Doi: https://doi.org/10.37497/JMRReview.v3i00.59

Journal of Medical Residency Review

THE CARDIOPROTECTIVE EFFECTS OF SEMAGLUTIDE IN OBESE PATIENTS: LITERATURE REVIEW

Os efeitos cardioprotetores da semaglutida em pacientes obesos: revisão da literatura

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Abstract
Introduction: Obesity is an independent risk factor for cardiovascular disease (CVD) as it increases inflammation and oxidative stress in the body. Glucagon Like Peptide-1 (GLP-1 RA) agonist receptors, such as semaglutide, reduce weight, improve blood sugar levels, and promote cardioprotection. GLP-1 Ras extend the life of GLP-1, an incretin responsible for processes that decrease hyperglycemia, leading to weight loss. Objective: To understand the cardioprotective effects of semaglutide in obese patients. Method: We conducted a literature review focusing on identifying the cardioprotective effects of semaglutide use in obese patients. Results and Discussion: The hyperglycemic and pro-inflammatory state of obese individuals favors pro-thrombotic mechanisms and cardiovascular dysfunction. GLP-1 Ras mediate their effects through the GLP-1 receptor, showing a reduced risk of CVD as they have beneficial effects on reducing blood pressure, weight, lipid levels, and glucose. Semaglutide acts as a long-acting GLP-1 RA, demonstrating a greater ability to reduce weight within this class, and works by stimulating insulin secretion by pancreatic beta cells and reduces glucagon production by alpha pancreatic cells. Conclusion: According to the literature, it is possible to consider that semaglutide promotes cardioprotection in obese patients. However, further studies are still needed to confirm this relationship and achieve greater efficacy in treatment.
Keywords: Cardioprotective effects, Semaglutide, Obesity .

Resumo
Introdução: A obesidade é um fator de risco independente para doenças cardiovasculares (DCV), pois aumenta a inflamação e o estresse oxidativo no organismo. Os receptores agonistas do peptídeo semelhante ao glucagon (GLP-1 RA), como a semaglutida, reduzem o peso, melhoram os níveis de glicose no sangue e promovem a cardioproteção. GLP-1 Ras prolonga a vida do GLP-1, uma incretina responsável por processos que diminuem a hiperglicemia, levando à perda de peso. Objetivo: Compreender os efeitos cardioprotetores da semaglutida em pacientes obesos. Método: Realizamos uma revisão de literatura com foco na identificação dos efeitos cardioprotetores do uso de semaglutida em pacientes obesos. Resultados e Discussão: O estado hiperglicêmico e pró-inflamatório de indivíduos obesos favorece mecanismos pró-trombóticos e disfunção cardiovascular. GLP-1 Ras medeiam seus efeitos através do receptor GLP-1, mostrando um risco reduzido de DCV, pois têm efeitos benéficos na redução da pressão arterial, peso, níveis lipídicos e glicose. A semaglutida atua como um AR GLP-1 de ação prolongada, demonstrando uma maior capacidade de redução de peso dentro desta classe, e atua estimulando a secreção de insulina pelas células beta pancreáticas e reduzindo a produção de glucagon pelas células alfa pancreáticas. Conclusão: De acordo com a literatura é possível considerar que a semaglutida promove cardioproteção em pacientes obesos. Porém, mais estudos ainda são necessários para confirmar essa relação e alcançar maior eficácia no tratamento.
Palavras-chave: Efeitos cardioprotetores, Semaglutida, Obesidade.

Introduction

Obesity, characterized by inflammation and oxidative stress, stands as an independent risk factor for cardiovascular diseases (CVD), which remain a leading cause of global mortality (RYAN ET

AL., 2020). Given the significant exacerbating role of obesity in CVD, interventions aimed at achieving effective and sustained weight loss, coupled with lifestyle modifications, offer promising avenues for independent cardiovascular benefits. (SINGH, KRAUTHAMER, & BJALME-EVANS, 2021)
Guidelines for treating overweight and obesity include lifestyle modifications such as physical exercise, calorie intake reduction, and behavioral therapy, practices that can also reduce the risk of developing cardiovascular complications. (CHAO ET AL., 2021). Often, these interventions intersect with the usage of anti-obesity medications (AOM), particularly for individuals with a body mass index (BMI) ≥ 30 kg/m² or ≥ 27 kg/m² with obesity-related comorbidities like type 2 diabetes, hypertension, or dyslipidemia.

Certain medications, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exemplified by semaglutide, not only induce weight loss and improve glycemia but also confer cardioprotective effects in individuals at risk of or with preexisting cardiovascular disease (BAGGIO & DRUCKER, 2021). Therefore, they are used as one of the medications to fight against obesity and other diseases in which they provide benefits.

GLP-1 RA was initially developed to treat type 2 diabetes mellitus, and effects on glycemia and weight loss were observed. However, studies were conducted and made it clear that GLP-1 receptor agonists were indeed able to decrease cardiovascular risk as well. (PEDROSA et al., 2022)
GLP-1 RAs extend the half-life of GLP-1, an incretin essential for processes counteracting hyperglycemia, including insulin secretion stimulation, glucagon secretion inhibition, and gastric emptying deceleration (GOLDENBERG & STEEN, 2019). Despite its therapeutic potential, clinical use of GLP-1 is hindered by its short half-life in circulation (1-2 minutes), attributable to rapid enzymatic degradation by dipeptidyl peptidase (DPP4) and neutral endopeptidase (NEP) (CHRISTOU et al., 2019). Thus, this study endeavors to elucidate the mechanisms underlying semaglutide's actions within the body and its interplay with the cardiovascular system.

Objective

To understand and evaluate the cardioprotective effects of semaglutide in obese patients.

Method

This is an integrative literature review. The search for articles that were reviewed focused on identifying the cardioprotective effects of semaglutide use in obese patients. Articles published in English and Portuguese language journals were included, as well as paid studies. The search also included the following descriptors: obese, semaglutide, cardioprotection.

Results and Discussion

Obesity and Disease Risk

The Body Mass Index (BMI) is calculated by dividing weight (in kilograms) by the square of height (in meters). According to the World Health Organization (WHO), obesity is defined as a BMI greater than or equal to 30 kg/m². However, this clinical measure lacks precision in distinguishing between muscle mass and fat, leading to diagnostic discrepancies. Therefore, complementary clinical assessments are necessary, such as measuring abdominal circumference to evaluate abdominal visceral fat, alongside analyzing the metabolic dysfunctions of the patient, given the multifaceted nature of obesity as a metabolic disorder (TIRANDI et al., 2024).

Obesity is intricately linked with traditional cardiovascular (CV) risk factors, including dyslipidemia, insulin resistance, type 2 Diabetes Mellitus, hypertension, and obstructive sleep apnea. Beyond its association with these risk factors, obesity directly promotes atherosclerosis, potentially leading to fatal outcomes. Studies indicate that the extent of adipose tissue deposits correlates with adverse cardiovascular events independently of other conventional risk factors. TIt has been proposed that the pro-thrombotic and pro-inflammatory state of these fat deposits plays a key role in the pathogenesis of CVD (LINGVAY et al., 2022).

Research has identified four phenotypes of obesity, each associated with distinct cardiovascular risks attributed to differing pathophysiological mechanisms. These phenotypes include: i) metabolically unhealthy normal weight (MUNW), ii) metabolically healthy overweight/obesity (MHO), iii) metabolically unhealthy overweight/obesity (MUO), and iv) sarcopenic obesity (SO) (PREDA et al., 2023).

Individuals categorized as MHO exhibit a heightened risk of myocardial infarction (MI), ischemic stroke, or cardiovascular death compared to those classified as MUO, along with increased

susceptibility to heart failure (HF) and atrial fibrillation (AF). Conversely, individuals within the MUO group demonstrate a higher prevalence of metabolic syndrome (MetS), left ventricular hypertrophy (LVH), HF with preserved ejection fraction (HFpEF), cardiovascular death, stroke, metabolic cardiomyopathy, arrhythmias, AF, MI, and epicardial adipose tissue deposition. Furthermore, the MUNW phenotype is associated with elevated risk of "inflammaging," characterized by low-grade, chronic inflammation linked with aging, leading to cellular senescence, altered mitochondrial function, disrupted autophagy, dysbiosis of the microbiota, and "metaflammation" due to increased nutrient intake, culminating in elevated inflammatory hormone levels such as leptin and fostering pro-inflammatory macrophages, thereby perpetuating inflammation, insulin resistance, and reactive oxygen species (ROS) production, resulting in tissue damage. Finally, individuals characterized by the SO phenotype exhibit a heightened risk of MetS, LVH, HF, cardiovascular death, stroke, metabolic cardiomyopathy, and epicardial adipose tissue deposition (PREDA et al., 2023).

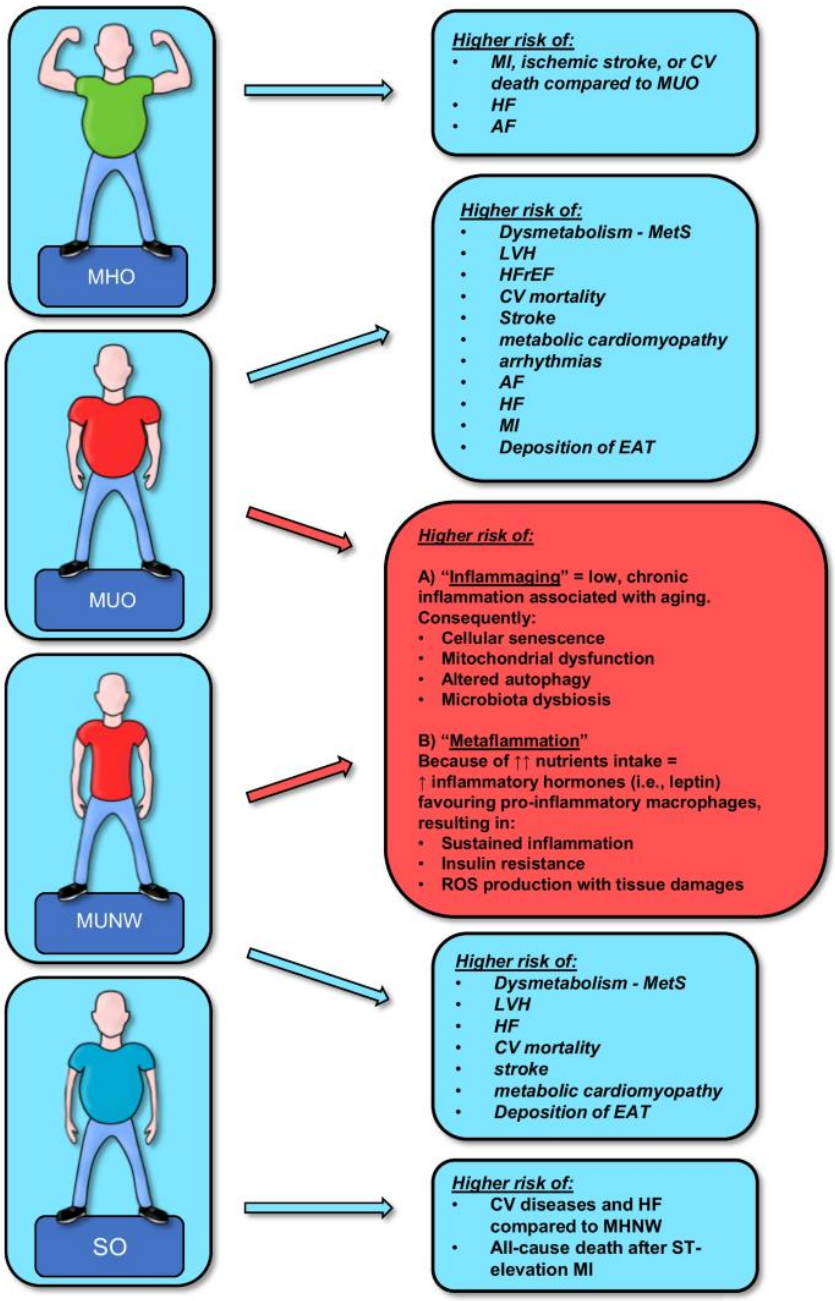

Figure 1: Obesity Phenotypes and Cardiovascular Risk.
Source: Preda et al. (2023).

Inflammation in Obesity and its Consequences on the CV System

Inflammation is the primary mechanism for the development of CV risk in obesity, and insulin plays a significant role in this condition as it triggers systemic inflammatory reactions and stimulates adipose tissue, besides its impact on lipid profile. Insulin stimulates increased triglyceride or free fatty acid metabolism in adipose tissue, resulting in the production of many fatty acid intermediates. Thus, these molecules lead to insulin receptor phosphorylation and inhibition of signaling through the activation of intracellular pathways such as c-Jun N-terminal kinase (JNK), IκB kinase (IKK) complex, and protein kinase C. Additionally, hypertrophic adipocytes and macrophages in the adipose tissue of obese individuals synthesize and release tumor necrosis factor-alpha (TNF-alpha), causing serine phosphorylation and tyrosine dephosphorylation of insulin receptors, leading to their inactivation and degradation (TIRANDI et al., 2024).

Therefore, the hyperglycemic and pro-inflammatory state of obese individuals favors pro-thrombotic mechanisms and cardiovascular dysfunction. Atherosclerosis is a disease characterized by irregular atheromas that advances into the lumen of medium and a large artery that is triggered by hyperinsulinemia, dyslipidemia, and hyperglycemia, as these conditions induce endothelial oxidative stress through glycation and its end products, activation of protein kinase C and the polyol/hexosamine pathway, endoplasmic reticulum stress, and mitochondrial dysfunction. Finally, reactive oxygen species (ROS) play an important role in the proliferation and apoptosis of vascular smooth muscle cells, which may result in atherosclerotic plaque instability and its potential rupture (TIRANDI et al., 2024).

Obese patients have a higher risk of developing comorbidities, consequently, they have a higher chance for cardiovascular complications, the most prevalent cause of death in these patients (SINGH; KRAUTHAMER; BJALME-EVANS, 2021).

Therefore, weight loss can reduce the risk of developing complications from obesity, such as CVD, but there are many challenges to achieving and maintaining appropriate weight. Thus, pharmacotherapy can be a means of assistance for individuals who need to lose weight and includes drugs such as GLP-1RAs (ARD et al., 2021).

Glucagon-like Peptide-1 Receptor Agonist Drugs - GLP1-RA

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), harness the beneficial physiological effects of GLP-1 by increasing GLP-1 receptor signaling well above normal levels, thereby reducing glucose with a low risk of hypoglycemia, producing weight loss (RYAN et al., 2020).

Consequently, the effects of GLP-1 RAs are mediated via the GLP-1 receptor, which is widely distributed in tissues such as the pancreas, gastrointestinal tract, heart, lungs, kidneys, and brain. Notably, GLP-1 receptors localized in the pancreas and brain have been implicated in the observed enhancements in glycemic control and body weight associated with semaglutide therapy (BAGGIO & DRUCKER, 2021).

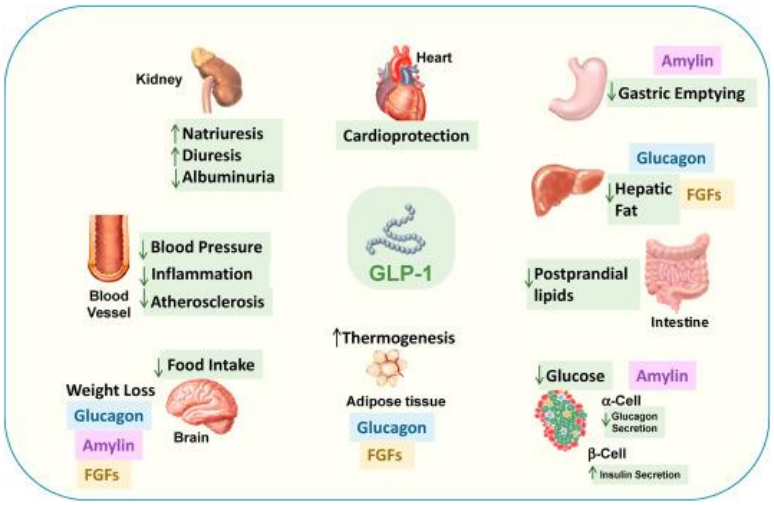

Figure 2 - Actions of GLP-1, amylin, fibroblast growth factors (FGFs), leptin, and glucagon in the major target organs relevant to metabolism.
Source: Baggio; Drucker (2021).

GLP-1 RAs have not demonstrated an increased cardiovascular risk during their developmental stages; rather, they have exhibited a reduction in this risk. This is attributed to their favorable effects on lowering blood pressure, facilitating weight loss, decreasing lipid levels, and even regulating glucose levels (RYAN et al., 2020). Consequently, the primary objectives of treatment with GLP-1Ras extend beyond mere weight reduction to encompass the mitigation of cardiometabolic complications (KOSIBOROD et al., 2022).

Semaglutide

Semaglutide is an analog of glucagon-like peptide-1 (GLP1), available in subcutaneous and oral formulations, functioning as a long-acting GLP-1 RA, with a half-life of approximately 7 days, and has been shown to have the greatest glucose reduction and weight loss power within the GLP-RA group. (RYAN et al., 2020) Thus, the drug is derived from human GLP-1 but has changes in its chemical structure such as: two amino acid substitutions at positions 8 and 34, acylation of lysine at position 26 with a connector composed of glutamic acid and a C-18 fatty acid side chain. These modifications promote a longer half-life for semaglutide, approximately 183 hours (approximately 1 week).

Semaglutide is primarily eliminated in the kidneys (CHRISTOU et al., 2019).

It is assumed that semaglutide may reduce CV risk in overweight/obese people, both through weight loss and, in part, through independent effects on CV risk factors and other metabolic parameters. Although the exact mechanisms behind the CV effects are not fully elucidated, data suggest that GLP-1 receptor agonists (GLP-1RAs), including semaglutide, may have direct and beneficial effects on the CV system (KOSIBOROD et al., 2022). Semaglutide subcutaneous 2.4 mg, a long-acting glucagon-like peptide 1 receptor agonist administered once weekly (GLP-1RA), was first approved for chronic weight management in June 2021 in the United States and since then, in several other countries. Semaglutide has been shown to reduce body weight by up to 16% when used in conjunction with lifestyle recommendations. GLP-1RAs, such as semaglutide, exert direct effects in various locations while it is postulated that they have direct CV effects (LINGVAY et al., 2022).

Therefore, semaglutide acts in the body by stimulating insulin secretion by pancreatic beta cells and decreasing glucagon production by pancreatic alpha cells, as well as reducing gastric emptying time and promoting weight loss (CHRISTOU et al., 2019).

Mechanisms of Action of Semaglutide in the Cardiovascular System

In the vessels, semaglutide is responsible for increasing endothelial cells expressing the GLP-1 receptor, so GLP-1 RAs favor vessel relaxation through the AMPK/Akt pathway and, by activating the nitric oxide synthesis pathway, they can also prevent endothelial activation dysfunctions by inhibiting NF-kB phosphorylation and undermining the pro-inflammatory expression of mediators such as endothelin-1 and interleukins (TIRANDI et al., 2024)

GLP-RA benefits both endothelial and vascular smooth muscle cells, as it inhibits the production of angiotensin-II and is directly associated with anti-inflammatory properties. (TIRANDI et al., 2024). Furthermore, regarding atherosclerosis, stability in the molecules has been demonstrated, reducing the accumulation of immune system cells in the vessel. Semaglutide reduces levels of TNF-α, vascular adhesion proteins, monocyte chemotactic protein-1, metalloproteinase1, intercellular adhesion molecules 1. GLP-1 RAs reduce systemic levels of pro-inflammatory cytokines while increasing anti-inflammatory mediators, such as adiponectin. GLP-1 treatment, therefore, reduces atherosclerotic inflammation, foam cell formation, and improves plaque stability by reducing matrix metallopeptidase-9 and facilitating collagen formation in the fibrous cap of the plaque. (TIRANDI et al., 2024)

It has been demonstrated that GLP-1 RA treatments can reduce 20-30% of epicardial fat, confirming the effects of these drugs in preventing CVDs. (TIRANDI et al., 2024)

Cardioprotective Effects of Semaglutide in Obesity

Research indicates a notably higher prevalence of left ventricular hypertrophy in obese individuals compared to non-obese counterparts. Consequently, obesity can precipitate anatomical and functional alterations in the heart, potentially culminating in cardiac fibrosis. Studies suggest that phenotypic changes in cardiac fibroblasts among obese individuals may contribute to the development of cardiac fibrosis. Furthermore, fibroblast activation triggered by metabolic syndrome, commonly associated with obesity, can instigate the release of extracellular matrix and subsequent fibrosis (PAN et al., 2022).

The heart consists of cardiomyocytes and non-cardiomyocytes (non-CM), both contributing to cardiac function. Pathophysiological processes in the heart, such as cardiac disorders, can occur due to cardiomyocyte hypertrophy, apoptosis, and autophagy, as well as the actions of non-CM. Among non-CM are fibroblasts, which can be converted into cardiomyocyte-like cells to aid in cardiac repair, and play a crucial role in cardiac remodeling, pathological processes, and the production of paracrine substances that modulate cardiomyocyte function, such as IL-11, responsible for cardiac hypertrophy and fibrogenic effects. In the event of cardiomyocyte injury, there is a proliferation of extracellular matrix, and fibroblasts are transcribed into myofibroblasts, potentially leading to fibrosis and subsequent cardiac hypertrophy (PAN et al., 2022)

GLP-1 is a target for the development of new strategies to reduce cardiovascular risk in obese individuals. This intestinal hormone regulates glucose metabolism, energy homeostasis, and has various effects, including cardiovascular effects. (RYAN et al., 2020)

Released in response to food intake, the GLP-1 peptide acts as a satiety signal, stimulates insulin release, inhibits glucagon secretion, and regulates gastric emptying. Additionally, at the cardiovascular level, it elicits benefits such as natriuresis, diuresis, blood pressure reduction, and inflammation mitigation (Ryan et al., 2020). Due to these properties, GLP-1 receptor agonists (GLP-1 RAs) have demonstrated a reduction in the risk of cardiovascular events, including semaglutide, a long-acting analog of GLP-1, known for its cardioprotective effects. Through its action on fibroblasts, semaglutide may effectively treat cardiac fibrosis in obese patients. Moreover, studies suggest that it inhibits the expression of Serpinh1 and Pcolce genes in fibroblasts, crucial players in obesity-induced cardiac fibrosis (PAN et al., 2022).

In a randomized clinical trial involving 17,604 patients analyzed over an average of 39.8 months, 8,803 received subcutaneous semaglutide 2.4 mg weekly, while 8,801 were in the placebo group. The results demonstrated a reduction in the incidence of death from cardiovascular diseases, non-fatal myocardial infarction, or non-fatal stroke among patients administered semaglutide, underscoring the drug's efficacy in cardiovascular outcomes (A. MICHAEL LINCOFF et al., 2023).

Conclusion

The literature confirms sufficient scientific evidence to consider semaglutide as a drug that promotes cardioprotection in obese patients. However, further studies are necessary to confirm its efficacy and deepen understanding of this relationship, potentially increasing the drug's usage in obesity treatment.

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