The Effects of Flutamide Treatment on Biochemical Parameters in Hirsute Patients

HİRSUTİSMLİ HASTALARDA FLUTAMİD TEDAVİSİNİN BİYOKİMYASAL PARAMETRELER ÜZERİNE ETKİSİ

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Summary

Objective: To determine the effects of flutamide 250-500 mg/day on serum lipids, apoproteins, Lp(a) and their interactions.

Design: Dept. of Obstetrics and Gynecology. Endocrinology and Biochemistry, Medical School of Erciyes University, Kayseri.

Methods: Sixty hirsute women were taken to the study. The Group I (n=20) received flutamide 250 mg daily, the Group II (n=20) received 500 mg/day flutamide (250 mg twice a day), and 20 healthy women were served as controls. Both treatments were administered oraly for 12 months. Serum total cholesterol triglycerides, HDL-cholesterol (LDL-C) were calculated by Friedewald formula, Total serum testosterone (T), free testostereno (fT) FSH, LH, E2, DHEAS, Androstenedione (A), 17-Hydroxyprogesterone (17-OHP), Sex hormone-binding globulin (SHBG), and PRL were determined.

Results: The hirsutism scores decreased in Group I and Group II from a mean of 17.00±5.34 to 4.11±2.47 (p<001), 17.47±4.90 to 5.12±3.14 (p<0.001) respectively. No significant differences between Group I and Group II at biochemical parameters (p<005). The elevation of serum triglyceride, total cholesterol, Apo B, Lp(a), LDL-cholesterol, and the decrease of HDL-cholesterol were observed in both treatment groups. No significant changes in the serum hormon levels were found between groups before and after treatment.

Conclusions: We suggest that flutamide therapy appears to be not effects on lipid profiles, apolipoproteins and Lp(a) levels. Peripheral androgenic blockage with flutamide does not modify the risk of CAD which increased in the hirsute patients.

Key Words: Flutamide therapy, Biochemical parameters

T Klin J Gynecol Obst 2001, 11:361-364

Özet

Amaç: Flutamid 250-500 mg/gün tedavilerinin serum lipidler, apoproteinler, Lp(a) ve üzerine etkisinin araştırılması.

Çalışmanın Yapıldığı Yer: Erciyes Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum, Endokrinoloji ve Biyokimya AD, Kayseri.

Materyel ve Metod: Çalışmaya 60 hasta alındı. Grup I (n=20) 250 mg/gün, Grup II (n=20) 500 mg/gün Flutamid verildi, ayrıca çalışmaya 20 sağlıklı kadın kontrol grubu olarak alındı. Her iki grubun tedavilerine 12 ay süreyle devam edildi. Serum total kolesterol, trigliserid, HDL-kolesterol, apoprotein A, apoprotein B, Lp(a) ölçüldü, LDL-kolesterol (LDL-C) Friedewald formülü ile hesaplandı. Total testosteron (TT), free testosteron (fT), FSH, LH, E2, DHEAS, androstenodion (A), 17 hidroksiprogesteron (17 OHP) sex hormon binding globulin (SHBG) ve PRL hormonları ölçüldü.

Sonuç: Hirsutism skorları Grup I ve Grup II'de sırasıyla 17.00±5.34'den 4.11±2.47 (p<0.001), 17.47±4.90'dan 5.12±3.14 (p<0.001)'e düştü. Biyokimyasal parametrelerde ise gruplar arasında belirgin fark gözlenmedi (p>0.005). Her iki tedavi grubunda serum total kolesterol, trigliserid, LDL-kolesterol, apoprotein B, Lp(a) seviyelerinde artış, HDL-kolesterol seviyelerinde azalma gözlendi. Serum hormon seviyelerinde tedavi öncesi ve sonrası belirgin değişiklik gözlenmedi.

Tartışma: Flutamid tedavisinin lipid profiline, apoproteinler ve Lp(a) seviyelerine etkili olmadığı kanaatindeyiz. Flutamid tedavisi ile yapılan periferik androjenik blokajın hirsute hastalarda CAD riskini azaltmadığı görülmektedir.

Anahtar Kelimeler: Flutamid tedavisi, Biyokimyasal parametreler

T Klin Jinekol Obst 2001, 11:361-364

Geliş Tarihi: 16.08.1999

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Hirsutism and acne are common cosmetic problems for women of reproductive age. The combination of mechanical hair removal and judicious use of medications will improve hair growth in most women (1). Antiandrogens have been introduced for the treatment of hirsutism because

of their ability to prevent androgens from expressing their activity at the target sites (2). There are several antiandrogen drugs having different structures related activities, these substances have either a steroidal structure, such as cyproterone acetat and spironolactone, or non-steroidal structure, e.g. flutamide (3). Flutamide is the only antiandrogen that blocks specifically the androgen receptor without glucocorticoid, progestational androgenic or estrogenic activity (4).

The lower high-density lipoprotein cholesterol (HDL-C) concentrations imply a potentially greater risk of coronary artery disease (CAD) compared with regularly menstruating nonhirsute nonhyperandrogenic women (5). Numerous studies suggest that patients with atherosclerosis are more exactly discriminated from patients without atherosclerosis by the finding of increased plasma apolipoprotein B (apo B) levels than by the findings of decreased HDL-C and increased LDL-C (6,7). Atherosclerosis in conjunction with low HDL-C and deficiency of apolipoprotein A_1 (apo A_1) has also been reported and authors suggest that plasma apo A_1 to be the most reliable of all lipid and lipoprotein fractions for predicting CAD in patients requiring angiography. Apo A_1 levels have also been shown to be better correlated with peripheral vascular disease than lipid parameters (7,8). After identification of lipoprotein-a (Lp(a)) by Berg in 1963 several investigators have confirmed that a high Lp(a) concentration is an independent risk factor for cardiovascular disease (9-11). Authors showed that the concentration of Lp(a) in serum cannot be influenced by age, diet, lifestyle, and other lipoprotein risk factors (11,12). Our previous studies showed that serum HDL-C decreases in non-treated hirsute patients, but serum apo A_1 and apo B levels were not significantly change (13).

No studies are reported concerning the Lp(a) serum concentration in hirsut patients treated with flutamide.

Thus in the present study, we aimed to determine the effects of flutamide 250-500 mg/day on serum lipids apoproteins, Lp(a), and their interactions.

Material and Methods

Sixty hirsute women were taken to the study. The group I (n=20) received flutamide (Eulexin; Schering Plough labo NV., Heist-op-den-Borg, Belgium) 250 mg daily, the group II (n=20) received 500 mg/day flutamide (50 mg twice a day), and 20 healthy women were served as controls. Both treatments were administered oraly for 12 months. Fifty-one percent and 60% of the women were polycystic ovary (PCO) in the group I and group II, respectively. Table 1 summarizes clinical details of the two treatment groups and control group.

The mean age, body mass index (BMI) and hirsutism scores were similar between patients, and controls. The study was approved by Ethical Committee of Erciyes University Medical School, and all subjects provided written and informed consent. It was proposed to patients with moderate to severe hirsutism according to the scoring system of Serriman and Gallwey as modified by Hatch et al. (14). Entery criteria was a score of 12 or greater. Hirsutism was graded by the same observer. All women had a slowly progressive hirsutism without evidence of virilization, pelvic mass, or elevated 17-hydroxyprogesterone levels. To be included in the study protocol, women had not to have received hormonal treatments in the three months preceding the study. Serum hCG was negative at the start of the protocol.

Table 1. Clinical characteristics of the hirsute patients treated with flutamide 250 mg/day (Group I), flutamide 500 mg/day (Group II) and controls

	Group I n=20	Group II n=20	Controls n=20
Age	22.65±4.01*	22.06±7.43	21.70±1.30
BMI	23.42±2.69*	23.41±3.45	23.70±2.05
FGS Basal	17.00±5.34**	17.47±4.90	3.05±0.83
FGS 12 months	4.11±2.47**	5.12±3.14	3.05±0.83

* p>0.05, compared with group II and controls
** p>0.05, compared with group II.

Estrogens were not co-administered during the study, and women had intrauterin devices or were adviced to use barrier methods of contraception during therapy. Peripheral venous blood samples were obtained in the overnight fasting state at 14 h. Serum HDL-cholesterol was measured by sodium phosphotungstate-Mg^{+2} method (15). Apolipoprotein A_1 and apolipoprotein B were measured by Orion Diagnostica Immunochemical method. The method is based on measurement of immunoprecipitation at 340 nm lipoprotein A was determined by Seckman array analyser Lp(a) kit. Serum total cholesterol and triglycerides were quantified using routine laboratory methods. LDL-cholesterol (LDL-C) was calculated by Friedewald formula (16).

(LDL-C)=(Total-C)-(TG/5+HDL-C)

Blood samples were collected in the follicular phase of the menstruel cycle at 8 a.m. and at three months intervals thereafter. After centrifugatton sera were stored at 20ºC until assayed. Total serum testosterone (T), free testosterone (fT), FSH, LH, E2, DHEAS, Androstenedione (A) and 17-Hydroxyprogesterone (17-OHP) were measured by radioimmunoassay (RIA) (DPC, Los Agneles). Sex hormone-binding globulin (SHBG) (Orion Diagnostica, Espoo, Finland), and PRL (ICN Biomedicals Inc. Costa Mesa, CA) were measured by iminoradiometric assay. The intra-assay and inter-assay precision coefficients of variation were 3.2 and 8.4% for FSH; 6.8 and 7.9% for LH; 5.2 and 5.5% for E2; 10 and 10.4% for T; 4.3 and 5.5% for fT; 8.3 and 9.2% for A; 3.9 and 7.0% for DHEAS; 5.6 and 4.5% for 17-OHP; 4.0 and 5.5% for SHBG; and 4.8 and 8.2% for PRL, respectively. All results were given as the means ± SD. Comparisons of values were made with the students-t test.

Table 2. Biochemical profiles in both treatment groups and controls[a]

	Group I n=20	Group II n=20	Controls n=20
Triglyceride (mmol/l)	0.88±0.29♣*	0.89±0.33*	0.67±0.18
Cholesterol (mmol/l)	5.08±0.84♣*	4.67±1.23*	3.79±1.01
HDL-Cholesterol (mmol/l)	1.14±0.29♣*	1.17±0.26*	1.36±0.19
Lipoprotein a (g/l)	0.22±0.12♣*	0.23±0.15*	0.08±0.04
ApoA1 (g/l)	1.38±0.21♣	1.30±0.17	1.32±0.17
ApoB (g/l)	1.27±0.26♣*	1.26±0.27*	1.09±0.21
$ApoA_1/ApoB_1$	1.06±0.25♣	1.09±0.24	1.19±0.37
LDL-Cholesterol (mmol/l)	3.76±0.49♣*	3.20±1.26*	2.30±0.79

[a] Values are means ± SD
♣ p>0.05, compared with group II value
* p<0.05, compared with control value

Table 3. Hormonal parameters before and after flutamide therapy in both treatment groups[a]

	Group I (n=20)		Group II (n=20)	
	Basal	12 months	Basal	12 months
FSH (IU/L)	4.01±1.66*	4.20±1.61	4.00±1.42*	4.01±1.28
LH (IU/L)	4.95±2.52*	5.15±1.03	5.08±1.17*	5.07±1.02
E_2 (pmol/L)	565.59±155.20*	557.91±158.44	566.06±108.80*	570.51±116.4
T (nmol/L)	2.23±0.70*	2.27±0.49	2.25±0.46*	2.27±0.55
freeT (pmol/mL)	1185±5.09*	10.50±5.47	10.40±1.63*	10.78±2.49
A (nmol/mL)	10.47±1.641*	10.19±3.42	10.99±3.31*	10.64±2.93
DHEAS (pmol/L)	14.61±451*	14.48±2.95	14.76±4.44*	14.90±5.77
17-OHP (nmol/L)	5.71±2.02*	7.05±5.14	5.84±2.05*	5.99±1.87
SHBG (nmol/L)	29.76±7.84*	30.04±8.83	29.46±7.28*	29.21±7.91
PRL (μg/L)	13.93±4.88*	12.34±4.13	12.92±3.53*	13.96±2.12

[a] Values are means ± SD
* p>0.05, compared with 12 months

Results

Clinical improvement in the degree of hirsutism was observed in all patients treated with flutamide 250 mg/day and 500 mg/day for 12 months. The modified Ferriman-Gallwey scores for hirsutism decreased in group I and group II from a mean of 17.00±5.34 to 4.11±2.47 (p<0.001), 17.47±4.90 to 5.12±3.14 (p<0.001), respectively. No significant alterations in any of liver functions, renal functions and blood counts parameters were observed. Table 2 summarizes biochemical detail of the two treatment groups and control. There is no significant differences between group I and group II at biochemical parameters (p<0.05). The elevation of serum triglyceride, total cholesterol. Apo B, Lp(a), LDL-cholesterol, and the decrease of HDL-cholesterol were observed in both treatment groups. The results of serum hormone levels before and after treatment were summarized in Table 3. No significant changes in the serum hormone levels were found between groups before and after treatment.

Discussion

Flutamide, an antiandrogen used to treat prostat cancer, but it used in various doses (250-750 mg/day) in treatment of hirsutism. Both endogenous and exogenous sex hormones play major roles in plasma lipoprotein and apolipoprotein metabolism (5). Patients with polycystic ovary syndrome (PCO) have hyperandrogenism associated with hypertriglyceridemia and low levels of plasma HDL-C (5,17).

Lipoprotein metabolism is of particular interest to clinicians concerned with the diagnosis and treatment of atherosclerosis. Increased HDL appears to retard or prevent the development of atherosclerosis (5,13).

In this study serum triglyceride, total cholesterol, Lp(a), Apo B, and LDL-cholesterol levels were in the normal range but it was high according to controls. The low HDL-C levels in women with hirsutism observed by other authors were seen in this study (13,18).

Dodin et al. (19) found that lipid profiles of nonhyperandrogenic women treated with flutamide (250 mg/day) were in the normal range for total cholesterol and HDL-C.

Cedeno et al. (20) reported that ketaconazol therapy may have beneficial effects on atherogenic lipid and lipoprotein patterns in women with hyperandrogenicity.

Our previous studies showed that serum HDL-C decreases and serum Apo A1 levels and Apo B levels not changed in non-treated hirsute women (13).

Kaiser et al. (21) reported that HDL-C slightly raised, and LDL fraction dropped after cyproterone acetate (Diane-35) therapy.

Low serum Apo A_1 levels and high serum Apo B levels or low Apo A_1/Apo B ratios were found in CAD (22,23).

In the current study we observed that flutamide does not appear to modify the levels of lipoproteins. There are no statistically differences between both treatment groups and controls at Apo A_1/Apo B ratio. Although it is not statistically significant Apo A_1 showed mild decrease and Apo B showed significantly increase in the both treatment groups.

Our results for Lp(a) were also higher at first sight in hirsut patients treated with flutamide (250-500 mg/day) compared to controls (Table 2). These differences were statistically significant ($p<0.001$). We have encountered no study concerning lipoprotein (a) in hirsute women.

In this study and our previouse study we found that flutamide (250 to 500 mg/day) had no effect on hormonal levels (Table 3) (24). These findings are agreement with the other studies (23,19).

In conclusion, we suggest that flutamide therapy appears to be not effects on lipid profiles, lipoproteins and Lp(a) levels. Peripheral androgenic blockage with flutamide does not modify the risk of CAD which increased in the hirsute patients.

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