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TO COMPARE THE EFFECTS OF METFORMIN HCL WITH DIET AND EXERCISE ON THE CARBOHYDRATE METABOLISM IN POLYCYSTIC OVARY SYNDROME

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ABSTRACT

To compare the effects of metformin HCl with diet and exercise on the carbohydrate metabolism in polycystic ovary syndrome a clinical trial was carried out on one hundred infertile females having polycystic ovary syndrome (PCOS) with ages between 20-40 years. They were enrolled from the infertility clinic of a private hospital in Karachi from 2001 to 2004. The patients were divided into group A (metformin treated group) and group B (diet and exercise treated group) each having fifty patients in all. Group A was given tablet metformin HCl 500 mg thrice daily while group B was kept on 30-60 minutes walk daily along with avoidance of excess sugars, oily food and red meat from their diet for a period of three months. Both groups were subjected to have fasting serum glucose (FSG) and fasting serum insulin (FSI) at day-0 and day-90. Significant reduction was found in group A in both the FSG and FSI which reduced from 92.74±13.0 mg/dl to 86±8.7 mg/dl) P=0.001) and 20.6±11.0 µU/ml to 9.8±5.6 µU/ml (P=0.001) respectively. Non significant reduction was observed in group B in both the parameters. FSG reduced from 92±11.1 mg/dl to 91±9.8 mg/dl (P=0.079) and FSI reduced from 18.8±5.0 µU/mlto 18.6±5.0 µU/ml (P=0.06). In conclusion metformin HCl increased the peripheral uptake and utilization of glucose probably which in turn increased the insulin sensitivity and reduced the insulin resistance in these patients having polycystic ovary syndrome.

Keywords: Polycystic ovary syndrome, carbohydrate metabolism, fasting serum glucose, metformin HCl, diet and exercise.

INTRODUCTION

Polycystic ovary syndrome is one of the most common endocrinopathy of women of childbearing age Goldenberg *et al*. (2005) with a prevalence estimated between 5 to 10% Knochenhauer *et al*. (1998), Kawadzki and Dunaif (1992). As a syndrome, it has multiple components reproductive, metabolic and cardiovascular with health implications across the life span. Androgen excess and insulin resistance, both of which have, strong genetic components, underlie much of the clinical presentation. The insulin resistance of the polycystic ovary syndrome appears to impart an increased risk of glucose intolerance, diabetes and lipid abnormalities and may enhance the development of macrovascular disease Ehrmann (2005). The association between a disorder of carbohydrate metabolism and hyperandrogenism was first described in 1921 by Achard and Thiers Achard *et al.* (1921), and was called "the diabetes of bearded women (diabetes des femmes a barbe). One of the first description of the complex phenotype today known as polycystic ovary syndrome was given by Stein and Leventhal in 1935 Stein and Leventhal (1935) who then named the condition as Stein Leventhal syndrome characterized by amenorrhoea, hirsutism, obesity and polycystic appearance of the ovaries etc.

Based on the prevalence of glucose intolerance in women Harris *et al*. (1987); the prevalence of glucose intolerance in PCOS "Dunaif *et al*. (1987) and on a conservative estimate of the prevalence of PCOS (~5%) it can be extrapolated that PCOS related insulin resistance contributes to approximately 10% of cases of glucose intolerance in premenopausal women Dunaif (1997). The pathway regulating carbohydrate metabolism is impaired in PCOS while insulin's action on steroidegenesis at the ovary is preserved despite the co-existence of peripheral insulin resistance Franks (1995). Insulin's action on steroidogenesis are mediated by pathways distinct from those which regulate the peripheral glucose disposal Nestler *et al*. (1998a). It now appears that Ras-Raf-MEK (mitoghen activated Protein Kinase) pathway is involved in the regulation of cell growth and metabolism whereas PI3-K (Phosphatidyl-inositol-3-kinase) pathway is involved in glucose uptake and disposal Cheatham *et al*. (1994).

Metformin HCl is a biguanide antihyerglycemic agent which improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). It does not produces hypoglycemia in either diabetic or non diabetic subjects and does not cause hyperinsulinemia. With metformin therapy insulin secretion remains unchanged while fasting insulin levels and day long plasma insulin response may actually decrease. Metformin decreases the body weight and has a tendency to improve the lipid profile, particularly when baseline values are abnormally elevated. Moreover by acting on the ovary and restoring normal ovarian activity metformin

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positively modulates the reproductive axis namely GnRH-LH episodic release and hence ovulation in females having PCOS Karim (2004).

Exercise is necessary for the loss of belly fat in diabetic women. Since diabetic women have metabolic problems similar to PCOS women, the study results are relevant. Either di*et al*one or diet plus exercise caused an average weight loss of 9.9 in three months. However, only the diet plus exercise group had a loss of visceral fat, which is the belly fat that surrounds internal organs Dunne and Slater (2005). Shedding even a modest amount of weight can help. In women with PCOS losing less than 10% of initial body weight has been shown to cut high levels of blood fats and blood sugar. Weight loss has been shown to improve insulin resistance Jayagopal *et al*. (2005).

With this background present study was designed to evaluate and compare the effects of metformin HCl with diet and exercise on the carbohydrate metabolism in patients having polycystic ovary syndrome.

MATERIALS AND METHODS

A total of one hundred infertile females having PCOS (polycystic ovary syndrome) were selected from the infertility clinic of a private hospital, Karachi. Eligibility criteria included women of reproductive age group with ages between 20-40 years having infertility, oligo-menorrhoea, obesity, hirsutism, fasting hyperinsulinemia (>10μU/ml) and fasting serum sugar level <6.1mmol/L (≤110 mg/dl) as ≥6.1mmol/L is WHO diabetic criteria, 2000. Consent was obtained from all study participants before they were enrolled in the study. Preliminary data, date of follow up visit and laboratory investigations of each patient were recorded on a specially designed proforma.

Study Design

This clinical trial was carried out from 2001 to 2004 with a study period of three months (90 days) on each patient. Following a thorough history and physical examination the total of hundred patients were divided into two groups A and B randomly. Even numbers of proformas for group A, metformin treated group and odd number of proformas for group B, diet and exercise treated group. Metformin HCl was started 500 mg once a day for one week and then increased to thrice daily for a period of three months. The initial week of therapy was not included in the study period. Group B patients were advised for exercise (30-60 minutes walk daily) and change in diet pattern (avoidance of oily foods, red meat and bakery products). Parameters of fasting serum glucose and insulin were done twice during the study i.e. at day zero and at day 90.

Analytical Methods

Fasting serum glucose was determined by enzymatic colorimetric method in which serum glucose is oxidized by glucose oxidase enzyme to gluconic acid and H_2O_2. The formed H_2O_2 then reacts under catalytic action of peroxidase with hydroxybenzoic acid and 4-amino-antipyrine to yield a red-violet quinoneimine dye. The quantity of this dye is proportional to the amount of glucose present in the sample.

Fasting serum insulin levels were measured by using IMX insulin reagent. Insulin assay is based on microparticle enzyme immunoassay (MEIA) technology. The IM system has been designed to perform immunoassays using fluorogenic enzyme substrates and flurescence polarization techniques. This enzyme immunoassays procedure typically uses a coated submicron microparticle as the means by which the analyte to be measured is

Table 1. Baseline (Day-0) Parameters of Patients (n=100)

S.No.	Parameters	Group A (n=50)		Group B (n=50)	
		Range	Mean±SD	Range	Mean±SD
1.	Fasting serum glucose (FSG) (mg/dl)	65-110	92.74±13	75-110	92±11.1
2.	Fasting serum insulin (FSI) (μU/ml)	10.4-51	20.6±11	10.2-30.4	18.8±5.0

Table 2. Sub-Groups of Parameters and their Percentage at Day-0 and Day-90 (n=100)

S. No.	Parameters	Subgroups		Group A (n=50)		Group B (n=50)	
				Day-0	Day-90	Day-0	Day-90
1.	Fasting serum glucose (FSG) (mg/dl)	(a)	<100	31 (62%)	45 (90%)	33 (66%)	38 (76%)
		(b)	100-110	19 (38%)	05 (10%)	17 (34%)	12 (24%)
2.	Fasting serum insulin (FSI) (μU/ml)	(a)	<10	0	27 (54%)	0	1 (2%)
		(b)	10-15	18 (36%)	16 (32%)	11 (22%)	12 (24%)
		(c)	> 15	32 (64%)	7 (14%)	39 (78%)	37 (74%)

Group A = Metformin treated group; Group B = Diet and exercise treated group.

captured for analysis. Assays which use this method are called the microparticle enzyme immunoassays (MEIA).

Statistical Analysis

The observations in both groups were recorded on day 0 and day 90 and evaluated by using student (paired) t-test for comparison from day 0 to day 90 (Programme SPSS Vol:10).

RESULTS

Baseline (day 0) parameter of the patients showed fasting serum glucose (FSG) ranging between 65-110 mg/dl in group A (metformin treated group) with a mean±SD of 92.74±13.0. The range of fasting serum glucose (FSG) in group B (diet and exercise treated group) was between 75-110 mg/dl with a mean±SD of 92±11.1 (Table 1).

The baseline fasting serum insulin (FSI) in µU/ml in group A had a range of 10.4-51 and in group B had a range of 10.2-30.4 with a mean±SD of 20.6±11.0 and 18.8±5.0 respectively (Table 1).

For observing the fasting serum glucose 9FSG) patients were divided into two sub groups of (a) having FSG < 100 mg/dl and (b) having FSG between 100-110 mg/dl. In metformin treated group A at day 0, 31 patients (62%) had FSG < 100 mg/dl which increased to 45 (90%) patients at day 90 while in diet and exercise treated group B initially subgroup (a) had 33 (66%) patients which increased to 38 (76%) patients at day 90 (Table 2).

For observing fasting serum insulin (FSI) the total patients (100) were divided into three subgroups (a) FSI <10 µU/ml, (b) FSI between 10-15 µU/ml and (c) FSI > 15 µU/ml. In metformin treated group A there was no patient in subgroup (a) at day 0 but it increased to 27 (54%) patients at day 90. In subgroup (b) there were 18 (36%) patients which reduced to 16 (32%) patients from day 0 to day 90. Whereas in subgroup (c) 32 (64%) patients were group at the beginning which decreased to 7 (14%) patients by the end of study (Table 2).

In group B subgroup (a) had none patient at day 0 which increased to 1 (2%) patient at day 90, subgroup (b) had 11 (22%) patients initially which increased to 12 (24%) at day 90, subgroup (c) had 39 (78%) at the beginning which reduced to 37 (74%) patients at day 90 (Table 2).

Significant reduction was found in FSG in group A from 92.74±13.0 to 86.00±8.7 mg/dl with a P value of 0.001 while non significant reduction was seen in group B from 92.00±11.1 to 91.00±9.8 mg/dl from day 0 to day 90 (Table 3).

Fasting serum insulin also showed a reduction which was significant in group A with P value of 0.001 and non significant in group B. FSI decreased from a mean±SD of 20.60±11.0 to 9.80±5.6 µU/ml from day 0 to day 90 in group A. the fall in mean±SD of group B was 18.8±5.0 to 18.60±5.0 µU/ml from day 0 to day 90 with a P value of 0.060 (Table 4).

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age women. It affects an estimated seven percent of females. While the biochemical imbalances that cause symptoms are becoming better understood, the trigger for PCOS is unknown PCO NWRC (2006). Exactly why and how PCOS develops is not quite clear. Most experts however, now agree that insulin plays a major role. Insulin is a powerful hormone that is released by the body's pancreas in response to eating food – especially carbohydrates. It transports sugar out of the blood and into muscle, fat and liver cells, where it is converted to energy or stored as fat. Many women with PCOS have insulin resistance. This means that the process of getting the sugar out of the

Table 3. Fasting Serum Glucose (FSG) at Day-0 and Day-90 (n=100)

Parameter	Group A (n=50)			Group B (n=50)		
	Day-0	Day-90	P-	Day-0	Day-90	P-
	Mean±SD	Mean±SD	value	Mean±SD	Mean±SD	Value
Fasting serum glucose (mg/dl)	92.74±13.0	86.00±8.70	0.001*	92.00±11.1	91.00±9.8	0.079

Table 4. Fasting Serum Insulin (FSI) at Day-0 and Day-90 (n=100)

Parameter	Group A (n=50)			Group B (n=50)		
	Day-0	Day-90	P-	Day-0	Day-90	P-
	Mean±SD	Mean±SD	value	Mean±SD	Mean±SD	Value
Fasting serum insulin (µU/ml)	20.60±11.0	9.80±5.60	0.001*	18.80±5.00	18.60±5.00	0.060

*Significant; Group A = Metformin treated group; Group B = Diet and exercise treated group.

blood and into the cells is defective – the cells are "resistant" to insulin.

The pancreas must secrete more and more insulin to get sugar out of the blood and into the cells. High levels of insulin or hyperinsulinemia can wreak havoc in the body causing any or all of the following conditions: polycystic ovaries, weight gain, and/or difficulty losing weight, increased risk of heart disease by increasing LDL and triglycerides, decreasing HDL and increasing clotting factors. The discovery of insulin's role in PCOS has brought hopes for better treatment. Treatment is no longer just aimed at treating the individual concerns but instead is now aimed at treating one of the underlying causes – insulin resistance. It is best treated with diet, exercise, weight loss if needed and insulin sensitizing medications Flutterweit and Mckittrick (2002).

In our study fasting serum glucose level (FSG) in metformin treated group A reduced significantly from 92.74±13.0 to 86±8.37 mg/dl. This is coinciding with the study of Morin-Papunen *et al*. (2000). He observed significant reduction in FSG level of 8 PCOS patients from 5.2±0.1 (92.85 mg/dl) to 4.9±0.1 (87.5 mg/dl) mmol//L (÷mmol/L by 0.056 conversion factor to get mg/dl) after 3 months of metformin therapy similar results were found by "Pasquali *et al*. (2000); whereas Marca *et al*. (2002), Kolodziejczyk *et al*. (2000) found non significant reduction in the fasting glucose level. On the contrary Nestler *et al*. (1998b) observed non significant increase in the FSG level from 78±3 mg/dl to 81±3 mg/dl after 35 days of treatment. Short period of this study is probably related to these results.

In group B i.e. diet and exercise treated group we have found non significant reduction in FSG which is coinciding with the findings of Pasquali *et al*. (2000), Kocak *et al*. (2002) while Nestler *et al*. (1998b) have reported a non significant increase in FSG level from 75±2 to 76±2 mg/dl.

Fasting serum insulin (FSI) level in group A also showed significant reduction in the mean fasting serum insulin level from 20.6±11.0 to 9.80±5.6 μU/ml which is matching with the studies of Nestler and Jakubowicz (1996), Kolodziejczyk *et al*. (2000), Morin- Papunen *et al*. (2000), Marca *et al*. (2002) whereas Moghetti *et al*. (2000) in a study of 23 caucasian women for 6 months with metformin 500 mg thrice daily found non significant decrease in fasting insulin level from 15.2±4.6 to 10.2±2.2 μU/ml. Longer duration of study of 6 months may be responsible for these results.

In group B mean fasting serum insulin (FSI) showed non significant results in our study which is coninciding with the results of Moghetti *et al*. (2000) and Nestler and Jakubowicz (1996). In contrast to this Crave *et al*. (1995) have reported significant reduction in FSI level. This is probably because inclusion criteria for this study was hirsutism and a BMI (body mass index) of > 25 while menstrual irregularities, anovulation and infertility were the main pre-requisites of our study.

In conclusion treatment with the insulin sensitizing agent metformin has produced beneficial effects on the carbohydrate metabolism (fasting serum glucose and fasting serum insulin) in patients having polycystic ovary syndrome in comparison to the conservatively managed group where the patients were subjected to exercise and diet control only. This is attributed to the reduction in insulin resistance and insulin sensitizing action of the metformin which makes it a novel therapy in the management of polycystic ovary syndrome – a common endocrine disorder.

REFERENCES

Achard, C. and Thiers, J. 1921. Le Virilisme Pilaire et son Association a I'insuffisance glycolytique (diabete des femmes a barbe). Bull Acad Natl Med. 86: 51-64.

Cheatham, B., Vlahos, CJ., Cheatham, L., Wang, L., Blenis, J. and Kahn, CR. 1994. Phosphatidylinositol 3-kinase activation is required for insulin stimulation of pp70 S6 Kinase, DNA synthesis and glucose transporter translocation. Mol Cell Biol. 14: 4902-11.

Crave, JC., Fimbel, S., Lejeune, H., Cugnardey, N., Dechaud, H. and Pugeat, M. 1995. Effects of diet and metformin administration on sex hormone binding globulin, androgens and insulin in hirsute and obese women. J Clin Endocrinol Metab. 80: 2057-62.

Dunaif A. 1997. Insulin resistance and the polycystic ovary syndrome: Mechanism and implications for pathogenesis. Endocrine Reviews. 18(6): 774-800.

Dunaif, A., Graf, M., Mandeli, J., Laumas, V. and Dobrjansky, A. 1987. Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance and/or hyperinsulinemia. J Clin Endocrinol Metab. 65: 499-507.

Dunne, N. and Slater, B. 2005. Natural Health solutions for PCOS. PCOS Review Newsletter. 19: 1-4.

Ehrmann, DA. 2005. Polycystic ovary syndrome. New Eng J Med. 352: 1223-36.

Franks, S. 1995. Polycystic ovary syndrome. N Engl J Med. 333:853-61.

Futterweit, W. and Mckittrick, M. 2002. The role that diet plays in PCOS. Healthology. 1-5.

Goldenberg, N., Glueck, CJ., Loftspring, M., Sherman, A. and Wang, P. 2005. Metformin-Diet benefits in women with polycystic ovary syndrome in the bottom and top quantities for insulin resistance. Metab Clin Exper Online. 54: 1-14.

Harris, MI., Hadden, WC., Knowler, WC. and Bennett, PH. 1987. Prevlaence of diabetes and impaired glucose tolerance and plasma glucose levels in US population aged 20-74 years. Diabetes. 36: 523-34.

Jayagopal, V., Kilpatrick, E. and Holding, S. 2005. Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J Clin Endocrinol Metab. 90(2): 729-33.

Karim, N. 2004. To observe the effects of metformin on the carbohydrate metabolism and ovulation in polycystic ovary syndrome. Ph.D. Thesis, University of Karachi, Karachi.

Kawadzki, J. and Dunaif, A. 1992. Diagnostic criteria for polycystic ovary syndrome: a rational approach In: Polycystic ovary syndrome, (eds. A dunaif, JR Givens, F Haseltine, GR Merriam, Cambridge, MA): Blackwell Scientific. 377-84.

Knochenhauer, ES., Key, TJ. and Kasharmiller, M. 1998. Prevalence of polycystic ovary syndrome in unselected black and white women of the southeastern United States: A prospective study. J Clin Endocrinol Metab. 83: 3078-82.

Kocak, M., Caliskan, E., Simsir, C. and Haberal, A. 2002. Metformin therapy improves ovulatory rates, cervical scores and pregnancy rates in clomiphene citrate resistant women with polycystic ovary syndrome. Fertil Steril. 77: 101-6.

Kolodziejczyk, B., Duleba, AJ., Spaczynski, RZ. and Pawelczyk, L. 2000. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertil Steril. 73: 1149-54.

Marca, AL., Morgante, G., Palumbo, M., Cianci, A., Petragtia, F. and Leo, VD. 2002. Insulin lowering treatment reduces aromatase activity in response to follicle stimulating hormone in women with polycystic ovary syndrome. Fertil Steril. 78: 1234-9.

Moghetti, P., Castello, R., Negri, C., Tosi, F., Perrone, F., Caputo, M., Zanolin, F. and Muggeo, M. 2000. Metformin effects on clinical features, endocrine and metabolic profiles and insulin sensitivity in polycystic ovary syndrome: A randomized, double blind, placebo controlled 6 month trial, followed by open Long term clinical evaluation. J Clin Endocrinol Metab. 85(1): 139-46.

Morin-Papunen, LC., Vauhkonen, I., Koivunen, RM., Ruokonen, A., Martikainen, HK. and Tapanainen, JS. 2000. Endocrine and metabolic effects of metformin versus ethinylestradiol-cyproterone acetate in obese women with polycystic ovary syndrome, a randomized study. J Clin Endocrinol Metab. 85: 3161-68.

Nestler, JE. and Jakubowicz, DJ. 1996. Decreases in ovarian cytochrome p450c17α activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. New Engl J Med. 335: 617-23.

Nestler, JE., Jakubowicz, DJ., DeVargas, AF., Brick, C., Quintero, N. and Medina, F. 1998a. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab. 83: 2001-5.

Nestler, JE., Jakubowicz, DJ., Evans, WS. and Pasquali, R. 1998b. Effects of metformin on spontaneous and clomiphene induced ovulation in the polycystic ovary syndrome. N Engl J Med. 338: 1876-80.

Pasquali, R., Gambineri, A., Biscotti, D., Vicennati, V., Gogliardi, L., Colitta, D., Fiorini, S., Cognigni, Ge., Filicori, M. and Morselli-labate, AM. 2000. Effect of long term treatment with metformin added to hypocaloric diet on body composition, fat distribution and androgen and insulin levels in abdominally obese women with or without the polycystic ovary syndrome. J Clin Endocrinol Metab. 85: 2767-74.

Polycystic ovary syndrome. 2006. Health Topics A-Z National Women's Health Resource centre (NWRC) healthy women. Org. Internet. 1-3.

Stein, IF. and Leventhal, ML. 1935. Amenorrhoea associated with bilateral polycystic ovaries. Am J obstet Gynecol. 29: 181-91.