ORIGINAL ARTICLE

The Effects of Pharmacologically Induced Hypogonadism on Mood in Healthy Men

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Background: The effects of declining androgen secretion on mood regulation and the potential psychotropic efficacy of androgen replacement in men are largely undetermined.

Objective: To examine the effects on mood of the acute suppression of testosterone secretion.

Design: A double-blind, placebo-controlled, crossover (self-as-own-control) study.

Setting: An ambulatory care clinic in a research hospital.

Participants: Thirty-one healthy adult men with no history of psychiatric illness or substance or anabolic steroid abuse.

Interventions: Men received depot leuprolide acetate (Lupron, 7.5 mg intramuscularly) every 4 weeks for 3 months. After the first month of Lupron alone, all men received (in addition to Lupron) testosterone enanthate (200 mg intramuscular) or placebo (sesame oil as color-matched vehicle) every 2 weeks for 1 month each in a crossover design. The order of administration of testosterone and placebo was randomly assigned and counterbalanced.

Main Outcome Measures: Mood and behavior rating scores (self-report and rater administered).

Results: With the exceptions of hot flushes, libido, and the feeling of being emotionally charged, none of the symptoms measured showed a significant difference across eugonadal, Lupron plus placebo, and Lupron plus testosterone conditions. Despite the absence of a uniform effect of Lupron plus placebo on mood, 3 men experienced clinically relevant mood symptoms during this induced hypogonadal condition. High baseline levels of sexual functioning predicted the greatest decline in sexual function during Lupron plus placebo.

Conclusions: These data, the first to describe the effects on mood of induced hypogonadism in healthy young men, suggest that short-term hypogonadism is sufficient to precipitate depressive symptoms in only a small minority of younger men. The predictors of this susceptibility remain to be determined.

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THE AGE-RELATED DECLINE IN circulating androgen levels progresses to hypogonadism in a substantial number of men[1,2] and may have a negative effect on bone metabolism, muscle mass, and, possibly, mood and behavior.[3-5] Androgens have been implicated in the regulation of mood by several types of evidence. First, in controlled clinical studies, supraphysiologic doses of androgens (eg, anabolic-androgenic steroids) induce prominent mood changes (hypomania, irritability) in approximately 5% of eugonadal men.[6-8] Second, in placebo-controlled clinical trials, physiologic doses of testosterone produce antidepressant-like effects in hypogonadal men in some[9-11] but not all[12] studies. Clearly, the mood effects of androgens are not uniformly observed in men, and the reported antidepressant response may reflect the reversal by testosterone of age-[13] or illness-related sarcopenia (reductions in muscle mass) and fatigue[10] instead of a direct action of androgen on mood. Moreover, several contextual factors could influence and, hence, complicate the interpretation of the inferences drawn about the relationship between androgens and mood, including impact of concomitant medical conditions, histories of psychiatric illness, substance abuse, and prior exposure to anabolic-androgenic steroids.[6,14-16] No study has examined the effects on mood of the acute withdrawal of testosterone in eugonadal healthy young men.

The purpose of this study was to address existing confounds by examining the effects on mood of the acute suppression of testosterone secretion with pharmacologically induced hypogonadism in young, healthy adult men with no history of psychiatric illness or substance or anabolic-androgenic steroid abuse.

METHODS

SUBJECT SELECTION

Subjects were men aged 18 to 45 years recruited through advertisements and referred from the National Institutes of Health (NIH) Normal Volunteer Office. All were medication free, had no significant medical illness (currently or in the past 2 years), and had normal laboratory results. Specifically, complete blood cell counts, blood chemistry, thyroid function tests (thyroid-stimulating hormone and free thyroxine), and prostate-specific antigen levels were within normal limits. Additionally, plasma total testosterone levels ranged from 355 to 992 ng/dL (12.3-34.4 nmol/L) (normal range, 300-1200 ng/dL [10.4-41.6 nmol/L]), and plasma prolactin levels were within normal limits (1-16 ng/mL) in all but 1 subject whose plasma prolactin was 29 ng/mL on repeat testing. The absence of current or past psychiatric illness was confirmed by a structured psychiatric diagnostic interview[17] and daily symptom self-ratings. Structured interviews were performed by 1 of 4 of us (P.J.S., M.A.D., N.A.H., or C.A.R.). Subjects were excluded from this study if they had a past or present psychiatric illness or evidence of persistent (>3-5 days) clinically significant mood and behavioral symptoms of moderate severity on the daily symptom rating form (see "Outcome Measures") during their screening phase. The protocol was reviewed and approved by the National Institute of Mental Health intramural research board, and oral and written informed consents were obtained from all subjects. All subjects were paid for their participation in this protocol according to the guidelines of the NIH Normal Volunteer Office.

PROCEDURE

This was a double-blind assessment of the effects of the acute induction of hypogonadism and subsequent replacement in a crossover design with testosterone and placebo. After a 2-month screening phase, men received 7.5 mg of intramuscular (IM) depot leuprolide acetate (Lupron; TAP Pharmaceuticals, Chicago, Ill) every 4 weeks for 3 months. Lupron alone was administered for the first 4 weeks. Subjects then received, in addition to Lupron, 200 mg of IM testosterone enanthate (Bristol-Myers Squibb, New York, NY) or 1.5 mL of IM placebo (sesame oil as color-matched vehicle) every 2 weeks for 1 month (ie, twice) and then crossed-over to the other replacement. The order of replacement was randomly assigned and counterbalanced. Men were seen at the National Institute of Mental Health clinic every 2 weeks throughout the study. Blood samples were obtained and symptom self-ratings were completed at each clinic visit on a biweekly basis throughout the study. Both subjects and raters were blinded to the order of replacement. All subjects were taking Lupron throughout the study, and therefore their endogenous testosterone secretion was suppressed, obviating the need for collecting samples at a uniform time point. Blood samples were taken solely to confirm hormone levels during each of the pharmacologically induced hormone conditions. Each individual came into the clinic at approximately the same time during the study, but the time of day for visits varied across individuals. Blood samples were centrifuged, aliquoted, and stored at −70°C until time of assay.

OUTCOME MEASURES

To assess the severity of mood symptoms, the following symptom rating forms were completed at baseline and during each hormonal condition: (1) a visual analogue scale[18,19] completed nightly for all symptoms; scores range from 0 (symptoms present in the extreme) to 100 (symptoms not present) and reflect the subject's symptoms at the time the ratings were completed; and (2) the Daily Rating Form, a 6-point Likert-type scale modified to include the symptoms measured in this study,[20] also completed nightly, to represent a composite rating for the previous 12 hours; scores range from 1 (symptoms not present) to 6 (symptoms present in the extreme). The Daily Rating Form symptoms consist of the following: avoidance of social activity; loss of enjoyment or interest; impaired function at work or home; irritability or anger; impaired concentration or distractibility; mood swings; feeling depressed, sad, low, or blue; feeling anxious or nervous; decreased eating; increased eating; more sleep, naps, or lying in bed; low energy; loneliness or feeling rejected; feeling physically restless or agitated; feeling powerful, emotionally charged, or pumped up; increased sexual interest; decreased sexual interest; disturbed sleep; drinking alcohol or using nonprescribed drugs; impulse to hurt self; impulse to hurt someone else; acting on impulse to hurt someone; daytime hot flushes; and nighttime hot flushes. Thirteen symptoms recorded by the visual analogue scale consisted of the following: rapidly changing mood, increased appetite or cravings, a global feeling (best ever/worst ever), impulse to hurt others, low self-esteem, impulse to hurt self, sadness, irritability, low energy, functional impairment, anxiety, extreme physical discomfort, and isolation and social avoidance. Four men did not complete the Daily Rating Form ratings, and 2 men did not complete the visual analogue scale ratings. The following standardized rating scales also were completed during each clinic visit: the Beck Depression Inventory (BDI), a measure of depression severity,[21] and the Spielberger State-Trait Anxiety Inventory, a measure of anxiety severity.[22]

Because measures of hostility have been correlated with testosterone levels in a variety of studies (albeit not uniformly),[23-30] we attempted to determine whether induced hypogonadism would be associated with a reduction in self-ratings of aggression. A subsample of 20 men completed rating forms that assessed changes in the subjects' experiences of aggression, anger, and impulsiveness as follows: (1) Buss-Durkee Hostility Inventory (a 75-item scale measuring the subscales of assault, indirect hostility [subject is not direct target of hostility], irritability, verbal hostility, guilt, suspicion, resentment, and negativity)[31,32]; (2) Anger, Irritability, and Assault Questionnaire[33] (a 42-item scale assessing variables such as irritability, verbal assault, indirect assault, direct assault, and anger); and (3) Barratt Impulsiveness Scale version 7B (a 48-item scale measuring risk taking, interpersonal behavior, motor behavior, self-assessment, and sensory stimulation).[34,35] (All 3 rating forms were modified to reflect a subject's experience during the 2 weeks prior to completing the scales.)

HORMONAL ASSAYS

Blood levels of testosterone, free testosterone, estradiol, and dihydrotestosterone were measured by radioimmunoassay, as described previously[36-41] (Quest Diagnostics, Baltimore, Md, and Covance Laboratories, Vienna, Va).

STATISTICAL ANALYSIS

The 7-day averages of the daily symptom scores were calculated during the fourth week of the 3 experimental conditions: baseline, Lupron plus testosterone, and Lupron plus pla-

Table 1. Hormone Levels During the Baseline Period and During the Administration of Lupron Plus Placebo or Testosterone in 31 Men

Hormone	Normal Range	Baseline, Mean ± SD	Lupron Plus Placebo, Mean ± SD	Lupron Plus Testosterone, Mean ± SD	ANOVA-R $F_{2,60}$ (*P* Value)
Testosterone, ng/dL	300-1200	462.6 ± 145.3	39.2 ± 27.0*†	730.1 ± 461.3‡	49.7 (<.001)
Free testosterone, pg/mL	11-41	30.0 ± 7.7	2.3 ± 1.8*†	37.7 + 12.4‡	139.7 (<.001)
Dihydrotestosterone, ng/dL	25-75	40.2 ± 14.9	9.5 ± 4.6*†	46.0 ± 28.1	38.1 (<.001)
Estradiol, pg/mL	10-50	25.4 ± 8.4	4.2 ± 1.8*†	26.3 ± 13.6	37.4 (<.001)

Abbreviation: ANOVA-R, analysis of variance with repeated measures.
SI conversion factor: To convert testosterone to nanomoles per liter, multiply by 0.0347; to convert estradiol to picomoles per liter, multiply by 3.67.
*$P < .01$ for hypogonadal vs baseline using post-hoc Bonferroni *t* tests (2 tailed).
†$P < .01$ for hypogonadal vs testosterone replaced using post-hoc Bonferroni *t* tests (2 tailed).
‡$P < .01$ for baseline vs testosterone replaced using post-hoc Bonferroni *t* tests (2 tailed).

cebo. Cross-sectional rating scores (for the BDI, Spielberger State-Trait Anxiety Inventory, Buss-Durkee Hostility Inventory, Anger, Irritability, and Assault Questionnaire, and Barratt Impulsiveness Scale version 7B) were taken from the last week of each phase. The averaged daily and single cross-sectional symptom scores were compared by analysis of variance with repeated measures (ANOVA-R) (Systat; SPSS Inc, Chicago, Ill), with hormonal condition (baseline vs Lupron plus testosterone vs Lupron plus placebo) as the within-subjects variable. Analyses of variance were reperformed using subject age as a covariate. Symptom-rating data during the first month (Lupron alone) were not included in the analysis because plasma testosterone levels increase (or flare) transiently after the first injection of Lupron. We examined differences in the number of men meeting a severity criterion score for the BDI (BDI score ≥7 for clinically relevant depressive symptoms[42]) across hormonal conditions with the Fisher exact test.

Plasma hormone levels obtained during the last 2 weeks of each add-back condition (testosterone or placebo) were averaged and compared by ANOVA-R with hormone condition as the within-subjects variable.

Seminal earlier studies[43,44] demonstrated that the behavioral response to hypogonadism and testosterone replacement in animals could be predicted by pretreatment levels of androgen-related behavior. To determine if these observations could be extended to humans, we assigned subjects to 1 of 2 categories defined by their baseline symptom scores on 2 behavioral symptoms, ie, sexual interest and feeling emotionally charged, identified by ANOVA as changing significantly across the 3 hormonal conditions. The 2 subject groups comprised the 10 subjects with the highest (high group) and lowest (low group) baseline scores on the 2 selected symptoms. Their scores for these 2 symptoms were reanalyzed by ANOVA-R with baseline symptom score (low vs high) as the between-subjects variable and hormonal condition as the within-subjects variable.

Post hoc Bonferroni *t* tests were performed within and between groups when indicated by significant ANOVAs. Two-tailed *t* tests were performed to compare baseline plasma levels of testosterone and estradiol between high and low baseline symptom groups.

To examine potential order effects on significant symptom measures, we repeated the ANOVA-R with order of receiving testosterone as a between-group factor. Additionally, to avoid any potential confound of the crossover design on the observed effects of Lupron plus placebo, we reanalyzed the data by ANOVA-R including baseline and only the first hormone treatment that each subject received (ie, pseudoparallel design).

Finally, Pearson correlation coefficients were performed to examine whether changes in symptom scores between the testosterone-replaced and hypogonadal conditions were associated with changes in testosterone levels across these conditions. Thus, for those symptoms that changed significantly across hormone conditions (ie, BDI scores, hot flushes, sexual interest, and feeling emotionally charged), correlations were performed with the following measures of testosterone: (1) the change in the average testosterone level recorded from the testosterone-replaced to the hypogonadal conditions and (2) the maximum change (calculated by identifying the highest level of testosterone obtained and subtracting it from the lowest plasma testosterone level during the hypogonadal state).

RESULTS

SUBJECT CHARACTERISTICS

Thirty-one men ranged in age from 23 to 46 years (mean ± SD, 30.8 ± 5.8 years). Fourteen men received Lupron plus testosterone first, and 17 received Lupron plus placebo first after 4 weeks of treatment with Lupron alone.

HORMONE MEASURES

Lupron plus placebo was associated with significantly lower plasma levels of testosterone, free testosterone, dihydrotestosterone, and estradiol than either the eugonadal (baseline) or Lupron plus testosterone conditions (**Table 1**). Plasma levels of both total testosterone and free testosterone were significantly higher during testosterone replacement than during baseline. No significant differences in plasma levels of dihydrotestosterone or estradiol were observed between baseline and Lupron plus testosterone.

SYMPTOM RATINGS

With the exception of hot flushes (both daytime and nighttime), libido, and feeling emotionally charged, there were no significant differences between the Lupron plus placebo condition and either the baseline or the Lupron plus testosterone conditions in the symptoms measured, including sadness, anxiety, irritability, mood lability, anhedonia, and decreased energy (**Table 2**). Hot flush (daytime and nighttime) severity significantly increased and both sexual interest and feeling emotionally charged sig-

Table 2. Symptom Ratings During the Baseline Period and During the Administration of Lupron Plus Placebo or Testosterone in 31 Men

Outcome Measure	Symptom	Baseline, Mean ± SD	Lupron Plus Placebo, Mean ± SD	Lupron Plus Testosterone, Mean ± SD	ANOVA-R F* (*P* Value)
Beck Depression Inventory	NA	0.5 ± 1.2	2.3 ± 3.2†‡	0.8 ± 1.5	7.34 (.001)
Spielberger State-Trait Anxiety Inventory	NA	25.6 ± 4.0	28.1 ± 9.5	29.1 ± 12.2	2.16 (NS)
Daily Rating Form	Sadness	1.2 ± 0.4	1.3 ± 0.5	1.3 ± 0.5	0.34 (NS)
	Anxiety	1.2 ± 0.4	1.1 ± 0.4	1.3 ± 0.7	1.49 (NS)
	Irritability	1.2 ± 0.2	1.3 ± 0.5	1.4 ± 0.5	1.83 (NS)
	Mood lability	1.2 ± 0.3	1.3 ± 0.6	1.2 ± 0.4	0.50 (NS)
	Anhedonia	1.2 ± 0.3	1.2 ± 0.4	1.4 ± 0.7	1.95 (NS)
	Decreased sexual interest	1.2 ± 0.3	2.6 ± 1.5†§	1.3 ± 0.7	21.2 (<.001)
	Increased sexual interest	1.7 ± 0.8	1.2 ± 0.3†§	1.9 ± 0.8	12.2 (<.001)
	Nighttime hot flushes	1.0 ± 0.0	1.8 ± 1.0†§	1.1 ± 0.3	13.31 (<.001)
	Daytime hot flushes	1.0 ± 0.0	1.8 ± 1.1†§	1.1 ± 0.2	14.20 (<.001)
	Emotionally charged	1.5 ± 0.8	1.2 ± 0.4†§	1.4 ± 0.6	4.46 (<.05)
	Decreased energy	1.5 ± 0.6	1.6 ± 0.8	1.6 ± 0.9	0.22 (NS)
	Hypersomnia	1.2 ± 0.4	1.4 ± 0.6	1.3 ± 0.8	0.76 (NS)
	Disturbed sleep	1.3 ± 0.5	1.5 ± 0.7	1.4 ± 0.7	1.06 (NS)
	Decreased eating	1.2 ± 0.4	1.1 ± 0.2	1.2 ± 0.4	0.42 (NS)
	Increased eating	1.3 ± 0.5	1.6 ± 0.9	1.4 ± 0.6	1.68 (NS)
	Physical agitation	1.3 ± 0.7	1.2 ± 0.6	1.3 ± 0.6	0.53 (NS)
	Impulse to hurt self	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.46 (NS)
Visual analog scale	Mood stability	74.2 ± 17.0	74.6 ± 19.8	73.0 ± 17.3	0.15 (NS)
	Social avoidance	65.4 ± 16.7	64.1 ± 18.1	62.3 ± 17.9	0.64 (NS)
	Decreased work productivity	64.5 ± 16.7	64.2 ± 18.7	61.1 ± 18.0	0.75 (NS)
	Impulse to hurt others	87.6 ± 15.6	90.6 ± 13.0	90.3 ± 12.5	1.45 (NS)
	Self-esteem	79.6 ± 20.0	71.3 ± 20.0	67.4 ± 19.2	0.67 (NS)

Abbreviations: ANOVA-R, analysis of variance with repeated measures; NA, not applicable; and NS, not significant.
*ANOVAs: for Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory, *df* = 2,60; for Daily Rating Form, *df* = 2,52, n = 27; and for visual analog scale, *df* = 2,56, n = 29.
†$P < .01$ for Lupron plus placebo vs baseline using post hoc Bonferroni *t* tests (2 tailed).
‡$P < .05$ for Lupron plus placebo vs Lupron plus testosterone using post-hoc Bonferroni *t* tests (2 tailed).
§$P < .01$ for Lupron plus placebo vs Lupron plus testosterone using post-hoc Bonferroni *t* tests (2 tailed).

nificantly decreased during Lupron plus placebo compared with both baseline and Lupron plus testosterone. There were no symptom differences between baseline and Lupron plus testosterone. Repeated ANOVA with age as a covariate resulted in an identical pattern of effects.

Beck Depression Inventory but not Spielberger State-Trait Anxiety Inventory scores significantly increased during Lupron plus placebo compared with baseline and Lupron plus testosterone. The increase in BDI score during Lupron plus placebo (mean ± SD, 2.3 ± 3.2) was statistically but not clinically significant and reflected the effects of 3 men who scored 7 or higher on the BDI during Lupron plus placebo compared with none during Lupron plus testosterone replacement (Fisher exact test, *P* not significant). One man met DSM-IV[45] criteria for a major depressive episode during Lupron plus placebo, and his BDI scores were 0 at baseline, 14 during Lupron plus placebo, and 1 during Lupron plus testosterone. We observed significant effects of order of hormone administration and a trend for a significant interaction between order of hormone administration and hormone condition on the scores of the BDI (ANOVA-R: effects of order, $F_{2,58} = 7.0$, $P < .01$; interaction, $F_{2,58} = 2.5$, $P = .09$). A similar pattern was observed for the symptom of decreased sexual interest (ANOVA-R: effects of order, $F_{2,50} = 19.5$, $P < .001$; interaction, $F_{2,50} = 4.1$, $P < .05$). Men receiving Lupron plus placebo first but not those receiving Lupron plus testosterone first experienced a significant increase in BDI scores (and a decrease in sexual interest) during Lupron plus placebo compared with baseline conditions ($t_{58} = 3.4$ and $t_{50} = 3.7$, respectively; $P < .01$).

Total scores on the Buss-Durkee Hostility Inventory, Anger, Irritability, and Assault Questionnaire, and Barratt Impulsiveness Scale version 7B did not change across hormonal conditions; however, several individual subscale scores changed significantly from baseline with study participation. Buss-Durkee Hostility Inventory assault scores decreased from baseline during both Lupron plus placebo and Lupron plus testosterone (with significant differences between baseline and Lupron plus placebo). A similar pattern of change was observed for the individual subscales of risk taking, motor behavior, and sensory stimulation on the Barratt Impulsiveness Scale version 7B (**Table 3**). There was no significant interaction between order of hormone administration and hormone condition on the scores of either the Buss-Durkee Hostility Inventory assault or the Barratt Impulsiveness Scale version 7B subscales.

Men were assigned to high (n = 10) and low (n = 10) symptom groups for the baseline symptoms of sexual interest and feeling emotionally charged. There were significant group × hormone condition interactions for both sexual interest and feeling emotionally charged (ANOVA-R:

Table 3. Symptom Ratings During the Baseline Period and During the Administration of Lupron Plus Placebo or Testosterone in 20 Men

Outcome Measure	Symptom	Baseline, Mean ± SD	Lupron Plus Placebo, Mean ± SD	Lupron Plus Testosterone, Mean ± SD	ANOVA-R $F_{2,38}$ (*P* Value)
Buss-Durkee Hostility Inventory	Assault	4.7 ± 2.0	4.0 ± 1.8*	4.2 ± 1.8	3.4 (<.05)
	Indirect hostility	3.5 ± 1.8	3.5 ± 2.0	3.3 ± 2.0	0.4 (NS)
	Irritability	3.2 ± 2.3	3.5 ± 2.7	3.2 ± 2.6	0.5 (NS)
	Verbal	7.4 ± 2.3	6.9 ± 2.9	6.9 ± 2.5	1.0 (NS)
	Guilt	2.0 ± 1.8	1.9 ± 2.0	2.3 ± 2.0	0.8 (NS)
	Suspicion	0.9 ± 1.3	0.9 ± 1.2	0.8 ± 1.1	0.6 (NS)
	Resentment	0.7 ± 0.9	0.8 ± 1.1	0.7 ± 1.3	0.1 (NS)
	Negativity	1.5 ± 1.2	1.3 ± 1.6	1.5 ± 1.6	0.3 (NS)
Anger, Irritability, and Assault Questionnaire	Irritability	6.6 ± 3.9	7.5 ± 3.9	7.1 ± 5.0	0.6 (NS)
	Verbal assault	8.8 ± 5.5	8.8 ± 4.2	9.8 ± 4.6	1.2 (NS)
	Indirect assault	2.1 ± 3.6	2.0 ± 2.4	3.0 ± 3.0	1.2 (NS)
	Direct assault	8.0 ± 4.2	7.9 ± 3.7	8.5 ± 3.5	0.3 (NS)
	Anger	2.2 ± 3.2	1.9 ± 3.2	2.5 ± 3.1	0.5 (NS)
Barratt Impulsiveness Scale version 7B	Risk taking	6.4 ± 6.5	3.3 ± 5.5†	3.7 ± 5.5‡	8.5 (.001)
	Interpersonal behavior	3.1 ± 2.9	3.6 ± 3.7	3.7 ± 3.0	0.4 (NS)
	Motor behavior	14.5 ± 6.6	12.2 ± 6.2	11.9 ± 5.4§	3.3 (.05)
	Self-assessment	15.7 ± 8.8	14.0 ± 9.1	15.0 ± 10.4	1.0 (NS)
	Sensory stimulation	6.5 ± 3.5	4.8 ± 2.9*	5.8 ± 2.8	3.7 (<.05)

Abbreviations: ANOVA-R, analysis of variance with repeated measures; and NS, not significant.
*$P < .05$ for Lupron plus placebo vs baseline using post hoc Bonferroni *t* tests (2 tailed).
†$P < .01$ for Lupron plus placebo vs baseline using post hoc Bonferroni *t* tests (2 tailed).
‡$P < .01$ for Lupron plus testosterone vs baseline using post hoc Bonferroni *t* tests (2 tailed).
§$P < .05$ for Lupron plus testosterone vs baseline using post hoc Bonferroni *t* tests (2 tailed).

$F_{2,36}=5.9$, $P<.01$, and $F_{2,36}=11.6$, $P<.001$, respectively). For both symptoms, scores for the high symptom group were significantly higher than those for the low symptom group during baseline (by definition) and Lupron plus testosterone but not during Lupron plus placebo (baseline: $t_{54}=5.8$, $P<.01$, and $t_{54}=5.5$, $P<.01$; Lupron plus testosterone: $t_{54}=3.6$, $P<.01$, and $t_{54}=2.5$, $P=.05$ [for increased sexual interest and feeling emotionally charged, respectively]). Men with high baseline sexual interest had a significant decrease in sexual interest during Lupron plus placebo ($t_{36}=5.0$, $P<.01$), and levels of sexual interest were restored to baseline levels during Lupron plus testosterone ($t_{36}=5.1$, $P<.01$, compared with Lupron plus placebo) (mean±SD, 2.3±0.4 [baseline], 1.2±0.3 [Lupron plus placebo], and 2.3±0.9 [Lupron plus testosterone]). The low symptom group reported no significant effects on sexual interest during Lupron plus placebo or during testosterone replacement (mean±SD, 1.0±0.1 [baseline], 1.0±0.04 [Lupron plus placebo], and 1.5±0.6 [Lupron plus testosterone]). The average percent decrease in sexual interest from baseline to Lupron plus placebo was 46% in high and 2.3% in low baseline symptom groups. A similar pattern was found for the symptom of feeling emotionally charged; for the low baseline emotionally charged group, scores remained low during all 3 conditions, whereas symptoms for men with high baseline decreased significantly from baseline to Lupron plus placebo ($t_{36}=5.8$, $P<.01$) and increased nonsignificantly during Lupron plus testosterone but not to baseline levels (mean±SD, 2.3±0.8 [baseline], 1.5±0.6 [Lupron plus placebo], and 1.8±0.7 [Lupron plus testosterone]).

A trend for an interaction between group (high vs low baseline sexual interest scores) and hormone condition ($F_{2,36}=3.1$, $P=.06$) was observed for BDI scores. Despite comparable baseline BDI scores, men with high baseline sexual interest, but not those with low baseline sexual interest, had a significant increase in BDI scores during Lupron plus placebo compared with their baseline scores ($t_{36}=3.1$, $P<.05$). During Lupron plus placebo, BDI scores in the high group also were significantly higher than the low group scores (mean±SD, 3.9±4.3 vs 0.8±1.0, $t_{54}=3.1$, $P<.01$). A comparable number of men who received placebo first (ie, more likely to develop mood symptoms) were in the high baseline group (n=7) as were in the low baseline group (n=6).

Baseline plasma testosterone and estradiol levels did not differ between men with high baseline symptoms and those with low baseline symptoms.

Finally, we observed a significant correlation between BDI scores and severity of nighttime hot flushes ($r=0.7$, $P<.001$). There were no significant correlations between symptom scores during hypogonadism and changes in testosterone levels ($r=0.1$-0.3, *P* not significant).

COMMENT

Few subjects in this study developed negative mood symptoms during an otherwise dramatic albeit brief (4-week) withdrawal and replacement of testosterone under double-blind conditions. Some measures of mood did worsen during Lupron plus placebo, but the response within individuals varied considerably. For example, while BDI scores significantly increased during Lupron plus placebo, this increase was almost entirely due to the emer

gence in 3 men of symptoms of depression (BDI scores, 7-14) lasting 7 to 14 days during Lupron plus placebo. The relevance of changes in testosterone levels to mood for only a subgroup of men was similarly demonstrated in 4 studies of anabolic-androgenic steroids, reporting that approximately 5% of healthy male volunteers (none of whom were hypogonadal or drug abusers) experienced clinically significant mood symptoms, such as hypomania, when administered supraphysiologic doses of testosterone.[6-8,15] Indeed, in our group of carefully screened healthy volunteers, we observed the onset of clinically significant mood symptoms during Lupron plus placebo (hypogonadism), in contrast to during supraphysiologic levels of androgens, in a small percentage (approximately 10%) of the sample. Similarly, substantial effects in a small subset of patients appear responsible for observed mood-elevating effects of testosterone in samples of depressed men.[11] Thus, a clinically significant mood response to induced hypogonadism or testosterone replacement in men appears to reflect a differential behavioral response to alterations in reproductive hormones, as previously reported in women,[46] which may be mediated by genetic factors.[47] In samples in which rates of physical and psychiatric illness are higher than those in our sample and similar to those found in the general population, it is conceivable that negative mood response to induced hypogonadism could be more prevalent.

It is possible that, as suggested in perimenopausal women, depression may occur secondary to severe hot flushes. Indeed, in this study, BDI scores were significantly correlated with ratings of hot flush severity but not sleep disturbance. However, the high prevalence rates of hot flushes (67% in our acutely hypogonadal men and approximately 70% in perimenopausal women)[48] stand in contrast to the relatively low rate of depression in these samples. Thus, although the severity of both hot flushes and depression may be correlated, the presence of severe hot flushes is not sufficient to produce depression. Men and women who develop depression in the context of hot flushes, therefore, display a differential sensitivity to the negative effects of either declining testosterone (or estradiol) levels or hot flushes on mood.

Baseline level of symptomatology appeared to differentiate the men's responses to hormone withdrawal and replacement. Men with higher baseline levels of sexual interest (and feeling emotionally charged) experienced significant declines in these measures during Lupron plus placebo. Neither differences in baseline symptom scores nor responses to Lupron plus placebo were predicted by baseline or treatment-related plasma testosterone or estradiol levels. High baseline levels of sexual interest also identified a group of men who experienced a significant increase in BDI mood scores during Lupron plus placebo. At baseline, BDI scores in the high sexual interest group did not differ from those in the low sexual interest group; however, the high but not the low sexual interest group experienced a significant increase in BDI scores during Lupron plus placebo. Our findings are similar to those of Grunt and Young[43] and Moore,[44] in which animals with the highest levels of sexual activity at baseline experienced the greatest declines and increases in sexual activity during hypogonadism and testosterone replacement, respectively. A floor effect may have prevented detection of a further decline in symptoms during Lupron plus placebo in the low symptoms group. Nonetheless, the restoration of significantly elevated sexual interest in the high group but not the low group, despite comparable elevations of testosterone, suggests that testosterone is critical for sexual interest but only in some men; that is, men differ in the sensitivity to this effect of testosterone. Thus, our data suggest that a behavioral phenotype can predict a disparate response to declining testosterone secretion, and this phenotype may contribute to the substantial variation in the observed symptomatic response to aging and reproductive senescence.

Lupron plus placebo or testosterone (sufficient to achieve physiologic levels) did not influence aggression and impulsivity in these healthy men, consistent with the findings of Tricker et al.[14] However, had we studied a group of men with high baseline levels of aggression or impulsivity, or had supraphysiologic levels of testosterone been achieved more uniformly, it is possible that a larger change in these symptoms would have been observed.[23-25] Nonetheless, even with doses substantially higher than those we used, Pope et al[7] observed only a low frequency (5%-10%) of idiosyncratic hypomanic reactions rather than frequent induction of aggression or impulsivity. Several subscale items did decline during both Lupron plus placebo and Lupron plus testosterone; consequently, we cannot rule out the possibility that a factor present at baseline, suppressed with Lupron and not replaced with testosterone, could be mediating changes in those subscale items. Conversely, decreased symptoms could have occurred consequent to study participation, although clearly other measures moved in the opposite direction (eg, BDI).

It is possible that a longer duration of hypogonadism than we induced may have a greater negative impact on mood than we observed. In support of this possibility, we did observe that the men who received Lupron plus placebo first had greater changes in BDI and sexual interest scores during hypogonadism compared with those receiving Lupron plus testosterone first. Those men randomized to first receive placebo were hypogonadal for 5 to 6 consecutive weeks (the 1-2 weeks following the flare during month 1 and 4 weeks in month 2), whereas those men first receiving Lupron plus testosterone were hypogonadal during only 4 consecutive weeks in month 3. However, even in those men receiving placebo first, mood changes during Lupron plus placebo were nonuniform and were mild in the majority of subjects. Further, 4 weeks has been reported by prior studies to be sufficient to result in mood changes (improvement) in hypogonadal men after testosterone replacement,[13,49] and it was obviously sufficient to induce hot flushes and lower libido in the men participating in this study. Finally, our findings are comparable to those in the existing literature on the relationship between depression and hypogonadism in men; that is, despite the prolonged hypogonadism associated with aging, the majority of men do not develop a depression. Between the ages of 60 and 70 years, 20% to 30%

of men may meet criteria for hypogonadism,[1] yet no comparable increase in the onset of depressive illness has been reported. Nevertheless, we should be cautious about generalizing our findings in young men, whose testosterone levels were pharmacologically manipulated, to changes in mood associated with reproductive aging in older men. Overall, our data suggest that acute androgen withdrawal, while associated with decreased libido and hot flushes, is not sufficient to uniformly alter mood in healthy, young adult men.

Our data fail to support a uniform adverse effect on mood of induced hypogonadism in healthy young men. Nonetheless, our findings are consistent with a literature suggesting that some men are differentially sensitive to alterations in androgenic steroids, such that they experience disturbed mood in association with marked increases or decreases in these steroids. Even for a behavior (sexual function) that is more clearly linked to changes in testosterone, our demonstration that a behavioral phenotype (level of libido) can predict the degree of improvement in libido following testosterone replacement suggests that testosterone will not serve as a panacea for age- or hypogonadism-related sexual disturbance. An examination of healthy, psychologically normal young men served our intent to isolate the behavioral effects of testosterone, so that they would not be confounded by other factors (past psychiatric history, medical illness, or behavioral maladaptation) that may impact the relationship between mood and hypogonadism. Consequently, the generalizability of our observations to other (eg, aging) populations awaits further study.

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William Kurelek's Description of The Maze

The Maze [1] depicts Kurelek's spirit, 5 groups of unhappy thoughts, and the outside world: "Spirit: The white rat curled up in the central cavity represents my spirit (I suppose). He is curled up with frustration from having run the passages so long without hope of escaping this maze of unhappy thoughts. They proceed as follows: 1. *Home Upbringing* (top and top right): I, as a small boy, rejected by my school mates; my fear of school bullies and the ridicule of school girls; fear of being rejected by my father and losing the companionship, food, shelter, and warmth of a home; my father's philosophy, the survival of the craftiest, pointed out by the plight of the foolish fish. 2. *Political* (top left): My one time attachment to Ukranian nationalism . . . the Ukraine being raped by Russia; my subsequent association with members of the Peace Movement, a Communist front organization; the end result of over-zealous political leaning, WAR (my physical fear of it). 3. *Sexual* (middle left): The merry-go-round of rag dolls and wallflowers represent my lack of feeling and direction for dancing; the bull, dragging along his impediment and galloping towards the cow in heat, represents my fear of the animal side of sex in me. 4. *My Social Relations* (bottom left): Choice between the hospital, with its ordeal of the panel (I in the test tube), interpreted in two ways, as a benevolent conspiracy, or as a malevolent persecution: or the outside world—I continuing to be the outcast, skirting the smooth level highway of life in the ditch behind the hedge, sensitive to being seen in the light. 5. *Life and Death* (middle and bottom right): (A) Museum of Hopelessness being life [painting of a mushroom cloud] and (B) the conveyer belt bearing the victim (me) inexorably to be crushed by the roller Death, I being one third there by the clock and (C) the last picture of me trying to convince myself that I am really mortal, using the secondhand information (the drawing) rather than examining the skeleton or coffin. *Outside World* (right-hand side of painting): . . . spiritual and cultural barrenness. . . . The loosened red ribbon [linking the 2 halves of the skull] bound together the head of a T. S. Eliot Hollow Man, and was untied by psychotherapy . . . but since the outside world is still unappealing, the rat remains inert. Before the head was opened, burrs (bitter experiences) choked the throat and pricked the sensitive underside of the tongue, and when it was opened the sawdust shavings (tasteless education) spilled out from the top of the tongue: mixed with the sawdust are symbols of (to me) equally tasteless Art, painting, literature, and music. The burrs also represent, in the eye socket, the successive evaluations of my character by any friend during the process of acquaintance, all repellent but hopeful till the last, when the heart is discovered to be a grub. On the tongue and in the throat, the Kurelek family (big burrs produce little burrs), representing my father as the hard domineering blue burr opening up the mushy yellow burr, my mother, to release a common lot of burrs, my brothers and sisters, and one unique orange one—myself. The last burr, spearing culture, is I at the University. The inverted one is I as a child, trapped painfully between two aspects of my father, the one I hated and the one I worshipped."[2(p1-4)]

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