ANNALES
UNIVERSITATIS MARIE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LVIII, N 2, 130 SECTIO D 2003

Department of Internal Medicine, Medical University of Lublin

WOJCIECH BARUD, ROBERT PALUSIŃSKI,
BOGUSŁAW MAKARUK, JANUSZ HANZLIK

Dihydrotestosterone treatment in men with coronary artery disease. I. Influence on sex hormones, lipid profile, insulin resistance and fibrinogen

Introduction of the term "andropause" in males, analogous to term "menopause" in females, markedly increased the interest in hormonal substitutive treatment of aging men. It is well known that testosterone (T) level declines with age and this phenomenon is associated with increased incidence of coronary artery disease as revealed in many epidemiological and clinical studies (5). The above observations point to the potentially beneficial effects of androgen supplementation. The most potent androgens are T and dihydrotestosterone (DHT). The latter is the product of conversion from T by the 5 alpha-reductase enzymes 1 and 2. DHT as a non-aromatizable androgen is not metabolized to estrogens and has a higher affinity to androgen receptor than T.

The aim of this study was to evaluate the effects of three months of DHT treatment in aging males with coronary artery disease on the levels of sex hormones, lipids, fibrinogen and insulin resistance.

MATERIAL AND METHODS

Patients with a history of prior myocardial infarction and no evidences of prostate cancer were considered eligible for the study. The group treated with DHT comprised eleven males at the mean age of 58.5 ± 5.4 years. In the control group there were eight males at the mean age of 58.1 ± 8.8 years treated with placebo. DHT, in the form of 0.7% gel for transdermal use, was a kind gift from Besins Iscovesco (Paris, France). Each patient was asked to apply every evening 2 doses of the study gel (32mg of DHT in the treated group) on the skin of the abdomen for three months. Ultrasonographic examination of prostate and measurement of serum prostate specific antigen (PSA) were performed in all subjects. The study protocol was approved by the University Ethics Committee and a written consent was obtained from each person before enrollment.

Blood samples were taken from antecubital vein at 8 in the morning. Blood cell count was assessed by hemoanalyzer Cell Dyn 1600 (Abbott). Total cholesterol (TC), triglicerydes (TGL) and blood glucose were measured by enzymatic methods (P.Z. Cormay, Lublin, Poland). High density lipoprotein cholesterol (HDL-C) was assessed by dextran sulphate precipitation method (P.Z. Cormay, Lublin, Poland). Low density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation [LDL-C = TC – (HDL-C + TGL/5)]. Fibrinogen concentration was measured using Multifibren U (Dade Behring GmbH, Marburg Germany). Fasting

plasma insulin level was determined by RIA kit (Medgenix, Fleures, Belgium). Total testosterone and estradiol (E_2) were measured by RIA, using a commercially available kit from Immunotech (Marseilles, France). The level of sex hormone binding globulin (SHBG) was measured by ELISA assay from DPC. Free testosterone index was calculated as total T/SHBG*100. PSA level was determined with the use of IRMA method from Cis. Insulin resistance was estimated from fasting plasma insulin and glucose using the "Homeostasis Model Assessment (HOMA)" (11). In each patient prostate volume was measured during ultrasonographic examination.

The results are expressed as Mean ± SD. A statistical analysis was performed using Statistica 5.5 for Windows software. Student's paired t test was used to compare measurements in the same group before and after DHT treatment. A p value <0.05 was considered statistically significant.

RESULTS

The data are presented in Table 1. A three-month DHT treatment significantly decreased the concentration of total T, free T index as well as E_2 level, with no changes in SHBG concentration and E_2/T ratio. DHT regimen did not alter the parameters of lipid profile. No changes in

Table 1. Anthropometric, hormonal, biochemical and hematological parameters in DHT and placebo treated group (mean ± SD)

	DHT		Placebo	
	before	after	before	after
Anthropometry				
Age (yr)	58.5 ± 5.4		58.1 ± 8.8	
BMI (kg/m^2)	28.0 ± 3.1	28.3 ± 2.8	28.7 ± 4.8	28.9 ± 4.9
Hormones				
Testosteron (nmol/l)	16.46 ± 5.53	12.56 ± 4.99**	14.04 ± 7.22	14.23 ± 6.44
T/SHBG (%)	36.36 ± 12.37	27.40 ± 9.44*	25.74 ± 10.01	26.44 ± 9.73
SHBG (nmol/l)	50.06 ± 24.06	48.39 ± 19.94	61.83 ± 49.35	61.75 ± 48.01
Estradiol (pmol/l)	91.82 ± 36.65	64.45 ± 23.14**	121 ± 17.9	118.2 ± 17.8
E_2/T	6.23 ± 3.75	6.33 ± 5.44	11.57 ± 7.47	10.54 ± 6.56
Biochemistry				
TC (mg/dl)	208.4 ± 17.7	216.7 ± 22.5	191.0 ± 54.4	191.1 ± 44.5
TGL (mg/dl)	137.5 ± 28.2	139.2 ± 32.1	124.4 ± 57.4	141.3 ± 64.6
HDL-C (mg/dl)	41.5 ± 11.7	44.8 ± 9.2	45.5 ± 10.2	46.8 ± 14.9
LDL-C (mg/dl)	139.4 ± 14.2	144.1 ± 23.8	120.6 ± 40.0	116.1 ± 29.0
Fasting glucose (mg/dl)	80.1 ± 10.9	80.2 ± 6.6	84.4 ± 6.7	82.9 ± 3.8
Fasting insulin (μIU/ml)	5.14 ± 4.56	4.79 ± 3.10	6.24 ± 2.15	5.83 ± 1.74
HOMA IR	1.12 ± 1.15	1.00 ± 0.70	1.34 ± 0.55	1.22 ± 0.43
Fibrinogen (mg/dl)	282.3 ± 56.4	265. ± 45.5	361.9 ± 104.0	326.0 ± 71.4
Hematology	15.3 ± 2.0	15.9 ± 2.1	14.4 ± 1.9	14.4 ± 1.8
Hemoglobin (g/dl)				
Red cell count (mln/μl)	5.06 ± 0.58	5.28 ± 0.67	4.59 ± 0.57	4.58 ± 0.39
Hematocrit (%)	45.1 ± 6.0	47.2 ± 6.0	42.8 ± 5.7	42.8 ± 5.3
Prostate				
PSA (ng/ml)	1.29 ± 0.77	1.23 ± 0.56	1.44 ± 1.20	1.40 ± 1.15
Prostate volume (ml)	34.3 ± 12.4	32.7 ± 9.2	42.5 ± 14.1	43.4 ± 13.6

* $P < 0.05$

** $P < 0.01$

blood glucose and insulin level or insulin resistance were observed in this group. Tendencies towards higher levels of haemoglobin, erythrocyte count and hematocrit in the treated group were noted, however these changes did not reach the level of statistical significance. Also, fibrinogen level did not change in the course of DHT treatment. Prostate volume and concentration of PSA in patients with active treatment remained unchanged throughout the study period. There were no significant changes in any evaluated parameter in the placebo group.

DISCUSSION

As it would be suspected, three months' DHT treatment significantly decreased the concentration of total T and free T index. The level of E_2 was also decreased but E_2/T ratio remained unchanged. The above observations are consistent with the data of Wang et al. on pharmacokinetics of transdermal DHT (15). They found that the dose of 32 mg of DHT per day over two weeks induced significant elevation of blood DHT together with decrease in T level. However, total androgen concentration (T+DHT) rose to 20-26 nmol/l, reaching values within the range considered normal for young, healthy men (11-44 nmol/l). E_2 concentration declined after 14 days of treatment and SHBG remained unchanged as it was observed in our study. Similar findings, in terms of SHBG, total T and free T level, were presented by Ly et al. (9). However, in their study a three months' DHT therapy was not associated with any significant changes in E_2 level. Kunelius et al. observed decrease of T, E_2 and SHBG concentrations in the course of six months' DHT treatment (8). The different effects of DHT on SHBG level may be related to the age of the study population. In middle-aged men with hypogonadism, androgen treatment was associated with decrease in SHBG, while in elderly males SHBG level was unchanged.

Until recently, androgens have been considered as factors inducing unfavorable changes in lipid profile and androgen treatment or even supplementation (in hypogonadism) were thought to be associated with increased risk of cardiovascular events. However, the results of many recent studies do not support these observations and suggest the opposite relations – males with high-normal levels of androgens seem to have better lipid profile than ones with hypogonadism (5). In our study, three months' DHT treatment had no adverse effects on blood lipids and even a trend towards higher levels of HDL was observed.

Yet, the results presented by others are not consistent, many point to beneficial effects of androgen supplementation on lipid profile. Hromadova et al. observed significant increase in HDL and decrease of LDL in young men with hypogonadism in the course of T treatment (6). Zgliczynski et al. administered T enantate parenterally to elderly males and noted decline in total cholesterol and LDL cholesterol without unfavorable changes of HDL (16). Interestingly, Dobs et al. observed that beneficial changes of lipid profile mediated by T supplementation in hypogonadal men were more pronounced in older patients (4).

The effects of DHT on blood lipids were also studied. Vermeulen and Deslypere noticed slight decrease in total and LDL cholesterol, non-significant decline of HDL cholesterol and no changes in HDL/total cholesterol ratio in aging men treated with transdermal DHT (14). Similar findings were published by Ly et al. They observed decrease in total cholesterol and LDL cholesterol with no significant changes of HDL and triglycerides in elderly males after DHT treatment (9). The other authors did not find any effects of DHT on the lipid levels (8).

Studies that revealed unfavorable effects of androgens on blood lipids usually involved high doses of synthetic androgen preparations, used in males without hypogonadism.

In our patients treated with DHT, neither glucose nor insulin levels changed throughout the study period. Also, insulin resistance remained unchanged in the course of treatment. Many studies investigated relations between sex hormones and insulin resistance or hyperinsulinemia in women, but in contrast very few addressed this problem in men. Moreover, results published so far are largely inconsistent. They roughly indicate that high doses of T or anabolic steroids

increase insulin resistance, but smaller doses used as a substitutive therapy do not have this effect or even induce beneficial changes (12). In the study by Cohen and Hickman anabolic steroids appeared to have deleterious effects on insulin sensitivity (1). On the other hand, T supplementation in males with hypogonadotropic hypogonadism did not induce insulin resistance (13). Marin et al. observed decrease in insulin resistance and fasting plasma glucose in obese males after T treatment. This phenomenon was most probably mediated by decrease in intra-abdominal fat content. The most pronounced improvement of insulin resistance was observed in males with the lowest levels of T (10). Like in our findings transdermal DHT had no significant effect on the level of glucose, insulin and insulin resistance (10).

Many clinical observations support the role of androgens in erythropoiesis. T is known to increase renal production of erythropoietin and directly induce erythropoietic stem cells in bone marrow. Androgen supplementation in hypogonadal men leads to the development of polycythemia. That is why the administration of androgens in patients with coronary artery disease may be unsafe. As a precaution, blood cell count in all enrolled patients was assessed in the course of our study. Three months' DHT treatment was associated with slight increase of hemoglobin concentration, red blood cell count and hematocrit value. Other authors reported similar findings (9). Literature search suggest that erythrogenic effect of T supplementation is more pronounced in older males than in young hypogonadal men. Sometimes this may even lead to cessation of the therapy. However, tight control of T levels within the range of normal values decrease the risk of the adverse effects in the course of treatment (7).

No significant changes in fibrinogen level were induced by DHT therapy in our patients. This is of great importance, since fibrinogen is one of the risk factors for coronary artery disease, and some studies indicate that there is an association between androgens and fibrinogen levels. However, rather beneficial effect of therapy should be expected because lower levels of androgens are associated with higher fibrinogen concentration (3). The lack of significant changes in fibrinogen in our study may be attributed to a short period of DHT administration.

There are conflicting opinions on the role of androgens in prostate pathology. They are considered a risk factor for benign prostate hyperthrophy and prostate cancer. In our patients treated with DHT no changes in prostate volume and PSA were observed. This is in line with findings of other authors who reported no adverse effects of DHT treatment on prostate (8,9) and even decrease of its volume by 15% (2). The latter effect may be related to the decrease of E_2 level induced by DHT supplementation. Estrogens synergise with androgens in the stimulation of prostate growth and their decrease in the course of DHT treatment may be responsible for the prostate shrinkage. Therefore, it seems reasonable to believe that transdermal DHT supplementation does not have any adverse effects on prostate of aging males.

CONCLUSIONS

1. Three months' transdermal DHT treatment of males leads to a decrease in endogenous testosterone and estradiol levels, without affecting estradiol/testosterone ratio.
2. DHT therapy is not associated with unfavorable changes of lipid profile, insulin resistance and fibrinogen level.
3. Short term DHT administration is safe for the prostate of aging males.

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SUMMARY

The effects of three months' transdermal dihydrotestosterone treatment were assessed in eleven men with coronary artery disease. Concentration of total testosterone level significantly decreased ($p < 0.01$) as well as free testosterone ($p < 0.05$) and estradiol levels ($p < 0.01$), without changes of sex hormone binding globuline and estradiol/testosterone ratio. DHT regimen did not alter the parameters of lipid profile. No changes of blood glucose, insulin, insulin resistance (HOMA) and fibrinogen were observed in this group. The tendency towards higher levels of hemoglobin, erythrocyte count and hematocrit did not reach statistical significance. Short term DHT administration in aging males was safe for prostate.

Wpływ leczenia dihydrotestosteronem u mężczyzn z chorobą wieńcową
I. Wpływ na hormony płciowe, profil lipidów, insulinooporność i fibrynogen

Oceniano wpływ trzymiesięcznego stosowania dihydrotestosteronu w postaci przezskórnej u jedenastu mężczyzn z chorobą wieńcową. Stwierdzono, że w wyniku podawania DHT w sposób statystycznie istotny obniżało się stężenie testosteronu całkowitego ($p < 0.01$), wskaźnik wolnego testosteronu ($p < 0.5$) oraz stężenie estradiolu ($p < 0.01$). Nie zmieniało się natomiast stężenie globuliny wiążącej hormony płciowe oraz stosunek estradiolu do testosteronu. Nie ulegały zmianie również wskaźniki gospodarki lipoproteinowej. Bez zmian pozostawało stężenie glukozy, insuliny, wskaźnik insulinooporności (HOMA) oraz stężenie fibrynogenu. Wzrost stężenia hemoglobiny, liczby erytrocytów i hematokrytu nie był statystycznie istotny. Krótkoterminowe podawanie DHT u starszych mężczyzn było również bezpieczne dla gruczołu krokowego.