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Comparison of metformin combined with finasteride *vs.* metformin alone on adiponectin, ghrelin and hirsutism outcomes in females with PCOS

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SUMMARY

Background: Polycystic Ovarian Syndrome (PCOS) is an important condition to consider when considering treatment of hyperandrogenism in women. Most women with PCOS have uneven menstrual cycles, infertility and hirsutism. Approximately 60-76 percent of women with PCOS have hirsutism, and 75-90 percent have hyperandrogenism, which is a major clinical characteristic of PCOS. Adiponectin is a protein produced by fat cells that are distributed in the body in areas of the body that are dependent on androgens. The gold standard for the clinical evaluation of hirsutism is the increased Ferriman-Galloway (mFG) score of eight. Adiponectin levels are inversely correlated with the fat content of the bloodstream. Small amounts of adiponectin are associated with insulin resistance, type 2 diabetes, metabolic syndrome and cardiovascular problems associated with obesity. Adiponectin is a peptide hormone that plays a key role in regulating energy balance, food intake and weight regulation. The current investigation was aiming at exploring the effect of metformin combined with finasteride vs. metformin alone on ghrelin, adiponectin and hirsutism outcomes in females with PCOS.

Objective: To investigate and compare the effects of metformin, finasteride and combinations of these medicines on adiponectin, ghrelin levels and hair growth in Iraqi women with Polycystic Ovarian Syndrome (PCOS).

Patients and methods: The current study included 150 patients aged 18 to 39 years. Patients were divided into three groups: the metformin group, who had a standard starting dose of 500 mg, which was increased by 500 mg every 1-2 weeks with food for three months. Thefinasteride group received a 5 mg daily dose for three months, while the combination group received both medicines at similar doses for the same period of time. Each group had 50 patients. This study included data on BMI, age, adiponectin, ghrelin and Ferriman gollwey score.

Results: After treatment, all three modalities of treatment, metformin, finasteride and combination were able to reduce mean BMI significantly ($p<0.001$) and the magnitudes of reduction were almost comparable in addition, after treatment, all three modalities of treatment were able to reduce mean free testosterone, and FGS, and to increase mean Ghrelin and Adiponectin significantly ($p<0.001$) and the magnitude of change caused by combination was the best.

Conclusion: In women with PCOS, the combination of finasteride and metformin increases the levels of ghrelin and adiponectin in the serum, effectively reducing androgen levels and hirsutism. However, it does not offer any additional weight loss benefits, which makes metformin a safer alternative.

Keywords: PCOS; FGS; Adiponectin; Ghrelin; Finasteride; Metformin; Body mass index; Free testosterone

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a widespread endocrine syndrome characterised through hyperandrogenism chronic anovulation, and resistance to insulin [1]. Hirsutism is a characteristic of excessive fine hair in a typical male pattern that is present in women and is a primary symptom of increased androgen ranks in women with (PCOS) [2]. During puberty, the increased number of androgens causes the follicles of the vaginal system to change in some areas to terminal hair, which is curlier bigger, and darker, and is more visible and known as sexual hair follicles [3], whereas pubic and axillary hair are sensitive to low levels of androgens, other areas may require higher androgen concentrations to grow terminal hair [4]. This process is mediated by free testosterone, the main active form of plasma testosterone [5]. The Ferriman-Gallwey (FG) scale measures hair growth in various areas sensitive to androgens. FG score 8 or higher on the FG scale designates hirsutism [3]. A score of 8 to 15 indicates minor hirsutism and a score of >15 indicate moderate or austere hirsutism. Among patients with PCOS, approximately 60-76 percent are Hirsutism [6]. Hirsutism is caused by a relationship between androgenic levels and hair follicle sensitivity to androgens [3]. Adiponectin is an adipokine known for its insulin sensitising, antioxidant and anti-atherogenic properties [7]. Adiponectin plays a role in the effect of hyperandrogenism and central obesity on resistance to insulin (IR) [8]. In women with PCOS, decreased adiponectin ranks have been related with T2DM, IR, dyslipidaemia and metabolic syndrome [9]. Enlarged adipocytes, low Adiponectin levels and increased waist circumference have been identified as possible factors contributing to PCOS insulin resistance [10]. Previous studies have shown a link between low levels of adiponectin and Polycystic Ovarian Syndrome (PCOS), which seems to be unrelated to obesity. Adiponectin has been proposed as a possible biomarker for identifying PCOS women at increased risk of developing diabetes and cardiovascular problems [11]. Ghrelin is involved in regulating the short-term intake of food and is antagonised by insulin and other anorexic hormones such as CCK and PYY. In a previous analysis by the authors, an imbalance between ghrelin and insulin levels was detected in women with obesity and PCOS [12]. In obese patients, particularly those with PCOS, ghrelin levels are reduced during fasting and suppression after meals is impaired [13]. The goal of the current training was to explore the influence of finasteride, metformin and their

combination on ghrelin, adiponectin and hirsutism in females with (PCOS).

PATIENTS AND METHOD

The current study of the product under investigation involved 150 patients aged (18-39) These patients were diagnosed with the disease (PCOS) by two obstetricians and gynaecologists in the criteria of Rotterdam (Rotterdam, 2003). Pregnant or breast-feeding women and women with co-morbid conditions (DM, hypertension, liver disease and kidney disease) were not allowed to participate in the training. Patients were separated into three groups: the finasteride group, who were preserved with 5 mg once everyday for 3 months. The metformin group customary a low dosage of 500 mg and increased by 500 mg every 1-2 weeks during meals for 3 months, and the combination group received both medicines at the same dose as above. Each groups consisted of fifty patients. The patients were recruited from a maternity and children's hospital in the Adiwaniyah province of Iraq. The training period expires on September 21, 2024 and is extended to December 31, 2025. The study included data on age and body mass index. Serum measurements of adiponectin and ghrelin were performed before and at 3 months after treatment using the Enzyme-Linked Immunosorbent Assay (ELISA) (Elabscience, China), in addition to serum measurements of free testosterone and Score (FGS) before and at 90 days post-treatment. The ethics committee of the College of Physicians of the University of Al-Kadisiyah approved the project. All participants were informed to give their written consent after a full explanation of the procedures and objectives of the study.

Statistical analysis was conducted using SPSS (version 23) and Microsoft Excel 2010. Data normality was assessed with the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation, along with minimum and maximum values. One-way ANOVA was used to compare mean differences among three groups. A paired samples t-test was used to assess mean changes before and after treatment within each group. A P-value ≤ 0.05 was considered statistically significant.

RESULTS

Comparison of mean ages between study groups is shown in **Tab. 1.** No significant difference in variation (p=0.633). The mean age of the metformin group was 27.78 ± 3.79 years, ranging from 18 to 36 years old. The mean age of the finasteride group was 27.72 ± 4.14 years, ranging from 18 to 39 years old. The mean age of the combined group was 28.38 ± 3.48 years, ranging from 21 to 39 years old.

Before initiation of treatment, comparison of mean Body Mass Index (BMI), mean free testosterone, mean Ferriman-Gallwey score (FGS), mean Ghrelin and mean Adiponectin revealed no significant differences (p>0.05), as shown in **Tab. 2.** After treatment, all three modalities of treatment, metformin, finasteride and combination were able to reduce mean BMI, mean free testosterone, and mean FGS, and to increase mean Ghrelin and mean Adiponectin significantly (p<0.001). Changes in mean

Tab. 1. Comparison of mean age among study groups.

Characteristic	Metformin group *n*=50	Finasteride group *n*=50	Combination group *n*=50	*p*
Age (years)				
Mean ± SD	27.78 ± 3.79	27.72 ± 4.14	28.38 ± 3.48	0.633 O NS
Range	18-36	18-39	21-39	
SD: Standard Deviation; *n*: number of cases; O: One way ANOVA; NS: Not Significant				

Tab. 2. Comparison of mean BMI, Free testosterone, FGS, Ghrelin, and Adiponectin among study groups.

Characteristic	Metformin group *n*=50	Finasteride group *n*=50	Combination group *n*=50	*P* (one way ANOVA)
BMI				
Before	29.14 ± 1.96	29.64 ± 1.75	29.79 ± 1.74	0.291NS
After	28.44 ± 1.88	28.31 ± 1.76	28.78 ± 1.72	<0.001***
p (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	-
Free testosterone				
Before	4.34 ± 0.53	4.29 ± 0.40	4.33 ± 0.48	0.272 NS
After	3.52 ± 0.52	3.34 ± 0.42	3.00 ± 0.45	<0.001***
p (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	-
FGS				
Before	12.66 ± 2.53	12.55 ± 2.43	12.60 ± 2.06	0.297 NS
After	11.18 ± 2.75	9.78 ± 2.86	8.98 ± 1.93	0.014*
p (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	-
Ghrelin				
Before	417.60 ± 42.74	420.72 ± 37.70	418.28 ± 38.26	0.341NS
After	462.74 ± 70.27	464.82 ± 51.79	486.28 ± 58.30	0.002**
p (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	<0.001***
Adiponectin				
Before	3.15 ± 0.40	3.20 ± 0.36	3.18 ± 0.35	0.198 NS
After	3.74 ± 0.54	3.49 ± 0.39	3.88 ± 0.55	<0.001***
p (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	-
Body Mass Index (BMI), Standard Deviation (SD), number of cases (n), Not Significant (NS), significant at p≤0.001 (***), mean ±SD, and Ferriman-Gallwey Score (FGS) were used to express the data.				

BMI were comparable among the all three modalities of treatment; however, with respect to other variables, the magnitude of change caused by combination was the best, **Tab. 2.**

DISCUSSION

In this study, the mean BMI before initiation of treatment ranged from 29.14 to 29.79 kg per m^2, with a total BMI range of 25.2 kg per m^2 to 26.7 kg per m^2 [14]. The Neubronner, et al. [14] in their study included 134 females with PCOS with a mean BMI of 25.14 (±) 6.46 kg, which is slightly lower than the BMI reported in this study, but still in overweight (>25 kg per m^2) according to the WHO BMI classification [15]. In this study and following treatment, all three treatment modalities, metformin, finasteride and combination, significantly reduced average BMI, and the magnitude of the reductions was almost comparable.

Diri, et al. [16] have conducted a study similar in design to the current study and their results are partly consistent with those of Diri, et al. [16] in terms of comparable reduction, but there is disagreement as to the statistical significance. Our study is the second on the combined effect of metformin and finasteride in PCOS women, following the work of Diri, et al. [16]. Based on the results of the current studies and those of Diri, et al. [16], the combination of finasteride and metformin will not have an additive effect on weight loss in PCOS women and treatment with metformin alone may be preferable to this goal. Regarding metformin, our results are consistent with those of previous authors [17]. Similarly, finasteride has been shown not to cause significant changes in average BMI in women with PCOS [18,19]. The mechanism by which metformin helps to reduce weight is by enhance insulin resistance and decreasing calorie intake. In addition, changes in gastrointestinal physiology and circadian rhythms induced by metformin also affect the oxidation and storage of lipids in the skeletal muscle liver, and adipose tissue [20-22].

Regarding testosterone, the current results are almost identical to the previous reports [16]. In females with (PCOS), metformin has been reported to reduce testosterone levels by approximately 20-25 percent [23]. The mechanism by which metformin is believed to reduce testosterone ranks are through the mitigation of hyperinsulinaemia [24-26], but other mechanisms may be involved [25,27-29]. Anti-androgenic medicinal products such as finasteride are used to reduce symptoms associated with hyperandrogenism in sick with (PCOS) [30]. The combination was able to significantly reduce the average FGS in the current study, which is in line with the preceding training [16]. The Ferriman-Galloway Test is used to assess hirsutism [31]. There have been previous reports of the effect of metformin on serum ghrelin levels in women with PCOS [32-34], but unfortunately no reports of the consequence of finasteride on ghrelin levels in women with PCOS. The main findings of the current study are therefore: the assessment of the combined effect of metformin and finasteride on serum ghrelin levels in PCOS women, the single effect of finasteride on serum ghrelin levels in PCOS women, and evidence that the combination of the two agents is superior to the use of a single agent when the aim is to increase serum ghrelin levels. Therefore, the improvement in ghrelin levels in the current study may be due to the decrease in Body Mass Index (BMI) [33], which in turn may explain the improvement in insulin sensitivity in women with PCOS as seen from changes in HOMA-IR. A decrease in BMI may indeed be proposed as a mechanism of action of metformin to increase ghrelin levels, but the mechanism of action of finasteride and synergistic effect when added to metformin are difficult to explain.

There are many previous reports of a single effect of metformin on serum adiponectin levels in PCOS women, but there are also some previous reports of a single influence of finasteride on serum adiponectin ranks [35]. Published articles were concerned with evaluating the correlation between serum testosterone levels and serum adiponectin levels [36-41]. The main findings of the current study are therefore: the evaluation of the combined effect of metformin and finasteride on serum adiponectin levels in PCOS women, the single effect of finasteride on serum adiponectin ranks in PCOS women, and evidence that the combination of the two agents is superior to the use of a single agent when the aim is to increase serum adiponectin levels.

However, conflicting findings on the effect of metformin on adiponectin serum levels in women with (PCOS) were documented in a meta-analysis [35] which showed a statistically significant increase in adiponectin serum levels after metformin treatment, which was correlated with significant improvements in other relevant parameters. In line with what was reported in the meta-analysis, medicinal products containing metformin may significantly increase the level of adiponectin in women with PCOS [42]. The latter two studies partially support the current study results regarding changes in adiponectin response to metformin, but the exact mechanism of action remains unclear and will require further experimental work.

CONCLUSION

In females with PCOS, the grouping of finasteride and metformin results in increased serum levels of ghrelin and adiponectin. This combination has been revealed to be more operative in controlling serum androgen ranks and reducing hirsutism in women with PCOS. There are no additional benefits of combining finasteride and metformin for weight loss in women with PCOS. Therefore, the use of metformin alone is the safer option.

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