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Comparison of Insulin Resistance Markers in Three Groups of Iraqi Females with PCOS Taking Metformin, Spironolactone, or a Combination of Both

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Annotation: Background: Polycystic ovarian syndrome (PCOS) is an endocrine disrupting syndrome that affects numerous women of childbearing age. While part of the mechanism of causation in PCOS has been identified, the exact etiology and pathophysiology are not fully understood. PCOS has been related with hormonal and metabolic changes and may predispose people to a number of other conditions such as obesity, metabolic syndrome, hypertension, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD).

Aim of the study: to compaire between the consequence of metformin alone versus metformin plus spironolactone combination regarding insuline resistance(insulin resistance test) in pcos Iraqi women

Patients and methods: The existing interventional prospective training included 150 patients between the ages of 18 and 40. Based on Rotterdam principles (Rotterdam, 2004), two obstetrics and gynecology specialists diagnosed those patients with polycystic ovarian syndrome (PCOS). In Iraq's Adiwaniyah Province, the Maternity and Pediatrics Teaching Hospital served as the source of the patients. The training is scheduled for September 1st, 2024, and is extended until March 1st, 2025.

Result; all three modalities of treatment, metformin, spironolactone and combination were able to reduce mean BMI, mean HOMA-IR, mean TyG, mean and TyG-BMI, mean TG/HDL significantly ($p < 0.001$). The amount of changes in variable initiated via combination was the best.

Conclusion; The combination of spironolactone and metformin is more operative improving insulin sensitivity in women with PCOS as evident from TyG index, TyG-BMI index and HOMA-IR and (TG/HDL) index than.

Keywords: PCOS; hyperandrogenism; insulin resistance; hirsutism;metformin; spironolactone.

Introduction:

The most prevalent endocrine condition that affects women through their reproductive years (1) this syndrome global prevalence between 8 and 13%(2) It is broadly documented that insulin resistance and hyperandrogenism production key parts in the aetiology (3)(4) Approximately 35 to 80 percent of PCOS patients have insulin resistance (IR), according to studies (5). PCOS IR can lead to metabolic disorders and complications. The following conditions are linked to an improved risk of disease: "metabolic syndrome," "impaired glucose tolerance," "diabetes mellitus," and "cardiovascular disease.". Patients with PCOS who have IR are at a considerably higher risk of developing diabetes and cardiovascular diseases because of the communal preferment and crosstalk between IR and androgen excess. Type 2 diabetes is known to develop as a result of damage to islet β cells and impaired glucose tolerance brought on by chronic pancreatic stress under IR **(6, 7)** PCOS has been linked to increased numbers of visceral adipose tissue as well as overall adiposity, which may boost the danger of fatness, cardiovascular illness, insulin fighting kind 2 diabetes in females with PCOS irrespective of their weightiness status (8)Within PCOS, clinical hyperandrogenism can be distinguished from biochemical hyperandrogenism in females displaying symptoms like acne, alopecia, or hirsutism. Nonetheless, in adolescents, hirsutism alone should be considered as a marker for biochemical hyperandrogenism (9). Patterns of hair loss can vary, appearing in a diffuse pattern, at

the crown, or in the vertex region (10). Hirsutism is characterized by the existence of coarse, dark terminal hairs following a male-like distribution (11) Elevated androgen levels are identified through increased free testosterone ranks (12,13)

The prevalence of hirsutism in PCOS is assessed to be 65–75 percent, while it affects 4–11 percent of women (14). We predicted that spironolactone plus metformin, as opposed to metformin alone, would reduce insulin resistance more significantly in the treatment of women with PCOS because insulin resistance is a significant factor in the pathophysiology of PCOS [15].

When treating type 2 diabetes, metformin is the most often prescribed medication. It reduces oxidative stress, stops hepatic gluconeogenesis, and increases peripheral tissue sensitivity to insulin. Additionally, this medication improves the metabolic syndrome in PCOS patients while lowering androgen ranks and raising sex hormone binding globulin (SHBG) ranks. Because of this, metformin is frequently used in women with PCOS (16), and the androgen receptor blocker spirolactone is crucial in the management of hyperandrogenism (17).

Patients, Materials and Methods

There were 150 patients in this study, ranging in age from 18 to under 40. Two obstetrics and gynecology specialists evaluated those patients for PCOS using the Rotterdam principles (Rotterdam, 2004). The Maternity and Pediatrics Teaching Hospital in Iraq's Adiwaniyah Province served as the source of the patients. The study began on September 1st, 2024, and was continued until March 1st, 2025. Co-morbidities such as diabetes mellitus, essential hypertension, liver, kidney, thyroid, hyperprolactinemia, congenital adrenal hyperplasia, and other endocrine disorders that resulted in hyperandrogenism, for instance Cushing disorder, as well as androgen-secreting tumors, were excluded from this study, as were women who were pregnant or nursing, and women who were taking cortisol, antidepressants, hypoglycemic agents, or hormonal contraceptives within 12 weeks.

The women were divided in to three category

Groups 1: The M group (n = 50), they received metformin as low dose of 500 mg and increase by 500 mg every 1-2 weeks, it is recommended to take a maximum daily dose of 2.5 g, writhe meal, per-oral, for 90 days.

Group 2: Is the MS group (n =50) and they received metformin as low dose of 500 mg and increase by 500 mg every 1-2 weeks, it is recommended to take a maximum daily dose of 2.5 g, writhe meal, per-oral for 90 days duration plus spironolactone 25mg(bid) for the same period.

Group 3:is the s group (n=50) and they received spironolactone 25mg(bid) Investigations were achieved at the standard and three months. Telephone meetings stood arranged three months later to

document adherence and any opposing reactions..

Ethical consideration

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

Microsoft Office Excel 2010 and the statistical package for social sciences (SPSS) version 23 were used to gather, compile, analyze, and existing the documents. Using the Kolmogorov-Smirnov test, quantitative (numerical) variables were first assessed for normality distribution. Then, normally distributed numeric variables stayed stated as mean (a measure of central tendency) and standard deviation (a measure of dispersion), along with minimum and maximum values.

The succeeding statistical investigations were used:

1. **One way ANOAV** was use to compare differences in means among three groups.

2. **Paired samples t-test** was employed to calculate the variation in the mean of numerical variables in each group prior to and following treatment..

At a P-value of 0 or less than 0.05, the level of significance was taken into consideration..

The average age by participating country is presented in Table 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 mean body mass index (BMI), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), triglyceride-glucose index (TyG), triglyceride-glucose- BMI index (TyG-BMI) and triglyceride/high density lipoprotein index (TG/HDL) are shown in table 2. After treatment, all three modalities of treatment, metformin, spironolactone and combination were able to reduce mean BMI, mean HOMA-IR, mean TyG, mean and TyG-BMI, mean TG/HDL significantly (p <0.001). the amount of changes in other variable caused by combination was the best.

Table 1: Comparison of mean age among study groups

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
Range	18 -39	18 -38	18 -39	NS

Table 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	27.47 ±3.80	28.01 ±3.36	0.033 *
P (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	
HOMA-IR				
Before	5.15 ±1.67	5.37 ±1.82	5.31 ±0.82	0.241 NS
After	4.43 ±1.57	4.98 ±1.26	3.84 ±0.60	<0.001 ***
P (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	
TyG-index				
Before	6.32 ±1.37	6.45 ±1.45	6.51 ±1.37	0.112 NS
After	5.52 ±1.32	5.95 ±1.44	4.94 ±1.25	<0.001 ***
P (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	
TyG-BMI index				
Before	186.22 ±47.99	181.94 ±48.17	184.64 ±44.09	0.262 NS
After	162.45 ±45.57	163.63 ±46.77	140.94 ±38.57	<0.001

				***
P (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	
TG/HDL				
Before	4.49 ±1.35	4.47 ±0.87	4.50 ±1.22	0.223 NS
After	3.80 ±1.32	3.97 ±0.87	3.74 ±1.31	0.041 *
P (paired-t-test)	<0.001 ***	<0.001 ***	<0.001 ***	

Discussion

In this study, after treatment, all three modalities of treatment, metformin, finasteride and combination were able to reduce mean HOMA-IR significantly and the magnitude of reduction caused by combination was the best. Current study results are thus in agreement with those of **(18,19)** since they showed that the use of either drugs alone was able to significantly reduce HOMA-IR, but, combination of both agents was more significantly efficient in reducing HOMA-IR. However, **(20)** found no added effect if both drugs were used in combination, thus, current results are in disagreement with them. Spironolactone has the potential to enhance insulin sensitivity by diminishing androgen levels, as well as decreasing body weight and (BMI) **(21)**. Indeed, the concomitant administration of spironolactone and metformin has the capacity to lower androgen levels, enhance insulin sensitivity, facilitate lipolysis, and increase glucose uptake and energy homeostasis in conjunction with metformin, eventually culminating in weight loss among patients. This might represent the primary apparatus of action for combination treatment **(19)**.

In this study, after treatment, all three modalities of treatment, metformin, Spironolactone and combination were able to reduce mean the (TyG) index significantly and the magnitude of reduction caused by combination was the best. With respect to **(18),** they showed that metformin use is effective in reducing total cholesterol level significantly, but, neither spironolactone alone, nor metformin were able to do so; however, they mentioned nothing in their study about the index TyG. Actually, after thorough search in available published article in Google website and in academic website, the researcher of the current study, did not found a similar design of a study that examined the combined effect of metformin and spironolactone on the index TyG; therefore, this point van be original in this study with an important finding that combination therapy provide efficient synergistic effect in improving TyG index in females with PCOS.

Indeed, a modern experimental training **(22)** has shown that Low-dose spironolactone conflicts dyslipidemia and hepatic inflammation through modifying PCSK9 in rat model of POCs **(19)** conducted an evaluation of the Triglyceride Glucose Index among patients with PCOS and determined that the TyG index exhibited superior performance compared to conventional lipid ratios, such as (TG/HDL-C), in forecasting insulin resistance (IR) and might serve as reliable indicators of IR in this cohort. Thus, the observed reduction in the mean values of TyG in the present study serves as an indicative measure of the effectiveness of both metformin and spironolactone in augmenting insulin sensitivity in women suffering from PCOS. Indeed, to the best of our information, this is the first training to show the synergistic effect of adding spironolactone to metformin to get better improvement of insulin sensitivity in women with PCOS.

In the current training, after treatment, all three modalities of treatment, metformin, Spironolactone and combination were able to reduce mean TyG-BMI significantly and the magnitude of reduction caused by combination was the best. In reference to **(18)**, their findings indicated that the administration of metformin is efficacious in significantly decreasing total cholesterol levels; however, neither spironolactone administered alone nor metformin exhibited similar efficacy, and their study did not address the index TyG-BMI. Actually, after thorough search in available published article in Google website and in academic website, the researcher of the current study, did not found a similar

design of a study that examined the combined effect of metformin and spironolactone on the index TyG-BMI; therefore, this point van be original in this study with an important finding that combination therapy provide efficient synergistic effect in improving TyG-BMI index in women with PCOS.

In the present research, after treatment, all three modalities of treatment, metformin, Spironolactone and combination were capable to decrease mean TG/HDL considerably (p <0.00 and the magnitude of reduction caused by combination was the best. The influence of metformin on ameliorating dyslipidemia in the present investigation is corroborated by the observations of preceding researchers **(23,24)**. In a multitude of studies, metformin has exhibited a advantageous effect on lipid profiles, albeit with some inconsistencies, across various facets of dyslipidemia; thus, the administration of metformin has directed to improved levels of (HDL) cholesterol, declined concentrations of (LDL) cholesterol, and/or lowered triglyceride levels **(25., 26)**.

With respect to spironolactone, a recent experimental study by **(22)** has shown that hepatic inflammation and Low-dose spironolactone combats dyslipidemia via modifying PCSK9 in rat model of POCs **(27)**, in their experimental study have shown that spironolactone improves lipid metabolism through ameliorating hepatic steatosis and inflammation. The latter two experimental studies are clearly supportive to the finding of current study that spironolactone alone or in combination is efficient in combating dyslipidemia in women with PCOS.

In the year 2009**, (28).** conducted a study examining the influence of spironolactone on serum lipid profiles in female patients diagnosed with hirsutism over a duration of three months, ultimately concluding that spironolactone may exert detrimental effects on serum lipoprotein concentrations by raising (LDL) ranks while diminishing (HDL) ranks throughout a brief treatment regimen. This subsequent observation is in stark opposition to the findings presented in the current study. Therefore, the role of spironolactone is still not very clear with respect to lipid metabolism and is in need for further clinical investigation to confirm the outcomes of the existing study.

Conclusion

The concomitant administration of spironolactone and metformin offers a superior strategy for women with PCOS to have improved insulin sensitivity, as shown by the HOMA-IR, TG/HDL, TyG, and TyG-BMI indices.

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