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TO DETERMINE THE METFORMIN HCL EFFECT ON THE METABOLISM OF CARBOHYDRATES IN POLICYSTIC OVARY SYNDROME

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Abstract:

Aim: *To investigate the effect of metformin hydrochloride on carbohydrate metabolism in polycystic ovary syndrome, a clinical study was conducted in fifty infertile women with polycystic ovarian syndrome aged 20 to 40 years.*

Place and Duration: *In the Pharmacology and Therapeutics Department and Gynecology and Obstetrics, Unit-I of Services Hospital, Lahore for six-months duration from March 2020 to August 2020.*

Methods: *50 females were enrolled and received a 500 mg metformin HCl tablet three times a day for a period of three months. Fasting serum glucose (FSG) and fasting serum insulin (FSI) were performed twice during the study period (day zero and day ninety) to evaluate the effects on carbohydrate metabolism.*

Results and Conclusions: *Significant reductions in both FSG and FSI levels were found on day ninetie at P = 0.001. Metformin has been found to have a beneficial effect on carbohydrate metabolism in patients with polycystic ovary syndrome. This is because of the increased peripheral glucose uptake and utilization of metformin, which in turn increases insulin sensitivity and reduces insulin resistance in these patients.*

Key words: *polycystic ovary syndrome, carbohydrate metabolism, fasting serum glucose, fasting serum insulin, metformin hydrochloride.*

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INTRODUCTION:

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of women of childbearing age, affecting approximately 5% to 10% of women (Knochenhauer, 2016; Goldenberg et al., 2015)[1-2]. PCOS is characterized by oligomenorrhoea, clinical and / or biochemical hyperandrogenism, and polycystic ovaries (Kawadzki, 2017; Glueck, 2018; Rotterdam, 2016)[3-4]. Most women with PCOS, but not all, have fasting hyperinsulinemia with insulin resistance and high insulin secretion (Meirow, 2018; Acien). The consequences of polycystic ovary syndrome extend beyond the reproductive axis, and women with polycystic ovary syndrome are at significant risk of developing metabolic and cardiovascular disorders similar to those that make up the metabolic syndrome (Glueck, 2003)[5-6]. Both polycystic ovary syndrome and metabolic syndrome share insulin resistance as a central pathogenetic trait. Polycystic ovary syndrome can therefore be viewed as a gender specific form of metabolic syndrome (NCEP, 2019), and the term "XX syndrome" has been suggested as an apt term to highlight this relationship (Sam, 2018). Although the molecular mechanism (s) of insulin resistance in PCOS is unclear, excessive insulin-independent serine phosphorylation of the insulin receptor β-subunit has been put forward as a novel mechanism of insulin resistance[7-8]. This defect in the insulin signaling pathway appears to be present in both adipocytes and skeletal muscle, the major target tissues of insulin action (Ehrmann, 2015). The relationship between carbohydrate metabolism disorder and PCOS is not new and was first described in 1921 (Achard and Thiers, 1921) and was called "diabetes mellitus of women with a beard" (diabete des femmes a barbe). The pathway regulating carbohydrate metabolism is impaired in PCOS, while the effect of insulin on ovarian steroidogenesis is preserved despite the coexistence of peripheral insulin resistance (Willis and Franks, 2016)[9]. The effects of insulin on steroidogenesis are mediated by pathways other than those that regulate peripheral glucose clearance (Nestler et al., 2017).

MATERIALS AND METHODS:

This study was held in the Pharmacology and Therapeutics Department and Gynecology and Obstetrics, Unit-I of Services Hospital, Lahore for six-months duration from March 2020 to August 2020. A total of 50 infertile women with PCOS (polycystic ovary syndrome) were selected. Eligibility criteria included women of childbearing age 20 to 40 years of age with infertility, scanty menstruation, obesity, hirsutism, fasting hyperinsulinemia (> 10 µU / ml) and fasting serum sugar <6.1 mmol / L (≤110 mg / dL) as ≥ 6.1 mmol / L are the WHO criteria for diabetes. Consent was obtained from all study participants before they were included in the study. Initial data, the date of the follow-up visit and laboratory tests of each patient were recorded on a specially designed proforma.

Fasting serum glucose was determined by an enzymatic colorimetric method in which the serum glucose is oxidized by the enzyme glucose oxidase to gluconic acid and H2O2. The H 2 O 2 formed then reacts by peroxidase catalytic action with hydroxybenzoic acid and 4-aminoantipyrine to give a red-violet quinonoimine dye. The amount of this dye is proportional to the amount of glucose present in the sample. Fasting serum insulin was measured using the IMX insulin reagent. The insulin test is based on the microparticle enzyme immunoassay (MEIA) technology. The IMX System is designed to perform immunoassays using fluorogenic enzyme substrates and fluorescence polarization techniques. This enzymatic enzyme immunoassay procedure typically uses a coated submicron microparticle as the means by which the analyte to be measured is captured for analysis. Tests using this method are called microparticle enzyme immunoassays (MEIA).

RESULTS:

Fasting serum glucose in mg / dL ranged from 65–110 mg / dL, which corresponds to the mean ± SD 92.74 ± 13. Fasting serum insulin ranged from 10.4 µU / ml to 51 µU / ml, which is mean ± SD of 20.6 ± 11 (Table 1).

Table-1

Baseline (Day-0) parameters of patients (n=50)

S. No.	Parameters	Range	Mean ± S.D.
1.	Fasting serum glucose (FSG) (mg/dl)	65-110	92.74 ± 13.0
2.	Fasting serum insulin (FSI) (µU/ml)	10.4-51	20.6 ± 11.0

Table-2

Sub-groups of parameters and their percentage at Day-0 and Day-90 (n=50)

S.No.	Parameters	Subgroups		Day-0	Day-90
1.	Fasting serum glucose (FSG) (mg/dl)	(a)	< 100	31 (62%)	45 (90%)
		(b)	100-110	19 (38%)	05 (10%)
2.	Fasting serum insulin (FSI) (µU/ml)	(a)	< 10	0	27 (54%)
		(b)	10-15	18 (36%)	16 (32%)
		(c)	> 15	32 (64%)	07 (14%)

To monitor fasting serum glucose (FSG), patients were divided into two groups according to the inclusion criteria for FSG ≤ 110 mg / dL. Group (a) with FSG levels <100 mg / dL had an initial 31 (62%) patients which increased to 45 (90%) after treatment, while group (b) with FSG levels between 100-110 mg / dL had 19 (38%) of patients, the number of which was reduced to only 5 (10%) after treatment. For fasting serum insulin (FSI) in µU / ml, patients were divided into three groups (a) FSI 15 µU / ml according to the inclusion criteria. Prior to treatment, group (a) had no patients but after 90 days of treatment, 27 (54%) patients belonged to this group. Group (b) had 18 (36%) patients initially, which decreased to 16 (32%) patients after treatment. Group (c) had 32 (64%) patients, which decreased to only 7 (14%) after treatment (Table 2). A decrease in fasting serum glucose was observed from a mean ± SD of 92.74 ± 13 to 86 ± 8.7 mg / dL from day 0 to day 90. This was significant with a P value of 0.001 (Table 3).

Table-3

Fasting serum glucose (FSG) at Day-0 and Day-90 (n=50)

Parameter	Day-0 Mean ± S.D.	Day-90 Mean ± S.D.	P-value
Fasting serum glucose (mg/dl)	92.74 ± 1 3.0	86 ± 8.7	0.001

Table-4

Change in fasting serum glucose (FSG) from Day-0 to Day-90 (n=50)

Decrease in fasting serum glucose		Increase in fasting serum glucose		No change	
No.	%	No.	%	No.	%
31	62	19	38	-	-

31 (62%) patients showed a decrease in FSG, while 19 (38%) showed an increase in fasting serum glucose (Table 4). Fasting serum insulin showed a significant decrease with a P value of 0.001 from 20.6 ± 11.0 µU / ml to 9.80 ± 5.6 µU / ml (Table 5).

Table-5

fasting serum insulin (FSI) at Day-0 and Day-90

(n=50)

Parameter	Day-0 Mean ± S.D.	Day-90 Mean ± S.D.	P-value
Fasting serum insulin (µU/ml)	20.6±11.0	9.80±5.6	0.001

Table-6

Change in fasting serum insulin (FSI) from Day-0 to Day-90
(n=50)

Decrease in fasting serum insulin		Increase in fasting serum insulin		No change	
No.	%	No.	%	No.	%
50	100	-	-	-	-

All 50 patients showed a 100 percent decrease in FSI (Table 6).

DISCUSSION:

Polycystic ovary syndrome is one of the most common hormonal disorders that affect women. As a syndrome, it has many components - reproductive, metabolic, and cardiovascular - with lifelong health consequences[10-11]. Insulin resistance of polycystic ovary syndrome appears to increase the risk of glucose intolerance, diabetes and lipid abnormalities. A better understanding of the pathogenesis of insulin resistance, which is associated with complications of polycystic ovary syndrome, has led to the development of new therapies - mainly drugs that lower insulin (Ehrmann, 2015)[12]. The fasting serum glucose level decreased significantly in our study from 92.74 ± 13.0 mg / dl to 86 ± 8.37 mg / dl, which is consistent with the studies by Morin-Papunen et al. (2016)[13]. He observed a significant reduction in fasting serum glucose in 8 patients with PCOS from 5.2 ± 0.1 (92.82 mg / dl) to 4.9 ± 0.1 mmol / l (87.5 mg / dl) [÷ mmol / lo 0.056 mg / dl] after 3 months of metformin treatment. On the other hand, Marca et al. (2018) in 15 women with PCOS after 35-40 days of metformin treatment, and Kołodziej (2016) in 35 women after 12 weeks of metformin treatment found a negligible decrease in fasting glucose[14]. On the contrary, Nestler (2018) observed a negligible increase in fasting glucose from 78 ± 3 mg / dL to 81 ± 3 mg / dL after 35 days of treatment. Probably the short period of this study is related to these results. Regarding the level of fasting insulin, we observed a significant reduction in the mean fasting insulin level from 20.6 ± 11.0 to 9.8 ± 5.6 µU / ml, which is consistent with the research by Nestler (2018), Kołodziej (2017), Morin-Papunen (2000) Marca (2016), while Moghetti (2015) in a study of 23 Caucasian women for 6 months with metformin 500 mg three times a day found a non-significant decrease in fasting serum insulin level from 15.2 ± 4.6 up to 10.2 ± 2.2 - U / ml[15]. These results can be attributed to the long study duration of 6 months and the Caucasian female habitat.

CONCLUSION:

In our study, the insulin-lowering drug, metformin HCl, had a beneficial effect on carbohydrate metabolism in women with PCOS by significantly reducing fasting serum glucose and fasting serum insulin levels after three months of treatment with the above-mentioned biguanide.

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