REVIEW

Comparing The Effects of Metformin and Exercise-Based Lifestyle Interventions for Symptom Management of Polycystic Ovary Syndrome (PCOS): A Literature Review

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is a common hormone problem characterized by androgen excess and typically leads to the development of small cysts in the ovaries, insulin resistance, hirsutism, irregular menstrual cycles, and hyperandrogenism. While there is no cure for PCOS, treatments like metformin and lifestyle modifications work to manage individual symptoms. While studies in the past have compared individual effects of metformin and lifestyle modifications, specifically aerobic exercise. This review compared the effects of metformin treatment and exercise interventions on metabolic symptoms, such as high blood glucose and insulin levels in PCOS.

Methods: A literature search using Pubmed and Google Scholar was conducted. A total of five articles focusing on metformin were included in the review; some focusing inclusively on the drug itself, others comparing lifestyle modifications alone and modifications combined with metformin. In this review, the lifestyle modification was aerobic exercises, taking the form of exercise regimes (walks, marching in place, or supervised fitness sessions).

Results: Results show that metformin improves metabolic symptoms, including blood glucose and insulin levels, significantly more than lifestyle interventions alone; however, if both treatments were combined, these effects were more profound.

Discussion: Metformin serves as an effective treatment for metabolic and hormonal symptoms, consequently improving PCOS symptomology. Although exercise is shown to be less effective than metformin, the addition of exercise to metformin treatment further ameliorates symptomology.

Conclusion: Combining metformin and aerobic exercise demonstrates the greatest impact on managing PCOS symptoms. Future studies should examine the standardization of an aerobic exercise regimen and pharmaceutical treatments for the management of PCOS.

Keywords: polycystic ovary syndrome; PCOS; aerobic exercise; lifestyle modification; metformin; metabolic syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder estimated to affect 4-20% of reproductive-aged women worldwide [1]. It is a complex disorder with several presentations, including hirsutism, acne, and male-pattern alopecia [2]. Today PCOS is commonly diagnosed according to the Rotterdam criteria, in which it requires at least two of the following features: oligoovulation or anovulation, hyperandrogenism, and polycystic ovaries [3].

Comorbidities associated with PCOS are obesity, insulin resistance, cardiovascular diseases, obstructive sleep apnea, endometrial hyperplasia, and certain types of cancers, all of which can exacerbate symptoms [3]. Currently, there is no known all-encompassing cure for PCOS. Still, several treatments are given for symptom management, such as oral contraceptives, antiandrogens, or glucocorticoids for hyperandrogenism, insulin-sensitizing

Feng | URNCST Journal (2024): Volume 8, Issue 1 DOI Link: <u>https://doi.org/10.26685/urncst.525</u> agents, and lifestyle modifications for insulin resistance and weight management.

Metformin, an established oral insulin-sensitizing agent, is typically used to treat type two diabetes by regulating blood glucose and insulin levels [4]. Recently, it has been explored as a treatment option for PCOS. Patients with PCOS are more susceptible to metabolic syndrome, a cluster of conditions that increase the risk of heart disease, stroke, and type two diabetes [5]; thus, metformin can be used to ameliorate these symptoms and prevent its onset [6]. In healthy patients, body mass index (BMI) is considered normal if it is $\leq 25 \text{kg/m}^2$ [7], normal low-density lipoprotein (LDL) cholesterol is below 100 mg/dL [8], and normal follicle-stimulating hormone (FSH) levels between 4.7 to 21.5 mlU/mL [9]. Metformin use in overweight women with PCOS has shown improvements in BMI, LDL cholesterol, and reduced FSH levels. These factors are thought to be directly influenced by metformin's effect on

ovarian steroid production [10]. With clinical follow-up, the benefits of metformin on metabolic syndrome can be sustained for more than three years [6].

However, metformin has limitations, including adverse effects that can range from gastrointestinal side effects, with the most severe being vomiting and diarrhea [11,12]. Moreover, new evidence suggests that due to obese patients' additional insulin resistance, metformin may not be able to work effectively for patients with a higher BMI [4].

Due to this added barrier, other treatment options beyond pharmaceuticals are studied, including lifestyle modifications [13,14]. Since obesity has been associated with more severe symptomology in women with PCOS, there is a rationale for promoting weight loss [10,15]. Weight loss, even as little as 5% of body mass, has been associated with the amelioration of symptoms such as insulin resistance and anovulation [16]. It has been shown that abdominal fat loss lowers inflammation and improves hyperandrogenism and metabolic function [2].

Lifestyle modifications are considered the gold standard of treatment for PCOS [6]. This approach focuses on the principles of lifestyle medicine, which is a preventative approach that works to change a patient's behavior and habits for the management of chronic conditions and illnesses [17]. Lifestyle medicine comprises six pillars: nutrition, exercise, sleep, stress management, avoidance of risky substances, and healthy relationships [17]. Exercise is the most examined of these six pillars to promote weight loss in women with PCOS. It is specifically emphasized that moderate physical activity, not including strenuous exercise, should improve cardiometabolic function and regulate glucose and androgen levels via weight loss [2,18]. These findings highlight the importance of lifestyle modifications for PCOS management; however, limited studies show the generalizability of these results to women with a higher BMI.

Despite the treatments available for PCOS, there is yet to be a single universal standard of treatment for symptom management. Given the lack of established treatment standards [11,12,14,18], this review investigated the effects of metformin treatment and exercise on metabolic parameters, including BMI, blood glucose, and insulin levels in PCOS. This review compared the effects of metformin and lifestyle modification in managing symptoms of PCOS. The findings of this study provide insights into the clinical management of PCOS and extend the understanding of the role of lifestyle modifications in PCOS.

Methods

Literature Search Strategies

A database search was conducted on July 2nd, 2023 on PubMed and Google Scholar using the keywords PCOS, exercise, and metformin combined by an "AND" function. Meta-analyses and reviews were excluded using the database filtering system. Articles written in English and published after 2010 were considered.

Study Selection

The studies selected were all randomized controlled trials that compared the metabolic effects of metformin and exercise in PCOS. Articles were included if participants were over 18 but before menopause, had a BMI >18.5, and had a diagnosis of PCOS as per the Rotterdam Criteria. Studies were screened to exclude participants with significant and severe pathology that could interfere with the study's completion. This includes participants who had undergone fertility treatments and other treatments known to interfere with metabolic outcome measures of PCOS (i.e., hormone treatments, hormonal contraceptives, drugs known to interfere with metformin) in the six months prior to each study. Participants who had a history of any other disorder known to cause PCOS symptoms, commonly androgen-secreting tumours, diabetes, and Cushing's syndrome, also were excluded.

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[19] guidelines were used to assess the quality of the studies. Each study included in the review has been assessed for quality using the CASP checklist. Insulin level changes before and after intervention were used to ensure CASP checklist standards were met.

Results

Figure 1 shows the identification process of eligible articles. A total of 1518 primary studies were retrieved from PubMed and Google Scholar. No duplicate articles were found. After screening, 1410 articles were removed and 108 articles were individually screened for title and abstract. A total of 5 articles were included that compared metformin usage with aerobic exercise in PCOS (see Table 1). The study durations ranged from 12 weeks to 1 year. The effects of metformin and aerobic exercise were evaluated by assessing biomarkers like insulin levels, weight, hormone levels, inflammatory markers, and changes in the BMI of participants. Blood tests and in-lab measurements were used to track these changes.

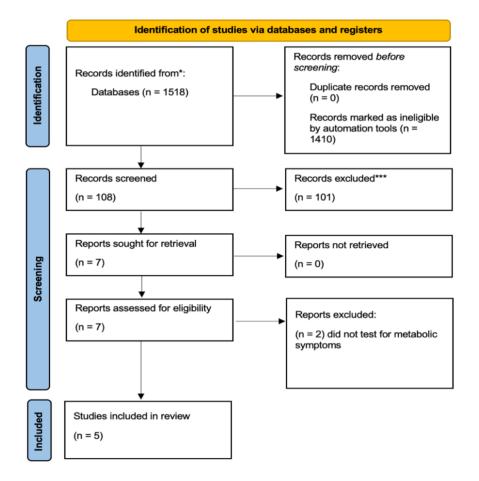


Figure 1. Identification of studies following PRISMA guidelines (figure created with Microsoft Word).

Metformin versus Lifestyle Modification

Of the five articles examined, only two compared the efficacy of lifestyle modification (aerobic exercise) to metformin. Fux Otta et al. (2010) found that combining metformin with lifestyle modification yielded significant results in waist circumference, fasting insulin levels, and testosterone levels (p = 0.007, p = 0.003, and p = 0.02, respectively), while participants that only received lifestyle modification yielded no significant results after four months of treatment [21]. Tiwari et al. (2019) also found similar results; participants that only received lifestyle modification treatment did not show significant changes in testosterone and insulin levels at 3 or 6 months, except for 2 participants who had improved insulin levels at six months [24]. In the metformin group, 83% of participants showed significant improvement in insulin levels after three months and all participants showed significant results after 6 months [24]. Combining metformin with aerobic exercise yielded a significantly higher reduction in waist circumference than with aerobic exercise alone. Despite the higher mean weight loss seen in the metformin group, there were no significant differences in BMI between the two groups [24].

Metformin and Lifestyle Modification

Metformin treatment has been shown to significantly impact BMI, weight, and waist circumference. Mandel et al. (2017) found a significant reduction in participants' weight and BMI [20], while Wior et al. (2010) found that metformin significantly reduced waist circumference and fasting insulin levels (p = 0.007 and p = 0.003respectively) [21]. When combining aerobic exercise with metformin, there was a more profound reduction in participant waist circumference (p < 0.001) [22].

To evaluate the effects of aerobic exercise, biochemical inflammatory markers were examined. Elbandrawy et al. (2022) found that metformin treatment led to a significant reduction of interleukin-6 (IL-6), tumor necrosis factor (TNF), and C-reactive protein (CRP) in patients, with the most significant reduction when combined with aerobic exercises (p = 0.01, p = 0.01, p = 0.001 respectively) [23]. Tiwari et al. (2019) found a significant change in testosterone levels at six months following metformin treatment (p = 0.0001) [24]. On the contrary, Ladson et al. (2011) found testosterone levels in the metformin treatment group to be lower at three months than at six months, although a total attrition rate of 66.7 % has been reported [22]. By itself, aerobic exercise was found to have no

significant effects on BMI, waist circumference, waist-tohip ratio, and fasting insulin levels [20,21,22]. The effects of exercise on BMI are also inconsistent; two studies found that there was no significant reduction in BMI [20,24], while Wior et al. (2010) found no significant effects in BMI [21]. While Tiwari et al. (2019) found no statistical differences in BMI (p = 0.090), there were significant differences after six months in participant weight when treated with lifestyle modification with and without metformin (p = 0.043) [24]. Ladson et al. (2011) found that aerobic exercise without metformin significantly reduced participant waist circumference (p = 0.001) but had no significant effects on fasting insulin levels (p = 0.38) [24].

Author & Year of Study	Sample Size	Age	Outcome Measures	Intervention	Duration	Significant Results
Elbandrawy et al. (2022)	n=40 (normal weight)	<i>M</i> =26.7	IL-6, TNF-α, and CRP	Metformin vs. Metformin and aerobic exercise (low to mid intensity)	12 weeks	Significant reduction of IL-6, TNF- α , and CRP in both groups; a larger decrease in the aerobic exercise added group
Tiwari et al. (2019)	N=66 (54% obese, 14% overweigh t, 32% normal weight)	<i>M</i> = 24.5	Menstrual cycle duration, acne, acanthosis nigricans, hirsutism, anthropometric parameters, serum testosterone	Metformin and fixed exercise schedule vs. Placebo and fixed exercise schedule	6 months	The Metformin group showed better results on anthropometric parameters, although both groups had significant results; significant changes in oral glucose tolerance and serum testosterone in the metformin group
Mandal et al. (2017)	N=96	N/A	Weight, BMI, menstrual cycle, ovulatory response, hormonal changes	Metformin vs. Dietary modification and exercise	Metformin only (3 months-1 year)	Metformin shows significant results in the restoration of menstrual cycles, ovulation, and hormone levels
Wior et al. (2010)	N=30	20-34 years	BMI, waist/hip ratio, blood pressure, hirsutism, menstrual patterns, serum concentrations of gonadotropins, androgens, progesterone, glucose, insulin, and lipids	Lifestyle modification vs. Metformin vs. Placebo	4 months	Significant improvement in BMI and menstrual cycle in lifestyle modification and metformin groups, improvement in insulin levels, hip/waist ratio, and testosterone only found in metformin group
Ladson et al. (2011)	N=114	21-39 years	Ovulation rates, testosterone	Lifestyle modification and placebo vs. Lifestyle modification and metformin	6 months	Testosterone was lower in the metformin group at 3 months but not 6, significant weight loss in both groups

Table 1. Summary of Examined Studies

Discussion

Polycystic ovarian syndrome is an endocrine disorder diagnosed using the presence of oligoovulation or anovulation, hyperandrogenism, and polycystic ovaries. Excess androgen can result in metabolic and hormonal issues, and PCOS is therefore commonly treated with hormonal treatments or lifestyle modifications. This review examined the effects of metformin and physical activity on the metabolic symptoms of PCOS, including blood glucose and insulin levels. The reviewed studies showed that metformin has a strong and consistent effect on restoring metabolic function by inducing weight loss and regulating blood glucose and insulin levels. In all five reviewed articles, metformin improved metabolic symptoms more than exercise regimens. When metformin and exercise were combined, significant improvements in metabolic symptoms compared to metformin treatment alone were reported. Metformin also improved hormonal levels across studies and generally improved hyperandrogenism by regulating testosterone levels [6]. This finding is consistent with the findings of Kazerooni Dehghan-Kooshkghazi (2003),showing and that improvements in metabolic function lower high testosterone levels, reducing the effect of hyperandrogenism [25].

Results show that metformin treatment had a more profound effect on treating metabolic symptoms, including inflammation, of PCOS compared to exercise alone [23]. When a combination of the two treatments was administered, the positive effects were even greater than metformin treatment. The degree of the positive effects seen from metformin treatment varied across studies, but all studies found that metformin had significantly more positive effects on insulin, glucose, and hormone levels when compared to exercise. However, Ladson et al. (2011) found that at six months, the effects of exercise alone were equal to that of combined exercise and metformin treatment on androgen levels. This suggests that there was no added benefit of metformin treatment on androgen levels after the six months mark, which has also been reported by another study [26]. This study found that among women administered with 850 mg of metformin, which was consistent with the dosage administered by Ladson et al. (2011), lifestyle changes alone led to weight loss, which improved hormonal symptoms. However, Ladson et al.'s (2011) results should be interpreted cautiously. The study had an attrition rate of 66.7%, which limited the power of the study to find differences between the two treatment groups. Needless to say, the findings of these two studies provide insight into the importance of weight loss, regardless of treatment type, for the metabolic symptoms of PCOS.

Metformin is highly effective at treating the metabolic symptoms of PCOS, such as glucose and insulin levels [2]. It does this by decreasing the production and absorption of glucose in the body and increasing the effectiveness of insulin without increasing secretion [27]. Metformin can also indirectly improve a number of symptoms such as the regulation of LDL cholesterol, FSH, and hormone levels through the regulation of metabolism. Given the multifactorial nature and interconnected symptoms of PCOS, metformin treatment effectively improves several symptoms which can improve quality of life and ovulation [10]. A body of evidence showed the efficacy of metformin treatment for women with PCOS [2,10], including those who were classified as overweight. This shows that several interconnected symptoms of PCOS can be improved by targeting insulin and glucose levels. Metformin indirectly reduces high BMIs that can contribute to the pathogenesis and degree of PCOS symptomatology [28].

In conjunction with metformin, aerobic exercise can also help reduce BMI to improve symptoms further. Previous studies have shown its beneficial effects on both metabolic and androgenic symptoms of PCOS [29]. combined with especially when other lifestyle modifications such as diets. These studies have also established that the primary outcome of these lifestyle modifications is moderate weight loss, which improves metabolic and androgenic symptoms [29]. Although strenuous exercise could have negative effects due to increased possibility of inflammation from platelet activation, which negatively impacts cardiovascular symptoms by increasing blood pressure and risk of heart failure [2], further research should be done on the duration and frequency of moderate aerobic exercise. Given the side effects and risks of using metformin, aerobic exercise may be considered an alternative for those in poor health.

This review was a snapshot of current comparisons between exercise and metformin usage to manage metabolic symptoms in women with PCOS. This study has several strengths. A single experiment that compares metformin and exercise interventions assures that the inclusion and exclusion criteria, experimental environment, and methodology were kept constant between the two groups. This is advantageous because it allows for a more accurate comparison between the two groups, as the number of external factors that may affect results is reduced compared to between-study reviews. While previous studies have compared generalized lifestyle modifications, limited studies disaggregated lifestyle modifications into the six pillars and focused exclusively on exercise. By focusing on exercise alone for this review, it allows for the effects of exercise to be distinguished from other lifestyle modifications such as dieting, restorative sleep, and stress management.

This study is not without limitations. The lack of a standardized exercise regimen acts as a limitation in this review that made comparisons between exercise interventions and pharmaceutical interventions challenging. The small sample size of studies that directly compare metformin to exercise also limits the strength of the conclusions. Future studies should expand the scale of this review to create an accurate and up-to-date depiction of metformin treatment's administration and effectiveness. Furthermore, a standardized lifestyle intervention for managing PCOS symptoms should be explored to direct the

incorporation of lifestyle intervention treatments in the clinical management of PCOS.

Conclusions

The current lack of a standardized treatment method to treat PCOS symptoms warrants investigation into the efficiency of different treatments. This review evaluated metabolic symptoms of PCOS through a combination of metformin and aerobic exercise. Some studies examined the applications of metformin and aerobic exercise separately, while others compared their efficacy. Metformin has constantly been shown to ameliorate metabolic function by inducing weight loss and regulating hormone levels. When combining metformin and aerobic exercise, more drastic results were observed. While aerobic exercise alone cannot keep up with metformin's effects in the short term, after six months of treatment, the effects on testosterone were comparable to that of the metformin treatment. A key point in PCOS symptom management is weight loss, which can be induced by metformin or aerobic exercise. Moderate weight loss, driven by a combination of metformin and exercise, as shown to lead to improvements in metabolic and androgenic symptoms. By targeting insulin and glucose levels, metformin works jointly with exercise to lower BMI and waist circumference.

While there have been few studies that examine the complementary relationship of metformin and aerobic exercise for symptom management of PCOS, studies examining general lifestyle modifications and varying pharmaceuticals are not new. This study adds to the literature on effective PCOS symptom management by directly comparing metformin and exercise-based lifestyle interventions. This is important because metformin and exercise effectiveness can be directly compared within the same experiment, rather than between two different experiments that may have different methods or parameters. Direct comparisons of these two treatment methods can better inform the effects of metformin or exercise as standardized treatments or interventions to be integrated into clinical practice. The main limitation of our study is the limited number of a studies that explored the role of both metformin and exercise within the same experiment, which make it difficult to draw conclusions. In addition, a lack of standardized exercise intervention between the articles reviewed makes the validity of the conclusions about exercise effectiveness weaker. Future studies should expand this review's scale to accurately depict metformin and exercise treatment effectiveness.

List of Abbreviations Used

PCOS: polycystic ovary syndrome BMI: body mass index LDL: low density lipoprotein FSH: follicle stimulating hormone PRISMA: preferred reporting items for systematic reviews and meta-analyses

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This study did not require ethics approval and/or participant consent because it is a review article.

Authors' Contributions

AG: made contributions to drafting the abstract, intro, methods, and discussion, collected and analyzed data, screened and selected articles, and gave final approval of the version to be published.

JW: made contributions to drafting the abstract, intro, results, and conclusion, collected and analyzed data, and gave final approval of the version to be published. AG and JW are co-first authors

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