLD and type 2 diabetes, causes reduced glucose uptake by muscles and liver and increased hepatic gluconeogenesis. This results inhibition of lipolysis of adipose tissue and increased hepatic lipogenesis. This also leads to increase concentration of glucose and free fatty acids [10].

The first stage of NAFLD development is attributed to impaired metabolism of free fatty acids (FFA) in the liver. Excessive calorie consumption leads to increased burden of free fatty acids on the liver. At one point, it is no longer able to effectively oxidize them, start to re-esterify them to triglycerides (TG) and secrete them in the form of VLDL. As a result, TGs start to accumulate in hepatocytes and causing steatosis [1, 3].

As mentioned above, insulin resistance is observed in these patients. Consequently, there is unrestricted lipolysis and FFA flow to the liver. Increased hepatic de novo lipogenesis, which further increases TG deposition in hepatocytes. This long-term process leads to lipotoxicity in hepatocytes and chronic inflammation. The effect of which is cell apoptosis and fibrosis [1]. However, this is not the only disturbed process. Overactivation of the mitochondrial fat oxidation pathway known as the tricarboxylic acid cycle is observed [1]. There is overloading of the endoplasmic reticulum, dysfunction of the mitochondria. It results in the release of reactive oxygen species (ROS) and toxic forms of the lipid intermediates such as ceramides and diacylglycerols [1].

Inflammation is also exacerbated by decrease level in adiponectin (which has anti-inflammatory effects) and increase in leptin and pro-inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) [1].

All these processes intensify insulin resistance, which is also the cause by, and create a vicious cycle [1].

The gold standard for NAFLD diagnosis is liver biopsy. Unfortunately, it is an invasive, time-consuming and expensive test. It is also not a perfect test for screening [8, 13]. Therefore, other diagnostic methods such as ultrasound and MRI are also used [13]. Blood biomarkers are constantly being sought. The most used parameters are alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT). It has been noted that patients with type 2 diabetes mellitus and NAFLD have mild to moderate levels of these parameters compared to patients with diabetes mellitus and without NAFLD, but they also may be normal and are not specific for this diagnosis [4, 8, 13]. Now, the only recommended treatment is lifestyle modification and 7-10% weight loss. This is associated with low efficacy. Only 3-6% of patients achieving weight loss [9, 15]. In addition, most patients return to their initial body mass [10]. Studies using magnetic resonance spectroscopy have shown that in

overweight patients, a 10%weight loss by lifestyle modification can reduce TG levels even 60% [1]. Currently, the most effective treatment of the obesity in these patients is bariatric surgery. It reduces inflammation and leads to resolution of NASH in up to 85% [1, 12, 16].

Incretin hormones such as GLP-1 are present in our bodies and after meal are secreted by intestinal L-cells [14]. They potentiate insulin secretion stimulated by the glucose rise after a meal. It is known as the incretin effect. They also inhibit secretion of glucagon and slow gastric emptying [12]. They reduce insulin resistance and improve peripheral insulin sensitivity by inhibiting gastric emptying and reducing appetite, leading to weight loss [13, 14]. They lower free fatty acid concentrations by increasing glucose reuptake by liver and muscle [14]. Additionally, they have cardio- and nephroprotective effects [4, 7, 10].

GLP-1 acts through receptors which are located in the gut, central nervous system and alpha and beta pancreas cells. The literature reports that this receptor can be also presented in the peripheral nervous system, heart, lungs, and kidneys [10].

Patients with NAFLD have increased dipeptidylpeptidase-4 (DPP-4) activity, which inactivates GLP-1, and decreased expression of the GLP-1 receptors in liver. In this regard, these individuals have lower levels and reduced sensitivity to incretin hormones (mainly GLP-1) [1,12,17].

There are no approved drugs for the treatment of NAFLD. There are tested products whose mechanism of action affects inflammation, oxidative stress, metabolic dysregulation, weight loss, and gut-liver axis regulation are under investigation [1].

Agonists of the GLP-1 receptor (GLP-1R) are divided into two categories. The first group consists of exenatide and lixisenatide. Their amino acid sequence has low homology compared to endogenous GLP-1. The second group substances include liraglutide and semaglutide. They have high homology with the human GLP-1. Compared to the endogenous molecule, which has a degradation time of 1.5 minutes, GLP-1 receptor agonists have a long-lasting effect [10].

Potential mechanisms of action of GLP-1 analogues in NAFLD

1. Weight reduction:

   GLP-1 analogues act on the central and peripheral nervous systems. Primarily by acting on the hypothalamus and brainstem, they increase feelings of satiety and fullness after a meal, thereby reducing appetite [1, 10]. GLP-1, by stimulating its receptor in the central nervous system, reduces the expression of serotonin (5-HT2A) receptors in the

hypothalamus, leading to a decrease in appetite [10]. Stimulation of GLP-1 receptors in the arcuate nucleus inhibits meal initiation and affects meal termination via the lateral parabrachial nucleus [10]. An additional cause of weight loss may be the activation of NK cells and induction of fibroblast growth factor 21, which promotes the conversion of white adipose tissue to brown adipose tissue [18].

Treatment with GLP-1R agonists results in weight loss of 2-7 kg, with dose- and formulation-dependent effects [1, 10].

The effect of exenatide on weight loss and reduction of hepatic steatosis in patients with NAFLD has been demonstrated, among others, in studies by Ding X. et al [12, 19] and Dutour A. et al [20]. It has been suggested that the neurological mechanisms of action of liraglutide and semaglutide are different, which would explain the differential efficacy in weight loss [10].

Liraglutide has been shown to cause an average weight loss of 3.4-6.1% [10, 21].

Semaglutide has the highest efficacy in weight loss among the GLP-1 analogues, with a mean weight loss of 9.6-14.4% demonstrated at a dose of 2.4 mg/week [10, 22].

In addition, a randomized trial conducted by Rubino D.M. et al. (STEP 8) showed that at week 68, weight loss of at least 10% (recommended for NAFLD treatment) was achieved in 70.9% of patients treated with 2.4 mg/week semaglutide and 25.6% of patients treated with 3 mg/day liraglutide [10, 23].

2. Impact on insulin resistance:

   Weight loss is one of the reasons for insulin resistance reduction with GLP-1 analog treatment. It is believed that this is not the only mechanism. GLP-1 analogues administered to healthy population reduce glucose production in the liver. They caused reducing hepatic lipogenesis, lowering the concentrations of toxic FFA and metabolites of TG produced during lipolysis [1]. The role of GLP-1 analogues in insulin sensitization also has been documented.

   Exenatide stimulates phosphorylation of phosphoinositide-dependent kinase-1 (PDK-1), protein kinase B (Akt), and protein kinase c (PKC), which are key effectors in signalization of the insulin pathways [12, 14, 24]. A study in rats showed that GLP-1 and their analogues, in muscle and adipose tissue increased glucose metabolism. They also affect fat synthesis from fatty acids [12, 14].

Work on exenatide has shown that exenatide stimulates the expression of glucose transporter type 4 on the plasma membrane of these cells, it facilitates glucose uptake by skeletal muscle [12].

3. Reduce liver steatosis:

   Reduction of hepatic steatosis is one of the goals of NAFLD treatment. TG accumulation in the liver is reduced by exenatide [10, 24].

   A 12-week study in patients with obesity, type 2 diabetes and NAFLD conducted by Shao et al. confirmed a reduction in hepatic steatosis [25, 26]. Another study showed similar results, after 26 weeks of exenatide treatment with a 24% reduction in liver fat content [20, 26].

   Such an effect was also shown for liraglutide. Liraglutide reduces liver fat content by 44% [10, 27]. Additionally randomized trial comparing liraglutide with placebo confirmed these results. This study showed that liraglutide reduced steatosis and hepatocyte ballooning, such an effect was not present in the placebo group [10, 28].

4. Incretin effects:

   It was noticed that patients with NAFLD have lower levels of incretin hormones, mainly due to increased degradation by DPP-4 and reduced production of these hormones [1, 9, 15]. This indicates the potential efficacy of GLP-1R agonists in the treatment of NAFLD.

5. Influence on inflammation and oxidative stress:

   In this group of patients, it is observed a decrease in the concentration of adiponectin, the anti-inflammatory factor. The initiation of treatment with GLP-1 analogues increases adiponectin concentration [18]. It has been shown that liraglutide decreases the concentration of leptin. It has a positive effect on the leptin-adiponectin ratio. This causes regulation of fatty acid oxidation, the activity of acetyl-CoA carboxylase and fatty acid synthase. It leads to reduction of the abnormalities associated with NAFLD [1].

   In addition, studies report that GLP-1 analogues slow down the secretion of inflammatory cytokines by NK cells and increase the release of the anti-inflammatory interleukin-10 by acting on cAMP (cyclic adenosine monophosphate) [12]. These substances also suppress the inflammatory response in the gut, where they inhibit the secretion of inflammatory factors by lymphocytes [12].

As mentioned above, mitochondrial dysfunction is observed in NAFLD. This dysfunction increases levels of reactive oxygen species (ROS). Their enlargement concentration damages cellular DNA and causes apoptosis and cellular necrosis. Exenatide and liraglutide through the JNK (c-Jun N-terminal kinases) pathway and by increasing the secretion of antioxidant enzymes enhance antioxidant effects [12]. Their immunomodulatory effects suggest the chance of use in the treatment of NAFLD and NASH.

"Liraglutide Efficacy and Action in NASH (LEAN)", a very important study should be mentioned here. This is a double-blind, randomized trial. It tested the effect of liraglutide on NASH. The results were evaluated by liver biopsy. Resolution of NASH after 48 weeks of treatment was confirmed in 39% of the study group and 9% of the control group [4, 12, 28]. Similar results were seen with semaglutide. In 59% of patients with NASH and liver fibrosis treated with semaglutide 0.4 mg, resolution of NASH without worsening of fibrosis was achieved (compared to 17% on placebo). The inflammatory biomarkers reduction was also observed [12, 29, 30, 31].

6. Liver fibrosis:

   Long-lasting oxidative stress and hepatic inflammation result in hepatic fibrosis. In this process are also involved: higher levels of TGF- β (transforming growth factor betha), increases in tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase (MMP) (which are profibrogenic markers) and proliferative markers such as TNF-α and TGF-β. Balestrieri et al. showed that GLP-1 analogues in diabetic patients reduced the expression of TNF-α and MMP [12, 32]. It has also been proven that liraglutide inactivates murine hepatic stem cells [12].

   In studies where 0.4 mg/day semaglutide was administered subcutaneously showed that it was effective in reducing the progression of fibrosis [10, 29, 30].

   The protective effect of GLP-1R agonists may be found in their reduction of the expression of three collagen genes responsible for liver fibrosis [10].

   There are no studies reporting the effectiveness of GLP-1 analogues on existing liver fibrosis.

7. The gut-liver axis:

   GLP-1 receptor agonists, through their influences on reducing intestinal motility, inhibiting chylomicron synthesis and secretion, reduce postprandial hyperlipidemia [1].

For several years it has been known that the intestinal microbiota has an impact on obesity and liver damage [12]. The intestinal microbiota affects the release of incretin hormones and through this on intestinal motility and glucose metabolism. GLP-1 receptor agonists inhibit lipoprotein lipase activity, which is associated with increased lipid accumulation in the liver. The beneficial microbiota removes products of bacterial origin such as short-chain fatty acids, which are substrates for hepatic gluconeogenesis. They by the preventing the passage of some bacterial products improve the function of the intestinal barrier [12].

Patients with NAFLD have different microbiota composition. This dysbacteriosis reduces the expression of the GLP-1 receptors, which impairs the signaling of the gut-hepatic-brain axis and this is a mechanism of GLP-1 resistance. In mice fed a high-fat diet, liraglutide treatment restored the bacterial balance. This could not be replicated in mice fed a methionine-choline-deficient diet [12, 29, 30].

8. Effects on ALT, AST:

   ALT and AST are one of the liver damage markers. Unfortunately, they are not very sensitive. Patients with NAFLD and higher levels of these biomarkers have a higher risk of progression to NASH [10]. A 10% weight loss (without pharmacology) in patients with NAFLD and obesity decrease AST and ALT levels [10].

   So far, many studies confirm the effect of GLP-1R agonists in reducing biomarkers of liver damage [10, 13, 28, 29, 30, 33].

   Lixisenadide is a drug that compared to placebo, in overweight/obese patients with type 2 diabetes, normalizes ALT levels. However, there are no studies in people with NAFLD [1].

   A reduction in liver injury parameters such as ALT, AST, GGT has been showed in a 12-week clinical trial with exenatide. These were significantly lower than in the control group, suggesting a liver protective effect [12, 25, 26]. Normalization of these parameters achieved up to 40% patients treated with exenatide [10].

   In patients with type 2 diabetes and/or obesity, ALT and AST reduction is also achieved by liraglutide at a dose of 1.8 mg/day [4, 10]. Such results have also been shown for semaglutide and it was a dose-dependent effect [10, 29, 30]. At week 52 of semaglutide treatment, ALT normalization was achieved in 25%-46% patients with elevated baseline ALT compared to 18% of placebo group [4].

Side Effects

GLP-1 analogues are well tolerated by patients [15, 34]. The most frequently reported adverse effects are gastrointestinal problems such as nausea, diarrhea, flatulence and abdominal pain. Their frequency increased with higher doses of the drug [13, 15]. No serious adverse events were observed [13]. The symptoms subsided usually 1-2 weeks after a target dose was established [15].

Conclusions

The globalization of obesity and metabolic syndrome has made NAFLD the most common cause of chronic liver disease [12]. In recent years, we have gained new knowledge into the pathophysiology of NAFLD. Considering the metabolic nature of the disease, lifestyle modification should not be the only treatment strategy [14]. Therapy should act on pathways such as the gut-liver axis, oxidative stress and inflammation. From this perspective, GLP-1 analogues appear to be an ideal therapy. GLP-1R agonists, registered to treat diabetes type 2 and obesity, have been shown to be effective in alleviating NAFLD and possibly preventing from NASH [12]. They increase insulin sensitivity have positive effects on lipid and glucose metabolism, oxidative stress and inflammation [12, 14]. Reducing inflammation is an important part of reducing the risk of NAFLD progression and development of HCC. They increase the protective effect on the cardiovascular system [10], while being a safe therapy [15].

It is hoped that in the coming years the efficacy of these drugs in NAFLD will be confirmed and they will be approved for this indication [1].

Disclosures

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