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MAJOR RESULTS ABOUT THE REAL EFFECT OF LIRAGLUTIDE ON REDUCING CARDIOVASCULAR RISK PREDICTORS: SYSTEMATIC REVIEW OF CLINICAL UTILITY

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ABSTRACT

Introduction: Obesity portrays a multifactorial disease and presents a serious public health problem, with an alarming epidemic character. There are about two billion overweight and obese people in the world, and Brazil is in fifth place in the world ranking. This scenario is of concern as overweight promotes increased mortality related to the development of cardiorespiratory and metabolic diseases. Liraglutide (LG) is an analog of the hormone GLP-1. Incretins are hormones secreted through endocrine cells that are located in the small intestine epithelium and can control glycemic levels and decrease the weight to treat obesity. **Objective:** The aim of this study was to evaluate, through a systematic review, important clinical results on the real effect of Liraglutide in reducing the predictors of cardiovascular risk in patients with and without diabetes, as well as the assessment of patient survival. **Methods:** Following literary search criteria with the use of the MeSH Terms that were cited in the item on "Search strategies", a total of 68 clinical studies and reviews that were submitted for eligibility analysis were checked, and after that, 19 studies were selected, following the rules of systematic review-PRISMA. **Major findings and Conclusion:** LG is a GLP-1 receptor agonist that has been successfully used in the treatment of type 2 diabetes for several years. It was concluded that weight loss in obese non-diabetic patients was reasonable, with a high incidence of nausea in the treatment group. Weight loss is associated with an improvement in Quality of Life, and when compared by age and obesity. The underlying mechanism may be improved glycemic control, which leads to reduced expression of apoCIII, a key regulator of hypertriglyceridemia in hyperglycemic patients. Therefore, clinical studies have shown that 12-month LG treatment in addition to ongoing hypoglycemic therapy significantly improves all major CVD risk factors and reduces cardiometabolic risk, as shown by visceral fat index values.

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INTRODUCTION

Obesity portrays a multifactorial disease and presents a serious public health problem, with an alarming epidemic character (Davies, 2017). There are about two billion overweight and obese people in the world, and Brazil is in fifth place in the world ranking, with about 18 million people reaching up to 70 million overweight individuals (IBGE, 2019). Still, in this context, recent surveys identified that 18.9% of Brazilian adults (age ≥ 18 years) are obese and about 53.8% are overweight (Mooradian, 2019 and Alonso-Troncoso, 2016). This scenario is of concern, as overweight promotes an increase in mortality related to the development of cardiorespiratory and metabolic diseases (Siskind, 2019). Thus, cardiovascular disease (CVD) is a major contributor to long-term mortality, requiring aggressive modification of CVD risk (Siskind, 2018 and Patel, 2019). However, it is unclear how coronary artery disease (CAD) and dyslipidemia affect clinical outcomes and how the management of these factors may affect survival (Patel, 2019). Currently, there are different therapeutic measures that can be offered to overweight or

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obese patients such as dietary reeducation, therapies, exercise and medications, endoscopic and surgical procedures (Siskind, 2018). They will be selected according to the patient's clinical status, with pre-screening, and the criteria based on BMI and associated comorbidities (Patel, 2019). Liraglutide (LG) is an analog of the hormone GLP-1 (glucagon-like peptide-1) [9]. Incretins are hormones secreted through endocrine cells that are located in the small intestine epithelium and can control glycemic levels and decrease weight for obesity treatment (Matikainen, 2019; Mikhail, 2019 and Fujishima, 2012). LG is a drug that acts beneficially on the pathophysiology of diabetes and obesity, these pathophysiologies that contribute to lower productivity at work and school, compromising the quality of life and also causing disruptions in social and family life (Shyangdan, 2010; Vilsboll, 2012 and Kahal, 2019). As literary support in this context, several studies have shown the beneficial effect of LG on weight reduction as well as improvement in the quality of life (Qol) (Cataldi, 2018; Matikainen, 2019; Nuffer, 2015 and Faria, 2010). In January 2010 LG was approved by the FDA for the treatment of type 2 diabetes. As it has a significant weight loss side effect it has been used by people without type 2 diabetes (Jothydev, 2012 and Matyjaszek-Matuszek, 2018). Therefore, the present study evaluated, through a systematic review, important clinical results about the real effect of Liraglutide in reducing the predictors of cardiovascular risk in patients with and without diabetes, as well as the assessment of patient survival.

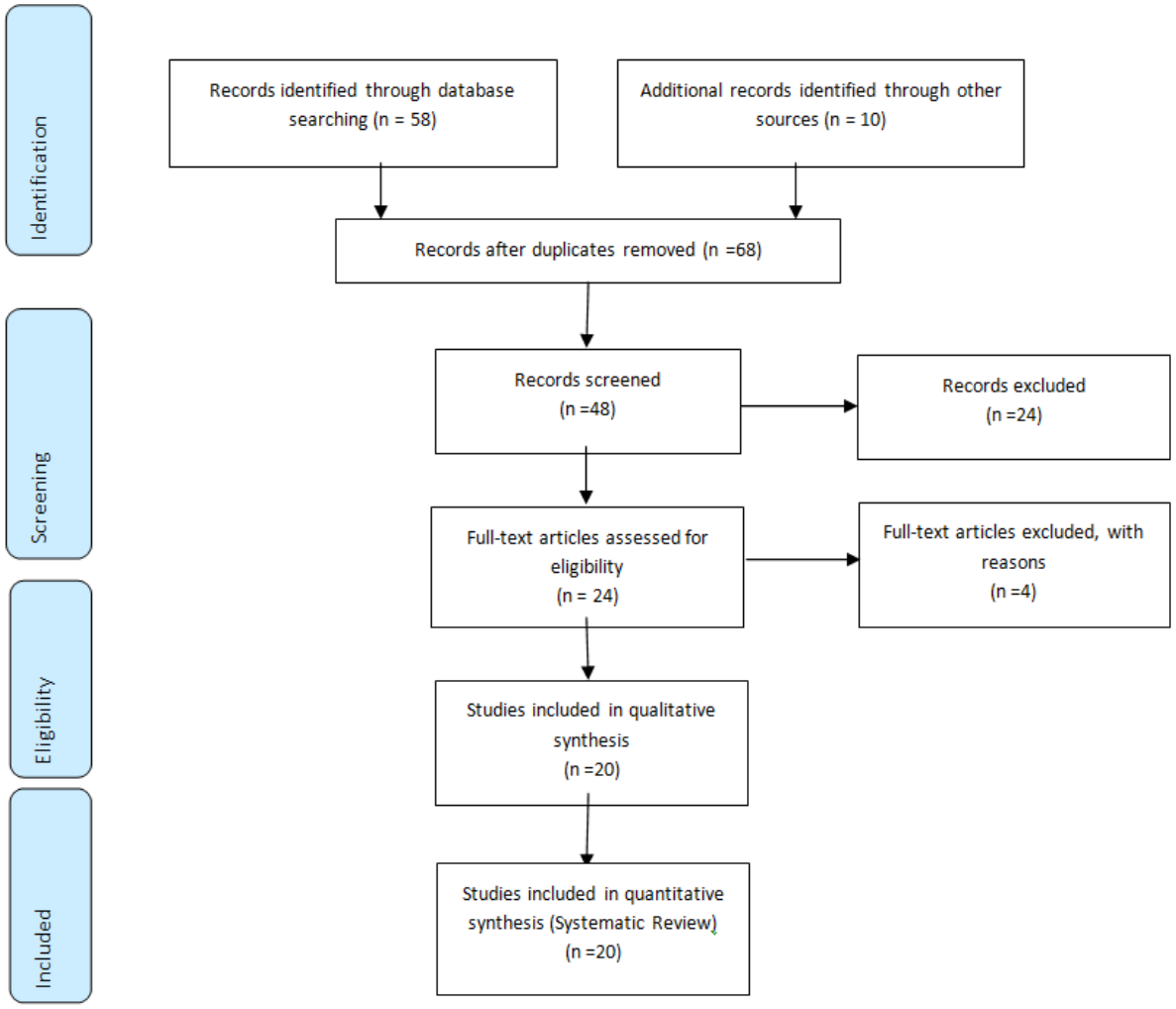
MATERIALS AND METHODS

Study Design: Following literary search criteria with the use of the *MeSH Terms* that were cited in the item on "Search strategies", a total of 68 clinical studies and reviews that were submitted to the eligibility analysis were checked, and after that, 20 studies were selected, following the rules of systematic review-PRISMA (Transparent reporting of systematic reviews and meta-analyzes-http: //www.prisma-statement.org/).

Search Strategy and Information Sources: The search strategy was performed in PubMed, Embase, Ovid and Cochrane Library, Web of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: - search for MeSH Terms: Anti-obesity drug. Liraglutide. Cardiovascular risk. Diabetes. Survival. Clinical importance, and - use of boolean "and" between mesh terms and "or" among historical findings.

Risk of Bias: According to the Cochrane model for risk of bias in the present study, the overall assessment resulted in 2 studies with high bias risk and 3 studies with uncertain risk. In addition, there was an absence of funding source in 6 studies and four studies did not disclose the information on the declaration of conflict of interest. Liraglutide (LG) is a glucagon-like peptide-1 receptor agonist (GLP-1) that has been successfully used to treat type 2 diabetes for several years (Davies, 2017; IBGE, 2019 and Russom, 2015).

Flow Chart



Weight loss has been well described as an added benefit with LG therapy, which has led the manufacturer to evaluate and develop a higher dose formulation specifically for the treatment of obesity (Mooradian, 2016). LG at 3 mg/day was approved by the US Food and Drug Administration for this indication in December 2014 (Alonso-Troncoso, 2019 and Siskind, 2018). One study of 5,908 participants involved 5 randomized, double-blind, placebo-controlled clinical trials. Participants were randomized to either the LG group or a comparison group (placebo or Orlistat). The aim of this study was to assess whether cardiovascular risk increased with LG treatment. The composite primary outcome of this time-to-event analysis was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome was analyzed using a Cox proportional hazards model. With LG 3.0 mg, 8 participants had cardiovascular events positively (1.54 events / 1000 person-years) compared with 10 participants in the comparator group (3, 65 events / 1000 person-years). The risk rate for LG 3.0 mg compared to comparators was 0.42 (95% confidence interval, 0.17-1.08). Treatment with LG 3.0 mg was not associated with excess cardiovascular risk (Davies, 2017).

In addition to the effects on glycemic control and body weight, GLP-1 receptor agonists may favorably affect other important CVD risk factors. Thus, a retrospective study evaluated the effects of 12-month LG treatment on major CVD risk factors in 115 outpatients with type 2 diabetes (60 men and 55 women) with stable hypoglycemic, antihypertensive and/or hypolipidemic. Clinical and anthropometric data, metabolic and lipid profile, as well as visceral adiposity index, an obesity-related cardiovascular risk factor, were observed in all participants at baseline and after 12 months of treatment. LG treatment was associated with a significant reduction in baseline fasting blood glucose (-42.1 mg / dl, p <0.05), HbA1c (-1.5%, -17 mmol / mol, p <0.05), body weight (-7.1 kg, p <0.05), waist circumference (-6.8 cm, p <0.001), total cholesterol (-27.4 mg / dl, p < 0.05), LDL cholesterol (-25.4 mg / dl, p <0.05), triglycerides (-56.1 mg / dl, p <0.05) and non-HDL-C (-36.6 mg / dl, p <0.05) and an increase in HDL cholesterol concentrations (+9.3 mg / dl, p <0.001), a significant reduction in systolic and diastolic blood pressure (-14.7 mmHg, P < 0.001 and -9.0 mmHg, P <0.05, respectively) and a decrease in visceral weevil index values (-1.6, p <0.001). Therefore, 12-month LG treatment in addition to ongoing hypoglycemic therapy significantly improves all major CVD risk factors and reduces cardiometabolic risk, as shown by visceral fat index values (Vilsboll, 2004).

In addition, efforts to reduce the risks of diabetes may contribute to declining cardiovascular mortality. Few antihyperglycemic drugs have been conclusively shown to have cardioprotective effects. These include metformin, liraglutide, semaglutide, dulaglutide, and sodium-glucose-2 co-transporter inhibitors. Statins are the cornerstone of treatment for people with established CAD or at risk for CAD. In patients with persistent low-density lipoprotein cholesterol (LDL-C) levels> 70 mg / dL, the addition of ezetimibe or subtilisin inhibitors of pro-protein Kexin type 9 (PCSK9) is recommended. In general, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be included in the treatment regimen. The goal is to have blood pressure <140/90 mmHg, while a lower target <130/80 mmHg is recommended in patients with CAD or proteinuria (> 1 g / day). Antiplatelet aspirin therapy should be restricted to people with established CAD or with multiple risk factors for CAD (Mooradian, 2019). Also in this sense, the worldwide prevalence of type 2 diabetes mellitus has increased in parallel with that of obesity. Thus, a retrospective observational cohort study including 187 patients treated with LG for at least one year evaluated the metabolic efficacy of LG in clinical practice. Thus, HbA1c levels and weight decreased significantly in the first 12 weeks, and the reduction persisted at 12 and 24 months in all studied subgroups. Mean weight and HbA1c decreases after 24 months were 8.5 kg and 1.7%, respectively. HbA1c values <7% were achieved by 42% of patients at 12 months and 40% at 24 months. Also, treatment with LG allowed the reduction of insulin dose. No serious adverse events were observed. Cardiovascular risk decreased from high to moderate-low. Under standard clinical conditions, LG achieved a better metabolic response than observed in clinical trials. Efficacy at 12 weeks of treatment is a good predictor response (Alonso-Troncoso, 2018). To broaden responses with the use of LG, a meta-analysis study evaluated whether glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce antipsychotic-associated body weight gain in patients with schizophrenia when compared. to the controls. Individual data from study participants randomizing patients to GLP-1RA or control were meta-analyzed. The primary endpoint was the difference in body weight between GLP-1RA and control; Secondary outcomes included cardio-metabolic variables and adverse drug reactions (ADRs). Multiple linear regression was performed including gender, age, the severity of psychosis, metabolic variable, ADRs, and GLP-1RA agent. Three studies (exenatideonce-weekly = 2; liraglutide once daily = 1) provided data at participant level (n = 164, age = 40.0 ± 11.1 years, body weight = 105.8 ± 20, 8 kg). After 16.2 ± 4.0 weeks of treatment, body weight loss was 3.71 kg (95% CI = 2.44-4.99 kg) higher for GLP-1RA versus control (p <0.001), number needed to treat ≥5% body weight loss = 3.8 (95% CI = 2.6-7.2).

Waist circumference, body mass index, HbA1c, fasting glucose, and visceral adiposity were significantly lower with GLP-1RA. Gender, age, the severity of psychosis, nausea, any ADR and GLP-1RA agent had no significant impact on outcomes. GLP-1RAs body weight loss was higher for clozapine / olanzapine-treated patients (n = 141) than other antipsychotics (n = 27) (4.70 kg, 95% CI = 3.13-6.27 vs 1.5 kg, 95% CI = - 1.47-4.47) (p <0.001). Nausea was more common with GLP-1RA than control (53.6% vs. 27.5%, p = 0.002, number needed for damage = 3.8). Thus, GLP-1RAs are effectiveandtolerable for antipsychotic-associated body weight gain, particularlyclozapine / olanzapine-treatedpatients (Siskind, 2018). In another scenario, patients with type 2 diabetes and nonalcoholic fatty liver disease present a considerable residual risk of cardiovascular disease. Treatment with LG may reduce the risk of cardiovascular disease. Thus, the effects of LG intervention on ectopic fat deposits, hepatic lipogenesis and fat oxidation, postprandial lipid metabolism, and blood glucose in humans with type 2 diabetes were investigated. The effect of LG was investigated in 22 patients with type 2 diabetes. 2 properly controlled. Patients were blindly randomly allocated to LG 1.8 mg or placebo once daily for 16 weeks. As LG is known to promote weight loss, the study included dietary advice to achieve similar weight loss in the placebo and LG groups. Cardiometabolic responses to a high-fat mixed meal were measured before and at the end of the LG intervention. As a result of this work, weight loss at week 16 was similar between the groups: -2.4 kg (-2.5%) in

the liraglutide group and -2.1 kg (-2.2%) in the liraglutide group. placebo. HBA1c improved 6.4 mmol / mol (0.6%) in the liraglutide group (P = 0.005). Liver fat decreased in both groups, 31% in the liraglutide group and 18% in the placebo group, but there were no significant changes in de novo liver lipogenesis rate or in the levels of β-hydroxybutyrate, a marker of fat oxidation. Significant postprandial decreases were observed in triglycerides only in plasma, chylomicrons, and VLDL and remaining particle cholesterol after treatment in the LG group. Fasting and postprandial apoCIII concentrations decreased after LG intervention and these changes were closely related to blood-glucose-lowering. In the relative importance analysis, approximately half of the changes in postprandial lipid were explained by reductions in apoCIII concentrations, while less than 10% of the variation in postprandial lipid was explained by reductions in weight, glycemic control, liver fat, or responses. of postprandial insulin. Therefore, 16-week LG intervention yields multiple improvements in cardiometabolic risk factors that were not seen in the placebo group, despite similar weight loss. There was also a marked reduction in the remaining postprandial atherogenicparticles. The underlying mechanism may be improved glycemic control, which leads to reduced expression of apoCIII, a key regulator of hypertriglyceridemia in hyperglycemic patients (Matikainen, 2019).

A recent 2019 study reviewed the cardiovascular effects of LG, including macrovascular and microvascular events, its use in heart failure, and their effects on heart rate and blood pressure. Thus, the impact of LG on cardiovascular outcomes was examined in a large study published in 2016, the LEADER study. This study included 9,340 patients with advanced type 2 diabetes and high initial cardiovascular risk. The primary outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. After a median follow-up of 3.8 years, patients randomized to LG had a significant reduction in the composite primary endpoint compared to patients randomized to placebo, the hazard ratio (HR) 0.87; 95% CI 0.78-0.97. Death from cardiovascular causes was significantly reduced with liraglutide therapy (HR, 0.78; 95% CI 0.66-0.93), as well as death from any cause (HR, 0.85; 95% CI 0.74-0). ,97). In 2017, LEADER researchers reported that nephropathy events were significantly lower after LG therapy than placebo (HR 0.78; 95% CI 0.67-0.92), but there was no significant difference in events. retinopathy. Meanwhile, other studies have suggested that LG use may be harmful in patients with severe heart failure, in part due to increased heart rate. LG is a useful therapy in patients with advanced type 2 diabetes complicated by CVD (Mikhail, 2019). To show the beneficial effects of weight loss with LG use and the outcome on quality of life and depression in obese young women with polycystic ovary syndrome (PCOS) and controls. In a cross-sectional study, 36 obese women were recruited (19 PCOS, 17 controls), 33.9 ± 6.7 years versus 33.5 ± 7.1 years and weight 102.1 ± 17.1 versus 100.4 ± 15. , 1 kg respectively. The combination of the two groups revealed significant ($p < 0.05$) improvement in physical (82.6 ± 11.2 vs. 78.9 ± 13.6), psychological (62.4 ± 16.5 vs. 57, 5 ± 16.4) and social (76.6 ± 15.3 vs. 71 ± 16.8) WHOQOL-BREF components at six months. Weight loss is associated with an improvement in the quality of life, and when compared by age and obesity, PCOS was not independently associated with reduced quality of life or depression (Cataldi, 2018). Intervention with LG for 16 weeks produces multiple improvements in cardiometabolic risk factors that were not observed in the placebo group, despite similar weight loss (Nuffer, 2015) Of particular importance was a marked reduction in the remaining postprandial atherogenic particles. The underlying mechanism may be improved glycemic control, which leads to reduced expression of apoCIII, a key regulator of hypertriglyceridemia in hyperglycemic patients (Nuffer, 2015). In a study of 564 participants, LG was tested as an adjunct in the treatment of obesity in obese individuals without DM2. Participants received subcutaneous LG once daily at doses of 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg. It was concluded that weight loss in obese non-diabetic patients was reasonable, with a high incidence of nausea in the treatment group (Jothydev, 2012). The efficacy and safety of LG have been evaluated in overweight and obese DM2 patients. Of these patients, 85.71% had diagnosed diabetes less than 12 weeks before LG therapy (Faria, 2010). After 3 months of treatment with LG at a dose of 1.8 mg/day, an average reduction of 5.02kg was obtained, and after 6 months the reduction in body weight was 8.65kg. This reduction may be of great importance in DM2 management (Matyjaszek-Matuszek, 2018).

Limitations

To achieve higher satisfactory anti-obesity goals, the use of Liraglutideshould be optimized and tailored to specific patient subpopulations, applying dose adjustments if necessary. In the present review, we postulate that gender may be among the factors that influence the activity of new obesity drugs, both by pharmacokinetic and pharmacodynamic factors. Although evidence from pre-marketing clinical studies suggests that no dose adjustments by gender are required for any of these new drugs, these studies were not specifically designed to identify gender-related differences.

Conflicts of interest: There are no conflicts of interest.

Conclusion

Clinical studies have shown that 12-month LG treatment in addition to ongoing hypoglycemic therapy significantly improves all major CVD risk factors and reduces cardiometabolic risk, as shown by visceral fat index values.

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