T pellets - tx endometriosis/fibroids/PMS ? dose

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DATA: Hormone Therapy with Pellet Implants

Hormone replacement therapy by pellet implantation has been used with great success in the United States, Europe and Australia since 1938 and found to be superior to other methods of hormone delivery (Greenblatt 49, Mishnell 41, Cantrill 84, Stanczyk 88). It is **not** experimental. Pellets deliver **consistent**, physiologic levels of hormones and avoid the fluctuations of hormone levels seen with other methods of delivery (Greenblatt 49, Thom 81, Cantrill 84 Stanczyk 88).

Hormones delivered by the subcutaneous implants bypass the liver, do not affect clotting factors and do not increase the risk of thrombosis (Notelovitz 87, Seed 00). Bioidentical testosterone delivered subcutaneously by pellet implant is cardiac protective, unlike oral, synthetic testosterone (Sands 97, Worboys 00).

Testosterone delivered by pellet implantation, does not adversely affect blood pressure, lipid levels, glucose or liver functions (Burger 84, Farish 84, Fletcher 86, Barlow 86, Notelovitz 84, Stanczyk 88, Davis 95, 00, Handelsman 96, Sands 97, Seed 00, Cravioto 01). In addition, testosterone is a vasodilator (Perusquia 10).

Pellets are **superior** to oral and topical hormone therapy with respect to relief of menopausal symptoms (Staland 78, Cardoza 84). Testosterone implants have consistently been shown to improve insomnia, sex drive, libido, hot flashes, palpitations, headaches, irritability, depression, aches, pains, and vaginal dryness (Glaser 11, Staland 78, Thom 81, Brincat 84, Davis 95, 00, Cravioto 01).

Hormone replacement therapy with estradiol and testosterone implants is **superior** to oral and topical (both the patch and gel) hormone replacement therapy for **bone density** (Savvas 88, 92, Davis 95, Anderson 97). The **consistent, adequate** levels of testosterone delivered by pellet implant are important in maintaining bone mineral density (Aminoroaya 05) while also being available as a substrate for the production of estradiol (Simpson 02, 03). The pellets not only prevent bone loss, they actually **increase** bone density (Savvas 88, Studd 90, Garnett 91, Savvas 92, Naessen 93, Holland 94, Studd 94, Davis 95, Anderson 97, Seed 00, Panay 00).

Testosterone implants in women have been shown to improve lethargy, depression, loss of libido, and hot flashes without attenuating the beneficial affects of estradiol on cardiac and lipid profiles (Farish 84, Fletcher 86, Sands 97, Seed 00). Testosterone, delivered by pellet implant does not affect the menstrual cycle (Dewis 86) and has been used to treat endometriosis and uterine fibroids (Greenblatt 49). Testosterone pellet implants have also been used to successfully treat severe pre-menstrual syndrome unresponsive to other forms of therapy, without adverse effects (Dewis 84).

Testosterone, delivered by subcutaneous pellet implant has been shown to improve hot flashes, heart discomfort, sleep problems, depressive mood, irritability, anxiety, physical fatigue, memory loss, migraine headaches, sexual problems, bladder problems (incontinence), vaginal dryness, joint and muscular discomfort in both pre-menopausal and post-menopausal patients without adverse drug events (Glaser 11).

Pellets do not have the same risk of breast cancer as the synthetic progestins or synthetic Methy-testosterone. In fact, studies show a **reduction** in the incidence of breast cancer with the implantation of **testosterone** pellets (Dimitrakakis 04, Tutera 09).

BT

Even after over 20 years of therapy with hormone implants, the risk of breast cancer is not increased (Gambrel 06). In breast cancer survivors, hormone replacement therapy with pellet implantation does **not** increase the risk of cancer recurrence or death (Natrajan 02) as does estrogen in combination with the synthetic progestins (Habits Trial 04). Hormone replacement therapy with testosterone pellet implantation has an extremely low incidence of side effects (Glaser 11) and high compliance rate (Gambrell 06).

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Testosterone replacement therapy in men with subcutaneous implants (pellets) has been show to be effective, convenient and safe (Handelsman 90, 92, 97, Kelleher 01, 04, Conway 88, Jockenhoval 96, Zacharin 03, Schubert 03, Dunning 04).

The testosterone implant is licensed in England for women. The 75 mg testosterone implant is FDA approved in the US (July 13,1972, male patients). Other doses need to be compounded by trained pharmacists.

> The *75 mg pellet* is a sterile product is cylindrically shaped and weighs approximately 77mg (75mg testosterone). The inactive ingredients include 0.2mg stearic acid USP and 2mg polyvinylpyrroidone USP.

The routine doses of testosterone delivered by pellet implantation in recent studies are between 800 and 1200 mg in men. The pharmacokinetics and pharmacodynamics are well established showing that these doses deliver reproducible physiologic levels of testosterone for 4-6 months. The studies show that pellets have a zero order release rate. Although individuals vary, the 75 mg testosterone pellet has a consistent release rate approximately 0.5 mg of testosterone per day for a total of approximately 6 mg per day for 12 pellets. A 6-9 mg daily production of testosterone is a 'physiologic' level produced by the testicles.

Testosterone implants have a near linear release rate. Peak serum testosterone levels with the implants are usually seen at month one. Therapeutic testosterone levels at month one, are expected at the upper limits of normal for healthy young males (800-1100 ng/dL). By month 4 to 5 testosterone levels drop to below 500-600 ng/dL at which time symptoms return and the pellets are reinserted. Each individual has their own reproducible levels where symptoms return.

Testosterone implants have been used in women. Doses used in studies are as low as 50 mg and up to 225 mg. In the United States, common doses are100 to 225 mg. There are minimal side effects at these doses (an increase in facial hair and mild acne), which may be reduced by lowering the dose, if the patient chooses. If measured, serum treatment levels are elevated above non-treatment levels at month one (Burger 84, Dewis 84, Gambrel 06, Thom 81, Glaser 09). Urine and saliva levels remain normal. There are no signs of androgen excess at these treatment levels. Symptoms return when testosterone levels reach the upper end of endogenous ranges (Burger 84). End organ response to testosterone remains optimal (i.e., relief of depression, increase in bone density, relief from insomnia, relief from aches and pains, lessened anxiety, improved memory and concentration, increased energy, etc.). Testosterone implants last between 2.5 and 5 months in female patients. Individual treatment doses and treatment ranges are established and are reproducible. Long-term studies with up to **30 years** follow up, confirm the safety of testosterone therapy and absence of adverse drug events with the pellet implant (Gambrel 06, Traish10).

In a paper published in the journal 'Menopause' in 2004, '*Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy*' women were referred for testosterone supplementation for the following indications:

- Complaints of emotional lability
- Fatigue and loss of stamina
- Impaired concentration and memory
- Breast tenderness
- Loss of libido

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- Sleep disturbance
- Muscle weakness

Patients received testosterone implant containing 50-150 mg of testosterone every 5 months in addition to conventional estrogen or estrogen/progestin therapy. The testosterone dose was titrated to alleviate symptoms (listed above), **improve bone mineral density** and minimize adverse affects (slight increase in facial hair and acne).

The addition of testosterone, delivered by pellet implant, was shown to reduce the incidence of breast cancer in women treated with conventional hormone therapy. In women, not on synthetic progestin therapy (which is known to increase the incidence of breast cancer RR 1.69-2.00), the incidence of breast cancer was lower than 'no hormone therapy'.

Testosterone therapy alone, delivered by pellet implant is effective for the relief of both physical and psychological symptoms in **pre-menopausal and post-menopausal** patients. Symptoms of testosterone deficiency/hormone imbalance are often seen prior to menopause. Many women begin to experience symptoms by age 35-40, when testosterone production has declined by half (Zumoff 95).

Testosterone alone has previously been reported to be more effective than estrogen/testosterone or estrogen therapy for relief of somatic and psychological symptoms (Sherwin 85). Uninterrupted sufficiency of circulating testosterone supports the production of estradiol by aromatase in estrogen dependent tissues (brain, bone, muscle, skin, cardiac, vascular tissue, fat and breast tissue) and affords protection against estrogen deficiency. Also, low circulating levels of estrogen have no bearing on estrogen produced locally. This may explain why **continuous delivery** of testosterone by pellet implant is so effective in post-menopausal patients.

Subcutaneous testosterone therapy is **safe** and extremely **effective** in pre and post-menopausal patients as well as men.

For additional information on the benefits of testosterone, please refer to:

Glaser R, York AE, Dimitrakakis C. Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). *Maturitas*. 20011;68:355-361.

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.

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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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Review

Testosterone therapy in women: Myths and misconceptions

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ABSTRACT

Although testosterone therapy is being increasingly prescribed for men, there remain many questions and concerns about testosterone (T) and in particular, T therapy in women. A literature search was performed to elucidate the origin of, and scientific basis behind many of the concerns and assumptions about T and T therapy in women.

This paper refutes 10 common myths and misconceptions, and provides evidence to support what is physiologically plausible and scientifically evident: T is the most abundant biologically active female hormone, T is essential for physical and mental health in women, T is not masculinizing, T does not cause hoarseness, T increases scalp hair growth, T is cardiac protective, parenteral T does not adversely affect the liver or increase clotting factors, T is mood stabilizing and does not increase aggression, T is breast protective, and the safety of T therapy in women is under research and being established.

Abandoning myths, misconceptions and unfounded concerns about T and T therapy in women will enable physicians to provide evidenced based recommendations and appropriate therapy.

Contents

Abbreviations: T, testosterone; E2, estradiol; DHT, dihydrotestosterone; U.S., United States; AR, androgen receptor; ER, estrogen receptor.

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1. Introduction

Testosterone (T) therapy is being increasingly used to treat symptoms of hormone deficiency in pre and postmenopausal women. Recently, especially with the advent of the T patch, additional research has been, and is currently being conducted on the safety and efficacy of T therapy. However, particularly in the United States (U.S.), there still exist many misconceptions about T and T therapy in women. This review addresses, and provides evidence to refute, some of the most common myths.

A major source of misconceptions regarding T therapy in women arises from epidemiological studies implicating elevated (endogenous) T levels with certain diseases. This data is misleadingly delivered to produce a pathogenic model of these diseases without enough evidence or plausibility to support a causative role. False conclusions repeated often enough, especially when supported with anecdotal observations, create 'myths' that become widely accepted, even in the absence of any biological or physiological rationale.

Another source of confusion concerning the safety of T therapy in both men and women is the extrapolation of adverse events (e.g., mental status changes, aggression, cardiac and liver problems, endocrine disturbances, abuse potential) from high doses of oral and injectable anabolic-androgenic steroids to T therapy, despite a lack of evidence. In this review, testosterone (T) refers only to bio-identical (human identical molecule) testosterone, not to oral, synthetic androgens or anabolic steroids.

In England and Australia, T is licensed and has been used in women for over 60 years. However, as of 2013, in the U.S., there is no licensed T product for women and human/bio identical T is regulated as a 'schedule 3' drug and included as a 'class X' teratogen.

2. 'Top 10' myths about testosterone use in women

2.1. Myth: Testosterone is a 'male' hormone

Even in scientific publications, T has been referred to as the 'male hormone'. Men do have higher circulating levels of T than women; however, quantitatively, T is the most abundant active sex steroid in women throughout the female lifespan (Fig. 1) [1]. T is measured in 10-fold higher units than estradiol (E2), i.e., nanograms/dl or micromolars compared to picograms/ml or picomolars for E2. In addition, there are exponentially higher levels of proandrogens: dihydroepiandrosterone sulfate (DHEAS), dihydroepiandrosterone (DHEA) and androstenedione, supplying significant amounts of T to the androgen receptor (AR) in both sexes. In fact, the measured ranges of androgen precursors are similar in men and women.

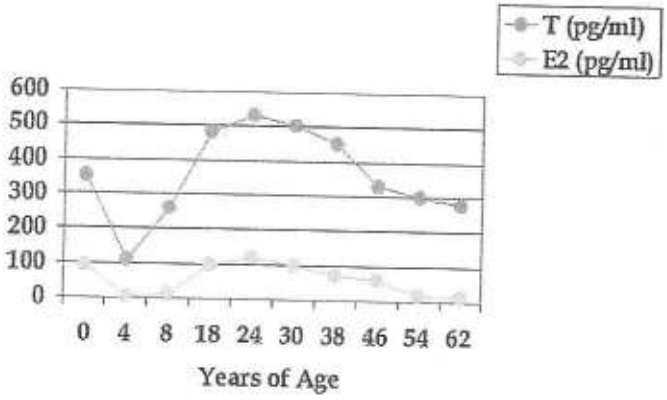

Fig. 1. Throughout the female lifespan, testosterone (T) is the most abundant active steroid. T levels are significantly higher than estradiol (E2) levels, adapted from Ref. [1].

Despite any clear rationale, estrogen was assumed to be the hormone of 'replacement therapy' in women. However, as early as 1937, T was reported to effectively treat symptoms of the menopause [2]. From a biologic perspective, women and men are genetically similar, having both functional estrogen receptors (ERs) and functional androgen receptors (ARs). Interestingly, the AR gene is located on the X chromosome. T, in balance with lower amounts of E2, is equally important for health in both sexes. In addition, T is the major substrate for E2 and has a secondary effect in both sexes via the ER.

Fact
Testosterone is the most abundant biologically active hormone in women

2.2. Myth: Testosterone's only role in women is sex drive and libido

Despite many recent publications, T's role in sexual function and libido is only a small fraction of the physiologic effect of T in women. Functional AR's are located in almost all tissues including the breast, heart, blood vessels, gastrointestinal tract, lung, brain, spinal cord, peripheral nerves, bladder, uterus, ovaries, endocrine glands, vaginal tissue, skin, bone, bone marrow, synovium, muscle and adipose tissue [3,4].

Testosterone and the pro-androgens decline gradually with aging in both sexes. Pre and post-menopausal women, and aging men, may experience symptoms of androgen deficiency including dysphoric mood (anxiety, irritability, depression), lack of well being, physical fatigue, bone loss, muscle loss, changes in cognition, memory loss, insomnia, hot flashes, rheumatoid complaints, pain, breast pain, urinary complaints, incontinence as well as sexual dysfunction. These symptoms of androgen deficiency are becoming increasingly recognized in women, and treated with T therapy [5–7]. Rating scales for symptoms of androgen deficiency have been developed in an effort to standardize severity of symptoms and to measure treatment effectiveness. Functional, biologically active, ARs are located throughout the body in both sexes: to assume that androgen deficiency does not exist in women, or that T therapy should not be considered in women, is unscientific and implausible.

Fact
Testosterone is essential for women's physical and mental health and wellbeing

2.3. Myth: Testosterone masculinizes females

It has been recognized for over 65 years, that T effect is dose dependent and that in lower doses, T 'stimulates femininity' [8]. Although pharmacologic doses of T and supra-pharmacological doses of T used to treat female to male transgender patients, may result in increased facial hair growth, hirsutism, and slight enlargement of the clitoris; true masculinization is not possible. Unwanted androgenic side effects are reversible by lowering the T dose; however, because of the dose dependent beneficial effects of T, many women prefer to treat the side effects rather than lower the dose [9,10].

As previously mentioned, in the U.S. androgens are listed as a 'class X' teratogen. Although 400–800 mg/d of danazol, a potent synthetic androgen, can result in clitoromegaly and fused labia (without long term effects) in some female fetuses; there is no evidence that T, delivered by pellet implant (i.e., a daily dose of 1–2 mg) or topical T has any adverse effect on a fetus, even in animal studies [11,12]. Animal studies have shown that virilization of a female fetus requires extremely high doses of T (>30 times normal

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maternal levels, >50–500 times 'human' T doses) administered over an extended period of time [12–14].

There is a significant rise in (endogenous) maternal T levels during pregnancy, up to 2.5–4 times non-pregnancy ranges. However, the placenta buffers hormone diffusion and is a source of abundant aromatase, which metabolizes maternal T [15,16]. T stimulates ovulation, increases fertility and has been safely used in the past to treat nausea of early pregnancy without adverse effects [8].

Fact
Outside of supra-pharmacologic doses of synthetic androgens, testosterone does not have a masculinizing effect on females or female fetuses

2.4. Myth: Testosterone causes hoarseness and voice changes

Hoarseness is common, affecting nearly 30% of persons at some point in their life, with 6.6% of the adult population affected at any given time. Hoarseness is more prevalent in women than men. Most common causes of hoarseness are inflammatory related changes due to allergies, infectious or chemical laryngitis, reflux esophagitis, voice over-use, mucosal tears, medications and vocal cord polyps. There is no evidence that T causes hoarseness. In addition, there is no physiological mechanism by which T could be expected to do so. T deficiency is listed as a 'cause' of hoarseness [17]. Physiologically, this is consistent with the anti-inflammatory properties of T.

Although a few anecdotal case reports and small questionnaire studies have reported an association between 400 and 800 mg/d of danazol and self-reported, subjective voice 'changes' [17,18]; a prospective, objective study demonstrates the opposite. 24 patients receiving 600 mg of danazol therapy daily were studied at baseline, 3 months and 6 months. The authors reported that there were no vocal changes that could be attributed to the androgenic properties of danazol [19]. This is consistent with the findings of our current, 1 year, prospective study examining voice changes on pharmacologic doses of subcutaneous T implant therapy in women (under publication).

Although high doses of anabolic steroids in female rats can cause irreversible vocal cord changes, there is no evidence that this is true for T replacement doses in humans. If a patient experiences voice changes or hoarseness on T therapy, a standard workup should be performed.

Fact
There is no conclusive evidence that testosterone therapy causes hoarseness or irreversible vocal cord changes in women

2.5. Myth: Testosterone causes hair loss

There is no evidence that T or T therapy is a cause of hair loss in either men or women. Although men do have higher T levels than women, and men are more likely to have hair loss with age, it is unreasonable to assume that T, an anabolic hormone, causes hair loss. Hair loss is a complicated, multifactorial, genetically determined process that is poorly understood. Dihydrotestosterone (DHT), not T, is thought to be the active androgen in male pattern balding. Female 'androgenic' alopecia refers to a (male) pattern of hair loss in women, rather than the etiology.

Although some women with PCOS and insulin resistance have higher T levels, and do have hair loss, this does not prove causation. Hair loss is common in both women and men with insulin resistance [20,21]. Obesity and insulin resistance increase 5-alpha reductase, which increases conversion of T to DHT in the hair follicle [22]. Also, obesity, age, alcohol, medications and sedentary lifestyle increase aromatase activity, lowering T and raising E. Increased DHT, lowered testosterone, and elevated estradiol levels can contribute to hair loss in genetically predisposed men and women; as can many medications, stress and nutritional deficiencies.

Approximately one third of women experience hair loss and thinning with aging, coinciding with T decline. We have previously reported that two thirds of women treated with subcutaneous T implants have scalp hair re-growth on therapy. Women who did not re-grow hair on T were more likely to be hypo or hyperthyroid, iron deficient or have elevated body mass index. In addition, none of 285 patients treated for up to 56 months with subcutaneous T therapy complained of hair loss, despite pharmacologic serum T levels on therapy [10].

Fact
Testosterone therapy increases scalp hair growth in women

2.6. Myth: Testosterone has adverse effects on the heart

Men have higher levels of testosterone than women: men have a higher incidence of heart disease; however, it is illogical to assume that T causes or contributes to cardiovascular (CV) disease in either sex. Unlike anabolic and oral, synthetic steroids, there is no evidence that T has an adverse effect on the heart. In addition, it is not physiologically plausible.

There is overwhelming biological and clinical evidence that T is cardiac protective [23]. T has a beneficial effect on lean body mass, glucose metabolism and lipid profiles in men and women; and has been successfully used to treat and prevent CV disease and diabetes [24]. T acts as a vasodilatorin both sexes, has immune-modulating properties that inhibit atheromata, and has a beneficial effect on cardiac muscle [25–27].

Low T in men is associated with an increased risk of heart disease and mortality from all causes [28,29]. In addition, low T is an independent predictor of reduced exercise capacity and poor clinical outcomes in patients with heart failure. Similar to men, T supplementation has been shown to improve functional capacity, insulin resistance and muscle strength in women with congestive heart failure [30].

Testosterone is a diuretic. However, T can aromatize to E2, which can have adverse effects including edema, fluid retention, anxiety, and weight gain. Medications, including statins and anti-hypertensives, increase aromatase activity and elevate E2, indirectly causing side effects from T therapy.

Fact
There is substantial evidence that testosterone is cardiac protective and that adequate levels decrease the risk of cardiovascular disease

2.7. Myth: Testosterone causes liver damage

Although high doses of oral, synthetic androgens (e.g., methyltestosterone) are absorbed into the entero-hepatic circulation and adversely affect the liver; parenteral T (i.e., subcutaneous implants, topical patch) avoids the entero-hepatic circulation and bypasses the liver. There are no adverse affects on the liver, liver enzymes or clotting factors [31]. Non-oral T does not increase the risk of deep venous thrombosis or pulmonary embolism unlike oral estrogens, androgens and synthetic progestins.

Despite the concern over liver toxicities with anabolic steroids and oral synthetic androgens, there are only 3 reports of hepatocellular carcinoma in men treated with high doses of oral synthetic methyl testosterone. Even benign tumors (adenomas) were exceedingly rare with oral androgen therapy.

Fact
Non-oral testosterone does not adversely affect the liver or increase clotting factors

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2.8. Myth: Testosterone causes aggression

Although anabolic steroids can increase aggression and rage, this does not occur with T therapy. Even supra-pharmacologic doses of intramuscular T undecanoate do not increase aggressive behavior [32].

As previously mentioned, T can aromatize to E2. There is considerable evidence in a wide variety of species, that estrogens, not T, play a major role in aggression and even hostility through action at ER alpha [33,34].

In women, we previously reported that subcutaneous T therapy decreased aggression, irritability and anxiety in over 90% of patients treated for symptoms of androgen deficiency [5]. This is not a new finding: androgen therapy has been used to treat PMS for over 60 years.

Fact
Testosterone therapy decreases anxiety, irritability and aggression

2.9. Myth: Testosterone may increase the risk of breast cancer

As early as 1937 it was recognized that breast cancer was an estrogen sensitive cancer; that T was 'antagonistic' to estrogen and could be used to treat breast cancer as well as other estrogen sensitive diseases including breast pain, chronic mastitis, endometriosis, uterine fibroids and dysfunctional uterine bleeding [8]. However, some epidemiological studies have reported an *association* between elevated androgens and breast cancer. Notably, these studies suffer from methodological limitations, and more importantly, do not account for associated elevated E2 levels and increased body mass index. In addition, the 'cause and effect' interpretation of these inconsistent observational studies conflicts with the known biology of T's effect at the AR. AR signaling exerts a pro-apoptotic, anti-estrogenic, growth inhibiting effect in normal and cancerous breast tissue [35,36].

Clinical trials in primates and humans have confirmed that T has a beneficial effect on breast tissue by decreasing breast proliferation and preventing stimulation from E2 [37,38]. It is the T/E2 ratio, or the balance of these hormones that is breast protective. T does not increase, and likely lowers the risk of breast cancer in women treated with estrogen therapy [39]. Although T is breast protective, it can aromatize to E2 and have a secondary, stimulatory effect via estrogen receptor (ER) alpha.

T combined with an aromatase inhibitor (subcutaneous implant) has been shown to effectively treat androgen deficiency symptoms in breast cancer survivors and is currently being investigated in a U.S. national cancer study as potential therapy for these symptoms, as well as, aromatase induced arthralgia [40,41].

Fact
Testosterone is breast protective and does not increase the risk of breast cancer

2.10. Myth: the safety of testosterone use in women has not been established

There are many excellent reviews on the safety of parenteral T therapy in women [6,7]. Testosterone implants have been used safely in women since 1938. Long-term data exists on the efficacy, safety and tolerability of doses of up to 225 mg in up to 40 years of therapy [9,42]. In addition, long term follow up studies on supra-pharmacologic doses used to 'female to male' transgender patients report no increase in mortality, breast cancer, vascular disease or other major health problems [43,44].

Many of the side effects and safety concerns attributed to T are from oral formulations, or are secondary to increased aromatase activity, subsequent elevated E2 and its effect at the ER. Aromatase activity increases with age, obesity, alcohol intake, insulin resistance, breast cancer, medications, drugs, processed diet and sedentary lifestyle. Although often overlooked or not addressed in clinical studies, monitoring aromatase activity and symptoms of elevated E2, is critical to the safe use of T in both sexes.

Fact
The safety of non-oral testosterone therapy in women is well established, including long-term follow up

3. Conclusion

Adequate T is essential for physical, mental and emotional health in both sexes. Abandoning myths, misconceptions and unfounded concerns about T and T therapy in women will enable physicians to provide evidence based recommendations and appropriate therapy.

Contributors

Rebecca Glaser and Constantine Dimitrakakis contributed equally to the research and the writing of the manuscript.

Competing interest

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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.

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)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

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

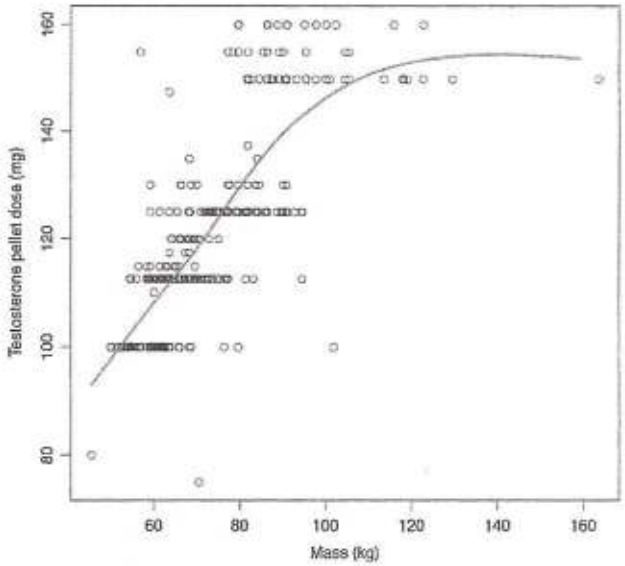

Fig. 2. Testosterone pellet dose (mg) implanted compared to patients reported weight in kilograms. The testosterone pellet dose prescribed to the each patient depended strongly, in a non-linear fashion, on her weight.

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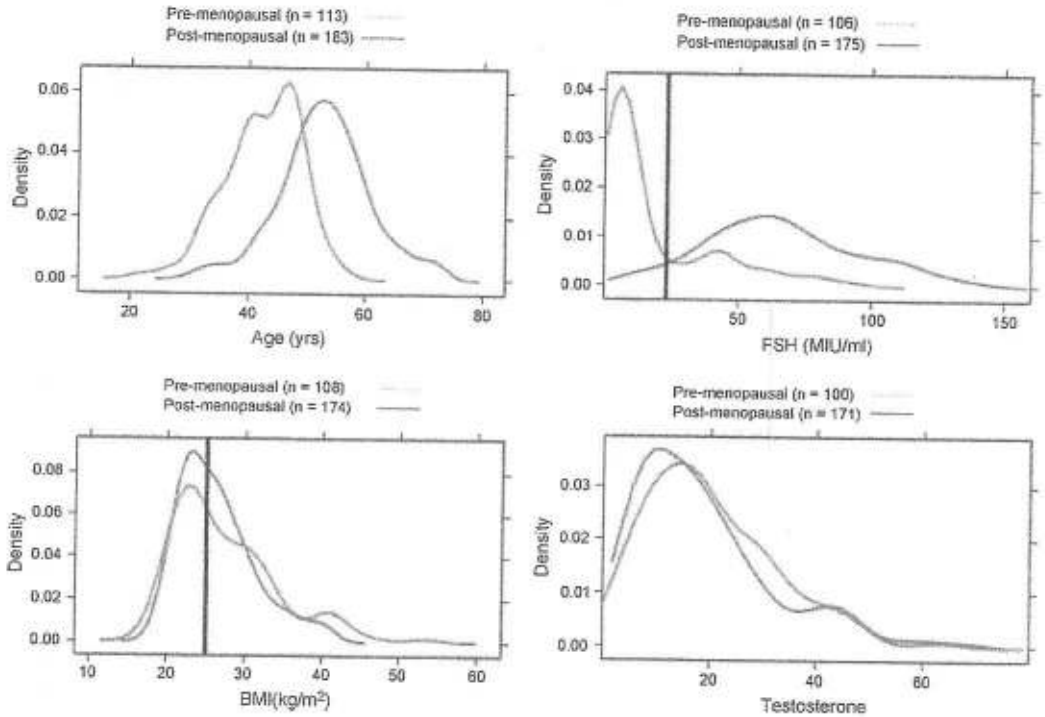

Fig. 3. Patient demographics distribution: pre- and post-menopausal age, FSH, BMI and total testosterone. Age (mean): pre-menopausal, 42.7 years. Post-menopausal, 53.0 years. FSH: 26.4% of pre-menopausal patients had an FSH > 23 MIU/ml (vertical line). 5.7% of post-menopausal patients had an FSH < 23 MIU/ml. BMI (mean): pre-menopausal, 27.6 kg/m². 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 questionnaire 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/m²), 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/m² (range 19.29–53.16,

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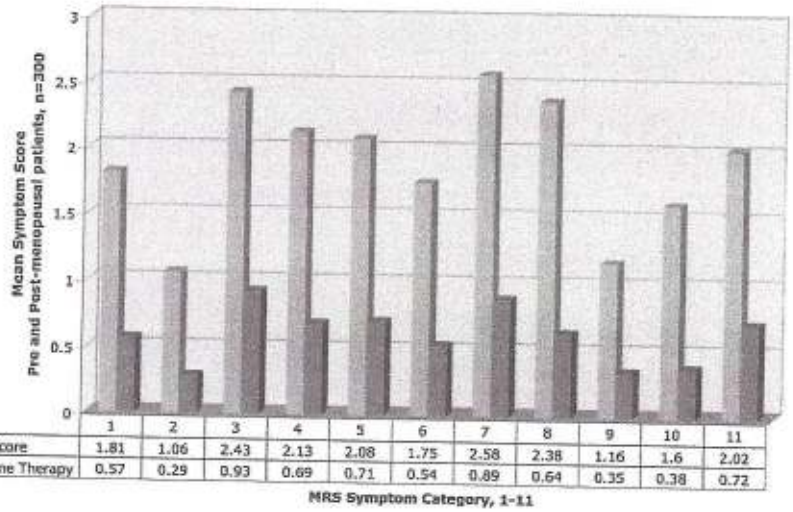

	1	2	3	4	5	6	7	8	9	10	11
Baseline Score	1.81	1.06	2.43	2.13	2.08	1.75	2.58	2.38	1.16	1.6	2.02
Testosterone Therapy	0.57	0.29	0.93	0.69	0.71	0.54	0.89	0.64	0.35	0.38	0.72

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 ($N = 300$).[a] Statistically significant improvement ($P < 0.0001$) was demonstrated in each of the 11 MRS symptom categories. [a]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^2), 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 and16 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)[1] 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^2) 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.

[1] (1)–(11) denotes MRS individual symptom categories.

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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).

	n	Scores before (SD)	Scores after (SD)	Absolute change (SD)	Percent (%) change	P[a]
Combined cohort						
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
Pre-menopausal patients						
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
Post-menopausal patients[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

[a] Paired t-test for dependent samples: significance of the absolute difference.
[b] 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.

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].

Table 2
MRS score improvement by testosterone, relative to severity of symptoms at baseline.

Severity score of complaints at baseline range (mean)	N[a]	Improvement total score mean (SD)	Improvement psychological score mean (SD)	Improvement somatic score mean (SD)	Improvement urogential 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.
[a] Only patients who completed all questions on both baseline and follow-up MRS questionnaires were included in this analysis.

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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 neuroprotective 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.

They say higher levels than endogenous "normals" are needed

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