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The Effects of Flutamide on Lipid Profile, Insulin Sensitivity, Hirsutism and Gonadotropins in Women With Polycystic Ovary Syndrome

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Abstract: In this study, we evaluated metabolic changes and the effects of flutamide in 22 women with PCOS. Flutamide was administered for a 6-month period in a dose of 750 mg/day. The basal and after treatment body mass index, waist: hip ratio, blood glucose, insulin, lipids, Ferriman-Gallwey scoring (FGS), gonadotropins, testosterone, trasaminazed and glucose: insulin (G:I) ratio were measured. For comparison, ANOVA was used. The sixth month mean FGS was significantly lower than the basal values (18.5±7.4 and 12.5±4.5, P<0.01). The mean basal G:I ratio was 3.31±1.12 and 6.21±2.53 at the sixth month. The sixth month G:I ratio was significantly higher (P<0.001). The total and LDL-cholesterol were decreased by flutamide (from 144±23 to 123±23 and from 88±32 to 60±25 mg/dl respectively. P<0.02 and P<0.01), whereas, the HDL-cholesterol level was increased with flutamide (from 44.8±3.9 to 46.5±3.2 mg/dl and P<0.001). LH (from 14.7±6.7 to 8.4±3 mIU/ml), LH/FSH ratio (from 3.4±1.7 to 1.9±0.6), total testosterone (from 0.87±0.29 to 0.61±0.18 ng/ml) and free testosterone (from 4.29±1.18 to 2.14±0.9 pg/ml) were decreased by flutamide (P<0.05). Thus, we reached three conclusions:1-Flutamide may improve insulin insensitivity. 2-In PCOS, flutamide decreases total and LDL-cholesterol, and increases HDL-cholesterol. 3-Flutamide may improve the LH/FSH ratio and induce a decrease in testosterone.

Key Words: insulin sensitivity, PCOS, flutamide, hirsutism and lipids.

Introduction

The most common disorder is women resulting in chronic anovulation with estrogen present is polycystic ovary syndrome (PCOS) (1). A total of 5-10% of these women are affected by PCOS (2). In addition to hirsutism, hyperandrogenism leads to metabolic aberrations such as insulin resistance, dyslipidemia and cardiovascular disease (3). Although some explanations are available, the causes of these aberrations are not clear. The roles of insulin and sex hormones in the regulation of lipid metabolism have been well defined (4). Hyperandrogenism is not only associated with increased waist: hip ratio, but also leads to increased visceral fat accumulation and decreased serum HDL levels (5, 6). Decreased insulin sensitivity in PCOS can be diagnosed using the fasting glucose: insulin ratio (G:I ratio), which is easily obtainable, safe, highly sensitive and specific (7). Legro RS et al. (7) reported that the cut-off value of this ratio is 4.5, and, below this ratio, it is accepted that there is insulin resistance in non-Hispanic white PCOS women (7). Correction of hyperandrogenism and insulin resistance in PCOS may improve lipid and other metabolic disturbances. The treatment of PCOS with flutamide, a 5 alpha-reductase inhibitor and pure antiandrogen, is associated with significant improvements in insulin resistance.

The purpose of this study was to study the metabolic changes of PCOS and explain the effect of flutamide in women with PCOS

Material and Methods

Thirty women with PCOS were selected for study. However, 8 patients did not return for clinical checks (26.6%), and the remaining 22 patients (73.3%) were investigated. The diagnosis of PCOS was confirmed by the presence of chronic anovulation and hyperandrogenism. Hyperandrogenism was confirmed by an increased level of at least two of the following plasma androgens: total testosterone, free testosterone, androstenedione, and an

increased LH/FSH ratio. The characteristic LH/FSH ratio in plasma was greater than 2 (8). The diagnosis of PCOS was verified by ultrasonography. The patients who took part in the study were evaluated for diabetes mellitus, adrenal disorders such as Cushing Syndrome and congenital adrenal hyperplasia, hyperprolactinemia and other endocrinopathies. Patients with these disorders were then excluded from the study. Furthermore, smokers and/or drinkers were also excluded from the study. All measuremenets were taken within 10 days of the onset of the menstrual cycle in women with menses (n=6, 27.3%). In oligo-amenorrheic patients (n=16, 72.7%), measurements, after the basal evaluations, could be taken at any time. All basal measurements were performed at 08:00 AM after overnight fasting. Blood samples were collected in order to determine serum levels of total testosterone, free testosterone, androstenedione, fasting serum insulin, fasting blood glucose, FSH, LH, fasting insulin, total cholesterol, HDL-cholesterol, triglyceride, ALP, SGOT, SGPT and DHEA-sulphate. LDL levels were determined using the Friedwald equation. Insulin sensitivity was calculated using the fasting glucose: insulin ratio. Ratios under 4.5 were taken to signify impaired insulin sensitivity. In patients suspected of having adrenal enzyme deficiency, the serum 17-OH progesterone level was measured and, when appropriate, an ACTH stimulation test was performed. After the basic metabolical and physical measurements, all patients received oral flutamide (Eulexin tb 250 mg Schering-Erkim.) for 6 months at a dose of 750 mg/day. Flutamide treatment was started on the first day of the menstrual cycle in women with menses. In amenorrheic women, it was possible to start flutamide treatment at any time. No special diet was imposed on the patients. All the patients were informed that they were being studied. Because flutamide has no contraceptive effect, barrier or intrauterine contraception was suggested for sexually active women. We wished to prevent any possible gestation. At the third and sixth months of treatment, BMI, WHR, fasting blood glucose (FBG), fasting insulin (FI), triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, Ferriman-Gallwey scoring, LH, FSH, total testosterone, free testosterone, SGOT, SGPT, alkaline phosphatase (ALP), the LH:FSH ratio and glucose: insulin ratio were re-evaluated.

Analytical Procedures

Fasting blood glucose, serum total cholesterol, SGOT, SGPT and ALP levels were determined with a Beckman Cx-5 Delta autoanalyzer. HDL-Cholesterol levels were measured using Rawdox (CH-2652), using a direct enzymatic assay for the in vitro quantitative determination of HDL-cholesterol. Serum insulin levels were measured using the. Access Immunoassay system with access ultrasensitive insulin kits (Beckman, USA). The total testosterone and FSH levels of the serum samples were analysed using ECLIA (Boehringer Manheim Elecsys 2010 immunoassay analyser). Free testosterone levels were determined using the ICN pharmaceuticals Inc. DHEA-S, and androstenedione levels were calculated using DHEA-S RIA kits and an androstenedione RIA kit (competitive RIA technique-orho-clinical diagnostics Amersham, UK). Serum 17-OH progesterone levels were determined by using an Active17 alfa OH progesterone RIA DSL-5000 diagnostic systems laboratories, Inc. (Texas, USA) LKb-Wallac 1275. For the determaniton of LH in the serum, a Magia analyzer (Enzyme linked, colorimetric Immunoassay-ELISA) was used. For all the measurements, the intra-and interassay coefficients of variation were 1.46-9.5% and 2.94-10.8%, respectively. The finding were recorded as the mean±standard deviation (m±sd). The results were stored in an SPSS computer programme. The means were compared using the analysis of variance (ANOVA). If there was any significant difference between groups, as determined using ANOVA, we used the Tukey HSD procedure to determine which values were statistically different.

Results

The mean age of the patients was 23.7±7.8 years. BMI, WHR, fasting blood glucose (FBG), fasting insulin (FI) and hormone changes in the patients are presented in Table 1. The total cholesterol, triglyceride, HDL-cholesterol and hepatic transaminase levels of the patients and their changes related to the treatment are presented in Table 2. Time related changes in fasting insulin, fasting blood glucose and G:I ratio are shown in Figure 1. The serum androstenedione, DHEA-S and 17-OH progesterone levels of the patients were 2.16±0.56, 2.45±1.12 and 1.62±2.23 respectively. The serum 17-OH progesterone levels were within the normal range in all of the patients. Menstruation occurred at various times during the treatment period in a total of 6 patients (1 at the 4th month, 2 at the 5th month, 3 at the 6th month). In these patients, the mean serum LH level was 8.98±1.65 (basal), 6.68±1.08 at the 3rd month and 4.21±1.26 at the 6th month. The mean serum FSH level was 3.17±0.39 (basal), 2.29±0.96 at the 3rd month and 2.96±0.17 at the 6th month. The mean LH:FSH ratio was 2.84±0.44 (basal), 3.4±1.39 at the 3rd month and 1.43±0.47 at 6th

Table 1. The parameters of the patients, and their time-related changes.

	Basal	Third month	Sixth month	P
BMI (kg/m^2)	26.9±7.8	26.4±6.5	26.4±6.4	NS
WHR	1.19±0.27	1.2±0.24	1.22±0.23	NS
FG score (point)	18.5±7.4	14.9±6.3	12.5±4.5	<0.01
LH (mIU/ml)	14.7±6.7	11.6±5.2	8.4±3.0	0<0.001
FSH (mIU/ml)	5.43±4.7	4.2±2.4	4.1±1.9	NS
LH/FSH	3.4±1.7	3.3±2.3	1.9±0.6	<0.01*
Total Tes. (ng/ml)	0.87±0.29	0.71±0.2	0.61±0.18	<0.002*
Free Tes. (pg/ml)	4.29±1.18	3.01±0.97	2.14±0.91	<0.0001**
FBG (mg/dl)	88±10	89.8±8.3	85.5±9.6	NS
FI (micIU/ml)	30.5±14.3	24.0±13	24.0±13	NS
G:I ratio	3.31±1.12	4.58±1.69	6.21±2.53	<0.001*

* = Compared basal-sixth month.

** = Compared with both basal-third month and basal-sixth month.

NS = Non Significant (Post hoc Tukey HDS procedure was applied).

Table 2. Metabolic values of the patients.

	Basal	Third month	Sixth month	P
T. Chol (mg/dl)	144±23.8	134.4±26.3	123±23.7	<0.02
Trigl (mg/dl)	77.6±38.7	83.5±36.3	78.2±31.1	NS
HDL-Chol (mg/dl)	41.8±3.9	44.6±3.2	46.5±3.2	<0.001
LDL-Chol (mg/dl)	88.4±32.2	72.9±29.2	60.7±25.1	<0.01
SGOT (IU/L)	27.4±9.5	26.6±7.6	28.8±7.4	NS
SGPT (IU/L)	26.9±13.1	26.3±11.5	26.1±10	NS
ALP (IU/L)	72.0±23.1	70.7±16.1	73.8±18.2	NS

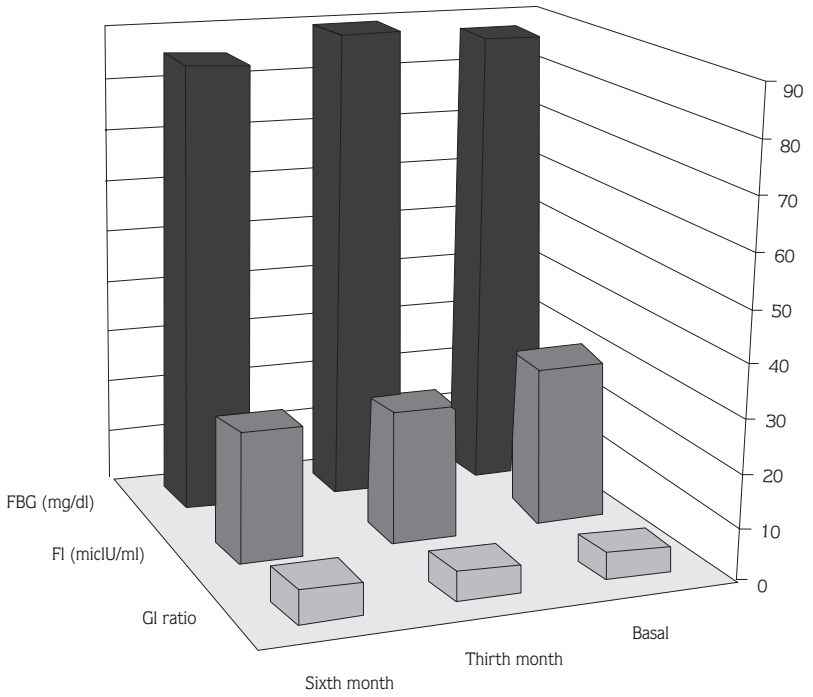

Figure 1. Time-related changes of fasting blood glucose, fasting insulin, and G:I ratio of the patients.

month. The mean total testosterone was 1.01±0.11 (basal), 0.87±0.08 at the 3rd month and 0.84±0.05 at the 6th month. The mean free testosterone was 3.44±0.48 (basal), 2.56±0.39 at the 3rd month and 93.5±6.07 at the 6th month. The mean fasting insulin was 41.8±4.56 (basal), 33.6±4.78 at the 3rd month and 20±2.3 at the 6th month. The mean fasting glucose: insulin ratio was 2.33±0.27 (basal), 2.81±0.61 at the 3rd month and 4.76±0.83 at the 6th month. The mean serum LH, LH:FSH ratio, total testosterone, free testosterone and fasting insulin level decreased, but the G:I ratio increased with treatment. The number of these patients was not high enough to allow statistical analysis.

Discussion

Legro RS et al. (7) reported that the fasting G:I ratio may be useful as a screening test for insulin resistance in non-Hispanic white PCOS women. In this report, it was also demonstrated that this test is easily applicable, safe and highly sensitive. For this reason, we used fasting the G:I ratio for the evaluation of insulin sensitivity. In our patients, before the treatment the G:I ratio was lower than the cut-off value, but this ratio increased with flutamide treatment. In addition on the increase in the G:I ratio, androgen levels also improved with flutamide treatment. This is in accordance ith falling circulating insulin levels, by a variety of mechanisms, causing a decrease in the androgen level in women with PCO. The effects of antiandrogen treatment on insulin sensitivity has been reported in various studies. However, these reports gave different results. In women treated with gosorelin, a decrease in serum androgen concentrations and an improvement in insulin sensitivity were determined (9). Testosterone administration in oopherectomized female rats resulted in a rapid deterioration in insulin sensitivity (10). The results of our study show that flutamide may improve insulin sensitivity. In non-obese PCO women, significant correlations were found between testosterone-LDL levels and insulin-triglyceride levels (11). Peiris et al. (12) demonstrated that, in premenopausal women with upper body fat localisation, the decline in hepatic insulin extraction and diminution in peripheral insulin sensitivity were in part mediated by increased androgenic activity. In this study, both pre and post-treatment BMI and WHR values were compared. However, no significant changes were found. Fasting blood glucose and fasting insulin levels did not change with flutamide. However, the G:I ratio was improved with flutamide treatment. This suggests that flutamide treatment may improve lipid profile in PCOS via improvement in insulin sensitivity. In previous related studies, it was found that flutamide did not cause any improvement in insulin resistance when measured with OGTT and a hyperinsulinemic-euglycemic clamp procedure (13). Therefore, a comparison of the G:I ratio and hyperinsulinemic-euglycemic clamp procedure in PCOS is required. Although flutamide is accepted as being a pure antiandrogen, there is evidence that it has other biological activities such as inhibition of adrenal 17-20 and 5-alpha reductase (8). In women treated with flutamide, the FG score decresaed during the treatment. This indicates that flutamide is effective in the treatment of hirsutism in PCOS. Flutamide also induced a significant drop in total and free testosterone. No significant side-effects or changes in liver enzymes were observed. Our data demonstrate that hirsutism in PCOS may markedly respod to treatment with flutamide alone without significant side effects, even if administered in relatively high doses such as 750 mg/day. This finding is in agreement with previous results (14, 15). It has been claimed that the gonadotropin levels of patients who use flutamide does not change after treatment (16). In our study, the increase in insulin sensitivity may be responsible for this. We were unable to measure sex hormone binding globulin (SHBG) levels due to lack of technical support. Androgens decrease SHBG on the contrary estrogens (17). It has been pointed out in previous studies that hepatic production of SHBG may be inhibited by insulin (18). Our study demonstrated that both total testosterone and free testosterone levels decreased with treatment. In our study, flutamide had no meaningful effect on insulin levels, but it caused an increase in the G:I ratio. A improvement in insulin sensitivity may decrease ovarian androgen production. Therefore, it may also decrease total testosterone levels. In six amenorrheic patients (27.7%), menstruation occurred with flutamide treatment. The serum LH, LH:FSH ratio, total testosterone, free testosterone and fasting insulin levels of these patients decreased. However, the G:I ratio increased with flutamide treatment. The number of these patients was not high enough to allow us to compare the results statistically. Improvements in the serum hormon profile and G:I ratio may be responsible for this development. Patients who use flutamide may develop elevated levels of hepatic transaminases (19). In our study, flutamide did not cause changes in SGOT, SGPT or alkaline phospatase levels. We concluded that:

1. Flutamide improves insulin sensitivity when the glucose/insulin ratio is used to determine insulin sensitivity.

2. Flutamide treatment in PCOS decreases total and LDL-cholesterol levels, and increases HDL-cholesterol. This treatment may improve, the LH:FSH ratio in PCOS.

3. Flutamide induces a significant drop in total and free testosterone. Liver enzymes are not affected. Our data demonstrate that hirsutism in PCOS can rapidly and markedly respond to treatment with flutamide alone without significant side effects even if administered in relatively high doses such as 750 mg/day.

References

1. Carr BR. Disorders of the ovary and female reproductive tract in Williams Textbook of Endocrinology. Wilson JD, Foster DW (Ed.) Eighth edition. Wilson and Foster. W.B. Saunders Company. 1992, p.768.
2. Dunaif A, Givens JR, Haseltine F: The polycystic ovary syndrome. Cambridge: Blackwell, 1992.
3. Wild RA, Painter PC, Coulson PB, Carruth KB, Ranney GB. Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 61: 946-951, 1985.
4. Ek I, Arner P, Berqvist A, Carlstrom K, Wahrenberg H. Impaired adipocyte lipolysis in nonobese women with the polycystic ovary syndrome: a possible link to insulin resistance? J Clin Endocrinol Metab 81: 952-960, 1997.
5. Pasquali Rcassimiri F, Cantobelli S: Insulin and androgen relationship with abdominal body fat distribution in women with and without hyperandrogenism. Horm Res. 39: 179-187, 1993.
6. Lovejoy JC, Bray GA, Bourgeois MO, Macchiavelli R, Rood JC, Greenson C, Partington C: Exogenous androgens influence body composition and regional body fat distribution in obese postmenopausal women - a clinical research centre study. J Clin Endocrinol Metab. 81: 2198-2203, 1993.
7. Richard S. Legro, Diane Finegood, Andrea Dunaif. A: Fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 83: 2694-2698, 1998.
8. Alan Goldfien and Scott E Monroe: Ovaries, basic and clinical endocrinology. Fifth edition. Appleton and Lange. Prentice-Hall International Inc. 1997 pp: 462.
9. Dahlgren E, Landin K, Krotkiewski M, Holm G, Janson PO: Effects of two antiandrogen treatments on hirsutism and insulin sensitivity in women with PCOS. Hum Reprod Oct; 13 (10) 2706-11, 1998.
10. Holmang A, Larsson BM, Brezinska Z, Bjorntorp P: Effects of short-term testosterone exposure on insulin sensitivity of muscles in female rats Am J Physiol. Jun: 262 (6 pt 1): E 851-5, 1992.
11. Graf MJ, Richards CJ, Braun V: The independent effects of hyperandrogenemia, hyperinsulinemia, and obesity on lipid and lipoprotein profiles in women. Clin Endocrinol (Oxf) Jul: 33 (1): 119-31, 1992.
12. Peiris AN, Mueller RA, Struve MF, Kissebah AH: Splanchnic insulin metabolism in obesity. Influence of body fat distribution. J Clin Invest. Dec; 78 (6): 1648-57, 1986
13. Diamanti-Kandarakis E, Mitraakou A, Hennes MM, Platonissiatis D, Kaklas N, Spina J, Georgiadou E; Hoffmann RG, Kissebah AH, Raptis S: Insulin sensitivity and antiandrogenic therapy in women with polycystic ovary syndrome. Metabolism Apr; 44 (4): 525,31, 1995.
14. Pucci E, Genazzani AD, Monzani F, Angelini F, Gargani M, Barletta D, Luisi M; Genazzani AR: Prolonged treatment of hirsutism with flutamide alone in patients affected by polycystic ovary syndrome. Gynecol Endocrinol. Sep; 9 (3): 221-8, 1995.
15. Falsetti L, De Fusco D, Eleftheriou G, Rosino B: Treatment of hirsutism by finasteride and flutamide in women with polycystic ovary syndrome. Gynecol Endocrinol Aug; 11 (4): 251-7, 1997.
16. Cesur V, Kamel N, Uysal AR, Erdoğan G, Baskal N. The use of antiandrogen flutamide in the treatment of hirsutism. Endocr J. Oct; 41 (5): 573-7, 1994.
17. Alan Goldfien and Scott E Monroe Ovaries. Basic and Clinical Endocrinology. Fifth Edition. Appleton and Lange. Prentice-Hall International Inc. 1997.
18. Nestler JE, Powers LP, Matt DW, Steingold KA, Plymate SR, Rittmaster RS, Clore JN, Blackard WG: A direct effect of hyperinsulinemia on serum SHBG levels in obese women with the PCOS. J Clin Endocrinol Metab. 72; 83-89 1991.
19. Wyskowski DK, Freiman JP Tourtelot JB, Horton ML: Fatal and nonfatal hepatotoxicity associated with flutamide. Ann Intern Med 118: 860-864 1993.