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NEW TREATMENTS FOR OBESITY: DOUBLE AGONIST TWO GIP/ GLP-1 RECEPTORS – TIRZEPATIDE

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Abstract: Goal: This study seeks to validate the mechanisms of action, the clinical effectiveness and the safety of Tirzepatide as a new therapeutic option for the treatment of obesity. Methodology: Review of bibliographic literature developed from September to November 2023. The research was carried out in the PubMed Central database with a search strategy: (Tirzepatide) AND (Obesity). It was found a total of 156 articles and selected, after application of criteria of inclusion and exclusion, 19 articles were included in the study. **Discussion:** Obesity is a very prevalent pathology in the world population, which induces various metabolic alterations capable of affecting quality and life expectancy. Among the research for more effective pharmacological treatments, Tirzepatide has stood out as a promising therapeutic option, with a significant reduction in body weight. This drug is a dual agonist of the GIP/GLP-1 receptor, approved for DM2 therapy by the FDA in May 2022. The different studies analyzed demonstrate effects such as improved glycemic control, reduction of HbA1c levels, reduction of triglyceride levels, Best blood pressure and insulin values in the world. Also, because it has greater activity as the GIP receptor when compared to GLP-1, it has better effects in controlling glucose and body weight. **Final considerations:** Tirzepatide demonstrated clinical efficacy in weight loss and improvement of various markers. The current studies also clarify their mechanism of action and safety, meanwhile, to the majority of the population as carriers of DM2. Logo, it is necessary to develop research that seeks to understand the use of this medication in other patient profiles, not necessarily type 2 diabetics.

Keywords: Tirzepatide, Obesity, Pharmacological Treatment.

INTRODUCTION

Obesity is characterized as a chronic disease, resulting from excessive accumulation of adipose tissue in the body (PAPAMARGARITIS D. et al., 2022). Various risk factors are associated with this condition, including harmful habits such as an inadequate diet and a sedentary lifestyle. Furthermore, both the birth with low weight and the natural development process are also contributors to the development of obesity (CAKLILI O. T. et al., 2023). The increasing prevalence of obesity at a global level is cause for concern, considering that such a condition triggers various metabolic alteration, predisposing the individual to serious conditions such as high blood pressure, type 2 diabetes mellitus and cardiovascular diseases, with a consequent reduction in the quality and expectation of life (PAPAMARGARITIS D. et al., 2022). Scientific literature highlights that the magnitude of weight loss is directly related to better metabolic and clinical parameters, promoting a better quality of life in the biological, psychological, physical and social spheres (JEON E. et al., 2023).

The therapeutic approach to obesity in adults is multifaceted, encompassing lifestyle modification – which combines nutritional reeducation with regular physical exercise –, bariatric surgery and pharmacological interventions (PAPAMARGARITIS D. et al., 2022). The World Health Organization (WHO) uses the Body Mass Index (BMI) as a parameter to classify nutritional status, with a BMI between 25 and 29.9 being considered overweight, and a BMI between 30 and 39.9 being considered obese. According to the guidelines of the American Association of Clinical Endocrinology (AACE), it is recommended that individuals with a BMI equal to or greater than 27 and comorbidities associated with obesity, in addition to adopting changes in lifestyle, may be candidates for the use of antiobesity medications, being Pharmacotherapy is specifically indicated when the BMI reaches or exceeds 30, regardless of the presence of comorbidities (BESHIR S. A. et al., 2023).

Recently, Tirzepatide, a synthetic analog of the incretins GIP and GLP-1, emerged as a new therapeutic agent, initially approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes mellitus in 2022. However, it is approved for Its use in obesity treatment in individuals who do not have DM2 is still in process (JEON E. et al., 2023). The results of the randomized, placebo-controlled clinical study (SURMONT-1) reveal the effectiveness of Tirzepatide in promoting weight loss in obese individuals without DM2, achieving and exceeding the primary objective of a 5% reduction in body weight. in comparison with the placebo group (ABDEL-MALEK M. et al., 2023).

The administration of Tirzepatide is carried out weekly, via subcutaneous injection, with dosage adjustment according to medical guidance. It is effective in promoting glycemic control and significant weight loss in patients with type 2 diabetes mellitus, being contraindicated in individuals with type 1 diabetes mellitus or in treatment with other GLP-1 receptor agonists. In cases of concomitant insulin therapy, the introduction of Tirzepatide must be carried out with caution, adjusting insulin doses to minimize the risk of hypoglycemia (POPOVICIU M. S. et al., 2023).

This article, through a literature review, aims to validate the mechanisms of action, clinical efficacy and safety of Tirzepatide as a new therapeutic alternative in obesity treatment.

METHODOLOGY

This is a narrative bibliographic review developed in accordance with the criteria of the PVO strategy, an acronym that represents: population or research problem, changes and failure. Used for research elaboration through its guiding quest: "What are the mechanisms of action of Tirzepatide, and what is its clinical efficacy and safety in obesity treatment?" In this sense, in accordance with the parameters mentioned above, the population or problem of this research refers to obese adult patients and the analysis of two possible therapeutic effects of Tirzepatide in the treatment of obesity through the decrease in body fat percentage, as well as its effects. adverse and safe. This is how you search for information carried out by means of research in the PubMed Central (PMC) database. The research terms are used in combination with the Boolean term "AND": (Tirzepatide) AND (Obesity). This search found 156 items, subsequently submitted to the selection criteria. The criteria include: articles in English and Portuguese languages published in the period from 2018 to 2023 that address topics the proposed for this research, studies of the type of systematic review, literature review, meta-analyses, observational studies and randomized clinical trials (RCT), available in full. The exclusion criteria are: duplicate articles, made available in summary form, which do not directly address the studied proposal and which do not address the other inclusion criteria. A total of 19 articles were selected to compose the present study.

DISCUSSION

Metabolically healthy obesity (MHO) is characterized by the absence of significant metabolic disorders or cardiovascular problems, despite the individual being obese or overweight. Obesity treatment offers a wide variety of approaches, which range from lifestyle interventions to healthy lifestyles. Pharmacological interventions, each with its advantages and limitations. In recent years, medical research has become more advanced in the search for more effective pharmacological treatments for obesity. Among these innovations, Tirzepatide has stood out as a promising therapeutic option. This medication represents a notable advance in obesity pharmacotherapy, targeting both obesity and the commonly associated comorbidity, type 2 diabetes (DM2), and its ability to promote weight loss often surpasses that of other medications used for this purpose. In the SURMOUNT-1 study, it was demonstrated that body weight reduction can average, on average, 10-15.9% when combined with lifestyle modifications, including diet and physical exercises. Its use is weekly, leading to nausea and its most common collateral effect (PAPAMARGARITIS D. et al., 2022; CAKLILI O. T. et al., 2023).

Among the options available for obesity treatment, we highlight: Phentermine/ Topiramate, which combines an anorectic agent with a mood stabilizer, acting on the central nervous system to reduce appetite. The average weight reduction with its use was 10.9%, and its most common side effects include constipation, insomnia, paresthesia, sinusitis and non-palate alterations (PAPAMARGARITIS D. et al., 2022). Or Orlistate, a lipase inhibitor, which reduces fat absorption, resulting in a discrete weight reduction, as long as it is accompanied by a diet with low lipid intake. Furthermore, there is an additional benefit of reducing the occurrence of cardiovascular events in patients with metabolic syndrome. Its collateral effects include steatorrheia and reduced absorption of liposoluble vitamins (CAKLILI O. T. et al., 2023). Bupropion/Naltrexone, which is in the nutritional reward system and is also used in the treatment of opioid and alcohol

dependence, is also used in depression. This combination shows reduction, on average, a 5% reduction in body weight, promoting an increase in energy expenditure, satiety and reduced appetite. The most prevalent adverse effects are headache, constipation, xerostomia, anxiety, dizziness and vomiting, which impairs cardiovascular safety and remains uncertain (PAPAMARGARITIS D. et al., 2022; CAKLILI O. T. et al., 2023). Liraglutide and Semaglutide, which act as agonists of the GLP-1 receptor, reducing caloric intake through central nervous system effects. Liraglutide, in daily dosage, was the first class to be approved for obesity treatment and can lead to an average weight reduction of up to 6%. Furthermore, it offers potential benefits in reducing the incidence of DM2 in pre-diabetics and in reducing cardiovascular events in patients with DM2 and previous cardiac diseases. The most common adverse effects are gastrointestinal, including nausea, vomiting, and diarrhea. Semaglutide, used in a weekly dose due to its prolonged period, subsequently emerged with similar benefits and adverse effects over the years of Liraglutide, in addition to promoting better control over nutrition, reducing the rate of gastric waste and reducing two dietary deficiencies, resulting in an Average reduction of 14.9% of body weight, more than the dose of Liraglutide (PAPAMARGARITIS D. et al., 2022; CAKLILI O. T. et al., 2023). Amylin, a peptide secreted by insulin in the pancreas, exerts beneficial effects in weight reduction, controlling appetite, slowing gastric emptying and inducing a feeling of satiety. This is the development of amylin analogs for obesity treatment. Pramlintide, one of its analogues, in addition to controlling appetite, also has antiglycemic effects. Another analogue, or Cagrilintide, is a promising therapy for weight loss, surpassing Liraglutide in effectiveness. There are also studies on drugs to combine Cagrilintide with Semaglutide for the treatment of obesity and diabetes. Finally, Setmelanotide, a melanocortin-4 receptor agonist, demonstrates effectiveness in weight reduction, especially in patients with specific genetic deficiencies. These advances represent promising treatments for obesity and its comorbidities (ABDEL-MALEK M. et al., 2023). It is relevant to note that all of the aforementioned treatments require the implementation of lifestyle modifications, such as alterations in diet and even physical activities, as essential complementary measures to optimize their therapeutic effectiveness (PAPAMARGARITIS D. et al., 2022; CAKLILI O. T. et al. al., 2023).

For obese patients with DM2, a comparative analysis revealed that basal insulin offers better glycemic control in the elderly, except when compared to Semaglutide or Tirzepatide. However, generally speaking, these agents demonstrate equivalent or superior glycemic control, resulting in a uniform reduction in body weight and a lower risk of severe hypoglycemia. The most recent agents, such as Semaglutide and Tirzepatide, surpass the previous representatives of the class of GLP-1RAs. Therefore, the use of IBGLMs is preferably recommended in patients with DM2 who do not achieve treatment goals, including lifestyle modifications and the use of current medications (LAZZARONI E. et al., 2021).

It is crucial to highlight that the obesity treatment choice must be based on an individualized assessment, considering the needs, preferences and clinical conditions of each patient. Furthermore, more research and clinical experience may be necessary to determine the exact position of Tirzepatide in relation to other medications not treating obesity (ABDEL-MALEK M. et al., 2023).

Tirzepatide, among the dual agonists of two GIP/GLP-1 receptor, is the most advanced in

its development and the first drug approved for DM2 therapy by the FDA in May 2022. According to the data obtained from the SURMOUNT-1 trial, or drug can become an important therapy for obesity treatment as an alternative to bariatric surgery procedures, according to Gallwitz B. (2022).

Tirzepatide is a GIP/GLP-1 chimeric peptide with a 39 amino acid peptide chain component. The linear peptide is covalently linked to a portion of the fatty diacid C20 on the side chain of the amino acid Lys20. When compared to other peptides linked to fatty acids, the side chain allows binding to albumin after skin injection, increases biological half-life and delays enzymatic degradation. The affinity of Tirzepatide's binding to GIP and GLP-1 receptors is high, according to Gallwitz B (2022). In vitro studies demonstrate the drug's ability to activate GIP receptors with comparable quality to native GIP. You have also activated the GLP-1 receiver, for 13 times more it fails in comparison with the native GLP-1. It is concluded, therefore, that Tirzepatide is capable of stimulating glucose-dependent insulin secretion by activating the GIP and/or GLP-1 receptor. Second Gallwitz B. (2022), a rodent study showed that the administration of Tirzepatide led to a loss of body weight, through mechanisms of reduced food intake and increased energy expenditure.

Copur S. et al (2023) showed in their work that Tirzepatide is a glucose-reducing drug that is at the same time. Its agonistic effects are doubled in the receptors of the glucose-dependent insulinotropic peptide (GIP) and the glucagon-like peptide 1 (GLP-1). Despite the dual actuation, there is greater activity of the GIP receptor when compared to the GLP-1 receptor, which results in an unbalanced dual agonist with the tendency of the GIP and GLP-1 receptors. In a multicenter randomized, double-blind, Phase 3 clinical trial, with 478 patients with type 2 diabetes mellitus poorly controlled by diet and exercise, and without insulin therapy, Copur et al (2023) elucidated that, during a period of 40 weeks only with the use of the drug Tirzepatide, there was an improvement in glycemic control, with reductions in our HbA1c levels (- 1.87% at a dose of 5 mg/week, – 1.89% at a dose of 10 mg/week, – 2.07% in the 15 mg/week dose, + 0.4% in the placebo group) and weight reduction (range: 7.0–9.5 kg). Furthermore, the study concluded that treatment with Tirzepatide is not inferior to treatment with Semaglutide, regardless of the dosage given, in terms of glycemic control and weight reduction during the clinical trial.

Studies over time will show that this tendentious signal has a better effect in not controlling glucose and body weight in comparison with corresponding and impartial agonists. GLP-1 is located in the distal ileum and in the colon, this being an incretin hormone, while GIP, another incretin hormone, is released by K cells, located in the duodenum and in the colon. The incretin hormones have their secretion induced by nutrients, neuroendocrine stimuli in the intestine and by microbial factors. GIP and GLP-1 increase insulin secretion, as well as its peripheral sensitivity, concomitantly with slower gastric emptying and gastrointestinal neurological regulation with regard to peristalsis. As GIP increases glucagon secretion by pancreatic alpha cells, or suppresses GLP-1, it generates a favorable balance between lipolysis and hypoglycemia, according to Copur S. et al (2023). According to Copur et al (2023), Tirzepatide for being a glycose-lowering agent that adjusts GIP and non-GLP-1, showed highly beneficial results, including two metabolic parameters, such as HbA1c, serum glucose in blood and snow. of triglycerides/lipoproteins, besides considerable weight loss, the drug may be used for the treatment of diabetes and obesity.

It is concluded that Tirzepatide is a biased and unbalanced drug that, through its dual action, has benefits in terms of glycemic control, weight reduction and improvement of metabolic parameters. Copur S. et al (2023).

Lempesis I. G. et al. (2022) showed in their work that Tirzepatide is a drug that acts as a dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). However, it is worth highlighting the effects of GIP and GLP-1 on the human body, exerting actions related to glycemic control, increased insulin secretion, cardioprotection and improved functioning of adipose tissue. To find this information, Wilson J. M. et al. (2020) revealed that to obtain these effects it is necessary to use a dose-dependent dose, observing more results in a dose of 15mg compared to 10mg, showing that Tirzepatide reduces triglyceride levels, being one of the ways to improve the lipid profile. two users of the medication. Enteroendocrine K cells are responsible for the secretion of GIP, as well as L cells, also enteroendocrine, are responsible for the secretion of GLP-1. Both molecules use incretin hormones, which support food intake and are secreted in the intestine, potentiating the mechanisms of insulin-secreting beta cells of the pancreas. The release of these hormones causes slower gastric emptying, increased insulin secretion and peripheral sensitivity. (LEMPESIS I. G. et al., 2022). Lempesis I. G. et al. (2022) highlights that drugs analogous to GLP-1 are not used in the treatment of obesity, since they present satiety-promoting and anorectic structures, influencing the food reward networks and the motivational drive to overeat. Complementing this information, Forzano I. et al. (2022) demonstrated that GLP-1 reduces food intake, delays gastric emptying and reduces levels of low-density lipoprotein (LDL), cholesterol and triglycerides. On the other hand, Campbell J. E. et al. (2023) showed in their research that GIP exerts a direct action in beta cells for insulin production and an indirect action through communication between alpha and beta cells, being considered predominant in insulin secretion. Therefore, evident hairs work of Campbell J. E. et al. (2023) and Lempesis I. G. et al. (2022) that the current Tirzepatide showed significant improvements in arterial pressure, lipid profiles and insulin values in the body. Potentializing this fact, it was observed in these investigations that patients who used Tirzepatide in doses of 10mg and 15mg in comparison with the placebo obtained a reduction of approximately 15% and 20% in weight loss respectively. It is also worth noting that after receiving Tirzepatide, you receive a Fast Track designation for obesity treatment by the Food and Drug Administration.

According to Gallwitz B. (2022), the neuroendocrine cells of the intestinal mucosa secrete incretin hormones, which are potent stimulators of postprandial insulin secretion, responsible for about 70% of postprandial secretion. This phenomenon has been described as an effect of incretin, and also explains that glucose ingested orally leads to a higher insulin response, when compared to that administered intravenously. However, the main incretin hormones are the glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP).

It is worth highlighting that GIP loses its insulinotropic effect in patients with DM2 and chronic hyperglycemia, while GLP-1 is capable of maintaining the stimulation of insulin release. Consequently, parenteral administration of GLP-1 stimulates insulin secretion, being capable of normalizing plasma glucose. However, or native GLP-1, because it is degraded in minutes by the enzyme dipeptidyl-peptidase-IV (DPP-4), is not suitable for treatment in hyperglycemic individuals with DM2, according to Gallwitz

B (2022).

According to Gallwitz B. (2022), healthy volunteers and patients with DM2 in the SURPASS-4 study have comparative pharmacokinetics. Exposure to the drug increases in proportion to the dose following subcutaneous injection, regardless of the location of application. The maximum plasma concentration time (tmax) varies from 8 to 72 hours, with bioavailability being 80%. After 4 injections, one each week, the balance in the plasma concentrations has been achieved. About 99% of bioavailable Tirzepatide is bound to plasma albumin. The hydrolysis of the amide and the proteolytic cleavage of the structure of the Tirzepatide peptide, as well as the β oxidation of the portion of C20 fatty acid, are only responsible for the metabolic clearance of the drug. These metabolites are only excreted through urine and feces. My life span is approximately 5 days. However, given this information, I was given a subcutaneous injection regimen once a week. The pharmacokinetics of Tirzepatide are slightly altered by age, sex, race, body weight, ethnicity, or kidney and liver function. According to recent studies, the activity of the CYP enzyme is not influenced by Tirzepatide. It is worth noting that the absorption of drugs or concomitant therapy with Tirzepatide may be reduced or delayed; This effect is explained by the delay in gastric evacuation due to Tirzepatide.

FINAL CONSIDERATIONS

The analysis of this study on obesity highlights the importance of an open and personalized therapeutic approach. Recognizing obesity as a serious global health problem, there is an obvious need for treatments that go beyond changes in diet and physical exercise. A holistic approach, considering genetic, psychological, social and environmental factors, is essential. Among emerging therapies, Tirzepatide has shown significant potential. This medication, acting as a dual agonist of two GLP-1 and GIP receptors, plays an important role in the regulation of appetite and does not control glycemia. Its effectiveness in promoting weight loss and HbA1c reduction becomes a valuable addition to the arsenal against obesity. The selection of Tirzepatide must be individualized, taking into consideration, the patient's medical history, associated comorbidities and tolerance of side effects.

The approach to treating obesity is not limited to weight loss, but also aims to improve the quality of life and reduce the risks associated with health. Recognizing obesity as a continuous and personalized journey, Tirzepatide represents an important innovation that can improve the health and well-being of the patient in a comprehensive way.

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