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Preliminary Clinical Experience with Androgen Administration for Pre- and Postmenopausal Women with Hypoactive Sexual Desire

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The present study examined effects of testosterone on hypoactive sexual desire in pre- and postmenopausal women (treated) compared with an age-matched reference group (reference). Treated participants received 100 mg of testosterone cypionate in oil injected intramuscularly (i.m.) monthly for 3 months. We measured salivary testosterone and scores on the Sexual Desire Inventory pretreatment and posttreatment. Treated and reference participants' baseline testosterone was equivalent, however, treated participants exhibited

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higher testosterone levels than did reference participants posttreatment. As expected, treated participants exhibited lower baseline sexual desire than did reference participants and showed a significant increase in sexual desire posttreatment. This research suggests that testosterone may effectively alleviate hypoactive sexual desire, even in women with normal testosterone levels.

Hypoactive sexual desire (HSD) is the most common sexual complaint among women (Davis, 1998; Michael, Gagnon, Laumann, & Kolata, 1994; Talakoub et al., 2002). Recent estimates of prevalence range from 27% to 33% in nonclinical samples of women aged 18–59 years in the United States (Michael et al., 1994; Laumann, Paik, & Rosen, 1999) and from 21% to 53% among Canadian women of reproductive age (Fisher, Boroditsky, & Bridges, 1999). The etiology of HSD is multifaceted and may involve a range of factors from the biological to psychosocial. Basson (2001) found that all women seeking clinical attention for HSD reported a dynamic interplay of more than one causal factor. For example, psychosocial correlates of HSD include inability to relax (Frank, Anderson, & Rubenstein, 1978), poor marital adjustment (Stuart, Hammond, & Pett, 1987), and insufficient emotional intimacy (Basson, 2001). Psychological approaches to the treatment of HSD address these or other issues through individual or couple counseling and therapy.

Endocrine foundations of HSD have also been investigated. Research suggests that androgens are the primary hormones supporting female sexual desire (reviewed in Bachmann, 2002). Although there is strong evidence of a link between low levels of estrogens and sexual dysfunctions (e.g., dyspareunia; Decker et al., 2003; reviewed in Basson, 2002; Traish, Kim, Munarriz, Moreland, & Goldstein, 2002), estrogenic deficiencies appear to be causally linked to "mechanical" difficulties, including decreased vaginal lubrication and genital blood flow, and not to low sexual desire, per se (Sarrel, 2000).

Low androgen levels and HSD are two signs of a condition tentatively referred to as hypoandrogenism (Bachmann, 2002) or female androgen insufficiency syndrome (Bachmann et al., 2003). However, there is little consensus regarding the threshold levels of androgen that define this syndrome or that are required for normal sexual desire (Basson, 2001).

Despite these unresolved issues, HSD is associated with low androgens, primarily testosterone (T; e.g., Sarrel, 2000; Sherwin, 1988). For example, Basson (2001) reported that 25% of patients seeking attention for sexual dysfunctions exhibited androgen deficiencies. Further evidence supports the low androgen–HSD relationship. In a small clinical study of 12 premenopausal women with HSD, eight exhibited low levels of T (Guay, 2001). Women with HSD have significantly lower T than controls with intact sexual drives (Riley & Riley, 2000). A similar relationship between androgens and sexual

desire exists in postmenopausal women; Guay and Jacobson (2002) found that nearly 75% of postmenopausal women with HSD had lower androgens than published norms. Davis, Gilbert, Misiowiec, and Riegel (2003) found that pre-, peri- and postmenopausal women receiving androgen supplementation with and without estrogen replacement therapy (ERT) perceived improvements in their sexuality, including constructs relevant to sexual desire. Finally, Goldstat, Briganti, Tran, Wolfe, and Davis (2003) found that in healthy premenopausal women presenting with low libido and T in the lower three quartiles of the normal range, T therapy increased sexual self-ratings. Thus, evidence supports an association between sexual desire and androgen levels.

Testosterone is synthesized in females from three major sources: the adrenal glands, the ovaries, and conversion in adipose or other peripheral tissues from prohormones (Bachmann, 2002; Burger, 2002; Luu-The, Dufort, Pelletier, & Labrie, 2001). HSD originating from androgen deficiencies may result from ovarian or adrenal deficits. Ovarian androgen output decreases with age as ovarian tissues begin to atrophy (Bachmann, 2002; Burger, Dudley, Cui, Dennerstein, & Hopper, 2000; Davis, 1999), but there is no dramatic decrease in androgen levels associated with natural menopause. In contrast, it has long been established that women experiencing surgical menopause have decreased levels of androgens and sexual desire (Waxenberg, Drellich, & Sutherland, 1959).

HSD experienced by women in surgical or natural menopause is alleviated by androgen treatment, above the benefits gained from ERT. This includes naturally menopausal (Greenblatt, Barfield, Garner, Calk, & Harrod, 1950; Lobo, Rosen, Yang, Block, & Van Der Hoop, 2003; Sherwin, 2002) and surgically menopausal women (Gelfand, 1999; Shifren et al., 2000). Although ERT has been shown to maintain vaginal lubrication, increase pelvic blood flow, and decrease vaginal atrophy (Sarrel, 2000), it acts to increase sex-hormone binding globulin (SHBG), which actually decreases bioavailable T. ERT without androgens may well have a negative impact on sexual desire because of the increase in SHBG and the corresponding decrease in bioavailable T (Basson, 1999).

Androgens and sexual desire have been examined largely in correlational studies (e.g., Riley & Riley, 2000). Few studies of androgen supplementation have employed reference groups, except studies of ERT in naturally postmenopausal women (e.g., Sherwin, 2002). Munarriz et al. (2002) examined effects of androgens on sexual desire in women and found that as androgens increased from the lower third to upper half of the normal female range, sexual function, including sexual desire, improved. However, this study did not control for use of ERT or oral contraceptives and lacked both a control group and statistical treatment. Guay (2001) examined androgen treatment, which improved sexual desire in six of eight women presenting with HSD and low androgen levels, although again there was no control group or statistical treatment. In a well-controlled study, Tuiten et al.

(2000) found that a single dose of T increased genital arousal in healthy premenopausal women, which was significantly associated with "sexual lust." However these women did not have HSD, and sample size was small.

Overall, research has established that psychosocial and androgenic factors influence female sexual desire. Statistically evaluated research using ERT and androgens in postmenopausal women has examined androgens and sexual desire correlationally as well as experimentally. To our knowledge, there is no statistical study that uses a reference group and controlling for variables that influence T to examine T administration without ERT in women with HSD. The current study examines the effects of T treatment in women seeking attention for HSD compared with a reference group.

METHODS

Participants

Participants were offered enrollment in the study by the clinical coinvestigators while receiving care from them. Participants were explicitly reassured that their decision to participate or not to participate in this research would not affect their medical care in any way. Women were excluded from participation if they had any major health conditions or a known sexual dysfunction other than HSD.

Women presenting with HSD who elected to be treated by T and who consented to participate constituted the treatment group. Age-matched patients presenting for routine annual pelvic examinations and who consented to participate constituted the reference group. Pre- and postmenopausal women were recruited. Some women in both groups were using antihypertensives, but no women were using hormonal contraceptives, ERT, or psychotropic medications. The treated women were treated only with T and did not receive adjunct counseling.

Initially, the research sample included 37 participants. With attrition, the final sample was 33: premenopausal reference ($N = 3$, mean age = 40, $SD = 6.24$); postmenopausal reference ($N = 11$, mean age = 54.82, $SD = 6.78$); premenopausal treated ($N = 5$, mean age = 36, $SD = 3.16$), although one woman discontinued prior to completion; postmenopausal treated ($N = 14$, mean age = 49.79, $SD = 8.71$). There was no significant difference in age between treatment and reference groups. Reported reasons for attrition included: distance from doctor's office, dislike of injections, scheduling conflicts, unwelcome mood disturbances, and unwanted excess hair.

Materials

Women in the treated group received a 1-mL dose of T cypionate (Depotestosterone, Upjohn), injected IM in oil at 100 mg/ml 1 time per month

for 3 months. We chose this dose because of past clinical experience suggesting effectiveness without undesirable side effects.

We used the Sexual Desire Inventory (SDI; Spector, Carey, & Steinberg, 1996) to assess sexual desire. We modified the SDI by adding one question, "During the last month, *how often* have you had sexual thoughts?" We scored the SDI was in accordance with Spector et al. (1996), except that we inflated the total SDI scores by the addition of the extra item. The SDI produces total, solitary, and dyadic SDI scores. In Spector, Carey, & Steinberg (1998), the SDI showed a test-retest reliability of 0.76 over a 1-month period. The SDI has been validated in other studies (Galyer, Conaglen, Hare, & Conaglen, 1999; King & Allgeier, 2000; Spector & Fremeth, 1996; Spector et al., 1996). In the present study, the dyadic and total SDI subscales showed excellent reliability, with alpha coefficients greater than 0.88; the solitary subscale showed internal consistency, with the alpha coefficient greater than 0.65.

Procedure

All participants gave informed consent. To assess baseline HSD in treated women, the clinical coinvestigators conducted a clinical evaluation through interviews, examining the participants' clinical histories, including information about past sexual function, sexual arousal, orgasms, other sexual events, and frequency of sexual night dreams, sex play, and sexual thoughts. Scores ranged from slightly to extremely inhibited sexual desire.

At the first testing point, participants provided a baseline saliva sample and completed the pretreatment SDI. We chose saliva because it yields a direct measure of the bioavailable fraction of the hormone. Saliva and serum-free T concentrations are highly correlated, $r = 0.91$ (Navarro, Juan, Bonnin, & Villabona, 1986), $r = 0.94$ (Wang, Plymate, Nieschlag, & Paulsen, 1981). At the second testing point, participants provided the second baseline saliva sample, and treated women received the first T injection. Treated women received a second injection approximately 1 month after the first injection. At the third testing point, all participants provided the first posttreatment saliva sample, and treated women received the third injection. At the fourth testing point, all participants provided the second posttreatment saliva sample and completed the posttreatment SDI.

Thus, we measured bioavailable T at four points via saliva samples, two at pretreatment and two at posttreatment. We measured SDI scores twice, one pretreatment and one posttreatment. For premenopausal treated and reference participants, testing occurred during menses and at midcycle at pretreatment and during their third menstrual cycle. For postmenopausal women, testing occurred at two points separated by 2 weeks at pretreatment and 3 months following. Most samples were collected between 8:30 a.m. and 9:45 a.m.; four were collected between 10:00 a.m. and 10:30 a.m.; and five samples were collected between 1:30 p.m. and 4:15 p.m.

Saliva Collection

To ensure optimal quality of the saliva, we asked participants not to eat, drink (except plain water), smoke, or brush their teeth for one hour before saliva collection. The participants rinsed their mouths with water, and we provided an inert sugar-free gum to stimulate saliva flow. Saliva was collected in polystyrene culture tubes that had been pretreated with sodium azide. Following collection, the tubes were kept covered at room temperature for 18–24 hr to allow separation to occur. The tubes were then stored at −20°C until analysis.

Radioimmunoassays

Specimens were thawed at 4°C and centrifuged at 3000 rpm for 15 min. Because we anticipated low concentrations of T in some of the women, we submitted 2 mL of the supernatant to a double ether extraction and reconstituted it in one mL phosphate buffer. We then assayed the extract using a single Coat-a-Count kit for total T (Diagnostic Products Corporation (DPC), Los Angeles, CA), modified for use with saliva. The calibrators were diluted 1:20 and, to further increase detectability at the low end of the curve, we added a 5 pg standard, giving a range of 5–800 pg. For the assay, 200 uL of sample was pipetted into an antibody-coated tube, and 1 mL of ^{125}I tracer was added. The tubes were allowed to incubate for 22 hr at room temperature, then decanted and counted in a gamma counter. All specimens were assayed in duplicate. The sensitivity was calculated at 5 pg, and the intra-assay coefficient of variation averaged across low, medium, and high pools was 10%.

The DPC kit has demonstrated superior validity for the measurement of T in women (Taieb et al., 2003). The antiserum is highly specific for T, with negligible cross-reactivity with other steroids except dihydrotestosterone (<3.5%). We did not include women taking oral contraceptives in the present study, thus eliminating any risk of cross-reactions with progestogens in the 19-nortestosterone series.

The values used for statistical analysis are mean T concentrations across the two duplicates.

RESULTS

Changes in bioavailable T and sexual desire were analyzed with 2 (time: pre- versus posttreatment) × 2 (group: treatment versus reference) mixed effects analyses of variance (ANOVA), using the Statistical Package for the Social Sciences, v.11, for Windows. We used Tukey's HSD post hoc tests to explore statistically significant interactions.

TABLE 1. Testosterone Levels and Sexual Desire Inventory (SDI) Scores as a Function of Testosterone Treatment

Measure	Reference		Treated		Pre vs. Post	Treated vs. Cont	Interaction
	Pre	Post	Pre	Post			
Testosterone range: 5 pg/mL (min)–77.15 (max)	13.86^a	12.50^a	10.08^a	29.49^b	**		**
SDI total range: 12–89	63.08^a	65.67^a	28.13^b	65.03^a	***	**	***
SDI dyadic scale; range: 7–54	36.35^a	37.81^a	16.08^b	35.56^a	***	**	***
SDI solitary autosexual scale; range: 2–23	7.21^a	7.96^a	4.33^b	10.06^a	***		**

Note. Means with common superscripts do not differ at the .05 level by Tukey's Honestly Significant Difference tests; * = .05; ** = .01, *** = .001.

Testosterone (T) Levels

We removed two extreme outliers from the T analyses; one had T levels over 150 standard deviations from the mean, the other was over 8.5 standard deviations from the mean. This likely reflects blood contamination of the saliva. One woman had a pretreatment T value below assay sensitivity and was also excluded.

There was a significant Time × Group interaction effect, $F(1, 28) = 14.64$, $p = .001$, as well as a significant main effect of time, $F(1, 28) = 11.06$, $p = .002$, and a trend for a main effect of group, $F(1, 28) = 3.78$, $p = .062$, on levels of T. Post hoc tests (see Table 1) revealed no difference between groups in pretreatment means, however, treated women exhibited significantly higher T posttreatment compared to pretreatment, $q(4, 26) = 7.03$, $p < .01$, and significantly higher T posttreatment than did reference women, $q(4, 26) = 6.16$, $p < .01$.

Sexual Desire

Some women skipped questions on the SDI, so the total SDI score ($n = 5$) or the dyadic SDI score ($n = 1$) could not be calculated.

There was a significant interaction of Time × Group, $F(1, 25) = 30.56$, $p < .001$, as well as significant main effects of time, $F(1, 25) = 40.50$, $p < .001$, and group, $F(1, 25) = 12.82$, $p = .001$, on total SDI scores. Post hoc tests revealed that treated women had significantly lower sexual desire precompared with posttreatment, $q(4, 25) = 9.44$, $p < .01$. Treated women also had significantly lower sexual desire prior to treatment, compared with reference women, $q(4, 25) = 8.44$, $p < .01$. We note that treated women's overall sexual desire following treatment was equivalent to reference women's sexual desire at that time.

Autosexual desire—the desire for self-stimulation—as measured by the SDI solitary subscale, also showed a significant interaction of Time × Group, $F(1, 30) = 8.99$, $p = .005$, as well as a main effect of time, $F(1, 30) = 15.23$, $p < .001$. Post hoc tests revealed that prior to treatment, treated women had significantly lower autosexual desire scores than they reported posttreatment, $q(4, 30) = 9.86$, $p < .01$. We note that treated women's autosexual desire, following treatment, was equivalent to reference women's sexual desire at that time.

Desire for couple sexual interaction, as measured by the SDI dyadic subscale, also showed a significant interaction of Time × Group, $F(1, 29) = 27.97$, $p < .001$, as well as main effects of time, $F(1, 29) = 37.79$, $p < .001$, and group, $F(1, 29) = 15.28$, $p = .001$. Post hoc tests revealed that prior to treatment, treatment group women had significantly lower dyadic sexual desire than they did posttreatment, $q(4, 29) = 8.99$, $p < .01$. Prior to treatment, treatment group women also had lower dyadic sexual desire than did reference group women, $q(4, 29) = 8.57$, $p < .01$. We note that following treatment, treatment group women's levels of dyadic sexual desire were equivalent to those of reference group women.

For nearly all indicators of sexual desire, reference group women did not differ pre- to posttreatment; treatment group women reported less sexual desire than did reference group women prior to treatment; and treatment and reference group women reported equivalent sexual desire following treatment.

Menopausal Status, Testosterone, and Sexual Desire

We analyzed menopausal status for exploratory reasons. Changes in bioavailable T and sexual desire were analyzed with a 2 (time: pre- versus posttreatment) × 2 (group: treatment versus reference) × 2 (menopausal status: pre- versus postmenopausal) repeated measures ANOVA. There were no significant interactions involving menopausal status for either T or the SDI solitary subscale. There was a significant interaction of Time × Menopausal Status, $F(1, 23) = 10.26$, $p < .004$, as well as a significant interaction of Time × Group × Menopausal Status, $F(1, 23) = 9.64$, $p = .005$, for overall sexual desire. Reference group women remained constant over time, whereas treatment group women showed a significant increase in SDI scores to levels comparable to reference group women. Premenopausal treatment group women appeared to have a larger increase in sexual desire than did Postmenopausal Treatment Group women. There also was a significant interaction of Group × Menopausal Status for the SDI dyadic subscale, $F(1, 27) = 5.17$, $p = .031$, such that reference and treatment group women differed in dyadic sexual desire, and premenopausal reference Group women had higher dyadic sexual desire than did postmenopausal reference group women.

DISCUSSION

The goal of this study was to investigate the effects of androgen treatment without ERT on sexual desire in women presenting for treatment of HSD compared with age-matched reference group women. This investigation showed highly consistent positive effects of androgen treatment on bioavailable T and on sexual desire levels among treated women. Because this pilot study was not performed double-blind and did not include a placebo control group, results should be interpreted with caution and viewed as preliminary clinical findings. Following androgen administration, treated women exhibited significantly higher levels of T compared with pretreatment or reference women. This is consistent with previous reports (e.g. Munnariz et al., 2002). In contrast with Davis (1998), who stated that only women with hormonal components to their sexual dysfunction would benefit from androgen replacement, our study found an increase in sexual desire in treated women despite their having baseline T levels equivalent to the reference group. Perhaps women with HSD are more sensitive to T (see Bancroft, 2002, for a theoretical treatment of these issues), a possibility that highlights the present gap in knowledge regarding regular levels of androgens in women. This also suggests that HSD diagnosis should not be dependent on androgen levels.

Treated women had significantly lower sexual desire scores on the SDI than did reference group women at baseline, consistent with their subjective complaints of low sexual desire. Consistent with previous reports (Guay, 2001; Munarriz et al., 2002), androgen administration led to increases in sexual desire. Other studies of sexual parameters, including those of relevance to sexual desire, also report increases following T administration (Goldstat et al., 2003; Davis et al., 2003). Significantly higher scores on all scales of the SDI were observed posttreatment for treated women compared to pretreatment. Thus, androgen treatment seemed effective at increasing solitary desire, or the desire for self-stimulation, as well as dyadic desire, or the desire for partner-related stimulation. Further research should examine whether lower doses of T, accompanied by fewer androgenic side effects, are as effective at increasing sexual desire as those used in this study. Transdermal therapies would also likely be less aversive to participants than injections.

Androgen treatment-related increases in sexual desire may have been the result of expectancy effects in this study, although studies using T in conjunction with ERT have found similar increases in sexual desire (e.g., Sherwin, 2002). Further clinical study should focus on randomized, double-blind, placebo-controlled trials to definitively rule out expectancy effects. In addition, T has beneficial effects on mood and energy, which may in turn be associated with increases in sexual parameters (Bancroft, 2002; Davis et al., 2003; Decker et al., 2003). It is possible that the increases in sexual desire following T administration are secondary to positive effects on these variables. Although women with HSD would still experience increased sexual

desire with T administration, further study should determine whether T acts to increase sexual desire directly or through mediating variables.

Although the etiology of HSD is complex and multifaceted, it appears that hormonal treatment may be effective at increasing sexual desire, perhaps even for women who do not show a baseline androgen deficiency. Previous research has shown the beneficial effects of androgens in addition to ERT in naturally postmenopausal women (Sherwin, 2002) and in surgically postmenopausal women (Gelfand, 1999). Correlational studies have also found associations between increased androgens and increased sexual desire (e.g., Riley & Riley, 2000). Munarriz et al. (2002) and Guay (2001) both examined the effects of androgen supplementation on sexual desire, but ours is the first study, to our knowledge, that statistically demonstrates the effects of androgen supplementation on HSD in women using no other exogenous hormones. As well, we used large enough samples in the present study to explore potential interactions of menopausal status. Our findings are in agreement with Tuiten et al. (2000), who found that testosterone administration was associated with increased sexual lust in a small sample of eight healthy premenopausal women but they extend these results to longer-term treatment in a clinical population of women with HSD and to both pre- and postmenopausal women, suggesting that T administration may be an effective way of alleviating HSD.

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