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Clinical trial paper

The benefits of androgens combined with hormone replacement therapy regarding to patients with postmenopausal sexual symptoms

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Abstract

Objective: To evaluate the benefits and risks of hormone replacement therapy (HRT) combined with methyltestosterone (MT) in postmenopausal women with sexual dysfunction.
Design: This study was a randomized, double-blind, placebo-controlled and crossover trial. Eighty-five women using HRT were divided into four treatment groups: GI–HRT plus placebo for 4 months; GII–HRT plus MT 2.5 mg/day for 4 months; GIII–HRT plus placebo for 2 months and then replaced with HRT plus MT 2.5 mg/day for 2 months; GIV–HRT plus MT 2.5 mg/day and then replaced with HRT plus placebo for 2 months. Blood was collected at baseline, after 2 months (T1) and 4 months (T2) of treatment for hormone determinations of estradiol, FSH, total and free testosterone, GOT, GPT, glucose, total and fractions of cholesterol and triglycerides. All participants answered clinical questions and a validated questionnaire of modified McCoy's sex scale.
Results: The association of HRT with MT 2.5 mg/day did not significantly change liver enzymes or increase cardiovascular risk factors. The patients of GII, GIIII and GIV when using MT presented amelioration of sex symptoms, mainly satisfaction and desire ($p < 0.01$); however, GIII at T1 (1.3 ± 0.3) presented similar problem score results as compared to GIII at T2 (1.5 ± 0.6).
Conclusion: All data suggest that combined HRT-androgen therapy may be beneficial for postmenopausal women receiving HRT who continue to complain of sexual difficulties or for postmenopausal women with sexual complaints who are not undergoing estrogen therapy.

Keywords: Sexual disturbance; Postmenopause; Methyltestosterone; Hormone replacement therapy

1. Introduction

The androgen decline associated with menopause may contribute to muscle wasting, osteoporosis, loss of energy, changes in mood and depression, decreased

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libido and finally impaired sexual function. Although androgens do not change significantly in relation to the menopausal transition, their levels fall slowly with age [1]. In fact, there is a decline in the adrenal and ovarian androgen production, including dehydroepiandrosterone (DHEA), DHEA sulfate androstenedione and testosterone after menopause [1–5]. In addition, some authors considered that testosterone might be the hormone of sexual desire and motivation [4–6]. However, some authors disagree about the notion that local vaginal disturbances are related to androgen level reduction [7–9]. Some authors suggested that low sexual desire might be related to problems with marriage or partner relationship [10].

The administration of hormone replacement therapy (HRT) does not completely resolve climacteric symptoms such as reduced libido, insomnia and the loss of physical energy in some naturally menopausal subjects nor in those undergoing surgically induced menopause [11–15]. In some of these cases, the addition of androgens to HRT has not only been shown to be more efficacious in resolving vasomotor symptoms than the administration of estrogens alone [16] but has also been found to improve some aspects related to the psychosexual sphere and quality of life [17]. However, there is controversy regarding sexual decline in women.

Although some authors reported that the female sexual decline was related more to decreasing estradiol than to androgen levels [16,18], other studies pointed to the importance of testosterone in improving complaints concerning sexual disturbance [3,4,10,12]. In fact, Kaplan and Owett [19] described the female androgen deficiency syndrome that correlated the reduction in libido and interest in sex with the low levels of testosterone. However, androgens present some side effects. In fact, some studies reported some concerns about testosterone treatment, such as reduction in HDL-cholesterol, increase in LDL-cholesterol and liver disturbance, as well as some virile signs [20–23].

Some authors have emphasized the beneficial effects of estrogen–androgen combinations on muscular and bone mass (the main risk factor for fractures) and the lipid profile, which is a well-recognized parameter of cardiovascular risk [17,24]. However, it has also been recently pointed out that the reduction in cardiovascular risk observed during treatment may only be partially explained by the favorable changes in lipid profiles induced by HRT. However, other authors did not confirm those benefits [25]. In addition, the WHI study found that combined continuous conjugated equine estrogens and medroxyprogesterone acetate (CEE/MPA) increased the relative risk of coronary heart disease and stroke [26].

Because androgens combined with HRT are still thought to be a useful therapeutic option, particularly in surgically castrated patients, it may be worth evaluating their effects on sexual phenomena. The aim of this study was to evaluate whether the addition of androgens to HRT might interfere with sexuality and cardiovascular risk in postmenopausal women.

2. Patients and methods

This study was a randomized, double-blind, placebo-controlled and crossover trial designed to investigate the extent to which methyltestosterone 2.5 mg/day (Diosynth, Apeldoorn, Netherlands) combined with HRT (conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 5 mg/day, Wyeth, São Paulo, Brazil) improved sexual symptoms, affected hepatic enzyme levels and increased cardiovascular risk in postmenopausal women. All patients volunteered to enter the double-blind investigation because they were dissatisfied with their current treatment with HRT for sexual function. Before the administration of HRT, all participants had intact uterus, amenorrhea for at least 1 year, absence of any type of hormonal treatment during the previous 12 months, serum follicle-stimulating hormone (FSH) levels exceeding 40 IU/l and estradiol (E_2) < 25 pg/ml.

This trial was approved by the institutional review board and involved 85 patients followed at the Outpatient Menopause Clinic of the Gynecology Department, Federal University of São Paulo/"Escola Paulista de Medicina". All patients had been on HRT for at least 1 year and gave their informed consent regarding the new regimen. None of the patients were suffering from any major diseases (hypertension, heart disease, diabetes, renal or peripheral vascular diseases) and none of them had undergone surgical removal of the uterus or ovaries while using HRT.

Subjects for the present study consisted of women aged 49–63 years who attended screening and visits to establish baselines. To be eligible for this study, women had to report complaints of sexual dysfunction

Table 1
Design of treatment

	Treatment		
	Baseline	0–60 days	61–120 days
GI	HRT	HRT + P	HRT + P
GII	HRT	HRT + MT	HRT + MT
GIII	HRT	HRT + P	HRT + MT
GIV	HRT	HRT + MT	HRT + P

HRT, hormone replacement therapy; MT, methyltestosterone; P, placebo.

acquired in the postmenopausal period and to regularly use HRT. In addition, all participants were sexually active and satisfied with the performance of their partners. None of patients took other medications or had other health problems or postmenopausal symptoms that could interfere with their sexual life including hot flashes, insomnia and other psychosomatic symptoms. The duration of the study was from June 2001 to March 2002.

After initial screening, 85 women were selected from over 400 patients and underwent mammography, transvaginal pelvic ultrasound and a pap test before being assigned to the four different regimens of treatment in a sequence determined by a computerized random-number generator. All patients received a numerical randomized envelope, which had a letter inside labeled GI, GII, GIII and GIV corresponding to HRT plus placebo for 4 months; HRT plus methyltestosterone 2.5 mg/day for 4 months; HRT plus placebo for 2 months and then replaced with HRT plus methyl testosterone 2.5 mg/day for 2 months; HRT plus methyltestosterone 2.5 mg/day for 2 months and then replaced with HRT plus placebo for 2 months, respectively (Table 1). Lactose capsules were used as placebo in this study. Five patients ceased to participate in this study because of abnormal uterine bleeding ($n = 1$) and private reasons ($n = 4$).

During the study, the subjects and study personnel were not informed about the regimens of treatment. To avoid compromising the double-blind design, the occurrence of side effects or physical changes, such as menstrual bleeding was recorded by an independent gynecologist. Study drugs were packaged in two 30-day flasks (30 capsules each). The patients were instructed to take one capsule of each flask per day during the study. The follow-up was conducted by a gynecologist who did not participate in the screening part of this study or the distribution of the drugs. Also, this physician evaluated the patients for acne and hirsutism using the semiquantitative scale and Ferriman–Gallwey scoring system, respectively.

When establishing baseline, the patients also underwent a transvaginal ultrasound (TVS) evaluation to measure endometrial thickness. The ultrasound examinations were performed using Toshiba SAL-38B real-time ultrasound equipment fitted with a 5.0-MHz probe. The endometrial echo was measured using the thickest area of the endometrium in the superior third of the uterine body. Thickness was determined in the anteroposterior direction from the echogenic interface of the endometrium–myometrium junction on both sides. The operator, who performed all examinations, was blinded to the patient's clinical data. Also, blood pressure was measured by another physician with a mercury sphygmomanometer after the participant had been sitting quietly for at least 5 min.

At each time point, height and weight were measured with subjects wearing lightweight clothing and no shoes; BMI (calculated as kg/m^2) was used as an estimate of obesity. After fasting for 12 h, blood samples were obtained by vein puncture at baseline and after 2 (T1) and 4 months (T2) to test the levels of total cholesterol, its high-density lipoprotein (HDL) and low-density lipoprotein (LDL) fractions, triglycerides, glucose, hepatic enzymes, free and total plasma testosterone. Total cholesterol was assayed by means of the colorimetric enzymatic CHOD-PAP test, HDL-cholesterol by homogeneous colorimetric enzymatic HDL plus test and triglycerides by colorimetric enzymatic GPO-PAP test; all three assays being performed with Hitachi 917 equipment with Roche reactants. Total testosterone and estradiol were measured by means of the colorimetric enzymatic IMMUNOLITE 2000 test (DPC, Los Angeles, CA). The analytical sensitivity for total testosterone is 15 ng/dl (0.5 nmol/l) and the percentage of croos-reactivity with methytestosterone is 0.8% (DPC). Free testosterone was determined using the Coat-A-Count kit (DPC). Glucose, GOT (glutamyl oxaloacetic transaminase) and GPT (glutamyl pyruvic transaminase) were measured using a commercial kit (Bioclin, Belo Horizonte, Brazil). The SHBG was measured by a solid-phase, two-site chemiluminescent enzyme immunometric assay using the Immulite 2000 automated analyzer (DPC), intra-assay and interassay

Table 2
Modified McCoy sex scale

Unless otherwise stated, answer intensity questions with: 0 = none; 1 = a little bit; 2 = moderately; 3 = quite a bit; 4 = extremely				
(1) Are you satisfied with your present frequency of sexual activity?	0	1	2	3
(2) How many times a day have you had sexual thoughts or fantasies during the last month?	0	1	2	3
(3) How enjoyable is sex for you?	0	1	2	3
(4) How often do you feel aroused or excited (for instance increased heart beat, flushing, vaginal wetness, heavy breathing)?	0	1	2	3
(5) How often do you have an orgasm during sex?	0	1	2	3
(6) How often do you suffer from lack of vaginal lubrication (wetness) during sex?	0	1	2	3
(7) How often do you suffer from pain associated with intercourse?	0	1	2	3

CVs are 6.5% and 8.7%, respectively; the detection limit is 0.2 nmol/l.

A validated questionnaire of the modified McCoy's sex scale [13] for Brazilian women on sexual behavior was also applied for baseline, T1 and T2, which was filled out on each visit in the presence of an observer. This questionnaire covers sexual experience and responsiveness during the last 30 days and contains seven items (Table 2). Each answer received a score from 0 to 3 where a high value indicated a high degree of satisfaction. Items 2 and 4 were grouped into the variable desire, 6 and 7 into "problems" and 2, 3, 4 and 5 into "satisfaction".

3. Statistical methods

The results are expressed as means and standard deviation (S.D.) and analyzed using two-way ANOVA and the multiple comparisons of Turkey. A $p = 0.05$ was considered statistically significant. The power analysis assumed a clinically meaningful difference for points between the four treatment groups with respect to the primary endpoint. Under these assumptions, 85 women were needed for 80% power.

4. Results

Patients were predominantly Caucasian in all groups. Table 3 shows that there were no statistically significant differences between the four patient groups in terms of age, years of menopause, maximum or minimum blood pressure and TVS or time in use of HRT. None of participants reported signs of hyperandrogenism, such as hair loss, facial hair or sebaceous secretions during all periods of this study (there is not a difference among groups in relation to acne semiquantitative scale and Ferriman–Gallwey scoring system). The side effects reported by three patients

Table 3
Clinical data of selected participants at baseline

	Baseline			
	GI	GII	GIII	GIV
Age (year)	56.6 ± 4.9	55.4 ± 4.7	55.9 ± 5.3	57.8 ± 4.2
Years after menopause	3.4 ± 1.3	3.3 ± 1.8	3.6 ± 1.6	3.5 ± 1.5
Max. BP (mmHg)	124 ± 9.7	124 ± 12.6	128 ± 7.9	126 ± 11.7
Min. BP (mmHg)	73 ± 9.5	74 ± 6.9	73 ± 8.2	74 ± 9.7
TVS (mm)	5.3 ± 1.4	4.7 ± 1.5	4.9 ± 1.6	4.8 ± 1.4
Use of HRT (months)	14.7 ± 2.9	14.1 ± 3.1	15.3 ± 3.3	14.8 ± 4.2

BP, blood pressure; TVS, transvaginal ultrasound; HRT, hormone replacement therapy.

Table 4
Hormonal profile of participants during the study

		GI	GII	GIII	GIV
Estradiol (pg/ml)	Baseline	50.9 ± 14.4	58.8 ± 11.5	61.5 ± 15.8	50.6 ± 15.6
	T1	52.9 ± 14.1	55.6 ± 9.5	63.9 ± 10.6	50.4 ± 10.8
	T2	57.2 ± 15.9	52.1 ± 17.8	62.6 ± 9.1	52.7 ± 19.1
FSH (IU/l)	Baseline	26.7 ± 5.9	29.3 ± 5.3	27.3 ± 3.4	26.7 ± 3.8
	T1	29.7 ± 5.9	23.6 ± 3.9	26.5 ± 6.2	22.8 ± 6.4
	T2	25.2 ± 7.2	23.6 ± 4.7	23.6 ± 4.9	24.8 ± 8.4
TT (ng/dl)	Baseline	32.9 ± 5.1	34.2 ± 9.7	31.6 ± 7.3	31.5 ± 5.7
	T1	33.4 ± 5.9	60.2 ± 5.7[a]	29.8 ± 2.9	63.1 ± 4.9[b]
	T2	28.9 ± 3.1	65.1 ± 4.9[c]	60.8 ± 4.1[d]	35.1 ± 6.2
FT (pg/ml)	Baseline	0.7 ± 0.1	0.7 ± 0.2	0.6 ± 0.3	0.7 ± 0.1
	T1	0.7 ± 0.3	4.1 ± 0.6[e]	0.7 ± 0.2	4.3 ± 0.5[f]
	T2	0.7 ± 0.2	4.5 ± 0.5[g]	4.1 ± 0.5[h]	0.7 ± 0.2
FT index	Baseline	1.07 ± 0.17	1.06 ± 0.31	1.04 ± 0.21	1.08 ± 0.19
	T1	1.09 ± 0.19	5.3 ± 0.58[i]	0.88 ± 0.11[j]	5.61 ± 0.55
	T2	0.99 ± 0.11	5.56 ± 0.69[k]	5.15 ± 0.76[l]	1.18 ± 0.31

TT, total testosterone; FT, free testosterone; FT index, total testosterone (ng/dl)/SHBG (nmol/l) × 3.47; (a) $p < 0.01$ compared to baseline of all groups, GI and GIII; (b) $p < 0.01$ compared to baseline of all groups, GI and GIII; (c) $p < 0.01$ compared to baseline of all groups, GI and GIV; (d) $p < 0.05$ compared to baseline of all groups, GI and GIV; (e) $p < 0.01$ compared to baseline of all groups, GI and GIII; (f) $p < 0.01$ compared to baseline of all groups, GI and GIII; (g) $p < 0.01$ compared to baseline of all groups, GI and GIV; (h) $p < 0.05$ compared to baseline of all groups, GI and GIV; (i) $p < 0.01$ compared to baseline of all groups, GI and GIII; (j) $p < 0.01$ compared to baseline of all groups, GI and GIII; (k) $p < 0.01$ compared to baseline of all groups, GI and GIV; (l) $p < 0.05$ compared to baseline of all groups, GI and GIV.

of GII who informed nervousness and aggressiveness after 2 months of treatment. Also, there was no statistically significant difference in endometrial thickness and blood pressure between the groups at any of the considered time points.

Levels of estradiol, total and free testosterone and FSH are presented in Table 4. Regardless of the treatment group, plasma levels of estradiol and FSH did not significantly change during the study. The total and free testosterone levels at baseline were not statistically different between the groups (values of total testosterone were superior to 15 ng/dl in all groups). Also, the free testosterone index of all groups was similar (Table 4). In addition androgen values (including the free testosterone index) significantly increased in the methyltestosterone-treated groups. However, in the crossover treatment groups (GIII and GIV), the levels of testosterone were low only when patients received placebo.

Table 5 shows the liver enzyme (GOT and GPT) values. There was no statistically significant difference between the four groups of patients in terms of baseline and after treatment. Additionally, no statistically significant changes in cardiovascular risk factors, such as glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and BMI were observed over time in any group.

The results of sex scale are shown in Table 6. The grouped desire and satisfaction scores were similar in all groups at baseline. Methyltestosterone treatment increased those scores: GII and GIV at T1, GII and GIII at T2. However, the problem score results were not as consistent as desire and satisfaction scores. No statistical difference was observed at baseline and T1 between GI and GII. However, GII presented a significant reduction in this score when the baseline result was compared to T1 and T2 data. Although GIII problem score at T1 was lower than that at baseline and the GIV result significantly decreased at T2, the crossover group (GIII and GIV) data failed to prove the methyltestosterone benefits to the problem score because the GIV values at T1 were similar to those at T2.

5. Discussion

Testosterone is an important metabolic and sex hormone produced by the ovary throughout a woman's

Table 5
Liver enzymes and cardiovascular risk factors during the study

		GI	GII	GIII	GIV
GOT (mU/ml)	Baseline	18.5 ± 2.7	19.1 ± 4.5	18.1 ± 2.3	16.4 ± 2.6
	T1	19.3 ± 3.4	19.7 ± 1.9	18.1 ± 1.8	18.6 ± 3.2
	T2	19.8 ± 3.1	20.9 ± 5.4	18.7 ± 2.8	17.9 ± 2.3
GPT (mU/ml)	Baseline	22.2 ± 2.4	22.7 ± 3.7	21.8 ± 3.3	23.1 ± 4.7
	T1	24.1 ± 2.3	24.1 ± 3.5	22.3 ± 3.2	25.2 ± 2.5
	T2	24.4 ± 4.4	26.1 ± 6.1	21.9 ± 3.1	24.5 ± 4.9
Glucose (mg/dl)	Baseline	83.7 ± 9.1	79.8 ± 14.6	83.8 ± 11.7	86.3 ± 11.2
	T1	79.3 ± 11.5	84.1 ± 9.1	84.5 ± 8.7	78.5 ± 9.6
	T2	79.5 ± 11.9	85.1 ± 12.5	77.4 ± 8.6	83.5 ± 10.1
Total cholesterol (mg/dl)	Baseline	213.1 ± 46.9	195.4 ± 28.8	209.4 ± 34.1	210.2 ± 41.3
	T1	184.7 ± 40.9	183.6 ± 25.5	181.6 ± 39.7	194.1 ± 38.9
	T2	187.6 ± 35.1	170.5 ± 16.6	176.1 ± 43.3	204.6 ± 37.8
HDL-cholesterol (mg/dl)	Baseline	49.1 ± 10.4	52.7 ± 14.6	50.8 ± 6.9	49.1 ± 15.5
	T1	45.6 ± 115.5	40.8 ± 14.6	51.7 ± 9.4	39.6 ± 15.3
	T2	48.9 ± 15.9	44.7 ± 7.8	42.7 ± 9.4	40.4 ± 7.2
LDL-cholesterol (mg/dl)	Baseline	160.1 ± 26.9	140.4 ± 28.8	152.4 ± 34.1	156.2 ± 31.3
	T1	130.7 ± 20.9	140.6 ± 25.5	121.6 ± 39.7	157.1 ± 38.9
	T2	130.6 ± 25.1	130.5 ± 16.6	140.1 ± 43.3	162.6 ± 37.8
Tryglirecides (mg/dl)	Baseline	129.3 ± 38.5	135.5 ± 33.5	141.1 ± 39.1	135.2 ± 35.2
	T1	132.6 ± 35.2	142.5 ± 32.9	139.8 ± 41.1	137.9 ± 34.2
	T2	141.2 ± 36.8	132.8 ± 39.5	145.6 ± 38.4	142.5 ± 36.7
BMI (kg/m^2)	Baseline	27.2 ± 3.6	26.9 ± 2.5	28.1 ± 3.4	27.9 ± 2.9
	T1	27.1 ± 3.4	27.4 ± 2.5	28.5 ± 3.2	27.8 ± 3.3
	T2	27.1 ± 3.2	28.2 ± 3.3	28.3 ± 3.3	27.4 ± 3.1

Table 6
Sex score of participants during the study

		GI	GII	GIII	GIV
Desire	Baseline	1.0 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	0.8 ± 0.3
	T1	1.1 ± 0.5	2.5 ± 0.4[a]	1.3 ± 0.5	3.1 ± 0.6[b]
	T2	1.0 ± 0.4	2.6 ± 0.5[c]	2.6 ± 0.6[d]	1.6 ± 0.3
Satisfaction	Baseline	0.4 ± 0.3	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.2
	T1	0.9 ± 0.2	1.9 ± 0.2[e]	1.4 ± 0.4	2.0 ± 0.3[f]
	T2	1.0 ± 0.3	2.1 ± 0.3[g]	2.4 ± 0.3[h]	1.3 ± 0.2
Problem	Baseline	1.9 ± 0.9	3.2 ± 0.8	2.8 ± 0.5	2.2 ± 0.7
	T1	1.6 ± 0.5	1.2 ± 0.3[i]	1.3 ± 0.3[j]	2.1 ± 0.7
	T2	1.4 ± 0.4	0.7 ± 0.3[k]	1.5 ± 0.6	0.6 ± 0.3[l]

(a) $p < 0.01$ compared to baseline of all groups and $p < 0.05$ compared to GI and GIII; (b) $p < 0.01$ compared to baseline of all groups, GI and GIII; (c) $p < 0.01$ compared to baseline of all groups and $p < 0.05$ compared to GI and GIV; (d) $p < 0.01$ compared to baseline of all groups and $p < 0.05$ compared to GI and GIV; (e) $p < 0.05$ compared to baseline of all groups, GI and GIII; (f) $p < 0.05$ compared to baseline of all groups, GI and GIII; (g) $p < 0.05$ compared to baseline of all groups, GI and GIV; (h) $p < 0.05$ compared to baseline of all groups, GI and GIV; (i) $p < 0.05$ compared to GII and GIII baseline; (j) $p < 0.05$ compared to GII and GIII baseline; (k) $p < 0.05$ compared to baseline of other groups and $p < 0.01$ compared to GII baseline; (l) $p < 0.05$ compared to baseline of all groups, GIV at T1 and GI and GIII at T2.

lifetime, with levels changing at different times of life and under certain medical conditions. Postmenopausal changes in sexual function may be related to decreasing production of ovarian and adrenal androgens [5,7,11–13]. Our results showed an improvement in desire and sensation score with an increase in testosterone levels without severe complaints or risks related to methyltestosterone administration.

Some studies reported that endogenous androgens had been observed to play an important role in psychosexual functioning in women during the menstrual cycle [24,27] and in the perimenopausal transition, during which testosterone levels decline [28]. However, there are some reports on androgen side effects in women, such as hirsutism, increased facial oiliness, acne, deepening voice, hostility, weight gain, alopecia, elevated liver functions, lower HDL levels and (rarely) carcinoma [29,30]. However, other double-blind studies did not mention these side effects in menopausal women after estrogen–androgen treatment [11,17]. In addition, in a review of the safety literature on estrogen–androgen, Gelfand and Wiita [31] found that there are no published reports of serious hepatic or cardiovascular events with postmenopausal estrogen–androgen therapy. It is possible that administration together with estrogens may reduce the side effects of androgens on the liver and cardiovascular systems in women. This hypothesis is also supported by our results. This fact suggested that methyltestosterone 2.5 mg/day combined with HRT might be safe in sexual disturbance treatment for at least a short time.

In postmenopausal women, decrease in testosterone may be one of many possible causes of decreasing sexual desire and satisfaction; however, disorders of desire are complex and require careful study. Some studies demonstrate that testosterone replacement/supplementation may be appropriate for a small percentage of women who complain of decreased desire [2–8,11,13]. Many women experiencing the clinical symptoms of androgen deficiency and low free testosterone levels respond well to testosterone replacement therapy. In fact, our data demonstrated that an increase in free testosterone is related to improvement in sex activity frequency and enjoyable excitation, orgasm and fantasy. Regardless of androgen type, dose or administration route, other studies found results similar to ours. In fact, Davis et al. [32] observed that estrogen–androgen implants increased all measures of sexuality, except for the effects on fantasies that were not significant. On the other hand, Sherwin et al. [7] reported significant increases in sexual fantasies in surgically menopausal women treated with relatively high doses of androgens and estrogens in long-acting injectable preparations. Also, Sarrel et al. [11] demonstrated an enhancement of sexual function detected in an interview situation. Burger et al. [33] informed that women receiving estrogen and testosterone preparations reported improved sexual desire and enjoyment. Also, Lobo et al. [34] suggested that the increased circulating levels of unbound testosterone and suppression of SHBG provide a plausible hormonal explanation for the significantly improved sexual functioning in women receiving the combination of esterified estrogen and methyltestosterone. In addition, some authors showed a significant increase in satisfying sexual activity and sexual desire after the association between estrogen and testosterone in surgically menopausal women with hypoactive sexual desire disorder [35,36].

Sarrel [5] mentioned that this sexual disturbance is related to local vaginal changes and estrogen might effective for the treatment of this problem. In fact, the effects of estrogen therapy in improving psychological symptoms, maintaining vaginal lubrication, decreasing vaginal atrophy and increasing pelvic blood flow in postmenopausal women are well documented; however, some patients require more than estrogen alone to improve psychological dysfunction, decreased sexual desire or other sexual problems associated with menopause. In our study, all selected participants were regular users of HRT with lubrication problems and pain during intercourse. This fact suggested that those patients did not respond to estrogen for decrease in sexual disturbances related to local vaginal alterations or medroxyprogesterone acetate blocked the estrogen benefits regarding vaginal lubrication. Also, the effect of association with methyltestosterone combined with HRT on lack of vaginal lubrication and pain is not so clear based on our data.

6. Conclusion

Our data showed that estrogen–androgen therapy improved sexual sensation and desire in postmenopausal women without severe side effects,

changes in liver enzymes or increase in cardiovascular risk. This fact suggests that combined HRT-androgen therapy may beneficial for postmenopausal women receiving HRT who continue to complain of sexual difficulties or for postmenopausal women with sexual complaints who are not undergoing estrogen therapy without severe local vaginal changes.

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