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Treatment with percutanous testosterone gel in postmenopausal women with decreased libido – effects on sexuality and psychological general well-being

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Abstract

Objectives: To elucidate if percutanous treatment with 10 mg testosterone per day could enhance sexuality and psychological well-being in postmenopausal women presenting problems with low libido. Secondary to study the influence on blood lipids, hemoglobin and erythropoietin levels.
Methods: Fifty-three postmenopausal women participated. As a complement to their already on-going HRT, 10 mg of a testosterone gel (Testogel, Besins–Iscovesco) or placebo was administered. Treatment continued for three plus three months in a double blind, randomized, crossover design.
Results: The scores concerning "frequency of sexual activity, orgasm and intercourse", "sexual arousal, fantasies and enjoyment", "satisfaction with orgasms", and "interest in sex" were all significally improved for testosterone addition as compared to placebo both before and after crossover. Testosterone levels increased more than 10-fold during treatment while DHT-levels were more than doubled. Estrogen levels were not affected during the addition of testosterone. Liver enzymes, total cholesterol, triglycerides, HDL and LDL revealed no significant differences between any of the periods or groups. Endometrial thickness did not change significantly during treatment. Hemoglobin and erythropoietin remained unchanged. No significant differences in the number of experienced side effects were found.
Conclusion: Testosterone gel of 10 mg had positive effects on several aspects of sexual life such as frequency of sexual activity, orgasm, arousal, fantasies and sexual interest in postmenopausal women on HRT. Several psychological variables were positively influenced. The given dose resulted in too high serum levels. Even if no negative effects were observed, monitoring of serum levels and a decreased dose should be considered in future studies.

Keywords: Testosterone; Sexuality

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1. Introduction

In the past years an increasing interest has been noted in the use of estrogen–androgen treatment in postmenopausal women which has been shown to positively affect sexual motivation, well-being and bone density [1–4]. A change in body composition with an increased lean body mass and decreased fat mass has been found after treatment with a combination of oral methyltestosterone and estrogen as compared to estrogen alone [5]. Treatment with testosterone has also been shown to increase hemoglobin, an effect that could be mediated by erythropoietin [6,7].

All available preparations though, have some disadvantages and the side effects that have been reported are mainly related to dose, pharmacological properties and method of administration. In contrast to estradiol, oral testosterone treatment is not feasible due to hepatotoxicity and unfavorable changes of the lipid metabolism [8–11]. There is a concern about a possible adverse effect by androgens on the lipid profile and its long-term effects on CVD [12].

The ideal androgen preparation should be easy to administer, produce stable serum levels and not cause any negative effects on the liver.

Stable serum concentrations can be achieved by subcutaneous implants or transdermal patches [1,3]. This way of administration also avoids the first liver passage. The percutanous route could therefore prove to be a good alternative. In a previous pharmacological study [13], we evaluated the effects of three different doses of a transdermal testosterone gel in postmenopausal women and found that the 10 mg dose produced serum levels of testosterone within the normal range.

Objective: The primary objective of this study was to elucidate if percutanous treatment with 10 mg testosterone gel per day could enhance sexuality and psychological well-being in postmenopausal women on HRT presenting problems with low libido. Secondary objectives were to study the influence on blood lipids, hemoglobin and erythropoietin.

2. Material and methods

2.1. Subjects

Postmenopausal women between 50 and 65 years of age and complaining of total loss or significant decrease of libido during the postmenopausal period were invited to participate. Women who had experienced libido problems already before the menopause were excluded. All women had a preserved uterus and ovaries and were using combined estrogen/progestogen hormone therapy – cyclic or continuous – since at least two months. All women had a partner and none of the women had any experience of previous androgen therapy. They were all healthy and had no concomitant treatment besides their HRT. Women with heart disease, high blood pressure, malignant disease or other serious chronic disease were excluded. All women had serum concentrations of testosterone below 2.0 nmol/l. The study was approved by the local Ethics Committee at the Karolinska hospital. All women gave their written consent to participate in the study.

As a complement to their already on-going HRT, 10 mg of a testosterone-gel (1% testosterone hydroalcoholic gel testogel, Besins–Iscovesco, Paris, France) or the same amount of a placebo gel was administered in a standardized way each morning. The placebo gel was kept in an identical package and had the same physical properties as the active substance. Application was given to the outside of the thigh in a thin layer of approximately 15 cm^2. Treatment continued for three plus three months in a double blind, randomized, crossover design. Randomization was performed in blocks of eight and the code was kept in the local hospital pharmacy. A modified Swedish version of the McCoy questionnaire [14] was used to assess sexual life. This questionnaire covers sexual experience and responsiveness during the previous 30 days. It contains 21 items and the answers are given on a 7-point scale. Quality of life was evaluated with the “Psychological general well being – questionnaire” (PGWB) [15] presenting a total score as well as depicting anxiety, depression, self-control, vitality, health and well-being. Possible side effects concerning skin, acne, facial hair, clitoral enlargement and voice were actively asked for at each visit. Assessment of sexuality, PGWB and side effects as well as venous blood sampling and vaginal ultrasound for endometrial thickness was performed at baseline and then after three and six months. Liver enzymes, hemoglobin content and erythropoietin were assessed by routine hospital methods. Venous blood samples were taken between 7 and 10 a.m. after an overnight fast and serum was separated after centrifugation and stored at −20 °C pending analysis.

2.2. Analytical methods

The serum levels of total cholesterol and triglycerides (Ortho Diagnostics, Rochester, NY, USA) and HDL-cholesterol (Bayer Ltd., Suffolk, UK) were determined by routine clinical methods in the Department of Clinical Chemistry, Karolinska Hospital. LDL-cholesterol was calculated according to Friedewald's formula [16]. The detection limit and overall coefficient of variation were 1.29 mmol/l and 1.8% for total cholesterol and 0.11 mmol/l and 1.6% for triglycerides. The detection limits and within- and between-assay coefficients of variation were 0.3 mmol/l, 1.9 and 1.3% for HDL-cholesterol.

The serum concentrations of total testosterone were determined with radioimmunoassay (RIA) in untreated serum, using a commercial kit obtained from Diagnostic Products Corp., Los Angeles, CA, USA ("Coat-a-Count®" Testosterone). The serum concentrations of estradiol were determined with a chemiluminescence enzyme immunoassay, using a commercial kit obtained from the Diagnostic Products Corp., Los Angeles, CA (Immulite®). The detection limits and within- and between-assay coefficients of variation were 0.1 nmol/l, 6 and 10% for total testosterone and 73 pmol/l, 8 and 9% for estradiol. 5-dihydrotestosterone (DHT) was determined by RIA after destruction of cross-reacting testosterone by oxidative cleavage of the 4-ene double bond with potassium permanganate, using a commercial kit from Diagnostic Systems Laboratories Inc., Webster, TX, U.S.A.

2.3. Statistics

Sample size was estimated from earlier studies where the McCoy scale was used [4]. The coefficient of correlation between treatments was assumed to be 0.30. Based on this assumption, the minimum number of women needed was 40. Differences in scores from baseline were compared among groups. An analysis of variance for repeated measures (ANOVA) and binary responses (procedure Genmode in SAS®) was first applied to the sexual items and PGWB-scale to test for interaction ($p < 0.01$) caused by the order of randomization. As this was not the case for any of the variables a Friedman test was used to examine differences between the two treatments. Significant differences were then subject to a post hoc test to assess the effect of the treatment periods. Differences between the biological variables were examined by ANOVA.

3. Results

A total of 77 women were assessed for eligibility. Seventeen did no fulfill the exclusion criteria, in the majority of the cases because of a testosterone level >2 nmol/l, leaving 60 women to be randomized and participate in the study. Four women did not comply to medication and were therefore, excluded from further analysis. During the study one woman had a fracture, one developed a skin disease and in one a carcinoma of the uterus was diagnosed. This woman had an irregular shedding at inclusion and the endometrial biopsy revealed a carcinoma. This case was regarded as an inclusion failure and the tumor was judged to have been present prior to inclusion. Consequently 53 women were included in the statistical analysis (Fig. 1).

Mean ± S.D. age, weight and BMI for the 53 women completing the study were 55.4 ± 3.5 years, 65.4 ± 7.8 kg and 23.6 ± 2.8 kg/m^2. The scores in the sex questionnaire concerning "frequency of sexual activity, orgasm and intercourse", "sexual arousal, fantasies and enjoyment", "satisfaction with orgasms" and "interest in sex" were all significally improved for testosterone addition as compared to placebo both before and after cross over. For "vaginal lubrication" a significant improvement was seen only for the first period starting at baseline (Table 1).

For the questions concerning "pain during intercourse", "satisfaction with partner as a lover", "satisfaction with partner as a friend", "feeling of being sexually attractive to partner", "partners problem with impotence", no differences were found for either of the periods.

The total PGWB score as well as the subscales depicting "anxiety" and "positive well-being" demonstrated significant improvements both before and after cross over for the group receiving testosterone. For the subscales "self content" and "vitality" a significant difference was seen only for the first period starting from baseline. For the subscales concerning 'depressed mood' and 'general health' no differences between any of the two treatments or periods were found. (Table 2).

For the group receiving placebo at baseline no changes were seen for any of the questions when these

Table 1
Median values for the individual items of the McCoy questionnaire before and during testosterone treatment in 53 postmenopausal women on HRT

	Baseline	Placebo	Testosterone	*p*-value placebo vs. testosterone	*p*-value for three months placebo vs. testosterone	*p*-value for three months testosterone vs. placebo
1. Frequency of sexual activity	2	3	4	<0.001	<0.001	0.014
2. Sexual thoughts or fantasies	2	2	3	<0.001	0.014	<0.001
3. Sexual enjoyment	4	4	6	<0.001	<0.001	0.001
4. Aroused or excited	4	4	5	<0.001	0.001	0.012
5. Frequency of orgasm	3	4	5	<0.001	<0.001	0.016
6. Lack of vaginal lubrication	3	3	2	0.005	0.009	0.106
7. Pain during intercourse	1	1	1	0.49	n.s.	n.s.
8: Satisfaction with partner as a lover	5	6	6	0.57	n.s.	n.s.
9. Satisfaction with partner as a friend	6	6	6	0.64	n.s.	n.s.
10. Satisfaction with orgasms	5	5	5	0.0.12	0.066	0.021
11. Frequency of sexual intercourse	4	4	4	0.0168	n.s.	n.s.
12. Feeling of being sexually attractive	3	3	3	0.031	n.s.	n.s.
13. Feeling of being sexually attractive to partner	2	2	2	0.86	n.s.	n.s.
14. Interest in sex	5	5	3	<0.001	<0.001	<0.001
15. Partners problem with impotence	1	1	1	0.65	0.021	n.s.
16. Sexual feelings when you think of your partner	3	3	3	0.014	n.s.	n.s.
17. Sexual feelings when you remember something sexual that you experienced	4	3	4	0.108	n.s.	n.s.
18. Sexual feelings when you read a romantic or sexual sequence in a book	4	4	5	0.038	n.s.	0.029
19. Sexual feelings when you listen to music, or other sounds that could give sexual associations	3	3	4	0.025	0.031	n.s.
20. Sexual feelings when you notice special scents like perfumes	3	3	3	0.501	n.s.	n.s.
21. Sexual feelings when you see a movie or television-program with a sexual content	4	4	5	<0.001	0.024	0.002

Range of possible scores for all items were 1–7.

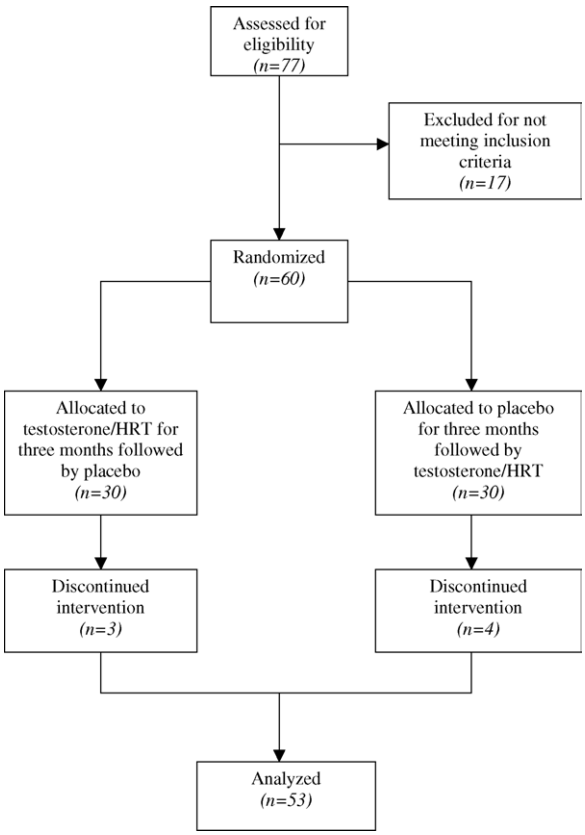

Fig. 1. Flow diagram of randomized study placebo/HRT or testosterone/HRT.

answers were compared to those found at crossover. Since there was no significance for any carry-over effects the results were analyzed together.

Testosterone levels increased more than 10-fold during treatment while DHT-levels were more than doubled (Table 3). Estradiol levels were not affected during the addition of testosterone. Liver enzymes (data not shown), total cholesterol, triglycerides, HDL, LDL and endometrial thickness as measured by vaginal ultrasound revealed no significant differences between any of the periods or groups. Also hemoglobin and erythropoietin remained unchanged during the whole study period. No significant differences in the number of experienced side effects such as headache, weight gain, increased appetite, acne, or facial hair were found between the active and placebo period (Table 4).

4. Discussion

Daily application of 10 mg of a percutanous testosterone gel as an addition to already ongoing HRT in postmenopausal women with libido problems resulted in a marked improvement in several aspects of sexual life. It is well known that serum androgen levels gradually fall in women after 20 years of age [17] and that women in their 40 s have about half the testosterone levels of women in their 20 s [18]. Instead of using a questionnaire with a total score it was decided to use a form with questions on an item level. This made it possible to get a more dynamic picture of which aspects of sexual life that were affected by treatment rather than presenting a "total sexual score". When examining the items, testosterone clearly improved the aspects of sexual life concerning "arousal", "excitement" and "fantasies".

Previously, when testosterone was administered using a 300 μg transdermal patch for 12 weeks to surgically postmenopausal women with loss of libido, pos-

Table 2
Median values for the individual items of the PGWB questionnaire before and during testosterone treatment in 53 postmenopausal women on HRT

	Baseline	Placebo	Testosterone	*p*-value placebo vs. testosterone	*p*-value for three months placebo vs. testosterone	*p*-value for three months testosterone vs. placebo
PGWB anxiety (5–30)	23	24	27	<0.001	0.007	0.033
PGWB depressed mood (3–18)	16	15	16	0.382	n.s.	n.s.
PGWB positive well-being (4–24)	15	16	17	0.010	0.022	0.011
PGWB self content (3–18)	16	16	16	0.031	0.022	n.s.
PGWB general health (3–18)	16	16	17	0.065	n.s.	n.s.
PGWB vitality (4–24)	14	17	18	0.005	0.002	n.s.
Total PGWB (22–132)	100	105	111	0.021	0.008	0.044

Range of possible score for each item is indicated.

Table 3
Serum hormones, lipids and endometrial thickness before and during testosterone treatment in 53 postmenopausal women on HRT

	Baseline	Placebo	Testosterone
Total testosterone (nmol/l)	0.74 ± 0.37	0.95 ± 1.00 n.s.	7.8 ± 5.2 $p < 0.001$
DHT (pmol/l)	407 ± 252	302 ± 272 n.s	993 ± 1034 $p < 0.001$
Estradiol (pmol/l)	255 ± 130	242 ± 130 n.s.	262 ± 142 n.s.
Total cholesterol (mmol/l)	5.44 ± 0.75	5.42 ± 0.85 n.s.	5.48 ± 0.81 n.s.
Triglycerides (mmol/l)	1.20 ± 0.46	1.26 ± 0.63 n.s.	1.25 ± 0.54 n.s.
HDL-cholesterol (mmol/l)	1.78 ± 0.32	1.70 ± 0.40 n.s.	1.70 ± 0.38 n.s.
LDL-cholesterol (mmol/l)	3.12 ± 0.74	3.17 ± 0.84 n.s.	3.23 ± 0.76 n.s.
Endometrial thickness (mm)	4.3 ± 2.4	4.6 ± 2.9 n.s.	4.5 ± 3.0 n.s.

Values given as mean ± S.D. Comparisons are made between baseline-placebo and baseline-testosterone.

Table 4
Side effects reported by 53 postmenopausal women during three months of the placebo/HRT or testosterone/HRT treatment

	Placebo	Testosterone
Influence on mood, headache, weight, appetite etc.	7	6
Skin related (acne, facial hair, hair on legs)	9	11
Total	16	17

itive effects on “pleasure, orgasm” and “frequency of sexual activity” were found [3]. In contrast to our study, no effects were seen on “thoughts-desire”, “arousal” or “receptivity”. It is probable that these differences are dose dependent as the mean testosterone level after treatment with the patch was 3.5 nmol/l while in our study as high as 7.8. Basal levels in both studies were identical with a mean value of 0.74 nmol/l. In our study, effects on the PGWB-score were found for “anxiety” and “well-being” as well as the “total score”. In comparison, treatment with the patch failed to demonstrate an effect on “anxiety” probably because of the same reason, i.e. differences in testosterone levels. To the best of our knowledge no study has yet been performed in which a correlation between endogenous testosterone levels and sexual life in postmenopausal women has been found. Considerations regarding treatment should therefore look more on the woman’s symptoms than on specific testosterone levels and it seems possible that an individualization of dosage can be performed depending on the woman’s response and what the specific goals for treatment are.

In order to determine the appropriate testosterone dose a previous study was performed in which three different doses, 10, 20 and 30 mg were given. We found that the 10 mg dose resulted in testosterone levels within the normal range, not exceeding 3.0 nmol/l after 2 weeks of treatment [13]. The higher supraphysiologic levels (mean 7.8 ± 5.2 nmol/l) now observed after a longer treatment period of three months are probably a result of an accumulation of testosterone in the skin. In spite of this finding no increased frequency of side effects compared to the placebo group was found. Mild side effects of testosterone such as increased facial hair growth and acne are most often reversible while other side effects such as clitorial enlargement and voice changes can be irreversible. In a study by Sherwin, where testosterone was given as an intramuscular injection, increased facial hair growth was found in 15–20% of the women [2]. Women in that study had testosterone levels between 7 and 10 nmol/l during the first week after injection.

In a study of nine women with long-term use of androgen seven had a clitorial enlargement. Five women of these women had used testosterone injections for more than five years and had testosterone levels of 6.6–14.9 nmol/l. A direct correlation between both duration of use as well as testosterone levels and clitoral size was found [19]. In the present study – in spite of high serum levels of testosterone – side effects during testosterone treatment were not different from placebo. Even so this risk must still be considered during longer treatments and regular monitoring of testosterone levels should be performed.

Also no changes in the lipid profile were observed which is probably a consequence of the route of administration. In studies where oral preparations have been used an unfavorable lipid profile has been observed

probably caused by altered liver protein synthesis [8]. It is therefore, preferable if a transdermal or parenteral method of administration can be used.

Testosterone is converted to estrogen in some target tissues and a concern in previous studies has therefore been an increased endometrial thickness. It has consequently been suggested that all women receiving testosterone should take progestogens to avoid hyperplasia of the endometrium [20]. All women in this study were on combined HRT and we found no increase in endometrial thickness during the six months study period.

Previously erythropoietin has been reported to increase during testosterone treatment and it has been suggested that androgens are a determinant of the red cell mass [6,7]. However, the observed rise in hemoglobin has been moderate and in our study hemoglobin levels remained unchanged during treatment.

In summary, 10 mg of a transdermaly applied testosterone gel had positive effects on several aspects of sexual life in postmenopausal women with ongoing HRT, such as frequency of sexual activity, orgasm, arousal, fantasies and sexual interest. Also several psychological variables were positively influenced. The given dose resulted, probably due to accumulation, in too high serum levels. Even if no negative effects of this were observed, monitoring of serum levels and a decreased dose, should be considered in future studies.

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