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Pharmacologically Induced Hypogonadism and Sexual Function in Healthy Young Women and Men

Peter J Schmidt^{1,*}, Emma M Steinberg¹, Paula Palladino Negro¹, Nazli Haq¹, Carolyn Gibson¹, and David R Rubinow²

¹ Behavioral Endocrinology Branch, National Institute of Mental Health, NIH, DHHS, Bethesda, MD, USA

² Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Abstract

Studies fail to find uniform effects of age-related or induced hypogonadism on human sexual function. We examined the effects of induced hypogonadism on sexual function in healthy men and women and attempted to identify predictors of the sexual response to induced hypogonadism or hormone addback. The study design used was a double-blind, controlled, crossover (self-as-own control). The study setting was an ambulatory care clinic in a research hospital, and the participants were 20 men (average \pm SD age = 28.5 \pm 6.2 years) and 20 women (average \pm SD age = 33.5 \pm 8.7 years), all healthy and with no history of psychiatric illness. A multidimensional scale assessing several domains of sexual function was the main outcome measure. Participants of the study received depot leuprolide acetate (Lupron) every 4 weeks for 3 months (men) or 5 months (women). After the first month of Lupron alone, men received (in addition to Lupron) testosterone enanthate (200 mg intramuscularly) or placebo every 2 weeks for 1 month each. Women received Lupron alone for 2 months, and then, in addition to Lupron, they received estradiol and progesterone for 5 weeks each. The results of the study: in women, hypogonadism resulted in a significant decrease in global measures of sexual functioning, principally reflecting a significant decrease in the reported quality of orgasm. In men, hypogonadism resulted in significant reductions in all measured domains of sexual function. Testosterone restored sexual functioning scores in men to those seen at baseline, whereas neither estradiol nor progesterone significantly improved the reduced sexual functioning associated with hypogonadism in women. Induced hypogonadism decreased sexual function in a similar number of men and women. No predictors of response were identified except for levels of sexual function at baseline. In conclusion, our data do not support a simple deficiency model for the role of gonadal steroids in human sexual function; moreover, while variable, the role of testosterone in sexual function in men is more apparent than that of estradiol or progesterone in women.

Keywords

sexual function; hypogonadism; estradiol; progesterone; testosterone; GnRH agonist

*Correspondence: Dr PJ Schmidt, Behavioral Endocrinology Branch, National Institute of Mental Health, Bldg 10 CRC, Room 6-5340, 10 Center Drive MSC 1276, Bethesda, MD 20892-1276, USA, Tel: + 1 301 496 6120, Fax: + 1 301 402 2588, E-mail: peterschmidt@mail.nih.gov.

DISCLOSURE

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INTRODUCTION

Studies of the effects of hypogonadism on sexual functioning in women have been confounded by the conditions under which hypogonadism occurs, including aging, surgical procedures, and coexisting gynecologic pathologies. In young men, decreased sexual functioning secondary to hypogonadism is more consistently demonstrated (Bagatell *et al*, 1994); however, the reductions are not uniformly observed, and predictors of the sexual response to hypogonadism or androgen replacement have not been identified. While imperfect in modeling natural conditions, hormone manipulation paradigms can eliminate many of the confounds that obscure the relationship between hormones and sexual function. In this study, we take advantage of two studies of the effects of induced hypogonadism on mood in young, healthy men and women, and ask whether similar hormonal manipulations alter sexual function.

A role for sex steroids in the regulation of sexual function in men and women has been inferred from several observations. First, therapeutic trials, many of which were placebo-controlled, reported the beneficial effects of sex hormone therapy in men and women in whom hypogonadism was secondary to medical or surgical castration (Floter *et al*, 2002; Shifren *et al*, 1985, ²⁰⁰⁰; Simon *et al*, 2005; Sherwin *et al*, 1985; Sherwin and Gelfand, 1987; Braunstein *et al*, 2005; O'Carroll *et al*, 1985; Anderson *et al*, 1999; Bhasin, 2000; Bagatell *et al*, 1994; Dennerstein *et al*, 1980; Davidson *et al*, 1979), reproductive senescence (Nathorst-Boos *et al*, 1993b, 2006; Sarrel, 1990, 1998; Wiklund *et al*, 1993; Myers *et al*, 1990; Sarrel *et al*, 1998; Lobo *et al*, 2003; Sherwin, 1991; Wang *et al*, 2000; Gray *et al*, 2005; Steidle *et al*, 2003; Seftel *et al*, 2004; Guay *et al*, 1995), or concurrent medical conditions (eg Kallman's syndrome or HIV) (Wang *et al*, 2000; O'Carroll *et al*, 1985; Snyder *et al*, 2000; Anderson *et al*, 1999; Arlt *et al*, 1999; Rabkin *et al*, 2000, 2006; Johannsson *et al*, 2002; Carani *et al*, 2005). These data suggest (albeit indirectly) that deficiencies of sex hormones could underlie a decrease in sexual function in both men and women. Second, some basal hormone studies have observed correlations between blood levels of sex steroids and sexual functioning, while other studies have observed lower sex hormone levels in subjects with decreased sexual function compared with asymptomatic control groups (Schiavi *et al*, 1991; Cawood and Bancroft, 1996; Santoro *et al*, 2005; Basar *et al*, 2005; Modelska *et al*, 2004; Trivison *et al*, 2006; Beutel *et al*, 2005; Kennedy *et al*, 1997; Nyunt *et al*, 2005; Dennerstein *et al*, 1994, ²⁰⁰²; Slob *et al*, 1996; Adams *et al*, 1978; Bancroft *et al*, 1980; Meuwissen and Over, 1992; Doering *et al*, 1974). Finally, several longitudinal studies have demonstrated the reduction of sexual function under the following circumstances: after medical or surgical castration; after the development of hypogonadism secondary to a variety of medical illnesses; after the administration of medications that inhibit sex hormone production (Marberger *et al*, 2006); and during age-related reproductive senescence (Dennerstein *et al*, 2002; Koster and Garde, 1993).

Despite these findings, the role of gonadal steroids in the regulation of sexual function in humans remains controversial for several reasons. First, the results of therapeutic trials are difficult to interpret since hormone therapy may have effects independent of those on sexual function. For example, mood, energy, muscle mass, and strength improve with androgen therapy and might, therefore, contribute indirectly to the observed beneficial effects of androgens on sexual functioning (Grinspoon *et al*, 2000). Second, the results of basal hormone studies are inconsistent, since men and women with low sex hormone levels do not uniformly report low levels of sexual function (Trivison *et al*, 2006; Santoro *et al*, 1996; Burger *et al*, 1995, 1999, ²⁰⁰⁰; Leiblum *et al*, 2006; Sternbach, 1998; Bachmann *et al*, 1985; Greendale *et al*, 1996; Davidson *et al*, 1983; Vermeulen, 2001). Finally, a substantial proportion of both men and women (30–50%) report no change in libido after medical or surgical castration despite obvious losses of reproductive endocrine function (Bagatell *et al*,

1994; Bremer, 1959; Dennerstein *et al*, 1977, 2002; Chakravarti *et al*, 1977; Tauber, 1940; Elit *et al*, 2001; Madalinska *et al*, 2005; Zussman *et al*, 1981).

Several characteristics could influence the impact of declining or suppressed gonadal steroid secretion on sexual functioning, including the magnitude of the decrease in sex hormone levels from baseline, the level of hormone during hypogonadism (ie below a threshold of hormone levels at which impaired sexual function occurs), sex, age, duration of hypogonadism, and baseline phenotype (eg level of sexual function), as well as the presence of concurrent symptoms such as depression (Isidori *et al*, 2005; Beutel *et al*, 2005; Cawood and Bancroft, 1996; Nilsson *et al*, 1995; Kratzik *et al*, 2004; Finkelstein *et al*, 1998; Schiavi and White, 1976; Schiavi *et al*, 1994). Indeed, in a preliminary study using an undimensional evaluation of libido, we observed that baseline levels of sexual functioning predicted the response to hypogonadism and hormone replacement in a group of men with GnRH agonist-induced hypogonadism (Schmidt *et al*, 2004). These observations are important clinically as they could predict those individuals in whom hormone therapy would improve sexual function.

In this study, we attempted to examine the role of gonadal steroids in human sexual functioning as follows: first, we assessed the impact of the acute short-term induction of hypogonadism on sexual functioning. Second, we evaluated potential sex differences in the response to induced hypogonadism. Finally, we examined the impact of several other variables that might predict a differential response to hypogonadism or hormone therapy in humans, including age, mood symptoms, and hormone levels. Our main hypothesis was that induced hypogonadism would impair sexual functioning across multiple domains in groups of men and women. A secondary hypothesis was that considerable variability would be demonstrated in the impact of hypogonadism on sexual functioning in men and women (Wallen, 1990, 2001; Herzog *et al*, 2005; Zehr *et al*, 1998).

METHODS

Subject Selection

Men (between age 18 and 45 years) and women (between age 18 and 55 years) were recruited through advertisements in local newspapers or referred from the NIH Normal Volunteer Office, and participated between November 1994 and March 2003. All were participants in a larger study examining the effects of GnRH agonist-induced hypogonadism and sex hormone replacement on measures of mood and brain function. Given the original focus of this study, in women we evaluated the effects of the two principal ovarian steroids, estradiol and progesterone, whereas the effects of testosterone were evaluated in men only. Estradiol, testosterone, and progesterone (or its neurosteroid metabolites) all have been implicated in the regulation of appetitive behaviors including sexual motivation in both animals and humans (Frye, 2007; Evans and Foltin, 2006; Dreher *et al*, 2007). All participants were medication free and free of significant medical illness (current or in the past 2 years) confirmed by history, physical examination, and routine laboratory tests.

None of the men and women reported problems with their mood, sleep, sexual function, or sexual relationships. Women reported regular menstrual cycle function (21–35 days). The absence of current or past psychiatric illness was confirmed by a structured psychiatric diagnostic interview (Spitzer *et al*, 1990). Additionally, all subjects completed daily visual analog scale self-ratings (sadness, anxiety, and irritability) for at least 2 months to exclude the presence of premenstrual mood symptoms in women or other mood disturbances.

The protocol was approved by the National Institute of Mental Health Intramural Research Board, and written informed consent was obtained from all subjects. Subjects were paid for

their participation in this protocol according to the guidelines of the NIH Normal Volunteer Office.

Procedure

Hormonal manipulation protocol—All women received 3.75 mg of depot Lupron (leuprolide acetate, purchased from TAP Pharmaceuticals, Chicago, IL) by intramuscular injection every 4 weeks for 5 months (Figure 1). Lupron alone was administered for the first 8 weeks. All women then received, in addition to Lupron, 17 β estradiol (0.1 mg/ day) (E) by skin patch (Alora, active and placebo patches were supplied by Watson Pharmaceuticals, Salt Lake City, UT) or progesterone suppositories (200 mg b.i.d.) (P) (NIH Pharmacy, Bethesda, MD) for 5 weeks each. The two replacement regimens were separated by a 2-week washout period.

All men received 7.5 mg of depot Lupron by intramuscular injection every 4 weeks for 3 months. Lupron alone was administered for the first 4 weeks. Subjects then received, in addition to Lupron, testosterone enanthate (200 mg) (T) or placebo (1 ml sesame oil) given by intramuscular injection every 2 weeks for 1 month. A placebo comparison was included in men to blind the timing of the addition of testosterone, whereas in women no placebo phase was included since the order of estradiol and progesterone addback was randomly assigned.

In both men and women, the order of receiving hormone replacement (ie, T vs placebo in men, and E vs P in women) was randomly assigned and counter-balanced.

Subjects were seen at the NIMH clinic at least every 2 weeks throughout the study, and blood samples were obtained and symptom rating scales were completed. Both subjects and raters (NH, PJS) were blinded to the order of replacement. Blood samples were employed solely to confirm hormone levels during each of the pharmacologically induced hormone conditions (see Table 2). Individuals came into the clinic at approximately the same time during the study, although the time of the day for each visit varied across individuals. Blood samples were centrifuged, aliquoted, and stored at -70°C until time of assay.

Outcome Measures

Sexual functioning was evaluated by a uniquely modified version of the Derogatis Interview of Sexual Functioning-Self Report (DISF-SR) (Derogatis, 1997), a multidimensional scale with separate forms designed for men and women. The DISF-SR scale was selected for this study because it sampled several domains of sexual function. Additionally, in contrast to the majority of other measures of sexual function, the DISF-SR was available in forms adapted for both men and women and, therefore, potential sex differences could be evaluated. Finally, the reliability and validity of DISF-SR (and other scales measuring sexual function) have been determined by comparing scores between symptomatic and asymptomatic samples; however, this study employed a repeated measure, self-as-own design; consequently, the capability of the scale to distinguish normal from abnormal sexual function was less of a concern. Questions focus on five domains (ie, subscales) of sexual functioning: (1) sexual cognition and fantasy (eg erotic thoughts and dreams), (2) sexual arousal (eg level of arousal during sexual behaviors), (3) sexual behavior and experience (eg masturbation, foreplay, and intercourse), (4) quality of orgasm, and (5) sexual drive and relationship (eg level of satisfaction with sexual relationships). We requested and were given permission to modify the DISF-SR specifically for this study by the author and copyright holder, Leonard R Derogatis, PhD. Such permission used by the authors (PJS, DRR) should in no way be construed as an endorsement of this approach to measurement. The DISF was modified from the original for this study as follows. First, the sampling interval within

which sexual function is measured was reduced from a 30-day to a 7-day interval. Second, the scale was converted from a nine-point Likert-type scale (0–8) to a 100 mm visual analog scale (0–100) (range—not at all to very frequently). Finally, a seventh question was introduced in section IV (quality of orgasm) of the male version to examine feelings of closeness and togetherness with partner, an item that was present in the female scale and also relevant to male sexual function. The modified scale has both a total score and individual domain scores (subscale) as follows: maximum total scores of 2500 in women and 2600 in men, maximum scores for each domain of 500, except for quality of orgasm (no. 4—score of 600 in women and 700 in men), and sexual drive (no. 5—score of 400 in both men and women) (Figure 2).

The modified version maintained the same five domains as the original, and except for one question (mentioned above), the remaining 25 questions were the same (in both female and male interviews). The DISF was administered at baseline (start date of Lupron) in both men and women. In men, the DISF also was administered during the last weeks of placebo and T replacement; whereas in women, the DISF was administered at the end of Lupron alone (hypogonadism) and during the last week of each hormone replacement condition (E and P). Symptom rating data during the first month were not included in the analysis since steroid levels increase (or ‘flare’) transiently after the first injection of Lupron. Additionally, to evaluate coexisting mood symptoms all participants completed the Beck Depression Inventory (BDI) (Beck *et al*, 1961) at the same time that the DISF was completed.

Statistical Analysis

In both women and men, serum hormone levels, BDI, and total DISF scores at each time point were compared by analysis of variance with repeated measures (ANOVA-R; Systat, SPSS, Chicago, IL), with hormone condition (women [four levels]: baseline, hypogonadal, E, and P; men [three levels]: baseline, hypogonadal, and T) as the within-subjects variable. Additionally, in both men and women we examined the effects of hormone condition on individual domains of sexual functioning by performing separate ANOVA-Rs on each of the DISF subscales (ie nos. 1–5).

To examine possible sex differences in response to hypogonadism, Z-scores were calculated for baseline and hypogonadal DISF scores (ie, total and individual subscale scores) in the women and compared with those in men by ANOVA-R with sex as the between-subjects variable and hormone condition (baseline and hypogonadal) as the within-subjects variable. Z-scores were calculated using the average and standard deviations of the baseline DISF scores in each sex to permit comparisons across men and women despite differences in total maximum DISF scores. Additionally, we operationally defined a substantial decline in sexual function as a 50% or greater reduction in the total DISF score relative to baseline scores. This criterion was intended to serve as a proxy for a clinically significant decrease in sexual function (Alexander *et al*, 2004) and was based on a similar threshold employed in pharmacologic studies of depression, in which a 50% improvement in rating scores is considered to be clinically significant. We compared the number of men and women who experienced a 50% or greater reduction (relative to baseline) in their total DISF scores by χ^2 analysis. We performed an identical analysis employing a less conservative 30% cutoff score as the threshold.

In a prior report (Schmidt *et al*, 2004) with a larger sample of men (ie $n = 31$), 20 of whom participated in this study, men who received placebo first and, therefore, were exposed to two consecutive months of hypogonadism reported greater declines in sexual function during hypogonadism than those men receiving T replacement first (ie the first month of Lupron alone was followed by 1 month of T prior to the third month during which they received Lupron plus placebo). Thus, we repeated our analyses of sex differences in DISF

scores after hypogonadism with only those men who were exposed to two consecutive months of hypogonadism to match (and control for differences in) the duration of hypogonadism in the women in this study.

In our earlier report, in which we employed a multi-symptom inventory in the male subjects of the current study, we also observed that baseline levels of sexual interest predicted subsequent behavioral response to both hypogonadism and T replacement (Schmidt *et al*, 2004). To replicate these observations with a more comprehensive measure of sexual function in men and to determine if these observations could be extended to women, we first assigned subjects to one of two categories defined by their baseline DISF total scores and then compared subjects in the lowest ($n = 6$) and highest ($n = 6$) tertile baseline scores. DISF scores (total and subscale) were re-analyzed within each sex by ANOVA-R, with baseline total DISF score (low vs high) as the between-subjects variable and hormonal condition as the within-subjects variable.

Finally, men and women were grouped for comparison as follows: (1) those with a 50% or greater reduction in the total DISF scores during hypogonadism compared with baseline and (2) those with the highest and lowest tertiles of baseline DISF scores (as described above). We examined whether these differences in sexual function were associated with specific characteristics at baseline, during hypogonadism, or that changed between baseline and hypogonadism. Two-tailed Student's *t*-tests (all *t*-tests had Bonferroni corrections for the number of comparisons made unless indicated) were performed comparing the following baseline measures: age; blood hormone levels (ie, men: total T, free T, E, and dihydrotestosterone [DHT]; women: total T, E, and P), including measures at baseline, during hypogonadism, and the difference (Δ) between measures at baseline and during hypogonadism; and BDI scores at baseline, during hypogonadism, and the change in BDI scores between baseline and hypogonadism. Pearson correlation coefficients were employed to investigate possible relationships between changes in DISF scores and changes in blood hormone levels.

RESULTS

Subject Characteristics

In total, 20 men ranging in age from 22 to 42 years (mean \pm SD, 28.5 \pm 6.2 years) and 20 women ranging in age from 19 to 47 years (mean \pm SD, 33.5 \pm 8.7 years) participated in the study. All participants were Caucasian except for two African-American women. Eleven men received placebo first and, therefore, were exposed to two consecutive months of hypogonadism as were all 20 women. All subjects were sexually active, and their marital status was as follows: men—single ($n = 12$), married ($n = 6$), and divorced ($n = 2$); women—single ($n = 13$), married ($n = 5$), and divorced ($n = 2$). In women, there were no significant effects of hormone condition on BDI scores (ANOVA-R $F_{3,57} = 0.5$, $p = \text{NS}$), whereas in men a significant effect of hormone condition on BDI scores was observed (ANOVA-R $F_{2,38} = 3.7$, $p = 0.04$), which reflected a small but statistically significant increase in BDI scores during the hypogonadal state (Table 1). This increase in BDI score reflected the influence of two men who developed clinically significant mood symptoms and had BDI scores of 14 and 6, respectively, during hypogonadism (consistent with data in the larger group of subjects reported previously) (Schmidt *et al*, 2004).

DISF Symptom Ratings

Comparisons across hormone conditions in women and men—In women, induced hypogonadism significantly decreased DISF scores compared with those at baseline (Table 1). DISF scores during hypogonadism did not differ from those during either E or P.

All DISF subscale scores also showed a reduction during hypogonadism, E, and P compared with baseline; however, the only decrease that met statistical significance after adjustment for five comparisons (ie, the five subscales) was subscale four (quality of orgasm). As observed with the total DISF scores, the subscale scores during hypogonadism, E, and P did not differ significantly.

In men, total DISF scores during hypogonadism were significantly decreased compared with scores during both baseline and T. All five subscale scores significantly decreased during hypogonadism compared with baseline conditions and during hypogonadism compared with T (see Table 1).

We observed identical patterns of results when we repeated these analyses after excluding those men ($n = 1$) and women ($n = 5$) over 40 years of age.

Comparisons between men and women during baseline and hypogonadism—

Standardized total DISF scores (ie, Z-scores) were significantly higher in men compared with women during both baseline and hypogonadism and significantly decreased in both sexes during hypogonadism compared with baseline. Each of the individual DISF subscales demonstrated a similar significant effect of hormone condition (decreased during hypogonadism), and in scales nos. 2 and 4 (ie, arousal and orgasm), we observed significant effects of sex (higher in men) and a sex by hormone condition interaction, reflecting greater decline in men than women during hypogonadism. An identical pattern of effects was observed when the nine men who received T replacement before placebo were excluded from the analysis.

Eight men (40%) and seven women (35%) experienced a 50% or greater decline in total DISF scores during hypogonadism: ($\chi^2 = 0.12, p = 0.7$); similarly, 12 men (60%) and 14 women (70%) experienced a 30% or greater decline in total DISF scores during hypogonadism. Five of the eight men who experienced a 50% or greater decline in total DISF received placebo first.

Comparisons between those with high and low baseline DISF scores—

Women with low and high total DISF scores at baseline had significantly different responses to induced hypogonadism (Figure 2). No significant effects of hormone condition were observed in the low baseline symptom group (t_{30} (range) = 1.0–1.4, $p = \text{NS}$), with no significant differences between hypogonadism, E, and P compared with baseline. In contrast, the women with high total DISF scores at baseline had significantly lower scores during hypogonadism, E, and P compared with baseline conditions, (t_{30} (range) = 4.6–5.4, $p < 0.01$).

In men, a similar pattern of effects was observed, with the absence of significant differences (between hypogonadism and baseline or T) in the low baseline symptom group (t_{20} (range) = 0.1–1.6, $p = \text{NS}$), whereas in the high baseline symptom group significantly lower DISF scores were observed during hypogonadism compared with baseline and T conditions ($t_{20} = 6.1$ and 7.5, respectively, $p < 0.01$).

As a caveat, when data were re-analyzed using baseline DISF scores as a covariate, the significance of the effect of hormone condition was reduced to marginally significant levels ($p = 0.05$ and 0.01 (women and men, respectively)).

Mood and Hormonal Measures

Characteristics of those with and without a clinically significant response to hypogonadism—

Women with and without a 50% or greater reduction in total DISF

scores were not distinguished by any variables, including total T and P (Student's t -values ranged from 0.9 to 1.0), with the exception of significantly lower baseline plasma E levels (in those women with a 50% reduction in DISF scores) (Student's $t_{17} = 2.8, p = 0.013$) and a significantly greater decline in plasma E levels from baseline to hypogonadism in those without a 50% decrease (Student's $t_{17} = 15.9, p = 0.02$). These findings reflected the presence of outlier values in the women without a 50% decrease that spuriously elevated mean baseline E levels. When three women with luteal phase plasma levels of E (ie, > 100 pg/ml) were eliminated from the analysis, there were no differences between the groups. There were also no differences in plasma E levels between groups of women during hypogonadism (Student's $t_{17} = 1.3, p = \text{NS}$).

Similarly, no significant differences were observed between those men with and without a 50% or greater reduction in total DISF scores during hypogonadism (relative to baseline) in the following measures: age; BDI scores (at baseline, during hypogonadism, or the change in BDI score from baseline to hypogonadism); and plasma hormone levels (total and free T, DHT, and E) at baseline or during hypogonadism as well as the difference in plasma hormone levels between baseline and hypogonadism (Δ). (Student's t -values ranged from 0.7 to 1.0).

Finally, no baseline differences were observed between the high and low baseline symptom groups in either men or women (Student's t -values ranging from 0.5 to 1.0).

Hormone measures of experimental condition—Blood hormone levels confirmed the creation of the intended hormone conditions (Table 2). As expected, blood levels of T in women remained suppressed relative to baseline for the duration of the study (ie, despite E or P addback).

Hormonal correlates of DISF scores—No significant correlations were seen between the changes in hormone levels across conditions and the corresponding change in total DISF scores in either men or women.

DISCUSSION

Our hypotheses were that induced hypogonadism would impair sexual functioning across multiple domains and that there would be considerable variability in the impact of hypogonadism on sexual functioning in both men and women. Both of these hypotheses were confirmed, albeit with sex differences in the domains of sexual functioning influenced by induced hypogonadism. The findings of this study have implications for clinicians' expectations about the impact of hypogonadism on an individual's sexual function and, possibly, for the selection of men and women who would be appropriate candidates for hormone therapies targeted at improving sexual function. First, in women, short-term induced hypogonadism was associated principally with a significant decrease in the reported quality of orgasm, whereas in men, hypogonadism significantly reduced all domains of sexual function measured by the DISF. In men, testosterone replacement restored sexual function to that observed at baseline, whereas in women, neither estradiol nor progesterone replacement reversed the reduction in sexual functioning caused by hypogonadism. Despite the reduction in sexual function observed on a group basis, only 40% of men and 35% of women reported substantial decreases in sexual function during induced hypogonadism (ie, 50% or greater decline in total DISF scores relative to baseline). Second, we observed no sex differences in the proportion of participants who responded with a substantial decline in sexual function during hypogonadism. Third, those participants with and without a significant decline in DISF scores during hypogonadism were not distinguished by any measure, including baseline mood symptom ratings (ie, BDI scores) and both baseline and

post GnRH agonist hormone measures. Finally, men and women with high baseline DISF scores responded differently to hypogonadism than those with lower baseline DISF scores. Thus, levels of sexual function at baseline (ie, total DISF score) in both men and women predicted the magnitude of the decline in sexual function during hypogonadism and, in men, the improvement in sexual function after testosterone replacement. This study was designed to evaluate the effects of hypogonadism and sex steroid replacement on measures of mood; sexual function was not a primary outcome measure. However, the hormone manipulations performed represented a unique opportunity to examine the effects of hypogonadism (albeit short term) on measures of sexual function in young healthy men and women. The absence of a T replacement arm in women and the relatively small sample sizes limit our conclusions about the source of the decline in libido in women. Nonetheless, short-term hypogonadism was associated with a decline in measures of sexual function in both men and women.

In men, the reduced sexual function during hypogonadism was restored to baseline levels by testosterone replacement. These data in men are consistent with previous reports of impaired sexual functioning in hypogonadal men and the restoration of sexual function with testosterone replacement (Bhasin, 2000; Guay *et al*, 1995; Anderson *et al*, 1999; Snyder *et al*, 2000; Seftel *et al*, 2004; Isidori *et al*, 2005; Steidle *et al*, 2003; Gray *et al*, 2005; O'Carroll *et al*, 1985; Wang *et al*, 2000; Davidson *et al*, 1979; Kwan *et al*, 1983). The observed changes in sexual function in men during induced hypogonadism occurred independent of significant changes in mood symptoms (an increase in negative mood was reported in only two men). The reduction in global sexual function could be related to loss of testosterone, its 5 α -reduced metabolite DHT, estradiol (synthesized from testosterone within the brain by aromatase), or one of testosterone's neurosteroid metabolites such as androsterone. Indeed, androsterone levels are implicated in the reduced libido observed in this trial. In a subsample of these men in whom lumbar punctures were performed, we observed that CSF androsterone levels but not CSF measures of T or DHT correlated with the symptom of decreased sexual function (Bloch *et al*, 2006).

In women, we observed a similar effect of hypogonadism on total DISF scores; however, in contrast to the effects of testosterone in men neither estradiol nor progesterone replacement restored sexual function to levels reported at baseline. The failure of estradiol to enhance sexual function is consistent with some (Nathorst-Boos *et al*, 1993a; Alexander *et al*, 2004; Lobo *et al*, 2003; Sherwin, 1985; Myers *et al*, 1990), but not all (Dennerstein *et al*, 1980, 2002; Finkelstein *et al*, 1998; Sarrel, 1990, ¹⁹⁹⁸; Sarrel *et al*, 1998; Sherwin, 1991; Nathorst-Boos *et al*, 1993b; Wiklund *et al*, 1993), studies reporting an association between estradiol levels and sexual function. While we did observe sexual function to decline in association with hypogonadism-induced decreases in ovarian estradiol secretion (perhaps consistent with earlier studies), sexual function was not restored by estradiol replacement. Blood levels of both estradiol and progesterone increased during each of their respective replacement conditions, but only slight nonsignificant increases in DISF scores accompanied these changes. Nonetheless, it is possible that had we studied a larger sample of women with decreased libido, or had we employed higher doses or provided a longer duration of therapy of estradiol (or possibly progesterone), a larger impact on sexual function would have been observed. The doses employed in this study, however, were adequate to reduce hot flashes (estradiol and progesterone) and self-reports of vaginal dryness (estradiol only). While no statistically significant effects of estradiol on sexual functioning were observed, an improvement in sexual function after estradiol was observed and, therefore, a type II error cannot be ruled out. Blood levels of both testosterone and DHT remained suppressed in women throughout all three hormone conditions in which DISF scores were reduced relative to baseline. Blood testosterone levels were decreased by approximately 30% during Lupron-induced hypogonadism compared with baseline and, therefore, changes in testosterone (or one of its androgen or neurosteroid metabolites) could mediate the observed decline in

sexual function and quality of orgasm in women (Simon *et al*, 2005; Sherwin *et al*, 1985; Lobo *et al*, 2003; Nathorst-Boos *et al*, 2006; Braunstein *et al*, 2005; Sherwin and Gelfand, 1987; Shifren *et al*, 2000; Floter *et al*, 2002; Davis *et al*, 2006; Leiblum *et al*, 2006; Santoro *et al*, 2005). However, since testosterone was not administered to women in this study, we only can speculate about this possible relationship.

The robust decline in the reported quality of orgasm during hypogonadism contrasts with the results of many, but not all, studies examining the effects of testosterone therapy on domains of sexual function in women. Studies by Sherwin *et al* (1985) and Floter *et al* (2002) observed testosterone to enhance arousal and motivational aspects of sexual function in hypogonadal women, but neither quality of orgasm nor sexual behavior was increased. Although the Sherwin data (Sherwin *et al*, 1985) suggested that orgasm and sexual behavior were influenced less by androgens, more recent studies employing transdermal testosterone have observed improvements in all domains of sexual function, including orgasm and frequency of intercourse (Simon *et al*, 2005; Shifren *et al*, 2000; Braunstein *et al*, 2005; Nathorst-Boos *et al*, 2006).

Despite significant changes on a group basis, only 35% and 40% of women and men, respectively, experienced a substantial (50% or greater) decline in DISF scores during hypogonadism. At first glance, the proportion of participants in whom hypogonadism reduced sexual function seems remarkably small; however, these data are consistent with several prior studies in which rates of moderate to severe sexual dysfunction ranged from 20% to 50% in women postmenopause or post-oophorectomy (with studies of women post-oophorectomy reporting higher rates of clinically significant loss of libido compared with the natural menopause) (Leiblum *et al*, 2006; Bremer, 1959; Dennerstein *et al*, 1977, 2002; Chakravarti *et al*, 1977; Koster and Garde, 1993; Elit *et al*, 2001; Madalinska *et al*, 2005; Bachmann *et al*, 1985; Teplin *et al*, 2006). The rate of reduced sexual function in men (40%) is lower than the rates of post-castration loss of sexual function of 50% or greater reported by some case series (Bagatell *et al*, 1994; Bremer, 1959; Tauber, 1940; Basaria *et al*, 2002). Our data demonstrate that induced hypogonadism, at least short term, does not result in a clinically significant loss of sexual function in all men and women. Thus, as with many other non-reproductive behaviors, there is a differential response of sexual function to changes in reproductive function, with only a proportion of subjects experiencing a significant change in behavior despite a similar decrease in sex steroid hormone secretion. These data also could explain the findings of several treatment studies in which sex hormone therapy was not uniformly effective in enhancing libido (Seftel *et al*, 2004; Isidori *et al*, 2005; Davidson *et al*, 1979).

Several factors have been reported to modify the behavioral response to declining or loss of sex steroid secretion, including age, sex, extent of hormone suppression, quality of relationship with partner, coexisting stress or mood symptoms, or levels of adrenal hormones (Gray *et al*, 2005; Koster and Garde, 1993; Beutel *et al*, 2005; Cawood and Bancroft, 1996; Bachmann *et al*, 1985; Davidson *et al*, 1983; Basar *et al*, 2005; Nilsson *et al*, 1995; Kratzik *et al*, 2004; Finkelstein *et al*, 1998; Schiavi and White, 1976; Schiavi *et al*, 1994). However, with the exception of baseline DISF scores, no baseline characteristic was associated with the level of impaired libido during hypogonadism, including age (although all participants were of a similar young age), depression scores during hypogonadism, hormone levels during either baseline or hypogonadal conditions, and change in hormone levels across conditions. Men and women with higher baseline levels of sexual function (high group) experienced the greatest loss of sexual function during hypogonadism; however, these participants were not distinguished by any other characteristic measured in this study. These data are consistent with and extend our previous observations in men (Schmidt *et al*, 2004) as well as those in animals by Grunt and Young (1952, 1953), who

reported that baseline levels of sexual activity predicted the response to castration and testosterone replacement in male guinea pigs. A floor effect may have prevented detection of a decline in DISF scores during hypogonadism in the low symptom group. Baseline DISF scores clearly contributed to the results we observed; nonetheless, the effect of hormone condition cannot solely be attributed to those with elevated baseline DISF scores. An important role for sex steroids in at least some men and women is suggested both by the loss of sexual function in men and women in the high baseline sexual function groups and by the restoration of normal sexual function by testosterone in the high baseline sexual function men (but not in the low symptom groups despite comparable changes in sex steroids). Thus, our data and those of others (Gray *et al*, 2005) suggest that a behavioral phenotype could predict a disparate response to changes (either decreases or increases) in sex steroid secretion. This phenotype could contribute to the heterogeneity of the changes in sexual function during reproductive aging in both men and women.

This study has several limitations: first, the duration of hypogonadism was relatively brief, and it is possible, therefore, that a longer duration of hypogonadism would have resulted in a larger proportion of men and women developing clinically significant losses of sexual function or different patterns of loss with respect to specific domains of sexual function. Indeed, in our earlier report (Schmidt *et al*, 2004), in a larger sample, those men exposed to two consecutive months of hypogonadism reported a greater decline in sexual function. Nonetheless, the relative proportion of women affected in this study is comparable to rates of significant loss of sexual function in previous studies in women after oophorectomy or natural menopause (Leiblum *et al*, 2006; Dennerstein *et al*, 1977, 2002; Chakravarti *et al*, 1977; Koster and Garde, 1993; Elit *et al*, 2001; Madalinska *et al*, 2005). Indeed, even in men, studies have reported that a loss of sexual function is not observed in 100% of hypogonadal men (Bagatell *et al*, 1994; Bremer, 1959). Second, although we controlled for several factors that could contribute to sexual function, including age, concurrent symptoms, and sex, we did not obtain detailed information about the quality of the relationships in participants (Bachmann *et al*, 1985). We also did not measure adrenal hormones (cortisol and dehydroepiandrosterone (DHEA)) (Basar *et al*, 2005), although neither baseline DHEA nor cortisol secretion would be predictably altered by GnRH agonist treatment. Finally, we studied young healthy men and women, and the rate of sexual dysfunction after hypogonadism could be higher in older subjects or in those with concurrent medical illnesses. Thus, our findings should not be generalized to older men and women.

Future studies should investigate other possible biological or environmental contributors to the difference in behavioral response to permit a better characterization of this hormonally vulnerable group of men and women.

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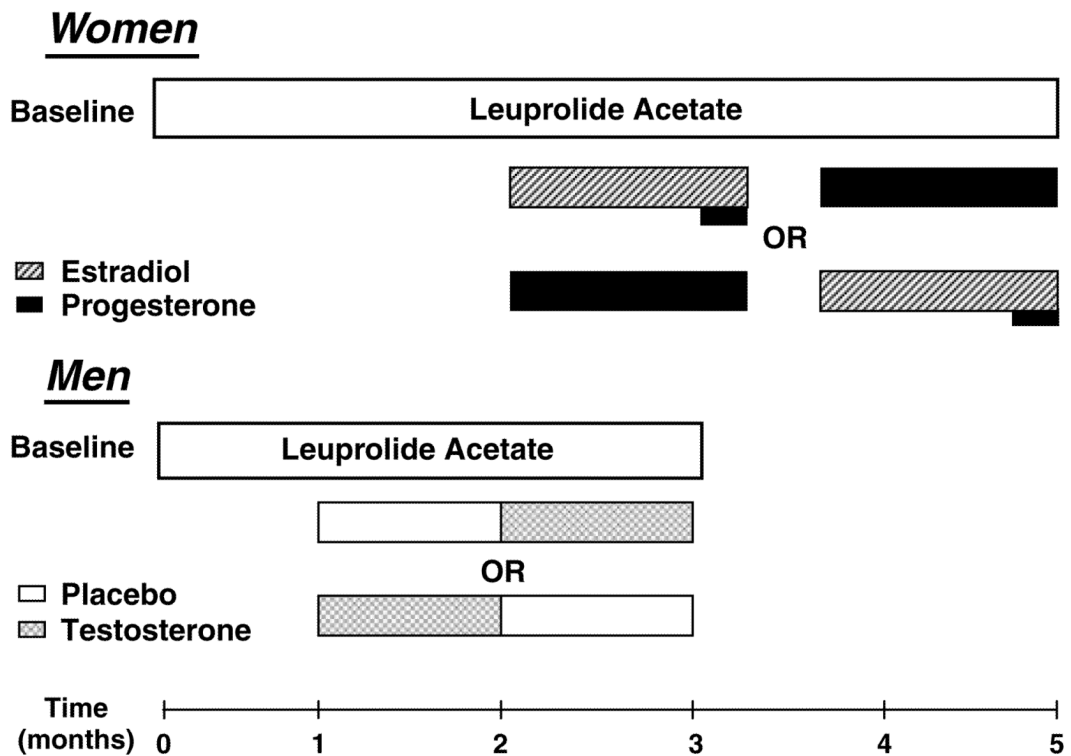


Figure 1.

All women received 3.75 mg of depot Lupron (leuprolide acetate; TAP Pharmaceuticals, Chicago, IL) by intramuscular injection every 4 weeks for 5 months. The first injection of Lupron was administered during the follicular phase between days 2–6 after the onset of menses. Lupron alone was administered for the first 8 weeks. All women then received, in addition to Lupron, 17 β estradiol (0.1 mg/day) (E) by skin patch (Alora; Watson Pharmaceuticals, Salt Lake City, UT) or progesterone suppositories (200 mg b.i.d.) (P) (NIH Pharmacy, Bethesda, MD) for 5 weeks each. The two replacement regimens were separated by a 2-week washout period. Subjects were administered both patches and suppositories (active or placebo, depending upon the treatment phase) daily throughout the entire replacement period to ensure that the double blind was maintained. During the last week of E, all women received 1 week of active P suppositories in addition to E to precipitate menses. All women received prepackaged 1-week unit-dose supplies of suppositories that were formulated and coded (weeks 1–5) by the NIH Pharmacy Department. All men received 7.5 mg of depot Lupron by intramuscular injection every 4 weeks for 3 months. Lupron alone was administered for the first 4 weeks. Subjects then received, in addition to Lupron, testosterone enanthate (200 mg) or placebo (1 ml sesame oil) given by intramuscular injection every 2 weeks for 1 month. All men received 1 month each of testosterone replacement (T) and placebo. A placebo comparison was included in men to blind the timing of the addition of testosterone, whereas in women no placebo phase was included since the order of estradiol and progesterone addback was randomly assigned. In both men and women the order of receiving hormone replacement (ie, T vs placebo in men, and E vs P in women) was randomly assigned and counter-balanced.

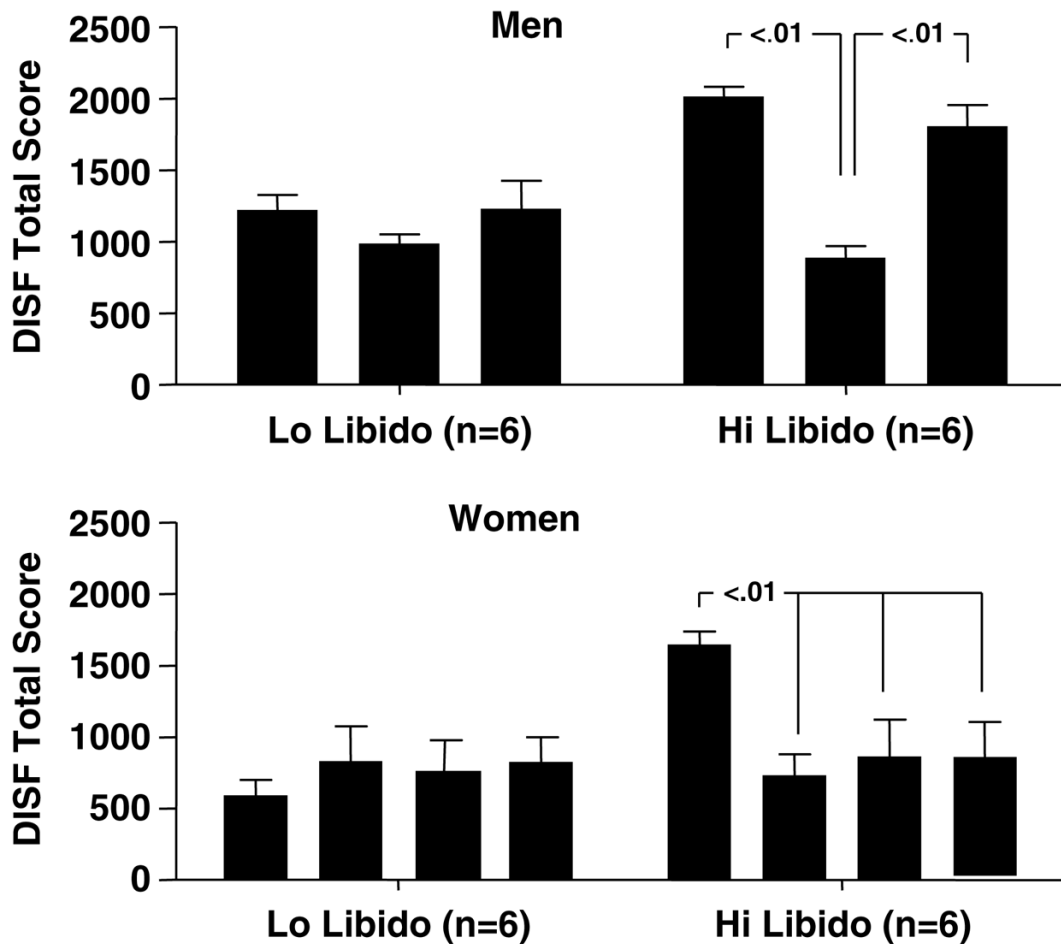


Figure 2.

In men, a significant interaction between baseline symptom group (high vs lo,w) and hormone condition was identified by ANOVA-R ($F_{2,20} = 9.7, p < 0.003$). Men with high baseline DISF scores ($n = 6$) had a significant reduction in total DISF scores during hypogonadism compared with both baseline and T-replaced conditions, and a significant increase in DISF scores after T replacement compared with hypogonadism. Men with low baseline DISF scores ($n = 6$) showed no significant differences in DISF scores across hormone conditions. Similarly, women with high baseline DISF scores ($n = 6$) showed a significant reduction in DISF scores during hypogonadism (and during estrogen and progesterone conditions) compared with baseline scores, whereas women with low baseline DISF scores ($n = 6$) showed no significant change across hormone conditions (ANOVA-R group \times hormone condition, $F_{3,30} = 9.8, p = 0.001$). In women, total DISF scores were significantly greater in the 'high' group at baseline only ($t_{40} = 3.8, p < 0.01$; otherwise $p = \text{NS}$). Whereas, in men, total DISF scores were significantly higher in the 'high' compared to the 'low' baseline symptom group during both baseline and T ($t_{30} = 3.4$ and 4.7 , respectively, $p < 0.01$). No significant interactions between subscale scores and group or hormone condition were observed in either men or women.

Table 1

The Effects of Induced Hypogonadism and Sex Hormone Replacement on DISF Scores in Healthy Adult Women ($n = 20$) and Men ($n = 20$)—Mean (SD) (Range)

	Baseline	Lupron alone	Lupron+E	Lupron+P	Lupron+T
<i>DISF Total</i>					
Women	1179.7 (466.8)	715.5 (437.1)**	919.2 (532.6)*	820.6 (434.9)*	—
	(324–2041)	(60–1692)	(97–1833)	—	—
Men	1632.5 (358.5)	886.8 (333.6)**‡	—	—	1506.6 (420.9)
	(836–2294)	(181–1577)	—	—	(689–2128)
<i>DISF Subscales (SS)</i>					
Cognition no. 1					
Women	226.4 (106.3)	149.4 (128.0)	205.1 (132.0)	178.1 (105.6)	—
Men	275.9 (98.0)	140.7 (87.8)**‡	—	—	249.5 (120.7)
Arousal no. 2					
Women	191.0 (111.3)	114.3 (98.2)	157.3 (110.1)	137.7 (111.2)	—
Men	336.8 (91.1)	150.3 (86.5)**‡	—	—	300.9 (112.5)
Behavior no. 3					
Women	187.6 (110.9)	99.6 (83.5)	139.1 (104.6)	133.5 (71.8)	—
Men	208.6 (103.8)	109.4 (71.9)**‡	—	—	200.9 (91.0)
Orgasm no. 4					
Women	343.1 (156.9)	196.5 (141.7)**	232.0 (169.2)**	211.3 (151.3)**	—
Men	546.1 (88.7)	327.9 (160.0)**‡	—	—	504.2 (135.0)
Drive no. 5					
Women	231.7 (88.1)	155.8 (74.9)	185.8 (89.8)	160.0 (75.6)	—
Men	265.2 (68.1)	158.5 (80.9)**‡	—	—	251.2 (81.6)
<i>BDI</i>					
Women	2.1 (5.1)	3.0 (2.9)	2.0 (3.0)	2.2 (3.0)	—
Men	0.4 (1.0)	2.2 (3.2)	—	—	0.9 (1.6)

Post hoc comparisons: women and men compared with baseline—

* $p < 0.05$;

**
 $p < 0.01$.

Men only: Lupron alone vs T replaced—

[†] $p < 0.05$,

[‡] $p < 0.01$.

Otherwise $p = NS$.

BDI—all comparisons $p = NS$.

In women, we observed a significant effect of hormone condition on total DISF scores (ANOVA-R: $F_{3,54} = 5.1, p = 0.009$).^a Compared with baseline, the total DISF scores were significantly lower during hypogonadism, and remained significantly lower during P ($F_{54} = 3.0, p < 0.05$) and lower at a trend level of significance during E administration ($F_{54} = 2.2, p = 0.05$). There were no significant differences in the total DISF scores during hypogonadism compared with either E or P (F_{54} (range) = 0.9–1.7, $p = NS$). All DISF subscale scores were lower; however, only subscale four (quality of orgasm) showed a significant decrease during hypogonadism, E, and P compared with baseline (F_{54} (range) = 2.8–3.7, $p < 0.05$ with six comparisons). DISF subscale scores during hypogonadism, E, and P did not differ significantly.

In men, total DISF scores during hypogonadism were significantly decreased compared with scores during both baseline and T (ANOVA-R: $F_{2,38} = 31.0, p < 0.001$). All DISF subscale scores significantly decreased during hypogonadism compared with baseline conditions (ANOVA-R: $F_{2,38}$ (range) = 9.3–32.3, $p \leq 0.001$) (t_{190} (range) = 3.6–7.9, $p < 0.01$). Additionally, scores were decreased during hypogonadism compared with T (t_{190} (range) = 3.3–6.4, $p < 0.01$) in subscale nos. 1, 2, and 4; $p < 0.05$ in subscale nos. 3 and 5.

Total DISF scores were significantly higher in men compared with women during both baseline and hypogonadism (ANOVA-R: significant effects of sex ($F_{1,38} = 12.2, p = 0.001$)); total DISF scores significantly decreased in both men and women during hypogonadism compared with baseline ($F_{1,38} = 44.4, p < 0.001$), but there was no significant sex by hormone condition interactions ($F_{1,38} = 2.4, p = 0.13$). Total DISF scores remained significantly higher in men after scores in both sexes were standardized (ie, Z-scores) (effect of sex: $F_{1,38} = 6.5, p = 0.02$; effect of hormone condition: $F_{1,38} = 48.7, p < 0.001$). Individual DISF subscales demonstrated a significant decrease during hypogonadism in both men and women ($F_{1,38}$ (range) = 18.6–46.4 (range), $p < 0.001$). Additionally, scores of subscale nos. 2 and 4 (arousal and orgasm, respectively) were significantly greater in men compared with women (effect of sex: $F_{1,38} = 8.9$ and $7.9, p < 0.01$) and declined to a greater extent in men compared with women (sex by hormone condition interaction: $F_{1,38} = 11.4$ and $7.4, p \leq 0.01$).

^aTo avoid violating sphericity assumptions, Greenhouse–Geisser adjustments of the degrees of freedom were employed to calculate the observed p -values, since in some comparisons the variance of the differences in scores between hormone conditions was large.

^bDISF ratings were not completed by one woman during P replacement and, therefore, her ratings were not included in the analysis comparing DISF scores in women across the four hormone conditions.

Table 2

Blood Hormone Levels in Women and Men during Baseline, Lupron Alone (Hypogonadism), Estradiol (E), Progesterone (P), or Testosterone (T) Replacement Conditions

	Baseline	Lupron alone	Lupron+E	Lupron+P	Lupron+T
<i>Total T (ng/dl)</i>					
Women	32.3 (14.9)	19.7 (6.9) [#]	23.3 (9.9)	21.3 (9.7)	—
Men	444.5 (89.2)	34.1 (25.0) [#]	—	—	374.8 (157.0)
<i>E (pg/ml)</i>					
Women	59.4 (43.8)	7.7 (4.4)	93.6 (66.6)	7.8 (8.0)*	—
Men	25.5 (8.6)	4.3 (1.7)*	—	—	21.3 (12.1)
<i>P (ng/ml)</i>					
Women	1.8 (3.7)	0.6 (0.4)	0.5 (0.2)	13.0 (10.1) ⁺	—
<i>Free T (pg/ml)</i>					
Men	30.2 (6.4)	2.5 (2.2)*	—	—	24.6 (8.8)
<i>DHT (ng/dl)</i>					
Men	38.1 (12.6)	10.2 (5.0) ⁺	—	—	33.6 (19.2)

Women: total testosterone (total T)—ANOVA-R demonstrated a significant effect of hormone condition ($F_{3,54} = 8.8, p < 0.001$); reflecting significantly decreased total T levels during the hypogonadal state as well as during E and P ($^{\#}t_{54} = 3.4-4.8$ (range), $p < 0.01$), with no significant differences in total T levels between E or P and the hypogonadal state ($t_{54} = 0.7-1.1$ (range), $p = NS$). Estradiol (E)—plasma E levels were significantly lower during both hypogonadism and P compared with both baseline and E (ANOVA-R $F_{3,54} = 20.8, p < 0.001$; $^*t_{54} = 4.0-6.6$ (range), $p < 0.01$), whereas there were no significant differences between baseline and E ($t_{54} = 2.6, p < 0.1$ (trend)). Progesterone (P)—P levels were significantly higher during P compared with all three other hormone conditions (ANOVA-R: $F_{3,54} = 27.3, p < 0.001$; $^{\dagger}t_{54} = 7.1-7.9$ (range), $p < 0.01$). P levels were not significantly different across baseline, hypogonadism, and E conditions ($t_{54} < 1.0, p = NS$).

Men: blood levels of total testosterone (total T) ($F_{2,38} = 71.4, p < 0.001$), free testosterone (free T) ($F_{2,38} = 97.2, p < 0.001$), dihydrotestosterone (DHT) ($F_{2,38} = 33.4, p < 0.001$) and estradiol (E) ($F_{2,38} = 30.9, p < 0.001$) were significantly lower during hypogonadism compared to both baseline and T ($^{\#}$ total T, † DHT, and E ($t_{38} = 6.2-13.2$ (range), $p < 0.01$)). Blood hormone levels did not differ between baseline and T ($t_{38} = 1.4-2.5$ (range), $p = NS$) although there was a trend for a significant difference in free T levels between baseline and T ($t_{38} = 2.6, p = 0.05$).

Hormone assays: blood hormone levels reported in this study were measured in single blood samples obtained during the clinic visit when the DISF scale was completed.

In men, serum levels of total testosterone (total T), free testosterone (free T), estradiol (E), and dihydrotestosterone (DHT) were measured by radioimmunoassay as described previously (Furuyama *et al*, 1970; Abraham, 1973; Vermeulen *et al*, 1971; Abraham *et al*, 1972; Jiang and Ryan, 1969; Ito and Horton, 1970) by Quest Diagnostics (Baltimore, MD) and Covance Laboratories (Vienna, VA). The intra- and interassay coefficients of variation were respectively 5.7 and 14.0% for free T, 4.4 and 16.9% for total T, 7.7 and 11.0% for E, and 8 and 9% for DHT.

In women, serum levels of total T, E, and progesterone (P) were measured by radioimmunoassay as described previously (Furuyama *et al*, 1970; Wu and Lundy, 1971; Ito and Horton, 1970) by Esoterix (Calabasas Hill, CA). The intra- and interassay coefficients of variation were respectively 6.6 and 8.9% for total T, 5.5 and 10.9% for E, and 7.5 and 5.8% for P. Free T and SHBG levels were not performed in women because of the unreliability of current assays for measuring low levels of free T and SHBG in women (Rosner *et al*, 2007).

The laboratory normal range for the androgen measures were as follows: women: total T = 10–55 ng/dl; free T = 50–120 pg/ml; DHT = 25–75 ng/dl.