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A Comparative Evaluation: Metformin Vs. Metformin With Probiotics In Adolescents With PCOS: Impact On Testosterone Levels, Acne And Hirsutism

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ABSTRACT
Objective: This study aimed to compare the effects of metformin alone versus metformin combined with probiotics on testosterone levels, acne severity, and hirsutism in adolescents with PCOS.
Methods: In a randomized, double-blind, placebo-controlled trial, 80 adolescent females aged 13-19 with PCOS were enrolled. Participants were randomized into two groups: Group A received 500 mg of metformin twice daily, while Group B received the same metformin dosage plus daily probiotics (Lactobacillus acidophilus, Bifidobacterium bifidum, and Lactobacillus rhamnosus) for 12 weeks. Serum testosterone levels, acne severity (using a standardized grading scale), and hirsutism scores (using the modified Ferriman-Gallwey scoring system) were measured at baseline and after 12 weeks.
Results: Both groups showed significant reductions in serum testosterone levels, acne severity, and hirsutism scores. Group B exhibited a more substantial decrease in testosterone levels (53.21 ± 12.7 ng/dL vs. 60.32 ± 10.4 ng/dL, p=0.03) and acne severity (1.83 ± 0.16 vs. 2.12 ± 0.21, p=0.04) compared to Group A. However, there was no significant difference in the reduction of hirsutism scores between the groups (p=0.13). Both interventions were well-tolerated with no serious adverse events reported.
Conclusion: The addition of probiotics to metformin treatment significantly enhances the reduction of testosterone levels and improves acne severity in adolescents with PCOS compared to metformin alone. These findings suggest that probiotics may be a beneficial adjunct therapy in managing hyperandrogenism-related symptoms in PCOS.

Keywords: Polycystic Ovary Syndrome (PCOS), Metformin, Probiotic, Testosterone, Hirsutism, Acne

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a hormonal disorder that affects women during their reproductive years. Approximately 116 million women worldwide are affected, which is about 3.4% of the global population (1). PCOS is linked to chronic anovulation and infertility, as well as hormonal and metabolic imbalances like insulin resistance, hyperandrogenism, hypercholesterolemia, and systemic inflammation (2). According to the revised Rotterdam criteria, PCOS is commonly defined by the presence of at least two out of three symptoms: oligo-/amenorrhea, polycystic ovarian morphology, and clinical or biochemical hyperandrogenism (3). Additionally, PCOS is associated with several comorbidities, such as depression, obesity, insulin resistance, and Hashimoto's thyroiditis (4).

As the exact mechanisms of PCOS are still not fully understood, therapeutic options primarily target specific symptoms. Lifestyle changes, weight loss, and the off-label use of metformin are among the most commonly recommended and prescribed interventions for addressing obesity, insulin resistance, and other metabolic symptoms associated with PCOS (5).

Recent studies have shown that the gut microbiome is essential for human health and disease (6). Gut microbes offer numerous benefits, such as protecting against pathogens, regulating the immune system, and maintaining intestinal barrier integrity (7). The gut microbiome also influences host metabolism, and different gut microbiome profiles are associated with chronic diseases (8). Since the gut microbiome regulates various physiological functions that are compromised in PCOS, such as energy homeostasis, glucose metabolism, and systemic inflammation, it is suggested that the gut microbiome could play a role in the development of PCOS (9, 10).

According to the "Dysbiosis of Gut Microbiota" theory, the gut microbiome is believed to activate the host's immune system, resulting in a chronic inflammatory response. This inflammation can impair insulin receptor function, leading to insulin resistance. Consequently, hyperinsulinemia disrupts follicular development and stimulates excess androgen production by the ovarian thecal cells(11).

Moreover, alterations in the gut microbiome have been found to be associated with hyperandrogenism, indicating that testosterone levels may impact the composition of the gut microbiome in women (12). Probiotics are dietary supplements comprising live microorganisms, intended to restore the gut microbiome.Therefore, the study aim to reveal the effects of metformin monotherapy compared to metformin combined with probiotics on testosterone levels, acne and hirsutism severity in adolescents diagnosed with PCOS.

MATERIAL AND METHODS

Study Design: This study employed a randomized, double-blind, placebo-controlled trial design to compare the effects of Metformin alone versus Metformin combined with probiotics on testosterone levels, acne score, and hirsutism score in adolescents diagnosed with Polycystic Ovary Syndrome (PCOS).

Participants: The study included adolescent females aged between 13 and 19 years, diagnosed with PCOS according to the Rotterdam criteria. Participants with other endocrine disorders, metabolic diseases, or those taking medications affecting hormonal profiles were excluded from the study.

Sample Size Calculation: A total of 80 participants were involved. Sample size was calculated based on previous studies assessing similar outcomes, aiming for a power of 80% and a significance level of 0.05.

Randomization and Blinding: Participants were randomly assigned to one of two groups: Group A receiving Metformin alone and Group B receiving Metformin with probiotics. Randomization was performed using computer-generated random numbers. Both participants and investigators were blinded to group assignment.

Interventions:

- Group A: Participants received Metformin at a dose of 500 mg orally twice daily.
- Group B: Participants received Metformin at the same dosage as Group A along with probiotics (Lactobacillus acidophilus, Bifidobacterium bifidum, and Lactobacillus rhamnosus) once daily.

Duration of Intervention: The intervention period lasted for 12 weeks.

Outcome Measures:

1. **Testosterone Levels:** Serum testosterone levels were measured at baseline and after 12 weeks of intervention using standard laboratory techniques.

Acne Severity: acne severity was evaluated using standardized acne grading scales at baseline and at the end of the intervention period. Acne severity was rated as follows:

- **Acne score 0:** No acne
- **Acne score 1:** ≤ 15 comedones + ≤ 10 papules + ≤ 5 pustules (Mild acne)
- **Acne score 2:** > 15 comedones or > 5 papules or > 5 pustules and < 5 nodulocystic lesions (Moderate acne)
- **Acne score 3:** ≥ 5 nodulocystic lesions (Severe acne)

This rating system is based on the criteria by Charoenvisal et al., 1996.

2. **Hirsutism Score:** Hirsutism was evaluated using the modified Ferriman-Gallwey scoring system at baseline and post-intervention.

Statistical Analysis: Data analysis was performed using appropriate statistical methods. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on the distribution. Categorical variables were expressed as frequencies and percentages. Comparison between groups was done using independent sample t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. A p-value < 0.05 was considered statistically significant.

Ethical Considerations: The study was conducted following the principles outlined in the Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was obtained from all participants or their legal guardians before enrollment in the study. Participants were assured of confidentiality, and their rights and well-being were protected throughout the study.

RESULTS

Participant Characteristics: A total of 80 adolescent females diagnosed with PCOS were enrolled in the study and randomized into two groups: Group A (Metformin alone, n=40) and Group B (Metformin with probiotics, n=40). There were no significant differences in baseline characteristics between the two groups, including age, body mass index as mentioned in Table 1

Table 1: Baseline Characteristic of Adolescent diagnosed PCOS

Baseline Characteristics	Group A Metformin Alone (n=40)	Group B Metformin + Probiotics (n=40)
Age (years)	18.5 ± 1.2	18.6 ± 1.1
Body Mass Index (BMI)	28.3 ± 4.5	28.1 ± 4.6

Effect on Testosterone Levels: At the end of the 12-week intervention period, both Group A and Group B showed a significant reduction in serum testosterone levels compared to baseline ($p < 0.05$). There was was also statistically significant difference in the reduction of testosterone levels in the combination group Group B as compared to Group A (p)

Effect on Acne Severity: Both intervention groups demonstrated a significant improvement in acne severity scores from baseline to week 12 (p). There was a significant difference in the improvement of acne severity between the Group A and Group B (p).

Effect on Hirsutism Score: A significant reduction in hirsutism scores was observed in both groups from baseline to week 12 (p). However, there was no statistically significant difference in the reduction of hirsutism scores between Group A and Group B (p).

Table 2: Effect of Interventions on Testosterone Levels, Acne Severity, and Hirsutism Score

Outcome Measure	Group A (Metformin alone)	Group B (Metformin with Probiotics)	p-value
Change in Testosterone Levels (ng/dL)			
Baseline	73.7 ± 9.4	74.2 ± 8.9	0.178
At 24th week	60.32 ± 10.4	53.21 ± 12.7	0.03
p-value	0.04	0.001	
Change in Acne Severity Score			
Baseline	2.56 ± 0.19	2.64 ± 0.23	0.153
At 24th week	2.12 ± 0.21	1.83 ± 0.16	0.04
p-value	0.02	0.001	
Change in Hirsutism Score			
Baseline	17.1 ± 1.8	17.6 ± 1.9	0.13
At 24th week	14.8. ± 1.7	13.3 ± 1.4	0.01
p-value	0.007	0.001	

Adverse Events: Overall, both interventions were well-tolerated, with no serious adverse events reported in either group. Minor gastrointestinal symptoms such as bloating and diarrhea were reported by a small percentage of participants in group A (Metformin alone).

DISCUSSION:

In our study, Metformin treatment has been shown to reduce hyperandrogenism and its clinical manifestations. Particularly, testosterone levels significantly declined after 24th week of therapy, with the most substantial decrease observed in women who initially had the highest levels of hyperandrogenemia. This suggests that metformin may be particularly effective for women with severe hyperandrogenemia, leading to improved clinical outcomes like acne and hirsutism.

A study investigated the effects of metformin treatment on hirsutism, acne, hormonal patterns, and body weight in adolescent girls with PCOS. Eighteen girls aged 15 to 18 participated in the study. Each subject received a daily dose of 1,700 mg of metformin tablets for six months. The results indicated that all participants experienced significant reductions in testosterone, and free testosterone levels (13). Another study conducted by Se et al., administering probiotics for 12 weeks to women with PCOS led to a significant increase in serum SHBG and a significant decrease in serum total testosterone and mFG scores. However, it did not affect serum DHEAS levels compared to placebo. To the best of our knowledge, data on this topic are still limited (14). In a recent study there has been significant reduction in acne severity in women with polycystic ovary syndrome (PCOS) (15, 16). This is likely due to the connection between acne vulgaris and insulin resistance in females with PCOS. Additionally, recent studies have found that Metformin is an effective adjunct therapy for treating moderate to severe acne vulgaris in patients without previous diagnoses of PCOS or androgen excess (17, 18).

An uncontrolled study by Kolodziejczyk et al. assessed the effects of a 12-week course of metformin (500 mg three times daily) on hormonal and clinical indices in 39 women with PCOS. Acne severity was scored as follows: 0 = no acne, 1 = minor acne (only on the face), 2 = moderate acne (only on the face), and 3 = severe acne (on the face and chest or back). The results showed a significant reduction in acne severity scores, from 1.45 to 1.14 ($p < 0.001$), in patients taking metformin (19). Similarly, a study by Israni et al. investigated the effects of metformin on acne vulgaris and other hyperandrogenism conditions in women with PCOS. Seventeen women meeting the Rotterdam criteria for PCOS completed three months of metformin therapy (1–1.5 g per day). The study reported a significant 71% reduction in acne severity scores after three months of treatment (20).

Studies have also confirmed that lowering testosterone levels can effectively mitigate hyperandrogenemia in overweight women with PCOS, leading to improvements in clinical symptoms such as excess hair, acanthosis nigricans, and acne (21, 22).

To the best of our knowledge, this is the first study to directly compare the effects of metformin monotherapy to a combination of metformin and probiotics on testosterone levels, acne severity, and hirsutism in adolescents with PCOS. Our findings indicate that the addition of probiotics to metformin treatment significantly enhances the reduction of testosterone levels and improves acne severity compared to metformin alone. This suggests that probiotics may serve as a valuable adjunct therapy

for managing hyperandrogenism-related symptoms in PCOS. Further research is warranted to explore the long-term benefits and underlying mechanisms of this combined treatment approach.

CONCLUSION

In conclusion, our study highlights the efficacy of metformin in reducing hyperandrogenism and improving clinical symptoms in women with PCOS, particularly in those with severe hyperandrogenemia. Additionally, the combination of metformin and probiotics shows promising results in further enhancing the reduction of testosterone levels and improving acne severity. These findings underscore the potential of probiotics as adjunct therapy in managing PCOS-related symptoms. Further investigation into the

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