Comparison between the Effect of Vitamin D Supplementation and Metformin on Insulin Resistance in Women with Polycystic Ovarian Syndrome

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Abstract

Background: Women with polycystic ovarian syndrome (PCOS) often lack vitamin D, with a blood 25-hydroxy vitamin D (25OHD) level of <20 ng/ml seen in 67–85% of PCOS patients. Decreased 25OHD values were connected to insulin resistance, ovulatory and menstrual anomalies, poor pregnancy efficiency, obesity, hirsutism, hyperandrogenism, and higher cardiovascular illness risk factors, according to observational investigations. Vitamin D insufficiency may worsen PCOS symptoms. **Aim:** Find out how individuals with PCOs syndrome respond to vitamin D treatment in terms of their hormonal profile (FSH, LH), insulin resistance, and in individuals with PCOS syndrome, contrast the impact of vitamin D therapy vs metformin on insulin resistance. **Subjects and methods:** the study conducted at AL Zahraa University Hospital at the outpatient clinic of obstetrics and gynecology Participants including 60 women suffering from PCOS. The study was randomly assigned to three groups. **Results:** Comparing the post-treatment fasting insulin, fasting glucose insulin ratio, HOMA-IR level, FSH, LH, fasting G, fasting insulin, and fasting insulin/fasting glucose insulin ratio across the three groups revealed a substantial variation. Age, BMI, pretreatment FSH and LH levels, fasting insulin, fasting glucose, fasting glucose insulin ratio, and HOMA-IR level did not significantly vary between the three groups. **Conclusion:** In women with PCOs, the efficacy of metformin and vitamin D supplementation together is superior to that of metformin or vitamin D treatment alone in reducing insulin resistance.

Key Words: vitamin D, insulin, PCOs syndrome.

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Introduction:

The most prevalent endocrine illness in women of reproductive age is polycystic ovarian syndrome (PCOS), which may affect up to 18% of this group. **(March et al., 2010).**

Polycystic ovaries, menstrual abnormalities, infertility, and biochemical (increased androgen) and clinical (hirsutism and/or acne) hyperandrogenism are all symptoms of PCOS. **(Alexander et al., 2009).**

Women with PCOS often lack vitamin D, with 67–85% of them having blood levels of 25-hydroxy vitamin D (25OHD) < 20 ng/ml. Decreased 25OHD values were connected to insulin resistance, ovulatory and menstrual anomalies, worse pregnancy outcome, hirsutism, obesity, hyperandrogenism, and higher cardiovascular illness risk factors, according to observational investigations. Vitamin D insufficiency may worsen the symptoms of PCOS. **(Wehr et al., 2009).**

There is a growing realization that vitamin D is critical for reproductive health. receptors for vitamin D The placenta, endometrium, and ovary have all been discovered to have VDRs. (Pal et al., 2008). Calcium dysregulation, which is linked to vitamin D insufficiency, helps women with PCOS develop follicular stoppage, which affects menstruation and fertility. **(Ozkan et al., 2010).** with nocturnal enuresis (3).

Although there is currently little data to support the potential advantages of vitamin D supplements in this group, vitamin D deficiency may contribute to the exacerbation of PCOS, and there may be a place for vitamin D supplement in the therapy of

this condition. **(March et al., 2010).**

In certain cases, women with PCOS may take the diabetic medication metformin to reduce their insulin and blood sugar levels. This helps PCOS-afflicted women maintain regular menstrual cycles, initiate ovulation, and reduce miscarriage risk. Long-term usage also reduces the risk of heart illness and diabetes brought on by high insulin concentrations. **(Ehrmann et al., 2005).**

Women with PCOS may be treated with metformin, which lowers insulin levels and encourages normal ovarian function. The ideal way to utilize metformin is in conjunction with a nutritious diet, weight loss, and regular exercise. **(Barbieri et al., 2007).**

Patients and Methods

This is prospective intervention clinical study with intention to treat, conducted at AL Zahraa University Hospital at the outpatient clinic of obstetrics and gynecology, for 2 years starting from October 2015 to October 2017. Participants including 60 women suffering from PCOS (as regard the 2004 Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group's definition) and coming with different complains.

Inclusion Criteria:

Patients in this research were determined to have PCOS if at least two of the following three conditions were present: Clinical (alopecia, acne, and hirsutism) & Or/Biochemical Hyperandrogenism, Oligo & Or/Anovulation, Polycystic Ovaries on US Evaluation, and (a rise in both free and total testosterone).

Exclusion criteria:

ingestion of vitamin D today, hypoalbuminemia, coagulation disease, nephrotic syndrome, liver failure, recognized causes of liver cirrhosis or liver malfunction accompanied with ascites uncontrolled hypertension, A medical condition or medicine (such as epilepsy) that affects how vitamin D is metabolized as well as a known hypersensitivity to metformin hydrochloride.

All the subjects were submitted to:

Full History Taking, Complete General and Gynecological Evaluation and Investigation.

Biochemical Assay including:

Fasting Insulin level.

Fasting blood sugar.

FSH/LH ratio.

Calculation of fasting glucose/ insulin ratio

Calculation of the homeostatic model assessment of Insulin resistance (HOMA-IR) utilizing the formula below:

Fasting plasma insulin value X the fasting plasma glucose value / 405 according to Legro RS. Castracane VD & Kauffman RP).

Pelvic U/S: The existence of 12 or more follicles measuring 2 to 9 mm in diameter in any one ovary or an enlarged ovarian volume >10 cm3 are the key indicators for PCOS identification.

The study's cases were divided into three groups at random, The Randomization Was Based on The Day Of Patient Attendance Into The Clinic.

Group A (20 women): who was prescribed vitamin D therapy 2000 IU per day for three months (in the form of VIDROP 1 ml/day) (Medical Union Pharmaceuticals, company).

Group B (20 women): who was prescribed combined therapy both vitamin D 2000 IU/ day + metformin 500mg 3times/day for three months.

Group C (20 women): who was prescribed metformin therapy 500 mg 3times /day for three months (CIDOPHAGE 500mg) (CID company).

Through repeated measurements of FSH, LH serum fasting insulin, fasting glucose, fasting glucose/insulin ratio, and HOMA-IR three months later, the efficacy of medications was calculated.

Statistical Analysis:

One-way ANOVA was utilized to compare numerical variables across groups if its assumptions were met; otherwise, the Kruskal-Wallis test was employed. Unpaired T-test was utilized to compare two groups. When necessary, post hoc analyses were performed using the Mann-Whitney test or the Tukey's HSD test.

Chi-square test (x^2) was utilized to compare categorical data between groups.

A variation was deemed statistically substantial if the p value was < 0.05.

A variation was deemed statistically substantial if the p value was <0.001.

A variation was deemed statistically insignificant if the p value was > 0.05.

Results:

Table (1): Display the age of participants in the various groups as one of their clinical features.

	Age					ANOVA	
	Range			Mean	± SD	F	P-value
Group A	19	-	33	23.300	± 4.111	1.889	0.171
Group B	19	-	29	25.200	± 2.898		
Group C	20	-	34	26.500	± 3.979		

Group A: ranged in the age from 19-33 years old (mean 23.300± SD 4.111).

Group B: ranged in the age from 19-29 years old (mean 25.200 ± SD 2.898).

Group C: ranged in the age from 20-34 years old (mean 26.500 ± SD 3.979).

There is no substantial variation between the three groups according to age as p- value (0.171).

Table (2): Compares pre and post treatment BMI for different groups

Groups	BMI						Difference		Paired T-test	
	Pre			Post						
	Mean	±	SD	Mean	±	SD	Mean	SD	t	P-value
Group A	29.790	±	4.843	28.310	±	3.493	1.480	1.570	2.980	0.015*
Group B	32.410	±	5.104	30.400	±	3.618	2.010	1.869	3.401	0.008*
Group C	32.310	±	3.950	30.690	±	3.729	1.620	1.135	4.513	0.001*

There was significance difference in group A before and after treatment according to BMI being less in post treatment (mean 1.480, SD 1.570) p-value (0.015).

There was significance difference in group B before and after treatment according to BMI being less in post treatment (mean 2.010, SD 1.869) p-value (0.008).

There was significance difference in group C before and after treatment according to BMI being less in post treatment (mean 1.620, SD1.135) p-value (0.001).

Table (3): Compares pre and post treatment FSH level for different groups.

Groups	FSH						Difference		Paired T-test	
	Pre			Post						
	Mean	±	SD	Mean	±	SD	Mean	SD	t	P-value
Group A	5.307	±	1.551	4.962	±	1.351	0.345	0.496	2.199	0.055
Group B	6.543	±	2.101	5.436	±	1.488	1.107	1.051	3.330	0.009*
Group C	5.99	±	2.088	4.442	±	0.760	1.511	1.23	3.886	0.001*

There was no significance difference in group A before and after treatment according to FSH level, p-value (0.055).

There was significance difference in group B before and after treatment according to FSH level being less in post treatment (mean 1.107, SD 1.051) p-value (0.009).

There was no significance difference in group C before and after treatment according to FSH level, p-value (0.509).

Table (4): Compares pre and post treatment LH level for different groups

Groups	LH						Difference		Paired T-test	
	Pre			Post						
	Mean	±	SD	Mean	±	SD	Mean	SD	T	P-value
Group A	9.544	±	3.509	6.278	±	1.786	3.266	2.535	4.074	0.003*
Group B	10.713	±	5.194	5.197	±	1.736	5.516	3.737	4.667	0.001*
Group C	7.501	±	2.602	5.165	±	2.090	2.336	0.862	8.567	<0.001*

There was significance difference in group A before and after treatment according to LH level being less in post treatment (mean 3.266, SD 2.535) p-value (0.003).

There was significance difference in group B before and after treatment according to LH level being less in post treatment (mean 5.516, SD 3.737) p-value (0.001).

There was significance difference in group C before and after treatment according to LH level being less in post treatment (mean 2.336, SD 0.862) p-value (<0.001).

Table (5): Compares pre and post treatment fasting insulin level for different groups.

Groups	FI						variation		Paired T-test	
	Pre			Post						
	Mean	±	SD	Mean	±	SD	Mean	SD	t	P-value
Group A	31.750	±	8.591	27.350	±	7.647	4.400	1.384	10.053	<0.001*
Group B	36.820	±	9.136	17.320	±	3.645	19.500	6.195	9.954	<0.001*
Group C	34.380	±	7.195	22.290	±	5.004	12.090	4.437	8.616	<0.001*

There was significance difference in group A before and after treatment according to FI level being less in post treatment (mean 4.400, SD 1.384) p-value (<0.001).

There was significance difference in group B before and after treatment according to FI level being less in post treatment (mean 19.500, SD 6.195) p-value (<0.001).

There was significance difference in group C before and after treatment according to FI level being less in post treatment (mean 12.090, SD 4.437) p-value (<0.001).

Table (6): Compares pre and post treatment fasting glucose insulin ratio for different groups.

Groups	FG/I					Difference		Paired T-test	
	Pre			Post					
	Mean	±	SD	Mean	±	SD	Mean	SD	t	P-value
Group A	2.770	±	0.722	3.169	±	0.910	-0.399	0.204	-6.195	<0.001*
Group B	2.388	±	0.559	4.865	±	0.941	-2.477	0.615	-12.737	<0.001*
Group C	2.432	±	0.408	3.715	±	0.601	-1.283	0.483	-8.396	<0.001*

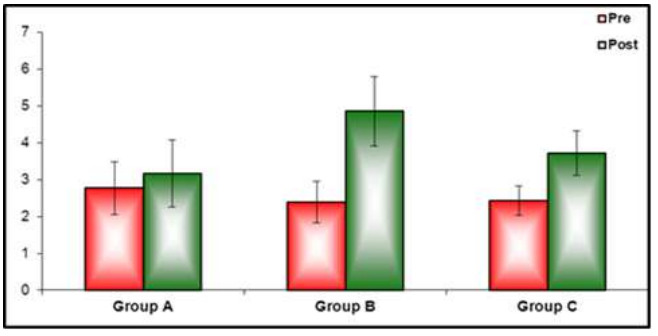

Figure (1): Compares pre and post treatment fasting glucose insulin ratio for different groups

There was significance difference in group A before and after treatment according to FG/I ratio level being more in post treatment (mean -0.399, SD 0.204) p-value (<0.001).

There was significance difference in group B before and after treatment according to FG/I ratio level

being more in post treatment (mean -2.477, SD 0.615) p-value (<0.001).

There was significance difference in group C before and after treatment according to FG/I ratio level being more in post treatment (mean -1.283, SD 0.483) p-value (<0.001).

Table (7): Compares pre and post treatment HOMA-IR for different groups.

Groups	HOMA-IR						Difference		Paired T-test	
	Pre			Post						
	Mean	±	SD	Mean	±	SD	Mean	SD	t	P-value
Group A	6.548	±	1.966	5.482	±	1.686	1.066	0.356	9.467	<0.001*
Group B	7.639	±	1.921	3.489	±	0.804	4.150	1.275	10.290	<0.001*
Group C	6.950	±	1.789	4.467	±	1.274	2.483	0.992	7.912	<0.001*

There was significance difference in group A before and after treatment according to HOMA-IR being less in post treatment (mean 1.066, SD 0.356) p-value (<0.001).

There was significance difference in group B before and after treatment according to HOMA-IR being less in post treatment (mean 4.150, SD 1.275) p-value (<0.001).

There was significance difference in group C before and after treatment according to HOMA-IR being less in post treatment (mean 2.483, SD 0.992) p-value (<0.001).

Discussion:

Anovulatory infertility, menstrual abnormalities, and hirsutism are all often brought on by the genetically complicated endocrine illness known as polycystic ovary syndrome (PCOS), which affects women. **(Azziz, 2005).** PCOS seems to be linked to an elevated risk of metabolic anomalies, such as hyperinsulinism and insulin resistance, type 2 diabetes, dyslipidemia, cardiovascular illness, and endometrial cancer. **(Legro, 2008).**

Hyperinsulinemia and insulin resistance are common metabolic disorders in PCOS. Recently, it was shown that insulin resistance and blood values of 25OHD are negatively associated in women with PCOS. **(Mahmoudi, 2009).** Additionally, prior research has revealed a connection between the polymorphisms in the vitamin D receptor (VDR) gene and insulin sensitivity, PTH and 25(OH)D values in the blood. **(Baroncelli et al., 2008).**

In our study there is improvement in fasting serum insulin level in vitamin D group from (31, 750±8, 591) to (27.350± 7.647) with p-value <0.001.

And in group B (vitamin D+ metformin) from (36.820 ± 9.136) to(17.320± 3.615) with p-value <0.001.

In group C (metformin) from (34.380 ±7.195) to (22.290 ±5.004) with p-value <0.001.

But there is substantial improvement in group B rather than the other 2 groups with p-value <0.001.

Also, our study result demonstrated that there is improvement in fasting G/I ratio in the three groups with p-value <0.001. But the improvement more noticeable in combined group (vitamin D+ metformin) with p-value < 0.001.

This outcome is line with research done by **Thys-Jacobes et al. (1999)** on the impact of vitamin D in 13 women with PCOS shown that improvement only in 7 women in decrease insulin resistance by fasting G/I ratio.

Additionally, our research supports a study from the Framingham Offspring Study, which found that levels of 25 (OH) D were negatively correlated with fasting plasma glucose, insulin values, and HOMA-IR. This study had 808 non-diabetic people. In comparison to participants in the lowest tertile, those in the highest tertile of plasma 25 (OH) D values had reduced HOMA-IR, fasting plasma glucose, and insulin values (12.7%, 1.6%, and 9.8%, respectively). **(Kotsa et al., 2009).**

It has been shown that the majority of PCOS sufferers have insulin resistance. Furthermore, it has been demonstrated that in obese individuals, the 25 (OH) D level is negatively linked with insulin resistance. **(Wehr et al., 2009).** Additionally, it seems that PTH values are greater in PCOS women. **(Panidis et al., 2005).**

Through promoting the development of insulin receptors in peripheral tissues, vitamin D may directly rise insulin sensitivity. The equilibrium of calcium within extracellular and intracellular tissues is disturbed by a lack of vitamin D, which inhibits the release of insulin. **(Pittas et al., 2007).** Through promoting the development of insulin receptors in peripheral tissues, vitamin D may directly rise insulin sensitivity. The equilibrium of calcium within extracellular and intracellular tissues is disturbed by a lack of vitamin D, which inhibits the discharge of insulin. **(Jorde and Figenschau Y 2009).**

Yildizhan et al. (2008) revealed that A deficiency in vitamin D was seen in 67% of PCOS patients. In line with earlier research **(Wehr et al., 2009).**

According to the results, there is a significant correlation between BMI and 25(OH)D in PCOS women, which is in line with earlier research. It is still unclear if vitamin D deficiency causes obesity or whether obesity is a result of vitamin D deficiency. Conversely, obesity may cause low

levels of circulation vitamin D by storing vitamin D in fat cells. **(Wehr et al., 2009).** In research done by **Gennarelli (2005),** Skinfold measures revealed that compared to controls, women of healthy weight with PCOS had greater levels of total body fat and a propensity to store more adipose tissue in truncal-abdominal locations. It has been shown that women with PCOS who have this kind of fat have high insulin resistance. **Wortsman et al. (2000);** revealed that in comparison to non-obese patients, the rise in 25(OH)D values 24 hours after exposure to whole-body UV radiation was 57% reduced in obese people. Conversely, individuals who are fat may avoid sunlight, which is important for the skin's production of vitamin D. **(Wehr et al., 2009).**

Low vitamin D consumption may be a predictor of obesity, and there is proof linking low vitamin D value to obesity **(Hahn et al., 2006 &Kamycheva et al., 2003).**

Our study result demonstrated that there was improvement in HOMA-IR in three groups as p-value (0.008) A substantial variation was noticed between group A& group B as regard HOMA-IR being less in group B than group A, p-value (0.006).

This is in agree with research done by **Taiwan et al. (2009)** In a randomized clinical experiment, 60 PCOS individuals with infertility were split into three equal groups. Each day, 400 IU of vitamin D was given orally to group 1. The identical treatment for Group 1 was given to Group 2, plus 1,500 mg of metformin daily. Metformin 1,500 mg/day was given to group 3. Three months were spent treating the patients. They evaluated the influence of vitamin D on menstrual abnormalities, insulin resistance, and infertility in three groups of 20 PCOS-afflicted women, the majority of whom had oligomenorrhea. The vitamin D and metformin group showed higher improvement in menstrual abnormalities, while the variations between the groups were not statistically significant, presumably due to the small sample numbers. A significant, randomized clinical trial with a bigger sample sizes may be able to show a more direct connection between vitamin D-metformin therapy and regular menstrual cycles. Additionally, they discovered a statistically substantial variation in follicular development, insulin level, and therefore insulin resistance by HOMA-IR between the vitamin D-metformin and vitamin D groups. This indicates that the vitamin D-metformin group had a greater response to therapy than the other two groups.

In the research done by **Velazquez et al. (1997),** After six months of metformin medication, which decreased insulin and androgen levels while controlling menstrual periods, fertility was recovered in PCOS patients.

These individuals' low dietary calcium intake and the need of calcium and vitamin D for bone health and fertility point to potential therapy modalities. These two medications—calcium-vitamin D and metformin—seem to work better together than they do alone to treat menstrual irregularities, reduce insulin resistance, and promote follicular maturation.

Also, A study done by **Duran and colleagues (2010)** revealed that three weeks after taking an orally single dosage of 300,000 units of vitamin D3, the concentration of 25-hydroxyvitamin D3 dramatically rose from 16.9±16 ng/ml to 37.1±14.6ng/ml (p: 0.027).

HOMA-IR considerably lowered from 4.41±1.38 to 3.67±1.48 (p: 0.043), which is consistent with our findings even though glucose and insulin values were not substantially lower.

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