sciendo

Review • DOI: 10.2478/ahem-2023-0001 • AHEM • Vol. 77/2023 • 1-8

AHEM

Advances in Hygiene and Experimental Medicine
Postępy Higieny i Medycyny Doświadczalnej

GLP-1 analogues in the treatment of obesity and non-alcoholic fatty liver disease

Review

Kacper Deska[1]*, Bartłomiej Bąk[2], Marcin Kosmalski[3], Tadeusz Pietras[3]

[1]Medical University of Lodz: Uniwersytet Medyczny w Lodzi, Łódź, POLAND
[2]Military Medical Academy Memorial University Teaching Hospital in Łódź
[3]Department of Clinical Pharmacology, 1st Chair of Internal Medicine, Norbert Barlicki Memorial University Teaching Hospital No. 1 in Łódź

Received 05 April, 2022, Accepted 20 October, 2022

Abstract

Type two diabetes has become a civilization disease in the recent years, and the accompanying obesity, metabolic syndrome and non-alcoholic fatty liver are often the inseparable components of the clinical presentation in patients with diabetes of this type. The treatment of each of these elements is important for optimal metabolic control of the patients, as well as directly affecting their life expectancy. However, The ideal solution would be to take as few drugs as possible, preferably drugs that have a beneficial effect on several coexisting diseases at the same time. In the recent years, there have been more and more reports about the pleiotropic effect of drugs affecting the incretin axis - GLP-1 analogues. The presented paper provides an overview of the latest knowledge on the effect of GLP-1 receptor agonists on weight reduction and reduction of changes in the course of non-alcoholic fatty liver disease.

Keywords

psoriasis • psoriatic arthritis • lifestyle • diet

1. Introduction

The components of metabolic syndrome are currently becoming important public health issues in developed countries. Metabolic syndrome includes abdominal obesity, hypertension, type 2 diabetes (T2DM), atherogenic dyslipidemia, and, according to the latest concepts, also nonalcoholic fatty liver disease (NAFLD). A common pathogenetic factor in obesity, NAFLD, and T2DM is insulin resistance and its effects. All components of metabolic syndrome usually coincide, although in some cases obesity is accompanied by NAFLD but diabetes does not occur, or T2DM along with nonalcoholic fatty liver develops in slim subjects; these may be individuals with greater deposition of visceral fat, even though body mass index (BMI) does not indicate obesity [1]. Two major European studies reported NAFLD prevalence rates of 42.6% to 69.5% in large samples of T2DM patients [2].

According to the 2021 World Health Organization (WHO) data, 14% of the population suffers from obesity worldwide and 39% are overweight. In 2013, 382 million people suffered from T2DM. It is estimated that NAFLD could affect up to 25% of the world's population, and in highly developed countries 17% to 46% of the population suffers from it. According to a meta-analysis conducted in 2019, the prevalence of NAFLD in patients with diabetes reaches 55.5%. The highest percentage of co-occurrence of these two entities—68.0%—has been recorded in European countries [3]. Research on drugs used in the treatment of metabolic syndrome is focused on groups of drugs that would be effective in treating obesity, insulin resistance, diabetes, and NAFLD. The group that probably meets these conditions most closely are GLP-1 analogues. Originally, these drugs were introduced for the treatment of T2DM. Recent studies indicate their effectiveness also in the treatment of obesity and NAFLD. The aim of the presented paper is to review the literature on the possible importance of GLP-1 analogue therapy in the treatment of obesity and NAFLD.

2. Mechanism of action of GLP-1 analogues

The concept of the so-called incretin axis (entero-pancreatic axis) was created by Crutzfeldt and developed for the purposes

* E-mail: kadeska2701@gmail.com

of pharmacotherapy of T2DM by Drucker and Nauck [4]. The substances contained in food, such as carbohydrates, amino acids, and fatty acids, interact with specific cells of the epithelium of the ileum and colon: L and K cells. As a result of this interaction, L cells of the epithelium secrete glucagon-like peptide 1 (GLP-1), and K cells (in response to glucose) secrete insulin-stimulating glucose-dependent insulinotropic polypeptide (GIP). They constitute a humoral pathway of influence on pancreatic islet cells, which, in addition to the neuronal and metabolic pathway, affects the postprandial secretion of insulin. GLP-1 is a stronger stimulator of beta cells than GIP, inhibiting glucagon secretion at the same time. Intestinal peptides act on Langerhans islet cells through specific receptors and are rapidly degraded by peptidases, especially dipeptidyl peptidase-4 (DPP-4) [EC 3.4.14.4] [4].

The literature emphasizes a number of additional activities of GLP-1, such as: slowing gastric motility, lowering blood pressure (also by acting on the myocardium), stimulating the satiety center, and a neuroprotective effect [5]. According to some authors, GLP-1 also exerts regenerative and protective effects on pancreatic islet beta cells, however, these views have not been fully documented experimentally and clinically.

Therefore, the effect on the incretin axis for glycemic control is very attractive from a theoretical point of view. For therapeutic purposes, however, it is necessary to synthesize peptides resistant to DPP-4, or to use substances inhibiting this enzyme, while prolonging the duration of action of endogenous intestinal peptides. In metabolic syndrome and T2DM, the incretin effect is reduced mainly by weakening the secretion of GLP-1, which causes a decrease in insulin secretion. The drugs that affect the activity of the incretin axis are currently important in the treatment of diabetes and the components of metabolic syndrome [6].

The first of the drugs belonging to the group of GLP-1 analogues was exenatide, introduced in 2005. In the following years, liraglutide, semaglutide, lixisenatide, dulaglutide, and albliglutide were included in the therapy. Their action, like the effect of endogenous GLP-1, is based on glucose-dependent stimulation of insulin secretion with inhibition of glucagon secretion.

3. The use of GLP-1 analogues in the treatment of obesity – literature review

The SCALE study, the results of which were published in 2013, demonstrated that in a 12-month follow-up of non-diabetic patients using 3.0 mg liraglutide doses in combination with a reduced-calorie diet and increased physical activity, the patients taking liraglutide achieved statistically greater weight reduction than those in the placebo group [7]. In a meta-analysis by Monami et al., liraglutide compared to placebo was shown to bring statistically significant improvements in BMI in both diabetic and non-diabetic patients. The authors also point out that extending liraglutide therapy from 6 to 12 months also has a beneficial effect on the BMI and metabolic parameters in patients with obesity [8].

Table 1. Comparison of the dosage and the possibility of using the individual GLP-1 receptor agonists available on the Polish market as monotherapy, including the trade names of the products. LAR: a form of long-acting release preparation

GLP-1 receptor agonist	Dosing frequency	Registration in monotherapy	Trade name of the product
Exenatide LAR	1 x week	no	*Bydureon*
Dulaglutide	1 x week	yes	*Trulicity*
Lixisenatide	1 x day	no	*Lyxumia*
Liraglutide	1 x day	yes	*Victoza*
Semaglutide	1 x week	yes	*Ozempic*

To confirm the effectiveness of semaglutide in supporting the treatment of obesity, randomized, double-blind, multicenter and international clinical studies referred to in the literature as STEP (Semaglutide Treatment Effect in People with obesity) were conducted. By the time of publication of this paper, the results of 7 studies (STEP 1-6, STEP 8) have been published, in which a total of 5727 subjects took part [9–14]. Each compared the effects of 2.4 mg dose of semaglutide, administered subcutaneously once a week, to placebo or another obesity treatment drug. The study group consisted of adults suffering from obesity or overweight, with or without concomitant T2DM. In each study, all groups were treated for obesity using non-pharmacological methods: a low-calorie diet (energy supply reduced by 500 kcal/day) and an increase in moderate-intensity exercise by 150 min/week.

In STEP 1, the mean change in the patients' body weight from the baseline to week 68 was -14.9% in the semaglutide group compared to -2.4% in the placebo group. In absolute terms, this corresponds to a change in body weight of -15.3 kg in the semaglutide group versus -2.6 kg in the placebo group [9].

The STEP 2 study was the only one conducted on obese patients with concomitant T2DM. Adults with a body mass index of at least 27 kg/m2 and glycated hemoglobin of 7-10% who had been diagnosed with T2DM at least 180 days before screening were included in the trial. The patients were randomly assigned to one of 3 groups: with subcutaneous application of 2.4 mg semaglutide or 1.0 mg semaglutide once weekly, or to the placebo group. The duration of the study was 68 weeks. The approximate change in mean body weight from the baseline to week 68 was -9.6% for 2.4 mg semaglutide compared with -3.4% for placebo [10].

The STEP 3 study was a withdrawal trial project to assess the change in body weight after switching from semaglutide to placebo. At week 68, the estimated mean change in body weight from the baseline was -16.0% for semaglutide versus -5.7% for placebo. More participants treated with semaglutide compared to placebo lost at least 5% of their baseline body weight (86.6%

vs. 47.6%, respectively). A higher percentage of participants in the semaglutide group compared to placebo achieved a weight loss of at least 10% or 15% [15].

The STEP 4 phase was preceded by a 20-week preparatory period in which the patients had to demonstrate weight loss (10.6%, on the average). Then, they were randomly assigned to two groups. Over the 48 weeks of continuous use of semaglutide, the mean change in body weight from week 20 to week 68 was -7.9% compared with +6.9% after switching to placebo [11].

The longest-running study was the STEP 5 phase. Over a 104-week period, the average weight loss of patients on continuous treatment with 2.4 mg semaglutide reached 15.2% compared with 2.6% for placebo [14].

The STEP 6 study was conducted entirely on Asian populations from Japan and South Korea. The estimated mean change in body weight from the baseline to week 68 was -13.2% in the 2.4 mg semaglutide group and -9.6% in the 1.7 mg semaglutide group compared with -2.1% in the placebo group. The area of visceral abdominal fat was reduced by 40.0% among the 2.4 mg semaglutide group participants and 22.2% among the participants in the 1.7 mg semaglutide group compared with 6.9% in the placebo group [12].

The STEP 7 study was completed in January 2022, but its results have not yet been published.

The STEP 8 study was the only one to compare the effectiveness of weight-loss treatment in patients using liraglutide and semaglutide in the adopted strict dosage regimen. Among overweight or obese adults without diabetes, weekly subcutaneous semaglutide versus once daily subcutaneous liraglutide, added to dietary and physical activity recommendations, resulted in a significantly greater weight loss at week 68. (The mean weight change from the baseline was -15.8% for semaglutide vs. -6.4% for liraglutide) [13].

The most common adverse reactions to subcutaneous semaglutide 2.4 mg/week were transient gastrointestinal disorders: nausea, vomiting, flatulence. They ranged from mild to moderate and resolved with time during the therapy. Acute pancreatitis as a severe complication of semaglutide therapy was rare, whereas it was found to be more common in the semaglutide groups than in the placebo group (STEP 1: 3 patients, STEP 2: 1, STEP 3: 0, and STEP 4: 1).

In 2019, Jabbour et al. conducted an analysis of the effectiveness of treatment and the effect on body weight of exenatide, the combination of exenatide with dapagliflozin, exenatide with metformin and dapagliflozin with metformin. The research demonstrated that the greatest degree of weight reduction was obtained with the combination of exenatide and dapagliflozin. Interestingly, the highest percentage of body weight reduction and the highest numerical value of weight loss were obtained in patients with a high baseline BMI, and the reduction values decreased the lower the baseline body weight was [16].

Thus, it seems that supporting weight reduction in patients suffering from obesity with drugs from the GLP-1 analogues group is both effective and safe. It is therefore reasonable to consider the use of semaglutide for weight control in obese patients without concomitant T2DM.

4. GLP-1 analogues for the treatment of non-alcoholic fatty liver disease

The term *non-alcoholic fatty liver* describes degenerative and inflammatory changes in the liver caused by metabolic diseases involving histological changes typical of alcoholic disease. The histopathological changes include degenerative changes in the hepatocytes (hydrocele and steatosis) and the occurrence of Mallory corpuscles. In the case of disease progression, inflammatory changes (histopathological neutrophil infiltration) with subsequent parenchymal fibrosis of the liver may intensify.

NAFLD complications may include the development of non-alcoholic steatohepatitis, cirrhosis, or hepatocellular carcinoma.

The reported most common causes of NAFLD include obesity, diabetes, surgical procedures performed to support the treatment of obesity, extensive resection of the small intestine, and abetalipoproteinemia. Patients with fatty liver disease, which is a consequence of the use of drugs such as perhexillin, amiodarone, glucocorticosteroids, synthetic estrogens, and many others, also qualify for this group [1,17].

There is no effective causal treatment for fatty liver. There are attempts to treat it with pioglitazone, alpha-tocopherol, statins, or ursodeoxycholic acid, but they do not resolve the disease [18].

Clinical studies of the role of incretin drugs in the therapy of fatty liver disease are currently underway. The results of multicenter randomized controlled trials to date show that liraglutide reduces fatty liver disease and improves insulin sensitivity as well as the results of histopathological investigations in patients with non-alcoholic steatohepatitis (NASH). In addition, it reduces chronically elevated levels of alanine aminotransferase and promotes weight reduction (reducing the feeling of hunger and increasing the feeling of satiety) [19].

A 2021 meta-analysis carried out by Gostal et al. demonstrated that the use of GLP-1 analogues significantly affects the level of lipid content in the liver cells. The study included eight randomized clinical trials, giving a total population of 615 patients with T2DM and NAFLD. In addition, patients using GLP-1 analogues demonstrated a reduction in the levels of alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transpeptidase, which is associated with a reduction in the level of inflammation within the liver and an improvement of hepatic function. This is probably the first meta-analysis conducted exclusively in patients with T2D and NAFLD, which gives a strong signal that GLP-1 analogues improve liver function and histopathological image [20].

Almost all human studies with exenatide twice daily, evaluating the endpoints associated with NAFLD, include patients with T2D. Several case series and open-label studies suggest that exenatide treatment alone or in addition to standard diabetes therapies may lead to improved liver biomarkers and liver fat reduction in T2D patients [21]. However, it has not been investigated by biopsies whether exenatide is able to alleviate the histological characteristics of NAFLD/NASH, so it remains in the realm of conjecture whether it is the result of beneficial metabolic effects, or beneficial effects on the liver in general.

In the second study from the Liraglutide Efficacy and Action in Diabetes (LEAD) program, a total of 154 patients with T2D participated in a sub-study to assess liver fat content with computed tomography (CT) using the liver-to-spleen attenuation index. This ratio increased significantly from the baseline after 26 weeks of treatment with liraglutide 1.8 mg/day, indicating a reduction in hepatic steatosis. It did not change in the patients treated with lower doses of liraglutide, glimepiride, or placebo [22,23]. In another study, 6 months of treatment with liraglutide 1.2 mg/day significantly reduced liver fat content in patients with poorly controlled T2D, as assessed by 1H magnetic resonance spectroscopy [24].

The LEAN study later became the first study to evaluate the effects of liraglutide on liver function. Fifty-two patients with NASH were randomized to 48 weeks of treatment with liraglutide (1.8 mg/day) or placebo. In that study, 39% of patients treated with liraglutide achieved histological resolution of NASH, compared with 9% in the placebo control group; a reduction in fibrosis was also observed in patients using liraglutide [25]. The latter study had greater methodological advantages than the previously mentioned study, resulting from the availability of liver biopsies at the baseline and after treatment, in addition to the imaging methods, which are burdened with greater error.

In April 2021, a phase 2 clinical study investigating the efficacy and safety of three doses of semaglutide administered subcutaneously once daily compared to placebo in patients with non-alcoholic steatohepatitis was completed. A total of 320 patients (230 of whom had stage F2 or F3 fibrosis) were randomly assigned to receive semaglutide at 0.1 mg, 0.2 mg, and 0.4 mg doses, or placebo. The study showed that treatment with semaglutide resulted in a significantly higher percentage of patients with resolution of hepatitis than placebo. However, the study did not show a significant difference between the groups in the improvement percentages of patients with fibrosis [26].

5. Attempts to explain the beneficial effects of GLP-1 analogues on obesity and NAFLD

Under physiological conditions, endogenous GLP-1 produced by neurons in the nucleus of the solitary band expressing preproglucagon exhibits anorexigenic activity by proopiomelanocortin (POMC) neurons in the arcuate nucleus that express the GLP-1R receptor. There are a few data and medical experiments in the PubMed database which suggest that in addition to the direct excitatory effect on POMC neurons, GLP-1 signaling also acts indirectly—presynaptically activating the POMC neurons, enhancing the anorexigenic effect. In addition, the research of He et al. showed that liraglutide directly activated arcuate POMC neurons through TrpC5 channels, activating an analogous intracellular transmission pathway such as adipocyte-derived leptin. Liraglutide also indirectly increases the excitatory tension of POMC neurons. Thus, these results suggest that the use of GLP-1 agonists could potentially enhance the long-term anorexigenic effect of leptin through direct and indirect central effect on the POMC neurons [6,27,28].

GLP-1 receptors are widely expressed in the central nervous system (CNS) and are present both in cell bodies and neuronal fiber endings, as well as in astrocytes and microglia [29]. Treatment with therapeutic GLP-1R agonists, such as exenatide and liraglutide, resulted in increased neurogenesis in the dentate gyrus, and some data suggest that GLP-1R may exert a protective effect on the mitochondria of neurons in the CNS mediated by activation of the PI3K/Akt pathway and elevated levels of the antiapoptotic protein Bcl-2 [30]. Liraglutide treatment was also shown to be able to alleviate mitochondrial fragmentation by increasing the levels of Mfn-2 and OPA-1, and at the same time intensify the phosphorylation of DRP-1, thereby promoting mitochondrial fusion, which prevents the loss of hippocampal neurons in a mouse model of Alzheimer's disease 5 × FAD (diabetes is an independent risk factor for dementias) [31–33].

Neurons in the nucleus of the solitary band with preproglucagon (PPG) expression are the main source of GLP-1 in the CNS. They activate areas of the brain involved in the regulation of eating behaviors [34].

Stimulation of the PPG-secreting neurons is not fully understood. It has been suggested that this may be due to stimulation of the vagus nerve by pancreatic GLP-1 and subsequent transport of the signal through interneurons to the appropriate neurons. However, there are not enough such connections in the brain. It was therefore hypothesized that PPG-secreting neurons receive their signal mainly from the neurons that express the oxytocin receptor, suggesting that central and peripheral GLP-1 signaling may facilitate its anorexigenic action through two independent circuits [35].

In a 2019 study conducted in Boston by Farr et al., brain activation in response to food images was not altered by liraglutide compared to placebo. When checked for BMI/body weight, liraglutide increased the activation of the right orbitofrontal cortex in response to food signals. A counterregulatory increase in reward-associated orbitofrontal cortex activation in response to nutritional signals can be observed when neuroimaging data are controlled for changes in BMI, indicating changes in the CNS that may lead to a subsequent plateau of weight loss [36].

Chronic use of GLP-1 receptor agonists is expected to improve insulin sensitivity of tissues, mainly by significant weight reduction. However, this effect can be independent of the amount of body fat. In 2013, Seghieri et al. demonstrated that GLP-1 inhibits endogenous glucose production under conditions where insulin and glucagon in plasma cannot change and glucose concentrations are predetermined [37]. A similar experiment, but carried out on people, was conducted in 2016 by Gastaldelli et al., showing that administration of exenatide, prior to an oral glucose load test, results in an increase in glucose uptake by hepatocytes, with lower plasma insulin concentrations than in the placebo group at the same time [38]. The results of the above experiments indicate a direct effect of GLP-1 either on the hepatocytes or on the inhibition of glucose production in the liver by the neuronal system. The ambiguity is because it has not yet been established whether a receptor for GLP-1 is present on the surface of hepatocytes [37–42].

The study conducted in 2021 by Oliveira et al. focused on the interaction of liraglutide with brown adipose tissue. Liraglutide has been shown to have an additive effect to β3-adrenergic stimulation in brown adipose tissue, and to increase the activity of deiodinase 2 in brown adipose tissue. The above finding indicates the possibility of activating intracellular pathways typical of thyroid hormones, complementing the currently known mechanisms of action of GLP-1 analogues on weight loss [43].

As mentioned above, the GLP-1R receptor has not been shown to be present on hepatocytes. Despite this, the in vivo and in vitro studies conducted to date have shown that the use of GLP-1 analogues has a beneficial effect on reducing lipid accumulation and lipogenesis in the liver. One hypothesis explaining the mechanism of action of GLP-1 analogues in reducing progression and reducing fatty changes in the liver is associated with a decrease in the expression of protein tyrosine phosphatase 1 (SHP1) with subsequent activation of the AMP-activated protein kinase (AMPK). SHP1 is widely recognized as a modulator of insulin action in hepatocytes and hepatic glucose metabolism. Increased expression of this protein is involved in the pathogenesis of insulin resistance and NAFLD as a negative regulator. In 2019, Yu et al. conducted a study on mice assessing the contribution of liraglutide to the SHP1/AMPK pathway. They showed that anti-lipotoxic effects (inhibition of lipid storage, inhibition of hepatic lipogenesis) may result from indirect inhibition of SHP1 and activation of AMPK in hepatocytes. It was probably the first study of this type in the world [44–47].

Kim et al. conducted in 2021 a study using double long-acting GLP1/2 agonists administered subcutaneously to laboratory mice for fatty liver lesions with subsequent transplantation of intestinal microflora. The transplantation of intestinal microflora had an additive effect on the liver with the parallel use of incretin analogues, and thereby on weight reduction, fat accumulation in the liver, inflammation, and fibrosis of the liver. This provides another example of the multifactorial pathogenesis of fatty liver disease [48].

6. Conclusion

Body weight and liver cell steatosis are associated with the anorexigenic effects of GLP1 analogues, as well as with their direct effects on adipose tissue cells and hepatocytes. The effect of GLP-1 analogues on diabetes-related obesity and NAFLD requires further research in the field of clinical sciences, as well as basic sciences. It is difficult to develop a model of molecular changes explaining the reduction of body fat and steatosis of the liver cells by GLP-1 analogues. Numerous studies at the molecular level do not allow development of a clear model of this action at the moment.

Authors' contribution

K.D.: Research concept and design, Supervising the project, Writing – Original Draft Preparation, Literature review; **B.B.:** Research concept and design, Supervising the project, Writing – Review and Editing, Literature review; **M.K.:** Writing – Review and Editing, Literature review, Final proofreading and approval of the version for publication; **T.P.:** Writing – Review and Editing, Final proofreading and approval of the version for publication.

ORCID

Kacper Deska https://orcid.org/0000-0002-5416-5711
Bartłomiej Bąk https://orcid.org/0000-0002-6810-1153
Marcin Kosmalski https://orcid.org/0000-0003-0609-9657
Tadeusz Pietras https://orcid.org/0000-0003-1771-3819

Conflict of interest

The authors have no potential conflicts of interest to declare.

References

[1] Kosmalski M., Ziółkowska S., Czarny P., Szemraj J., Pietras T.: The coexistence of nonalcoholic fatty liver disease and type 2 diabetes mellitus. J Clin Med., 2022; 11: 1375

[2] Blachier M., Leleu H., Peck-Radosavljevic M., Valla D.C., Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol., 2013; 58: 593–608

[3] Younossi Z. M., Golabi P., de Avila L., Paik J. M., Srishord M., Fukui N., Qiu Y., Burns L., Afendy A., & Nader F. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol., 2019; 71: 793–801

[4] Drucker D.J., Nauck M.A. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. The Lancet, 2006; 368: 1696–705

[5] Filippatos T.D., Panagiotopoulou T.V., Elisaf M.S.. Adverse effects of GLP-1 receptor agonists. Rev Diabet Stud RDS., 2014; 11: 202

[6] He Z., Gao Y., Lieu L., Afrin S., Cao J., Michael N.J., Dong Y., Sun J., Guo H., Williams K.W. Direct and indirect effects of liraglutide on hypothalamic POMC and NPY/AgRP neurons— Implications for energy balance and glucose control. Mol Metab., 2019; 28: 120–134

[7] Wadden T.A., Hollander P., Klein S., Niswender K., Woo V., Hale P.M., Aronne L.; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes., 2013; 37: 1443–51

[8] Monami M., Dicembrini I., Marchionni N., Rotella C.M., Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. Exp Diabetes Res., 2012: 672658

[9] Wilding J.P.H., Batterham R.L., Calanna S., Davies M., Van Gaal L.F., Lingvay I., McGowan B.M., Rosenstock J., Tran M.T.D., Wadden T.A., et al. STEP 1 Study Group: Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med., 2021; 384: 989-1002

[10] Davies M., Færch L., Jeppesen O.K., Pakseresht A., Pedersen S.D., Perreault L., Rosenstock J., Shimomura I., Viljoen A., Wadden T.A., et al., STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. The Lancet., 2021; 397: 971–984

[11] Rubino D., Abrahamsson N., Davies M., Hesse D., Greenway F.L., Jensen C., Lingvay I., Mosenzon O., Rosenstock J., Rubio M.A., et al., STEP 4 Investigators. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults With overweight or obesity: The STEP 4 randomized clinical trial. JAMA., 2021; 325: 1414–1425

[12] Kadowaki T., Isendahl J., Khalid U., Lee S.Y., Nishida T., Ogawa W., Tobe K., Yamauchi T., Lim S., STEP 6 investigators. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol., 2022 10: 193–206

[13] Rubino D.M., Greenway F.L., Khalid U., O'Neil P.M., Rosenstock J., Sørrig R., Wadden T.A., Wizert A., Garvey W.T., STEP 8 Investigators. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults With overweight or obesity without diabetes: The STEP 8 Randomized Clinical Trial. JAMA., 2022; 327: 138–150

[14] Wegovy™ demonstrated significant and sustained weight loss in two-year study in adults with obesity, Available at: https://www.prnewswire.com/news-releases/wegovy-demonstrated-significant-and-sustained-weight-loss-in-two-year-study-in-adults-with-obesity-301417583.html (Accessed September 26, 2022)

[15] Wadden T.A., Bailey T.S., Billings L.K., Davies M., Frias J.P., Koroleva A., Lingvay I., O'Neil P.M., Rubino D.M., Skovgaard D., et al., STEP 3 Investigators. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 Randomized Clinical Trial. JAMA., 2021; 325: 1403–1413

[16] Jabbour S.A., Frías J.P., Guja C., Hardy E., Ahmed A., Öhman P. Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly, or dapagliflozin, added to metformin monotherapy, on body weight, systolic blood pressure, and triglycerides in patients with type 2 diabetes in the DURATION-8 study. Diabetes Obes Metab. czerwiec 2018; 20: 1515–9

[17] Basu R, Noureddin M, Clark JM. Nonalcoholic fatty liver disease: Review of management for primary care providers. Mayo Clin Proc., wrzesień 2022; 97: 1700–16

[18] Kosmalski M., Drzewoski J., Szymczak-Pajor I., Zieleniak A., Mikołajczyk-Solińska M., Kasznicki J., Śliwińska A.. Irisin is related to non-alcoholic fatty liver disease (NAFLD). Biomedicines, 2022; 10: 2253

[19] Cichoż-Lach H. Obesity and non-alcoholic fatty liver disease. In: Clinical Obesitology. Bielsko-Biała: Alfa-Medica Press; 2021: 206–15

[20] Ghosal S., Datta D., Sinha B. A meta-analysis of the effects of glucagon-like-peptide 1 receptor agonist (GLP1-RA) in nonalcoholic fatty liver disease (NAFLD) with type 2 diabetes (T2D). Sci Rep. 11 listopad 2021; 11: 22063

[21] Klonoff D.C., Buse J.B., Nielsen L.L., Guan X., Bowlus C.L., Holcombe J.H., Wintle M.E., Maggs D.G. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin., 2008; 24: 275–286

[22] Armstrong M.J., Houlihan D.D., Rowe I.A., Clausen W.H., Elbrønd B., Gough S.C., Tomlinson J.W., Newsome P.N. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther., 2013; 37: 234–242

[23] Jendle J., Nauck M.A., Matthews D.R., Frid A., Hermansen K., Düring M., Zdravkovic M., Strauss B.J., Garber A.J.; LEAD-2 and LEAD-3 Study Groups. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monothera-

py or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes Obes Metab., 2009; 11: 1163–72

[24] Petit J.M., Cercueil J.P., Loffroy R., Denimal D., Bouillet B., Fourmont C., Chevallier O., Duvillard L., Vergès B. Effect of liraglutide therapy on liver fat content in patients with inadequately controlled type 2 diabetes: The Lira-NAFLD Study. J Clin Endocrinol Metab., 2017;102: 407–415

[25] Armstrong M.J., Gaunt P., Aithal G.P., Barton D., Hull D., Parker R., Hazlehurst J.M., Guo K.; LEAN trial team, Abouda G., et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016; 387: 679–690

[26] Newsome P.N., Buchholtz K., Cusi K., Linder M., Okanoue T., Ratziu V., Sanyal AJ, Sejling AS, Harrison SA; et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med., 2021; 384: 1113–1124

[27] Péterfi Z., Szilvásy-Szabó A., Farkas E., Ruska Y., Pyke C., Knudsen L.B., Fekete C. Glucagon-like peptide-1 regulates the proopiomelanocortin neurons of the arcuate nucleus both directly and indirectly via presynaptic action. Neuroendocrinology, 2021; 111: 986–997

[28] Müller T.D., Finan B., Bloom S.R., D'Alessio D., Drucker D.J., Flatt P.R., Fritsche A., Gribble F., Grill H.J., Habener J.F., et al. Glucagon-like peptide 1 (GLP-1). Mol Metab., 2019; 30: 72–130

[29] Heppner K.M., Kirigiti M., Secher A., Paulsen S.J., Buckingham R., Pyke C., Knudsen L.B., Vrang N., Grove K.L. Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein and binding in the male nonhuman primate (Macaca mulatta) brain. Endocrinology, 2015; 156: 255–267

[30] Hamilton A., Patterson S., Porter D., Gault V.A., Holscher C. Novel GLP–1 mimetics developed to treat type 2 diabetes promote progenitor cell proliferation in the brain. J Neurosci Res., 2011; 89: 481–489

[31] Athauda D., Foltynie T. The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action. Drug Discov Today, 2016; 21: 802–818

[32] Spielman L.J., Gibson D.L., Klegeris A. Incretin hormones regulate microglia oxidative stress, survival and expression of trophic factors. Eur J Cell Biol., 2017; 96: 240–253

[33] Timper K., Del Río–Martín A., Cremer A.L., Bremser S., Alber J., Giavalisco P., Varela L., Heilinger C., Nolte H., Trifunovic A., et al. GLP-1 receptor signaling in astrocytes regulates fatty acid oxidation, mitochondrial integrity, and function. Cell Metab., 2020; 31: 1189–1205.e13

[34] Brierley DI, Holt MK, Singh A, de Araujo A, McDougle M, Vergara M, Afaghani MH, Lee SJ, Scott K, Maske C, et al. Central and peripheral GLP–1 systems independently suppress eating. Nat Metab. 2021; 3(2): 258–273.

[35] Głombik K., Detka J., Budziszewska B. Hormonal regulation of oxidative phosphorylation in the brain in health and disease. Cells, 2021;10: 2937

[36] Farr O.M., Upadhyay J., Rutagengwa C., DiPrisco B., Ranta Z., Adra A., Bapatla N., Douglas V.P., Douglas K.A.A., Nolen-Doerr E., et al. Longer-term liraglutide administration at the highest dose approved for obesity increases reward-related orbitofrontal cortex activation in response to food cues: Implications for plateauing weight loss in response to anti-obesity therapies. Diabetes Obes Metab., 2019; 21: 2459–2464

[37] Seghieri M., Rebelos E., Gastaldelli A., Astiarraga B.D., Casolaro A., Barsotti E., Pocai A., Nauck M., Muscelli E., Ferrannini E. Direct effect of GLP-1 infusion on endogenous glucose production in humans. Diabetologia., 2013; 56: 156–161

[38] Gastaldelli A., Gaggini M., Daniele G., Ciociaro D., Cersosimo E., Tripathy D., Triplitt C., Fox P., Musi N., DeFronzo R., et al. Exenatide improves both hepatic and adipose tissue insulin resistance: A dynamic positron emission tomography study. Hepatology, 2016; 64: 2028-2037

[39] Gupta N.A., Mells J., Dunham R.M., Grakoui A., Handy J., Saxena N.K., Anania F.A. Glucagon–like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. Hepatology, 2010; 51: 1584–1592

[40] Pyke C., Heller R.S., Kirk R.K., Ørskov C., Reedtz-Runge S., Kaastrup P., Hvelplund A., Bardram L., Calatayud D., Knudsen L.B. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology, 2014; 155: 1280–1290

[41] Seghieri M., Christensen A.S., Andersen A., Solini A., Knop F.K., Vilsbøll T. Future perspectives on GLP-1 receptor agonists and GLP-1/glucagon receptor co-agonists in the treatment of NAFLD. Front Endocrinol (Lausanne), 2018; 9: 649

[42] Svegliati-Baroni G., Saccomanno S., Rychlicki C., Agostinelli L., De Minicis S., Candelaresi C., Faraci G., Pacetti D., Vivarelli M., Nicolini D., et al. Glucagon-like peptide-1 receptor activation stimulates hepatic lipid oxidation and restores hepatic signalling alteration induced by a high-fat diet in nonalcoholic steatohepatitis. Liver Int., 2011; 31: 1285–1297

[43] Oliveira F.C.B., Bauer E.J., Ribeiro C.M., Pereira S.A., Beserra B.T.S., Wajner S.M., Maia A.L., Neves F.A.R., Coelho M.S., Amato A.A. Liraglutide activates type 2 deiodinase and enhances β3-adrenergic-induced thermogenesis in mouse adipose tissue. Front Endocrinol (Lausanne). 2022; 12: 803363

[44] Marín-Juez R., Jong-Raadsen S., Yang S., Spaink H.P. Hyperinsulinemia induces insulin resistance and immune suppression via Ptpn6/Shp1 in zebrafish. J Endocrinol., 2014; 222: 229–241

[45] Lu Y., Jiang Z., Dai H., Miao R., Shu J., Gu H., Liu X., Huang Z., Yang G., Chen A.F., et al. Hepatic leukocyte immunoglobulin-like receptor B4 (LILRB4) attenuates nonalcoholic fatty liver disease via SHP1-TRAF6 pathway. Hepatology. 2018; 67: 1303–1319

[46] Xu E., Forest M.P., Schwab M., Avramoglu R.K., St-Amand E., Caron A.Z., Bellmann K., Shum M., Voisin G., Paquet M., et al. Hepatocyte-specific Ptpn6 deletion promotes hepatic lipid accretion, but reduces NAFLD in diet-induced obesity: potential role of PPARγ. Hepatology, 2014; 59: 1803–1815

[47] Yu P., Xu X., Zhang J., Xia X., Xu F., Weng J., Lai X., Shen Y. Liraglutide attenuates nonalcoholic fatty liver disease through adjusting lipid me-

tabolism via SHP1/AMPK signaling pathway. Int J Endocrinol., 2019; 19: 1567095

[48] Kim E.R., Park J.S., Kim J.H., Oh J.Y., Oh I.J., Choi D.H., Lee Y.S., Park I.S., Kim S., Lee D.H., et al. A GLP-1/GLP-2 receptor dual agonist to treat NASH: Targeting the gut-liver axis and microbiome. Hepatology, 2022; 75: 1523–1538