THE LIRAGLUTIDE USE IN THE TREATMENT OF TYPE TWO DIABETES AND OBESITY: LITERATURE REVIEW

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ABSTRACT

The Diabetes *Mellitus* type two (DM2) is a chronic, progressive, multifactorial, non-transferable, is related to a group of syndromes or metabolic disorders whose main features to non-production of insulin by the pancreas or the blocking of the cellular response to insulin produced, then taking place a deficiency in the secretion and/ or action of the hormone insulin. The latest class introduced on the market is based on the activity of incretin (hormones produced by the gastrointestinal tract, which enhance the secretion of insulin after food intake). The Liraglutide is an analog of glucagon-like peptide-1, and represents an innovative, secure and sustainable strategy for patients with DM2, it is an incretin hormone that is released from the gastrointestinal tract in order to increase insulin secretion by pancreatic beta cells. Glucagon-like peptide-1 significantly increases insulin-dependent glucose secretion, decreases glucagon secretion, increases sensitivity to insulin, slows gastric emptying, and decreases the appetite with agonist action on its receptors. This study aimed to review the literature through the use of liraglutide in the treatment of DM2, as well as investigate the prospects and security of the use of liraglutide in obesity and contribute to subject the technical upgrade.

KEYWORDS: Diabetes *Mellitus* type two, obesity, analogue of glucagon-like peptide-1, Liraglutide.

1. INTRODUCTION

Physical inactivity triggered by modern life and then obesity poor diet contributes directly in the etiology of diabetes mellitus type 2 (DM2) in adults, regardless of body mass index or family history of diabetes. It is known that this metabolic disorder is considered a global pandemic whose prevalence has reached epidemic proportions quickly, the main disease involving the endocrine pancreas and today is one of the most important causes of morbidity and mortality[1 2,3,4].

The DM2 is one of the most frequent chronic diseases and continues to grow in number, social and economic importance, thus representing a huge economic burden on health institutions[4]. Thus, then obesity poor diet and physical inactivity triggered by modern life contribute directly in the etiology of type 2 diabetes in adults, regardless of body mass or history of diabetes in the family index. It is known that this metabolic disorder is universal reality, whose prevalence has reached epidemic proportions quickly, the main disease involving the endocrine pancreas and today is one of the most important causes of morbidity and mortality in the general population[12].

When ingest nutrients, there is the release of gut hormones known as incretins, in which perform an important function sum that is the increase of postprandial insulin secretion. The incretins are related to the physiological regulation of blood glucose levels, since the main incretins are GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide)[5].

Liraglutide is an analog of GLP-1 is an innovative, secure and sustainable strategy for patients with DM2. It is an incretin hormone that is released from the gastrointestinal tract in order to increase insulin secretion by pancreatic beta cells. GLP-1 significantly enhances the secretion of insulin-dependent glucose, decreases glucagon secretion, delays gastric emptying, decreases appetite and its agonist action on receptors resulting in weight reduction[6].

Individuals without diabetes and overweight are making use of this drug as slimming. Because it is a new drug, liraglutide has proven its effectiveness in these cases and it is not known the dangers of this use. Thus, this study aimed to review the literature through the use of liraglutide to treat DM2, as well as investigate the prospects and security of the use of liraglutide in obesity and contribute to technical theme update.

2. MATERIAL AND METHODS

This article is a literature review. The aim of this study was discussing the use of liraglutide in diabetic patients and investigates the prospects and security of the use of liraglutide in obesity.

Sites were surveyed covering existing publications in Pubmed database (National Center for Biotechnology

Information), SciELO library (Sientifc Electronic Library online) and books of the Faculty Inga library collection, including studies that have addressed the issue since 2000 to 2015 using the following key words: type 2 diabetes, obesity, analogue of glucagon like peptide-1 and liraglutide.

3. DISCUSSION

Diabetes *Mellitus*

According to the International Diabetes Federation, the prevalence of diabetes worldwide in 2011 reached 366 million people, and the expectation is that this number will reach 552 million in 2030. Studies in the literature used electronic data stored in the Primary Care System Ministry of Health in Brazil where the prevalence of diabetes *mellitus* (DM) has been above 10% between 2002 and 2007 in most states[7,8].

The incidence of diabetes is often omitted in these studies of prevalence because the diagnostic criterion used is the fasting plasma glucose. From 2010 through the use of glycated hemoglobin and possible association of this with fasting glucose for diagnosis, the prevalence of DM can increase by up to 50% in people over 50 years[4].

Diabetes is a chronic, progressive, multifactorial and non-communicable disease is related to a group of syndromes, metabolic disorders whose main characteristics of the non-production of insulin by the pancreas or blocking the cellular response to insulin produced, then occurring a deficiency in the secretion and / or action of the hormone insulin. It is the primary metabolic syndrome with numerous complications and are closely related to other conditions or set of symptomatology[6,9,10,11].

Diabetes is not a disease relatively simple; it is a heterogeneous group of syndromes that can be total or partial. According to the American Diabetes Association (2008) 12, the criteria for diagnosis in short are the following symptoms: polyuria, unexplained weight loss, polydipsia, plasma glucose concentration random greater than 200 mg/ dL, plasma glucose concentration in 126 fasting mg/ dL or plasma glucose concentration greater than 200 mg/ dL within 2 hours after ingestion of an oral glucose load[12,13]. Furthermore, the American Diabetes Association (2008) 12 adopts four clinical classifications DM: diabetes *mellitus* type 1 (insulin dependent) diabetes mellitus type 2 (non-insulin dependent diabetes), gestational diabetes and diabetes due to other causes (e.g. , medications or genetic defect)[13].

DM1 comprises 5-10% of all cases of DM, affects children and young adults (under 20 years), but some latent forms may occur later. The disease is characterized by destruction of pancreatic beta cells, resulting in complete loss of endogenous insulin secretion, postprandial glucose concentrations increase due to a lack of insulin stimulation by elevated hepatic glucose production, and hypersecretion of glucagon by the absence the compensatory compliance insulin. Symptoms include polydipsia, polyphagia, polyuria and loss of body mass. As for the causes can be: idiopathic, which is unaware of the cause of this destruction, or autoimmune disease, attributed to targeted autoimmune processes against these cells, naqual there is presence of autoimmunity markers (antibodies against the cells of the islet or anti-insulin antibodies) triggered by genetic predisposition, environmental factors and may be further infections or conditions such as tumors. A person with type 1 diabetes are insulin dependent and need of exogenous insulin (injected subcutaneously) to control their blood sugar levels, thus preserve life and prevent ketoacidosis. When untreated appear nausea, vomiting, dehydration, coma and ultimately death (Table 1)[13,14,15].

Type 2 diabetes is the most common form of diabetes affected group, affecting around 90% of diabetic patients. As previously mentioned it is a metabolic disease, progressive, multifactorial and global presence, which directly affects the quality and style of life of diabetic patients. These patients can be reduced by 15 years of age or older, where most have cardiovascular complications. DM 2 is associated with three physiological changes: impaired insulin secretion due to dysfunctions in pancreatic beta cells (especially in the postprandial state), peripheral resistance to insulin, and an inability to suppress glucagon secretion (Table 1)[3,16].

Table 1. Characteristics of Diabetes Type I and Type II

	Type 1	Type 2
Age at the onset	Usually during childhood or puberty.	Often over 35 years
Nutritional status at the beginning	Often malnourished	Generally the presence of obesity
Prevalence	5 to 10% of diagnosed diabetics	90 to 95% of diagnosed diabetics
Genetic predisposition	Moderate	Too strong.
Defect or disability	The beta cells are destroyed, eliminating the production of insulin	Inability of beta cells to produce appropriate amounts of insulin; insulin resistance; other defects

Source: Clark, M. A., Finkel, R., Rey, J. A., Whalen, K., 2013.

In the development of DM2 above adipose tissue requires increased acquisition of insulin hormone and in patients with DM2 notes a considerable resistance to this, due to a reduction in insulin receptors or a failure of the

cellular transport mechanism, causing a rise on the blood glucose, triggering the hyperinsulinemia frame[1,2,17].

Gestational diabetes has its onset or first recognition during the period of pregnancy and is defined as carbohydrate intolerance. In this phase it is important to keep the blood glucose controlled rates because uncontrolled can cause fetal macrosomia, shoulder distorted, and neonatal hypoglycemia[13].

The incretins effect and the Glucagon Like Peptide-1 hormone

The incretins are gastrointestinal hormones described since 1960. Its "incretin effect" is characterized by a greater increase in insulin secretion when glucose administered orally and compared with parenteral administration of an isoglycemic infusion[4].

The glucose-dependent insulinotropic polypeptide (GIP) and Peptide-1 (GLP-1) glucagon are the two most important incretinics hormones. GLP-1 and GIP are small peptides, formed by 30 and 42 amino acids respectively released by the L enteroendocrine cells which are located in the distal ileum and colon and the K cells in the duodenum, respectively, since both stimulate insulin release only when the concentration of blood glucose is elevated, by increasing the secretory capacity of the endocrine pancreas and thus has improved glycemic levels[4].

GLP-1 controls blood glucose levels, which in their physiological concentration, stimulates insulin secretion endogenous glucose-dependent, also lowers glucagon secretion (with deletion of production of hepatic glucose) so that it has reduced the rate of gastric emptying and therefore the calorie intake. GIP in turn slows gastric emptying with less intensive and does not inhibit glucagon secretion[4].

Native GLP-1 and GIP are slightly degraded by the proteolytic enzyme dipeptidyl peptidase-IV (DPP-IV), which cleaves the two N-terminal amino groups of the peptides giving inactive metabolites. With the activation of the DPP-IV has the degradation of GLP-1 and formation of metabolite GLP-1 starch, which does not activate the GLP-1 receptor. Thus, there has been an increase in insulin secretion during an intravenous infusion of GLP-1 in diabetic patients with this functional beta cell; Its metabolite not regulates insulin secretion and glucose metabolism[4].

Clinical uses of liraglutide

Liraglutide has about 97% homology with GLP-1 and was recommended for marketing authorization under the trade name Victoza®. Liraglutide stimulates insulin secretion and improves beta cell function (including restoring glucose sensitivity) in a glucose-dependent manner, thereby helping to reduce the concentration of glucose in the blood. Moreover, decreases glucagon secretion inappropriately high, also in a glucose-dependent manner, which results in reduced hepatic glucose production. Thus, when the blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. On the other hand, when the blood glucose is low, liraglutide suppresses glucagon secretion and lowers insulin secretion[18,19].

Thus, liraglutide is an attractive alternative for the treatment of DM2, it has significantly improved glycemic control with a low potential for hypoglycemia (because your glucose mechanism of action dependent), and has greater efficiency and conservation in the function the beta cells. Treatment should be started preferably in the early stages of DM2, where the clinical benefits are more relevant than in the final stages, where the degree of deterioration of beta cell function can no longer allow this recovery, because it is not recommended replacement of insulin by these later stages liraglutide[19].

The Liraglutide has a pharmacodynamic and pharmacokinetic profile suitable for subcutaneous administration, and it must be administered once a day[20]. The initial dose is 0.6 mg per day. After at least one week, the dose should be increased to 1.2 mg, depending on the clinical response after at least one week, the dose may be increased to 1.8 mg. It is not recommended daily doses greater than 1.8 mg.

The chain fatty acids allows liraglutide structures that form heptamers (micelles aggregate type) delaying the absorption at the site of subcutaneous injection, and provides protection against degradation by DPP-4 inhibitor. The maximum concentration is observed after 10-14 hours of your application and its half-life is 11-13 hours, providing a 24-hour action fraction[20].

The pharmacokinetics of liraglutide is not affected by gender, age or location. After the start of treatment, steady state concentration is achieved after 3 to 4 days [20].

Liraglutide to decrease body weight

Many seek for the ideal body, and are subject to think that being thin is the key to a healthy life[21]. The search for the ideal body weight loss and this model is not as quick and easy as well as it depends on what the person will present his body. And for the dream ideal body requires discipline and a different lifestyle, programmed with rules, change of physical, psychological behavior and nutritional education. When the recognition of the difficulties arises, or unsatisfactory results for this method people seek other solutions such as bariatric surgery, and the most common solution for medication, which often dispense medical advice[22]. However the obsession of people wants to be within the standards proposed by the company direct them to use increasingly improbable methods. Seduced by the desire for immediate weight loss, individuals end up opting for drugs that provide these effects[22 23, 24].

It was found after consistent observations that glucose reduction mechanism in the blood of liraglutide involves a slight delay in gastric emptying, decreasing food intake after a meal, reducing hunger and energy consumption, and thus the drug reduces the weight and body fat, including visceral adipose tissue, and consequently reduces waist circumference, improves lipid profile, and it has also benefits the cardiovascular risk profile[3,19,20].

According to a multicenter analysis, published in 2011 conducted in three countries with 929 patients with DM2 and use of liraglutide, been found that, liraglutide used in dosage of 0.6, 1.2 and 1.8 mg, a reduction of hemoglobin glycated (HA1c) 1.36% 1:45% is 1.39%, respectively, and it was also observed reduction in weight 1.8 to 2.4 kg[25].

Another US study, which aims to compare the use of liraglutide with glimepiride, showed a greater decrease in the levels of HA1c using the first drug and concluded that single dose of liraglutide provides effective glycemic control and not associated to gain weight, as reported that administration of 1.2 mg, the liraglutide demonstrated an improvement of 0.84% and, as the dosage of 1.8 mg, an improvement of 1.14%, whereas only 0.51% glimepiride. The study also reported average weight loss with the use of liraglutide at a dose of 1.2 mg 2.05 kg and at a dose of 1.8 mg, the loss was 2.45 kg, however glimepiride led to a weight gain 1.12 kg[26].

Auspar (2014)[20] conducted a study with liraglutide administered at varying doses of 1.2, 1.8, 2.4, 3.0 and 4.8 mg / kg, gave a reduction of 5.5 kg to 7.2 kg body weight, registering a percentage of 76% effectiveness of liraglutide in individuals who lost weight with their use compared to other drugs.

Therefore, the weight loss was reported as a side effect, however beneficial. Liraglutide is a relatively new drug; more studies are needed to assess their long-term effects and its use in non-diabetic obese.

Nonetheless, major side effects reported liraglutide are nausea, vomiting, diarrhea, negative effects on the thyroid gland, particularly in patients with pre-existing disease such as increased blood calcitonin, goitre and thyroid tumors. The use is also contraindicated in patients with own or family history of medullary thyroid cancer and in patients with multiple endocrine neoplasia syndrome type 2. In addition, the drug is not recommended for patients with significant renal impairment[27].

4. CONCLUSION

The obesity followed a poor diet and physical inactivity triggered by modern life contributes directly in the etiology of DM2 in adults, regardless of body mass index or history of diabetes in the family.

Liraglutide is the first human GLP-1 analogue approved for the treatment of DM2 in Brazil its use is approved by the National Health Surveillance Agency to market since March 2010.

This analog has a homology of 97% and is a safe, effective and innovative strategy for patients with DM2, and improve glycemic control (as it stimulates insulin secretion) this drug decreases the secretion of glucagon so dependent on glucose, reduces body weight due to delayed gastric emptying (feeling of fullness), improved function of β cells, reduces postprandial lipids, controlling systolic blood pressure, minimizes the risk of hypoglycemia.

However its use is not recommended for weight loss in non-diabetic obese patients. Although there are studies that try to prove the efficacy of liraglutide for the treatment of obesity, yet there is no indication in obese patients in Brazil, but several people are using for weight loss. So we need to examine further tests to prove their results and safe for weight loss. Thus, to date its use is indicated only as an adjunct to diet and exercise to improve glycemic control in adults with DM2.

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