Diversitas Journal
ISSN 2525-5215
Volume 8, Número 4 (out./dez 2023) p.2723 – 2731
https://diversitasjournal.com.br/diversitas_journal

Metformin, Liraglutide and Semaglutide: Antidiabetic drugs used for the purpose of weight loss

ANDRADE, Sâmia Moreira de[1]; ANDRADE, Maria Victória Macedo de[2]; FARIA, Pedro Henrique Almeida de[3]; ROSA, Luís Marcelo Vieira[4]; COSTA, Plínio Robson Cavalcante[5]; PIRES, Luiz Gustavo Freitas[6]

(1) 0000-0002-2310-2515; Centro Universitário Santo Agostinho. São Luís, MA, Brasil. E-mail: samia.andrade27@hotmail.com
(2) 0009-0005-7534-2755; Faculdade Facimp Wyden. Sítio Novo, MA, Brasil. E-mail: 1mariavictoria10@gmail.com
(3) 0009-0002-5799-4117; Faculdade Facimp Wyden. Imperatriz, MA, Brasil. E-mail: pedrodealmeidafaria@gmail.com
(4) 0000-0002-8960-6871; Universidade Federal do Maranhão. São Luís, MA, Brasil. E-mail: marcelorosa.ma@gmail.com
(5) 0000-0002-9692-3701; Faculdade Facimp Wyden. Imperatriz, MA, Brasil. E-mail: pliniocosta774@gmail.com
(6) 0000-0003-2508-1815; Pontifícia Universidade Católica do Paraná. Curitiba, PR, Brasil. E-mail: gustavopires78@gmail.com

ABSTRACT

The present study aimed to carry out a bibliographical survey of antidiabetic drugs used for weight loss and their consequences for human health. The drugs most commonly reported in the literature were Metformin, Liraglutide and Semaglutide. The three drugs proved to be effective in weight loss, with Liraglutide having the most pronounced effect, including in clinical studies. Metformin and Semaglutide have been shown to reduce weight, especially when associated with the practice of physical exercise and a change in eating style. However, these drugs have not yet been approved for the purpose of weight loss, and a series of side effects have been reported, mainly associated with the gastrointestinal system, such as nausea, vomiting and diarrhea. Based on the evaluated data, the best way to reduce body weight remains the practice of physical activity and lifestyle changes, and since such practices are not enough, one can opt for the use of anorectics with the proper prescription. and guidance from a health professional. We also highlight the greatest need for the pharmacist, who is responsible for the interface between the drug and the patient, in the education process to avoid the irrational use of antidiabetic drugs in order to lose weight.

RESUMO

O presente estudo objetivou realizar um levantamento bibliográfico de medicamentos antidiabéticos utilizados para emagrecimento e suas consequências para a saúde humana. Os medicamentos mais comumente relatados na literatura foram Metformina, Liraglutida e Semaglutida. Os três medicamentos demonstraram ser efetivos no emagrecimento, tendo a Liraglutida efeito mais pronunciado, inclusive em estudos clínicos. Metformina e Semaglutida demonstraram reduzir peso principalmente quando associados à prática de exercício físico e mudança de hábito alimentar. Entretanto, esses medicamentos ainda não foram aprovados com a finalidade de emagrecimento, e uma série de efeitos colaterais foram relatados, principalmente associados ao sistema gastrointestinal como náusea, vômito e diarreia. Com base nos dados avaliados, a melhor forma de reduzir o peso corporal continua sendo a prática de atividade física e mudança do estilo de vida, e uma vez que tais práticas não são suficientes pode-se optar pelo uso de anorexígeno com a devida prescrição e orientação de um profissional de saúde. Visando a integralidade do cuidado para com os usuários, é de suma importância a participação de uma equipe multiprofissional, sendo destacada a figura do farmacêutico, responsável pela interface entre o medicamento e o paciente, no processo de educação para evitar o uso irracional de medicamentos antidiabéticos no intuito de emagrecer.

ARTICLE INFORMATION

Article process:
Submitted: 02/07/2023
Approved: 19/10/2023
Published: 02/11/2023

Keywords:
Diabetes, Obesity, Slimming, Antidiabetic drugs, Rational use of drugs

Palavras-Chave:
Diabetes, Obesidade, Emagrecimento, Uso racional de medicamentos

DOI: 10.48017/dj.v8i4.2720

INTRODUCTION

By 2045, it is predicted that 693 million adults worldwide will be affected by diabetes (Cole & Florez, 2020). Currently, in Brazil alone, there are more than 16.5 million people with this disease, making it the leading country in Latin America with individuals suffering from diabetes (Sousa et al., 2020). This is a disease characterized by hyperglycemia and complications that include ocular and renal microvascular disease and a variety of clinical neuropathies (Balaji et al.). Patients have a metabolic disorder caused by complete or partial deficiency of insulin by the pancreas and/or a decrease in its action in tissues (Fonseca & Rached, 2019).

The severity of the symptoms depends on the type of diabetes, which can be primarily classified as type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is autoimmune, with destruction of pancreatic β-cells and subsequent issues with insulin release. On the other hand, T2DM results from compromised pancreatic beta cells that hinder the individual's ability to use insulin (Padhi et al., 2020).

Another disease with a significant impact on public health and a crucial relationship with environmental factors is obesity, owing to the increased consumption of processed foods, excessive sodium, fats, and sugar in diets (Nilson, 2020). This disease affects approximately 300 million adults and is characterized by the excessive accumulation of adipose tissue in the body (Mendes; Bastos et al., 2019).

Early studies in 1998 conducted by Lee & Morley demonstrated that metformin reduces food intake and induces weight loss in obese individuals with type II diabetes, indicating that obese diabetic patients benefit from glycemic control treatment, as the medication also helps control weight. other antidiabetic medications such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists also reduce body weight by contributing to a negative energy balance, reducing appetite, and thus food intake, as well as promoting delayed gastric emptying (Wilding, 2018). However, this apparent benefit has led to the emergence of a practice that is becoming increasingly common: the use of antidiabetic medications for weight loss even in non-diabetic individuals.

Self-medication is recognized as a global public health problem, defined as the consumption of one or more medications not prescribed by a physician and not controlled by medical health organizations (Santos, 2019). This practice can pose a serious risk to individuals, who may experience changes in bowel movements, diarrhea, anxiety, confusion, insomnia, mood alterations, and violent behavior (Santos, 2019; Silva, 2013).

The central question of this study is: What are the effects of metformin, liraglutide, and semaglutide on weight loss? The aim of this study is to conduct a literature review on

antidiabetic medications used for promoting weight loss and assess their consequences for human health.

Metformin

Metformin belongs to the biguanide class and exerts its effects by activating Adenosine Monophosphate-Activated Protein Kinase (AMPK). This results in the reduction of gluconeogenesis in the liver, increased glucose sensitivity in muscles, and anorectic effects in the hypothalamus (Marques et al., 2021). Studies have shown that metformin can reduce the weight of individuals diagnosed with childhood obesity, regardless of gender or ethnicity (Freemark & Bursey, 2001; Srinivasan et al., 2006). Furthermore, the use of metformin led to a decrease in the Body Mass Index (BMI) when combined with regular physical activity and improvements in dietary habits (Gaia & Souza, 2018).

In a long-term study conducted by the Diabetes Prevention Program in obese individuals without diabetes, metformin was able to achieve an average weight loss of 2.1 kg, suggesting that its use is safe and sustainable (Marques et al., 2021). However, as observed by Siqueira & Frigeri (2018) in a series of evaluated studies, despite the reduction in BMI indicating metformin's effectiveness, its actual efficacy is questioned, as the values obtained may not be sufficient for individuals to no longer be considered obese. Therefore, it is important to note that the isolated use of metformin may not be sufficient for weight loss and its maintenance, requiring a multidisciplinary approach that includes regular physical activity and lifestyle changes. Additionally, it is essential to mention that metformin is not yet approved for the purpose of weight loss, as studies focused on this treatment are limited or lack rigor in their implementation. Furthermore, this medication is not without side effects, such as the risk of lactic acidosis (Marques et al., 2021), as well as nausea, fatigue, and vomiting, and it is contraindicated for patients with severe renal insufficiency or liver disease (Gonçalves & Abreu, 2021).

Liraglutide

Liraglutide is a drug with a 97% homology to human glucagon-like peptide 1 (GLP-1) and is approved for the treatment of type 2 diabetes. Its action involves interacting with the glucagon-like peptide-1 receptor (GLP-1R), which stimulates insulin secretion and suppresses glucagon release by the pancreas (Marso et al., 2016). This medication is sold under the brand names Victoza, Saxenda, and Xultophy, all of which are available in injectable form. Its effect on weight loss is associated with its appetite suppression and the slowing of gastric emptying (Mehta et al., 2017).

A comprehensive analysis of studies indicates that liraglutide can successfully achieve weight loss parameters of 5% or more and 10% or more reduction from baseline, making it a pharmacological option for obesity treatment at a daily dose of 3 mg (Nuffer & Trujillo, 2015; Scott, 2015). This medication also stimulates weight reduction in patients with type 2 diabetes, reducing adipose tissue, body fat mass, and fat percentage (Jendle et al., 2009). Liraglutide has advanced in clinical research, yielding interesting results, such as those reported in phase III trials where treatment with liraglutide significantly improved body weight compared to a placebo in obese non-diabetic patients (Wadden et al., 2013).

However, reported adverse reactions include nausea, vomiting, diarrhea, constipation, dry mouth, dyspepsia, gastroesophageal reflux, upper abdominal pain, flatulence, belching, abdominal distension, reduced appetite, irritation at the injection site, asthenia, fatigue, hypoglycemia, cholelithiasis, dizziness, dysgeusia, insomnia, increased lipase, and amylase levels (pancreatic enzymes) (Sousa, 2021). Additionally, liraglutide slows gastric emptying, which may interfere with the action of other medications, including those properly prescribed for obesity treatment. Its use in individuals over 75 years old is not recommended (Son & Kim, 2020).

Semaglutide

Semaglutide is marketed under the brand names Rybelsus, Wegovy, and Ozempic. It has a mechanism of action similar to liraglutide, acting on the GLP-1R and promoting insulin secretion and glucagon inhibition. The primary difference is that, unlike liraglutide, semaglutide has a longer half-life, requiring only once-weekly administration.

Studies have shown that semaglutide is effective in weight reduction but have primarily focused on diabetic patients who genuinely require the medication (Ahrén et al., 2018; Aroda et al., 2022). This consideration is crucial, as Martínez et al. (2020) have pointed out that the use of semaglutide, without exercise and dietary changes, may result in a rebound effect, stimulating an increase in body weight. Indeed, evidence suggests that its effect on weight loss is more pronounced when combined with physical activity (Lundgren et al., 2021). Additionally, a range of side effects have been reported, primarily gastrointestinal effects like nausea, vomiting, and diarrhea (Weber et al., 2023). Therefore, the use of semaglutide for weight loss remains the subject of significant scientific debate, and the lack of robust evidence and the need for further in-depth studies limit its recommendation for obesity treatment (Freitas et al., 2023).

It is worth noting that few studies are being conducted to evaluate the real impact of the inappropriate use of antidiabetic medications, as the majority of these studies were carried out in controlled research settings. Therefore, there should be a greater effort to better

characterize the irrational use of these medications for weight loss. Below is a table (**Table 1**) summarizing the three main antidiabetic medications used for weight loss, their mechanisms of action, weight loss outcomes in studies, and side effects.

Table 1.

Summary of the primary antidiabetic medications used for weight loss, their mechanisms of action, weight loss outcomes in studies, and side effects.

Medication	Mechanism of action	Use in weight loss	Side effects
Metformin	Activation of AMPK, and consequent reduction in gluconeogenesis in the liver, greater sensitivity to glucose in the muscle and anorexic effects in the hypothalamus.	Studies indicate a reduction in body weight with the use of metformin. However, it does not seem to be an effective medicine since the values obtained were not enough for the individual to stop being obese.	Lactic acidosis, nausea, tiredness and vomiting.
Liraglutide	Activation of the glucagon-like peptide-1 receptor (GLP-1R), with consequent stimulation of insulin secretion and suppression of glucagon by the pancreas.	Studies demonstrate that Liraglutide is capable of stimulating body weight reduction in patients with type 2 diabetes, and obese patients without diabetes.	Nausea, vomiting, diarrhea, constipation, dry mouth, dyspepsia, gastritis, gastroesophageal reflux, upper abdominal pain, flatulence, eructation, abdominal distension, reduced appetite, application site irritation, asthenia, fatigue, hypoglycemia, cholelithiasis, dizziness, dysgeusia, insomnia, increased lipase and amylase and delayed gastric emptying.
Semaglutide		Studies have shown that Semaglutide is effective in reducing weight, however, without physical exercise and changing eating habits it can cause a rebound effect in the individual.	Rebound effect, nausea, vomiting and diarrhea.

CONCLUSIONS

In recent years, there has been an increase in the consumption of antidiabetic medications purely for the purpose of weight reduction, with the most common ones being Metformin, Liraglutide, and Semaglutide. Despite their pronounced effects on weight loss, the use of these medications for obesity is not yet approved by drug regulatory agencies, making their use inappropriate for this purpose. The best way to reduce body weight continues to be through physical activity and lifestyle changes, and when such practices are insufficient, the use of anorexigenic drugs can be considered with the proper prescription and guidance from a healthcare professional. We also emphasize the need for a multidisciplinary team to ensure comprehensive care for users. The role of the pharmacist is particularly noteworthy as they are responsible for the interface between the medication and the patient in the process of educating to prevent the irrational use of antidiabetic medications for weight loss. Future studies should be conducted to deepen our understanding of this topic, particularly regarding the long-term use of these medications and their consequences for human health.

REFERENCES

Ahrén, B., Atkin, S. L., Charpentier, G., Warren, M. L., Wilding, J. P., Birch, S., & Leiter, L. A. (2018). Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes, Obesity and Metabolism*, 20(9), 2210-2219. https://doi.org/10.1111/dom.13353

Aroda, V. R., Bauer, R., Christiansen, E., Haluzík, M., Kallenbach, K., Montanya, E., Rosenstock, J., & Meier, J. J. (2022). Efficacy and safety of oral semaglutide by subgroups of patient characteristics in the PIONEER phase 3 programme. *Diabetes, Obesity and Metabolism*, 24(7), 1338-1350. https://doi.org/10.1111/dom.14710

Balaji, R., Duraisamy, R., & Kumar, M. P. (2019). Complications of diabetes mellitus: A review. *Drug Invention Today*, 12(1).

Cole, J. B., & Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nature reviews nephrology*, 16(7), 377-390. https://doi.org/10.1038/s41581-020-0278-5

Fonseca, K. P., & Rached, C. D. A. (2019). Complicações do diabetes mellitus. *International Journal of Health Management Review,* 5(1). https://doi.org/10.37497/ijhmreview.v5i1.149

Freemark, M., & Bursey, D. (2001). The effects of metformin on body mass index and glucose

tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. *Pediatrics*, 107(4), e55-e55. https://doi.org/10.1542/peds.107.4.e55

Freitas, G. C. P. L., Vasconcelos, M. C. D. H. V., Bisneta, A. I. S., Parra, R. L. O., Pereira, M. E. B., Negreiros, M. E. L., & Sobrinho, F. E. R. A. (2023). Efeitos do uso de semaglutida como opção farmacológica para o emagrecimento em adultos com IMC> 25 Kg/m²: uma revisão de escopo. *Research, Society and Development*, 12(4), e9012440955-e9012440955.

Gaia, C. G.; & Souza, N. B. (2018). Eficácia e riscos da utilização da metformina com finalidades diferentes para a qual foi desenvolvida. *Faculdade de Atenas*, 1(1), 1-18.

Gonçalves, L. S., & Abreu, T. P. (2021). O uso off label de medicamentos para o tratamento da obesidade no Brasil. *Revista Ibero-Americana de Humanidades, Ciências e cação*, 7(10), 1165-1177. https://doi.org/10.51891/rease.v7i10.2654

Jendle, J., Nauck, M. A., Matthews, D. R., Frid, A., Hermansen, K., Düring, M., & LEAD-2 and LEAD-3 Study Groups. (2009). Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. *Diabetes, Obesity and Metabolism*, 11(12), 1163-1172. https://doi.org/10.1111/j.1463-1326.2009.01158.x

Lee, A., & Morley, J. E. (1998). Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. *Obesity research,* 6(1), 47-53. https://doi.org/10.1002/j.1550-8528.1998.tb00314.x

Lundgren, J. R., Janus, C., Jensen, S. B., Juhl, C. R., Olsen, L. M., Christensen, R. M., & Torekov, S. S. (2021). Healthy weight loss maintenance with exercise, liraglutide, or both combined. New England Journal of Medicine, 384(18), 1719-1730. doi: 10.1056/NEJMoa2028198

Marques, G. J. R., Luiz, G. G., Neves, J. F., & Castro, L. A. (2021). O uso off label da metformina e fluoxetina para emagrecer e possíveis riscos à saúde. *Revista Saúde dos Vales*, 1(1) 1-24.

Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F., Nauck, M. A., & Buse, J. B. (2016). Liraglutide and cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine*, 375(4), 311-322. DOI: 10.1056/NEJMoa1603827

Martínez, R., López-Trinidad, L. M., Kapravelou, G., Arrebola, F., Galisteo, M., Aranda, P., & López-Jurado, M. (2020). A combined healthy strategy for successful weight loss, weight maintenance and improvement of hepatic lipid metabolism. *The Journal of*

Nutritional Biochemistry, 85, 108456. https://doi.org/10.1016/j.jnutbio.2020.108456

Mehta, A., Marso, S. P., & Neeland, I. (2017). Liraglutide for weight management: a critical review of the evidence. *Obesity science & practice*, 3(1), 3-14. https://doi.org/10.1002/osp4.84

Mendes, J. D. O. H., de Cássia Bastos, R., & Moraes, P. M. (2019). Características psicológicas e relações familiares na obesidade infantil: uma revisão sistemática. Revista da Sociedade Brasileira de Psicologia Hospitalar, 22(2), 228-247. https://doi.org/10.57167/Rev-SBPH.22.216

Nilson, E. A. F., Andrade, R. D. C. S., Brito, D. A. D., & Oliveira, M. L. D. (2020). Custos atribuíveis a obesidade, hipertensão e diabetes no Sistema Único de Saúde, Brasil, 2018. Revista Panamericana de Salud Pública, 44, e32.

Nuffer, W. A., & Trujillo, J. M. (2015). Liraglutide: a new option for the treatment of obesity. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 35(10), 926-934. https://doi.org/10.1002/phar.1639

Padhi, S., Nayak, A. K., & Behera, A. (2020). Type II diabetes mellitus: a review on recent drug based therapeutics. *Biomedicine & Pharmacotherapy*, 131, 110708.

Santos, K. P. et al. Perigo dos medicamentos para emagrecer. *Revista de Iniciação Científica e Extensão*, v. 2, n. 1, p. 37-45, 2019.

Scott, L. J. (2015). Liraglutide: a review of its use in the management of obesity. *Drugs*, 75, 899-910. https://doi.org/10.1007/s40265-015-0408-8

Silva, L. F. O. et al. Prevalência do uso de medicamentos para emagrecer entre universitárias. *Revista Científica de Enfermagem*, v. 3, n. 7, p. 19-26, 2013.

Siqueira, L. O., & Frigeri, F. C. (2018). Uso da metformina como agente emagrecedor. *RBONE-Revista Brasileira de Obesidade, Nutrição e Emagrecimento*, 12(71), 285-292.

Son, J. W., & Kim, S. (2020). Comprehensive review of current and upcoming anti-obesity drugs. Diabetes & metabolism journal, 44(6), 802-818. doi: https://doi.org/10.4093/dmj.2020.0258

Sousa, D. T. C., Meneses, F. G., Silva, G. L. M., & Cipriano, V. T. F. (2021). Risco do uso indiscriminado de medicamentos para emagrecimento Risk of indiscriminate use of medicines for slimming. *Brazilian Journal of Health Review*, 4(6), 28589-28602. doi:10.34119/bjhrv4n6-402

Sousa, J. C., Altino, I. P., de Andrade, S. M., Cunha, M. A., de Araújo, B. A. C., & de Oliveira, E. H. (2020). Dieta cetogênica para pacientes com diabetes mellitus tipo II. *Research, Society and Development*, 9(7), e117973972-e117973972. https://doi.org/10.33448/rsd-v9i7.3972

Srinivasan, S., Ambler, G. R., Baur, L. A., Garnett, S. P., Tepsa, M., Yap, F., ... & Cowell, C. T. (2006). Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. The Journal of Clinical Endocrinology & Metabolism, 91(6), 2074-2080. https://doi.org/10.1210/jc.2006-0241

Wadden, T. A., Hollander, P., Klein, S., Niswender, K., Woo, V., Hale, P. M., & Aronne, L. (2013). Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. International journal of obesity, 37(11), 1443-1451. https://doi.org/10.1038/ijo.2013.120

Weber, T. P., Bosco, I. E., Barroso, L. M., de Paiva, J. C. M., Passos, X. S., & Antunes, M. J. C. (2023). Uso do medicamento semaglutida como aliado no tratamento da obesidade. *Revista Científica Multidisciplinar*, 4(2), e422731-e422731. https://doi.org/10.47820/recima21.v4i2.2731

Wilding, J. P. (2018). Medication use for the treatment of diabetes in obese individuals. *Diabetologia*, 61(2), 265-272. https://doi.org/10.1007/s00125-017-4288-1