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Testosterone and Sexual Desire: A Review of the Evidence

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Abstract

Sexual desire is driven by complex interactions between various biopsychosocial factors including neuroendocrine regulation, mental state, and cultural values. Herein we perform a narrative review to describe the underlying physiology of sexual desire and summarize the current literature linking testosterone to sexual function. The following search terms were used to identify articles on the Medline and PubMed databases: "libido," "testosterone replacement therapy," "androgen receptor," and "sexual desire." Only articles in English were included. Several animal and human studies have implicated the pivotal role of testosterone (T) in regulating the physiological pathways underlying sexual desire. Functional imaging studies have identified several regions in the brain that are activated by sexual stimuli and these androgenic pathways. A strong correlation between serum T levels and libido in men has been reliably and repeatedly demonstrated. An important clinical application of this association is the improvement of sexual desire secondary to testosterone replacement therapy in hypogonadal men. We summarize the current literature on the neuroendocrine role of testosterone in sexual desire and its dose-dependent relationship with libido.

Keywords: testosterone; androgens; sexual desire; libido; hypogonadism

Introduction

The male sexual response cycle was first conceptualized by Kaplan in 1974 as four distinct phases: desire, arousal, orgasm, and resolution.[1] Sexual desire is defined as the forces that lead an individual to initiate and maintain human sexual behavior, and can be triggered by both intrinsic and external stimuli.[2] Desire has been further categorized into three separate components, including drive (biological factors including the neuroendocrine system), motive (psychological factors including mental and relationship state), and wish (cultural factors including ideals and values).[3]

From a biological perspective, several studies have demonstrated that hormones, particularly androgens,

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play a critical role in regulating sexual desire.[4,5] Testosterone (T) has been shown to account for variations in sexual desire between the genders as well as among individuals of the same gender.[6] Although sexual desire is a multifactorial process, herein we aim to summarize the physiology of T in male sexual desire and describe the current literature regarding the role of T in libido, sexual desire, and replacement therapy. We hypothesized that current literature adequately describes the physiological mechanisms of desire, but that further research is required to fully explore the relationship between T and sexual function.

Methods

We identified articles for this review through article database search on Medline and PubMed. The following search terms were used to identify articles: "libido," "testosterone replacement therapy," "androgen receptor," and "sexual desire." Only articles written in English were included in this review. There was no preference given to more recently published articles.

Physiological Pathways of Sexual Desire

Sexual desire arises from a complex interaction of distinct areas of the brain that respond to endogenous androgens. Androgen receptors (ARs) are expressed in several regions of the brain including the temporal lobe, hypothalamus, amygdala, midbrain, preoptic, prefrontal, and frontal areas, as well as the cingulate gyrus.[7] The mediobasal hypothalamus and limbic system have been identified as the regions of the brain most involved in regulating sexual desire, and correspondingly have the highest expression of ARs.[7] These regions in the mesocorticolimbic system have also been shown to locally synthesize androgens.[7]

Animal studies have served as the foundation for elucidating androgenic modulation of sexual desire. Raskin et al demonstrated that mice selectively lacking AR expression exhibited impaired sexual behavior, defined as attempts to mount, thrust, or ejaculate with the introduction of a female mouse.[8] Similarly, Beach and Pauker, and Beach and Holz examined male hamsters and rats after castration versus subsequent androgen administration and showed that reintroduction of androgens restored copulatory behavior.[9,10] These studies suggest that both androgens and ARs are necessary for the presence of sexual desire and behavior.

Regions of the brain activated during sexual desire have also been identified in human studies. Stoléru et al aimed to identify the areas in the male brain that are activated with visual sexual stimuli utilizing positron emission tomography and statistical parametric mapping.[11] Compared with emotionally neutral control video clips and humorous control video clips, the regions of the brain with the highest activity during viewing of sexually explicit video clips included the bilateral inferior temporal gyri, the right anterior insula, the right inferior frontal gyrus, the head of the right caudate nucleus, and the left anterior cingulate gyrus.[11] In addition, plasma T level was significantly positively correlated with increased cerebral blood flow to these regions during visually evoked sexual arousal ($p < 0.001$).[11]

Park et al utilized functional magnetic resonance imaging (fMRI) to decipher the neuroanatomy of the brain activated by visual sexual stimulation.[12] Erotic visual stimulation significantly activated the inferior frontal lobe, cingulate gyrus, insula gyrus, corpus callosum, thalamus, caudate nucleus, globus pallidus, and inferior temporal lobes in healthy men.[12] Furthermore, the authors examined hypogonadal men; among this population, only the inferior temporal and thalamic areas were significantly activated with sexual visual stimulation. However, after T supplementation, fMRI showed activity similar to healthy men with significant activation of the same regions of the brain as healthy men.[12]

In sum, both animal and human *in vivo* studies have reliably demonstrated that androgenic pathways within the brain play a pivotal role in regulating sexual desire and arousal.

Testosterone and Sexual Desire

Various studies have analyzed the association between T and sexual desire. Travison et al conducted an epidemiological study to assess the relationship between self-reported libido and serum T concentrations among 1632 men enrolled in the Massachusetts Male Aging Study at three different time points: baseline, 9-year follow-up, and 15-year follow-up.[13] Libido was measured with a score ranging from 0 to 14 based on self-reported frequency of sexual desire, sexual thoughts, fantasies, and erotic dreams, with low libido defined as a score <7. Libido and T concentration were significantly correlated ($p < 0.001$); furthermore, low libido score was predictive of low T levels ($p = 0.002$).[13]

Likewise, Corona et al demonstrated an inverse correlation between T levels and hypoactive desire, independent of age, in a retrospective study of 3714 men (mean age 53.2 ± 12.5 years).[14] In this study, reduced libido was assessed using question no. 14 from the

structured interview for erectile dysfunction, "Did you have more or less desire to make love in the last 3 months?" Many other studies have specifically evaluated the role of androgens in regulating libido in older men, as age-related reduction in T levels has been extensively documented.[15–17] Hsu et al assessed the longitudinal relationship between androgen status and sexual desire among men aged 70 years and older from the Concord Health and Aging in Men Project at baseline and at 2-year follow-up.[18]

Sexual desire was determined by the question, "How much desire for sex do you have now, compared with when you were 50?" with responses dichotomized into categorical variables of decreased versus not decreased. The authors found a significant correlation between T levels and sexual desire ($p < 0.001$); for each standard deviation decline in T levels, there was an adjusted odds ratio of 1.19 (95% confidence interval [CI], 1.05–1.35) for decline in sexual desire.[18] Together, these studies suggest a physiological correlation between serum T levels and libido.

In addition, Wu et al performed a cross-sectional study utilizing questionnaires to survey a random population of men from The European Male Aging Study across eight centers and demonstrated an inverse relationship between decreasing T levels and increasing sexual symptoms of low sexual desire as well as poor morning erection and erectile dysfunction.[19] Moreover, the authors identified the threshold of 8 nmol/L of total T and 160 pmol/L of free T for decreased sexual desire. Specifically, a reduction of 1 nmol/L in total T below this threshold of 8 nmol/L was associated with an odds ratio of 1.48 (95% CI, 1.20–1.83) for a low frequency of sexual thoughts.[19] These findings were then replicated in a prospective manner.[20]

Likewise, Cunningham et al performed a cross-sectional study across 12 sites in the United States to interrogate the association between sex hormones and sexual function among 788 men who were active participants in the testosterone trials.[21] Inclusion criteria for participants included men aged 65 years or older with self-reported sexual dysfunction, diminished vitality, and/or mobility limitation, as well as an average of two total T levels ranging from 100 to 275 ng/dL.[21]

Specifically, men qualified for the sexual function trial if they endorsed reduced libido, scored ≤20 on the sexual desire domain of the Derogatis Interview for Sexual Function, and had a partner willing to have sexual intercourse at least twice a month ($n = 470/788$, 60%).[21] The investigators found that mean sexual desire ($p = 0.02$), erectile dysfunction ($p = 0.05$), and sexual activity ($p = 0.01$) all increased significantly with free T. Similarly, total T was marginally associated with desire ($p = 0.055$), and significantly associated with erectile function ($p = 0.005$) and sexual activity ($p = 0.03$).

Overall, these studies provide evidence supporting a strong association between serum T levels and libido in men.

Testosterone Replacement Therapy and Libido

The aforementioned studies have served as the underlying rationale for treatment of hypogonadal men with testosterone replacement therapy (TRT) (Table 1).[22] Seftel et al revealed that T supplementation in hypogonadal men (total $T \leq 300$ ng/dL, $n = 406$, mean age 58 years) significantly improved sexual function.[23] The men were randomized to three groups: T gel (50 and 100 mg/day), T patch, versus placebo. Primary end points evaluated at 30 and 90 days post-treatment included frequency of intercourse, frequency of nighttime erections, and sexual desire measured on a Likert-type scale.

At day 30, a significant increase from baseline sexual desire was noted for those on 100 mg/day T gel compared with those on 50 mg/day T gel (increase by 1.2 vs. 0.4, $p < 0.001$), T patch (1.2 vs. 0.7, $p < 0.0013$), and placebo (1.2 vs. 0.4, $p < 0.001$).[23] This increase in sexual desire among men on 100 mg/day T gel continued at day 90 compared with 50 mg/day T gel (1.0 vs. 0.5, $p = 0.0165$), T patch (1.0 vs. 0.6, $p = 0.0317$), and placebo (1.0 vs. 0.5, $p = 0.0035$).[23] Improved frequency of nighttime erections and sexual intercourse was also observed with T supplementation. Thus, these data support a strong dose-dependent relationship between restoring serum T in hypogonadal men and improvement in sexual function.

Similarly, Wang et al demonstrated that transdermal T significantly improved sexual function among otherwise healthy hypogonadal men ($T \leq 300$ ng/dL, $n = 277$, age 19–68 years) across 16 centers in the United States.[24] Men were randomized into three groups: 50 mg/day T gel ($n = 73$), 100 mg/day T gel ($n = 78$), and T patch ($n = 76$). Sexual function and mood were evaluated through questionnaires assessing sexual daydreams, anticipation of sex, sexual interaction, orgasm, erection, masturbation, ejaculation, and intercourse on days 0, 30, 60, 90, 120, 150, and 180 during gel and patch application.

Sexual desire significantly increased after transdermal T treatment without any group differences

Table 1. Improvement in Sexual Desire Secondary to Treatment of Hypogonadal Men with Testosterone Replacement Therapy

Study	Subjects	Intervention(s)	Primary end point	Outcome
Seftel et al[23]	Hypogonadal men with T_{total} ≤300 ng/dL $n=406$	T gel 50 mg/day T gel 100 mg/day T patch	Libido measured on Likert-type scale at days 30 and 90	Day 30 100 mg/day T gel superior vs.: 50 mg/day T gel ($p<0.001$) T patch ($p<0.0013$) Placebo ($p<0.001$) Day 90 100 mg/day T gel superior vs.: 50 mg/day T gel (<0.0165) T patch ($p=0.0317$) Placebo ($p=0.0035$)
Wang et al[24]	Hypogonadal men with T_{total} ≤300 ng/dL $n=277$	T gel 50 mg/day T gel 100 mg/day T patch	Questionnaire on sexual dreams, anticipation of sex, sexual interaction, orgasm, erection, masturbation, ejaculation, and intercourse at days 0, 30, 60, 90, 120, 150, and 180	Libido increased after transdermal T without any intergroup differences ($p=0.0001$)
Steidle et al[25]	Hypogonadal men with AM $T\leq 10.4$ nmol/L $n=406$	T gel 50 mg/day T gel 100 mg/day T patch	Questionnaire regarding performance, motivation, spontaneous erections, desire, enjoyment (with and without a partner), and satisfaction with erection duration at day 90	Only 100 mg/day T gel superior vs. placebo for improved erections ($p<0.001$), sexual motivation ($p<0.05$), libido ($p<0.01$), and sexual performance ($p<0.05$)
Finkelstein et al[27]	Induced hypogonadism in healthy men with 3.6 mg goserelin acetate at weeks 0, 4, 8, 12 $n=400$	Cohort 1 ($n=198$) placebo, 1.25, 2.5, 5, or 10 g of topical 1% T gel daily for 16 weeks Cohort 2 ($n=202$) Additional anastrozole 1 mg daily	Questionnaire of health-related quality of life previously validated among patients with prostate cancer undergoing ADT	Cohort 1 Libido decreased with declining T doses Cohort 2 Libido declined significantly in placebo group compared with that in men in the three highest dose groups

ADT, androgen deprivation therapy; AM, ante meridiem or morning.

($p=0.0001$).[24] Sexual performance also significantly increased ($p=0.0001$); however, there was a greater increase among the T gel groups compared with the T patch group ($p=0.0113$).[24] These data confirmed the dose-dependent relationship between T and sexual desire.

Steidle et al conducted a multicenter randomized controlled trial and demonstrated that 100 mg/day T gel significantly improved sexual desire among 406 hypogonadal men (AM $T\leq 10.4$ nmol/L).[25] Sexual functioning was assessed through a previously validated questionnaire and included the following components: performance, motivation, spontaneous erections, desire, enjoyment (with and without a partner), and satisfaction with erection duration and size at day 90.[26]

Compared with men in the placebo group, men who received 100 mg/day T gel showed a significant improvement for spontaneous erections ($p<0.001$), sexual motivation ($p<0.05$), sexual desire ($p<0.01$), and sexual performance ($p<0.05$).[25] However, this same effect was not seen in men who received 50 mg/day of T gel or T patch versus placebo, suggesting a dose-dependent effect and superior efficacy with 100 mg/day T gel.

The restorative function of TRT in improving sexual function observed in men with baseline hypogonadism has also been demonstrated in healthy men with induced hypogonadism. In a randomized controlled trial, Finkelstein et al administered 3.6 mg goserelin acetate at weeks 0, 4, 8, and 12 to suppress endogenous gonadal steroids to 400 healthy men aged 20–50 years. In cohort 1 ($n=198$), participants were then randomized to receive 0 g (placebo), 1.25, 2.5, 5, or 10 g of topical 1% T gel daily for 16 weeks.[27] In cohort 2 ($n=202$), patients also received anastrozole 1 mg daily to block the aromatization of T to estrogen.

Sexual desire was measured through a self-administered questionnaire on health-rated quality of life previously validated among patients with prostate cancer undergoing androgen deprivation therapy.[28] Sexual desire decreased progressively with declining testosterone doses among men in cohort 1. In cohort 2, sexual desire declined significantly in men who

received placebo compared with men in the three highest dose groups and declined more in men who received 1.25 g of T daily versus men in the two highest dose groups. These findings reinforce that T levels are intimately associated with libido in a step-wise dose-dependent manner and that exogenous T is able to restore sexual desire in chemically castrated men.

Overall, these studies provide substantial evidence supporting the utility of TRT in increasing sexual desire in hypogonadal men. However, further studies are required to further characterize optimal methods of administration for individual patients.

Conclusions

In conclusion, this review summarizes the endogenous androgen neuroendocrine system and describes studies evaluating the role of T in human sexual desire and function. Limitations of this review include study inclusion criteria, which did not analyze studies published in languages other than English. Future systematic reviews should be conducted to further analyze the current literature in a regimented manner. Sexual desire is a sequela of complex multifactorial interactions among various biopsychosocial influences.

Both animal and human studies have solidified the role of androgens in the neuroendocrine pathways that regulate sexual desire, and this association has been validated in numerous clinical studies. The strong relationship between T and sexual desire underlies the clinical foundation of TRT in hypogonadal men, with data suggesting increased efficacy in a dose-dependent manner and with superiority of gel over patch application.

Authors' Contributions

V.N. conducted literature review. V.N., A.L., and T.H. contributed to the writing of the article and associated table.

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Abbreviations Used

ADT = androgen deprivation therapy
AM = ante meridiem or morning
ARs = androgen receptors
CI = confidence interval
fMRI = functional magnetic resonance imaging
T = testosterone
TRT = testosterone replacement therapy