Effects of metformin on polycystic ovary syndrome: a randomized, double-blind, placebo-controlled study

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Abstract

Background and objectives: Metformin improves manifestations of polycystic ovary syndrome (PCOS) by reducing insulin resistance. The objective of this study was to determine how metformin, in combination with lifestyle changes, affects the clinical manifestations of PCOS.

Materials and Methods: Patients with PCOS attending the outpatient of a tertiary care hospital were enrolled in the study. Revised Rotterdam Consensus 2003 criteria were used to diagnose cases of PCOS. Clinical information, anthropometric measurement, serum progesterone and polycystic ovarian morphology (PCOM) of each subject were recorded in a prescribed data sheet at baseline and after a period of nine months. Randomized placebo controlled double blind design was used to assign participants in respective groups. Participants were randomly assigned to receive 9 month course of either metformin (1500 mg/day) or placebo. Both groups were advised regarding schedule of lifestyle modification. Outcome variables were clinical manifestations related to metabolic, reproductive and androgenic status of PCOS.

Results: Out of 80 enrolled PCOS cases, 49 completed the study (metformin=26, placebo=23). The mean age of the study participants of metformin and placebo groups was 23.52±5.18 and 22.09±3.58 years respectively (p=0.262). Menstrual cycle significantly improved in both the study groups (before vs. after - metformin: 19.2% vs. 76.9%, p=0.003; placebo: 19.2% vs. 47.8%, p=0.02) after 9 months, but compared to placebo group no such significant (p=0.12) improvement occurred in metformin group. Severity of hirsutism, presence of acne, serum progesterone level and ovulatory status improved significantly in both groups after completion of the study. Except acanthosis nigricans, other metabolic manifestations did not significantly improve in metformin compared to placebo group after the intervention. While comparing the percentage changes, body mass index (BMI) and waist circumference (WC) reduced significantly in metformin than placebo group (BMI in kg/m^2- metformin vs. placebo: -3.63±8.22 vs. +1.42±6.67, p= 0.024; WC in cm - 2.81±7.74 vs. +1.68±7.89, p= 0.05). No significant adverse event was observed in metformin group.

Conclusion: Metformin, in conjunction with lifestyle modifications, has favorable impacts on clinical manifestations of PCOS.

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Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder of women of reproductive age. The prevalence of PCOS has been reported between 2 to 19.9% in different population of the world using different diagnostic criteria [1-11].

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PCOS has been associated with the risk of type 2 diabetes mellitus (T2DM) and metabolic syndrome [12]. Insulin resistance and obesity are the common features seen in PCOS women. About 60-70% and up to 88% women with PCOS are reported to have insulin resistance and obesity respectively [13]. Recent evidences have shown an important implication of insulin resistance in the pathogenesis of PCOS irrespective of obesity or over weight [14,15]. So, the presence of insulin resistance has prompted widespread use of insulin sensitizing agents in the treatment of PCOS [16]. Among the insulin sensitizers, metformin is the most commonly used agent for the treatment of PCOS [17]. In PCOS patients, metformin has been reported to act by restoring ovulation, and by reducing the weight, circulating androgen levels, risk of miscarriage and gestational diabetes mellitus [13]. Metformin is more effective in reducing hirsutism also [18]. Pioglitazone, another widely used insulin sensitizer, is more effective in reducing menstrual irregularity and ovulation (odds ratio= 2.31) than metformin, but associated with weight gain. Apart from the use of insulin sensitizing agents, lifestyle modifications also have therapeutic value in the management of clinical manifestations of PCOS. It helps especially in reduction of weight, waist circumference and hirsutism [19]. Combination effects of lifestyle modification and insulin sensitizer have been reported to be better than each modality of treatment alone especially in reducing body mass index (BMI) and improving menstrual irregularity [20]. In view of the above, the present study was undertaken to determine whether metformin or placebo, in conjunction with lifestyle changes, could affect the clinical manifestations of patients with PCOS.

Materials and methods

The research protocol was approved by the Institutional Review Board (IRB) of BSMMU (No.BSMMU/2014/05). Informed written consent was obtained from all participants. At the end of the study period, PCOS patients in placebo group were offered treatment with metformin based on the study findings.

Study type and population: This randomized double blind placebo-controlled study was conducted at the Department of Endocrinology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Patients with PCOS attending the outpatient clinic of Endocrinology department were enrolled. Diagnosis of PCOS was based on Revised Rotterdam Consensus 2003 criteria [21]. Patients with significant hyperprolactinemia (prolactin >25 ng/ml), abnormal thyroid function tests (thyroid stimulating hormone level - outside the normal reference), congenital adrenal hyperplasia and patients under medications that likely to influence hormonal profiles were excluded. Anyone wishing to have pregnancy was also excluded. Sample size was calculated by [n= $2\sigma^2$ $(Z_\alpha + Z_\beta)^2$ / $(\mu_1 - \mu_2)^2$] formula based on the mean±SD changes of BMI from a similarly designed study [22].

Intervention: After confirmation of diagnosis, patients were randomly allocated to either metformin or placebo group by lottery method in a double blind process. Both groups were provided advice regarding schedule of lifestyle modification. Each patient was advised regarding lifestyle modifications that included a weight-based diet [calorie calculated (weight maintenance Kcal ± 500 Kcal) and diet chart provided], brisk walking for at least 30 minutes at least five days a week and behavioral modification as appropriate [23]. Metformin was prescribed as 1500 mg/day in three divided doses for 9 months. Each tablet of metformin contained metformin HCl BP 500 mg, along with inactive ingredients of povidone, microcrystalline cellulose, croscarmellose sodium and magnesium stearate as excipient. Placebo tablet contained all the ingredients of excipient except metformin. Both metformin and placebo tablets were coded and dispensed in identical blister package.

Follow-up schedule: Each patient was scheduled for five visits within a period of nine months whereupon a window period of 14 days was permitted for the 2nd to 5th visits. In each follow up visit, patients were asked about the practice of lifestyle modification schedules and intake of investigational product (IP). Patients who did not follow all the schedules of lifestyle modifications at least five days a week were considered as noncompliant. Similarly, they were also asked to

bring the empty blisters of the IP. The blisters were counted and the participants who missed to take ≥5% of the IP were also labeled as noncompliant. Noncompliant participants were excluded from final analysis.

Outcome variables: The main outcome variables were metabolic (BMI, WC, blood pressure), reproductive (menstrual cycle, ovulation by progesterone level and polycystic ovarian morphology) and androgenic (modified Ferriman-Gallwey score and acne and acanthosis nigricans) manifestations of PCOS. Weight (kilogram) and height (meter) were measured by calibrated bathroom scale and mounted measuring tape respectively to calculate BMI (kg/m^2). Waist circumference (in centimeter) was measured by measuring tape at the level of umbilicus. Asian criteria was used to categorize BMI as under nutrition, optimal, overweight and obese by the cut-offs values of 18.5, 23 and 25 kg/m^2 respectively, and WC by the cut-off value of 80 cm [24]. Blood pressure was measured by calibrated sphygmomanometer (mm-Hg) and was categorized by metabolic syndrome criteria (cut-off of 130/85 mm-Hg) [25]. Hirsutism was measured by using modified Ferriman-Gallway (mFG) score and classified into mild, moderate and severe with the total score of 8 – 15, 16 – 25 and ≥26 respectively [26]. Acne was observed over face. Acanthosis nigricans was checked on neck, axilla and groin. Missing of at least three menstrual periods in a row was labeled as amenorrhea and without menstruation regularly for more than 35 days termed as oligomenorrhea. Menstruation occurring for consecutive two months was considered as regular menstruation.

Investigations: Blood samples from each participant were collected aseptically for biochemical investigations at the time of enrollment and after nine months. Fasting blood glucose (FBG) was measured by glucose oxidase method and serum luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone (TT), and progesterone were measured by chemiluminescent microparticle immunoassay at diagnosis during follicular phase of menstrual cycle. Serum progesterone ≥5 ng/ml was considered as indication of ovulation [27]. Ultrasonogram

(TOSHIBA Aplio 500 imaging machine) was done by trans-abdominal or trans-vaginal route depending on the marital status of the patient during follicular phase of menstrual cycle by skilled sonologists.

Data recording: A standardized questionnaire was used to obtain information regarding the age, personal and family history, obstetric, menstrual and gynecological history, medical diseases, and medications. Clinical information, anthropometric measurement, results of biochemical tests and polycystic ovarian morphology (PCOM) of each subject were recorded in a prescribed data sheet at baseline and after nine months during the last follow up visit (4th). Compliance and side-effects were recorded in all the follow up visits.

Data analysis: All data were processed by the SPSS program (version: 22.0). Values were expressed as frequencies (%) or mean±SD or median (interquartile range, IQR). Nominal variables namely occupation, personal and family history, acne, acanthosis nigricans, WC, BP and ovulation categories, inference of ultrasonography findings and side-effects at each visit were analyzed by using Pearson's Chi square/ Fisher's exact test between groups and McNemer test (two related samples) within each group (intervention: before vs. after). Ordinal variables (menstrual cycle, BMI category and severity of hirsutism) were tested by Chi-square test/Fisher's exact test between groups and Wilcoxon signed ranks test within group. Normally distributed quantitative variables (age, BMI, WC, BP, FBG, biochemical results) were analyzed by independent student's t test between groups and paired-t test within group. Skewed variables (mFG score, progesterone, TSH, prolactin, LH/FSH) were analyzed by Mann-Whitney-U test between groups and Wilcoxon rank sum test within each group. A two-tailed $p<0.05$ was taken as statistically significant.

Results

Initially, a total 80 women with PCOS were enrolled in the study. Out of 80, 49 PCOS patients completed the study. After unblinding, it was observed that 26 cases were in metformin group and 23 were in placebo group. Out of the rest 31 cases, 4 participants became pregnant before

reaching the end point (Metformin = 1, placebo = 3), and 27 were dropped out due to incomplete visit (metformin= 9, placebo= 9) or noncompliant to lifestyle modification or intake of IP (metformin = 4, placebo = 5) (Figure-1).

The mean age of the total study participants of metformin and placebo groups was 23.52±5.18 and 22.09±3.58 years respectively (p=0.262). Other baseline characteristics of the two groups were similar with respect to occupation, personal and family history and biochemical parameters (Table 1).

Table-2 shows the status of metabolic manifestations in PCOS patients before and 9 months after intervention. Compared to placebo group, the metabolic manifestations, except acanthosis nigricans, did not significantly improve in metformin group 9 months after the intervention. Compared to metformin group, the rate of acanthosis nigricans was significantly higher in placebo group at baseline (metformin vs. placebo: 19.2% vs. 52.2%, p=0.02) and remained significantly higher after the end of intervention also (7.7% vs. 39.1%, p=0.015). BMI (25.17±5.62 vs.
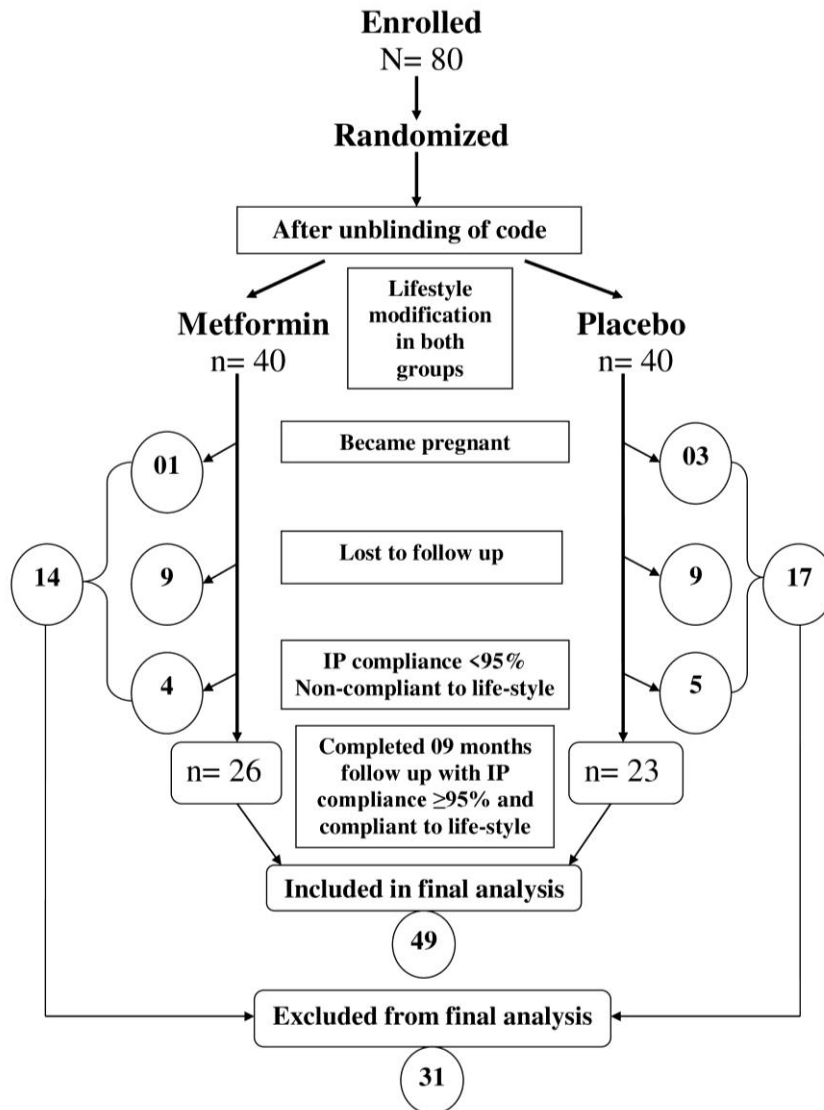

Figure-1: *Chart showing the enrollment, intervention and follow up scheme of the study participants.*

Table-1: *Baseline characteristics of the study population (N= 49)*

Variables	Metformin group	Placebo group	p
Number of participants	26	23	
Age (years), mean ± SD	23.52±5.18	22.09±3.58	0.262[†]
Occupation, no. (%)			
Housewife	9 (34.6)	8 (34.8)	
Service holder	2 (7.7)	1 (4.3)	1.00[¶]
Student	15 (57.7)	14 (60.9)	
Personal history, no. (%)			
Menstrual regulation/abortion	3 (11.5)	2 (8.7)	1.00[¶]
Subfertility	4 (15.4)	6 (26.1)	0.483[¶]
Family history, no. (%)			
Polycystic ovary syndrome	4 (15.4)	1 (4.3)	0.353[¶]
Hirsutism	6 (23.1)	11 (47.8)	0.082[¶]
Subfertility	3 (11.5)	6 (26.1)	0.273[¶]
Obesity	16 (61.5)	17 (73.9)	0.382[¶]
Diabetes mellitus	19 (73.1)	19 (82.6)	0.506[¶]
Hypertension	19 (73.1)	20 (87.0)	0.299[¶]
Investigations, mean±SD			
Fasting blood glucose, mmol/L	4.66±0.43	4.74±0.44	0.527[†]
S. ALT, U/L	49.58±16.13	47.87±21.80	0.755[†]
S. creatinine, mg/dl	0.81±0.13	0.78±0.16	0.487[†]
S. TSH, mIU/ml	2.22±1.10	2.49±1.36	0.447[†]
S. prolactin, ng/ml	16.14±21.12	11.12±5.66	0.275[†]
S. LH/FSH ratio	1.60±1.25	1.46±1.12	0.671[†]
S. Total testosterone, ng/ml	8.11±3.98	8.88±3.10	0.461[†]

Note: [¶]*Pearson's Chi-square/ Fisher's Exact test was done as appropriate;* [†]*Independent-samples t test or* *Mann-Whitney U test was done as appropriate*

24.10±5.17, p=0.021), WC (85.23±13.38 vs. 82.54±12.90, p=0.046), systolic (110.96±12.65 vs. 106.54±11.98, p=0.003) and diastolic BP (75.0±9.06 vs. 70.38±8.59, p=0.002) significantly improved in metformin group after intervention while no such changes occurred in placebo group. BMI, WC and BP categories did not improve in either group after 9 months of intervention.
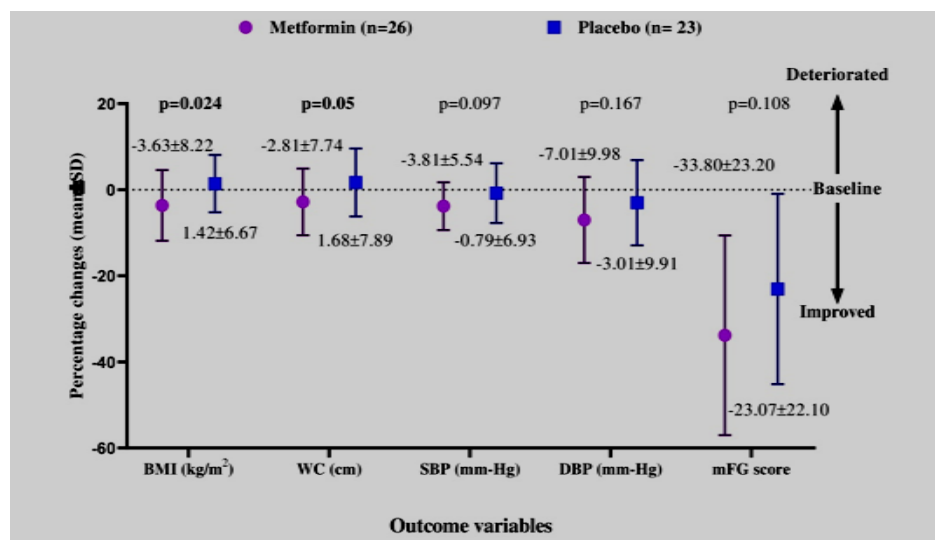
The status of reproductive and androgenic manifestations of the study groups before and after the intervention is shown in Table-3. Before intervention, all the characteristics of both the groups were similar. Menstrual cycle significantly improved in both the study groups (before vs. after-metformin: 19.2% vs. 76.9%, p=0.003; placebo: 19.2% vs. 47.8%, p=0.02) after 9 months, but no such significant (p=0.12) improvement occurred in metformin group compared to placebo group. Severity of hirsutism, presence of acne, serum progesterone level and ovulatory status improved significantly in both metformin and placebo groups after 9 months of study period. Only, mFG score, hirsutism, serum progesterone level and ovulatory status (decrease of anovulation rate by -53.8% vs. 95.7%, p=0.001) improved significantly (p=0.05,

Table-2: *Metabolic manifestations of the study groups before and after intervention (N= 49)*

Parameters	Metformin (n= 26)			Placebo (n= 23)			P values for Metformin vs. Placebo	
	Before	After	p	Before	After	p	Before	After
BMI, kg/m^2 (mean±SD)	25.17 ±5.62	24.10 ±5.17	**0.021***	25.77 ±5.89	25.96 ±5.43	0.545*	0.715[¶]	0.226[¶]
BMI category, no. (%)								
Underweight	2 (7.7)	2 (7.7)		3 (13.0)	2 (8.7)			
Optimal	9 (34.6)	8 (30.8)	0.206[‡]	4 (17.4)	4 (17.4)	0.739[‡]	0.321[¥]	0.591[¥]
Overweight	3 (11.5)	9 (34.6)		3 (13.0)	5 (21.7)			
Obese	12 (46.2)	7 (26.9)		13 (56.5)	12 (52.2)			
WC (cm, mean±SD)	85.23 ±13.38	82.54 ±12.9	**0.046***	84.74 ±11.88	85.80 ±11.24	0.428*	0.893[¶]	0.352[¶]
WC category, no. (%)								
Non-obese	7 (26.9)	11 (42.3)	0.219[‡]	9 (39.1)	7 (30.4)	0.625[‡]	0.542[¥]	0.554[¥]
Centrally obese	19 (73.1)	15 (57.7)		14 (60.9)	16 (69.6)			
Systolic BP, mm Hg, mean±SD	110.96 ±12.65	106.54 ±11.98	**0.003***	111.96 ±9.62	110.87 ±9.96	0.487*	0.760[¶]	0.179[¶]
Diastolic BP, mm-Hg, mean±SD	75.0 ±9.06	70.38 ±8.59	**0.002***	73.91 ±7.06	72.17 ±7.95	0.247*	0.645[¶]	0.455[¶]
BP category, no. (%)								
Normal	23 (88.5)	24 (92.3)	1.000[‡]	20 (87.0)	22 (95.7)	0.500[‡]	1.00[¥]	1.000[¥]
Elevated	3 (11.5)	2 (7.7)		3 (13.0)	1 (4.3)			
Acanthosis, no, (%)								
No	21 (80.8)	24 (92.3)	0.250[‡]	11 (47.8)	14 (60.9)	0.375[‡]	**0.020[¥]**	**0.015[¥]**
Yes	5 (19.2)	2 (7.7)		12 (52.2)	9 (39.1)			

*Paired-T test or †Wilcoxon signed ranks test or ‡McNemer test was done to compare within each intervention group. Comparisons between study groups were done by ¶independent-samples T test or ¥Pearson's Chi-square/Fisher's exact test

Figure-2: *Comparison of percentage changes of clinical manifestations of the study population after the completion of the study from baseline*

Table-3: *Reproductive and androgenic manifestations of the study groups before and after intervention (N= 49)*

Parameters	Metformin group (n= 26)			Placebo group (n= 23)			Metformin vs. Placebo (p value)	
	Before	**After**	**p**	**Before**	**After**	**p**	**Before**	**After**
Menstrual cycle								
Eumenorrhea	5 (19.2)	20 (76.9)		1 (19.2)	11 (47.8)			
Oligomenorrhea	18 (69.2)	3 (11.5)	**0.003**[‡]	18 (78.3)	7 (30.4)	**0.020**[‡]	0.297[¥]	0.12[¥]
Amenorrhea	3 (11.5)	3 (11.5)		4 (17.4)	5 (21.7)			
Modified FG score	8.15 ±5.20	5.15 ±3.99	**<0.001**[‡]	9.39 ±3.85	7.35 ±4.14	**<0.001**[‡]	0.354[Ѧ]	**0.05**[Ѧ]
Severity of hirsutism								
Insignificant	12 (46.2)	22 (84.6)		6 (4.3)	12 (52.2)			
Mild	11 (42.3)	3 (11.5)	**0.001**[‡]	16 (69.6)	10 (43.5)	**0.014**[‡]	0.185[¥]	**0.021**[¥]
Moderate	3 (11.5)	1 (3.8)		1 (4.3)	1 (4.3)			
Acne								
Absent	17 (65.4)	23 (88.5)	**0.031**[‡]	12 (52.2)	18 (78.3)	**0.031**[‡]	0.394[¥]	0.448[¥]
Present	9 (34.6)	3 (11.5)		11 (47.8)	5 (21.7)			
S. progesterone, ng/ml	1.55 ±2.58	5.16 ±5.20	**0.006**[‡]	0.94 ±0.85	0.82 ±1.34	0.670[‡]	0.263[Ѧ]	**<0.001**[Ѧ]
Ovulatory status								
Ovulation	3 (11.5)	12 (46.2)	**0.022**[‡]	0 (0.0)	1 (4.3)	–[‡]	0.237[¥]	**0.001**[¥]
Anovulation	23 (88.5)	14 (53.8)		23 (100.0)	22 (95.7)			
PCOM								
Absent	4 (15.4)	5 (19.2)	1.00[‡]	2 (8.7)	3 (13.0)	1.00[‡]	0.671[¥]	0.706[¥]
Present	22 (84.6)	21 (80.8)		21 (8.7)	20 (87.0)			

Data are expressed as frequency (%) as appropriate; within parentheses are percentages over column total of respective qualitative variable; FG (Ferriman-Gallwey), PCOM (polycystic ovarian morphology); [‡]Wilcoxon rank sum test or [‡]McNemer test was done to compare within each intervention group; Comparisons between study groups were done by [Ѧ]Mann-Whitney U test or [¥]Pearson's Chi-square/Fisher's exact test

p=0.021, p=0.001,) in metformin group compared to placebo after 9 months of intervention. PCOM did not improve in either group after 9 months of intervention.

Figure-2 shows the comparison of percentage changes (mean±SD) of clinical manifestations after the completion of the study (9 months) from baseline in metformin and placebo groups. The improvement of BMI and WC were significant in metformin than placebo group [metformin vs. placebo- BMI (kg/m^2): -3.63±8.22 vs. +1.42±6.67,

p= 0.024; WC (cm): -2.81±7.74 vs. +1.68±7.89, p= 0.05]. The SBP, DBP and mFG score improved in the metformin group but the changes were not statistically significant [metformin vs. placebo- SBP (mm-Hg): -3.81±5.54 vs. -0.79±6.93, p= 0.097; DBP (mm-Hg): -7.01±9.98 vs. -3.01±9.91, p= 0.167; mFG: -33.80±23.20 vs. -23.07±22.1, p=0.108]. On subgroup analysis based on BMI classification, both the study groups with BMI <23 kg/m^2 gained weight and the percentage changes of BMI was significantly higher in placebo group [metformin (n= 11) vs. placebo (n= 7): 0.56±7.2 vs. 8.34±4.30

Table-4: *Adverse effects of intervention drugs in the study population (N= 49)*

Adverse effects	No. of follow up visit	Metformin group (n= 26)	Placebo group (n= 23)	P value†
		Number (%)		
Loose motion	1st	17 (65.4)	4 (17.4)	0.001
	2nd	9 (34.6)	6 (26.1)	0.552
	3rd	10 (38.5)	4 (17.4)	0.125
	4th	4 (15.4)	1 (4.3)	0.353
Abdominal pain	1st	12 (46.2)	8 (34.8)	0.562
	2nd	9 (34.6)	7 (30.4)	0.771
	3rd	8 (30.8)	8 (34.8)	1.00
	4th	5 (19.2)	2 (8.7)	0.424
Nausea	1st	11 (42.3)	5 (21.7)	0.143
	2nd	5 (19.2)	6 (26.1)	0.734
	3rd	6 (23.1)	2 (8.7)	0.254
	4th	1 (3.8)	3 (13.0)	0.330
Vomiting	1st	3 (11.5)	0 (0.0)	0.237
	2nd	7 (26.9)	2 (8.7)	0.145
	3rd	3 (11.5)	1 (4.3)	0.612
	4th	3 (11.5)	1 (4.3)	0.612

†*Pearson's Chi-square or Fisher's exact test was done as appropriate*

kg/m^2, p= 0.021]. On the other hand, both BMI and WC reduced in both study groups with BMI ≥25 kg/m^2 and the percentage changes of reduction [metformin (n= 12) vs. placebo (n= 13): BMI: -7.77±8.35 vs. -1.33±2.44 kg/m^2, p=0.024; WC: -6.06±7.75 vs. -0.58±5.29 cm, p=0.049] were significantly higher in the metformin group.

Among the gastrointestinal adverse effects, only loose motion occurred significantly at a higher rate in metformin group [1st follow up visit: 65.4% vs. 17.4%, p=0.001] than placebo group. Other adverse effects were similar in rates in both groups. Frequency of loose motion and nausea improved in metformin group and abdominal pain reduced in placebo group with progression of time (Table-4).

Discussion

This randomized placebo controlled double blind study showed the beneficial effects of addition of metformin with lifestyle modifications on reduction of BMI and WC without causing significant side-effects in patients with PCOS. We observed that metformin with lifestyle modification led to the reduction of BMI. Most of the studies found similar results and few studies also found that metformin reduced insulin resistance even without reducing BMI, in PCOS [22]. Pouliot et al. showed that higher WC is predictive of abnormal endocrine and metabolic function and is associated with increasing risk of cardiovascular disease [28]. In our study, the mean reduction of WC in metformin group was 2.81 cm. Other investigators have also reported reduction of WC, though some reported no changes in WC after treatment with metformin [17,29,30]. We found that metformin, in combination with lifestyle changes, significantly reduced BMI and WC especially in obese patients. A recently published systematic review and meta-analysis of randomized controlled trials (RCTs) showed that metformin significantly reduced WC in PCOS patients [31].

In the present study, there was significant improvement of menstrual irregularity in both metformin and placebo groups. Therefore in the present study, it was not clearly possible to discriminate the impact of metformin on this issue as lifestyle modification was practiced by the

participants of both groups. Improvement of menstrual cycle was found in metformin group in several other studies [29,30,32-34]. However, improvement observed in the placebo group indicated the role of lifestyle modification even without significant change in BMI. Some studies found higher regularization of menstrual cycle by modification of lifestyle than metformin alone. However, the combination therapy seemed to be better than the lifestyle therapy alone.

In the present study hirsutism improved in both metformin and placebo groups. However, we observed significantly greater decrease of mFG score in metformin compared to placebo group after 9 months of study period. The results indicated that metformin and lifestyle modification together had better effect on hirsutism rather than either one alone. Contrary to our findings, some studies reported lack of beneficial effect of metformin on hirsutism in PCOS [33,34]. However, those studies observed the effect of metformin on women with high baseline mFG score and for a period of only six months. The effect of metformin on the hair follicles to reduce the state of hirsutism might not be apparent if the treatment duration is below six months as the hair turnover cycle is more than three months. Therefore, it may not be possible to make any inference on the action of metformin in reducing hirsutism unless treatment for adequate period is provided.

As in our cases, improvement of acne in metformin group is also supported by observations of others [32,35]. There was no significant change of polycystic appearance of ovaries in either group after nine months of study period. However, ultrasonogram of ovaries lacked description of status of ovarian follicles.

Four women conceived during the study, three of which were in the placebo group and one in the metformin group. Assessment of impact of metformin on fertility probably requires a longer duration of follow-up. One study found that after six months of metformin therapy, menstrual regularity was achieved in 86% women and 50% were ovulatory at six months [36]. We also found significantly higher rate of ovulation in the metformin group. Costello and Eden, also found similar improvement in obese PCOS patients [37].

There were no serious adverse events in either the metformin or placebo group. However, metformin was associated with more minor gastrointestinal events. But, the adverse events gradually improved over time.

The main strength of this study was its randomized double blind placebo controlled design and its long duration. The study findings also illustrated the importance of life style modification in management of clinical manifestations of PCOS. In conclusion, the present study showed that metformin with lifestyle modifications had considerable favorable impacts on clinical manifestations, particularly in terms of androgenic activity, weight loss, WC, BMI, and menstrual irregularity in PCOS patients. Effect of metformin therapy on fertility of PCOS cases needs longer duration of follow-up.

Authors' contributions

NA, HB and MAH designed the study protocol. NA, TS and AB collected the data; NA, MSM, TS and MAH did the statistical analysis; NA, MSM, AB and HB prepared the manuscript. MAH and HB supervised and coordinated the study and edited the manuscript. All authors read and approved the final manuscript.

Competing interests

None of the authors have any conflict of interest to declare.

Ethics approval and consent to participate and publish

Prior to commencement, the research protocol was approved by the Institutional Review Board (IRB) of BSMMU (No.BSMMU/2014/05). Informed written consent was taken from all participants to participate in the study and publish the study findings.

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