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## Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS)

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### ABSTRACT

**Objectives:** This study was designed to measure the beneficial effects of continuous testosterone therapy, delivered by subcutaneous implant, in the relief of somatic, psychological and urogenital symptoms in both pre- and post-menopausal patients, utilizing the validated Health Related Quality of Life (HRQOL), Menopause Rating Scale (MRS).

**Study design:** 300 pre- and post-menopausal women with symptoms of relative androgen deficiency, were asked to self-administer the 11-item MRS, at baseline and 3 months after their first insertion of the subcutaneous testosterone implant. Baseline hormone measurements, menopausal status and BMI, were assessed to determine correlation with symptoms and clinical outcome.

**Main outcome measurements:** Changes related to therapy were determined. Total MRS scores as well as psychological, somatic and urogenital subscale scores were compared prior to therapy and following testosterone implant therapy.

**Results:** Pre-menopausal and post-menopausal females reported similar hormone deficiency symptoms. Both groups demonstrated similar improvement in total score, as well as psychological, somatic and urogenital subscale scores with testosterone therapy. Better effect was noted in women with more severe complaints. Higher doses of testosterone correlated with greater improvement in symptoms.

**Conclusion:** Continuous testosterone alone, delivered by subcutaneous implant, was effective for the relief of hormone deficiency symptoms in both pre- and post-menopausal patients. The validated, HRQOL questionnaire, Menopause Rating Scale (MRS), proved a valuable tool in the measurement of the beneficial effects of testosterone therapy in both cohorts.

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### 1. Introduction

Androgen production in women declines steeply in the early reproductive years [1]. A woman of 40 has half the mean plasma total testosterone of a 21-year old [2].

Symptoms of relative androgen deficiency (RAD) including diminished sense of well-being, dysphoric mood (sadness, depression, anxiety, and irritability), fatigue, decreased libido, hot flashes,

bone loss, decreased muscle strength, changes in cognition and memory, and insomnia may occur prior to cessation of menses [3]. Pre-menopausal patients frequently report 'menopausal symptoms', most of which are not related to estradiol levels [4].

Subcutaneous testosterone therapy delivered by pellet implant has been used with success in female patients since 1938. Published data demonstrates efficacy as well as safety in doses of 75 mg up to 225 mg [5–9]. In addition, significantly higher doses (500–1800 mg) of subcutaneous testosterone have been safely used, to treat breast cancer patients [10].

Testosterone, delivered by pellet implant has been used in pre-menopausal females and shown not to affect the menstrual cycle [11,12]. Testosterone is not excreted in breast milk and has been used to treat post-partum depression and fatigue during the lactation period [13]. Testosterone alone has been reported to be more effective than estrogen–testosterone or estrogen therapy for relief of somatic and psychological symptoms in post-

**Abbreviations:** HRQOL, Health Related Quality of Life; MRS, Menopause Rating Scale; IRB, Institutional Review Board; BMI, body mass index.

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**Symptoms:**

	none	mild	moderate	severe	extremely severe
Score =	0	1	2	3	4
1. Hot flashes, sweating (episodes of sweating).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Irritability (feeling nervous, inner tension, feeling aggressive) .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Anxiety (inner restlessness, feeling panicky).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints) .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Fig. 1.** Menopause Rating Scale (MRS) 11 symptom categories with severity scale. The scoring is straightforward: the score increases point by point with increasing severity of subjectively perceived complaints in each of the 11 items (severity expressed in 0–4 points in each item). By checking these 5 possible boxes of “severity” for each of the items, the respondent provides her personal perception. Details on this open access MRS may be found at <http://www.menopause-rating-scale.info/>. ©ZEG Berlin.

menopausal patients as well as safe, even in pharmacologic doses [14].

This study was designed to measure the effectiveness of continuous testosterone therapy, delivered by subcutaneous implant, in the relief of somatic, psychological and urogenital symptoms in both pre- and post-menopausal patients using the self-administered, validated Health-Related Quality of Life (HRQOL) questionnaire, Menopause Rating Scale (MRS) (Fig. 1).

**2. Methods**

**2.1. Study group**

As part of a 10-year, prospective Institutional Review Board (IRB) approved trial on the effect of subcutaneous testosterone implants on the incidence of breast cancer (Dimitrakakis, Glaser), patient reported outcomes, HRQOL (Health Related Quality of Life), were used to evaluate the interventional effectiveness of this therapy on quality of life. There was no selection bias. 300 consecutive, newly enrolled pre- and post-menopausal women were accrued over a 24-month period from October 2007 through September 2009. Written informed consent was obtained on all patients. Patients with a pre-existing diagnosis of non-invasive or invasive breast cancer were excluded from participating in this study. Patients were either self-referred or referred by their physician for testosterone implant therapy for symptoms of relative androgen deficiency including; hot flashes, insomnia, depression, anxiety, fatigue, memory loss, migraine headaches, sexual problems, vaginal dryness, urinary symptoms, pain and bone loss.

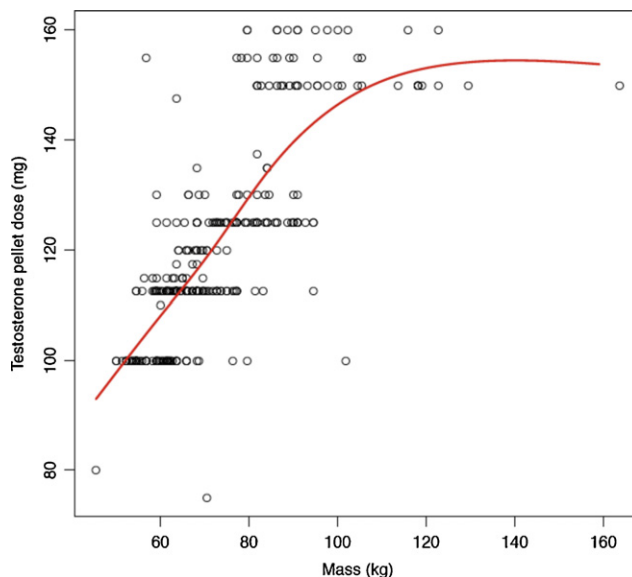
**2.2. Clinical testing**

Serum assays for estradiol, testosterone, free testosterone and FSH were performed at baseline. Estradiol and FSH were measured by chemiluminescence. Total and free testosterone, were measured by liquid chromatography tandem mass spectrometry and tracer equilibrium dialysis, calculation or direct analog/RIA. Intraassay

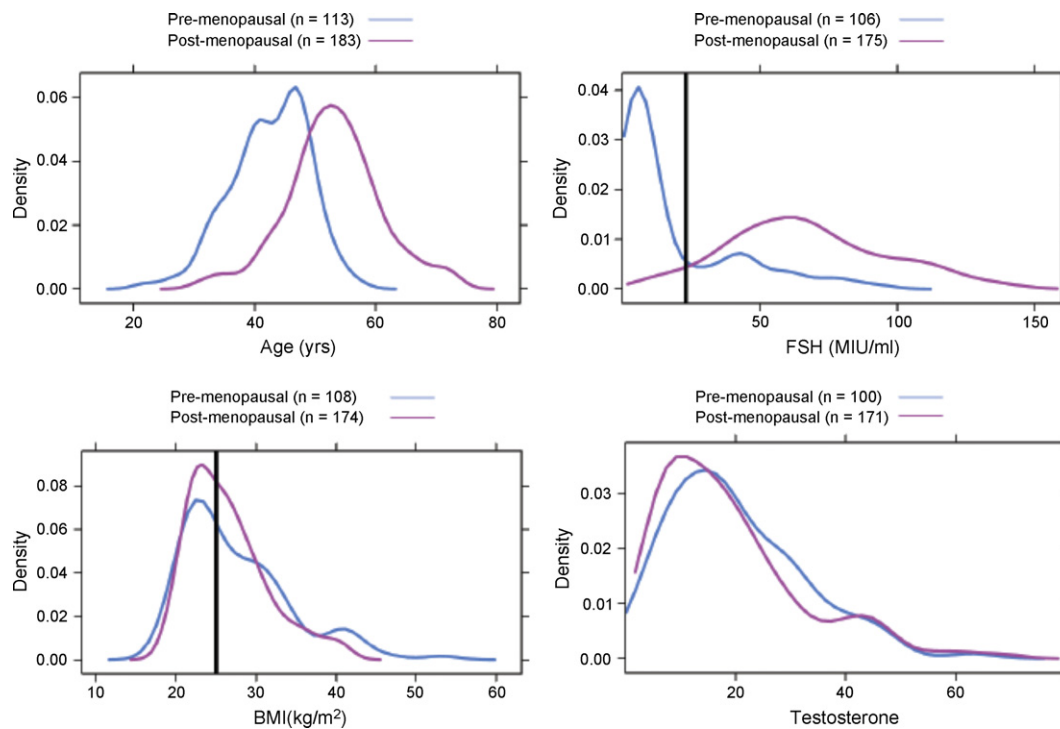
coefficients of variations were as follows: estradiol 9%, FSH 5%, total testosterone 9% and free testosterone 12%.

**2.3. Therapy**

The mean dose of subcutaneous testosterone implanted at the first visit was 121 mg. The range was between 75 mg and 160 mg with the following distribution: 75–80 mg (2 patients), 100 mg (64 patients), 110–120 mg (106 patients), 125–135 mg (73 patients), and 150–160 mg (55 patients). The initial testosterone dose was partially based on weight with a higher dose being used in heavier patients (Fig. 2). An approximate initial testosterone dose in mg of



**Fig. 2.** Testosterone pellet dose (mg) implanted compared to patients reported weight in kilograms. The testosterone pellet dose prescribed to the each patient depended strongly, in a non-linear fashion, on her weight.



**Fig. 3.** Patient demographics distribution: pre- and post-menopausal age, FSH, BMI and total testosterone. Age (mean): pre-menopausal, 42.7 years. Post-menopausal, 53.0 years. FSH: 26.4% of pre-menopausal patients had an FSH > 23 MIU/ml (vertical line). 5.7% of post-menopausal patients had an FSH < 23 MIU/ml. BMI (mean): pre-menopausal, 27.6 kg/m<sup>2</sup>. Post-menopausal, 26.5 kg/ml. Testosterone: similar distribution in pre- and post-menopausal patients.

twice the patients weight in kg has been successfully used in this clinical practice. Initial and subsequent dosage may be adjusted based on the avoidance of possible side effects of androgen therapy (e.g. increase in facial hair or mild acne) and adequacy of clinical response. No systemic estrogen therapy was prescribed.

The 3.1 mm (diameter) testosterone implants were compounded by a single pharmacy (Cincinnati, OH). The pellets were implanted subcutaneously through a 5 mm incision in the upper gluteal area under local anesthesia using a disposable trocar kit in a simple, 1-min procedure. The implants completely dissolve and do not need to be removed. In clinical practice (RG), we have found subcutaneous testosterone to be consistently absorbed and clinically more effective than topical testosterone.

#### 2.4. HRQOL measurement and statistical analysis

The patient's initial severity of symptoms and subsequent hormone related changes were evaluated using the validated Health-Related Quality of Life (HRQOL) questionnaire, Menopause Rating Scale (MRS) (Fig. 1).

The MRS was initially developed (a) to assess symptoms of aging/menopause (independent from those that are disease-related), (b) to evaluate the severity of symptoms over time, and (c) to measure changes related to hormone therapies [15–17]. A 5-point rating scale permits the patient to describe the perceived severity of complaints of each item (none 0, mild 1, moderate 2, severe 3, and extremely severe 4) by checking the appropriate box (Fig. 2). Three dimensions (sub-scales) of symptomatic complaints are identified: psychological, somatic and urogenital. The composite score for each of the sub-scales is based on adding up the scores of the items of the respective dimension scores. The corresponding questions for each of the calculated three sub-scales include: somatic sub-scale, questions 1, 2, 3, 11, psychological subscale, questions 4, 5, 6, 7 and urogenital sub-scale, questions 8, 9, 10 [16].

The MRS was self-completed by the patient at their initial clinic visit, prior to therapy (baseline assessment). A follow up ques-

tionnaire was also self-completed 12 weeks following their first testosterone pellet insertion (after therapy). Total scores and composite sub-scale scores were calculated per MRS protocol [15].

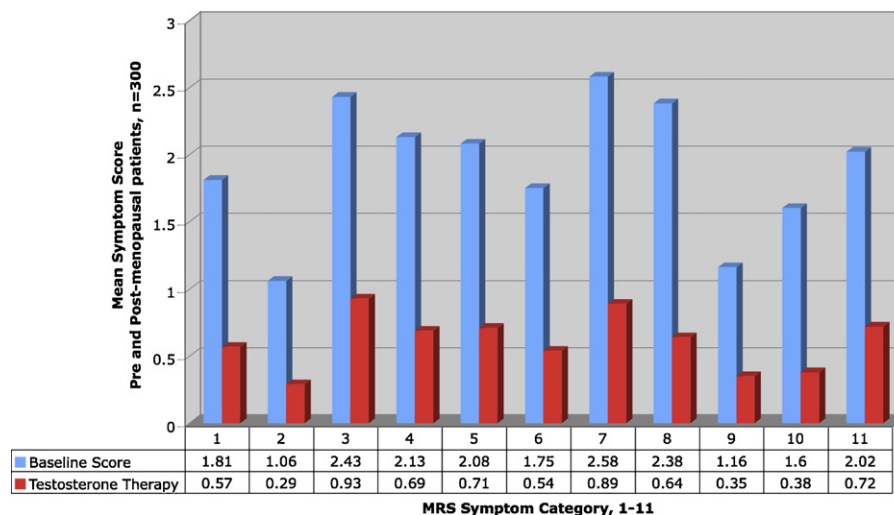
The statistical program R (R Development Core Team, 2009) was used for all data analysis. Paired Wilcoxon tests were used to compare the mean score values for each of the 11 symptoms before (baseline) and after testosterone treatment. The Spearman's rank correlation coefficient (Spearman's rho) analysis was used to screen relationships between individual variables including menopausal status, baseline testosterone levels, free testosterone levels (divided into upper, mid and lower thirds), estradiol levels and body mass index (BMI) (dichotomized to <25 and >25 kg/m<sup>2</sup>), on 'incidence/severity of symptoms at baseline' and 'response to therapy'. For this procedure, software from the R-package 'Hmisc' was used. Paired *t*-tests were used to compare the total scores and sub-scale scores. The smoothed estimates in the patient demographics density plots were calculated with a kernel density function provided in the R statistical package.

To investigate whether testosterone dose correlated with response to therapy, Spearman's rank correlation coefficient was calculated between testosterone dose and the degree of improvement in individual symptoms, as well as MRS total and sub-scale scores in pre- and post-menopausal patients. In addition, to determine whether the testosterone dose, independent of weight, correlated to the degree of improvement for any of the 11 symptom categories, and MRS total and/or sub-scale scores, the dose was first modeled as a function of weight using a generalized additive model (R-package 'Mgcv'). Then, Spearman's rank correlation was calculated between the adjusted dose and the degree of improvement.

### 3. Results

#### 3.1. Patient demographics

The mean age of our cohort of patients was 51.7 years. Mean body mass index (BMI) was 26.89 kg/m<sup>2</sup> (range 19.29–53.16,



**Fig. 4.** Pre- and post-testosterone therapy symptom scores in combined cohort. Comparisons between mean score values before and after testosterone treatment in each of the 11 MRS symptom categories for all patients ( $N=300$ ).<sup>a</sup> Statistically significant improvement ( $P<0.0001$ ) was demonstrated in each of the 11 MRS symptom categories. <sup>a</sup>Mean baseline score in blue and mean post-testosterone therapy score in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

median 25.63 kg/m<sup>2</sup>), with 132 patients having a BMI < 25 and 168 patients having a BMI > 25 (Fig. 3).

One hundred and eight (36.0%) of the 300 study subjects were pre-menopausal, 106 (35.3%) reported non-surgical, spontaneous menopause (last menstrual cycle greater than 12 months), 57 (19.0%) were surgical-menopausal (bilateral oophorectomy with or without hysterectomy), and 29 (9.6%) had a hysterectomy with one or both ovaries intact. Although not diagnostic for menopause, for the purpose of our study, patients having a hysterectomy with one or both ovaries intact were stratified to pre-menopausal ( $n=5$ ) if FSH levels were <23 MIU/ml and post-menopausal ( $n=20$ ) if FSH levels were >23 MIU/ml, the post-menopausal reference range for serum FSH defined by the clinical laboratory used. Eighty-eight (31.3%) of the 281 patients tested had FSH levels <23 MIU/ml whereas one hundred and ninety-three (68.7%) of the 281 patients tested had an FSH > 23 (Fig. 3).

Two hundred and twenty eight (87%) of 262 patients tested for free testosterone had a value in the lower third of the reference range. Twenty-nine (11%) of the 262 patients had a free testosterone in the middle third and five (2%) had a free testosterone in the upper third. There was no difference in distribution of free testosterone between pre- and post-menopausal patients ( $P=0.6$ ). In addition, there was no significant difference in total testosterone levels between pre- and post-menopausal patients ( $P=0.2$ ) (Fig. 3). Patients were treated based on clinical symptoms and therapy was continued based on clinical response. No patient was excluded from therapy based on baseline serum hormone levels. Patients were re-evaluated and re-treated with testosterone implants between 12 and 16 weeks when symptoms returned. Routine follow up serum testosterone levels are no longer obtained, as we found them to lack clinical relevance due to intra- and inter-individual variation, circadian variation and a lack of clinical correlation with outcome.

### 3.2. Response to therapy

In this cohort of 300 combined pre- and post-menopausal women, the clinical improvement after testosterone implant therapy was statistically significant in each of the 11 individual symptom categories studied,  $P<0.001$  in all cases (Fig. 4).

Means of the scoring points of the total scale and three sub-scales can be seen at baseline (before therapy) and after therapy

with subcutaneous testosterone implants in Table 1. In both pre- and post-menopausal patients as well as in the combined cohort of our patients, statistically significant declines of the mean scores were observed after treatment. This indicates an improvement of the HRQOL according to MRS total scale and in each of the three sub-scales: psychological, somatic and urogenital ( $P<0.001$ ). The percent change, i.e. improvement, of complaints during treatment relative to the baseline score is also presented in Table 1.

### 3.3. Clinical subgroups, MRS individual symptom categories (1)–(11)<sup>1</sup> and correlations

A higher incidence ( $P<0.05$ ) of psychological complaints, including depressive mood (4), irritability (5) and anxiety (6) were observed in pre-menopausal patients, while post-menopausal patients were more likely to report somatic complaints including hot flashes (1). Vaginal dryness (10), a urogenital complaint, was also more prevalent in post-menopausal patients. Both groups responded to subcutaneous testosterone therapy demonstrating a statistically significant improvement for both predominating and less common symptom categories.

Neither estradiol levels nor free testosterone levels at baseline correlated with incidence/severity of presenting symptoms or response to therapy in any category ( $P>0.05$ ), including Hot flashes and sweating (1). Patients with higher baseline total testosterone levels presented with fewer complaints of sexual problems (8). No other correlation between symptoms or response to therapy and initial testosterone levels was demonstrated.

Higher BMI (dichotomized to <25 and >25 kg/m<sup>2</sup>) correlated with a higher incidence of depressive mood (4), physical and mental exhaustion (7) and joint and muscular discomfort (11) ( $P<0.05$ ). Patients with higher BMI had a greater improvement in physical and mental exhaustion (7) with testosterone therapy ( $P<0.05$ ).

For each of the 3 sub-scales as well as total score, patients who presented with more severe symptoms demonstrated greater improvement on therapy (Table 2). The more severe the complaints were before treatment, the better the effect regarding relative improvement of symptoms measured by the MRS.

<sup>1</sup> (1)–(11) denotes MRS individual symptom categories.



**Table 1**

Testosterone treatment related improvement in combined cohort, pre-menopausal and post-menopausal patients. MRS mean (SD) scores at baseline (scores before) and following testosterone therapy (scores after) for total scale and for each sub-scale. Mean (SD) improvement of scores after therapy (absolute change and percent change).

	<i>n</i>	Scores before (SD)	Scores after (SD)	Absolute change (SD)	Percent (%) change	<i>P</i> <sup>a</sup>
<b>Combined cohort</b>						
Total scale	269	21.0 (8.0)	6.8 (4.9)	14.2 (7.6)	67.8	<.0001
Psychological subscale	287	8.5 (3.9)	2.8 (2.5)	5.7 (3.8)	66.7	<.0001
Somatic subscale	292	7.3 (3.4)	2.5 (1.9)	4.8 (3.2)	65.7	<.0001
Urogenital subscale	288	5.2 (2.9)	1.4 (1.6)	3.8 (2.5)	73.4	<.0001
<b>Pre-menopausal patients</b>						
Total scale	104	20.9 (7.3)	6.5 (4.7)	14.4 (7.6)	69.1	<.0001
Psychological subscale	108	9.4 (3.6)	3.0 (2.5)	6.4 (3.8)	68.0	<.0001
Somatic subscale	112	6.6 (3.2)	2.2 (1.7)	4.5 (3.2)	67.4	<.0001
Urogenital subscale	110	4.9 (2.7)	1.3 (1.6)	3.6 (2.4)	73.4	<.0001
<b>Post-menopausal patients<sup>b</sup></b>						
Total scale	162	21.1 (8.5)	6.9 (5.0)	14.2 (7.6)	67.2	<.0001
Psychological subscale	176	8.0 (4.1)	2.7 (2.4)	5.3 (3.7)	65.9	<.0001
Somatic subscale	176	7.7 (3.3)	2.7 (2.0)	5.0 (3.1)	64.6	<.0001
Urogenital subscale	174	5.3 (3.0)	1.4 (1.7)	3.9 (2.6)	73.4	<.0001

<sup>a</sup> Paired *t*-test for dependent samples: significance of the absolute difference.

<sup>b</sup> Post-menopause: last menstrual cycle > 12 months, surgical menopause with bilateral oophorectomy or post hysterectomy with retained ovarian function and FSH > 23 MIU/ml.

### 3.4. Testosterone dose, effect, side effects and adverse drug events

In all individual MRS symptom categories (1–11), excluding dryness of the vagina (10) and anxiety (6), higher doses of testosterone correlated with greater clinical improvement ( $P < 0.05$ ). In addition, after adjusting for dosage based on total body weight, greater improvement in Hot flashes, sweating (1), heart discomfort (2), sleep problems (3), depressive mood (4), physical and mental exhaustion (7), sexual problems (8) and joint and muscular discomfort (11) correlated with higher testosterone dose ( $P < 0.05$ ).

In post-menopausal patients, higher testosterone doses correlated with greater improvement in MRS total score and all three sub-scores: somatic, psychological and urogenital ( $P < 0.001$ ). In pre-menopausal patients, higher testosterone doses correlated with greater improvement in MRS total score ( $P < 0.05$ ) and urogenital sub-score ( $P < 0.01$ ). However, in pre-menopausal patients, higher testosterone doses did not correlate with greater improvement in either the psychological or somatic sub-scores ( $P > 0.05$ ).

A common concern is whether testosterone therapy may increase aggression and irritability. In our study over 90% of patients reported less irritability (feeling nervous, inner tension, feeling aggressive) on testosterone therapy whereas only 4.4% of patients reported a mild increase in these symptoms.

Known androgenic side effects include a possible increase in facial hair and mild acne. Some women reported a slight increase in facial hair, but no patient in this cohort discontinued therapy for that reason. Only three patients discontinued testosterone therapy due to 'lack of effect'. Three additional patients discontinued therapy for non-medical reasons. There were no adverse drug events reported. No patient extruded a pellet or required antibiotic therapy for local infection.

**Table 2**

MRS score improvement by testosterone, relative to severity of symptoms at baseline.

Severity score of complaints at baseline range (mean)	<i>N</i> <sup>a</sup>	Improvement total score mean (SD)	Improvement psychological score mean (SD)	Improvement somatic score mean (SD)	Improvement urogenital score mean (SD)
5–8 (7.11)	9	4.44 (1.88)	1.56 (1.24)	1.56 (0.88)	1.33 (1.80)
9–15 (12.35)	60	7.43 (3.57)	2.78 (2.15)	2.37 (2.05)	2.28 (2.19)
16+ (24.44)	198	16.92 (6.70)	6.94 (3.59)	5.60 (3.00)	4.38 (2.46)

Mean (SD) improvement in MRS score based on baseline severity of symptoms (mild: 5–8; moderate 9–15; severe: 16+) for total and sub-scale categories. The more severe the symptoms, the greater the improvement in total, psychological, somatic and urogenital scores.

<sup>a</sup> Only patients who completed all questions on both baseline and follow-up MRS questionnaires were included in this analysis.

### 3.5. Follow-up data (Cohort treated with testosterone therapy for over one year)

We have collected follow-up data on 285 patients treated for over one year (mean 28.1 + 10.4 months) with testosterone implants. Mean testosterone implant dose was 133.3 + 26.8 mg and mean interval of insertion was 13.8 + 3.8 weeks. Although dosing is individualized based on patient response, dose continued to correlate with weight ( $P < 0.001$ ). There have been no adverse effects on blood sugar, insulin resistance, diabetes, or lipid profiles (data not shown).

## 4. Discussion

Testosterone therapy alone, delivered by subcutaneous implant in adequate doses, was effective for the relief of psychological, somatic and urogenital symptoms in both pre-menopausal and post-menopausal patients as measured by the self-administered, validated HRQOL Menopause Rating Scale (MRS).

Symptoms of relative androgen deficiency may occur prior to menopause, cessation of ovulation and reduction of estradiol levels. In our study, one third of the patients were pre-menopausal, and were successfully treated with continuous testosterone therapy. We also demonstrated that testosterone alone relieves symptoms in post-menopausal women.

Our results showed that a single serum measurement of testosterone was not useful in the diagnosis of androgen deficiency. Neither the incidence/severity of symptoms nor treatment effect correlated with baseline free or total testosterone levels, consistent with previous studies [18,19].

In our clinical practice, we have found that heavier women require higher doses of subcutaneous testosterone to relieve symptoms. In this study, patients with higher BMI presented with more severe symptoms of depressive mood (4), physical and mental exhaustion (7) and joint and muscular discomfort (11). These patients also reported greater improvement in physical fatigue and mental exhaustion (7). The greater improvement in symptoms may be due to the higher doses of testosterone prescribed in these heavier patients, supporting weight-based dosing.

This study confirmed what prior studies have reported, that testosterone effect is dose dependent [19,20]. Published data supports the safety and efficacy of the testosterone implant doses used in this study [5–9]. Post-implant therapeutic serum testosterone ranges, above endogenous levels, have been established in the literature and previously duplicated in this clinical practice (data not shown) [5–7]. In contrast, maintaining serum testosterone levels within ranges for endogenous production in women has been shown to be inadequate for therapeutic effect [21].

In line with previous studies [7] hot flashes, sweating, heart discomfort, sleep problems, depressive mood, irritability, and anxiety all significantly improved on continuous, subcutaneous testosterone therapy. Physical fatigue as well as chronic joint and muscular pain, also significantly improved on therapy. This was not surprising as testosterone is both anti-inflammatory and anabolic. That may also explain the statistically significant improvement in bladder problems, including bladder incontinence (9), with continuous testosterone therapy. Memory and concentration improved which is consistent with previous studies and testosterone's neuro-protective effects [5,22]. As expected, sexual problems (desire, activity, satisfaction) improved with testosterone implant therapy.

A major weakness of the present study is the absence of a control group receiving placebo implant. However, this was not approved as a randomized controlled trial at the outset and a placebo control group was beyond the initial protocol purposes. This study is not a classical clinical trial to prove the effect of the testosterone implant where a comparison group would be essential, but rather a cohort study utilizing patient reported outcomes to assess symptoms and to evaluate medical care intervention, i.e. changes related to hormone therapy. In this context, with the well-known reliability of the MRS results published by other authors, the absence of a placebo group does not invalidate the data nor allay the interpretation of these results. Correlation of improvement in symptoms relative to the dose of testosterone, even after adjustment for weight, argues against placebo effect. Noteworthy is that 98% of patients returned for testosterone implant therapy when symptoms returned.

A possible explanation of the observed clinical improvement is that testosterone acts directly via the androgen receptor to ameliorate androgen deficiency related symptoms. The other hormonal path that may be involved is the aromatization of testosterone to estradiol in estrogen dependent tissues such as brain, bone, fat, muscle, cardiac, vascular and breast tissue. Adequate levels of continuous testosterone, provided by the subcutaneous implant, most likely protect against estrogen deficiency thus explaining why testosterone alone is effective therapy in post-menopausal patients. In our clinical practice (not included in this cohort of 300 patients), an aromatase inhibitor is used in combination with testosterone when estrogen is contraindicated (i.e. breast cancer survivors).

Testosterone therapy alone does not require endometrial protection [23,24] thus avoiding the adverse effects of synthetic progestin therapy including the documented increase in breast cancer [25]. Hormones delivered by the subcutaneous route avoid the enterohepatic circulation, bypass the liver, do not affect clotting factors and do not increase the risk of thrombosis [26,27]. Also, subcutaneous testosterone does not adversely affect lipid profiles [5,26]. Testosterone's lack of adverse, and possible protective effect

on breast tissue [9,28–30] is an additional benefit to be considered and is the endpoint of our 10-year prospective IRB approved study.

The Menopause Rating Scale (MRS) was a valuable tool in determining the beneficial effects of testosterone therapy in both pre- and post-menopausal patients.

Although this study is short-term (first pellet implant), in clinical practice significant symptom control is maintained as long as therapy is continued. All female patients are monitored as part of an ongoing prospective study on testosterone pellet implants and the incidence of breast cancer. No unexpected adverse drug events have been reported in over 1200 women treated with over 7000-testosterone pellet implants in up to 5 years of therapy.

## 5. Conclusion

This study has shown for the first time that adequate doses of continuous *testosterone alone*, delivered by subcutaneous implant, was effective therapy for physical, psychological and urogenital symptoms in both pre- and post-menopausal women, suggesting a broader physiologic role for testosterone. Despite methodological limitations, our clinical observations along with existing data support the concept that testosterone administration improves quality of life. Long-term follow up studies are needed to further document the efficacy and safety of testosterone therapy in women.

## Contributors

RG Study design, lead author, Principal Investigator Testosterone Implant Breast Cancer Incidence/Prevention Trial, patient accrual. AY Statistical and data analysis, co-author. CD Study design, Principal Investigator Testosterone Implant Breast Cancer Incidence/Prevention Trial, co-author.

## Competing interest

None declared.

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Klaas Heinemann Jr., MD, MBA, PhD, ZEG Berlin, granted permission for Fig. 1. James Apesos M.D., Wright State University Boonshoft School of Medicine, Department of Surgery, Dayton, OH and Atrium Hospital, Middletown, OH. Co-Investigator, Testosterone Implant Breast Cancer Incidence/Prevention Trial, approved the manuscript.

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