Genital and Subjective Measurement of the Time Course Effects of an Acute Dose of Testosterone vs. Placebo in Postmenopausal Women

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ABSTRACT

Introduction. Recent research on the impact of testosterone (T) on female sexual function has yielded inconsistent results, and few studies have used physiological measures of genital arousal.
Aim. This study examined the effects of an acute dose of methyltestosterone (MT) on physiological (genital) and subjective sexual response in postmenopausal women.
Main Outcome Measures. Vaginal pulse amplitude (VPA) and self-reported sexual response.
Methods. Randomized, double-blind, crossover, placebo-controlled trial of 5 mg MT, consisting of two separate 8-hour visits. Participants were 10 postmenopausal women without sexual dysfunction. Participants viewed both neutral and erotic video segments during five post-dose trials while their genital and subjective responses were monitored.
Results. The Wilcoxon signed rank test indicated a significant difference in VPA between the T (M = 0.018, SD = 0.018) and placebo (M = 0.016, SD = 0.017) conditions at 4.5 hours post-dose ($P = 0.03$). Higher difference scores were noted for 80% of subjects during the T condition at 4.5 hours, in contrast with only 50% of subjects responding to T at the other four time points. No differences were found on VPA relative change scores or subjective sexual arousal scores. When summed across all five time points, genital and subjective measures were correlated regardless of medication condition (0.62 and 0.60 for self-reported physical and mental sexual arousal scores, respectively).
Conclusions. These findings in postmenopausal women combined with those of two previous investigations in premenopausal women demonstrate a probable acute-dose time delay for genital sexual effects of exogenous T with no change in self-reported sexual arousal. Further investigation is needed to determine whether acute dosing of T has a consistent and predictable impact on genital arousal that has promise for the treatment of any subgroup of women with sexual disorders. **Heard-Davison A, Heiman JR, and Kuffel S. Genital and subjective measurement of the time course effects of an acute dose of testosterone vs. placebo in postmenopausal women. J Sex Med 2007;4:209–217.**

Key Words. Testosterone; Sexual Response; Vaginal Pulse Amplitude

Introduction

Over the past three decades, attempts have been made to better understand the relationship between hormones and sexual functioning [1–5]. The effects of androgens are believed to be related to sexual motivation, arousability, and receptivity [3], with research indicating a relationship between testosterone (T) and autoerotic behavior [6] and sexual activity with a partner [7]. Panels of international experts in the field have concluded that intact sex steroids are one of three critical pathways necessary for maintaining sexual function [8] and outlined the contribution of adequate levels of T, particularly bioavailable T, to women's well-being, energy and sexual desire, receptivity and pleasure [9,10]. However, available research examining the connection between abnormal hormone levels and sexual dysfunction remains limited, and there are still no clear guidelines for treatment.

Research demonstrating the relationship between endogenous free testosterone (FT) and women's sexual experiences has been fairly inconclusive to date. Some studies indicate that endogenous FT is related to frequency of sexual intercourse [11,12], more satisfaction with partners [13], greater frequency of sexual interactions [13], sexual interest/desire [12,14], frequency of orgasm [12], and sexual awareness [14], but not with frequency of masturbation [11]. These findings indicate a positive relationship between FT and sexual interest and, at times, sexual behavior. Studies in women with a rapid decline in T (up to 50%, along with decreased estrogen) because of surgical menopause have also found higher rates of decreased sexual desire, arousal, satisfaction, and sexual activity compared with naturally menopausal women [10,15]. Alternatively, recent clinical and population-based studies have shown little correlation among endogenous measures of androgen and sexual parameters [16–20]. It is possible, however, that this lack of correlation may be due to a reduction of intracellular production of T in the women with sexual dysfunction, but this reduction would not be reflected by serum levels.

Exogenous T administration studies indicated that menopausal women not taking hormone therapy (HT) reported similar levels of sexual difficulty (loss of desire) to women on esterified estrogen (EE) therapy [21]. When T was included in HT, most studies have found positive effects in the areas of sexual activity and pleasure [22–27], although a recent review of randomized controlled trials indicated several limitations in this literature including use of measures with limited reliability/validity data, insufficient attention to statistical power, focus on group data vs. individual change, the magnitude of clinically significant improvement, the impact of supraphysiologic hormone levels, and the relationship between mood, quality of life, and sexual function [28]. Two recent randomized controlled studies were designed specifically to examine the impact of including methyltestosterone (MT) with EEs on sexual function in postmenopausal women. Both studies selected women who reported a decline in sexual desire or satisfaction. Women taking EE plus MT reported a greater change from baseline on self-reported "sexual sensation" [21], desire [21,29], frequency of interest/desire, and responsiveness [29]. Subjective genital response and frequency of sexual intercourse were not significantly different between groups [21]. These data suggest that chronic dosing of EE plus MT impacts both sexual desire and arousal (in the form of clitoral sensation and sensitivity) via hormonal mechanisms. In recent reviews of the literature on endocrine aspects of female sexual dysfunction and hypoactive sexual desire, the authors concluded that the limited data available indicate that T is effective in increasing sexual desire, arousal, and satisfaction, but caution that we still lack reliable biochemical measures to indicate who will benefit from treatment or clear guidelines regarding the safety of long-term use [30,31].

Studies using laboratory measures (vaginal photoplethysmograph or Doppler velocimeter) following *chronic* T supplementation have not found significant changes in genital response [32–34]. However, recent laboratory studies have examined the effects of an *acute* dose of T in sexually functional premenopausal women using a vaginal photoplethysmograph (vaginal pulse amplitude [VPA]). Tuiten et al. [35,36] used a time series design to measure vaginal response to neutral and erotic video segments at 1.5-hour intervals for 6 hours following administration of 0.5 mg T (sublingual). While T levels in the blood peaked at 15 minutes post-dose, the relative change in VPA and ratings of "sexual lust" were highest at 4.5 hours post-dose. A subsequent study measured only two time points (to eliminate repeated exposure to erotic material) and found an increase in vasocongestion at 4.5 hours but not in ratings of "genital sensations" and "sexual lust" [36]. Based on both findings, they concluded that an acute dose of T resulted in delayed genital, but not subjective, changes in sexual arousal. In contrast, blood levels peaked at 5.5 hours but there was no increase in genital or subjective sexual response when premenopausal women without sexual dysfunction were administered topical T, applied to the vaginal region [37].

These findings may have particular relevance in the context of the newly developing definitions of female sexual arousal disorder that include an examination of both physiological genital arousal and mental excitement (i.e., subjective arousal) [38]. A subgroup of women who have problems with genital but not subjective arousal has been identified in laboratory studies using both physiological and subjective measurements [39]. Alternatively, other researchers have demonstrated a subgroup of women with (unspecified) "arousal disorder" who showed normal genital responding but denied subjective arousal during the laboratory experience [40]. Women with low sexual desire have also reported decreased functioning in

other aspects of sexual function such as arousal, orgasm, and pleasure [15]. Altogether, these findings demonstrate the importance of examining both physiological (genital) and subjective components of female sexual arousal, particularly when studying the impact of exogenous hormonal (i.e., T) administration on women's sexual functioning.

Aims

Because of the potential role of T in both subjective sexual arousal and genital congestion, the present investigation examined the effects of acute T dosing on physiological (VPA) and subjective measures of sexual arousal in postmenopausal women. Past research has found an increase in VPA 4.5 hours following an acute dose of T in premenopausal women. The present study attempted to replicate the time course effects of acute T dosing in women and is the first to examine administration of an acute dose of T to postmenopausal women.

Methods

Participants

Ten sexually functional, healthy, postmenopausal women were recruited for a study of hormones and sexuality via advertisements in the local city newspaper and flyers posted at a major teaching hospital. Sexually functional women were included in the present study in an effort to establish normative data and improve our ability to detect the possible effects of T on sexual arousal without the influence of sexual dysfunction. All10 women we recruited were run according to protocol and none were lost to attrition. The mean age for participants was 56.8 years (SD = 4.26, range 50–62); nine were Caucasian, one was African American; seven were married (N = 3) or in a current relationship (N = 4); eight were employed at least part-time; all had completed at least some college.

In order to be included, participants were required to be 50–70 years of age, postmenopausal (not menstruated for 12 months or more), heterosexual (because of stimulus material presented), and sexually healthy (no reported problems with desire, arousal, orgasm or pain). Participants were excluded if they had taken antidepressant medications, antihypertensive medications, hormone-replacement therapy, or cold or allergy medications in the previous 6 months; had received androgen supplementation in the last 6 months; had a self-reported history of key health issues (cardiovascular problems, breast or uterine cancer, untreated hyper- or hypo-thyroidism, diabetes, severe genital trauma, severe dizziness, smoking); or were currently depressed or abusing alcohol. Women with hysterectomies were eligible.

Design and Procedure

We used randomized, double-blind, placebo-controlled crossover dosing to test a single dose of 5 mg MT vs. placebo. The study procedures were approved by the University of Washington Institutional Review Board Human Subjects Division and participants signed an informed consent form prior to initiation of any study procedures. Participants presented to the Sexual Psychophysiological Laboratory for two separate visits at 1–2-week intervals. All visits began at 8:30 AM to control for potential daily circadian fluctuations. Participants were instructed to refrain from any form of intense exercise, to limit their caffeine intake, and not to use any medications or alcohol for 12 hours prior to the visit.

Participants completed questionnaires that included demographic information, medical history, and sexual functioning in a private room where they also viewed videos. Participants were given either MT (5 mg) or placebo. They completed questionnaires assessing sexual arousal at baseline (prior to dosing).

Five trials were conducted during each visit at 1.5-hour intervals following the dosing (at 1.5, 3, 4.5, 6, and 7.5 hours post-dose). The duration of these trials was approximately 20 minutes. During each trial, we instructed participants to insert the vaginal probe and to remain as still as possible for the duration of the trial in order to minimize movement artifact. The video segments consisted of 5 minutes of neutral footage (nature documentary) and 5 minutes of erotic footage (heterosexual couples engaged in foreplay and intercourse). The five counterbalanced videos differed only in the content of the respective segments.

Main Outcome Measures

Physiological Assessment

Vaginal pulse amplitude response was measured using a vaginal photoplethysmograph. The software program AcqKnowledge III, version 3.3 (BIOPAC Systems, Inc., Santa Barbara, CA, USA) and data acquisition unit (model MP100WS, BIOPAC Systems, Inc., Santa Barbara, CA, USA) were used with a personal computer (Power Macintosh 6100/70, Apple, Cuppertino, CA, USA) to collect, convert (from analog to digital), and transform

data. A sampling rate of 60 samples per second was used for VPA throughout each trial consisting of a brief adaptation, 300 seconds of neutral film, 10 seconds of blank screen, and 300 seconds of erotic film.

Data preparation for statistical analysis involved multiple steps conducted in accordance with previous studies of this nature. The signal was bandpass filtered (0.5–30 Hz). The entire data record was visually inspected and unusual changes indicative of movement artifacts were removed. Mean scores for VPA were obtained by averaging individual calculations of peak-to-peak changes across 30-second intervals for neutral and erotic stimuli.

Subjective Assessment: Sexual Arousal

Subjective sexual response was measured at six time points: baseline (before administration of medication) and after each of five erotic film segments. The Tape/Film Scale (TFS), a self-report rating scale adapted from Heiman [41,42], was used to measure subjective sexual arousal, physical arousal, and current affect. Participants indicated on a 7-point Likert scale the degree to which they experienced each of 39 sensations, ranging from "not at all" (1) to "extremely" (7), and instructions were slightly modified for the baseline condition. The TFS includes items that combine to form subscales for physical and mental sexual arousal and positive and negative affect. The TFS was analyzed in previous studies using both individual items and subscales that were developed using face valid criteria. For this study, these scales included items that were empirically validated as having correlations of 0.80 or higher. The physical sexual arousal scale had a possible range of 7–49 and an alpha of 0.98. The mental sexual arousal scale had a range of 4–28 and an alpha of 0.95. A single question from this measure was also used to assess sexual desire.

Statistical Analyses

Based on a power analysis derived from data collected by Tuiten with premenopausal women, it was determined that a minimum of eight subjects were needed to provide a power over 0.80 for analyses of VPA data and questions regarding subjective sexual response.

Difference scores were derived for each trial by subtracting the erotic VPA mean for minutes 2, 3, and 4 from the neutral VPA mean for minutes 2, 3, and 4 (erotic-neutral). For comparison purposes, we also calculated relative change scores, another frequently used method for examining VPA scores that was used in both prior studies of acute dosing with T [35,36]. Relative change scores for each trial were derived using the following formula: (erotic-neutral/neutral). Difference scores have limitations because they are related to the neutral VPA (greater neutral response is correlated with greater difference scores). Although the relative change score does not have this limitation, there is no consensus in the field regarding which is superior because there is no way to determine whether changes in μHz are consistent across the entire scale and what these differences mean physiologically. Although other measures of genital response are under development to address these issues, VPA as measured by the vaginal photoplethysmograph remains the most frequently used at this time.

Wilcoxon signed rank tests, a nonparametric test for related samples, were used to determine differences between the T and placebo conditions for each of the five trials on physiological and subjective measures of sexual arousal. A nonparametric test was chosen because the data were nonnormally distributed and there was a low number (10). All correlations were run using data collapsed across the five trials, and relationships were evaluated using Pearson correlation coefficients with a Bonferonni corrected alpha of 0.0038.

Results

Physiological Measures of Sexual Arousal

The Wilcoxon signed rank test indicated a significant difference in VPA between the T ($M = 0.018$, $SD = 0.018$) and placebo ($M = 0.016$, $SD = 0.017$) conditions at 4.5 hours post-dose ($P = 0.03$). The means and standard errors for difference scores in the T and placebo conditions across five post-dose trials are presented in Figure 1. The mean response for placebo was not significantly higher than for T at 6 hours post-dose, although there was one strong responder. When looking at response to T as measured by difference scores, 80% of subjects showed a greater VPA response during the T condition at the 4.5-hour post-dose trial, in contrast with only 50% for all other trials. There were no significant differences between the T and placebo conditions at any of the five trials using the genital response measure of relative change in VPA scores. In order to explicate the discrepant findings between difference scores and relative change scores, we compared the means for T and placebo collapsed across trials. Findings indicated that the overall means were higher in the

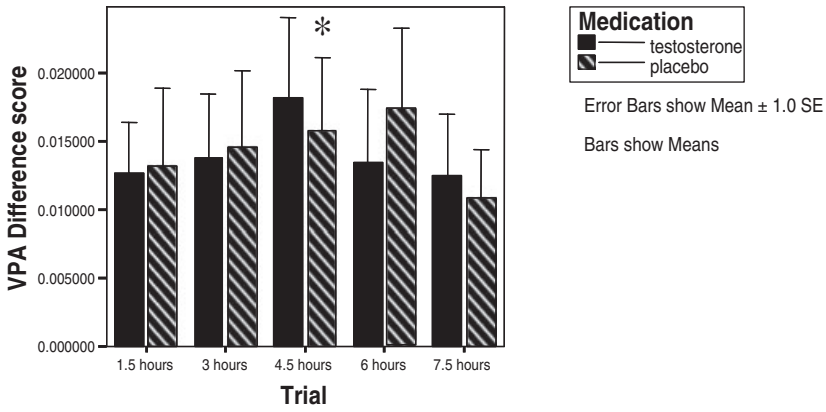

Figure 1 Genital response after methyltestosterone and placebo across five trials. VPA = vaginal pulse amplitude. *$P = 0.03$.

T (0.014 neutral; 0.029 erotic) than placebo (0.013 neutral; 0.027 erotic) condition, although ANOVAs indicated that these differences were not statistically significant, neutral: $F_{1,97} = 1.23$, ns; erotic: $F_{1,97} = 0.10$, ns.

Subjective Measures of Sexual Arousal

Subjective sexual arousal scores indicated that participants became sexually aroused to the erotic video. There were no significant differences on measures of subjective sexual arousal by visit or video across all trials. Wilcoxon signed rank tests indicated no significant differences in scores on scales of mental and physical sexual arousal for each of the five trials between the T and placebo conditions.

Mean mental arousal scores for the T and placebo conditions (collapsed across all trials) were 11.90 (SD = 6.67) and 11.41 (SD = 5.94), respectively (possible scores range from 4 to 28). Mean physical sexual arousal scores for the T and placebo conditions were 21.12 (SD = 12.31) and 20.50 (SD = 11.38), respectively (possible scores range from 7 to 49, see Figure 2). Mean sexual desire scores for the T and placebo conditions were 3.27 (SD = 1.79) and 3.24 (SD = 1.58), respectively (possible scores range from 1 to 7).

Relationship between Subjective and Physiological Measures of Sexual Arousal

Data were collapsed across all trials and both medication conditions to examine whether there was a link between genital and subjective arousal. There were significant ($P < 0.001$) positive correlations between VPA difference scores and mental sexual arousal ($r = 0.60$) and physical sexual arousal scales ($r = 0.62$). The single item assessing self-reported sexual desire was also positively related to VPA ($r = 0.52$).

Discussion

The present study was the first to test the sexual effects of an acute dose of oral T in postmeno-

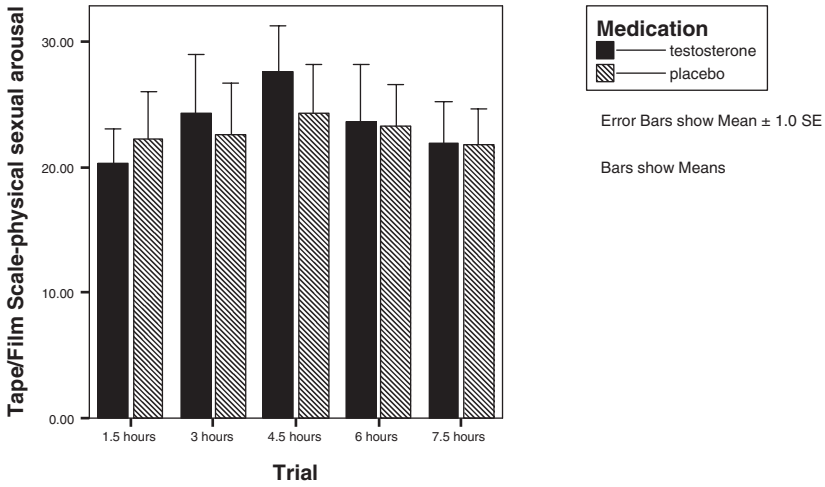

Figure 2 Subjective response after methyltestosterone and placebo across five trials.

pausal women. We found significant differences between T and placebo on VPA measures of difference scores for genital sexual arousal at 4.5 hours post-dose. This finding was not replicated in VPA measures of relative change for genital sexual arousal or measures of subjective sexual arousal. These results provide some support for two prior studies [35,36] and are of interest because they suggest a time delay in sexual effects following administration of T. They expand findings of this delay to healthy postmenopausal women using a different type of T (MT vs. T) and method of delivery (oral vs. sublingual). However, they are in contrast with a recent study that found that while T applied topically to the vaginal area did result in increased serum and FT levels, peaking at 5.5 hours post-dose, it did not impact genital responding over the next 8 hours [37]. All of the studies to date have found that subjective sexual arousal is not influenced by acute T administration. This is an important contribution to a still-emerging literature examining subjective or genital changes associated with acute dosing of T and builds the field of knowledge illustrating the influence of androgens and their method of administration on women's sexual functioning.

There were no significant differences between the T and placebo conditions for subjective measures of arousal at any of the five measurement trials. Perhaps this is due to the relatively low to moderate arousal reported by women across medication conditions, suggesting that the context of a sexual stimulus (e.g., partner interaction) is important in evoking intense arousal, and may override variations in hormone levels. It also may be due to the relatively small sample size. When summed across trials and medication conditions, genital and subjective arousals were significantly correlated, a finding that has not been consistent across studies using physiological measures of sexual arousal [41–45].

Interestingly, differences were found when comparing T and placebo on VPA measures of difference scores but not on VPA measures of relative change scores. When comparing means collapsed across trials for T and placebo conditions, the overall means were higher (though nonsignificantly) in the T than placebo condition for both the neutral and erotic video stimuli. These data suggest that T may be related to increased vaginal blood engorgement overall, independent from sexual stimuli.

Recent longitudinal research has indicated that while total T levels are unrelated to the menopausal transition, the FT index is actually higher in postmenopausal women not on HT [19], the population of women we studied. Measuring total T, FT, or sex hormone binding globulin (SHBG) levels for these women at baseline and after administration of MT would have allowed us to determine their current level of androgen function. Because MT requires a specific assay (it is not detectable by measuring total T or FT), we do not know how exogenously administered MT in this study impacted total or FT or what levels of MT resulted. However, it is likely that this 5 mg dose of MT caused supraphysiological activity at the level of the androgen receptors. In Tuiten's study of acute dosing, they reported no change in SHBG levels over 6 hours and noted a 10-fold increase in total T levels [35]. This is in contrast to chronic dosing studies indicating an increase in bioavailable T because of a decline in SHBG [29].

There are currently no data to indicate how intermittent, acute dosing with T would impact women's health and/or sexual responses. As noted previously, this is a large dose for women and would potentially create a several-fold increase in T on an intermittent basis resulting in supraphysiological activity at the androgen receptor. This may result in some sexual/behavioral responses that would not be seen with T supplementation designed to more closely replicate normal T levels. It is also difficult to predict whether such acute doses of T, even if they do result in increased genital congestion, would successfully impact sexual desire and interest, particularly given findings that subjective arousal does not increase and suggestions by some researchers that it is the combination of the activity of estrogen and androgen receptors that may impact the sexual effects of sex steroids [23,29,46,47]. Finally, it should be noted that the safety of an acute 5 mg dose of MT in women is unknown to date, and the possible risk of serious consequences (e.g., hyperlipidemia, metabolic syndrome) of using such high doses repeatedly would need to be carefully tested.

It is possible that exogenous T may result in an acute increase in peripheral (vaginal) response rather than a central (brain) response in the first 6 hours after administration. The lack of subjective changes in arousal in this study and others' [36,37] study appears to be consistent with data suggesting that serum T, FT, and dehydroepiandrosterone levels do not provide any predictive information for women's sexual functioning [16–20]. These findings contrast with the current conceptualization of T as the hormone primarily

responsible for sexual interest and enjoyment [2,48,49] and with studies of chronic T administration [24,50]. Further research on the physiological connection between T (endogenous levels or administered) and sexual arousal in women would be useful to clarify the temporal relationships between changes in androgen levels and genital and subjective sexual response patterns.

Conclusions

In this sample of 10 postmenopausal women, acute doses of MT 5 mg increased genital sexual arousal (VPA) at 4.5 hours post-dose using one of the two measures employed, indicating a time-delayed effect of exogenous T on vaginal congestion. We did not detect a significant change in self-reported feelings of sexual arousal. To our knowledge, this was the first study to examine the impact of acute T administration in postmenopausal women and represents one of only a few laboratory studies to study the effects of androgens in estrogen-deficient women.

Taking medication in order to enhance sexual function within such a specific time frame (4–5 hours after dosing) would have some limitations in clinical practice, perhaps similar to those reported by men using sildenafil, reducing spontaneity, and creating demand characteristics in the sexual encounter. On the other hand, some women with genital sexual arousal disorders may prefer as needed dosing to chronic HT. However, any clinical use is premature as there are important unanswered questions about the efficacy and safety of using T therapy in women.

Future research of acute dosing of androgens would need to address important issues such as safety and dosing along with both the speed of onset and duration of clinically significant effects on responding. Clinical guidelines advocate thorough assessment of medical and psychosocial factors in order to tailor any treatment regimen to each individual case, and current research suggests that there are numerous nonhormonal factors that affect sexual function with female sexual arousal disorders representing a heterogenous group [51,52]. Within this group, women who demonstrate lower levels of genital response as measured by VPA may be more likely to benefit from medication that increases genital responding [39]. Integrated designs (combining laboratory measures of genital responding and in-home use during partnered sexual activity) would be constructive to examine the relationship of acute doses of T to genital and subjective sexual response in particular populations of interest, such as women with sexual dysfunction, peri- and postmenopausal women, and women with known reduction of androgen production.

Overall, these findings add to research documenting an increase in genital congestion from exogenous T in postmenopausal estrogen-deficient women. However, we still have an as yet incomplete understanding of how T use and supraphysiological T activity will impact women's sexual and medical health.

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