

# The Effects of Transdermal Dihydrotestosterone in the Aging Male: A Prospective, Randomized, Double Blind Study

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The objective of the study was to investigate the effects of dihydrotestosterone (DHT) gel on general well-being, sexual function, and the prostate in aging men. A total of 120 men participated in this randomized, placebo-controlled study (60 DHT and 60 placebo). All subjects had nocturnal penile tumescence once per week or less, andropause symptoms, and a serum T level of 15 nmol/liter or less and/or a serum SHBG level greater than 30 nmol/liter. The mean age was 58 yr (range, 50–70 yr). Of these subjects, 114 men completed the study. DHT was administered transdermally for 6 months, and the dose varied from 125–250 mg/d. General well-being symptoms and sexual function were evaluated using a questionnaire, and prostate symptoms were evaluated using the International Prostate Symptoms Score, transrectal ultrasonography, and assay of serum prostate-specific antigen.

Early morning erections improved transiently in the DHT group at 3 months of treatment ( $P < 0.003$ ), and the ability to

maintain erection improved in the DHT group compared with the placebo group ( $P < 0.04$ ). No significant changes were observed in general well-being between the placebo and the DHT group. Serum concentrations of LH, FSH, E2, T, and SHBG decreased significantly during DHT treatment. Treatment with DHT did not affect liver function or the lipid profile. Hemoglobin concentrations increased from  $146.0 \pm 8.2$  to  $154.8 \pm 11.4$  g/liter, and hematocrit from  $43.5 \pm 2.5\%$  to  $45.8 \pm 3.4\%$  ( $P < 0.001$ ). Prostate weight and prostate-specific antigen levels did not change during the treatment. No major adverse events were observed.

Transdermal administration of DHT improves sexual function and may be a useful alternative for androgen replacement. As estrogens are thought to play a role in the pathogenesis of prostate hyperplasia, DHT may be beneficial, compared with aromatizing androgens, in the treatment of aging men. (*J Clin Endocrinol Metab* 87: 1467–1472, 2002)

ANDROGEN PRODUCTION declines with age in men, resulting in decreased serum concentrations of both total and bioavailable T (1–3). In healthy men, bioavailable free T declines by approximately 1%/yr between 40 and 70 yr (3) and by even more in unhealthy groups. Furthermore, the circadian rhythmicity of blood total T concentrations decreases with age (4). In contrast to menopausal symptoms in women, these age-related changes in testicular function are gradual, and the clinical picture may be difficult to recognize. However, a number of changes typically experienced by aging males have been attributed to a decline in circulating T levels. The symptoms are diminished energy, virility, and fertility and decrease in bone and muscle mass associated with an increase in adiposity (1–3, 5).

Improvement of clinical symptoms of andropause via androgen substitution therapy has long been recognized (6, 7). A number of androgen preparations have been tested to see whether androgen replacement could improve physical and mental well-being in aging men. T, the most frequently used androgen, has been administered orally, by injection, and recently via transdermal patches in hypogonadal men and in men suffering from andropause symptoms (8). Dehydroepiandrosterone has also been used for androgen replacement therapy,

and it has been shown to improve well-being in both aging women and men (9). More recently, percutaneous dihydrotestosterone (DHT) gel has become available as a method of androgen replacement (10). DHT, which cannot be aromatized to E2, may have advantages compared with aromatizing androgens (10). As E2 is thought to play a role in the pathogenesis of benign prostate hyperplasia, the treatment of andropause symptoms with nonaromatizing DHT may offer an advantage compared with aromatizing androgens. Furthermore, based on bioassay studies, DHT may have greater pharmacological potency than other available androgens (11).

To assess the efficacy and safety of DHT in the treatment of andropause symptoms we administered DHT gel or placebo transdermally to 120 men for 6 months, in a double blind, placebo-controlled monocenter study. In addition to andropause symptoms, special attention was paid to prostate tolerance, hematological parameters, and the lipid profile.

## Subjects and Methods

### Subjects

A total of 120 males, aged 50–70 yr (mean age, 58 yr), participated in this monocenter, double blind, randomized, placebo-controlled, parallel group study (Fig. 1, flow chart). Based on a telephone conversation or a clinic visit, 178 subjects were known to fulfill the symptom criteria, and they were asked to come for screening. Of them, 55 failed to enter the study because of abnormal lipid or liver parameters, high serum prostate-specific antigen (PSA;  $>10 \mu\text{g/liter}$ ), or other reasons. The subjects

Abbreviations: DHT, Dihydrotestosterone; FAI, free androgen index; Hb, hemoglobin; Hcr, hematocrit; I-PPS, International Prostate Symptoms Score; PSA, prostate-specific antigen.

were randomized to the DHT ( $n = 60$ ) or the placebo ( $n = 60$ ) group. The randomization codes identifying the treatment were kept in sealed envelopes and were broken only after all clinical and biochemical anal-

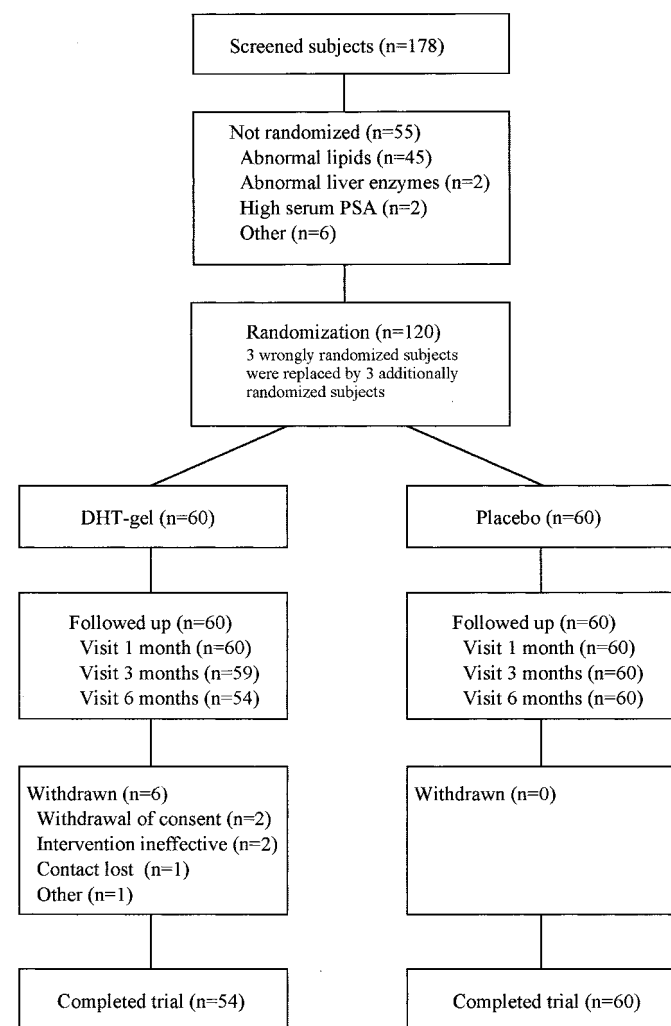


FIG. 1. Flow chart describing the progress of subjects throughout the study.

TABLE 1. Characteristics of the subjects

	All	DHT	Placebo	P value, DHT vs. PLACEBO
n	120	60	60	
Age (yr)	58.4 ± 5.3 <sup>a</sup>	58.3 ± 4.8	58.6 ± 5.7	NS
T ≤15 nmol/liter	51	25	26	NS
T <9 nmol/liter	5	3	2	NS
SHBG >30 nmol/liter	111	57	54	NS
SHBG >62 nmol/liter	22	11	11	NS
T ≤15 nmol/liter and SHBG >30 nmol/liter	43	22	21	NS
FAI	35.5 ± 10.8	35.3 ± 10.9	35.6 ± 10.7	NS
FAI (mean value in healthy men aged 20–49 yr)	76.9 ± 40.7 <sup>b</sup>			
FAI (mean value in healthy men aged 50–65 yr)	46.9 ± 16.4 <sup>b</sup>			
DHT (nmol/liter; mean value in healthy men aged 50–67 yr)	1.3 ± 0.7			

<sup>a</sup> Mean ± SD.

<sup>b</sup>  $P < 0.001$  compared with the study subjects.

yses were completed. None of the envelopes had to be opened before completing the study. Subjects included should have had rarefaction of nocturnal penile tumescence (once or less per wk; frequency of early morning erections together with libido are known to have correlation with serum androgen levels) and at least one of the following andropause symptoms: decreased libido, erectile dysfunction, urinary disorders, asthenia, or depressive mood. In addition, the subjects had to have a total serum T concentration of 15 nmol/liter or less (normal range, 9–32 nmol/liter) and/or an SHBG level greater than 30 nmol/liter (normal range, 14–62 nmol/liter). Although serum T levels of 15 nmol/liter or less and SHBG levels greater than 30 nmol/liter do not define all subjects as being hypogonadal or having low free T, these limits were used together with clinical symptoms to find men who would benefit from the treatment. The number of subjects in each category is given in Table 1. Five subjects in the DHT group and nine in the placebo group ( $P = 0.175$ ) had been treated earlier for impotence problems. The exclusion criteria with regard to prostate were prostate weight greater than 100 g, serum PSA level greater than 10  $\mu$ g/liter, acute prostatitis, abnormal prostate in clinical or ultrasonographic examination, or prostatectomy/transurethral resection of the prostate. The other main exclusion criteria were significant cardiovascular disease, abnormal lipid profile (total cholesterol >7.5 mmol/liter and/or triglycerides >1.7 mmol/liter), alcohol abuse, and uncured cancer. Furthermore, subjects with neurological impotence, major depression, or other psychiatric diseases, and those taking hormones or drugs affecting sexual function, lipid/hormone metabolism ( $\beta$ -blockers, methylodopa, clonidine, guanethine thiazide diuretics, spironolactone, digitalis, barbiturates, clofibrate, cimetidine, metochlopramide, or antidepressive and neuroleptic drugs), or hematological parameters were excluded. Three subjects (1 taking DHT: unstable hypertension; 2 taking placebo: coronary heart disease with metoprolol medication and skin cancer) were wrongly included in the study; therefore, 3 additional men were randomized. Six men in the DHT group dropped out before the end of the trial (Fig. 1). The reasons for drop-out were withdrawal of consent ( $n = 2$ ), lack of efficacy ( $n = 2$ ), contact lost ( $n = 1$ ), and acute pyelonephritis due to prostatitis ( $n = 1$ ). For comparison, the serum concentrations of DHT in 35 healthy men, aged 50–67 yr, and the free androgen index (FAI) in 146 healthy men, aged 20–65 yr, were analyzed.

The study was approved by the ethics committee of the University of Oulu, and all subjects signed an informed consent form. The subjects could discontinue the study any time, and a serious adverse event was considered an absolute stopping rule.

### Protocol

DHT and placebo gel were prepared and packed in identical tubes by Laboratories Besins Iscovesco (Paris, France). Both the study drug and placebo were opalescent gels with alcoholic odor, and they were applied on upper arms/shoulders and on abdomen if necessary. The DHT gel contained a 2.5% solution of DHT. After application the gel dried rapidly in a few minutes. The subjects were asked to wash their hands after

application and to pay attention to any skin irritation observed. All subjects administered 5 g DHT (125 mg DHT) or placebo gel daily for the first 30 d, whereafter the dose was adjusted by a outside person (*i.e.* blind to the principal investigators) on the basis of serum DHT measurement performed 20 d after study entry. If serum DHT was less than 5.8 nmol/liter, the men used a daily dose of 250 mg, if serum DHT was between 5.8–11.6 nmol/liter, the daily dose was 187.5 mg, and if serum DHT was over 11.6 nmol/liter, the daily dose was 125 mg. The purpose was to reach the upper limit of 5.8–11.6 nmol/liter, which has been found to be the range at which a daily dose of 5 g gel is used (12). The dose of placebo was adjusted randomly by an outside person; 30 subjects continued with 5 g, and 30 used either 7.5 or 10 g. All tubes were returned and weighed to ensure compliance, and no significant failures were observed. The effect of DHT on general well-being was evaluated by questionnaire (13 questions), which was modified from the Psychological General Well-Being scale (13), and 12 questions regarding sexual function were modified from the International Index of Erectile Function (14). For example, the scoring system for the early morning erections was: 1 = never, 2 = every other month, 3 = every month, 4 = every other wk, 5 = every week, 6 = two times a week or more. After the screening visit and entry, follow-up visits were made at 1, 3, and 6 months of treatment, and the subjects filled out the questionnaire before entry and at 3 and 6 months.

The prostate was palpated, and serum PSA was assayed at each visit. Transrectal ultrasonography of the prostate (Brüel & Kjaer Medical 3535, transducer 8551, 7 MHz, Naerum, Denmark) was carried out in three dimensions at the beginning of the study and at the last visit. Urinary symptoms were evaluated using the International Prostate Symptoms Score. Blood samples for T, E2, FSH, and SHBG measurements were drawn at 0 and 6 months and at each visit for other hormonal, hematological and biochemical analyses. All blood samples were taken after an overnight fast.

### Laboratory techniques

Serum DHT concentrations were measured by RIA after organic extraction and hydrophobic chromatography. The lower limit of quantification of serum DHT was 0.1 nmol/liter. The normal range for DHT was 1–10 nmol/liter, and the intra- and interassay coefficients of variation were 9.1% and 6.6%, respectively. In previous studies the basal serum levels of DHT have been found to be 1.5–2.0 nmol/liter in men between 50–70 yr of age (5, 15, 16) and 2.5–3.5 nmol/liter in men between 19–29 yr of age (16). Serum T concentrations were measured using a ACS:180 chemiluminescence system with an ACS:180 analyzer (Chiron Corp., Emeryville, CA). Serum E2 concentrations were measured by RIA (Orion Diagnostica, Turku, Finland). Serum SHBG, LH, FSH and PSA concentrations were quantified by two-site fluorimmuno-metric methods with kits obtained from Wallac, Inc. (Turku, Finland), using a 1235 AutoDELFLIA automatic immunoassay system. The intra- and interassay coefficients of variation were 4.0% and 5.6% for T, 5.7% and 6.4% for E2, 1.3% and 5.1% for SHBG, 4.9% and 6.5% for LH, 3.8% and 4.3% for FSH, and 1.2% and 3.8% for PSA, respectively. The FAI was calculated according to the equation:  $(T \times 100)/SHBG$ . Hematological analyses and biochemical measurements were performed using approved routine clinical chemistry methods (Oulu University Hospital).

### Statistics

The homogeneity of the two groups before inclusion and before treatment was analyzed using a *t* test in normally distributed variables (placebo, *n* = 60; DHT, *n* = 60). Wilcoxon's nonparametric test was used for variables with persisting skewed distribution, and  $\chi^2$  or Fisher exact test was used for qualitative variables. For comparison of main efficacy and biochemical parameters the repeated measures ANOVA was used (placebo, *n* = 60; DHT, *n* = 54).

## Results

After 1 month of DHT treatment, 23% of the subjects used a daily dose of 125 mg, 45% used 187.5 mg, and 32% used 250 mg. The serum concentrations of DHT and other hormones are shown in Table 2. For comparison, the FAI and serum

**TABLE 2.** Effects of DHT treatment on serum hormone parameters

Hormone	DHT			Placebo			<i>P</i> value, mean change DHT vs. placebo
	0 month	3 months	6 months	0 month	3 months	6 months	
DHT [nmol/liter (range)]	1.5 ± 0.6 (0.5–3.3)	9.3 ± 4.7 (1.6–24.8)	8.2 ± 4.6 (1.5–24.5)	1.5 ± 0.8 (0.1–5.0)	1.4 ± 0.8 (0.2–4.4)	1.5 ± 0.7 (0.2–4.2)	<0.001
Dose of DHT, 125 mg (5 g gel)	1.5 ± 0.7 ( <i>n</i> = 14)	9.5 ± 6.9	8.5 ± 6.5	1.6 ± 0.9 ( <i>n</i> = 30)	1.5 ± 1.0	1.6 ± 0.9	<0.001
Dose of DHT, 187.5 mg (7.5 g gel)	1.5 ± 0.6 ( <i>n</i> = 27)	9.0 ± 3.9	8.2 ± 4.8	1.4 ± 0.5 ( <i>n</i> = 22)	1.4 ± 0.6	1.4 ± 0.5	<0.001
Dose of DHT, 250 mg (10 g gel)	1.5 ± 0.7 ( <i>n</i> = 19)	9.2 ± 4.1	8.0 ± 2.8	1.2 ± 0.3 ( <i>n</i> = 8)	1.0 ± 0.4	1.2 ± 0.4	<0.001
T (nmol/liter)	16.1 ± 4.6		5.9 ± 3.9	15.9 ± 4.5		15.3 ± 5.1	<0.001
E2 (nmol/liter)	0.09 ± 0.03		0.05 ± 0.02	0.08 ± 0.02		0.09 ± 0.04	<0.001
SHBG (nmol/liter)	48.9 ± 17.3		38.7 ± 12.9	46.5 ± 16.6		42.7 ± 16.7	0.003
FSH (IU/liter)	6.5 ± 4.9		3.9 ± 3.8	5.7 ± 4.6		6.0 ± 5.3	<0.001
LH (IU/liter)	5.1 ± 2.9	2.4 ± 2.2	2.3 ± 1.8	4.5 ± 2.7	4.6 ± 3.1	4.6 ± 2.7	<0.001

DHT concentrations of healthy men are shown in Table 1. The score of early morning erection improved significantly in the DHT group during the first 3 months of treatment (from 3.0 to 3.9;  $P < 0.003$ ). The ability to maintain erections in subjects taking DHT improved significantly compared with that in subjects using placebo (Table 3). There were no statistically significant differences in general well-being, libido, mood, or vitality between the groups. However, the placebo effect was statistically significant in several questions: mood, briskness, self confidence, depression, activity, cheerfulness, and relaxation improved in both groups; libido, general interest in everyday life, and energy in the placebo group; and satisfaction with sexual life in the DHT group. Serum PSA concentrations did not change during the treatment. Similarly, prostate size and International Prostate Symptoms Score (I-PPS) remained unchanged (Table 4).

DHT treatment decreased serum concentrations of E2, T, and SHBG ( $P < 0.001$ – $0.003$ ; Table 2). Similarly, serum concentrations of LH and FSH decreased in the DHT group compared with the placebo group. DHT treatment did not affect serum lipid parameters (Table 4). No changes were observed in liver enzymes. Hemoglobin (Hb) and hematocrit (Hcr) values increased significantly in the DHT group compared with the placebo group (Table 4). In the DHT group, six men had Hb between 170 and 180 g/liter at least once during the treatment (normal range, 135–170), and one subject had Hb of 184 g/liter and Hcr of 55% (normal range,

40–54%) at 3 months, but the values decreased to 176 g/liter and 53% at 6 months. There were no major clinical adverse events during DHT treatment. Three subjects experienced mild headache during DHT treatment compared with two subjects in the placebo group. None of the subjects described skin irritation during the treatment, but one subject in the DHT group had hair growth on the left shoulder and upper arm. Two subjects in both groups suffered from mild depression during the study. Other reported adverse events were not considered to be related to the treatment.

## Discussion

This first placebo-controlled study carried out with DHT demonstrated a number of changes in both clinical and biochemical parameters in response to percutaneous DHT administration in men with relatively low bioavailable serum T levels and andropause symptoms. Treatment with DHT improved the ability to maintain erections and transiently improved early morning erections. However, these changes were small, though significant; therefore, their clinical importance remains uncertain. Six subjects in the DHT group and none in the placebo group dropped out before the end of the trial. We do not have a good explanation why only subjects in the DHT group stopped the study, but the difference in the dropout frequency between the groups was not statistically significant, and none of the reasons for dropping out were related to side-effects of the drug.

Androgens have been shown to have favorable consequences in the central nervous system by having a stimulating and maintaining effect on sexual function in men (17, 18). A number of androgen preparations have been used to treat hypogonadism (19). Treatment with percutaneous DHT gel increased serum total DHT levels 5-fold and led to concentrations that were clearly above the normal young adult male range (16). Although serum T concentrations decreased simultaneously with DHT administration by 50–70%, it is apparent that the total androgen effect increased signifi-

**TABLE 3.** Ability to maintain erection during intercourse

Treatment	0 month	3 months	6 months	<i>P</i> value, mean change DHT vs. placebo
Placebo	2.53 ± 1.44	2.65 ± 1.56	2.81 ± 1.56	0.04
DHT	2.26 ± 1.41	2.70 ± 1.50	3.24 ± 1.35	

Difficulties in maintaining erection during intercourse were scored from 1–6: 1, always; 2, in 75% of intercourses; 3, in 50%; 4, in less than 25%; 5, in less than 10%; and 6, never.

**TABLE 4.** Effects of DHT treatment on weight, prostatic weight, I-PPS score, and hematological, biochemical, and lipid parameters

Parameter	DHT				Placebo				<i>P</i> value, mean change DHT vs. PLA
	0 month	1 month	3 months	6 months	0 month	1 month	3 months	6 months	
Wt (kg)	79.5 ± 9.0		79.9 ± 8.8	79.5 ± 9.0	80.8 ± 9.2		81.1 ± 9.7	81.1 ± 9.3	NS
BMI	25.7 ± 2.1		25.8 ± 1.9	25.7 ± 1.9	26.1 ± 2.5		26.2 ± 2.6	26.1 ± 2.7	NS
Prostatic wt (g)	25.3 ± 10.0			25.9 ± 8.0	23.2 ± 7.8			25.5 ± 8.3	NS
I-PPS score	10.2 ± 6.3		8.6 ± 6.3	8.0 ± 5.3	8.0 ± 5.1		7.0 ± 5.7	6.9 ± 5.4	NS
Hematocrit (%)	43.5 ± 2.5	43.9 ± 2.8	46.0 ± 3.1	45.8 ± 3.4	43.4 ± 2.3	43.1 ± 2.5	42.9 ± 2.9	43.1 ± 3.0	<0.001
Red blood cells (10 <sup>12</sup> /liter)	4.7 ± 0.3			5.1 ± 0.4	4.7 ± 0.3			4.6 ± 0.4	<0.001
Hemoglobin (g/liter)	146.0 ± 8.2	149.3 ± 9.8	155.9 ± 9.7	154.8 ± 11.4	146.3 ± 8.2	146.5 ± 8.7	146.2 ± 9.4	145.8 ± 9.7	<0.001
PSA (μg/liter)	1.6 ± 1.6	1.6 ± 1.6	1.6 ± 1.4	1.6 ± 1.4	1.5 ± 1.2	1.5 ± 1.2	1.5 ± 1.2	1.5 ± 1.3	NS
Total cholesterol (mmol/liter)	5.6 ± 0.7			5.7 ± 0.7	5.7 ± 0.7			5.5 ± 0.8	NS
HDL cholesterol (mmol/liter)	1.1 ± 0.2			1.2 ± 0.2	1.1 ± 0.3			1.2 ± 0.3	NS
Triglycerides (mmol/liter)	1.2 ± 0.3			1.7 ± 0.9	1.2 ± 0.3			1.5 ± 0.8	NS



cantly, especially because serum SHBG levels decreased simultaneously. This is supported by the observation that percutaneous T and DHT have an equal androgen effect in patients with hypogonadism (20), and DHT may have even greater pharmacological potency than other androgens (11). Androgen replacement in older men has been reported to increase the sense of well-being (21). In our study we did not find significant effects of DHT gel on well-being or vitality. The reason for this is not clear, but it is possible that many subjects had erectile dysfunction before the study and had great expectations for treatment. As impotence is often multifactorial, and androgen supplementation of older men has generally not met with great success (21, 22), at least some subjects may have been disappointed with the treatment and did not pay attention to general well-being. Furthermore, as in previous studies (21), the placebo effect in this study was significant with regard to several aspects of general well-being. In addition, based on the inclusion criteria ( $T \leq 15$  nmol/liter and/or  $SHBG > 30$  nmol/liter) the subjects may have had only mild or moderate androgen deficiency. Although the FAI of the study subjects was significantly lower than that of healthy men of the same age and was half that seen in younger men, their serum DHT levels at baseline were comparable. This was expected, because serum DHT levels do not change markedly with advancing age (5), and therefore the measurement of DHT levels may not be useful when considering androgen decline or deficiency in aging men. Furthermore, if some of the effects of androgens, for instance on the central nervous system, are due to metabolism to estrogens, DHT as a nonaromatizable androgen may have a weaker effect. Alternatively, the instruments used to assess subjective symptoms may not be sensitive enough to detect small changes, which is always a problem in studies like this.

Growth and function of the prostate are controlled by sex steroids. This is supported by the observations that neither prostate hyperplasia nor cancer occur in castrated men or young men (23, 24). Furthermore, androgen deprivation by way of a variety of agents has been shown to reduce prostate size in benign prostatic hyperplasia and to lead to regression of prostate cancer (25, 26). However, regression of prostate size has been described only when almost complete suppression of circulating (27) or tissue (28, 29) DHT is achieved. It has also been recognized, although not proved, that the use of T in elderly men may carry a potential risk by enhancing the progression of preclinical to clinical cancer. It is known that androgens stimulate the growth of clinically diagnosed prostate cancer. In some studies the use of physiological T enanthate supplementation is reflected in stimulation of PSA (19, 26), although in several other studies this has not been observed (30). Holmång and associates (31) found that mean prostate volume increased by 12% during 8 months of treatment with T undecanoate. On the other hand, in many other studies no change in prostate volume during androgen treatment has been found (30). In our study serum PSA concentrations did not increase during DHT treatment, and prostate size remained unchanged. Nevertheless, it is recommended that men using androgen replacement therapy should be carefully screened and followed up periodically.

The mechanisms by which androgens affect the prostate

are not well established, but estrogens are thought to play a role. Experimental studies have shown the inability of non-aromatizable androgens to induce the early stage of prostate hypertrophy (32, 33). On the other hand, aromatizable androgens can induce prostate hyperplasia in monkeys, and this effect can be reversed with an aromatase inhibitor (34). Suzuki and associates (35) have shown that treatment with T combined with E2 stimulates more prostate growth in rats than T treatment alone. The results of a 1.8-yr survey of 37 men, aged 55–70 yr, treated with daily percutaneous DHT suggested that high serum levels of DHT effectively improved andropause symptoms while slightly, but significantly, reducing prostate size (10). In a previous study (20) as well as in the present study the administration of DHT decreased serum E2 levels by 50%. Although the above-mentioned findings and theories serve as a good basis with regard to the importance of estrogens in prostate function, further studies are needed to clarify the clinical significance of the decline of E2 concentrations during DHT treatment.

As expected and observed previously (15), serum FSH and LH concentrations decreased during DHT treatment as a result of the negative feedback effect. The long-term effect of DHT on testicular function, *e.g.* on spermatogenesis, is not yet known, but no evidence of irreversible effects exists (20).

It is well known that androgens have an anabolic effect. Androgens increase red cell mass and Hb concentrations mainly through a direct effect on erythropoietin synthesis in the kidneys, and inhibition of androgen secretion decreases Hb concentrations (36). We found that Hb increased significantly as early as after 1 month of DHT treatment. Similar effects on Hcr have been found earlier in long-term use of T in older hypogonadal men (19) and in normal aging males (31). This anabolic effect must be considered during the follow-up of subjects using DHT or other androgens; Hb and Hcr should be assessed after 3–6 months of treatment, and the dose should be decreased if necessary. Weight and body mass index did not change during the study. The possible effects of DHT on bone density as well as on body composition were not assessed, which may reduce the informativity of the study. These matters were considered carefully before the study, and because no significant changes, especially in bone density, were expected in 6 months of treatment they were not included.

Whether androgen therapy affects cardiovascular risk factors is not clear, although epidemiological studies have demonstrated higher risks in men with lower T levels (37, 38). Moreover, the effects of androgens on lipid metabolism are contradictory. Substitution of T in hypogonadal or T-deficient men has been associated with increases, decreases, or no change in serum high density lipoprotein levels (30, 39–43). In our study there were no changes in serum concentrations of total and high density lipoprotein cholesterol; overall the changes in serum lipids between DHT and placebo groups were modest, and the impact (*e.g.* risk or benefit of cardiovascular function) remains to be studied in long-term trials.

This study suggests that transdermal DHT gel may be a useful alternative for hormone replacement therapy in older men. Whether more significant improvement in sexual functions had been observed using higher doses of DHT remains

to be studied. DHT treatment resulted in hormonal changes that raise interesting questions about the significance of estrogens in prostate function. If estrogens play a role in prostate growth, as has been suggested, the use of nonaromatizable androgens may be beneficial compared with that of aromatizable androgens. Although no significant side-effects were noted, controlled follow-up trials of androgen replacement therapy in general are needed to clarify the possible long-term benefits and risks.

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### References

- Swerdloff RS, Wang C 1993 Androgens and aging in men. *Exp Gerontol* 28:435–446
- Nahoul K, Roger M 1990 Age-related decline of plasma bioavailable testosterone in adult men. *J Steroid Biochem* 35:293–299
- Gray A, Feldman HA, McKinlay JB, Longcope C 1991 Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts male aging study. *J Clin Endocrinol Metab* 73:1016–1025
- Bremner WJ, Vitiello MV, Prinz PN 1983 Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab* 56:1278–1281
- Barret-Connor E, von Mühlen D, Kritiz-Silverstein D 1999 Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo study. *J Clin Endocrinol Metab* 84:573–577
- Greenblatt RB, Oettinger M, Bohler CSS 1976 Estrogen-androgen levels in aging men and women: therapeutic considerations. *J Am Geriatr Soc* 24:173–178
- Reiter T 1963 Testosterone implantation: a clinical study of 240 implantations in ageing men. *J Am Geriatr Soc* 11:540–550
- Wang C, Swerdloff RS 1997 Androgen replacement therapy. *Ann Med* 29:365–370
- Morales JA, Nolan JJ, Nelson JC, Yen SSC 1994 Effects of replacement dose of dehydrotestosterone in men and women of advancing age. *J Clin Endocrinol Metab* 78:1360–1367
- De Lignieres B 1993 Transdermal dihydrotestosterone treatment of 'andropause'. *Ann Med* 25:235–241
- Griffin JE, Wilson JD 1998 Disorders of the testes and the male reproductive tract. In: Wilson JD, Foster DW, eds. *Williams' textbook of endocrinology*. Philadelphia: Saunders; 819–875
- De Ligniers B, Morville R 1980 Treatment of masculine hypogonadism by percutaneous administration of androgens. In: Mauvais-Jarvis P, Vickers CF, Weipierre J, eds. *Percutaneous absorption of steroids*. London: Academic Press; 273–283
- Wiklund I, Dimenas E, Wahl M 1990 Factors of importance when evaluating quality of life in clinical trials. *Control Clin Trials* 11:169–179
- Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishara A 1997 The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 49:822–830
- Wang C, Iranmanesh A, Berman N, McDonald V, Steiner B, Ziel F, Faulkner SM, Dudley RE, Veldhuis JD, Swerdloff RS 1998 Comparative pharmacokinetics of three doses of percutaneous dihydrotestosterone gel in healthy elderly men-clinical research center study. *J Clin Endocrinol Metab* 83:2749–2757
- Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Despres JP, Bouchard C 2000 Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: the heritage family study. *J Clin Endocrinol Metab* 85:1026–1031
- Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ 1994 Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. *J Clin Endocrinol Metab* 78:711–716
- Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ 1992 A long-term, prospective study of the physiologic and behavioural effects of hormone replacement in untreated hypogonadal men. *J Androl* 13:297–304
- Hajjar RR, Kaiser FE, Morley JE 1997 Outcomes on long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab* 82:3793–3796
- Kuhn JM, Laudat MH, de Lignieres B, Bricaire H, Lutton JP 1986 Traitement androgenique percutane des hypogonadismes masculins. Efficacite comparee de la testosterone et de la dihydrotestosterone: etude de 40 observations. *Contraception Fertil Sexuality* 14:1031–1036
- Tenover JS 1994 Androgen administration to aging men. *Endocrinol Metab Clin North Am* 23:877–892
- Korenman SG, Morley JE, Mooradian AD, et al. 1990 Secondary hypogonadism in older men: its relation to impotence. *J Clin Endocrinol Metab* 71:963–969
- Henderson BE, Ross RK, Pike MC, Casagrande JT 1982 Endogenous hormones as a major factor in human cancer. *Cancer Res* 42:3232–3239
- Horton R 1984 Benign prostate hyperplasia: a disorder of androgen metabolism in the male. *J Am Geriatr Soc* 32:380–385
- Frick J, Jungwirth A, Rovas E 1998 Androgens and the prostate. In: Nieschlag E, Behre HM, eds. *Testosterone*. Berlin: Springer-Verlag; 259–291
- Tenover JS 1992 Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab* 75:1092–1098
- Bosch RJLH, Griffiths DJ, Blom JHM, Schroeder FH 1989 Treatment of benign prostate hyperplasia by androgen deprivation: effects on prostate size and urodynamic parameters. *J Urol* 141:68–72
- Gormley GJ, Stoner E, Bruskewitz RC, et al. 1992 The effect of finasteride in men with benign prostate hyperplasia. *N Engl J Med* 327:1185–1191
- McConnell JD, Wilson JD, George FW, Geeller J, Pappas F, Stoner E 1992 Finasteride, an inhibitor of 5 $\alpha$ -reductase, suppresses prostate dihydrotestosterone in men with benign prostate hyperplasia. *J Clin Endocrinol Metab* 74:505–508
- Tenover JL 1996 Effects of androgen supplementation in the aging male. In: Odgers BJ, Vermeulen A, eds. *Androgens and the aging male*. New York: Parthenon; 191–221
- Holmäng S, Mårin P, Lindstedt G, Hedelin H 1993 Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in eugonadal middle-aged men. *Prostate* 23:99–106
- Walsh PC, Wilson JD 1976 The induction of prostate hypertrophy in the dog with androstenediol. *J Clin Invest* 57:1093–1097
- Pollard M, Snyder DL, Luckert PH 1987 Dihydrotestosterone does not induce prostate adenocarcinoma in L-W rats. *Prostate* 10:325–331
- Habenicht UF, Schwatz K, Neuman F, El Etreby MF 1987 Induction of estrogen-related hyperplastic changes in the prostate of Cynomolgus Monkey by androstenedione and its antagonization by the aromatase inhibitor 1-methyl-androsta-1,4-diene-3,17-dione. *Prostate* 11:313–326
- Suzuki K, Takezawa Y, Suzuki T, Honma S, Yamanaka H 1994 Synergistic effects of estrogen with androgen on the prostate: effects of estrogen on the prostate of androgen-administered rats and 5 $\alpha$ -reductase activity. *Prostate* 57:169–176
- Shahidi NT 1973 Androgens and erythropoiesis. *N Engl J Med* 289:72–80
- Barret-Connor E 1992 Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. *Ann Intern Med* 117:807–811
- Simon D, Charles MA, Nahoul K, Orssaud G, Kremiski J, Hully V, Joubert E, Papoz L, Eschwege E 1997 Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: the Telecom Study. *J Clin Endocrinol Metab* 82:682–685
- Bagatell CJ, Bremner WJ 1995 Androgen and progestagen effects on plasma lipids. *Prog Cardiovasc Dis* 38:255–271
- Bagatell CJ, Heiman JR, Matsumoto AM, Rivier JE, Bremner WJ 1994 Metabolic and behavioural effects of high dose exogenous testosterone in healthy men. *J Clin Endocrinol Metab* 79:561–567
- Ozata M, Yildirimkaya M, Bulur M, Yilmaz K, Bolu E, Corakci A, Gundogan MA 1996 Effects of gonadotropin and testosterone treatment on lipoprotein(a), high density lipoprotein particles, and other lipoprotein levels in male hypogonadism. *J Clin Endocrinol Metab* 81:3372–3378
- Sorva R, Kuusi T, Taskinen M-R, Perheentupa J, Nikkilä EA 1988 Testosterone substitution increases the activity of lipoprotein lipase and hepatic lipase in hypogonadal males. *Atherosclerosis* 69:191–197
- Zgliczynski S, Ossowski M, Slowinska-Szednicka J, Brzezinska A, Zgliczynski W, Soszynski P, Chotkowska E, Szrednicki M, Sadowski Z 1996 Effect of testosterone replacement therapy on lipids and lipoproteins in hypogonadal and elderly men. *Atherosclerosis* 121:35–43