

Review Article

Metformin and Weight Loss in Patients with Polycystic Ovary Syndrome

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Abstract

Introduction: Polycystic ovary syndrome is the most prevalent endocrinopathy in women of reproductive age. One characteristic of this disease is an association with various cardiovascular risk factors, including obesity, overweight, and insulin resistance. It is therefore important to study weight loss associated the use of metformin, which is widely prescribed to patients with polycystic ovary syndrome, in this population.

Material and Methods: A systematic review using only randomized clinical trials with placebo or control group using or not lifestyle change measures and systematic reviews.

Results: Based on the quality criteria for this review, a total of 14 studies were included and expanded the period of 2011 to 2014.

Conclusion: The use of high-dose metformin (>1500 mg per day) is associated with an average weight loss of 2.7 kg in 6 months; however, physical activity and diet were more efficient than metformin alone. When metformin is used in association with hormonal treatment, in the form of the oral contraceptive pill, a slight attenuation in weight loss is observed.

Keywords: Polycystic Ovary Syndrome; Weight Loss; Obesity; Overweight; Metformin

Abbreviations

AC: Abdominal Circumference;

ATP: Adenosine Triphosphate;

BMI: Body Mass Index;

cAMP: Cyclic Adenosine Monophosphate-Dependent Protein Kinase;

CR: Cardiovascular Risk;

IR: Insulin Resistance;

LDL-C: Low-Density Lipoprotein Cholesterol;

Metsyn: Plurimetabolic Syndrome;

OHC: Oral Hormone Contraceptive;

PCOS: Polycystic Ovary Syndrome;
T2DM: Diabetes Mellitus

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrinopathy in women of reproductive age, occurring in approximately 6–15% of this population [1]. One of the hallmarks of PCOS is menstrual irregularity, which affects approximately 80% of patients. The pathophysiology of menstrual irregularity is related to chronic anovulation, and the symptom has a direct impact on fertility [2]. Another common manifestation, hyperandrogenism, is typically associated with hirsutism; acne and/or alopecia may also occur, with devastating effects on the patient's self-esteem [3].

In addition to reproductive and dermatological implications, metabolic effects [4] play an important role by increasing cardiovascular risk (CR). Metabolic effects include an increased prevalence of insulin resistance (IR), diabetes mellitus (T2DM) [5,6], hypertension [7], dyslipidemia [8], atherosclerosis [9], and obesity [10]. The risk of metabolic syndrome (MetSyn) is also increased in this typically overweight and obese population [4].

While the etiology of PCOS remains unknown [2], the disease is characterized by a high prevalence of overweight and obesity; a major challenge in the treatment of PCOS is to identify the best intervention for weight loss.

The association between PCOS and obesity, overweight, and subcutaneous fat accumulation is well established; these features are observed in 40–85% of women with PCOS, regardless of age [12] and tendency to accumulate subcutaneous fat. The association of abdominal fat and PCOS is independent of body mass index (BMI), and affects 30–70% of patients [13]. Abdominal adiposity is understood to play a major role in the pathophysiology of this disease; a 5% weight loss, even in non-obese patients, results in an improvement in hyperandrogenic symptoms and menstrual irregularity, with the return of ovulation [14].

Lipolysis of abdominal fat increases IR and the production of inflammatory markers, resulting in an enhanced CR [15,16], and PMS, which prevalence accounts for 50% of PCOS patients [17]. Metformin may improve IR and facilitate weight loss, with a consequent reduction in CR.

Metformin, a biguanide, is associated with low rates of hypoglycemia, and is considered the first line drug in the treatment of type 2 diabetes and prediabetes [19,20]. Lactic acidosis is a rare but potentially serious side effect, with an incidence in the literature of 3/100,000 per year of use [21]; more commonly reported are gastrointestinal side effects, including nausea, vomiting, diarrhea, flatulence, abdominal pain, and indigestion. Al-

though usually mild and transient, gastrointestinal disturbance is reported by 10–50% of PCOS patients treated with metformin.

Metformin reduces atherogenesis and oxidative stress, and facilitates the redistribution of body fat by inhibiting the accumulation of subcutaneous fat [22]. Metformin also improves the lipid profile by decreasing the level of low-density lipoprotein cholesterol (LDL-C) [23], and is reported to ameliorate nonalcoholic hepatic steatosis [24].

However, analysis of the use of metformin and the evolution of prediabetes in T2DM patients indicates that metformin-associated improvements are slow to manifest, in comparison with improvements associated with lifestyle changes. The use of metformin was effective stopping the progression to DM in 38% of cases treated with the drug, compared with 52% of patients who instigated lifestyle changes [24].

The mechanism of action of metformin relies on a decrease in the production of hepatic glucose, and an increase in the uptake of circulating glucose by liver and muscle. Inhibition of hepatic gluconeogenesis by metformin occurs in the mitochondria; the drug acts to reduce the activity of the mitochondrial respiratory complex, thereby decreasing the production of adenosine triphosphate (ATP), resulting in inhibition of hepatic glucose and lipid production [2]. Moreover, metformin induces the activation of cyclic adenosine monophosphate-dependent protein kinase (cAMP), leading to increased fatty acid oxidation [25]. This provides a potential mechanism through which the drug may result in weight loss; however, the issue remains controversial in the literature, as not all studies show an association between metformin use and weight loss [26].

In PCOS patients, in addition to the benefits described above, metformin also acts on hyperandrogenism, and is associated with improvements in clinical and laboratory parameters, and ovulation. Notably, the latter effect does not imply an increased number of live births, when compared with a control group [27].

This review will address the use of metformin as a therapeutic treatment for weight loss and associated improvements in IR.

Material and Methods

Systematic review and literature survey in the PubMed, Embase and Cochrane Library being selected works considered of better methodological quality. Only randomized clinical trials with placebo or control group using or not lifestyle change measures and systematic reviews was selected, all papers that contain any confounding factor in the results were excluded.

We considered the use of work 1995 to 2015, the following terms are used to search "PCOS", "polycystic ovary syndrome", "IR", "metformin", "biguanides", "BMI", "weight loss", "obe-

sity “ , “ overweight “ and “ sensitizing drug insulin .”

Results

A total of 357 papers were identified that addressed the theme of the study. After reading and selection of works by the inclusion criteria of using only randomized double-blind clinical trials showing placebo control group, with the use of metformin as the only intervention in the study, results the selection of 14 works that follow described in Table 1.

Discussion

In contemporary clinical practice, overweight and obesity are the most prevalent diseases worldwide. Given that the complications of these diseases have a profound impact on morbidity and mortality, effective therapeutic interventions have been proposed. Despite the importance of this subject, data are scarce. A major difficulty is the identification of adequate interventions; in the majority of studies, lifestyle changes such as diet and/or physical activity are adopted alongside the use of drug therapy, as in the case of literature relating to the use of metformin. Moreover, many PCOS patients take oral hormonal contraceptives (OHCs), which may generate confusing data. Although the majority of the available literature demonstrates that use of OHCs is not associated with weight changes, studies specifically addressing this issue in PCOS patients are scarce [28]. The main studies on this topic are discussed below.

A major concern is the identification of the most effective metformin dose to induce weight loss in obese and overweight PCOS patients. In the present study, we considered two studies [29,30] with a total population of 35 patients treated with metformin at a dose of <1500 mg per day. When compared with a control group (n=36) for a period of 7 weeks, no differences in weight were observed.

The administration of a dose >1500 mg/day was reported in three studies, all of which included a control group in which no intervention was offered [31-33]. In these studies, the result was an average total weight loss of 2.7 kg in 6 months [34].

In total, we reviewed five studies [35-40], comprising a total population of 165 treatment group patients and 175 control group patients. No significant differences were observed between the groups in any of the studies, during a 6-month follow-up period, the greatest problem is the the short follow up, because the results could be even better in a long period of the. Taken together, these results indicate that metformin at a dose >1500 mg/day is associated with a reduction in weight and the waist circumference (WC) in PCOS patients. This may be interpreted as implying that combining dietary intervention with metformin treatment would achieve superior results. However, the results of our review indicated that, when diet alone was compared with diet plus metformin treatment, there was

no between-group difference in weight loss, despite a greater reduction in the WC of patients in the combination treatment group.

When combined lifestyle interventions (physical activity and dietary measures) are compared with metformin alone, greater improvements are observed those patients that changed their lifestyle. A study conducted in Saudi Arabia [41] concluded that the combination of caloric restriction and physical activity (moderate physical activity for 2 hours and 30 minutes or higher intensity activity for 1 hour and 15 minutes per week) was associated with greater weight loss, compared with that observed in patients using metformin alone. Over a period of 6 months, a weight reduction of approximately 10.3 kg was observed in the combined lifestyle interventions group, compared with 5.3 kg in the metformin alone group. While this study reported a weight loss greater than that reported by similar studies, the results suggest that lifestyle changes are more effective in reducing weight compared with metformin alone [41]. However, in a similar study performed in Brazil [42], between-group differences were limited to a higher decrease in WC in the exercise and diet group; no differences were observed between the lifestyle interventions and metformin alone groups in terms of weight loss. The two interventions described in this study did not differ significantly. It is worth mentioning the wide variation in the intensity of physical activity between different studies; patients in the Brazilian study performed only 90 minutes of moderate exercise per week. Population sampling also differed between these two studies; the sample size of the first study was 180 patients, compared with only 40 patients in the second study.

Further studies are required to address the use of hormonal contraceptives with metformin. The only existing study addressing this subject was conducted in the United States [43]. In this study, weight loss was observed in patients taking OHCs (desogestrel and ethinyl estradiol), although these patients presented a lower reduction in weight than with the use of isolated metformin. In the group of patients taking this biguanide, a weight loss of 1.3 kg and 3 kg was observed after 6 months and 1 year, respectively. This result suggests that it is possible to achieve the weight-related effects of metformin, alongside the endocrine benefits of OHC use.

Conclusion

The results of this review indicate that the use of metformin in PCOS patients promotes a weight loss of approximately 2.7 kg; this is a less substantial weight loss compared with that achieved by lifestyle changes. Therefore, metformin may be specifically indicated for the treatment of DM and impaired glucose tolerance in PCOS; the first-line treatment options for weight loss should be dietary change and physical activity.

The results of this review also show that concomitant use of metformin and OHC is associated with weight loss, although the degree of weight loss may be less than that achieved with metformin alone.

Further studies should be conducted in PCOS patients with the aim of assessing the impact of metformin on other measures related to body fat distribution.

Table 1. Description of selected studies, according to author, intervention, and follow-up duration.

Author	Intervention	Follow-up duration
Jakubowicz et al. [29]	Randomized, double-blind clinical trial Low-dose metformin (n=28) vs. Placebo (n=28)	7-8 weeks
Vandermolen et al. [30]	Randomized, double-blind clinical trial Low-dose metformin (n=12) vs. Placebo (n=15)	7 weeks
Fleming et al. [31]	Randomized, double-blind clinical trial High-dose metformin (n=26) vs. Placebo (n=39)	14 weeks
Kocak et al. [32]	Randomized, double-blind clinical trial High-dose metformin (n=28) vs. Placebo (n=28)	6 weeks
Yarali et al. [33]	Randomized, double-blind clinical trial High-dose metformin (n=16) vs. Placebo (n=16)	6 weeks

Gambineri et al. [35]	Randomized, double-blind clinical trial High-dose metformin and Diet (n=16) vs. Diet (n=16)	24 weeks
Kjotrod et al. [36]	Randomized, double-blind clinical trial High-dose metformin and Diet (n=19) vs. Diet (n=21)	16 weeks
Pasquali et al. [37]	Randomized, double-blind clinical trial High-dose metformin and Diet (n=18) vs. Diet (n=17)	24 weeks
Tang et al. [38]	Randomized, double-blind clinical trial High-dose metformin and Diet (n=69) vs. Diet (n=74)	24 weeks
Ladson et al. [39]	Randomized, double-blind clinical trial High-dose metformin and Diet (n=55) vs. Diet (n=59)	24 weeks
Esfahanian et al. [40]	Randomized, double-blind clinical trial High-dose metformin and Diet (n=17) vs. Diet (n=13)	12 weeks
Omar et al. [41]	Randomized, double-blind clinical trial High-dose metformin (n=180) vs. Diet+ physical activity (n=70) Observation: Healthy controls	24 weeks

Curi et al. [42]	Randomized, double-blind clinical trial High-dose metformin + Diet (n=18) vs. Diet+ physical activity (n=12)	24 weeks
Glintborg et al. [43]	Randomized, double-blind clinical trial High-dose metformin (n=30) vs. High-dose metformin + OHC (n=30)	48 weeks

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