

Clinical and biochemical outcome of patients with polycystic ovary syndrome managed with life style modification or combination with metformin

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Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder with diverse reproductive and metabolic features. It is caused by insulin resistance that is exacerbated by obesity. Lifestyle modification is the first line treatment in PCOS, but it is associated with low adherence and sustainability. In small studies, metformin improves outcomes such as menstrual cycle problem, reduces the features of hyperandrogenism (hirsutism) and metabolic parameters (lipid profile). This study aimed to compare clinical and biochemical outcome of patients with polycystic ovary syndrome managed with life style modification or combination with metformin.

Methods: This prospective interventional study was carried out at Endocrine OPD, BIRDEM, from November 2016 to March 2018. Newly detected cases of PCOS were taken as study sample. Sampling technique was purposive and then randomly selected into two groups; Group A (n=40) with lifestyle modification and Group B (n=40) with lifestyle modification plus metformin (500mg TDS). The clinical [weight, body mass index (BMI), waist circumference, menstrual problem, hirsutism) and biochemical [serum testosterone, LH, FSH, fasting lipid profile] outcome of intervention with lifestyle modification and combination with metformin was studied.

Results: Baseline characteristics of both groups had no significant difference. After 12 months, there was significant improvement in hirsutism, menstrual problem and significant decrease in weight, BMI, waist circumference in both groups. Among hormonal profile there was significant reduction of testosterone in Group B (p=0.01), whereas LH, FSH and LH: FSH ratio showed no significant difference. There was significant improvement of HDL (in both groups) and reduction of triglyceride (TG) (p=0.005, in group B). Outcome differences between two groups had shown significant improvement in weight, BMI, testosterone, HDL, TG level and on menstrual regulation. But there was no significant difference in waist and Ferriman-Gallwayscore in between groups.

Conclusion: lifestyle management is the first and most important step in the management of PCOS and addition of metformin to lifestyle modification appears to provide additional advantages. These results suggest the combination of lifestyle with metformin has a role to play in weight management: a key concern for women with PCOS. Addition of metformin also causes reduction of TG and testosterone, which is vital for PCOS management and found in this study.

Key words: polycystic ovary syndrome, life style modification, metformin, hirsutism.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder amongst women of reproductive age. PCOS is characterized by anovulatory menstrual cycle, infertility, hyperandrogenism and clinically manifested by irregular menstruation, hirsutism, obesity and acne thus resemble different metabolic syndromes.¹ It is a heterogeneous disorder of uncertain etiology, but there is strong evidence that complex interactions between genetic, environmental and behavioral factors contribute in pathogenesis of this syndrome.² Incidence of PCOS in women of reproductive age is reported to be 5 to 10%.³ The most widely used 1990 National Institutes of Health (NIH) criteria include clinical and/or biochemical

hyperandrogenism and chronic anovulation.⁴ The 2004 Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group) suggest PCOS should be diagnosed by two of the following three criteria: oligo-anovulation, clinical or biochemical hyperandrogenism and poly-cystic ovaries (PCOs) on ultrasound. Recent Androgen Excess and PCOS Society (AE-PCOS Society) criteria recommend that PCOS should be defined as clinical or biochemical hyperandrogenism associated with ovulatory dysfunction in the form of oligo-anovulation or PCO. Emerging data suggest obesity and PCOS has a bidirectional relationship. The more a person is obese the more chance of developing PCOS.⁶ Consistently, weight loss through lifestyle modification (comprising dietary modification, physical activity and/or behavioral change), medications (metformin, orlistat, incretinmimetics) or bariatric surgery improves insulin resistance, reduces hyperandrogenism and reduces PCOS clinical severity.⁷ Lifestyle management (LSM) is first line therapy in PCOS for prevention of weight gain.⁸ Metformin increases insulin sensitivity by decreasing gluconeogenesis, lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue and ovaries. In PCOS, metformin reduces insulin resistance and inhibits ovarian androgen production via its effects on steroidogenic acute regulatory protein and 17 α -hydroxylase. Based on current guidelines, metformin is indicated in PCOS in some scenarios to improve fertility⁶, for management of menstrual irregularity if women are unable to take OCPs and in co-existent prediabetes or diabetes, where lifestyle modification fails.⁹ Previous observational studies showed that LSM can be associated with clinical improvement in PCOS. Moderate weight loss during long term calorie restriction is associated with marked clinical improvement in menstrual function and fertility.¹⁰ In a retrospective study, weight loss is associated with improvement in ovulation, pregnancy outcome, self-esteem, and endocrine parameters in women who are infertile and overweight. In brief, changes in diet and lifestyle remain the primary choice in the management of reproductive and metabolic and cardiovascular (CV) sequelae in overweight and obese women with PCOS. Metformin is the primary insulin sensitizing drug to be used as an adjuvant to general lifestyle modification in patients who have impaired glucose tolerance (IGT) or overt type 2 diabetes. Furthermore, accumulating evidence shows that, in a subset of women with PCOS, metformin treatment may be effective for the improvement of reproductive function irrespective of insulin resistance and glucose intolerance.¹¹ This study was designed to compare clinical

and biochemical outcome of patients with polycystic ovary syndrome managed with life style modification or combination with metformin.

Methods

This prospective interventional study conducted in the BIRDEM General Hospital 1 and 2 in Endocrine OPD from November 2016 to March 2018. The women of reproductive age (15-40 Years) either married or unmarried already diagnosed as polycystic ovary syndrome without any intervention considered as study population. Subject selection was done as per inclusion and exclusion criteria. After full explanation of the study procedure informed written consent was taken. A detailed history was obtained. Data were collected in a structured questionnaire. After enrollment in the study, the study subjects were randomly divided into two groups. Group A gone through life style modification and Group B had combination of life style modification and metformin. Anthropometric measurements including height in cm, weight in kg and waist circumference (WC) in cm was. The BMI was calculated by dividing the weight (in kg) by the height (in m) squared to assess obesity. Each patient was counseled about drug side effect. They were sent to nutritionist to formulate a weight reducing diet plan and advised to walk at least 1 hour per day. The amount of terminal hair growth assessed using a modified Ferriman-Gallway method in which the upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back and upper arms were scored from 0 to 4. Subjects (Group A and Group B) were asked to follow up after 12 months with the hormonal (S. testosterone, LH, FSH), biochemical (fasting lipid profile) report. At that time clinical examination and anthropometric measurement was also done. Study subjects were made contact frequently over phone to inquire about compliance and any drug related side effect. If any side effect occurred then it was noted down and if not severe, subjects were counseled to continue the medication. After editing and coding, the coded data were directly entered into the computer by using SPSS software, version 22.0. Data cleaning validation and analysis were performed using the SPSS software. Categorical data were presented as percentage and continuous variable were expressed as mean \pm SD (standard deviation). An independent sample Student's t-test was used for comparison of means of continuous variables with normal or approximately normal distributions. The Chi-square test was used to analyze discrete variables. Confidence interval was set at 95% level. Statistical significance was set at $p < 0.05$.

Results

Total 80 patients were taken and divided in two groups equally. Baseline characteristics of the two groups shown in Table I and II and found no difference in two groups.

In Group A (LSM only), there are significant decrease in weight (mean change: -1.6, p-value <0.01), BMI (mean change: -0.54, p-value <0.001) waist circumference (mean change: -4.6, p-value <0.002) and improvement of hirsutism total score in the study subject (mean change: -3.6, p-value <0.01) at the end of the study. In Group B (LSM plus metformin), there are

significant decrease in weight (mean change: -4.33, p value <0.0001), BMI (mean change: -4.0, p value <0.001), waist circumference (mean change: -7.1, p-value: 0.006) and improvement of hirsutism total score in the study subject (mean change: -5.2, p-value: 0.004) at the end of the study as shown in Table III.

At the end of study period, there was significant decrease in testosterone level found in Group B (mean change: -1.7, p-value: 0.01) as shown in table 4. There is no effect on FSH and LH level and ratio after the end of the study period in two groups (Table IV).

Table I Baseline characteristic (clinical, anthropometric, hormonal and lipid profile) of the patients

Baseline characteristic	Group A	Group B	Difference in
Anthropometric and Clinical	Patients with life style modification (n=40)	Patients with lifestyle and Metformin therapy (n=40)	between group
Age (yr)	29.1 ± 4.3 (18-32)	30.4 ± 5.4 (19-36)	0.237 Ns
Weight (kg)	81.56 ± 2.95 (58-110)	82.0 ± 5.2 (54-112)	0.643 Ns
BMI (kg/m ²)	31.99 ± 0.79 (24-38)	31.7 ± 4.5 (23-37)	0.689 Ns
Waist (cm)	110.4 ± 8.5 (82-125)	112.9 ± 13.6 84-119	0.327 Ns
Ferriman-Gallwey score	17.7 ± 6.2 (10-26)	19.1 ± 8.9 (12-24)	0.417 Ns
Hormones			
Testosterone (ng/ml)	0.68 ± 0.15 (0.45-1.10)	0.63 ± 0.17 (0.34-1.23)	0.167 Ns
FSH(mIU/mL)	5.0 ± 1.9 (4-8)	4.8 ± 2.3 (5-9)	0.673 Ns
LH (mIU/mL)	8.7 ± 4.0 (07-19)	8.5 ± 2.0 (06-17)	0.778 Ns
LH/FSH ratio	1.74 (0.4-2.65)	1.98 (0.35-2.72)	0.737 Ns
Lipid parameters			
Cholesterol (mg/dL)	187.4 ± 55.4 (78-320)	186.0 ± 52.6 (65-345)	0.908 Ns
HDL (mg/dL)	37.1 ± 15.8 (28-65)	36.7 ± 13.2 (28-54)	0.903 Ns
LDL (mg/dL)	123.9 ± 45.7 (75-199)	121.8 ± 42.2(72-230)	0.831Ns
Triglycerides (mg/dL)	128.5 ± 87.4 (76-489)	125.8 ± 88.1 (74-565)	0.891 Ns

Ns= Not Significant (independent t test was done)

Table II Menstrual history of the PCOS patients at the baseline in between two groups

Menstrual characteristics	Group A	Group B	Difference in between group
	Patients with life style modification (n=40)	Patients with lifestyle and Metformin therapy (n=40)	
Menstrual duration	5.0 ± 0.57	4.8 ± 1.5	0.53 (t test)
Mean days ± SD	(02-17)	(03-21)	Ns
Number of menstrual cycles in last year. Mean days ± SD	5.46 ± 0.84 (02-08)	5.48 ± 0.53 (03-07)	0.89 (t test) NS
Amenorrhoea	11	14	0.58 (Chi square) NS
Oligomenorrhoea	29	26	0.61 (Chi square) NS

Table III Anthropometric effects after intervention in group A & group B

Variable	Patients with life style modification (Group A)			P value	Patients with lifestyle and Metformin (Group B)			P Value
	Baseline n=40	12th month n=32	Mean change (95% CI)		Baseline n=40	12th month n=33	Mean change (95% CI)	
Weight (kg)	81.56 ± 2.95 (80.61-82.50)	79.96 ± 2.65 (79.00-80.91)	-1.6 (-2.8 to -0.35)	0.01	82 ± 5.2 (80.33-83.66)	77.67 ± 3.3 (76.49-78.84)	-4.33 (-6.26 to -2.39)	<0.0001
BMI (kg/m ²)	31.99 ± 0.79 (31.73-32.24)	31.45 ± 0.65 (31.21-31.68)	-0.54 (-0.86 to -0.21)	0.001	31.7 ± 1.2 (31.31-32.08)	27.7 ± 3.88 (26.32-29.07)	-4.0 (-5.27 to -2.72)	<0.0001
Waist circumference (cm)	110.4 ± 8.5 (107.68-113.11)	105.8 ± 3.67 (104.47-107.12)	-4.6 (-7.51 to -1.68)	0.002	112.9 ± 13.6 (111.75-114.06)	105.78 ± 8.32 (102.82-108.73)	-7.1 (-12.13 to -2.10)	0.006
Ferriman-Gallwey score	17.7 ± 6.2 (15.71-19.68)	14.01 ± 6.4 (11.70-16.31)	-3.6 (-6.49 to -0.88)	0.010	19.1 ± 8.9 (16.25-21.94)	13.87 ± 6.76 (10.47-15.26)	-5.2 (8.74 to -1.71)	0.004

Note: Paired t test was done.

Table IV Hormonal effects after intervention in group A & group B

Variable	Patients with life style modification (Group A)			P value	Patients with lifestyle and Metformin (Group B)			P value
	Baseline n=40	12th month n=32	Mean change (95% CI)		Baseline n=40	12th month n=33	Mean change (95% CI)	
Testosterone (ng/mL)	7.3 ± 3.6 (6.1-8.4)	7.2 ± 3.5 (5.9-8.4)	-0.1 (-1.5 to 1.7) (6.4-8.5)	0.9 (5.0-6.5)	7.5 ± 3.4 (4.06-5.53)	5.8 ± 2.0 (4.27-6.32)	-1.7 (0.3-3.0)	0.01
FSH (mIU/mL)	5.0 ± 1.9 (4.39-5.60)	4.84 ± 1.28 (4.37-5.30)	-0.16 (-0.88 to 0.56)	0.659	4.8 ± 2.3 (4.06-5.53)	5.3 ± 2.89 (4.27-6.32)	0.50 (-0.66 to 1.6)	0.39
LH (mIU/mL)	8.7 ± 4.0 (7.4-9.9)	7.37 ± 3.87 (5.9-8.7)	-1.33 (-3.08 to 0.42)	0.134	8.5 ± 2.0 (7.8-9.1)	7.83 ± 1.78 (7.19-8.46)	-0.67 (-1.51 to 0.17)	0.11
LH: FSH Ratio	1.74	1.52	-0.12 (-0.06 to 1.08)	0.087	2.18	1.85	-0.33 (-0.17 to 2.03)	0.076

Note: Paired t test was done.

At the end of the study period, table 5 shows a significant improvement in HDL level in Group A (mean change: 6.8, p-value: 0.04) & more significant improvement in group B (mean change: 10.6, p-value: 0.001). There is no effect on LDL and Total Cholesterol level after the end of the study period in two groups. There is a significant decrease in TG level (mean change: 43.4, p-value: 0.005) in lifestyle and metformin intervention group (Table V).

At the end of the study, 22 (55%) and 30 (75%) women from Group A and B were menstruating regularly compared to none at baseline. In group A, amenorrhea 11 (27.5%) and oligomenorrhoea 29(72.5%), was significantly improved by 6 (15%) & 16 (40%) respectively. In group B, amenorrhea 14 (35%) and oligomenorrhoea 26 (65%), was significantly improved by 03 (7.5%) & 07 (17.5%) respectively as shown in Table VI.

Table V Lipid profile change after intervention between two groups.

Variable	Patients with life style modification (Group A)			P value	Patients with lifestyle and Metformin (Group B)			
	Baseline n=40	12th month n=32	Mean change (95% CI)		Baseline n=40	12th month n=33	Mean change (95% CI)	P Value
Cholesterol (mg/dL)	187.4 ± 55.4 (169.6- 205.1)	179.2 ± 53.7 (159.8- 198.5)	-8.2 (-32.4 to 16.08)	0.50	186.0 ± 52.6 (169.1- 202.8)	178.7 ± 50.3 (160.8- 196.5)	-7.3 (-30.2 to 15.60)	0.52
HDL (mg/dL)	37.1 ± 15.8 (32.04- 42.15)	43.9 ± 14.2 (38.7- 49.0)	6.8 (-0.11 to 13.48)	0.04	36.7 ± 13.2 (32.4- 40.9)	49.3 ± 9.5 (45.9- 52.6)	10.6 (4.3 to 16.84)	0.001
LDL (mg/dL)	123.9 ± 45.7 (109.2- 138.5)	118.2 ± 43.6 (102.4- 133.9)	-5.7 (-25.58 to 14.18)	0.57	121.8 ± 42.2 (108.3- 135.2)	119.8 ± 41.5 (105.0- 134.5)	-2.0 (-20.63 to 16.63)	0.83
Triglyceride (mg/dL)	128.5 ± 87.4 (100.5- 156.4)	120.1 ± 73.6 (93.5- 146.6)	-8.4 (-44.3 to 27.5)	0.64	135.8 ± 78.1 (110.8- 160.7)	90.4 ± 55.2 (70.8- 109.9)	-43.4 (-73.8 to - 12.9)	0.005

Note: Paired t test was done.

Table VI Menstrual effects after intervention in between two groups

Variable	Patients with life style modification (Group A)			Patients with lifestyle and Metformin therapy (Group B)		
	Baseline (n=40)	12th month (n=32)	P value	Baseline (n=40)	12th month (n=33)	P value
Amenorrhea	11	06	0.01	14	03	0.001
Oligomenorrhoea	29	16	0.01	26	07	0.001
Regular menstruation	0	18	0.001	0	30	0.001

Note: chi-square test was done

Outcome difference about clinical parameters after completion of the study Hirsutism mean score was improved (p-value is <0.08) and menstrual regularity was more improved (p-value <0.01) in lifestyle with Metformin intervention group than with lifestyle intervention alone. BMI (p-value 0,001) and Weight (p-value 0.0001) was significantly reduced in lifestyle with Metformin intervention group than lifestyle alone intervention group. There is no outcome difference in waist circumference (p-value 0.99) in between two intervention group. There is improved HDL level (p-value 0.05) and significant decreased in TG level (p-value 0.04) in life style intervention with Metformin

group than lifestyle intervention alone group. There is no outcome difference in serum cholesterol and LDL level in between two intervention group. There is significant outcome difference in testosterone (p-value 0.03) in lifestyle plus Metformin intervention group than lifestyle intervention alone group. There is no outcome difference in FSH, LH and FSH/LH ratio. All of these shown in Table VII. In group A 80% compliance and Group B 82.5% compliance rate. Drug induce adverse effect in lifestyle plus Metformin group was about 20% people complained abdominal discomfort, 7.5% diarrhoea, 12.5% nausea and vomiting 5%.

Table VII Outcome difference of all parameters after completion of the study in between two intervention groups

Variable (Clinical)	Lifestyle modification (Group A n=32) (Mean Change)	Lifestyle + Metformin (Group B n=33) (Mean Change)	P value
Ferriman-Gallwey score	-3.6 (-6.49 to -0.88)	-5.2 (8.74 to -1.71)	.08
Menstruation			
Regular	22	30	0.01
Weight (kg)	-1.6 (-2.8 to -0.35)	-4.33 (-6.26 to -2.39)	0.001
BMI (kg/m ²)	-0.54 (-0.86 to -0.21)	-4.0 (-5.27 to -2.72)	0.0001
Waist circumference (cm)	-4.6 (-7.51 to -1.68)	-7.1 (-12.13 to -2.10)	0.99
Total Chol (mg/dl)	-8.2 (-32.4 to 16.08)	-7.3 (-30.2 to 15.60)	0.57
HDL (mg/dl)	6.8 (-0.11 to 13.48)	10.6 (4.3 to 16.84)	0.05
LDL (mg/dl)	-5.7 (-25.58 to 14.18)	-2.0 (-20.63 to 16.63)	0.85
Triglycerides (mg/dl)	-8.4 (-44.3 to 27.5)	-43.4 (-73.8 to -12.9)	0.04
Testosterone (ng/mL)	-0.1 (-1.5 to 1.7)	-1.7 (0.3-3.0)	0.03
S.LH (mIU/ml)	-1.33 (-3.08 to 0.42)	-0.67 (-1.51 to 0.17)	0.87
S.FSH (mIU/ml)	-0.16 (-0.88 to 0.56)	0.50 (-0.66 to 1.6)	0.26
LH: FSH Ratio	-0.12 (-0.06 to 1.08)	-0.33 (-0.17 to 2.03)	0.96

Note: independent t test done

Discussion

PCOS is one of the most common endocrine disorders in woman of reproductive age. This is a prospective interventional study to investigate the effects of lifestyle alone or combination with Metformin on patients with PCOS. Total 80 patients were enrolled in this study and then randomly divided into group A (Subjects with lifestyle modification) and Group B (Subjects with lifestyle modification plus Metformin). Both groups were follow-up after 12 months and the dose of Metformin used 500 mg three times daily. There is no significant difference in baseline characteristics in between two groups. In study done by Barbieri¹² showed that, there was no significant difference among baseline characteristics (clinical, anthropometric, hormonal and lipid profile) in between groups. After 12 months of therapy, group A had 80% compliance. Whereas group B had 82.5% compliance. In Group A at the end of the study period, there is significant decrease in weight, BMI, waist circumference, and Hirsutism total score was significantly improved. Study done by Bruner et al¹³ showed similar results in their study after lifestyle intervention in PCOS obese patients. Lifestyle modification induced weight loss improves all metabolic parameters and also hyperandrogenism.^{10,11} This was supported by Brunner¹³, who mentioned weight reduction has shown to alleviate Hirsutism and acne. Linderbaum¹⁴ reported similar improvement of acne and Hirsutism after lifestyle modification. Study done by Hoeger⁵, didn't find significant changes of Hirsutism scores by lifestyle. At the end of the study period in group B, there is significant decrease in weight, BMI, waist circumference, and Hirsutism total score was significantly improved. Barbieri¹² showed that similar significant reduction in waist circumference and BMI in obese PCOS women after lifestyle plus Metformin intervention. Lord et al. 2003 showed that, the effect of Metformin on PCOS features could not confirm any weight-reducing effect. Menstrual dysfunction was significantly improved in both groups in this study. Similar study was done by Moran et. al. 2003 & Foster et. al. 2003 who reported that weight loss alone through lifestyle changes improves menstrual frequency & ovulation. Moghetiet. al¹⁷ showed that after Metformin treatment, mean frequency of menstruation improved in about 50% of subjects. Metformin therapy appears beneficial for improvement of menstrual cycle, ovulation

and hyperandrogenism in some women. These findings agreed with Lord.et.al (2003) who showed that Metformin is effective in achieving ovulation in PCOS. We found that the addition of Metformin to lifestyle had significant benefit on circulating androgen level. In this study testosterone level was significantly decreased in metformin treated group but not in LSM group. There is also no effect on FSH, LH level and LH: FSH ratio after the end of the study period in both groups. This observation agreed that, Metformin may have a direct effect on ovarian steroid-genesis.¹⁸ Another study showed that Metformin was effective in reducing total testosterone concentrations but had no effect on BMI or waist circumference.¹⁹ Similar result found in a double-blind placebo-controlled RCT of nine months revealed that metformin has significant beneficial effect on androgenous activity of PCOS.²⁰ Study done by Nahar etal showed that there are significant relationship between irregular menstrual cycle pattern and hormonal changes such as testosterone level.²¹ Our study also supported by other studies^{11,17}; who reported that, a fall in BMI showed an improvement in menstrual cycle; so as a fall in testosterone concentrations. There is more significant increase in HDL level in Group B then Group A and significantly decrease in TG level in group B. Metformin significantly decreased body fat and also raised circulating high-density lipoprotein cholesterol. PCOS patients treated with Metformin had a significant reduction in total cholesterol, LDL cholesterol and TG levels and an increase in HDL cholesterol levels^{17, 22}. Metformin inhibits ovarian steroidogenesis, increase lipolysis, decreases insulin resistance and decrease hepatic glucose output. For this reason the combination group may have shown more significant outcome.

Conclusion

The effects of lifestyle modification or combination with Metformin both are generally beneficial; the absolute changes are quite modest. This study shows that adding Metformin with LSM brings out improvement in clinical (wt, BMI, waist circumference, menstrual problem and Hirsutism score) and biochemical (S.Testosterone and triglyceride level). LSM is the core component of PCOS management. In conclusion lifestyle management is the first and most important step in the management of PCOS, addition of Metformin to lifestyle modification appears to provide additional advantages.

Conflict of interest: Nothing to declare.

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