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THE USE OF SEMAGLUTIDE (ANALOG OF GLP-1) IN THE TREATMENT OF OBESITY

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Abstract: Obesity is a complex pathology that affects virtually all stages of life, regardless of socioeconomic groups. GLP-1 analogues are potentially promising drugs for weight loss in obese or overweight adults and at least one comorbidity. An integrative review of the use of the GLP-1 analogue semaglutide in the treatment of obesity and weight loss therapy was reviewed, analyzing the STEP (Semaglutide Treatment Effect in People with Obesity) study.
Keywords: Obesity. Pharmacological treatment. LPG-1.

INTRODUCTION

Characterized by the excessive accumulation of body fat in the individual, obesity is a complex pathology that affects practically all stages of life, regardless of socioeconomic groups. (Barbosa, 2022). According to the Ministry of Health, in Brazil, 10% of the Brazilian population is obese and 40% are already overweight, therefore, half of the Brazilian population is on the obesity route (Nascimento, 2022). The pathogenesis of the disease is complex and results from an interaction between environment, lifestyle and genetic susceptibility. Obese patients are at higher risk for the development of cardiovascular diseases, gastrointestinal disorders, type 2 diabetes mellitus, musculoskeletal disorders, respiratory diseases and psychological disorders (Costa IM et al, 2021).

The use of drugs to treat obesity is increasingly frequent due to changes in eating habits, stress, sedentary lifestyle and body overvaluation (Nigro AHL, 2021).

GLP-1 analogues are potentially promising drugs for weight loss in obese or overweight adults and at least one comorbidity (Costa et al., 2021). Developed primarily for T2DM diabetes, and prescribed off-label for the treatment of obesity, GLP-1 analogues can be used long-term, or even continuously (Gomes and Trevisan, 2021). These drugs work by promoting body weight loss, suppressing glucagon release, slowing gastric emptying, improving insulin sensitivity and, consequently, reducing food consumption (Barros et al., 2021).

The GLP-1 receptor agonist liraglutide is approved for the treatment of people with obesity. However, the STEP (Semaglutide Treatment Effect in People with Obesity) study suggested greater efficacy of semaglutide, elucidating key aspects of the medical management of obesity in various races and ethnicities (Kushner RF, 2020).

This study aims to review, in an integrative way, the use of the GLP-1 analogue semaglutide in the treatment of obesity and in weight loss therapy.

METHODOLOGY

This is an exploratory literature review, organized through an integrative literature review. The collection of scientific data and the systematization of information come from scientific productions published from 2006 to 2022, in Portuguese and English, indexed in the Virtual Health Library (BVS), Scientific Electronic Library Online (SCIELO) and Google Scholar The collection of information used in the development of the work was based on the proposed theme, as well as its objectives.

RESULTS AND DISCUSSION

Food intake, an essential mechanism for energy metabolism, is regulated by complex hormonal, sensory and nervous arrangements, which range from the perception of odor, taste and appearance of the food, leading to the desire to eat (orexigenic effect), to signaling. post-digestive endocrine, which inhibit appetite, through the activation of peripheral nerve

afferents that project to the central nervous system (CNS) (Lopes et al., 2020).

The CNS receives and processes information from peripheral afferents, and then produces responses (efferents) in line with body demand. The interpretation of peripheral stimuli and generation of efferent signaling, an essential step in metabolic control, is performed by the hypothalamus and the brainstem (caudal portion) (Berthoud and Morrison, 2008).

The hypothalamus is the center that integrates peripheral signals, while the central ones are under the command of the brainstem and limbic system, thus resulting in the modulation of the stimulatory or inhibitory function of appetite. In the arcuate nucleus are concentrated the centers of hunger and satiety of the human organism. (Damiani and Damiani, 2011)

In the preprandial, prandial and postprandial period, several factors and signals integrate to stimulate the arcuate core centers to regulate appetite. The most potent orexigenic signaling comes from ghrelin, secreted by the oxyntic cells of the stomach when nutrient deprived (Lopes et al., 2020).

After ingestion, the first signal comes from stomach distention receptors, via the vagus nerve, stimulating the satiety center. Cholecystokinin (CCK) and peptide YY (PYY), along with incretins such as gastrin-inhibiting peptide (GIP) and glucagon-like peptide (GLP-1), are all secreted into the digestive tract in response to nutrients in the intestinal wall, have anorectic effects. Also leptin, secreted by adipocytes, has a potent anorectic role, and induces NPY blockade (Damiani and Damiani, 2011).

Studies have shown that neuropeptide Y (NPY) and the protein related to the Agouti gene (AgRP) in the hunger center stimulate the production of gamma aminobutyric acid (GABA), a substance capable of inhibiting the satiety center, and thus facilitating activation. of orexigenic mechanisms. On the other hand, the satiety center is composed of pro-opiomelanocortin (POMC) neurons and also of amphetamine and cocaine-related transcripts (CART), the latter with a direct anorexic role. POMC, in turn, acts as a precursor of several substances that act on melanocortin receptors (mainly MC4R), resulting in an anorectic effect (Berthoud and Morrison, 2008).

Incretins are hormones that are still the target of new studies, given that they have shown a fundamental role in appetite regulation. It is now known that they are produced and released by the digestive tract in response to the stimulation of nutrients in the intestinal wall. The main incretin is GLP-1, secreted by L cells in the ileum and colon, and GIP, secreted by K cells in the duodenum and jejunum (Lopes et al., 2020).

Currently, drugs that mimic the action of incretins are used for the treatment of type 2 diabetes mellitus (DM2), once their beneficial effects on pancreatic beta cells have been proven, by stimulating the proliferation, regeneration, and genesis of these cells (Chacra, 2006).). Complementary evidence has shown that GLP-1 also acts as a satiety in the CNS, thus interfering with appetite control (Souza, 2012).

Incretin peptides (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide, also called gastric inhibitory polypeptide [GIP]), are gastrointestinal peptides that stimulate glucose-dependent insulin secretion (Paulo et al., 2021).

Endogenous Glucagon-Like Peptide-1 (GLP-1) is a polypeptide formed by 31 amino acids, synthesized and secreted by the epithelial L cells of the small intestine and which receives stimulation by means of increased serum glucose levels.

The interaction with the GLP-1 receptor (GLP-1R) predominates in the upper intestinal tract, pancreatic islets, and visceral afferent nerves. (Reis et al., 2021). It is an endogenous incretin hormone whose action is linked to glucose metabolism. It reduces glucagon secretion by pancreatic beta cells and, consequently, hepatic gluconeogenesis, in addition to increasing insulin excretion by beta cells, helping to manage glycemia. Simultaneously, it delays gastric emptying, thus increasing its effect on satiety, since this delay allows for greater action of chemical and mechanical receptors in appetite regulation (Pasquel et al., 2021)

As the etiology of obesity is multifactorial, physical inactivity and food intake become significant targets in therapy and prevention. Currently, it is sought to use, together, pharmacological, dietary and behavioral therapies. In this sense, there is an interest in using GLP-1 analogue drugs as therapeutic agents (Pi-Sunyer et al., 2015)

Semaglutide is a long-acting GLP-1 analogue that mimics the effects of native GLP-1, which promotes TC by reducing energy intake, increasing satiety and satiety, and reducing hunger, as well as enhancing glycemic control (Knudsen and Lau, 2019).

Superior efficacy in weight loss with the GLP-1 receptor agonist semaglutide was demonstrated in STEP (Semaglutide Treatment Effect in People with Obesity) studies. In 2021, the FDA approved injection of 2.4 mg of semaglutide once a week for chronic weight management in adults who are obese or overweight and have at least one weight-related condition. The agency's decision made it the first drug approved for chronic weight management in adults with general obesity or overweight since 2014. The approval comes after the publication of the four phased trials.

3 STEP, each of which had the same co-primary endpoints of percent change in body weight and weight reduction of at least 5% from baseline to 68 weeks compared to placebo. Researchers used primary estimation to assess effects regardless of treatment interruption or rescue interventions (Schaffer, 2021).

The main STEP 1 study included 1,961 adults without diabetes who were obese or overweight with a weight-related comorbidity. The researchers randomly assigned participants "semaglutide 2.4 mg or placebo"; both groups received lifestyle intervention. The researchers found that the mean change in body weight from baseline to week 68 was -14.9% for the group and -2.4% for the placebo group, for an estimated treatment difference of -12.4 percentage points (95% CI, -13.4 to -11.5). Participants assigned to semaglutide lost an average of –15.3 kg versus –2.6 kg in the placebo group, for an estimated treatment difference of –12.7 kg (95% CI, –13.7 to –11.7) (Wilding et al., 2021).

STEP 2 included 1,210 overweight or obese adults diagnosed with type 2 diabetes. At 68 weeks, the estimated change in mean body weight from baseline was 9.6% with semaglutide 2.4 mg versus 3.4% with placebo, for an estimated treatment difference of 6.2 percentage points (CI 95%, 7.3 to 5.2). At week 68, more patients on semaglutide 2.4 mg achieved weight reductions of at least 5% versus placebo (68.8% versus 28.5%), for an OR of 4.88 (95% CI, 3, 58-6.64). One-third of subjects in this study achieved at least 20% weight loss or more (Davies et al., 2021).

STEP 3 evaluated the effect of semaglutide 2.4 mg on body weight in 611 adults with obesity but without diabetes when added to intensive behavioral therapy (30 counseling visits) with an initial low-calorie diet for 8 weeks. At 68 weeks, semaglutide plus intensive behavioral therapy and a low-calorie diet resulted in reductions in body

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weight of 16% versus 5.7% for placebo (P < 0.001) (Wadden et al., 2021).

STEP 4 evaluated continued weight loss or weight maintenance among 535 obese adults who continued semaglutide therapy beyond 20 weeks versus 268 participants who switched to placebo at 20 weeks. After randomization, the estimated mean weight change from week 20 to week 68 was -7.9% with continuation of semaglutide versus a mean increase of 6.9% among participants who switched to placebo, for a difference of -14.8 percentage points (95% CI, -16 to -13.5) (Rubino et al., 2021).

More than a third of participants who received semaglutide 2.4 mg had at least 20% weight loss and 11% of participants had at least 30% weight loss, approaching the effectiveness of bariatric surgery. However, nearly 10% of participants without diabetes and over 30% of participants with type 2 diabetes experienced less than 5% weight loss. Although the average and overall weight loss response is excellent for this drug, this distribution shows that some people will experience less than 5% weight loss (Schaffer, 2021).

CONCLUSION

Lifestyle intervention can often be insufficient to treat obesity; however, when combined with pharmacological treatments, clinically relevant weight loss and improvement in obesity complications can be achieved.

STEP studies demonstrated that semaglutide, a GLP-1 analogue, was superior in the treatment of obesity and weight loss, being reliable and effective for patients with and without diabetes, as an adjunct to intensive behavioral therapy plus hypocaloric diet, and with long-term administration for weight loss maintenance.

Monthly and brief lifestyle advice data is sufficient to produce an average weight loss of 15%. This has implications for the practical use of this drug in primary care.

REFERENCES

Barbosa MAS, Reis FRS, Marquez CO. Atenção farmacêutica no tratamento da obesidade envolvendo os análogos do Glucagon-like peptide 1 (GPL-1). Research, Society and Development 2022; 11(7): 1-12.

Barros MF et al. Ação da incretina GLP-1 e perspectivas para a redução da incidência de obesidade. Revista Transformar 2021; 15 (1): 483-497.

Berthoud HR, Morrison C. The brain, appetite, and obesity. Annu. Rev. Psychol. 2008; 59:55-92.

Brasil. Diretrizes da Sociedade Brasileira de Diabetes 2019-2020. Brasília: Sociedade Brasileira de Diabetes, 2019.

Chacra, A. R. Efeito fisiológico das incretinas. Johns Hopkins Advanced Studies in Medicine 2006; 6(7B): 613-17.

Costa IM et al. Uso de análogos de GLP-1 no tratamento da obesidade: uma revisão narrativa. Brazilian Journal of Health Review 2021; 4(2): 4236-4247.

Damiani D, Damiani D. Sinalização cerebral do apetite. Rev. Bras. Clin. Med. 2011; 9(2):138-45.

Davies M et al. 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. Lancet 2021; 397: 971–84.

Gomes HKBC, Trevisan M. O uso do Ozempic (semaglutida) como medicamento off- label no tratamento da obesidade e como auxiliar na perda de peso. Revista Artigos 2021; 29 (e7498): 1-7.

Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. Front Endocrinol (Lausanne) 2019; 10:155.

Kushner RF et al. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity 2020; 28(6):1050-1061.

Lopes GGC et al. Liraglutida e outros análogos do GLP-: nova perspectiva no tratamento do sobrepeso e obesidade. Atenas Higeia 2020; 2(3): 32-46.

Nascimento JC, Lima WMG, Trevisan M. A atuação do farmacêutico no uso da semaglutida (Ozempic): uma revisão integrativa. Brazilian Journal of Development 2021; 7(11): 1-25.

Nigro AHL. Medicamentos utilizados no tratamento da obesidade: revisão da literature. International Journal of Health Management Review 2021; 7(3): 1-17.

Paquel FJ, et al. Ensaio de alta hospitalar da liraglutida: Um estudo controlado randomizado comparando a segurança e eficácia da liraglutida versus insulina glargina para o manejo de pacientes com diabetes tipo 2 após a alta hospitalar. Diabetes Obes Metab, 2021; 23(6): 1351–1360.

Paulo MC et al. O uso do agonista do receptor GLP-1, semaglutida, como terapia para emagrecimento em pacientes obesos. Brazilian Journal of Surgery and Clinical Research 2021; 35(1): 54-59.

Pi-Sunyer X et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. New England Journal of Medicine 2015; 373(1):11-22.

Reis JRC et al. A prescrição de Peptídeo Semelhante a Glucagon 1 (GLP-1) no tratamento de pacientes portadores de diabetes tipo 2 e obesidade: uma revisão de literatura. Revista Eletrônica Acervo Médico 2022; 11:1-8.

Rubino D et al. 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(14):1414-1425.

Schaffer R. FDA approves once-weekly semaglutide for weight loss. Healio 2021. Disponível em: <https://www.healio.com/news/endocrinology/20210604/fda-approves- onceweekly-semaglutide-for-weight-loss>. Acesso em: 15 de julho de 2022.

Silva VG et al. Instruments used in psychological assessment in the treatment of Obesity: an integrative review. Research, Society and Development 2022; 11(1): 1-14.

Souza NB. Efeito das incretinas no tratamento do diabetes mellitus tipo 2. [dissertação na internet]. Criciúma (Brasil): Universidade do Extremo Sul Catarinense. Faculdade de Farmácia; 2012.

Wadden TA et al. Effect of Subcutaneous Semaglutide on Body Weight in Adults With Obesity. JAMA. 2021;325(14):1403-1413.

Wilding JPH et al. Once-Weekly Semaglutide in Adults with Overweight. N Engl J Med 2021;384:989-1002.