

Off-Label Use of Metformin for the Treatment of Obesity: A Risk or Success in Clinical Practice?

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ABSTRACT

Actually, metformin hydrochloride, an oral antidiabetic drug, has been used to treatment of obesity. Due to its effects associated to weight loss, patients are treated with this drug. In Brazil, the automedication is a recurring problem and has worsened with Covid-19 pandemic. The indiscriminate use without medical prescription of drugs such as metformin is worrying, mainly considering its off-label use. The aim this mini review was to discuss about the safety of off-label use of metformin in the treatment of obesity. This is a review of the literature carried out through a search in databases: PubMed, SciELO and MEDLINE; and Google Scholar. Articles were selected between 2018 and 2022. After reviewing the literature, it was observed that off-label use of metformin demonstrated efficacy as a therapeutic alternative for the treatment of obesity, in view of the importance of monitoring a pharmaceutical professional in the pharmacological treatment.

Keywords: Obesity; Off-Label Use; Metformin

Introduction

Obesity is considered a chronic disease, defined as the excessive or abnormal accumulation of fat in the body. It is a multifactorial disease, and its evolution occurs through relationships between social and environmental factors, such as: a high-calorie diet, sedentary lifestyle, and poor sleep quality. However, there are factors that are not controllable that make the weight loss process a challenge, they are hormonal and genetic factors [1]. The proportion of obese people in the Brazilian population increased from 12.2% in 2003 to 26.8% in 2019. In the same period, female obesity from 14.5% to 30.2%, while male obesity increased from 9.6% to 22.8%. Approximately 168,000 deaths per year in Brazil are caused by obesity. Cardiovascular diseases, Diabetes, respiratory diseases, and cancer represented about 75% of all causes of death in Brazil [2]. For therapeutic purpose, obesity treatments in adults include clinical guidance, food habit modification, pharmacological

treatment, and bariatric surgery, in cases of morbid obesity. Patients who initiate changes in life habits for at least 6 months, with changes in behavior, physical exercise, and diet, are advised to complement the treatment with pharmacological therapy. Managing obesity is a continuous process, it requires patient support and careful monitoring for effectiveness and safety [3]. Off-label use is defined as the use of drugs indicated by a group of professionals or a management system that has not been approved, based on the competent authorities, favoring the freedom of doctors to choose the most advantageous treatment for their patients [4,5].

Off-label use of a medication is practiced under the responsibility of the prescribing physician and may or may not be classified as a medical error, but most of the time, the use is made correctly, having as a counterpoint only the unapproved use [4]. Metformin is an antidiabetic drug used orally and is defined as a

first-line drug used in the treatment of Type II Diabetes Mellitus. It increases insulin sensitivity, thus reducing the rate of fat breakdown by inhibiting lipolysis, resulting in a decrease in free fat in the blood and liver, consequently facilitating the removal of fat in the body. Studies pointed the relationship between off-label use of metformin and weight reduction, or obesity are still lacking in depth. As many weight loss drugs were withdrawn from the pharmaceutical market, metformin emerged as a possible treatment [6,7]. Therefore, this mini review aimed to discuss about off-label use of metformin in the treatment of obesity in the clinical practice.

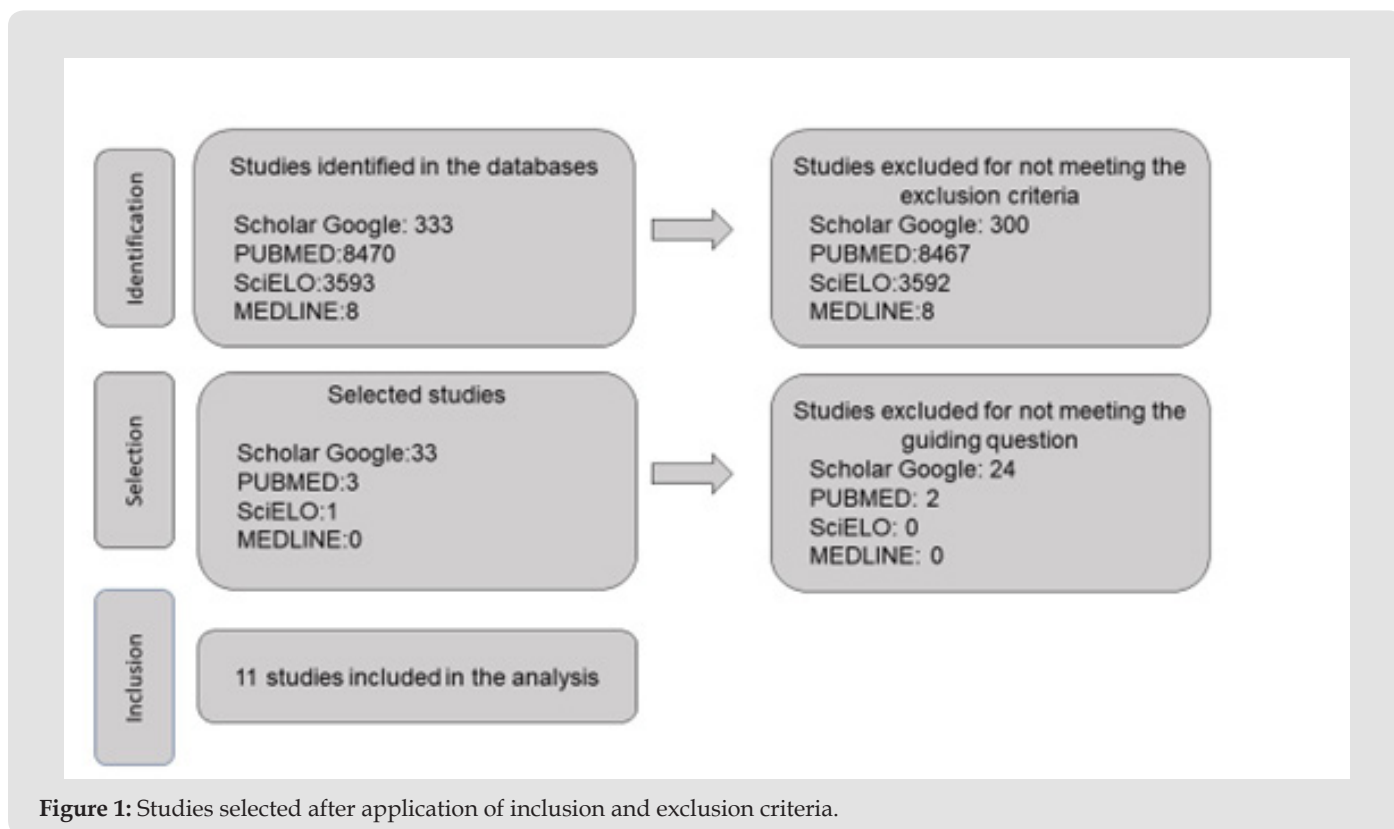
Methodology

This is a review study performed in databases such as: Medical Literature Analysis and Retrieval System Online (MEDLINE), Scientific Electronic Library Online (SciElo), and PUBMED. Google Scholar was also used and websites of Brazilian Ministry of Health

(BMH). There were difficulties in standardizing the descriptors and to obtain a wide variety of articles. Thus, the search pattern was changed according to database to find more articles. In MEDLINE database, Boolean operator AND was used: "Metformin and off label and obesity"; in PUBMED, Boolean operator OR: "Metformin or obesity or weight loss"; In SciELO: "Metformin, obesity", and in Google Scholar: "Metformin, off label, weight loss"; "Obesity, risks"; "Obesity, slimming". For this research, inclusion and exclusion criteria were used to select the articles. For inclusion criteria, articles published between 2018 and 2022, free access and written in Portuguese or English were selected. Articles that deviate from the main theme and duplicate articles were excluded.

Results

After a careful analysis of the articles, a flowchart (Figure 1) was constructed after application of inclusion and exclusion criteria. Then, 11 articles were chosen, read, analyzed, and summarized.



Discuss

Obesity

For Santos (2019) [8], obesity is a metabolic disease characterized by a disparity between energy intake and expenditure, causing a weight gain. A person is considered obese when its Body Mass Index (BMI) is greater than or equal to 30 kg/m². The normal

weight index varies between 18.5 and 24.9 kg/m². People who have BMI between 25 and 29.9 kg/m² are diagnosed with overweight and may already have some damage to their health [9]. There are genetic and external factors for the development of obesity such as: prolonged lack of food, increased intake of processed foods, decreased consumption of healthy foods and hormonal alterations. It is important to point out that obesity is associated with some

diseases that bring risks to human health as cardiovascular and renal diseases; Diabetes; arterial hypertension; cancers; asthma; digestive system and musculoskeletal diseases [10].

Non-Pharmacological and Pharmacological Treatment of Obesity

The treatment guidelines for obesity understand that people need to be focused on weight both in terms of individualized prevention and in accordance with the recommended treatment, which consists of diet, physical exercise, and bariatric surgery [11]. Conventional methods for reducing body weight require a change in people's behavior, which include the practice of physical exercises and a balanced diet [12]. Another method used for weight loss is through drug therapy, which is indicated for patients who have not achieved adequate weight loss through behavioral changes after six months of diet and physical exercises. The issue of pharmacological use requires constant support to the patient through monitoring for their safety and effectiveness by the doctor or pharmacist, through pharmaceutical care and anamnesis [3].

Off-Label Use of Metformin for Weight Loss

Metformin hydrochloride is one of the main choices for the treatment of Type II Diabetes Mellitus for patients. This disease is characterized by resistance of cells to the action of insulin and for this reason, it is not a viable option for treatment, but oral antidiabetics. It is a non-hypoglycemic drug from the biguanides group and derived from *Galega officinalis* L. It is worth emphasizing that the decrease in glycemia occurs essentially due to its hepatic and muscular actions that demonstrate insulin sensitizing action. In peripheral tissues that depend on insulin, essentially in skeletal muscle, there is an addition to obtaining glucose causing the glycemic reduction. While in liver cells, there is an increase in glycogenesis [12]. Patients who use metformin have effects such as a reduction in body weight. This effect occurs through an increase in insulin sensitivity, which reduces the rate of fat breakdown, resulting in a decrease in the release of fats into the blood and, as hence, to the liver, causing greater removal of fat in the body. Metformin causes a greater sensitivity to leptin, a hormone derived from fat cells that has a central effect in inhibiting appetite and increasing the patient's caloric expenditure, and consequently optimizes its effect, contributing to the reduction of body weight [7]. The use of this drug is safe and quite tolerable; however, it is not indicated for patients who are pregnant, insufficiency or have any relationship with the risk of hyperlactatemia [13]. Adverse effects of metformin include lactic acidosis, with restricted use only for patients with some diseases such as: liver, kidney, and lung [14]. The pharmacist performs an extremely important job about guiding patients who seek to resolve doubts about the correct use of medications, increasing adherence to treatment and managing risks related to their use. The pharmaceutical professional is

trained to raise awareness about the risks of self-medication and, most of the time, because he has a role of great responsibility that is to assist the patient and encourage the beginning and end of treatment [14].

Conclusion

Off-label use of metformin has obtained good results in the treatment of obesity, however it is not a drug used exclusively to this disease and weight loss is one of its side effect. Furthermore, it is important to consider non-pharmacological treatment as physical exercise, an adequate and healthy diet with caloric and nutritional balance. Changes in routine have the most impact on treatment, as it makes a healthy lifestyle in addition to bringing benefits to the body, such as: decreased blood sugar levels and decreased appetite. The association of metformin with non-pharmacological measures must be done by the prescriber to encourage more satisfactory results for the patient in the treatment of obesity.

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