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ORIGINAL ARTICLE

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Effect Of Short Term Administration Of Metformin On Endocrine And Clinical Parameters in Overweight/ Obese Polycystic Ovarian Syndrome (PCOS) Women

Uzma Firdous[1*], Mehir-un-Nisa Iqbal[1], Taseer Ahmed Khan[1]

[1]Department of Physiology, University of Karachi, Karachi, Pakistan

ABSTRACT

OBJECTIVE: This study was conducted to determine the effect of short term treatment of metformin on the clinical and endocrine characteristics of overweight/obese PCOS patients.

METHODOLOGY: This is the cohort study conducted on 180 Overweight/Obese PCOS subjects where 121 PCOS subjects were grouped as metformin (6 months) exposed and 59 PCOS subjects were grouped as metformin unexposed PCOS patients. A self-structured questionnaire was used along with blood samples for the estimation of insulin, testosterone, chemerin and omentin using Enzyme Linked Immunosorbent Assay (ELISA) while lipid profile was done using photometric methods.

RESULTS: The present study found the higher prevalence of obesity, abdominal fat, weight gain, menstrual irregularities, and infertility in all PCOS patients. There were significant differences in menstrual flow, menstrual irregularities, and infertility ($p < 0.05$) between studied groups. Non-significant differences were observed in the clinical manifestations of PCOS (hirsutism, acne and alopecia) and other clinical parameters ($p>0.05$). The studied groups showed higher levels of Insulin, testosterone, chemerin, and cholesterol but the difference was found to be non-significant ($p >0.05$). High HDL and low LDL levels were found in the metformin exposed PCOS group ($p<0.05$). Moreover, a significant negative correlation between testosterone and omentin ($p = 0.002$) was found in the metformin unexposed PCOS group.

CONCLUSION: The present study showed that short term metformin monotherapy in overweight PCOS women does not have significant effect on BMI, insulin, testosterone and adipokines levels while significant improvement was observed in menstrual irregularities, HDL and LDL levels in the metformin exposed group.

KEY WORDS: Insulin, Testosterone, Chemerin, Omentin.

*For Correspondence

Uzma Firdous

Lecturer, Department of Physiology
University of Karachi, Pakistan

Email: uzmaf@uok.edu.pk

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INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most common and challenging endocrinopathy afflicting 10-20% of the global and 20.7% of the Pakistani reproductive-aged women. Insulin resistance, hypothalamic pituitary ovarian dysfunction, hyperandrogenism, obesity, and alterations in adipokine release from adipose regions have been shown to contribute to the development of this disorder.

Menstrual disturbances, androgen excess, and anovulation are the prominent clinical features associated with this disorder[1].

Insulin resistance and hyperinsulinemia appear to be the leading causes of PCOS in women, affecting 50-70% of them[2]. PCOS women exhibit decreased insulin sensitivity and beta cell malfunction that eventually results in hyperinsulinemia, which is considered to be the leading cause of chronic oligo or anovulation, as well as hyperandrogenism. Ovarian hyperandrogenism induces a disruption in the recruitment of dominant follicles, resulting in larger ovaries, polycystic ovaries, hyperplasia, and luteinization of ovarian thecal or stromal cells as well as cutaneous manifestations of PCOS.

Android obesity is another frequently occurring condition present in 50-80% of PCOS women and it is independently associated with insulin resistance and hyperinsulinemia[3]. Higher prevalence of overweight and obese women are found in PCOS than their normal counterparts[4]. The excess body fat is believed to be the primary cause of derangement of adipocytes which is further accompanied with the development of obesity, insulin resistance, type II diabetes and metabolic syndrome[5]. Recent evidences have showed androgen excess increases

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ovarian chemerin levels with higher levels of serum chemerin levels and low levels of omentin in PCOS patients. Dyslipidemia is also observed in PCOS patients with high levels of total cholesterol, LDL- cholesterol and triglycerides while low levels of HDL-cholesterol.

Metformin is the most frequently prescribed antidiabetic agents to treat the aforementioned reproductive and metabolic consequences of PCOS. Metformin has been shown to decrease the blood glucose levels by stimulating the glucose uptake and inhibiting glycogenolysis, gluconeogenesis and intestinal glucose absorption. Meanwhile it also suppresses the process of the lipogenesis. Metformin is found to be effective in the amelioration of hyperinsulinemia driven hyperandrogenism and it also modulates the secretion of adipokines as well by lowering the serum chemerin levels and increasing omentin-1 levels in women.

Despite of its broad use worldwide in PCOS population large variation exists in the clinical response to metformin therapy and there is still uncertainty exist about the effectiveness of metformin in the PCOS women[6]. Recent literature reveals that in obese PCOS patients, the beneficial response of metformin therapy show variation in the duration and doses than their non-obese PCOS counterparts. To our knowledge, few studies have examined the response of the overweight/ obese PCOS patients to duration of treatment and with different doses of metformin[7] .The aim of this study is to investigate the effect of metformin (6 months) at a dose of 500mg, three

METHODOLOGY

Study Design and selection of study participants

The present study was conducted from July 2017 to June 2018 at ABC clinic (FOR BLIND REVIEW). The study design had been reviewed and approved by the Board of Advanced Studies and Research (BASR) at the University of ABC and was carried out in accordance with the Helsinki Declaration principles. After obtaining written informed permission, 180 overweight or obese PCOS participants aged 20-45 years with a BMI more than 25kg/m2 were chosen for the research. The individuals were divided into two groups: metformin exposed PCOS and metformin unexposed PCOS. The subjects assigned for the metformin exposed group were obese women who had menstrual irregularities, polycystic ovaries, clinical signs of hyperandrogenism, and reported the use of metformin drug (n=121) for at least 6 months, whereas the subjects chosen for the unexposed PCOS group were obese women who had visited the clinic for hormonal imbalance, menstrual irregularities and infertility and with no use of drugs (n=59) for the 6 months preceding the study.

Assessment of demographics, anthropometric and clinical parameters of PCOS

A self-structured survey questionnaire was designed with an emphasis on their BMI, physical activity, family history, stress history, menstrual and infertility history, ultrasound findings, age of menarche, length of menstrual cycle, gravidity, marital status, mood, clinical signs of hyperandrogenism (hirsutism, acne) based on the demographic and anthropometric data. According to WHO recommendations for South Asians, body mass index (BMI) and waist hip ratio (WHR) were calculated and reported. The modified Ferriman-Gallwey score (mFG) was used to evaluate the distribution pattern of body hair on a human body. Using the Global Acne Severity Scale (10), acne vulgaris was evaluated. All individuals had their venous blood samples drawn following an overnight fast of 12 hours for biochemical estimations.

Biochemical assessment

Plasma levels of hormones, insulin (Catalogue#: IN374S) and testosterone (Catalogue#: TE187S) were determined by CalibotechInc, ELISA Kit. The levels of chemerin (Catalog#: C3235) and omentin (catalog#: 11629) were assessed by Glory Science Co., Ltd ELISA kit while Lipid profile [TG (Lot #:17249O), Chol (Lot #:18OO3O), HDL (LOT # 6O116685), LDL (Lot #:6O1O9356) were performed by Quinica clinica aplicada (QCA) reagent, enzymatic kit method.

Statistical analysis

The SPSS statistical software (version 22.0) was used for carrying out all statistical analyses. The baseline characteristics of the studied groups were matched using the Whitney Mann U test. Independent samples t-test and Chi-square test were used to identify the relationship between the quantitative and qualitative variables respectively. The quantitative variables were further correlated using Pearson's correlation. Data were considered to be significant at $P < 0.05$.

RESULTS

Our study showed that out of the 18O PCOS subjects the mean age was found to be 26.31 ± O.54. Generalized obesity (69.4%), Centralized obesity (75%), weight gain (7o%), abnormal neck circumference (52%), sedentary life style (71%), stress (63%), age of menarche (12-14 years), amenorrhea (24.4%), oligonmenorrhea (41.1%), menstrual irregularity (3o%), normal menstrual flow (63.3%), polycystic ovaries (49%), infertile (51%), subfertile (21%), hirsutism (53.3%), acne (49.4%) were found in the subjects studied.

Those subjects who were not receiving metformin treatment have higher NC (χ^2 = 0.989, p-value <0.05), BMI (χ^2=8.058, p-value <0.05), light to moderate menstrual flow (χ^2=6.151, p-

value <0.05) and increased menstrual irregularities (χ^2=5.556, p-value <0.05). Moreover, non signficant variations were observed in the ultrasonographic features, menarchal age, length of menstrual cycle, infertility, hirsutism, acne, parity, alopecia, stress and sleep disturbances between the groups (p > 0.05).

The baseline characteristics of the metformin exposed and unexposed PCOS patients are summarized in Table 1.

This study found the higher levels of the Insulin, testosterone, chemerin, triglycerides and cholesterol levels in both the groups but no statistical differences was observed between the studied groups. However, HDL showed significantly higher mean values and LDL showed lower mean values in the metformin exposed PCOS group.

Hormonal and biochemical features of the exposed and unexposed PCOS subjects are presented in Table 2.

Characteristics	Mean ± S.E		p-value
	Metformin exposed PCOS group	Metformin unexposed PCOS group	
Age	26.07 ± 0.77	26.31 ± 0.54	0.683
BMI (kg/m2)	26.69 ± 0.75	28.70 ± 0.49	0.016
WC (cm)	91.47 ± 1.27	106.98 ± 18.40	0.247
WHR	0.86 ± 0.005	0.87 ± 0.007	0.343
Menstrual irregularity			0.018
Hirsuitism			0.561
Acne			0.334
Infertility			0.511

Table 1: Baseline characteristics of the Metformin Exposed and Unexposed PCOS patients. Results are presented as mean ±SEM. Significance was considered at the level of p≤0.05* (Mann Whitney U Test).

Furthermore, it was found that in the metformin unexposed PCOS group significant inverse correlation exist between testosterone and omentin (r = -0.40, p = 0.002) whereas no correlations were observed among other variables.

p: p-value compared between exposed and unexposed PCOS group (Independent T test)

*: Significance was considered at p ≤ 0.05 level

**: Significance was considered at p ≤ 0.05level

DISCUSSION

This study aimed to examine the short-term effects of metformin on the clinical, hormonal, and metabolic outcomes of obese and overweight PCOS patients. This study showed non-significant effect of metformin on BMI, WC, WHR, clinical

Biochemistry	Mean ± S.E		p-value
	Metformin exposed PCOS group	Metformin unexposed PCOS group	
Insulin	39 ± 17.3	48.38 ± 14.55	0.702
Testosterone	2.8 ± 0.07	2.979 ± 0.08	0.236
Chemerin	93.62±36.42	221.24± 79.7	0.226
Omentin	44.6 ± 14.3	23.428 ± 8.83	0.186
Triglycerides	93.87± 5.94	78.118 ± 6.3	0.084
Cholesterol	206.03± 8.40	206.35 ± 8.46	0.98
HDL-C**	49.48 ± 1.68	41.54 ± 1.52	0.002**
LDL-C*	80.96 ± 2.92	90.65± 3.68	0.045*

Table 2: Comparison of Hormonal & Biochemical Characteristics between Metformin Exposed and Unexposed PCOS Subjects. Data are presented as mean ±S.EM

manifestations of hyperandrogenism (hirsutism, acne and alopecia)[10,11]. Different studies have reported the conflicting results with respect to decrease in body weight and BMI after metformin use. This study found the significant effect of metformin in the reduction of menstrual flow and menstrual irregularities (p<0.05) in the metformin exposed group[12]. Our study showed the higher levels of insulin, testosterone, chemerin and omentin in both the PCOS groups[9]. The elevated plasma insulin acts synergistically with LH, resulting in decreased glucose transport, increased secretion and release of androgens and high cholesterol levels and ultimately infertility[13]. Furthermore, there was no significant effect of metformin on the levels of insulin, testosterone, chemerin and omentin in the metformin exposed group (p<0.05). The inefficacy of metformin in the improvement of body composition, clinical signs of hyperandrogenism and hormonal derangements in the metformin exposed PCOS group could be ascribed to obesity because patients in the present study were overweight or obese and had higher rates of weight gain. Numbers of studies have demonstrated that in obese PCOS women metformin shows the significant heterogeneity in the reduction of body weight and BMI. Several studies have supported the longer duration of metformin use for more than 3 months with higher doses to benefit from metformin therapy in overweight and obese PCOS patients[15,16].

In the present study, triglycerides and cholesterol levels did not change significantly in the studied groups (p> 0.05). High levels of HDL and low levels of LDL levels were observed in the metformin exposed group (p< 0.05)[17,18]. Recent studies have indicated that metformin causes the elevation of HDL-C while lowering of LDL-C and TGs levels. Although alterations in the levels of TGs and HDL-C takes longer time that is upto 12 months.

This study observed a significant inverse correlation between testosterone and omentin (p< 0.01) in the metformin exposed

			Insulin	Testosterone	Chemerin	Omentin
Metformin unexposed	r	Insulin	1	-0.124	0.01	0.111
	p			0.376	0.945	0.428
Metformin exposed	r	Insulin	1	-0.262	-0.008	-0.043
	p			0.123	0.964	0.809
Metformin unexposed	r	Testosterone	-0.124	1	-0.105	-.404**
	p		0.376		0.448	0.002
Metformin exposed	r	Testosterone	-0.262	1	-0.167	-0.211
	p		0.123		0.345	0.231
Metformin unexposed	r	Chemerin	0.01	-0.105	1	0.253
	p		0.945	0.448		0.065
Metformin exposed	r	Chemerin	-0.008	-0.167	1	.908**
	p		0.964	0.345		0
Metformin unexposed	r	Omentin	0.111	-.404**	0.253	1
	p		0.428	0.002	0.065	
Metformin exposed	r	Omentin	-0.043	-0.211	.908**	1
	p		0.809	0.231	0	

Table 3: Correlation of biochemical parameters in Metformin Exposed and Unexposed PCOS subjects. Pearsons Correlation test was used to test the association among the biochemical variables.r: Pearson coefficient , Statistically significant at the level of $p \leq 0.05$

group[19]. The correlation between insulin and testosterone levels was found to be non-significant[20,21]. The discrepancy in the findings might be related to the selection of only one type of androgen marker such as androstenedione or total testosterone as an indication of androgen excess because PCOS patients show altered pattern of biochemical hyperandrogenism. In the metformin unexposed PCOS group a significant negative correlation was observed between testosterone and omentin ($p< 0.05$) which is in concordance with the recent studies while significant positive correlation ($p< 0.01$) was found between chemerin and omentin which was in disagreement with the recent studies. Non-significant correlations were observed among other variables ($p > 0.05$).

It is reported that effectiveness of metformin in the improvement of ovulation and plasma insulin levels is inconstant depending on patients BMI[22,23]. In obese PCOS women ovulation rates are less than non-obese PCOS Women[24].

These findings reveal that PCOS patients responded to a very little degree in relation to short duration and normal dose of metformin. It is observed that low levels of the insulin, testosterone and chemerin are observed in metformin exposed group as compared to the metformin unexposed group. Nevertheless, these hormones did not show sensitivity to this particular dose of metformin. The effect of metformin on lipid profile was significant as proved by the other studies as well. Weight loss in PCOS women has been found to increase the ovulation and decrease the hyperglycemia, hyperlipidemia, hyperinsulinemia, hyperandrogemeia and free androgen index. This study suggests that the doses used in this study were suboptimal for overweight and obese PCOS women. Higher doses of metformin is believed to significantly reduces the BMI in over weight and obese PCOS[25].

CONCLUSION

The current study suggests that the short term treatment with metformin with sub optimal doses in overweight and obese PCOS patients resulted in nonsignificant treatment response. Longer duration of metformin use for 6-12 months and higher doses are required in these patients. Furthermore it is suggested that the clinical picture of metformin in PCOS patients is exacerbated by weight gain in obese PCOS females which shed light on the importance of weight spectrum to decrease the risk of PCOS. To make firm conclusions with regards to the clinical relevance of metformin in these overweight obese patients well designed randomized controlled trials with large sample sizes are required.

**: Correlation is significant at the level of 0.01 (2- tailed)

*: Correlation is significant at the level of 0.05 (2- tailed)

importance for the doctor and patient 8. Targeted programs focusing on interpersonal skills, analyzing audio-, video-tape encounters with patients, studying literature and arts, and importance of role models should be taught to them 9. Also, the variation in empathy among age groups should be looked into because of literature gap.

Conflict of Interest: The authors declare no conflict of interest.

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AUTHORS CONTRIBUTIONS

UF: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable.
MUNI: Conception, Design of the work, Acquistion, Data Analysis, and Drafting, Reviewed, Final approval, Agreement to be accountable.
TAK: Conception, Design of the work, Interpretation of data for the work, and Drafting, Reviewed, Final approval, Agreement to be accountable.

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