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THE EFFICACY OF ORAL SEMAGLUTIDE IN WEIGHT LOSS AND GLYCEMIC CONTROL

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Abstract: Goal: To analyze the effectiveness of oral Semaglutide in controlling diabetes and obesity, evaluating its reduction in body weight and glycated hemoglobin levels. Methods: The methodological approach of the study is a qualitative and descriptive bibliographic compilation, through an integrative literature review. The databases used for the research were the National Library of Medicine (PUBMED) and the Virtual Health Library (VHL). The descriptors used were: "semaglutide", "oral" and "weight", using the Boolean operator "AND". The inclusion criteria were studies published in the last five years, of the types Clinical Trial, Controlled Clinical Trial and Randomized Controlled Trial, in the English language and free access. Results: The impacts of using oral Semaglutide on weight loss and glycated hemoglobin levels were evaluated, showing positive results in all articles covered. The effectiveness of the treatment also showed a relationship with the dosage, showing better results at the maximum dose (14mg). Final considerations: Thus, it was observed that, with the use of this new route of administration of Semaglutide, favorable results are maintained for glycemic control and weight loss.
Keywords: Obesity, Diabetes Mellitus, Antiobesity Drugs, Hypoglycemic Agents.

INTRODUCTION

The increasing incidence of diabetes mellitus, as well as obesity, led to both being recognized as epidemics by the World Health Organization. Obesity is one of the biggest risk factors for the development of glucose intolerance and type 2 diabetes (DM2), and its prevalence around the world generates an alarming increase in the risk of cardiovascular morbidity and mortality (Cholot A, et al., 2018; Sala LL. and Pontiroli AE, 2020).

The measurement of Body Mass Index (BMI) is the most widely used assessment criterion to quantify and diagnose obesity, being defined as obesity when the individual's BMI value is ≥ 30kg/m2. Diabetes mellitus has several parameters for diagnosis, among which the most commonly used are fasting plasma glucose ≥ 126mg/dl, the oral glucose tolerance test with blood glucose ≥ 200mg/dl 2 hours after ingestion of 75g of glucose and free plasma glucose ≥200mg/dl, in addition to the glycated hemoglobin index (HbA1c), which despite not being used as a diagnosis, is the main parameter used to evaluate disease control (Fruh, SM., 2017; Gross JL, 2002).

The treatment of these two pathologies mirrors each other in many ways. Lifestyle changes are mandatory, including dietary adjustments, behavioral changes and the incorporation of physical exercise into daily life (Boles A, et al, 2017).

However, in relation to pharmacological treatment, most drug classes involved in the management of DM2 promote weight gain (Insulin, Sulfonylureas, among others). It would be important, however, that antihyperglycemic therapies do not contribute to overweight or obesity and, ideally, even promote weight loss (Eliaschewitz FG. and Canani LH, 2021).

With the aim of minimizing such unwanted side effects, new drugs were developed for the treatment of DM2, incretin modulators. These include: sodium glucose cotransporter 2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide 1 analogues (GLP-1 analogues); (Reddy PL and Isaacs D, 2015).

Incretins are hormones produced and released by the gastrointestinal tract when there is nutrient stimulation in the intestinal wall and are fundamental in regulating appetite. One of the main incretins is GLP-1, which is secreted by L cells in the ileum and colon (Lopes GGC, et al, 2020).

GLP-1 acts by reducing the secretion of

glucagon by pancreatic alpha cells, which leads to hepatic gluconeogenesis. It also stimulates the excretion of insulin by beta cells, helping with glycemic control. Furthermore, concomitantly, GLP-1 delays gastric emptying and decreases appetite (Costa IM, et al, 2021).

The first synthetic analogue of GLP-1, Exenatide, was approved by the Food and Drug Administration (FDA) in 2005 and in 2016 by the National Health Surveillance Agency (ANVISA), with daily subcutaneous administration. The new drug was used to treat diabetes and also showed favorable results for weight reduction. Since then, six other analogues have been introduced onto the market, four of which introduced a longer action as an innovation, which allowed a more comfortable dosage, with weekly subcutaneous application.

These medications are albiglutide, dulaglutide, exenatide and semaglutide (Bucheit JD, et al, 2020; Guimarães APSS, et al, 2022).

Subcutaneous Semaglutide showed superiority over other injectable therapies in its class. The drug promotes a reduction in appetite and reduces the desire for foods with a high lipid content, which leads to weight loss due to a calorie deficit. Furthermore, it also acts on plasma lipids, reduces systolic blood pressure and attenuates inflammation (Wright EE and Aroda VR, 2020).

Despite the many benefits of incretin analogues, subcutaneous administration remains a barrier to patient compliance. Minimal modifications were made in an effort to extend its bioavailability to be administered once a week, however converting a GLP-1 RA into tablet form presents a challenge as the digestion and absorption of an active compound is more complex, where it has to withstand the acidity of the stomach and penetrate intestinal structures with low permeability, maintaining a consistency that can eventually be circulated in the body (Bucheit JD, et al, 2020; Gupta V, et al, 2013).

Previous attempts to develop oral GLP-1 analogues have been unsuccessful due to absorption and degradation in the stomach. However, a new joint formulation of Semaglutide and sodium N-[8-(2-hydroxybenzoylamino] caprylate (SNAC) can overcome these barriers (Bucheit JD, et al, 2020).

Approved in September 2019 by the FDA and in April 2022 by ANVISA, Semaglutide Oral, branded Rybelsus, arrived on the market, with the innovation of a minimally invasive therapeutic approach. Despite this, the performance of this new formulation remains questioned (Guimarães APSS, et al, 2022). Therefore, the objective of this review was to analyze the effectiveness of oral Semaglutide in controlling diabetes and obesity, evaluating its reduction in body weight and glycated hemoglobin levels.

METHODS

The methodological approach of the study is a qualitative and descriptive bibliographic compilation, through an integrative literature review. The databases used for the research were the National Library of Medicine (PUBMED) and the Virtual Health Library (VHL). The search was carried out using the descriptors: "semaglutide", "oral" and "weight", using the Boolean operator "AND".

The literature review was carried out following the following steps: designation of the topic; definition of eligibility parameters; definition of inclusion and exclusion criteria; verification of publications in databases; analysis of the information found; analysis of the studies found and presentation of the results.

The inclusion criteria were studies published in the last five years, of the types Clinical Trial, Controlled Clinical Trial and

Randomized Controlled Trial, in the English language and free access. Literature reviews, summaries, case reports and meta-analyses were excluded, as well as duplicate articles that did not apply to the topic or that did not address the oral route of administration of Semaglutide.

RESULTS

A total of 270 results were generated from the initial search, of which 138 belong to the Pubmed database and 132 to the VHL database. After filtering searches older than 5 years, 135 and 129 titles remained, respectively. When selecting only those that corresponded to clinical trials and controlled clinical trials, 23 and 58 were counted, respectively.

By selecting only articles in the English language, 22 and 56 remained. By including only free full-text articles, these numbers were reduced to 13 and 39.

Finally, applying the exclusion criteria, nine articles were selected from Pubmed and seven articles from the VHL, totaling a complete analysis with 16 articles, as shown in figure 1.

After fully reading the selected works and evaluating the results, a comparative table was organized, which consists of: main author and year of publication, the number of individuals covered in the studies, the average weight reduction and the average reduction in glycated hemoglobin as represented in Table 1.

In relation to the 16 selected articles, 14 report positive impacts of the use of oral Semaglutide on both body weight and glycated hemoglobin index, suggesting its effectiveness in the treatment of obesity and diabetes mellitus.

Only one of the articles did not report changes in glycated hemoglobin, just as only one article did not mention changes in body weight.

Of the 16 articles, six recorded changes in weight and glycated hemoglobin associated with one or more dosages among the 3 standard doses (3mg, 7mg and 14mg), indicating progressive growth in results according to the dose increase.

10 of the studies, in turn, recorded their results using a single average value or a single numerical range, without specifying the doses.

One article described weight reduction only in percentage terms and not in kilograms.

None of the studies reported weight gain or an increase in glycated hemoglobin levels in the patients observed.

DISCUSSION

Of the selected articles, 15 consider changes in HbA1c, with reductions ranging between 0.5% and 1.92%. According to Roder ME, et al. (2019), at the same time that Semaglutide enhances insulin secretion by pancreatic beta cells, it suppresses glucagon secretion by pancreatic alpha cells and inhibits the rate of gastric emptying. The combined effect results in a reduction in glycemia by increasing glucose elimination in peripheral tissues, reducing hepatic glucose production and reducing postprandial glucose (Roder ME, et al, 2019).

Body weight is also addressed by 15 articles, not being mentioned by just one. With great variability in its results, reductions of 0.1kg to 6.9kg are observed. Weight loss during the use of semaglutide is caused by the delay in gastric emptying in the first postprandial hour, promoting early satiety, and by the action on GLP-1 receptors present in the arcuate nucleus of the hypothalamus, inhibiting appetite (Ard J, et al, 2021).

Six articles specified the doses used (3mg, 7mg and 14mg) and their respective impacts on glycated hemoglobin and body weight, recording progressive growth as the dose increased. The results are corroborated by Rasmussen MF, et al. (2020), who reports that mean HbA1c and mass levels decreased

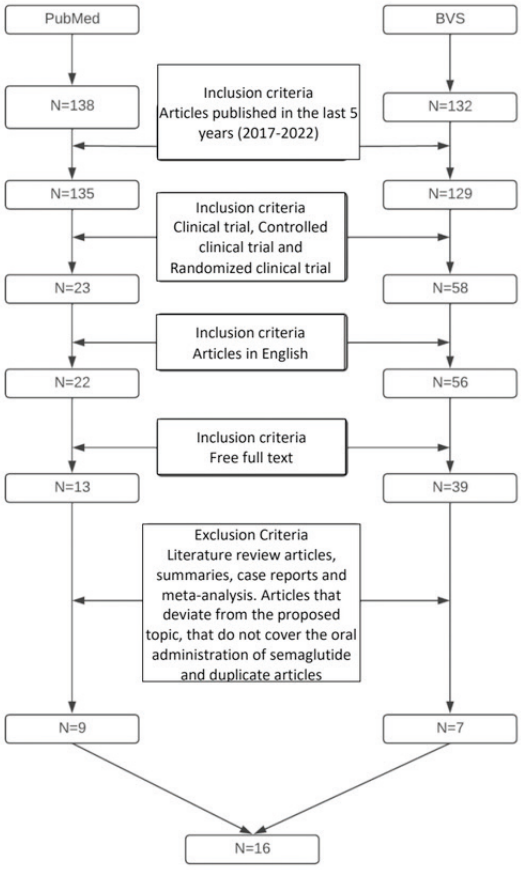

Figure 1: Flowchart of identification and selection of articles selected in the PubMed and Virtual Health Library databases.

*N= number of articles. SOURCE: Lopes CA, et al., 2022

AUTHOR AND YEAR	N= NUMBER OF INDIVIDUALS	AVERAGE WEIGHT REDUCTION	MEAN REDUCTION IN GLYCATED HEMOGLOBIN
Araki E, et al. (2021)	707	-0.6kg (3mg) -1.45kg(7mg) -2.75kg (14mg)	-0.7% (3mg) -1.1% (7mg) -1.55% (14mg)
Aroda VR, et al. (2019)	703	-0.1(3mg) -0.9(7mg) -2.3kg(14mg)	-0.7% (3mg) -1.2% (7mg) -1.4% (14mg)
Aroda VR, et al. (2021)	782	-	-0.6 – 1.1%
Buse JB, et al. (2020)	253	-2.8kg	-1.5%
Davies M, et al. (2017)	632	-2.1 – -6.9kg	-1.9%
Gibbons C, et al. (2020)	15	-2.7kg	-
Mosenzon O, et al. (2020)	1754	-4.2kg	-1.0%
Overgaard RV, et al. (2021)	2345	-3.77% of body weight	-1.58%
Pieber TR, et al. (2019)	253	-2.9kg	-1.4%
Pratley R, et al. (2019)	285	-4.4kg	-1.2%
Pratley RE, et al. (2021)	2836	-2.2 – 5kg	-1.1 – 1.5%
Rodbard HW, et al. (2019)	412	-3.8kg(14mg)	-1.3%(14mg)
Rosenstock J, et al. (2019)	1864	-1.2kg (3mg) -2.2kg (7mg) -3.1kg(14mg)	-0.6% (3mg) -1.0% (7mg) -1.3%(14mg)

Yale JF, et al. (2021)	452	-4.3kg	-0.9%
Yamada Y, et al. (2021)	458	-0.55kg (3mg) -1.07kg (7mg) -2.35kg (14mg)	-1.12% (3mg) -1.6% (7mg) -1.92% (14mg)
Zinman B, et al (2019).	731	-1.4kg (3mg) -2.9 kg (7mg) -3.7kg (14mg)	-0.5%(3mg) -0.9%(7mg) -1.2% (14mg)

Table 1: Schematization of the results of the articles according to main author and year of publication, number of individuals covered, average weight reduction and average reduction in glycated hemoglobin.

*mg: milligrams; kg: kilograms. SOURCE: Lopes CA, et al., 2022.

in a dose-dependent manner (from - 0.7 to -1.9% and -0.8kg to -3.7kg), with notably more significant outcomes with two higher doses (Rasmussen MF, et al, 2020).

According to Bruno BJ, et al. (2013), even with a large number of therapeutic proteins being discovered each year, oral administration continues to be a barrier. As a whole, protein and peptide drugs have low bioavailability when administered orally due to problematic barriers, including gastrointestinal proteases, epithelial barrier, and efflux pumps (Bruno BJ, et al, 2013). Despite this, the results of this study showed that of the 16 articles selected, all had positive effects on the variables addressed, suggesting that the oral formulation of Semaglutide did not impede the good performance of the drug, despite the various limitations of this route.

FINAL CONSIDERATIONS

Oral semaglutide has broad value in the future treatment of diabetes mellitus and obesity. Thus, it was observed that, with the use of this new route of administration of the drug, favorable results are maintained for glycemic control and weight loss. Therefore, it is in the interest of public health that new scientific research into this medicine is encouraged and that health professionals are informed about its therapeutic value.

REFERENCES

Araki E, et al. Efficacy and safety of oral semaglutide in Japanese patients with type 2 diabetes: A post hoc subgroup analysis of the PIONEER 1, 3, 4 and 8 trials. Diabetes Obesity Metab 2021;23(12):2785–2794.

Ard J, et al. Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists. Adv Ther, 2021;38(6):2821–2839.

Aroda VR, et al. Insights into the early use of oral semaglutide in routine clinical practice: The IGNITE study. Diabetes Obesity Metab, 2021;2177–2182.

Aroda VR, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care, 2019;1724–1732.

Boles A, et al. Dynamics of Diabetes and Obesity: Epidemiological Perspective. Biochim Biophys Acta, 2017;1863(5):1026–1036.

Bruno BJ, et al. Basics and recent advances in peptide and protein drug delivery. Ther Deliv, 2013;4(11):1443–1467.

Bucheit JD, et al. Oral Semaglutide: A Review of the First Oral Glucagon-Like Peptide 1 Receptor Agonist. Diabetes Technology & Therapeutics, 2020;22(1):10–18.

Buse JB, et al. Long-term efficacy and safety of oral semaglutide and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52-week, randomized, open-label extension of the PIONEER 7 trial. BMJ Open Diabetes Res Care 2020;8(2): e001649.

Chobot A, et al. Obesity and diabetes—Not only a simple link between two epidemics. Diabetes Metab Res Rev, 2018;34(7): e3042.

Davies M, et al. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes. JAMA, 2017; 318(15):1460–1470.

Eliaschewitz FG e Canani LH. Advances in GLP-1 treatment: focus on oral semaglutide. Diabetology & Metabolic Syndrome, 2021;13(1):99-108.

Gibbons C, et al. Effects of oral semaglutide on energy intake, food preference, appetite, control of eating and body weight in subjects with type 2 diabetes. Diabetes Obes Metab, 2021;23(2):581–588.

Gross JL, et al. Diabetes Melito: Diagnóstico, Classificação e Avaliação do Controle Glicêmico. Arq Bras Endocrinol Metab, 2002;46:16–26.

Guimarães APSS, et al. A semaglutida oral irá substituir a cirurgia metabólica? Revisão sistemática: Will oral semaglutide replace metabolic surgery? Systematic review. STUDIES IN HEALTH SCIENCES, 2022;3(2):736–757.

Gupta V, et al. Glucagon-like peptide-1 analogues: An overview. Indian J Endocrinol Metab, 2013;17(3):413–421.

Lopes GGC, et al. Liraglutida e outros análogos do glp-1: nova perspectiva no tratamento do sobrepeso e obesidade. Revista Atenas Higeia, 2020;2(3):36–42.

Mosenzon O, et al. Oral semaglutide in patients with type 2 diabetes and cardiovascular disease, renal impairment, or other comorbidities, and in older patients. Postgrad Med, 2020;37–47.

Overgaard RV, et al. Levels of circulating semaglutide determine reductions in HbA1c and body weight in people with type 2 diabetes. Cell Rep Med 2021;2(9):100387.

Pieber TR, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol, 2019;528–539.

Pratley RE, et al. Oral Semaglutide Reduces HbA1c and Body Weight in Patients with Type 2 Diabetes Regardless of Background Glucose-Lowering Medication: PIONEER Subgroup Analyses. Diabetes Ther, 2021;1099–1116.

Pratley RE, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet, 2019;394(10192):39–50.

Rasmussen MF, et al. The development of oral semaglutide, an oral GLP-1 analog, for the treatment of type 2 diabetes. Diabetol Int, 2020;11(2):76–86.

Reddy PL e Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drugs Context 2015;4:212-283.

Rodbard HW, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care, 2019;2272–2281.

Roder ME, et al. Clinical potential of treatment with semaglutide in type 2 diabetes patients. Drugs Context, 2019;8:212-585.

Rosenstock J, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA, 2019;321(15):1466–1480.

Sala L, et al. Prevention of Diabetes and Cardiovascular Disease in Obesity. Int J Mol Sci, 2020;21(21):8178-8201.

Wright EE e Aroda VR. Clinical review of the efficacy and safety of oral semaglutide in patients with type 2 diabetes considered for injectable GLP-1 receptor agonist therapy or currently on insulin therapy. Postgrad Med 2020;132(sup2):26–36.

Yale JF, et al. Use of once-weekly semaglutide in patients with type 2 diabetes in routine clinical practice: Results from the SURE Canada multicentre, prospective, observational study. Diabetes Obes Metab2021;2269–2278.

Yamada Y, et al. Efficacy and safety of oral semaglutide by baseline age in Japanese patients with type 2 diabetes: A subgroup analysis of the PIONEER 9 and 10 Japan trials. Diabetes Obes Metab 2022;24(2):321–326.

Zinman B, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. Diabetes Care 2019;42(12):2262–2271.