

ORIGINAL ARTICLE

EFFECT OF METFORMIN HYDROCHLORIDE IN CORRECTING HYPERINSULINEMIA AND HIGH LEPTIN LEVELS IN TREATMENT OF INFERTILE POLYCYSTIC PATIENTS

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Background: Research conducted over PCOS by various groups in the world indicated the effect of Metformin on PCOS. Previous studies suggest that Glucophage by reducing hyper-insulinemia is clinically useful in the treatment of polycystic ovary syndrome (PCOS). Our Objective was to observe the role of Glucophage in treating infertility of polycystic patients within three months in Group A and six months in Group B patients. Another aim was to assess the decrease in hyper-insulinemia and Leptin levels by Glucophage in our population. **Methods:** This study was carried out at the Department of Obstetrics and Gynaecology, Pakistan Institute of Medical Sciences, and Noor Specialised Clinic Islamabad, from Oct 2004 to Apr 2008. One hundred and seventy women in Group A and 145 in Group B fulfilling the clinical and biochemical criteria for PCOS were enrolled. Glucophage was started at an oral dose of 500 mg/day and maintained at 1500 mg for 3 months or 6 months in both Groups. Besides ultrasonography, serum FSH, LH, fasting insulin, fasting blood sugar, glucose insulin ratio, Quantitative Insulin Sensitivity Check Index (QUICKI) and leptin levels were performed. After three months in Group A and six months in Group B these criteria were again assessed. **Results:** After 3 and 6 months of Metformin therapy, significant reduction in biochemical parameters was observed such as fasting glucose, insulin and leptin. Data were analysed using SPSS by paired *t*-test and ANOVA. **Conclusion:** Six months treatment with Glucophage proved to be better option for infertile PCOS.

Keywords: Glucophage, PCOS, Hyperinsulinemia, Leptin

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of fertile age.^{1,2} By a 2003 international consensus conference, diagnosis is made by two out of three criteria: chronic oligo-ovulation or an ovulation after excluding secondary causes, clinical or biochemical evidence of hyper-androgenism, and radiological evidence of polycystic ovaries.³ Insulin resistance and its compensatory hyper-insulinemia contribute to the anovulation, hyper-androgenism, infertility and early pregnancy loss suffered by women with PCOS.⁴ Serum leptin concentrations in women with PCOS have been reported to be higher.⁵ Numerous studies show metformin treatment is associated with a decrease in leptin levels.⁶⁻⁹ Metformin probably improves ovulation in women with PCOS by reducing gluconeogenesis, improving insulin sensitivity, and reducing ovarian androgen production.¹⁰ In PCOS patients, metformin has been shown to be beneficial in reducing hyper-insulinaemia and hyper-androgenaemia while facilitating normal menses and pregnancy.¹¹⁻¹⁶ Our purpose was to study the effect of Glucophage in treating infertility of polycystic patients within three months in Group A and six months in Group B patients. Another aim was to assess the decrease in hyper-insulinemia and Leptin by Glucophage in our population.

MATERIAL AND METHODS

This prospective study was carried out at the outpatients department of Obstetrics and Gynaecology, Pakistan Institute of medical sciences and Noor Specialized clinic, Islamabad from October 2004 to April 2008. All patients had disturbed ovulatory function with chronic oligomenorrhea (cycle length >35 d; less than nine cycles per year) or amenorrhea (cycle length >12 week). Typical appearance of polycystic ovaries by ultrasound according to the criteria of the Rotterdam consensus meeting 2003 which all patients fulfilled. Patients with thyroid problem, tubal defects or on previous medications were excluded from the study. Patients with azospermic husbands were excluded from the study.

These patients were divided into two groups: Group A (Those who gave consent (n=170) to take Glucophage for three months). Group B (Those who gave consent (n=145) to take Glucophage for six months). In both groups the Glucophage drug (oral biguanide) by Merck was started in low dose to avoid its side effects. Initially the patients were advised to take 500 mg tablet daily, i.e., half tablet in morning and half in the evening for the first week and in the next week 500 mg tablet twice, i.e., one in the morning and one in the evening. In the third week the dose was increased to 500 mg three times daily. In Group-A 16 patients discontinued the treatment in a period of one month this

included two patients with tubal defects and in Group-B 11 patients discontinued the treatment after a period of 15 days, this included one patient with tubal defect. In Group-A total number of patients who continued with the treatment of Glucophage for three months was 154 and in Group-B 134 patients continued with the treatment for six months. Circulating blood samples taken before start of Glucophage therapy in Group-A and B and after Glucophage therapy for three months in Group A and six months in Group-B. Blood samples after overnight fast of the patient were tested for Insulin, Glucose and Leptin. Glucose was measured by the glucose oxidase technique (PAP method) by Merck Microlab 300. Serum Insulin levels were measured by ELISA (IBL) with intra and inter assays CVs of 5.3% and 5.6%, respectively. Serum Leptin levels were measured by ELISA (IBL) with intra and inter assay CVs of 5.95% and 11.55% respectively Fasting Glucose: Insulin ratio was calculated by dividing fasting serum glucose by fasting serum insulin. A sensitivity analysis of glucose and insulin by Quantitative Insulin Sensitivity Check Index (QUICKI) was performed. The formula for calculation of QUICKI was $=1/[\log(I_0)+\log(G_0)]$, where I_0 is the fasting insulin, and G_0 is the fasting glucose. The data was analyzed on SPSS using paired *t*-test and ANOVA.

RESULTS

In Group-A total number of patients who continued with the treatment of Glucophage for three months is 154 and in Group-B 134 patients continued with the treatment for six months. The age of the patients ranged from 20–42 years.

Group A –conceived patients: Fasting Blood Glucose and Insulin levels decreased highly significantly ($p<0.001$) after treatment with Glucophage for a period of three months. However, Glucose Insulin ratio, QUICKI and Mean Fasting Leptin levels showed no

significant ($p>0.05$) difference after treatment with Glucophage for three months as given in Table-1.

Group A –not conceived patients: Mean fasting Blood Glucose decreased highly significantly ($p<0.001$), however serum Insulin levels decreased significantly ($p<0.05$) after treatment with Glucophage for a period of three months. Mean serum Leptin levels showed no significant difference ($p>0.05$) between before and after treatment with Glucophage for three months (Table-1).

Comparison of patients conceived versus not conceived in Group-A: No significant difference was found in parameters.

Group B –conceived patients: Mean fasting Blood Glucose and Insulin levels decreased highly significantly ($p<0.001$) however Fasting Leptin level decreased significantly ($p<0.05$) after treatment with Glucophage. QUICKI increased highly significantly ($p<0.001$) and Glucose insulin ratio increased significantly ($p<0.05$) after treatment with Glucophage (Table-2).

Group B –not conceived patients: Mean fasting Blood Glucose and serum Insulin levels decreased highly significantly ($p<0.001$) Glucose Insulin ratio, QUICKI and serum Leptin levels showed no significant difference ($p>0.05$) after treatment with Glucophage (Table-2).

Comparison of patients conceived versus not conceived in Group-B: Mean Fasting blood glucose after treatment in patients who conceived (104.6 ± 0.89 mg/dl) and those who did not conceive (114.8 ± 1.23 mg/dl) showed significant decrease in level in patients who conceived ($p<0.001$).

Mean Fasting Insulin after treatment in patients who conceived (26.8 ± 0.69 μ IU/mg) and those who did not conceive (29.2 ± 0.68 μ IU/mg) showed highly significant decrease in level in the former in those patients who conceived ($t_{(132)}=1.75, p<0.05$).

Table-1: Biochemical parameters in conceived and not conceived polycystic patients before start of Glucophage therapy (Pre-treatment) and after giving Glucophage (Post treatment) for three months in Group A

Group-A	conceived patients (n=56)		not conceived patients (n=98)	
	Pretreatment (Baseline)	Post treatment (after 3 months)	Pretreatment (Baseline)	Post treatment (after 3 months)
Biochemical parameters				
Blood Glucose (mg/dl)	123.4 \pm 1.04	112.0 \pm 1.10***	124.0 \pm 0.96	114.4 \pm 1.23***
Insulin (μ IU/ml)	30.9 \pm 0.71	28.4 \pm 0.53***	30.4 \pm 0.55	28.9 \pm 0.47*
Glucose Insulin ratio	3.99 \pm 0.12	4.18 \pm 0.09	3.97 \pm 0.09	4.15 \pm 0.11
QUICKI	0.27 \pm 0.004	0.28 \pm 0.003	0.28 \pm 0.005	0.28 \pm 0.002
Leptin (ng/ml)	17.8 \pm 0.65	16.5 \pm 0.48	17.1 \pm 0.54	16.8 \pm 0.44

Values are given as Mean \pm SE, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

Table-2: Biochemical parameters in conceived and not conceived polycystic patients before start of Glucophage therapy (Pre-treatment) and after giving Glucophage (Post treatment) for six months in Group B

Group-B	conceived patients (n=86)		not conceived patients (n=48)	
	Pretreatment (Baseline)	Post treatment (after 6 months)	Pretreatment (Baseline)	Post treatment (after 6 months)
Biochemical parameters				
Blood Glucose (mg/dl)	120.7 \pm 0.73	104.6 \pm 0.89***	121.1 \pm 0.83	114.8 \pm 1.23***
Insulin(μ IU/ml)	31.0 \pm 0.61	26.8 \pm 0.69***	30.6 \pm 0.75	29.2 \pm 0.68**
Glucose Insulin ratio	3.97 \pm 0.09	4.41 \pm 0.13*	3.99 \pm 0.12	4.18 \pm 0.09
QUICKI	0.27 \pm 0.001	0.29 \pm 0.002***	0.27 \pm 0.004	0.28 \pm 0.003
Leptin(ng/ml)	17.5 \pm 0.56	15.8 \pm 0.48*	17.2 \pm 0.72	16.8 \pm 0.68

Values are given as Mean \pm SE, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

DISCUSSION

Our study demonstrates the usefulness of Glucophage therapy in decreasing hyper-insulinemia, high glucose and high leptin levels in the majority of PCOS women in our population. In this study the patients who conceived with Glucophage treatment for three months and six months there was decrease in mean fasting blood glucose and fasting insulin. The patients who were treated for six months with Glucophage showed significant increase in QUICKI and glucose insulin ratio. The decrease in fasting blood glucose and fasting insulin has been reported in previous western study.¹⁷ Glucose insulin ratio and Quicki did not show any significant change from baseline to post treatment values.¹⁸ In this study serum Leptin levels decreased significantly in those conceived patients who were treated for six months with Glucophage, but there was no decrease in serum leptin in patients who were treated for six months with metformin. Similar results were shown in a study in Italy after six months treatment with metformin.¹⁹ Similarly after 14 weeks treatment with Glucophage there was decrease in leptin levels.²⁰ Astonishingly in this study we found insulin levels which were high compared to other studies as described previously, however leptin levels were lower. This can be explained as obesity in PCOS is characterized by an increase in visceral fat²¹, i.e., an increase in the type of fat that relatively under secretes leptin compared with subcutaneous fat. These results may be explained by the presence of a PCOS-specific form of Insulin resistance in adipocytes, which impairs the effect of insulin on leptin secretion.²² Metformin therapy was well tolerated by the majority of our patients which is consistent with other studies.²³

CONCLUSION

In women with PCOS Glucophage treatment reduced hyper-insulinemia, fasting glucose and leptin levels. Six months treatment with Glucophage proved to be better option for infertile PCOS.

REFERENCES

- Vincenzo D L, Antonio LA M, Felice P. Insulin lowering agents in the management of polycystic ovary syndrome. *Hum Reprod* 2003;24(5):633–67.
- Myers EGR, Silva SG, Hafley G, Kunselman AR, Nestler JE, Legro RE. Estimating live birth rates after ovulation induction in polycystic ovary syndrome. *Contemp Clin Trials* 2005;26(3):271–80.
- Lanham MSM, Lebovic DI, Domino SE. Contemporary medical therapy for polycystic ovary syndrome. *Int J Gynecol Obstet* 2006;95:236–41.
- Cheang KI, Sharma ST, Nestler JE. Is metformin a primary ovulatory agent in patients with polycystic ovary syndrome? *Hum Reprod* 2006;22(11):595–604.
- Brezchiffa PR, Jakimiuk AJ, Agarwal SK. Serum immunoreactive leptin concentrations in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1996;81:4166–9.
- Morin-Papunen LC, Koivunen RM, Tomas C, Ruokonen A, Martikainen HK. Decreased serum leptin concentrations during metformin therapy in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1998;83:2566–8.
- Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Tapanainen JS. Insulin sensitivity, insulin secretion, and metabolic and hormonal parameters in healthy women and women with polycystic ovarian syndrome. *Hum Reprod* 2000;15:1266–74.
- Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, Fiorini S, Cognigni GE, Filicori M, Morselli-Labate AM. Effect of longterm treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000;85:2767–74.
- Koivunen RM, Morin-Papunen LC, Ruokonen A, Tapanainen JS, Martikainen HK. Ovarian steroidogenic response to human chorionic gonadotrophin in obese women with polycystic ovary syndrome: effect of metformin. *Hum Reprod* 2001;16:2546–51.
- Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, Montminy M, Cantley LC. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 2005;310:1642–6.
- Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism* 1994;43(5):647–54.
- Velazquez E, Acosta A, Mendoza SG. Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. *Obstet Gynecol* 1997;90:392–5.
- Morin-Papunen LC, Koivunen RM, Ruokonen A, Martikainen HK. Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. *Fertil Steril* 1998;69:691–6.
- Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;338(26):1876–80.
- Glueck CJ, Wang P, Fontaine R, Tracy T, Sieve-Smith L. Metformin-induced resumption of normal menses in 39 of 43 (91%) previously amenorrheic women with the polycystic ovary syndrome. *Metabolism* 1999;48:511–19.
- Moggetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, Zanolin E, Muggeo M. 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* 2000;85:139–46.
- Jakubowicz DJ, Seppala M, Jakubowicz S, Rodriguez-Armas O, Rivas-Santiago A, Koistinen H. Insulin reduction with metformin increases luteal phase serum glycodelin and insulin-like growth factor-binding protein 1 concentrations and enhances uterine vascularity and blood flow in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001;86:1121–26.
- Eisenhardt S, Schwarzmann N, Henschel V, Germeyer A, von Wolff M, Hamann A, Strowitzki T. Early Effects of Metformin in Women with Polycystic Ovary Syndrome: A Prospective Randomized, Double-Blind, Placebo-Controlled Trial. *J Clin Endocrinol Metab* 2006;91(3):946–52.
- Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D. Effect of longterm treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally

- obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000;85:2767–74.
20. Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab* 2002;87:569–74.
 21. Bjrnatorp P. The android woman—a risky condition. *J Intern Med* 1996;239:105–10.
 22. Ciaraldi TP, Morales AJ, Hickman MG. Cellular insulin resistance in adipocytes from obese polycystic ovary syndrome subjects involves adenosine modulation of insulin sensitivity. *J Clin Endocrinol Metab* 1997;82:1421–25.
 23. Morin-Papunen LC, Koivunen RM, Ruukonen A, Martikainen HK. Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. *Fertil Steril* 1998;69(4):691–6
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