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Liraglutide as an innovative and multifunctional drug for patients with obesity – the current state of knowledge and future prospects

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ABSTRACT

Introduction and purpose: Obesity is considered a disease of civilization representing a global health and social problem. Currently, 21% of adult Poles suffer from obesity, so every fifth patient contacted by a doctor is obese. The aim of this paper is to present a modern method of obesity pharmacotherapy.

Description of the state of knowledge: Obesity is a chronic disease, associated with excessive accumulation of adipose tissue, which causes a deterioration in the health and quality of life of an obese patient. The mainstay of obesity treatment is lifestyle modification. However, due to the high prevalence of obesity in developed countries and its serious consequences, pharmacological methods of obesity treatment were searched for. Currently, there are three drugs approved for the treatment of obesity in Poland: orlistat, a combined preparation of naltrexone + bupropion and liraglutide – agonist of a glucagon-like peptide-1 receptor. The effectiveness of one of them - liraglutide - is particularly significant, and the effect of this drug in reducing cardiovascular risk is also promising.

Conclusions: In the latest recommendations of the Polish Obesity Treatment Association, liraglutide is indicated as the drug of first choice for obese or overweight patients with a BMI ≥27 kg / m2, in whom coexisting: pre-diabetes, type 2 diabetes, arterial hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, metabolic syndrome, atherosclerosis or sleep apnea syndrome. However, there is still a need for further research into the efficacy and safety of liraglutide in this indication. Due to the presence of GLP-1 receptors in many

organs, the use of liraglutide in the future would probably extend to more diseases than obesity and type 2 diabetes.

Key words: liraglutide; obesity; GLP-1 analogues; anti-obesity drugs; weight loss medications

1. INTRODUCTION, METHODOLOGY AND PURPOSE

Obesity is a chronic disease, with no tendency to spontaneously resolve and witch often relapses, leading to many adverse health, psychological, social and economic consequences. Its numerous complications include the most common chronic diseases, the pathogenesis of which is closely related to metabolic disorders resulting from a long-term positive energy balance and excess body fat. Complications of obesity include mainly type 2 diabetes, arterial hypertension, dyslipidemia, atherosclerosis, non-alcoholic fatty liver disease, sleep apnea syndrome, but also chronic kidney disease, fertility disorders, osteoarthritis, and - which is rarely remembered - some malignant tumors [1,2]. The dangers of undiagnosed and untreated obesity have been particularly exposed by the COVID-19 pandemic. Epidemiological data clearly indicated obesity as one of the most important risk factors for the severe course of SARS-CoV-2 infection, the presence of which increases the risk of hospitalization and the need for intensive therapy, as well as the risk of death [3].

The negative consequences of obesity in the form of the development of numerous complications associated with it, deteriorating overall quality of life and shortening the life expectancy of obese patients, make doctors look for new methods of its treatment. Of course, the latest guidelines of Polish and international obesity treatment societies still provide the basis and the most important method of obesity treatment to modify the lifestyle. It includes changing your eating habits and increasing your physical activity. In terms of diet, the amount of calories supplied is reduced and attention is paid to the selection of food products. However, if it does not bring the expected results, pharmacological or surgical treatment should be considered [1,4,5].

The aim of this study is to present the current place and role of liraglutide - a drug from the group of GLP-1 (glucagon-like peptide-1) analogues - in the treatment of obesity, detailed indications for the implementation of such therapy, possible benefits of it - not only in relation to the treatment of obesity, but also its comparison with therapies with the use of other drugs registered for the treatment of obesity in Poland and of side effects.

The guidelines of obesity treatment societies and publications available in the PubMed, Google Scholar and MedRxiv scientific databases were analyzed by looking through keywords such as: “liraglutide”, “obesity”, “GLP-1 analogues”, “anti-obesity drugs” and “weight loss medications”.

2. DESCRIPTION OF THE STATE OF KNOWLEDGE

2.1. Obesity as a disease unit

The World Health Organization (WHO) defines obesity as a chronic complex disease defined by excessive adiposity that can impair health. It is in most cases a multifactorial disease due to obesogenic environments, psycho-social factors and genetic variants. In a subgroup of patients, single major etiological factors can be identified (medications, diseases, immobilization, iatrogenic procedures, monogenic disease/genetic syndrome). Body mass index (BMI), which is weight in kilograms divided by height in meters squared, is used to identify obesity. The BMI categories for defining obesity vary by age and gender in infants, children and adolescents. For adults, a BMI of 25.0 to 29.9 kg/m2 is defined as overweight and a BMI of 30 kg/m2 or higher is defined as obese: class 1 obesity - BMI 30–34.9 kg / m2; class 2 obesity - BMI 35–39.9 kg / m2; class 3 obesity (sometimes categorized as “severe” obesity) - BMI ≥40 kg / m2 [6]. BMI is not used for children and adolescents age 2 to 18 years; instead, it is recommended that a percentile scale based on the child’s sex and age be used. In this population, overweight is defined as a BMI in the 85th to 94th percentile, and obesity is a BMI at or above the 95th percentile. In the latest, eleventh version of the International Classification of Diseases (ICD-11), obesity is classified under the number 5B81, and in the tenth version currently in force in Poland (ICD-10) under the number E66 [7,8].

Obesity is a global health problem: it has been estimated that approximately 1.5 billion adults worldwide are overweight, among them about 200 million men and 300 million women are obese [9]. Even more alarming is the increasing trends in the prevalence of obesity in children and adolescents in developed and developing countries, leading to adverse effects in terms of both physical and mental health [10]. WHO reports an abrupt increase in global childhood obesity, from 32 million in 1990 to 41 million in 2016 [11].

The results of the survey by the Polish Centre for Public Opinion Research conducted in 2019 indicate that as many as 59% of adult Poles have excess body weight, and this percentage has increased by 13% over the last 10 years. This increase means that we will have to deal with the increasing incidence of type 2 diabetes, high blood pressure and other complications that will increase the risk of adverse cardiovascular events in the long run. The health consequences of excess body weight will be most pronounced in relation to obesity, which already affects 21% of adult Poles. It is impossible not to note that the rate of increase in the prevalence of overweight and obesity among children and adolescents in Poland is one of the highest in Europe. According to the report of the Organization for Economic Cooperation and Development (OECD) from 2019, due to the uncontrolled increase

in the prevalence of overweight and obesity, the average life expectancy in Poland will shorten by nearly 4 years by 2050 [12-15].
Every year over 2.8 million people worldwide die from overweight or obesity-related chronic diseases [16]. For every 5-unit increase in BMI above 25 kg/m2, overall mortality increases by 29%, vascular mortality by 41%, and diabetes-related mortality by 210% [17]. Measures of central adiposity, such as increased waist circumference, predict cardiometabolic risk, which cannot be directly determined by elevated BMI [18]. The Edmonton obesity staging system ranks excess adiposity on a 5-point ordinal scale and incorporates the person's obesity-related comorbidities and functional status. The system is intended to complement current measures and has been found to be a strong, independent predictor of increasing mortality; however, it is still unclear how to best incorporate the system into clinical practice [19].

2.2. Pharmacological methods of obesity treatment - indications and available medications

Adults living with obesity should receive individualized care plans that address their root causes of obesity and that provide support for behavioural change (e.g., nutrition, physical activity) and adjunctive therapies, which may include psychological, pharmacologic and surgical interventions.
All patients, regardless of body size or composition, would benefit from adopting a healthy, well-balanced eating pattern and engaging in regular physical activity. Aerobic activity (30–60 min) on most days of the week can lead to a small amount of weight and fat loss, improvement in cardiometabolic parameters, and weight maintenance after weight loss [20]. Weight loss and weight-loss maintenance require a long-term reduction in caloric intake. Long-term adherence to a healthy eating pattern that is personalized to meet individual values and preferences, while fulfilling nutritional needs and treatment goals, is an important element of managing health and weight.
The weight loss achieved with health behavioural changes is usually 3%–5% of body weight, which can result in meaningful improvement in obesity-related comorbidities [21]. The amount of weight loss varies substantially among individuals, depending on biological and psychosocial factors and not simply on individual effort.
The weight at which the body stabilizes when engaging in healthy behaviours can be referred to as the "best weight"; this may not be an "ideal" weight on the BMI scale. Achieving an "ideal" BMI may be very difficult. If further weight loss would bring significant health benefits for the patient, it should be pursued through additional therapeutic interventions: initially psychological and behavioural interventions, then pharmacological and surgical therapeutic options can be considered.
According to the Polish Obesity Treatment Guidelines, pharmacological obesity treatment can be - in combination with a diet with a correspondingly reduced caloric value and with increased physical effort - used in people who have not achieved a significant reduction in body weight and therapeutic goals as a result of dietary and behavioral treatment, as long as they meet the following criteria:

1) adults with BMI ≥30 kg / m2
2) adults with BMI 27-29.9 kg / m2 and ≥1 disease related to abnormal body weight, such as pre-diabetes or diabetes, atrial hypertension, dyslipidaemia or obstructive sleep apnea
3) adolescents aged ≥12 years, with a body weight> 60 kg and diagnosed with obesity taking into account the cut-off points specified in the international standard (according to the criteria International Obesity Task Force [IOTF] defined as the value of BMI determined for the age and sex of the patient, the achievement of which or exceeding of which entitles the diagnosis of obesity) [4].

Pharmacological treatment of obesity should not last <6 months, and its optimal duration should be ≥12 months, and it should be adjusted to the patient's individual needs: treatment goals - reduction of the initial body weight defined in percentage points and the expected improvement in health - and the planned pace of reduction body weight. Due to the chronic nature and recurrence of obesity, we use pharmacotherapy for as long as it is needed and effective. Stopping treatment too early may make it difficult to maintain weight and cause weight regain, especially if new, health-promoting lifestyle changes have not yet become established [4].
Currently, there are 4 drugs registered by the European Medicines Agency (EMA) for the treatment of obesity in the European Union:

1) orlistat
2) a preparation consisting of naltrexone hydrochloride and bupropion hydrochloride

and 2 analogs of the human glucagon-like peptide-1 (GLP - 1):

3) liraglutide
4) semaglutide - the newest, but at the time of publishing our article (November 2022), the preparation in the dose registered for the treatment of obesity is not yet available in Poland [4].

2.3. Mechanism of action of liraglutide

Liraglutide is an acylated analog of human glucagon-like peptide-1 (GLP-1) in which the amino acid sequence is 97% consistent with the amino acid sequence of the endogenous human GLP-1 molecule. Liraglutide in a preparation called Victoza® was approved in 2010 for the treatment of type 2 diabetes - the recommended dose

is subcutaneous administration of 1.8 mg daily [22]. The higher dose (3.0 mg subcutaneous daily) of liraglutide (Saxenda®) was approved by the FDA in 2014 and the EMA in 2015 for long-term weight management [23].
Liraglutide binds to and activates the GLP-1 receptor (GLP-1R). GLP-1 is secreted after meals from the distal ileum, proximal colon, and the vagal nucleus of the solitary tract, and it has multiple effects as an incretin hormone [24]. Its main role is to regulate blood glucose by inhibiting glucagon secretion and enhancing insulin secretion from the pancreatic β-cells in a glucose-dependent manner [25]. In addition, GLP-1 slows gastric emptying, induces post-prandial satiety and fullness, and reduces appetite and food consumption by working on the hypothalamus, limbic/reward system, and cortex [26]. The pharmacodynamics of liraglutide is very complex, as it acts at different levels to maintain glucose homeostasis by regulating the survival of pancreatic β-cell, insulin secretion, and eating behavior [27]. Liraglutide is more stable in plasma and strongly binds to the plasma proteins, thereby having a longer half-life (13 h) than the human endogenous GLP-1 (a few minutes) [28]. GLP-1 receptors are also found at specific sites in the heart, circulatory system, immune system, and kidneys. In atherosclerosis studies in mice, liraglutide prevented plaque development and reduced plaque inflammation. Additionally, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce plaque size in stable atherosclerosis [29].

2.4. The efficacy of liraglutide in the treatment of obesity

In 2009, the results of a study by Astrup et al. comparing the efficacy of different doses of liraglutide (1.2 mg, 1.8 mg, 2.4 mg, 3.0 mg), orlistat (360 mg daily) and placebo for weight reduction in obese patients without type 2 diabetes. The study was conducted in a group of 564 patients aged 18 to 65 years, with a BMI of 30-40 kg / m2, the follow-up period was 20 weeks. Apart from pharmacotherapy, the patients followed a low-energy diet and increased physical activity [30].
Regardless of dose, patients taking liraglutide achieved greater weight loss than those treated with orlistat or placebo. Mean weight loss in the liraglutide group was dose-related and ranged from: 1.2 mg - 4.8 kg, 1.8 mg - 5.5 kg, 2.4 mg - 6.3 kg , for a dose of 3.0 mg - 7.2 kg. The weight loss in the placebo and orlistat groups was 2.8 kg and 4.1 kg, respectively. The mean weight loss in the liraglutide group was from 2.1 kg to 4.4 kg greater than in the placebo group. The highest proportion of subjects who achieved a weight loss of ≥5% from baseline weight was reported among those taking a daily dose of 3.0 mg of liraglutide. In addition to the effect on body weight, liraglutide has also been shown to reduce blood pressure, irrespective of the dose, and in doses of 1.8-3.0 mg, it reduced the incidence of pre-diabetes [30].
Some of the patients enrolled in this study continued a 2-year follow-up to assess the efficacy of liraglutide in maintaining weight loss and its impact on the risk factors for cardiovascular disease. After 12 months, all patients previously taking liraglutide and placebo began the next phase of treatment. liraglutide - first at a dose of 2.4 mg (the dose considered most favorable based on the results of the previous 20-week follow-up), then at a dose of 3.0 mg. It turned out that almost 70% of patients taking the drug at a dose of 2.4 mg or 3.0 mg for 2 years maintained a minimum body weight of 5% from the baseline body weight, moreover, in this group lower blood pressure values, less abnormal glucose levels were observed, fasting and impaired glucose tolerance, mean values of fasting glucose and HbA1c were also lower [31].
The following three main randomized controlled trials were of greatest importance in confirming the clinical efficacy of liraglutide in the treatment of obesity: The Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) Obesity and Prediabetes, SCALE Diabetes, and SCALE Maintenance [32, 33, 34], assessed the effectiveness and safety of liraglutide.
In the SCALE obesity and prediabetes patients, including 61.2% of prediabetic participants, were randomized to receive liraglutide at a daily dose of 3.0 mg (n = 2487) or placebo (n = 1244). At the same time, all subjects followed a low-energy diet and increased physical activity. After the follow-up period (56 weeks), 63.2% of the liraglutide-treated patients and 27.1% of the placebo-treated patients achieved a minimum 5% reduction in body weight ($p < 0.001$). A minimum 10% reduction in body weight was achieved by 33.1% of those treated with liraglutide and 10.6% of those treated with placebo ($p < 0.001$). Moreover, blood pressure, lipid profiles, glycated hemoglobin - HbA1c (− 0.30% ± 0.28), and fasting glucose levels (− 7.1 mg/dL ± 0.8) improved in the liraglutide group as compared to those in placebo group [32].
The SCALE Diabetes assigned diabetic patients with obesity (n = 846) to receive 3 mg, 1.8 mg QD of liraglutide, or placebo for 56 weeks and reported weight reduction in the patients (6.0%, 4.7%, and 2.0%, respectively) [33]. Early weight reduction ≥ 4% was associated with greater weight loss with 3 mg of liraglutide (at 16 weeks) at the end of the study [35]. Compared to the 1.8 mg group, the 3.0 mg group had a greater improvement in HbA1c, fasting plasma glucose, Homeostatic Model Assessment for Insulin Resistance, and the number of hypoglycemic agents. In comparison to other anti-obesity drugs, one of the main benefits of liraglutide is that it does not contribute to the incidence of cardiovascular disease in obese patients with type 2 diabetes [36].
The SCALE Maintenance was designed to assess weight maintenance in non-diabetic participants who underwent a ≥ 4-week run-in with a low-calorie diet. Subjects (n = 422) who lost 5% or more of the initial body weight were assigned to the liraglutide 3.0 mg or placebo group for 56 weeks. Liraglutide group (3.0 mg) achieved an additional weight reduction of 6.2% as compared to 0.2% in placebo group [34].

2.5. Most common side effects of liraglutide in the treatment of obesity

SAXENDA® was evaluated for safety in 5 double-blind, placebo controlled trials that included 3384 overweight or obese adult patients treated with SAXENDA® for a treatment period up to 56 weeks (3 trials), 52 weeks (1 trial), and 32 weeks (1 trial). All patients received study drug in addition to a reduced-calorie diet and increased physical activity counseling. Patients received SAXENDA® for a mean treatment duration of 46 weeks (median, 56 weeks). Baseline characteristics included a mean age of 47 years, 71% women, 85% white, 39% with hypertension, 15% with type 2 diabetes, 34% with dyslipidemia, 29% with a BMI greater than 40 kg/m2, and 9% with cardiovascular disease. For all trials, dosing was initiated and increased weekly to reach the 3 mg dose [37]. The highest rates of adverse events were gastrointestinal; the top four were nausea, diarrhea, constipation, and vomiting. With regard to serious adverse events, pooled data reflected a rate of 6.3% (213 patients) in the liraglutide 3.0-mg treatment groups compared with 4.6% (89 patients) in the placebo groups. This translated to an estimated incidence of 93/1000 patients in the treatment groups compared to 71/1000 patients in the placebo groups. The most common serious adverse events in the liraglutide groups were hepatobiliary disorders and gallbladder disorders, whereas infections were most common in the placebo groups. When examining the adverse events that resulted in withdrawal from trials, pooled data showed a total of 331 patients (9.8%) who withdrew across the liraglutide 3.0-mg treatment groups compared with 83 (4.3%) who withdrew from placebo groups. Gastrointestinal disorders or symptoms were the most prevalent reasons for withdrawal in both the treatment and placebo groups, totaling 63% of all treatment group withdrawals and 30% of placebo withdrawals. Of note, most of the withdrawals across both groups occurred early, in the first 4–8 weeks of treatment [37].

2.6. Place of liraglutide in the current guidelines of the Polish Obesity Treatment Society

The guidelines of the Polish Obesity Treatment Society indicate that liraglutide at a dose of 3.0 mg:

a) should be used as the drug of choice in obese or overweight people with a BMI ≥27 kg / m2, in whom coexisting: pre-diabetes (impaired fasting glycemia and / or impaired glucose tolerance), type 2 diabetes, arterial hypertension, polycystic ovary syndrome or nonalcoholic fatty liver disease, metabolic syndrome, atherosclerosis and its clinical sequelae, sleep apnea syndrome,

b) it is effective and safe in the treatment of obese patients who are prepared for bariatric surgery or who have undergone bariatric surgery [4].

Liraglutide is available in a disposable pen injector as a solution for subcutaneous injection. The initial dose is 0.6 mg once a day subcutaneous and it should be gradually increased by 0.6 mg / day every ≥1 week, until the target dose is 3 mg once a day or the maximum tolerated dose. Gradually increasing the dose improves the tolerance of the drug and reduces gastrointestinal side effects. Treatment should be discontinued if the patient does not experience a reduction in baseline body weight after 12 weeks on a dose of 3.0 mg / day by at least 5% [4].

3. CONCLUSIONS

In our work, we wanted to emphasize the importance of obesity prevention and the need to change the perception of excess body weight not only as a risk factor for other chronic diseases, but also as a disease whose effective treatment significantly improves patients' health and long-term prognosis. The inclusion of pharmacotherapy in the treatment of obesity achieves significantly better results in weight reduction than using only nutritional treatment and lifestyle modification. Looking at the results of the clinical trials presented, liraglutide is very effective in the treatment of obesity in terms of both weight loss and its maintenance. Modern pharmacotherapy of obesity should also lead to a reduction in the risk of obesity complications and be individually tailored to the patient's needs, so as not only to help him achieve the assumed goal of weight loss, but also positively affect the course of other diseases and disorders that he has been diagnosed with. This is particularly true of risk factors for cardiovascular disease and the long-term cardiovascular safety of drugs. In this respect, liraglutide also appears to be the best drug currently used in the treatment of obesity - it is effective in reducing cardiovascular risk by lowering blood pressure and normalizing lipid profile. Moreover, it also has a positive effect on the carbohydrate metabolism - it lowers the values of: HbA1c, fasting plasma glucose, Homeostatic Model Assesment - Insulin Resistance index and also does not contribute to the incidence of cardiovascular disease in obese patients with type 2 diabetes. In the future, due to the presence of GLP-1 receptors in many organs, the use of liraglutide and other GLP-1 analogues could extend to more diseases than obesity and type 2 diabetes. We hope that this work will contribute to increasing researchers' interest in the effects of liraglutide and its potential new applications.

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