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# Use and preventive value of metformin in geriatric women with polycystic ovary syndrome

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**ABSTRACT**

**Objective:** To establish the effects of long-term use and preventive value of metformin in geriatric women with PCOS.

**Methods:** A search of published review articles was carried out in sites such as NCBI, ScienceDirect, Elsevier, Springer, Wolters Kluwer, among others, using the key words: “polycystic ovary syndrome”, “PCOS”, “Polycystic ovary syndrome and metformin”, “ effects of metformin and PCOS “,” insulin resistance and metformin “and” long-term sequelae of polycystic ovarian syndrome “.

**Results:** We retrospectively analyzed data specific to the randomized clinical trial of Pedersen et al. 2017, to determine the impact that treatment had for twelve months with metformin in three specific variables: weight, total cholesterol and HDL. The study was conducted in 40 Caucasian women from 18 to 39 years of age, with a fixed dose of metformin (2 g / day for 12 months), who met the Rotterdam criteria for PCOS in their genetic variant MATE1 with SOP7

**Conclusions:** It was confirmed that the establishment of twelve-month treatment with metformin in the randomized clinical trial of Pedersen et al. 2017 had a significant effect on the three specific variables: weight, total cholesterol and HDL.

**Keywords:** Metformin, Geriatrics, Syndrome, Ovaries, Polycystic

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## INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder of women of reproductive age that affects 4 to 18% of women and is characterized by broader metabolic characteristics that include obesity, dyslipidemia and insulin resistance.[1-5] The consensus of the European Society of Reproduction and Human Embryology / American Society of Reproductive Medicine (ESHRE / ASRM) established through the Rotterdam Criteria that at least two of the following characteristics are needed to make the diagnosis; Anovulation or oligoovulation with less than nine menstrual periods every 12 months, symptoms or biochemical evidence of hyperandrogenism; and at least twelve small follicles from 2 to 9 mm in at least one ovarioechography.[5-10]

It is estimated that insulin resistance plays a fundamental role in the pathogenesis of PCOS, since it leads to a compensatory increase in insulin production by pancreatic beta cells to control hyperglycemia, however, in the long term it leads to failure of this metabolic compensation and consequently to diabetes mellitus 2 (DM2). Likewise, hyperinsulinemia is considered to increase hyperandrogenism through a central role or by decreasing the circulating levels of sex hormone binding globulin. PCOS is not a simple reproductive disorder, but rather a condition that has long-term consequences and complications with a high impact on the morbidity and mortality of geriatric women. Pathologies such as type 2 diabetes mellitus, metabolic syndrome, vascular brain disease, hypertension, coronary heart disease and endometrial cancer are the main long-term sequelae of PCOS, of which the majority have been attributed to obesity and resistance to insulin, although neither situation is diagnostic criteria for the syndrome. Therefore, treatment strategies should focus primarily on the proper management of insulin resistance and obesity. Obesity in women with PCOS has an increased prevalence of 2.8 times (50 to 80%) compared to women who do not have the syndrome. In the original description of the syndrome by Stein and Leventhal in 1935, 60% were obese. Unfortunately, this condition, so common in women with PCOS, exacerbates the symptoms of the syndrome. The prophylactic use of metformin, an insilunisensitizing agent, in patients are PCOS, allows to reduce the risk of long-term sequelae, its pharmacological characteristics and efficacy will be described below. Metformin is a drug widely indicated in the treatment of type 2 diabetes, belonging to the group of biguanides, however, in addition to its use in patients with diabetes, its application has been widespread in women with PCOS. 9-11 In 1980 the association between hyperandrogenism and hyperinsulinemia in PCOS was discovered thanks to Burghen et als. Since 1996 it has been known that the administration of this drug reduced insulin and androgen levels in women with PCOS and since this date there have been many subsequent studies confirming this action.[4]

In the 1990s, metformin was shown to improve hyperandrogenism in obese and non-obese women with PCOS, this due to a reduction in hyperinsulinemia due to increased insulin sensitivity. In type 2 diabetes, the glycemic response to metformin is hereditary, although the genetic contribution is probably the result of individual variants throughout the genome rather than a few loci with large effect sizes. Similarly, genetic factors are likely to mediate the response to metformin in PCOS. Metformin works by improving the sensitivity of peripheral tissues to insulin, which results in a reduction in circulating insulin levels. Metformin inhibits hepatic gluconeogenesis and also increases glucose uptake in peripheral tissues and reduces oxidation of fatty acids.[12-13]

The systemic benefits of metformin therapy for women with PCOS are widely recognized, but knowledge of the molecular mechanisms of its action and to what extent it beneficially affects uterine function is limited. The mechanism of action of metformin is not yet It is well known, but appears to have several functions.[14] Metformin reduces insulin resistance, hepatic

gluconeogenesis and glucose uptake in the intestine, thereby improving insulin secretion from pancreatic β cells, thereby reducing glucose in the blood. It was also shown that metformin inhibits hepatic gluconeogenesis, by modulating the 5'-adenosine monophosphate activated protein kinase (AMPK), which depends on the regulation of the orphan nuclear small heterodimer receptor (SHP).[2] Serine-threonine protein kinase 11 (SK11) together with AMPK signals are involved in the suppression of genes, which encode gluconeogenic and lipogenic liver enzymes in the hepatic pathway induced by metformin.[3] In other studies, its mechanism of action is known to inhibit hepatic glucose production and increase peripheral insulin sensitivity to insulin, the latter effect is very useful in non-diabetic women who have PCOS and has demonstrated long-term improvement of the menstrual cycle, ovulation, hyperandrogenism and hirsutism.[4] Skeletal muscle accounts for more than 80% of the glucose uptake stimulated by insulin. In insulin resistant skeletal muscle cell cultures, metformin was able to restore insulin signaling defects, including reduction of insulin stimulated insulin receptor and phosphorylation of IRS-1, as well as phosphatidyl activity inositol 3-kinase (PI3K).[7]

It has been reported that chronic treatment with metformin inhibits the accumulation of lipids in human skeletal muscle and increases the activity of atypical basal and insulin stimulated protein kinase C (aPKC), without altering the basal and insulin stimulated activation of the PI3K dependent on IRS-1 and Akt (also known as protein kinase B, PKB) [7,11]. However, it was shown that treatment with acute metformin prevents insulin-induced suppression of oxidation of fatty acids in oxidative muscles[15]. Consequently, such lipid effects could contribute to improving insulin sensitivity and insulin stimulated glucose uptake.

Dyslipidemia is the most prevalent metabolic aberration in PCOS, which is most frequently represented by atherogenic dyslipidemia typical of IR states, that is, hypertriglyceridemia, decreased HDL cholesterol levels and increased small LDL cholesterol. and dense. Compared to healthy women, women with lean and obese PCOS had abnormal levels of phosphatidylcholine, free fatty acids and polyunsaturated fatty acids (PUFAs). In addition, oxidative stress in PCOS can participate in systemic inflammation and, together with IR and subsequent hyperinsulinemia, can influence the ovarian compartment and endothelial cells, resulting in hyperandrogenism, anovulation and CV disorders. It was shown that insulin and androgens may have opposite effects on lipid profiles in patients with PCOS9. Women with PCOS have an increased risk of cardiovascular disease as a result of the presence of insulin resistance and its related metabolic consequences, such as metabolic syndrome, type 2 diabetes and dyslipidemia, however, the actual prevalence of disease is unknown. cardiovascular in PCOS.[12]

The main side effects associated with metformin treatment are gastrointestinal symptoms of nausea, diarrhea, flatulence, bloating, anorexia, metallic taste and abdominal pain. These symptoms occur with varying degrees in patients and in most cases they resolve spontaneously. The severity of side effects can be reduced by the gradual administration of metformin and the assessment of dose increase guided by the severity of symptoms. An initial dose of 500 mg per day during the main meal of the day for 1 to 2 weeks may decrease side effects and allow tolerance to develop. A weekly or biweekly increase of 500 mg per day may be performed as necessary until a maximum dose of 2500 to 2550 mg / day is reached, depending on the clinical benefit and side effects. If the increase in the dose causes a worsening of the effects. Slow-release metformin may be associated with fewer side effects. Metformin can also cause malabsorption of vitamin B12 in the distal ileum in approximately 10 to 30% of patients, which is an effect that depends on age, dose and duration of treatment Rarely, lactic acidosis can occur , mainly in diabetic patients, which is a

serious condition that can be life threatening. However, unless there is a contraindication to take metformin such as kidney disease, the risk of lactic acidosis is negligible.[11-16]

## METHODS

A quantitative systematic review of review articles, original articles, experimental articles and meta-analyzes published from 2010 to 2018 was carried out on sites such as NCBI, ScienceDirect, Elsevier, Springer, Wolters Kluwer among others, using the keywords: "polycystic ovary syndrome", "PCOS", "Polycystic ovary syndrome and metformin", "effects of metformin and PCOS", "insulin resistance and metformin" and "long-term sequelae of polycystic ovarian syndrome".

## RESULTS

Specific data from the randomized clinical trial of Pedersen *et al*. 2017, to determine the impact that the treatment had during twelve months with metformin in three specific variables: weight, total cholesterol and HDL. The study was conducted in 40 Caucasian women 18 to 39 years of age, with a fixed dose of metformin (2 g / day for 12 months), who met the Rotterdam criteria for PCOS in their genetic variant MATE1 with SOP7.

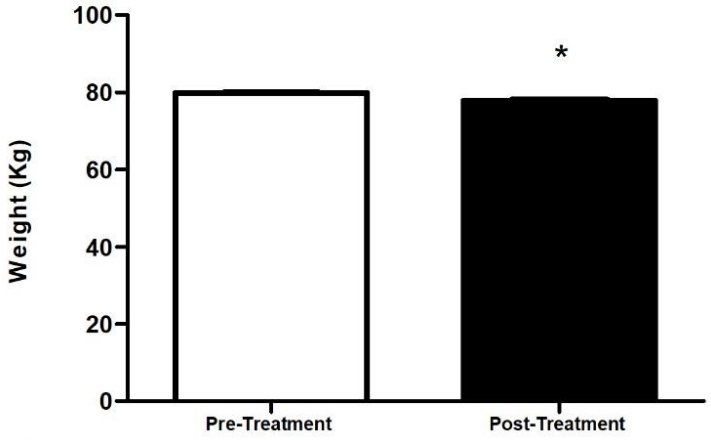


**Figure 1. Effects of 1 year of treatment with metformin on the weight of 40 patients with PCOS. P=0.0001 Pre-Treatment (79.9± 0.51Kg) and Post-Treatment (77.6±1.86Kg)**

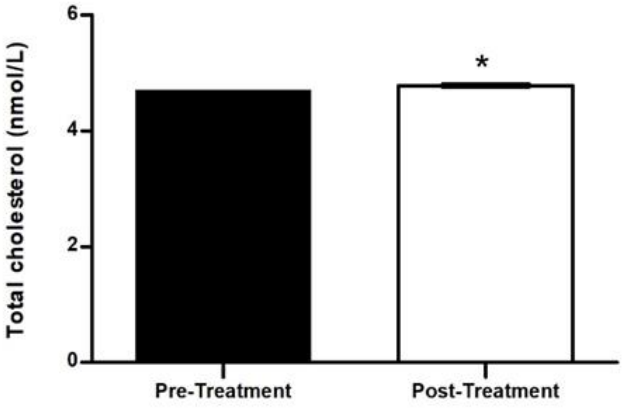


**Figure 2. Effects of 1 year of treatment with metformin on the total cholesterol of 40 patients with PCOS. P=0.0015 Pre-Treatment (4.7 nmol/L) and Post-Treatment (4.78±0.15 nmol/L)**

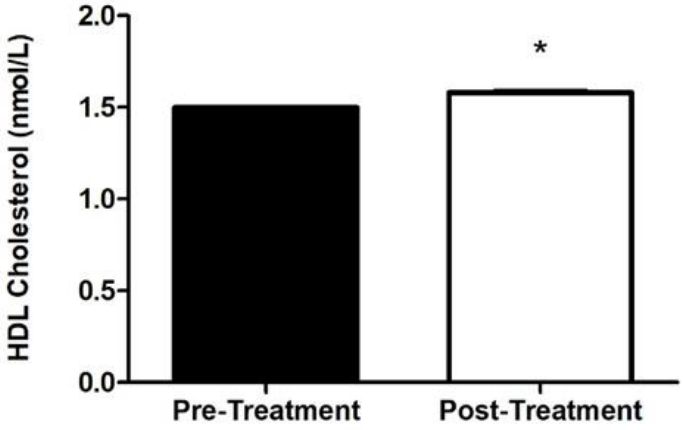


**Figure 3. Effects of 1 year of treatment with metformin on the HDL cholesterol of 40 patients with PCOS. P=0.0001 Pre-Treatment (1.5 nmol/L) and Post-Treatment (1.58±0.05 nmol/L)**

The effects of 1 year of treatment with metformin in the first variable analyzed (weight) of 40 patients with PCOS were: Pre-Treatment (79.9 ± 0.51kg) and Post-Treatment (77.6 ± 1.86kg) (Figure 1). The statistical analysis of the weight of the 40 Pre-Treatment and Post-Treatment patients was carried out with the T-student parametric test using GraphPad Prism 5.0 software and a value of p = 0.0001 was obtained.

Likewise, the effects of 1 year of metformin treatment in the second analyzed variable (total cholesterol) of 40 patients with PCOS were: Pre-Treatment (4.7 nmol / L) and Post-Treatment (4.78 ± 0.15 nmol / L) ( Figure 2). The statistical analysis of the total cholesterol of the 40 Pre-Treatment and Post-Treatment patients was carried out with the T-student parametric test using GraphPad Prism 5.0 software and a value of p = 0.0015 was obtained.

Finally, the effects of 1 year of metformin treatment on the third analyzed variable (HDL) of 40 patients with PCOS were: Pre-Treatment (1.5nmol / L) and Post-Treatment (1.58 ± 0.05nmol / L) (Figure 3 ). The statistical analysis of the HDL of the 40 Pre-Treatment and Post-Treatment patients was carried out with the T-student parametric test using GraphPad Prism 5.0 software and a value of p = 0.0001 was obtained.

## DISCUSSION

It was determined through the statistical analysis performed in the 40 patients with PCOS that the treatment with metformin for one year had a high impact on the three variables (weight, total cholesterol and HDL). The result of the effect on weight was very highly significant, which allows us to infer that one of the main causes of long-term sequelae in women with PCOS, obesity, can be controlled and even eliminated through the daily use of metformin and the sum of changes in the lifestyle of the patients. Likewise, the result of the effect on total cholesterol was highly significant, which means that total cholesterol may increase instead of decreasing in PCOS patients for two reasons, the first because in the analysis performed it was observed that the levels of DHL increased and this increase is inferred caused the increase in total cholesterol, and second is that it is essential to change the lifestyle of patients with diet and exercise to lower cholesterol levels despite the favorable increase that HDL favors. Finally, the result of the effect on HDL was very highly significant, since it increased after one year of treatment, which allows us to conclude that metformin treatment is directly involved in increasing the levels of “good cholesterol” in the blood, and is inferred This is the reason why total cholesterol levels increased.

## CONCLUSION

It was determined that treatment for 12 months with metformin the randomized clinical trial of Pedersen et al. 2017 had a significant effect on the three specific variables: weight, total cholesterol and HDL. Therefore, it is concluded that both lifestyle modifications, through the improvement of diet and exercise that produces weight loss, as well as metformin as a treatment for PCOS, represent the cornerstone of the effective improvement of Long-term health and thus avoid subsequent sequelae in geriatric women. The use of metformin in PCOS may show different results in the different analyzes since it depends largely on the variability of the patients in the phenotypes and their metabolic parameters, in the case of the analysis presented, the evidence shows a broadly positive effect, and despite not being evident until now, it is inferred that the prophylactic use of metformin would reduce the risk of disease and sequelae of PCOS in the long term in these patients. However, further studies must be carried out to establish determining criteria.

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