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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.

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Contents

1. Introduction.....	00
2. 'Top 10' myths about testosterone use in women.....	00
2.1. Myth: Testosterone is a 'male' hormone.....	00
2.2. Myth: Testosterone's only role in women is sex drive and libido.....	00
2.3. Myth: Testosterone masculinizes females.....	00
2.4. Myth: Testosterone causes hoarseness and voice changes.....	00
2.5. Myth: Testosterone causes hair loss.....	00
2.6. Myth: Testosterone has adverse effects on the heart.....	00
2.7. Myth: Testosterone causes liver damage.....	00
2.8. Myth: Testosterone causes aggression.....	00
2.9. Myth: Testosterone may increase the risk of breast cancer.....	00
2.10. Myth: the safety of testosterone use in women has not been established.....	00
3. Conclusion.....	00
Contributors.....	00
Competing interest.....	00
Funding.....	00
Provenance and peer review.....	00
References.....	00

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 micromolar compared to picograms/ml or picomolar for E2. In addition, there are exponentially higher levels of proandrogens: dihydroepiandrosterone sulfate (DHEAS), dihydroepiandrosterone (DHEA) and androstenedione, supplying significant amounts of T

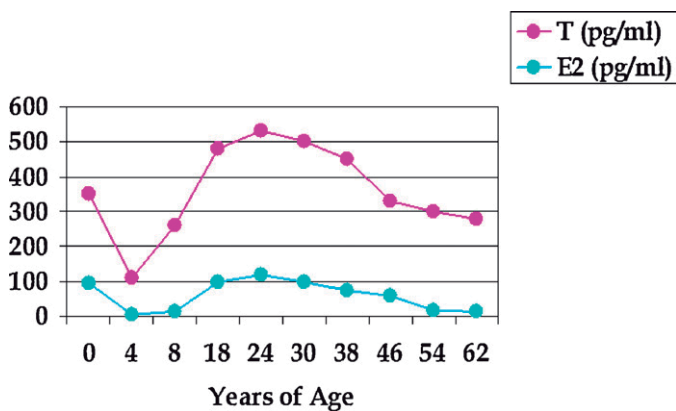


Fig. 1. Throughout the female lifespan, testosterone (T) is the most abundant active steroid. T levels are significantly higher than estradiol (E2) levels, adapted from Ref. [1].

to the androgen receptor (AR) in both sexes. In fact, the measured ranges of androgen precursors are similar in men and women.

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 vasodilator in 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 E<sub>2</sub>, which can have adverse effects including edema, fluid retention, anxiety, and weight gain. Medications, including statins and anti-hypertensives, increase aromatase activity and elevate E<sub>2</sub>, 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., methyl-testosterone) 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 effects 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

Neither author (RG, CD) has any competing interests.

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