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The impact of metformin combined with spironolactone *vs.* metformin alone on adiponectin, ghrelin and hirsutism out comes females with PCOS

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SUMMARY

Background: Anovulation and hyperandrogenism, in combination with ovarian morphological changes, insulin resistance, inappropriate secretion of gonadotropins and associated compensatory hyperinsulinaemia, remain hallmarks of PCOS, a most common endocrine disease that afflicts some women. Three groups of patients were identified: the M group (n=50) receiving metformin, the MS group (n=50) receiving metformin and spironolactone, and the S group (n=50) receiving spironolactone. According to the Rotterdam guidelines (Rotterdam, 2004), two obstetricians and gynaecologists diagnosed these patients with Polycystic Ovarian Syndrome (PMS). The patients were enrolled as of the Maternity and Pediatrics Teaching Hospital in Adiwaniyah Province, Iraq. The training is to start after September 1, 2024 and will last until March 1, 2025.

Results: All three treatment modalities, metformin, spironolacto,and combination were able to reduce themesn (BMI), mean total testosterone and the mean Ferriman-Gallstone (FGS) score and to significantly increase the mean ghrelin and the mean adiponectin ($p<0.001$). The magnitude of the reduction in Body Mass Index (BMI), total testosterone and the magnitude of the increase in mean ghrelin and mean adiponectin were best while using the combination.

Conclusion: Combination of spironolactone and metformin provide better approach for improving hirsutism out com in women with PCOS as evident from total testesteron concentration and (FGS)score in addition to improved levels of serum ghrelin and adiponectin.

Keywords: POS; Ghrelin; Adiponectin; Hirsutism; Metformin; Spironolactone

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is a heterogeneous and complex syndrome [1,2] characterised by prolonged ovulation, menstrual irregularities and hyperandrogenism, associated with infertility and metabolic disorders including hypertension and obesity [3]. Rendering to the Rotterdam principles, PCOS is characterized by at least two of the next: oligo- and/or anovulation, clinical and/or biological hyperandrogenism diagnosed by a transvaginal ultrasound scan [4]. Rumour has it that the adipose tissue is divided into White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT) which produces different sets of adipokines [5,6]. In females with PCOS, adipose tissue affects the metabolism and the endocrine signaling. Several human adipokines are recognized to distress the hypothalamus-pituitary-gonadal axis or to affect ovarian steroidogenesis. Adiponectin is secreted by WAT and recently, also by BAT [7]. Increased fat metabolism, regulation of glucose tolerance, maintenance of insulin sensitivity, protection against Type 2 Diabetes (T2D) and act as anti-inflammatory effects in macrophages [7]. The plasma adiponectin is thought to be a negative association for insulin resistance and is considered one of the most important markers of metabolic disease [7]. The dysfunction of the appetite regulator hormone ghrelin in women with pcos lead to inferior postprandial satiety and upper postprandial hunger than weight-matched controls [8]. Increased fasting ghrelin levels have been stated in females with PCOS [9], and decreased postprandial suppression of ghrelin, which is related with poor insulin sensitivity, and show to progress with weight eduction [8].

PATIENTS, MATERIALS AND METHODS

The study included 150 patients aged between 18 and 40 years old. These patients were evaluated (PCOS) according to the guidelines of the Rotterdam basis (Rotterdam, 2004). The patients were enrolled as of Maternity and Pediatrics Teaching Hospital in Adiwaniyah Province, Iraq. The training is dated September 2024 and extends to March 2025. Women who were pregnant or breast-feeding and co-morbid circumstances such as diabetes mellitus, essential hypertension, liver disease, thyroid disease, hyperproteinaemia, congenital adrenal hyperplasia, and other endocrine syndromes for instance Cushing's disorder and androgenic tumors, Medication within 12 weeks, including cortisol, hormonal contraceptives, antidepressant, hypoglycemic agents, stayed not included.

Groups 1: The M group (n=50) received metformin at a low dose of 500 mg and improved *via* 500 mg every 1-2 weeks, for 90 days the maximum daily dose is recommended to be 2.5 g, within meal per day.

Group 2: Is a group of patients with M S (n=50) who received metformin at a low dose of 500 mg and improved by 500 mg every 1-2 weeks for a 90-day period, plus spironolactone 25 mg(bid) for the same duration.

Group 3: Is the S group (n=50) and received spironolactone 25 mg(b) Phone meetings were set up three months later to document adherence and any opposing reactions.

Ethical deliberation

The University of Al-Qadisiyah College of Medicine's ethical review committee gave its approval to the study. All participants were informed to give an oral consent after full illustration of the aims and the procedures of the current study.

Method of statistics

The Statistical Package for Social Sciences (SPFS) version 23 and Microsoft Office Excel 2010 continued to be used for the collection, compilation, analysis, and storage of documents. Therefore, normally distributed numerical variables were given as mean (central trend index) and standard deviation (dispersive index), with minimum and maximum values. The Kolmogorov-Smirnov test was used to first evaluate the distribution of the mean values of the quantitative (numerical) variables. The statistical tests listed below were applied:

1. **One way ANOAV** stayed use to compare differences in means among three groups.
2. **Paired samples t-test** stayed used to evaluate the alteration in mean of numeric variables earlier and after management in each group.

Significance levels were deliberated at a P value of equal to or less than 0.05.

RESULTS

The average age by participating country is presented in **Tab. 1.** below. There no notable variation (p=0.322). The mean age of the metformin group was 25.64 years, with a range of 18 to 39 years. The mean age of the spironolactone group was 26.12 ±5.33 years, ranging as of 18 to 38 years. The mean age of the combined group was 24.38 ± 6.97 years, ranging as of 18 to 39 years old. Comparisons of the mean (BMI), the mean free testosterone, the mean FSH, the mean ghrelin and the mean adipocyte are given in **Tab. 2.** After treatment, all three treatment modalities, metformin, spironolactone and combination, were able to significantly reduce the mean total testosterone and mean ghrelin and the mean BMI and the Ferriman-Gallway Score (FGS) (p<0.001). The magnitude of the change in variables due to the combination was the best (**Tab. 1. and Tab. 2.).**

DISCUSSION

In the current study, the average BMI before treatment was significantly lower than the average after treatment in this study, all three treatment options, metformin, spironolactone and combination were effective in reducing the average BMI significantly. Several authors have conducted similar studies with similar design to this one [10-13]. They did not report any significant changes

Tab. 1. Comparison of the study groups' mean ages.

Characteristic	Metformin group *n* = 50	Spironolactone group *n* = 50	Combination group *n* = 50	*p*
Age (years)				
Mean ± SD	25.64 ± 5.41	26.12 ± 5.33	24.38 ± 6.97	0.322 O NS
Range	18 -39	18 -38	18 -39	

Tab. 2. Comparison of other variables among study groups.

Characteristic	Metformin group *n* = 50	Spironolactone group *n* = 50	Combination group *n* = 50	*P* (one way ANOVA)
BMI				
Before	29.32 ± 3.13	28.22 ± 3.88	28.17 ± 3.22	0.127 NS
After	29.25 ± 3.09	28.01 ± 3.36	27.47 ± 3.80	0.033*
P (paired-t-test)	<0.001***	<0.001***	<0.001***	-
Total testosterone				
Before	1.05 ± 0.17	1.06 ± 0.18	1.01 ± 0.21	0.201NS
After	0.92 ± 0.24	0.94 ± 0.23	0.69 ± 0.17	<0.001***
P (paired-t-test)	<0.001***	<0.001***	<0.001***	-
FGS				
Before	14.48 ± 3.27	14.20 ± 2.81	14.46 ± 2.55	0.148 NS
After	13.04 ± 3.28	12.34 ± 2.86	12.44 ± 2.80	0.019*
P (paired-t-test)	<0.001***	<0.001***	<0.001***	-
Ghrelin				
Before	321.00 ± 84.30	330.80 ± 87.99	328.40 ± 82.52	0.835 NS
After	355.80 ± 89.15	363.60 ± 90.07	384.60 ± 95.15	0.269 NS
P (paired-t-test)	<0.001***	<0.001***	<0.001***	<0.00***
Adiponectin				
Before	2.85 ± 0.56	2.86 ± 0.64	2.89 ± 0.55	0.910 NS
After	3.25 ± 0.71	3.27 ± 0.70	3.41 ± 0.73	0.488 NS
P (paired-t-test)	<0.001***	<0.001***	<0.001***	-

in mean BMI before or after treatment; however, a meta-analysis published by Zheng Y, et al. [13] showed that BMI can be significantly reduced by using both substances together, and that the combination is better than either of the two. As a meta-analysis, the conclusions of the study Zheng Y, et al. [13] are certainly stronger in statistical terms than those of the studies Diri H, et al. [11] and Long T, et al. [12] and the outcomes of the existing study are in line with the preceding ones. The combination of spironolactone and metformin will therefore have an additive effect on weight loss in females with PCOS. Other studies suggest that spironolactone can improve insulin sensitivity [14] in females with PCOS by one or more of the following mechanisms: first, spironolactone is a diuretic, so it helps the body to remove excess water and salt [15], secondly, spironolactone is an anti-androgen [16], which is known to cause central obesity and weight gain; and thirdly, obesity is related with insulin resistance. Regarding the potential of metformin to help women with PCOS, it is generally known that the medicine helps to weight loss [17,18].

In the current study, all three treatment modalities, metformin, spironolactone and combination, significantly reduced mean total testosterone, with combination being the most effective. Diri H, et al. [11] in their study, they evaluated the influence of metformin only, spironolactone alone and both agents in combination and found that both agents alone could significantly reduce testosterone levels, but that the combination of the two did have an additive effect compared to the use of the ethers alone. The outcomes of the current training are in complete contract with those of Long T, et al. [12] and Zheng Y, et al. [13] as they showed that both agents were effective in significantly reducing total testosterone levels and free androgenic indices when used alone, and that the best results were obtained when both were used in combination. Spironolactone acts as an antagonist of androgen receptors, exerting anti-androgenic effects by directly inhibiting androgen receptors, promoting aromatase activity and partially inhibiting androgen biosynthesis [19]. It has been shown that metformin can reduce testosterone levels by approximately 20 to 25 percent in women with a diagnosed with pcos [20].

In this study, all three treatment modalities, metformin, spironolactone and combination, significantly reduced average FGS, with the combination being the best. Based on the findings of Diri H, et al. [11], metformin alone was able to significantly improve FGS, whereas spironolactone alone was also effective in this respect, which supports the findings of the current study. Several previous reports [21-23] have shown a beneficial effect of the combination of metformin and spironolactone in the management of excessive hair growth in females with PCOS. The most likely mechanism for the efficacy of both metformin and spironolactone in improving hirsute may be due to the reduction of testosterone levels by both substances through different mechanisms, and a combination of both is likely to achieve the best result. In the current study, all three treatment options, metformin, spironolactone and combination, significantly increased mean ghrelin, with the combination being the best. Three previous studies [11-13], which are almost identical in design to the current study, did not mention any specific influence of metformin or spironolactone on serum ghrelin ranks in this cohort of PCOS patients. In fact, the current training is the first to explore the combined effect of metformin and spironolactone on serum ghrelin in women with PCOS, and the initial conclusion was that the combination was able to increase ghrelin better than the use of both substances separately. Additionally, existing literature has documented the effect of metformin on ghrelin serum concentrations in women with Polycystic Ovarian Syndrome (PCOS) [24-26]. Unfortunately, there are no trainings on the influence of spironolactone on ghrelin serum levels in this particular population. The main contributions of this study are therefore: an assessment of the synergistic effects of metformin and spironolactone on serum ghrelin ranks in PCOS women, an isolated effect of spironolactone on serum ghrelin levels in this demographic, and evidence that co-administration of both pharmacological agents leads to better results than use of a single agent when the aim is to increase serum ghrelin levels. In the current training, after treatment, all three modalities of treatment, metformin, spironolactone and combination were able to increase mean Adiponectin significantly and the magnitude of increase caused by combination was the best. Indeed, the three previous studies by Diri H, et al. [11], Long T, et al. [12] and Zheng Y, et al. [13], which have nearly similar design to current study, mentioned nothing about the sole influence of either metformin or spironolactone on adiponectin serum level in women with PCOS, in addition, they did not raise the issue of combination therapy effect on serum adiponectin level in such cohort of women. Actually, for the finest of our information, the current training is the first training to investigate the combination influence of metformin and spironolactone on serum adiponectin in females with PCOS and the original finding was that such combination is able to raise serum adiponectin better than using either agent alone.

Several trainings have shown a decrease in circulating adiponectin in females with (PCOS) [27,28], but no specific clinical experience has been obtained with spironolactone in sick with type 2 diabetes mellitus. Similarly, [29] a meta-analysis concluded that metformin treatment significantly increases the ranks of adiponectin in females with PCOS. The results of these two trainings partially confirm the results of the current study regarding changes in adiponectin levels in response to metformin. The exact mechanism by which metformin exerts its effect on increasing adiponectin levels remains unclear, but, given that previous studies have established a correlation between a decline in Body Mass Index (BMI) and an rise in adiponectin levels [29], it can be concluded that metformin has a important influence on weight loss in the female subjects in this study. As regards the mechanism of action of spironolactone on adiponectin, it can be attributed to the decrease in serum testosterone concentrations, as the existing literature has shown a negative relationship between testosterone and adiponectin levels in females with PCOS [30-34].

CONCLUSION

Combination of spironolactone and metformin provide better approach for improving hirsutism out com in women with PCOS as evident from total testesteron concentration, BMI and (FGS)score in addition to improved levels of serum ghrelin and adiponectin.

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