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Addition of testosterone to estrogen replacement therapy in oophorectomized women: effects on sexuality and well-being

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Key words: HORMONE REPLACEMENT THERAPY, ANDROGENS, TESTOSTERONE, SEXUALITY, WELL-BEING, MENOPAUSE

ABSTRACT

Objective To evaluate the effect of adding testosterone undecanoate 40 mg daily to estrogen replacement on sexual function, psychological well-being and self-esteem in surgically postmenopausal women.

Methods A letter of invitation to participate in the study was mailed to women who had undergone hysterectomy and bilateral oophorectomy for benign disorders during 1990–98. Fifty women, 45–60 years old, were consecutively recruited and randomly assigned to oral treatment with testosterone undecanoate 40 mg plus estradiol valerate 2 mg daily or placebo plus estradiol valerate 2 mg daily for 24 weeks. A double-blind design was chosen, with cross-over to the other regimen for another 24 weeks of treatment. Forty-four women completed the study. Outcome included scores on McCoy's sex scale questionnaire, the Psychological General Well-Being index and a self-esteem questionnaire, at baseline and after 24 weeks of either treatment. Serum concentrations of total testosterone, sex hormone binding globulin, free testosterone, dihydrotestosterone, androstenedione, estradiol, follicle stimulating hormone and luteinizing hormone were analyzed at baseline and after 24 weeks of both treatment regimens.

Results After 24 weeks, both treatment regimens had significantly improved some of the sexual variables. The addition of testosterone had a significantly better effect on the sex variables 'enjoyment of sex', 'satisfaction with frequency of sexual activity' and 'interest in sex'. The total McCoy score was significantly increased by both treatments, but there was a stronger effect when testosterone was also given. Although both regimens improved psychological well-being and self-esteem, we found no significant differences between testosterone–estrogen or estrogen alone at 24 weeks. Serum levels of all androgens, with considerable individual variation, increased significantly from baseline after 24 weeks of testosterone–estrogen treatment. Supraphysiological levels were achieved in a significant proportion of the women. Increases in estradiol and sex hormone binding globulin were less marked when testosterone was also given. Both treatments reduced gonadotropin levels.

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Conclusions The addition of testosterone undecanoate improved specific aspects of sexual function more than treatment with estrogen alone. Improvements in well-being and self-esteem were similar for both treatments. If testosterone undecanoate 40 mg daily should be used for clinical treatment, regular monitoring of androgen serum levels is needed.

INTRODUCTION

Treatment with estrogen is frequently given to replace the loss of ovarian function in women who have undergone hysterectomy and bilateral oophorectomy. Apart from synthesis of estrogen, the ovaries also contribute to serum androgen production. In both men and women, circulating androgen levels decline with age[1]. An androgen deficiency syndrome in the aging male has been energetically discussed, and some clinical criteria for this syndrome have been proposed. However, less information is available about androgen deficiency in women. Clinical experience shows that postmenopausal women often complain of persistent fatigue, reduced well-being and motivation, and low libido, despite adequate estrogen replacement[2,3]. After oophorectomy, serum testosterone levels in women decline rapidly by about 50%[4]. Thus, oophorectomized women form a well-defined group for studies of clinical symptoms and treatment of androgen deficiency.

Several preparations of testosterone in various doses and regimens have been used to treat this deficiency in women, but interpretation of the results of many studies has proved complicated[5,6]. Unlike estradiol treatment, oral testosterone cannot be given because of hepatotoxicity, and adverse effects on lipid metabolism[7]. Injections of testosterone have the disadvantage of causing fluctuating serum levels, but more stable testosterone levels can be achieved by subcutaneous implants or transdermal patches[3,5,8]. Testosterone undecanoate, an ester with a long-chain fatty acid linked to testosterone, was developed to overcome the low bioavailability and hepatic side-effects of an oral testosterone preparation. Most of this compound is absorbed by intestinal lymphatics, thereby avoiding the hepatic first pass[9]. Testosterone undecanoate has been used for a long time in men, but hardly any pharmacological studies have been carried out in women. In a recent short-term study, we gave testosterone undecanoate (40 mg/day) as replacement in postmenopausal women, and obtained serum levels of total testosterone of 3.2 (0.7–6.0) nmol/l[10].

This article reports the effects of testosterone undecanoate (40 mg/day) treatment in a randomized, double-blind, placebo-controlled, cross-over study. Surgically postmenopausal women were treated for 24 weeks with either estrogen–placebo or estrogen–testosterone. While endogenous androgens were low, the women did not complain of specific androgen deficiency symptoms at baseline. The primary end-points were sexual function, well-being and self-esteem.

METHODS

Participants

Women on the Stockholm county hysterectomy register during 1990–98 were mailed an invitation to participate in this study at the clinical trials unit at the Karolinska Hospital. After screening, 50 consecutive women were recruited. Inclusion criteria were age 45–60 years, a history of hysterectomy and bilateral salpingoophorectomy for benign disorders, such as fibroma and/or menorrhagia, body mass index (BMI) between 18 and 29 kg/m^2, blood pressure below 170 mmHg systolic and/or 105 mmHg diastolic and a normal mammogram within the past year. Exclusion criteria comprised previous use of hormone replacement therapy (within the past 2 months), other medication taken at the same time (other sex hormones, anabolic steroids, corticosteroids, danazol, calcium antagonists, beta-blocking agents, barbiturates, carbamazepines, griseofulvins, hydantoin, rifampicin, herbal/homeopathic therapy), history of or present premalignancies/malignancies, liver disease, cardiovascular, cerebrovascular or thromboembolic disorders, and present psychiatric disease. Furthermore, no regular use of tranquillizers and/or antihistamines, alcohol abuse or smoking of $\geq$ 10 cigarettes/day was allowed.

The study was a combined estrogen and testosterone trial, and specific symptoms, such as loss of libido or well-being, were not mandatory for inclusion. The mean age was 54.0 $\pm$ 2.9 years, mean BMI 25.7 $\pm$ 2.8 kg/m^2 and mean time since oophorectomy 4.6 $\pm$ 2.4 years. All women gave their written informed consent to participate, and the study was approved by the local ethics committee.

Study design, sample size, randomization and blinding

The study was randomized, double-blind and placebo-controlled. After inclusion and a wash-out period of 2 months, the women were randomly assigned to receive oral treatment with estradiol valerate 2 mg daily plus testosterone undecanoate 40 mg daily (E–T) or estradiol valerate 2 mg daily plus placebo (E–P). The treatment was continued for 24 weeks, and after cross-over switched to the other regimen for another 24 weeks.

Sample size was estimated from earlier studies using the McCoy sex scale questionnaire. The coefficient of correlation between treatments was assumed to be 0.30. Based on this assumption, the minimum number of women needed was 40.

The study medication used was individually numbered for each subject. The random assignment of subject code numbers over treatment groups was consecutively performed by the responsible trial nurse. Only the testosterone undecanoate and placebo were randomized, while the estrogen was given continuously to all women. Blinding was maintained until completion of the study.

Objectives and outcomes

The specific objective in this study was to evaluate the effects of adding testosterone undecanoate 40 mg daily to estrogen replacement in surgically postmenopausal women. The primary outcomes were sexual function, psychological well-being and self-esteem. Secondary objectives were effects on sex hormone levels and adverse events.

Interventions

McCoy's sex scale questionnaire was used to assess sexual life at baseline and after 24 weeks of each period of treatment. This questionnaire concerns a woman's sexual experience and responsiveness during the past 30 days, and contains 14 items on a 7-point scale regarding different aspects of sexual life, such as frequency of intercourse and orgasm, sexual pleasure and satisfaction with frequency of intercourse and orgasm, lubrication, dyspareunia, arousal, sexual fantasies and interest, feelings of attractiveness and satisfaction with partner. Each item and a total score were included.

Well-being was assessed with the Psychological General Well-Being (PGWB) index, concerning present emotional status and sense of subjective well-being or distress. It contains 22 questions and six subscales: vitality, self-control, well-being, general health, depressed mood and anxiety, and a total PGWB score. Both questionnaires are well established and have been used in previous studies of postmenopausal women[11,12].

All women were also asked to complete a third questionnaire deemed to assess self-esteem. This questionnaire comprised eight questions on a 1–4 scale, concerning a woman's view of her own abilities in social life and work. Each item and a total score were calculated.

The evaluation of side-effects included measurements of blood count, liver enzymes and serum creatinine after 6, 12, 24, 30, 36 and 48 weeks of treatment. Adverse events were recorded at each examination. Hirsutism and acne were classified as mild, moderate or severe. Clitoral enlargement was assessed by clinical examination.

Analytical methods

Venous blood samples were collected before and after 6, 12, 24, 30, 36 and 48 weeks of treatment. Serum was separated after centrifugation and stored at –20°C pending analysis. Serum concentrations of total testosterone were determined by radioimmunoassay (RIA) in untreated serum, using a commercial kit obtained from Diagnostic Products Corp., Los Angeles, CA, USA ('Coat-a-Count® Testosterone). 5α-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, USA. Serum concentrations of androstenedione were determined after extraction with diethyl ether by RIA, as described by Brody and co-workers[13,14]. Serum concentrations of sex hormone binding globulin (SHBG), estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH) were determined by chemiluminescence enzyme immunoassay, using commercial kits obtained from Diagnostic Products Corp. (Immulite®). Values of FSH and LH were expressed as U/l of 2nd IRP FSH 78/549 and 1st IRP LH 68/40.

Detection limits and within- and between-assay coefficients of variation were 0.1 nmol/l, 6% and 10% for total testosterone, 14 pmol/l, 4% and 8% for DHT, 0.6 nmol/l, 6% and 10% for androstenedione, 3 nmol/l, 5% and 8% for SHBG, 73 pmol/l, 8% and 9% for estradiol, 0.1 U/l, 8%

and 8% for FSH, and 0.7 U/l, 6% and 9% for LH, respectively.

Apparent concentrations of free testosterone were calculated from values for total testosterone, SHBG and a fixed albumin concentration of 40 g/l, by successive approximation using a computer program based on an equation system derived from the law of mass action[15].

Statistical analysis

Values are expressed as mean, median, standard deviation (SD) and centiles. The change from basal values was calculated using the Wilcoxon signed-ranks test. Differences between treatment periods were assessed using Fisher's permutation test, and we found no significant treatment-by-sequence group interaction, indicating a 'carry-over effect'. Correlations were assessed with Spearman's rank correlation test. Differences within groups were assessed using the χ^2 test. A p value < 0.05 was considered statistically significant.

RESULTS

Recruitment and participant flow

A total of 65 women were assessed for eligibility during a recruitment period of 6 months. Of these women, 15 did not fulfil the inclusion criteria. Fifty consecutive women were randomly assigned to treatment regimen A (starting with E–T then E–P) or B (starting with E–P then E–T). Five women were excluded owing to poor drug compliance, and one withdrew because of migraine during the E–P period. Thus, 44 women completed the study (Figure 1).

Baseline and outcomes

Endocrine data at baseline and after 24 weeks of E–P or E–T treatment are given in Table 1. Mean values for total testosterone, free testosterone, DHT and androstenedione had all increased significantly from baseline after 24 weeks of E–T treatment. The individual androgen values varied considerably, and 25 women exceeded the upper

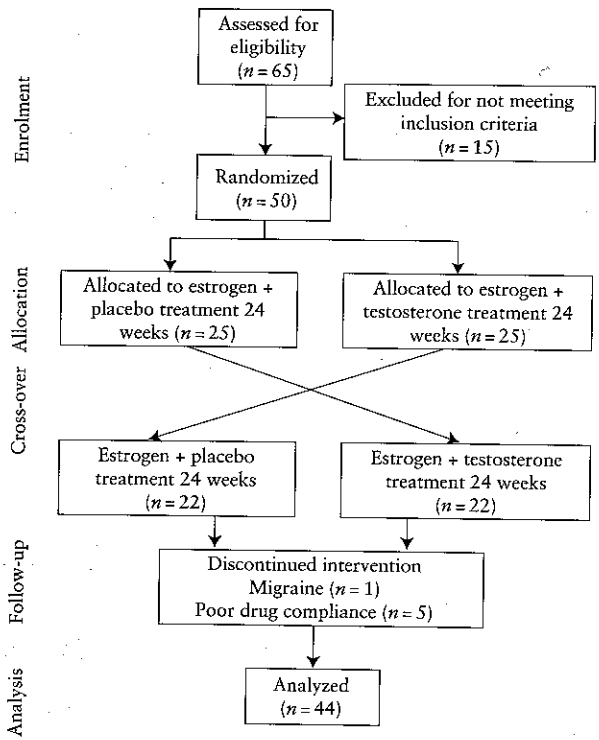

Figure 1 Flow diagram of randomized cross-over study

reference limit of total testosterone and free testosterone after 24 weeks of E–T treatment (Table 1). The increase in estradiol and SHBG during estrogen treatment was less marked when testosterone was added. Both treatment regimens reduced gonadotropin levels to a similar extent. The serum concentrations of total testosterone, free testosterone, androstenedione and DHT were significantly higher, while those of SHBG and estradiol were significantly lower after 24 weeks of E–T treatment than after E–P.

The effects on various aspects of sexuality, assessed by the McCoy sex scale questionnaire, are given in Table 2. 'Lubrication', 'dyspareunia', 'interest in sex' and 'sexual thoughts and fantasies' had improved significantly after 24 weeks on both regimens. While the women were taking testosterone, significant effects were also seen in 'enjoyment of sex', 'satisfaction with frequency of sexual activity', 'arousal', 'frequency of and satisfaction with orgasm' and 'feeling of sexual attractiveness to partner'. Of the 14 items on the questionnaire, only four variables related to sex remained unaffected during treatment. After 24 weeks of treatment, the addition of testosterone had a significantly better effect on the variables 'enjoyment of sex', 'satisfaction with frequency of sexual activity' and 'interest in sex'. The total McCoy score was significantly increased by both treatments, but the addition of testosterone exerted a stronger effect. Women with a low pretreatment score (< 4) for 'enjoyment of sex', 'interest in sex' and 'satisfaction with frequency of sexual activity' showed significantly more improvement at the end of both treatments ($p < 0.003$).

Table 3 indicates results of the Psychological General Well-Being index calculated for the subscores and as a total score. During both treatments, all subscores and total PGWB index had increased after 24 weeks. The response was most marked for 'positive well-being' and 'vitality', but there were no significant differences between the treatments in any of the subscores or total PGWB index.

Total self-esteem increased significantly from a median baseline value of 24.0 (25th–75th centiles 22.0–28.0) after 24 weeks of treatment with E–P (27.0, 23.0–30.0, $p < 0.007$) or E–T (26.0, 23.0–30.0, $p < 0.001$), but no significant differences were noted between E–T and E–P after 24 weeks in any of the self-esteem variables or the total index.

We found no correlations between McCoy, PGWB or total self-esteem variables, on the one hand, and hormones, on the other, after 24 weeks, neither in terms of absolute values or in terms of differences between treatment and basal values. Likewise, no significant correlations were found between age or time since oophorectomy and the McCoy, PGWB or total self-esteem variables (data not given).

Adverse events

There were no serious adverse events. A subjective increase in facial and/or thigh and lower abdominal hair growth was reported by three women during the E–T period and by three other women during the E–P period. The maximum intensity of hair growth was defined as mild by all women. Acne on the face and/or breast was seen in three

Table 1 Hormone concentrations at baseline and after 24 weeks of estradiol–placebo (E–P) or estradiol–testosterone (E–T) treatment ($n = 44$; mean ± SD). Clinical reference values for postmenopausal women are given

Hormone (normal range)	*Baseline*	*E–P 24 weeks*	*E–T 24 weeks*	*E–P vs. E–T 24 weeks*
Total T (nmol/l) (< 3)	0.8 ± 0.45	0.9 ± 1.3 NS	4.9 ± 4.1***	***
SHBG (nmol/l) (20–110)	60.2 ± 39.0	100.9 ± 41.8***	70.0 ± 27.4**	***
fT (pmol/l) (< 35)	15.4 ± 8.5	9.2 ± 6.3***	81.0 ± 64.1***	***
DHT (pmol/l) (< 700)	244.4 ± 121.1	282.2 ± 136.8 NS	4246.4 ± 4258.0***	***
A-4 (nmol/l) (1.0–6.0)	4.9 ± 1.8	4.3 ± 1.4**	8.1 ± 3.6***	***
E_2 (pmol/l) (< 100)	< 73	245.1 ± 151.3***	173.1 ± 100.4***	***
FSH (IU/l) (34–158)	83.3 ± 28.2	44.1 ± 26.4***	44.7 ± 26.5***	NS
LH (IU/l) (12–93)	36.5 ± 13.5	28.0 ± 14.0***	27.1 ± 15.2***	NS

**$p < 0.01$; ***$p < 0.001$; T, testosterone; SHBG, sex hormone binding globulin; fT, free testosterone; DHT, dihydrotestosterone; A-4, androstenedione; E_2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; NS, not significant

Table 2 Scores on McCoy sex scale questionnaire at baseline and after 24 weeks of treatment with estradiol–placebo (E–P) or estradiol–testosterone (E–T) (n = 44; mean, median (25th–75th centile)

McCoy item	*Baseline*	*E–P 24 weeks*	*E–T 24 weeks*	*E–P vs. E–T 24 weeks*
Enjoyment of sex	4.2, 4.0 (3.0–6.0)	4.7, 5.0 (4.0–6.0) NS	5.2, 5.5 (5.0–6.0)***	*
Satisfaction with frequency of sexual activity	4.0, 4.0 (3.0–5.0)	4.2, 4.0 (3.0–5.0) NS	4.7, 5.0 (4.0–6.0)**	*
Coital frequency	3.7, 4.0 (2.0–5.0)	3.9, 4.0 (2.0–5.0) NS	4.0, 4.0 (3.0–5.0) NS	NS
Sexual thoughts and fantasies	3.2, 3.0 (2.0–5.0)	3.8, 4.0 (3.0–5.0)*	4.0, 4.0 (3.0–5.0)***	NS
Arousal	4.3, 4.0 (3.0–6.0)	5.0, 5.0 (4.0–6.0) NS	5.1, 6.0 (4.0–6.0)**	NS
Lubrication	2.9, 2.0 (1.0–5.0)	2.0, 2.0 (1.0–3.0)***	2.1, 2.0 (1.0–2.0)**	NS
Frequency of orgasm during intercourse	4.2, 4.0 (3.0–5.8)	4.4, 4.5 (3.25–6.0) NS	4.6, 5.0 (4.0–6.0)**	NS
Satisfaction with orgasm	4.5, 4.5 (3.0–6.0)	4.8, 5.0 (4.0–6.5) NS	5.0, 5.0 (4.0–7.0)*	NS
Dyspareunia	1.9, 1.0 (1.0–2.0)	1.4, 1.0 (1.0–2.0)*	1.3, 1.0 (1.0–2.0)**	NS
Feeling of sexual attractiveness	4.1, 4.0 (3.5–5.0)	4.4, 4.0 (4.0–6.0) NS	4.5, 4.5 (4.0–6.0) NS	NS
Feeling of sexual attractiveness to partner	4.8, 5.0 (4.0–6.0)	5.0, 5.0 (4.0–6.0) NS	5.1, 5.0 (4.0–6.0)*	NS
Interest in sex	3.0, 3.0 (1.0–4.0)	3.8, 4.0 (3.0–5.0)*	4.3, 4.0 (3.0–6.0)*	*
Satisfaction with partner as a lover	5.2, 5.0 (4.0–6.0)	4.9, 5.0 (4.0–6.8) NS	5.2, 6.0 (4.0–6.0) NS	NS
Erectile dysfunction in partner	5.8, 7.0 (6.0–7.0)	5.9, 7.0 (5.5–7.0) NS	6.2, 7.0 (6.0–7.0) NS	NS
Total score	61.4, 61.0 (37.0–88.0)	68.7, 70.0 (28.0–94.0)**	72.1, 73.0 (41.0–94.0)***	*

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; NS, not significant

Table 3 Psychological General Well-Being (PGWB) index at baseline and after 24 weeks of estradiol–placebo (E–P) or estradiol–testosterone (E–T) treatment (n = 44; mean, median (25th–75th centile)

PGWB index	*Baseline*	*E–P 24 weeks*	*E–T 24 weeks*	*E–P vs. E–T 24 weeks*
Anxiety	23.1, 23.0 (20.8–26.0)	24.6, 25.5 (23.0–27.8)*	24.5, 25.0 (22.0–27.0)*	NS
Depressed mood	15.1, 16.0 (13.0–17.0)	16.2, 16.0 (16.0–18.0)***	16.3, 17.0 (16.0–18.0)***	NS
Positive well-being	15.3, 15.0 (12.0–18.0)	17.0, 18.0 (15.0–19.0)**	17.3, 18.0 (15.8–20.0)***	NS
Self-control	14.2, 15.0 (12.0–16.2)	15.3, 16.0 (15.0–17.0)**	15.8, 16.0 (15.0–17.0)***	NS
General health	15.0, 16.0 (12.8–17.0)	16.0, 17.0 (15.0–18.0)*	15.8, 16.0 (15.0–17.0) NS	NS
Vitality	15.8, 15.5 (13.0–19.0)	18.0, 18.0 (16.0–20.0)**	18.2, 19.0 (15.2–21.0)***	NS
Total score	98.4, 97.0 (84.0–113.0)	107.3, 110.5 (102.0–116.8)**	107.8, 112.0 (99.8–117.2)**	NS

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; NS, not significant

women during the E–T period and one during the E–P period. The acne was defined as mild to moderate. In one woman, both mild facial hair growth and acne occurred during E–T treatment. Five women reported a feeling of mild body swelling during the E–T period, but no weight gain was recorded. All side-effects were reversible. There was no change in blood count, liver enzymes or serum creatinine during the study.

DISCUSSION

Sexuality is a complex dimension of personality, influenced by hormonal, psychological and

cultural factors. Circulating estrogens and androgens may affect female sexuality in various ways. Estrogens are important for the physiological sexual response, whereas androgens are needed for sexual interest and desire[16]. Several questionnaires have been used to assess quality of sexual life, and therefore it is difficult to interpret previous studies in this field. In the present study we used the McCoy sex scale questionnaire[11,12], a well-established instrument covering various aspects of sexual function.

We found that 24 weeks of treatment with estrogen significantly improves 'sexual thoughts and fantasies', 'interest in sex', 'lubrication' and 'dyspareunia' in oophorectomized women. The effects on lubrication and dyspareunia are in accord with many previous studies in postmenopausal women, in which estrogen treatment improved sexual function by relieving vaginal symptoms[17,18]. Studd and colleagues reported that estrogens alone improved sexual satisfaction in women with atrophic vaginitis causing dyspareunia, whereas women having a low libido and no coital discomfort did not benefit. However, libido was improved by giving testosterone in addition to estrogen[19]. Also in the present study, the positive effects of estrogen on sexual function were enhanced by adding testosterone. After 6 months of treatment the total McCoy score was significantly higher on E–T treatment, compared with estrogen alone.

According to the McCoy scale, only a few items, such as satisfaction with partner and erectile dysfunction, were unaffected by the combined E–T treatment. The strongest effect was noted for 'enjoyment of sex' and 'sexual thoughts and fantasies'. Both these factors contribute to a basal sexual drive of desire and enjoyment, in which androgens apparently are important. We found that estrogen alone also enhances 'sexual thoughts and fantasies' and 'interest in sex', which may reflect an improvement in physical symptoms. On the other hand, the effect of the combined treatment on these variables was much more marked.

Oral estrogens counteract androgen effects by increasing SHBG, thereby reducing biologically active testosterone[20]. In our study, SHBG increased and free testosterone fell significantly from baseline values after 24 weeks of oral estrogen treatment. The addition of testosterone to oral estrogens partly counteracts these changes, and contributed to the improvement in sexual function found in our study. When comparing the two treatment regimens at 24 weeks, we found a significant difference in favor of E–T in the scores of the sexual items 'enjoyment of sex', 'interest in sex' and 'satisfaction with frequency of sexual activity'. Our results concerning androgen effects on sexual function are in accord with those reported in previous studies. Administration of testosterone preparations to various groups of women significantly improved items of sexual activity such as 'satisfaction', 'pleasure' and 'orgasm'[6], 'arousal'[5], and 'frequency of activity' and 'pleasure/orgasm'[8], compared with placebo or estrogen alone. However, the stimulatory effect of testosterone on sexual function in previous studies has been demonstrated in selected groups of women complaining specifically of reduced libido[6,8,19]. In the present study, we found evidence for sexual improvement after administration of testosterone even in women without pre-existing sexual dysfunction. Certainly, the results should be interpreted with caution, since supraphysiological androgen levels were achieved in a significant proportion of the women.

Although hormones are important for sexual function, it has been difficult to show correlations between libido and endogenous androgens. A negative correlation between the serum estradiol/testosterone ratio and coital frequency has been reported in perimenopausal women[11]. In a cross-sectional study of perimenopausal women, we found positive correlations between arousal, desire and satisfaction with endogenous androgens[21]. On the other hand, in a longitudinal study during the peri- and postmenopausal periods, Dennerstein and colleagues found that the relationship with the partner was the most important variable affecting sexuality, compared with hormones[22].

In the present study, we did not find any significant correlations between the various hormone levels and McCoy items after 24 weeks of treatment.

Treatment with estrogen alone has a positive effect on general well-being and quality of life[12,23]. The addition of an androgen to an estrogen has been reported to improve energy, well-being and mood even more in oophorectomized women during 3 months of observation[8,24]. In our study, a significant improvement was seen in nearly all subscores and total PGWB index after 24 weeks of E–P and E–T treatment. However, there were no apparent differences between the two regimens in any subscores or total PGWB index after treatment for 6 months. This lack of difference in contrast with previous findings, apart from study duration may also be due to variation in study

population. In our study, women were included who had no impairment in well-being and sexuality before treatment. The mean total PGWB score at baseline was 98 of a possible maximum of 132. This value is in good agreement with previous data from an unselected non-patient population of Swedish women (mean score 103)[25] and early postmenopausal women without symptoms (mean score 112)[26]. Relatively high baseline values give less room for significant increases. Still, we found both treatment regimens to improve total PGWB. An increase of more than 3.5 points has been suggested to be of clinical importance[27]. It could be that the PGWB questionnaire is not sensitive enough to discriminate between effects of estrogen and androgen on general well-being.

From a clinical point of view, a depressed mood might be due to low self-esteem. Mood is an important part of psychological general well-being. It has been suggested that a reduction in sexual interest is related to a low level of endogenous androgens and depressed mood[28,29]. Low concentrations of the major adrenal androgen dehydroepiandrosterone sulfate (DHEAS) were associated with depressed mood in postmenopausal women. Replacement with DHEA improves physical and psychological well-being[30]. We found a significant improvement in self-esteem from basal values after treatment with E–P or E–T after 24 weeks, but no significant difference between the treatments.

Until recently, little information on the effects of testosterone undecanoate in women has been available, although this compound has been used in men for decades. We found a dose of 40 mg/day, in spite of individual high androgen levels, to be well tolerated in oophorectomized women. Only a few mild side-effects were reported during 6 months of treatment. In a previous pharmacological study, peak serum levels were recorded 2–4 h after oral intake of testosterone undecanoate, then followed by a marked decline[10]. The present values (Table 1) were single point estimates, and the time interval from administration was not standardized. While no serious adverse events were observed during treatment, long-term effects were not investigated. It is evident that if testosterone undecanoate in a dose of 40 mg/day should be used for clinical treatment in individual women, regular monitoring of androgen serum levels is needed.

As expected, during treatment with estrogen alone, estradiol and SHBG increased and LH and FSH serum levels fell. When testosterone undecanoate 40 mg/day was added, circulating androgens increased significantly and estradiol levels fell slightly. In this study, we used estradiol valerate, which, like testosterone undecanoate, is dependent on esterase activity for the liberation of active hormone. Testosterone undecanoate may act as a competitive inhibitor of valerate hydrolysis[31,32].

In summary, the addition of testosterone undecanoate improved specific aspects of sexual function, compared with treatment with estrogen alone. Improvement in general well-being and self-esteem occurred with both estrogen–testosterone and estrogen–placebo treatment.

Conflict of interest Nil.

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