Evaluation of metformin treatment in patient with polycystic ovary syndrome in Kirkuk city

Received: 1/12/2010 Accepted: 13/6/2011

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Abstract

Background and objectives: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of fertile age, affecting 5-10% of the female population. The aim of the present study is to evaluate the endocrine and metabolic effects of metformin in patients with polycystic ovary syndrome in Kirkuk city.
Methods: Eighty female with polycystic ovary syndrome (PCOS), were classified in to two groups, the first group ,who received Clomifene citrate and Metformin hydrochloride included 45 patients and the second group , who received Clomifene citrate only (control group) included 35 patients. All study patients, were diagnosed as polycystic ovary syndrome and they were on treatment at least two months before blood sample collection. Laboratory assessment that obtained included serum, free testosterone, leptin and insulin glucose and lipid profile.
Results: No significant differences in median of, serum insulin, insulin resistance or serum leptin between study groups were observed. The median free serum testosterone was significantly lower (23 pg/ml) in those treated with metformin compared to those on ordinary treatment (50 pg/ml). Fasting serum glucose, HDL – cholesterol and total cholesterol were significantly higher in group without metformin (116.2 , 41.3 , 161.8 mg/dL respectively) compaired to group with metformin (101.5, 34.3 , 138.8 mg/dL respectively). The remaining biomarkers (serum LDL-cholesterol, serum VLDL-cholesterol and triglyceride) showed no statistically significant differences between two groups.
We conclude that metformin treatment has beneficial effects on serum, free testosterone, cholesterol and glucose in obese women with PCOS.
Key words: polycystic ovary syndrome, insulin resistance.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of fertile age, affecting 5-10% of the female population. The syndrome is characterized by chronic anovulation, hyperandrogenism, polycystic ovaries and decreased fertility.[1] PCOS is furthermore associated with insulin resistance, accumulation of abdominal fat and obesity (BMI >30 kg/m^2).[2] PCOS theca cells show increased activity of multiple steroidogenic enzyme such as 17-hydroxylase and 17,20 -lyase, resulting in raised androgen production, both basally and in response to LH. [3,4] Insulin can directly stimulate testosterone synthesis in human theca cells[5] and also contributes to increase adrenal secretion, in part by enhancing adrenal sensitivity to ACTH.[6] Insulin decreases sex hormone-binding globulin production by the

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liver, subsequently increasing free serum testosterone.[7] A potential contribution of leptin to the pathogenesis of PCOS was suggested by a recent study[8] in which a subgroup of women with PCOS was claimed to have higher leptin levels than controls.

Methods

Eighty female subjects with polycystic ovary syndrome (PCOS) were classified in to two groups: the first group Included forty five patients , their age ranged between 18 to 39 with a mean of (27.3 ± 4.7 years) , who received clomiphene (50 mg) two times a day from second day of menstrual cycle for five days , and (500 mg) of metformine two times all days and while the second group Included thirty five patients their age ranged between 18 to 38 with a mean of (27.3 ± 5.3 years) who received only clomiphene (50 mg) two times a day from second day of menstrual cycle for five days. All patients were attended to Azadi teaching hospital / department of obstetrics and gynecology (infertility management clinic) in Kirkuk city and the were on treatment at least two months before sample collection. Blood sample was obtained 12 hours after fasting without regarding to the day of menstrual cycle, the samples were used for determination of serum free testosterone, leptin ,insulin, lipid profile and glucose Insulin resistance index was calculated by the formula for homeostasis model assessment (HMOA) [9]:-

IRI = Fasting serum glucose(mmol/L) ×Fasting serum insulin(μIU)/ 22.5 Body mass index (BMI)[10] Was calculated as: BMI = Weight(Kg)/Height(m^2) Hormones was measured by a commercial ELISA kit Diagnostics biochem (Canada inc), glucose and lipid profile were measured through enzymetic colorimetric assays.

Statistical analysis: Statistical analyses were done using SPSS (Statistical Package for Social Sciences). Some of the quantitative variables for the present study were non-normally distributed like: Serum Insulin, Insulin resistance index, Free serum testosterone and serum Leptin. Such quantitative variables are best described with median instead of mean. The difference in median between 2 groups was assessed by Mann-Whitney test. The difference in mean between 2 groups was assessed by t-test. The statistical significance of association between 2 categorical variables was assessed by chi-square test. P value less than the 0.05 level of significance was considered statistically significant.

Results

Tables 1,2 showed the mean BMI which significantly higher among metformin treatment group (32 Kg/m^2) compared to its control (metformin negative group) (27.1 Kg/m^2). A significantly higher proportion of metformin group (55.6%) were obese/ morbid obese compared to its control group (25.7%).

Table1: The difference in mean BMI between the 2 study groups.

	Treatment with Metformin		P (t-test)
	Negative (N= 35)	Positive (N= 45)	
Body mass index (Kg/m2)			<0.001
Range	(20.8 - 35)	(23.1 - 52.7)	
Mean ± SD	(27.1± 4.03)	(32.0 ± 5.59)	

Table 2: The difference in distribution of BMI categories between the 2 groups.

	Treatment with Metformin				
	Negative		Positive		P (Mann-Whitney)
	N	%	N	%	
Body mass index (Kg/m2)-categories					0.001
Normal (<25)	10	28.6	2	4.4	
Overweight (25-29.9)	16	45.7	18	40	
Obese (30-39.9)	9	25.7	22	48.9	
Morbid obesity (40+)	0	0	3	6.7	

Table 3 showed absence of statistically significant difference in median serum insulin, insulin resistance or serum leptin between study subjects using additional metformin treatment and those on ordinary treatment for PCOS. The median free serum testosterone was significantly lower (23 pg/ml) in those treated with metformin compared to those on ordinary treatment only (50 pg/ml).

Table 3: The difference in median of selected serum parameters between those using additional Metformin treatment and their control group on ordinary treatment.

	Treatment with Metformin		P (Mann-Whitney)
	Negative (N=35)	Positive (N=45)	
Serum Insulin (μIU/ml)			0.29[NS]
Range	(2.3 - 99.5)	(4 - 71.5)	
Median	9.3	11.5	
Insulin resistance index			0.67[NS]
Range	(0.5 - 41.1)	(1 - 20)	
Median	2.5	2.9	
Free serum testosterone (pg/ml)			.005
Range	(0.06 - 100)	(0.01 - 90)	
Median	50	23	
Serum Leptin (ng/ml)			0.59[NS]
Range	(2.8 - 95.5)	(0.1 - 86.8)	
Median	28.5	32.8	

Table 4 showed the mean fasting serum, glucose, HDL – cholesterol and total cholesterol concentration were significantly higher in group on ordinary treatment (without metformin) (116.2, 41.3 and 161.8 mg/dL respectively) compaired to group with metformin (101.5, 34.3 and 138.8 mg/dL respectively). The remaining biomarkers (serum LDL-cholesterol, serum VLDL-cholesterol and triglyceride) showed no important or statistically significant differences between two study groups .

Prevalence of abnormal high level of serum hormones in both study groups showed in table (5), more than three quarter of study population had abnormally high serum, free testosterone, leptin and about quarter of them had high insulin, but the difference in prevalence was insignificant between the two study groups.

Table 4: The difference in some serum parameters between those using additional Metformin treatment and their control group on ordinary treatment

	Treatment with Metformin		P (t-test)
	Negative (N=35)	Positive (N=45)	
Fasting serum glucose (mg/dl)			0.004
Range	(81 - 190.8)	(72 – 136.8)	
Mean ± SD	(116.2± 27.7)	(101.5 ± 16.02)	
Serum LDL (mg/dL)			0.06[NS]
Range	(66.3 – 206.7)	(50.7 – 156)	
Mean ± SD	(118.17 ± 29.25)	(106.47 ± 26.13)	
Serum VLDL (mg/dL)			0.63[NS]
Range	(15.07 – 86.58)	(17.02 – 58.5)	
Mean ± SD	(25.74 ± 16.77)	(24.18 ± 11.31)	
Serum HDL (mg/dL)			<0.001
Range	(27.3 – 54.6)	(19.5- 58.5)	
Mean ± SD	(41.34 ± 7.02)	(34.32 ± 7.41)	
Serum Triglycerides (mg/dL)			0.59[NS]
Range	(26.4 – 431.2)	(35.2- 290.4)	
Mean ± SD	(128.48 ± 82.72)	(119.68 ± 56.32)	
Serum Cholesterol (mg/dL)			0.022
Range	(108 – 269.1)	(116 – 226.2)	
Mean ±SD	(161.85 ± 46.8)	(138.84 ± 41.34)	

Table 5: The difference in abnormal level of some serum parameters between the 2 study groups

	Treatment with Metformin				P (Chi-square)
	Negative		Positive		
	N	%	N	%	
Abnormally high free testosterone (>7 pg/ml)	32	91.4	35	77.8	0.1[NS]
Abnormally high serum Leptine (>11.1 ng/ml)	29	82.9	41	91.1	0.27[NS]
Abnormally high serum Insuline (> 25 µIU/ml)	9	25.7	12	26.7	0.92[NS]

Discussion

The study assessed metformin effect on metabolic profile (serum, lipid profile and glucose) and endocrine profile (serum, free testosterone ,insulin and leptin) in polycystic ovary syndrome. Majority of research supported the view that serum leptin concentration in women with PCOS are not significantly changed comparing with control group with similar BMI. [11,12]On the basis of our results, in spite of significant BMI difference between study groups , leptin levels did not shows significant difference , it was hypothesized by other study that changes in BMI are not accompanied by changes of leptin concentrations.[13] In our study, we observed that serum leptin levels were high in PCOS patients (both study group), percent of abnormally high serum leptin 82.9% in group without metformin treatment and 91.1% in group with metformin treatment, the high (serum leptin in PCOS women) may support the studies which suggested that the leptin may contribute to the pathogenesis of PCOS[15], this in agree with reports in the literature. [14,15,16] In various population around the world, it has been found the most women with PCOS have elevated levels of serum androgens; however, normal levels may be found in some women.[17] This finding clearly demonstrated in our study population who had 91.4% verus 77.8% high free testosterone in both study group. Our study demonstrated pronounced decline of circulating free testosterone level in group with metformin treatment these results appeared to suggest that metformin administration was high significantly reduce free testosterone, this in agreement with results obtained by studies[18,19] were postulated that metformin have a direct inhibitory effect on the expressioun of various enzymes involved thecal cell steroidgenesis and the thecal cells androgen prodction. Thus, the measurement of free testosterone provides a higher diagnostic yield for ovarian hyperandrogenism[20]. We observed significant reduction in glucose concentration in group with metformin treatment, this in agree with studies. [21,22] Lipid profile in women with PCOS have many abnormalities and vary depend on body weight, diet and ethinicity.[21] In our study, the effect of metformin on lipid profile was clearly demonstrated in serum cholesterol which was significantly decreased. This was in accord with the observations presented by studies[23,24] along with beneficial change in total cholesterol.

Conclusion

Beneficial effects of study does of metformin on study biomarkers showed, significant effect on serum (free testosterone ,glucose, cholesterol) in obese women with polycystic ovary syndrome ,with smaller in magnitude and non-significant effect on other study biomarkers .

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