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IMPACT OF SEMAGLUTIDE ON GLYCEMIC CONTROL AND POST-PRANDIAL GLUCOSE REDUCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract: **Objective**: To evaluate the potential of semaglutide as an adjuvant therapy in glycemic control and in the reduction of postprandial glycemia in patients with type 2 Diabetes Mellitus. **Methodology**: This narrative bibliographic review, conducted from April to May 2023, was developed according to the PVO strategy, an acronym that represents: population or research problem, variables and outcome. The literature search was performed on the PubMed database. After applying the inclusion and exclusion criteria, 17 articles were selected, published between 2017 and 2022, to compose the collection of this study. **Results**: Semaglutide has proven benefits for diabetic patients due to its ability to significantly reduce postprandial blood glucose by delaying gastric emptying, enhancing insulin secretion and inhibiting the secretion of the hormone glucagon. **Final considerations:** Despite being a recent drug, the literature converges to the consolidation of semaglutide as a promising medication in postprandial glycemic control in patients with type 2 Diabetes Mellitus, contributing to a better prognosis of the disease.

Keywords: Semaglutide; Glycemic control; Postprandial blood glucose.

INTRODUCTION

Type 2 Diabetes Mellitus (DM2) is a complex chronic condition that significantly impacts global health. It is characterized by insulin resistance and relative or partial deficiency in the secretion of this hormone by pancreatic beta cells, resulting in dysregulation of glycemic control. Inadequate glycemic control and subsequent prolonged hyperglycemia can lead to micro and macrovascular complications, in addition to an increased risk of hypertension, due to decreased production of nitric oxide by the endothelium (NIMAN S. et al., 2021).

To maintain adequate glycemic control,

T2DM patients need to adopt a multifaceted approach, which includes lifestyle changes and drug interventions (KIM H. S.; JUNG C.H., 2021). Within the wide range of drug therapies available, GLP-1 receptor agonists (GLP-1RAs) have stood out for their potential to regulate blood glucose without the risk of hypoglycemia (NIMAN S. et al., 2021; GOMEZ-PERALTA F., ABREU C., 2019).

The semaglutide, a member of the GLP-1RA family, is notable due to its availability in both subcutaneous and oral forms. The latter provides a valuable alternative for patients who have difficulties with injectable treatment, helping to improve treatment adherence (NIMAN S. et al., 2021). Both forms of administration are effective and have similar pharmacokinetic profiles after absorption (ARODA V. R. et al., 2022). In addition to its ease of administration, semaglutide has shown significant effects in reducing glucose, in addition to providing increased sensitivity to insulin, possibly due to weight loss associated with the treatment (KNUDSEN L.B.; LAU J., 2019).

The aim of this narrative review is to analyze in depth the impact of semaglutide on glycemic control and reduction of postprandial glycemia in patients with T2DM. And also compare the effectiveness of semaglutide with other available therapies, investigate the underlying mechanisms of action that contribute to these effects, and discuss the clinical and therapeutic implications of these findings for the general management of type 2 diabetes mellitus.

METHODOLOGY

The present study is a narrative bibliographic review carried out from April to May 2023, developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used for the development of the research through its guiding question: "What is the impact of semaglutide on glycemic control and reduction of postprandial glycemia in patients with type 2 diabetes mellitus, and how does this compare with other available therapies?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients with type 2 diabetes mellitus who used semaglutide to analyze its impact on the reduction of postprandial glycemia.

The literature search was carried out in the PubMed database. The following descriptors in Health Sciences (DeCS) were used in different combinations: ''Semaglutide'', ''Glycemic Control'' and ''Postprandial blood glucose''. The inclusion criteria defined for the selection of articles were: Reviews, systematic reviews, cohort studies, clinical trial, randomized clinical trial, meta-analysis, articles published in English, articles available in full that portray the theme addressed and articles published and indexed in these databases in the last 5 years. Exclusion criteria were: case reports, duplicate articles, available in summary form, or that do not directly address the studied proposal, and finally that did not meet the other inclusion criteria mentioned.

After associating the descriptors used in the searched bases, a total of 114 articles were found which, after applying the mentioned inclusion and exclusion criteria, led to the selection of 17 articles, published between 2017 and 2022, to compose the collection of the present study. Such articles were subjected to careful reading to collect data relevant to this research and the results were presented in a descriptive way, seeking to understand the impact of semaglutide in reducing postprandial glycemia in patients with type 2 diabetes mellitus, its clinical manifestations and complications, such as is its physiological action, in addition to the comparison of its

RESULTS

CLASS AND MECHANISMS OF ACTION OF GLP-1 RECEPTOR AGONISTS

The pharmacological treatment of T2DM has a wide variety of classes available. However, in recent years, the class of glucagon-like peptide-1 (GLP-1) analogues has been highlighted for its benefits (WEBB N. et al., 2018; ALSUGAIR H.A. et al., 2021). The relevance of this class is attributed to several characteristics: potential for reducing body weight; mitigation of cardiovascular risks resulting from micro and macrovascular complications; improved functional efficiency of pancreatic beta cells; delay in gastric emptying time; decreased risk of hypoglycemic events; and efficacy in maintaining glycemic stability (WEBB N. et al., 201; ZHONG P. et al., 2021).

GLP-1 analogues act on pancreatic beta cells to increase glucose-dependent insulin production while simultaneously restricting production of the hormone glucagon by pancreatic alpha cells. However, it is noteworthy that this effect on glucagon is not observed during hypoglycemic events (WEBB N. et al., 2018; NAUCK M.A. et al., 2021). In addition, there is an effect of these drugs on gastric emptying time, which is prolonged. The combination of these effects contributes to reducing the glycemic index and extending the period of satiety (NAUCK M.A. et al., 2021; IORGA R.A. et al., 2020).

Currently, these drugs are available in injectable form, except for semaglutide, which is also provided in an oral formulation. The class includes semaglutide, exenatide, lixisenatide, among others (ZHONG P. et al., 2021; NAUCK M.A. et al., 2021; ANDERSEN A. et al. 2021; DAVIES M. et al., 2017). The mechanisms of these drugs can be subdivided into short-acting and long-acting, with the subcutaneous formulation semaglutide being classified as long-acting, with high intermolecular affinity, which makes its effects last approximately 7 days (ZHONG P. et al., 2021). In addition, it is important to highlight that the drugs of the GLP-1 class can be used together with oral hypoglycemic agents and insulin therapy (NAUCK M.A. et al., 2021).

SEMAGLUTIDE AND GLYCEMIC CONTROL AND POSTPRANDIAL GLYCEMIC REDUCTION

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue with structure and pharmacokinetics that differ from those of other GLP-1 receptor agonists (GLP-1 RAs), since it shows about 94% homology sequence with native GLP-1 and high affinity for the GLP-1 receptor (WEBB N. et al., 2018; ZHONG P. et al., 2021; GOMEZ-PERALTA F., ABREU C., 2019). Additionally, it also suppresses appetite, leading to reduced energy intake through direct and indirect effects on the hypothalamus and postrema area of the brain, both of which are involved in regulating appetite and energy metabolism(ZHONG P. et al., 2021; NAUCK M.A. et al., 2021). From a pathophysiological standpoint, weight control and glycemic control appear to be mutually reinforcing, and injectable semaglutide has been shown to be more effective in maintaining long-term glycemic control and reducing body weight than other GLP-1 RAs, including liraglutide (ALSUGAIR H.A. et al., 2021).

Postprandial glycemia is an important risk factor for the development of complications related to diabetes mellitus. Fasting hyperglycemia and postprandial hyperglycemia are risk factors that can aggravate the condition of patients with DM2, and their homeostasis is essential to

reduce complications (DAHL K. et al., 2021). Among them, macrovascular alterations stand out, such as cardiovascular (CV) death, cerebrovascular accidents, peripheral arterial disease and microvascular disorders, such as diabetic retinopathy, diabetic peripheral neuropathy and diabetic nephropathy. In addition, high blood glucose can reduce the production of nitric oxide by the endothelium of blood vessels, which results in damage to the mechanism of vascular dilation, which may cause increased pressure in blood vessels, by increasing vascular resistance and consequently greater risk of hypertension. (NIMAN S. et al., 2021).

Currently, semaglutide is available in subcutaneous and oral presentations. Subcutaneous semaglutide is a long-acting GLP-1 analogue that can be used only once a week. In the oral presentation, semaglutide was co-formulated with sodium N-8-[2-hydroxybenzoyl] amino caprylate (SNAC), requiring daily administration (NAUCK M.A. et al., 2021; ANDERSEN A. et al 2021; DAVIES M. et al., 2017).

Long-acting GLP-1 analogues are capable of producing sustained stimulation of the GLP-1 receptor. This stimulation allows these drugs to lower both fasting and postprandial glucose by increasing insulin secretion and decreasing glucagon secretion. Therefore, long-acting GLP-1 analogues, such as semaglutide, promote effective glycemic control, with a significant reduction in HbA1c, acting both in controlling fasting and postprandial glycemia (NAUCK M.A. et al., 2021).

Diabetic patients with HbA1c of 8.0%, initially controlled only with exercise and diet, showed a decrease of 1.4% at 26 weeks and 1.6% at 30 weeks of monotherapy with oral semaglutide (14 mg) or subcutaneous (1.0 mg) (ZHONG P. et al., 2021). The incorporation of semaglutide as a second-line drug in the T2DM therapeutic regimen

improves glycemic control in patients who did not reach the HbA1c target (< 6.5%) with conventional treatments for T2DM alone (ARODA V. R. et al., 2022; WRIGHT E.E.J.; ARODA V.R., 2020). Combining insulin with a 7 or 14 mg oral placebo or semaglutide resulted in a 0.1%, 0.9%, and 1.3% reduction, respectively, in HbA1c levels after 26 weeks (OKAMOTO A. et al., 2021). A reduction in HbA1c was also observed in individuals with T2DM not controlled by insulin or metformin after the use of semaglutide (WRIGHT E.E.J; ARODA V.R., 2020; ZHONG P. et al., 2021).

Compared to other GLP-1 analogues such as liraglutide, exenatide, empagliflozin, sitagliptin and dulaglutide, the hypoglycemic effects achieved by semaglutide are similar or even more significant (ARODA V. R. et al., 2022). A study by Niman S. et al. (2021) proposed switching from conventional GLP-1 to subcutaneous semaglutide (0.92 mg) aimed at controlling T2DM. As a result, the authors observed a reduction from 6.72% to 6.45% in the HbA1c level after 3 months. At 6 months, 60% of these patients achieved HbA1c < 6.5%. This can be explained by the fact that, unlike other GLP-1 RAs, semaglutide exerts a direct action on the central nervous system, in regions such as the brainstem, lateral septal nucleus and hypothalamus.

One study analyzed the response of hormones that counter-regulate blood glucose homeostasis, especially glucagon, during the induction of hypoglycemia in patients using semaglutide, with an escalating dose every 4 weeks (0.25 - 0.5 - 1.0 mg) compared to placebo. It was observed that, although semaglutide acts by inhibiting glucagon secretion, during hypoglycemia there was an increase in the secretion of this hormone in both studied groups (semaglutide and placebo), in addition to a reduction in C-peptide levels (a marker of insulin production endogenous). These changes demonstrate that the

response to glucagon during hypoglycemia is not affected by semaglutide and, in the hypoglycemic condition, there is a reduction in the insulinotropic activity of semaglutide (KORSATKO S. et al., 2018).

The use of semaglutide has proven benefits for diabetic patients, thanks to its ability to significantly reduce postprandial blood glucose. According to Dahl K. et al. (2021) and Cornell S. et al. (2020), the ability of semaglutide to reduce blood glucose levels after meals is due to the delay in gastric emptying, the improvement of insulin secretion and the inhibition of the secretion of the hormone glucagon. These studies reinforce that the use of this glucagon-like peptide-1 (GLP-1) receptor agonist is an effective therapeutic option for the control of postprandial glycemia, which, in addition, presents a low risk of hypoglycemia compared to other secretagogues.

Regarding the semaglutide mechanisms that impact the reduction of postprandial glycemia, it is considered that the delay of gastric emptying is more important than the release of insulin in controlling this postprandial state (OKAMOTO A. et al., 2021). This happens because the reduction in the speed of gastric emptying results in a more prolonged absorption (DAHL K. et al., 2021). Furthermore, according to Cornell S. et al. (2020), this mechanism also reflects a slower passage of glucose to the duodenum. In terms of clinical applicability, oral treatment with semaglutide 14 mg has been shown to have a significant impact on fasting and postprandial glucose and lipid metabolism, and on delayed gastric emptying, particularly during the first hour after a meal (DAHL K. et al., 2021).

FINAL CONSIDERATIONS

Semaglutide, along with other GLP-1 receptor agonists (GLP-1 RAs), provides effective glycemic control and weight reduction with low risk of hypoglycemia in patients with type 2 diabetes mellitus., Semaglutide has shown promise, showing superiority in both postprandial and long-term glycemic control, in addition to more pronounced hypoglycemic effects compared to other secretagogues.

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