Journal of Andrology, Vol. 25, No. 6, November/December 2004

Restorative Increases in Serum Testosterone Levels Are Significantly Correlated to Improvements in Sexual Functioning

ALLEN D. SEFTEL,* RANDALL J. MACK,† ALLEN R. SECREST,† AND TED M. SMITH†

*From the *Department of Urology, Case Western Reserve University, University Hospitals of Cleveland, Cleveland VA Medical Center, Cleveland, Ohio; and †Auxilium Pharmaceuticals, Inc, Norristown, Pennsylvania.*

ABSTRACT: It is recognized that testosterone (T) levels decrease in men with age, as does sexual function. We hypothesize that T supplementation in hypogonadal men with sexual dysfunction will restore certain elements of sexual function. Hypogonadal male subjects (total T $\leq$ 300 ng/dL, n = 406, mean age 58 years) reporting one or more symptoms of low testosterone were randomized to T gel (50 mg/d and 100 mg/d), T patch, or placebo. Twenty-four–hour pharmacokinetic profiles for T were obtained. The 3 primary end points evaluated at 30 and 90 days posttreatment included a significant change in the frequency of intercourse and nighttime erections per 7-day week as well as a change in sexual desire measured on a Likert-type scale and calculated as a mean daily score. At day 30, a significant increase from baseline in sexual desire was noted for those on 100 mg/d T gel compared with those on 50 mg/d T gel, T patch, or placebo (1.2 vs 0.4, 0.7, and 0.4, respectively). A significant increase from baseline in the frequency of nighttime erections was also noted for those on 100 mg/d T gel compared with those on 50 mg/d T gel or placebo (51% of subjects in the 100 mg/d T gel group had an increase in frequency vs 30% for the 50 mg/d T gel group and 26% in the placebo group). Finally, a significant increase from baseline in the frequency of intercourse was evidenced for those on 100 mg/d T gel compared with those on T patch or placebo (39% of subjects in the 100 mg/d T gel group had an increase in frequency vs 21% for the T patch group and 24% in the placebo group). Similar results were seen for 100 mg/d T gel at day 90 for sexual desire and nighttime erections vs placebo. These data demonstrate a clear relationship between restoring serum T concentrations and improvement in certain parameters of sexual function. We propose that threshold T levels are needed in order to significantly affect improvements in sexual functioning.

Key words: Randomized controlled trial, androgen, gel, hypogonadism, sexual dysfunction.

J Androl 2004;25:963–972

It is recognized that serum testosterone (T) levels decrease below the eugonadal range in some men with advancing age. Restoration of T levels to the eugonadal range (300–1000 ng/dL) appears to correct many of the clinical abnormalities (impaired sexual function, negative changes in body composition, etc) commonly associated with hypogonadism (Wang et al, 2000; Steidle et al, 2003). With respect to hypogonadal males, a number of studies have demonstrated that T replacement therapy can significantly affect a number of the fundamental indicators of apposite sexual functioning, including intensity of libido, frequency of nocturnal erections, and frequency of sexual activity (O'Carroll et al, 1985; Burris et al, 1992; Arver et al, 1996). Furthermore, additional research in which an acute hypogonadal state was induced (in experimental animals and eugonadal males) not only confirmed the importance of physiological levels of T in maintaining normal sexual behavior but also highlighted the dose-response relationships between T levels and the various androgen-dependent processes, including sexual function (Fielder et al, 1989; Buena et al, 1993; Bagatell et al, 1994; Bhasin et al, 2001).

This study compared 3 active treatment regimens to a placebo regimen in a population consisting primarily of aging males with low serum T levels and the associated signs and symptoms of hypogonadism. We hypothesized that hypogonadal men with specific sexual dysfunction might receive benefit in their sexual functioning from T replacement therapy. Some results from this study have been reported previously—specifically, pharmacokinetic parameters related to serum T and dihydrotestosterone (DHT), body composition, mood, bone mineral density, and several safety parameters. In addition, significant improvements were noted relative to placebo in sexual desire, sexual performance (composite score based on the relative success of intercourse or masturbation), sexual motivation, and spontaneous erections (day or nighttime) (Steidle et al, 2003). This article focuses on the relation-

Supported by a grant from Auxilium Pharmaceuticals, Inc, Norristown, Pennsylvania.

Correspondence to: Allen D. Seftel, Department of Urology, Case Western Reserve University, University Hospitals of Cleveland, Cleveland VA Medical Center, 11100 Euclid Ave, Cleveland, OH 44106-5046 (e-mail: ads6@po.cwru.edu).

Received for publication March 11, 2004; accepted for publication June 12, 2004.

*Subject characteristics**

	T Gel				
	50 mg	100 mg	T Patch	Placebo	Total
Demographics					
n	99	106	102	99	406
Age (y)	58.1 ± 9.7	56.8 ± 10.6	60.5 ± 9.7	56.8 ± 10.8	58.0 ± 10.3
Height (cm)	178 ± 6	178 ± 8	178 ± 6	180 ± 7	179 ± 7
Weight (kg)	95.7 ± 13.4	95.7 ± 14.4	95.1 ± 13.5	98.5 ± 15.6	96.2 ± 14.2
Body mass index	30.0 ± 3.7	29.9 ± 3.3	29.9 ± 3.8	30.3 ± 3.8	30.0 ± 3.6
Testosterone (ng/dL)†	233.8 ± 57.0	232.0 ± 61.9	239.1 ± 68.9	228.5 ± 80.3	233.4 ± 67.4
Cause of hypogonadism‡					
Primary (n)	8	7	4	3	22
Secondary (n)	91	98	98	95	382
Aging (%)¶	70.7	58.1	66.7	61.2	64.1
Normogonadotrophic (%)¶	19.2	30.5	26.5	31.6	27.0

* T indicates testosterone; n, number of subjects. Demographic values are expressed as means ± 1 SD.
† Serum T concentration at 8 AM screening exam.
‡ Two subjects had a missing cause of hypogonadism.
¶ Percentage of total by treatment group. Distribution by cause is shown only if it occurred in ≥4% of subjects.

ship between the serum T levels obtained after T supplementation and sexual desire and 2 other primary indicators of male sexual function (frequency of nighttime erections and intercourse). These 2 parameters were selected on the basis of their clear and known association with low serum T levels, as well as their diagnostic usefulness in clinical practice.

Subjects and Methods

Subjects

Four hundred six male subjects were randomized and treated at 43 clinics in the United States. Approximately 100 subjects were randomized to each of 4 treatment groups (Table). The randomization was balanced with respect to treatment allocation within each center and was blinded with respect to the gel-treated groups. Subjects were between 20 and 80 years of age (mean age 58 years), had a morning T level ≤300 ng/dL (10.4 nmol/L) at screening (measured at a central laboratory), and had one or more symptoms of low T (ie, fatigue, decreased muscle mass, reduced libido, reduced sexual functioning of a nonmechanical [nonvascular] nature) as determined by the study investigators. Except for hypogonadism, the subjects were in generally good health.

The study was conducted in accordance with the Declaration of Helsinki and complied with Good Clinical Practice; all subjects signed an informed consent agreement that was previously approved by one of the study's participating institutional review boards.

Study Drugs

Topical T gel (Testim 1% [T gel]) was supplied by Auxilium Pharmaceuticals (Norristown, Pa). The 4 daily treatments were 50 or 100 mg/d T gel, matching placebo gel, and a transdermal T patch (Androderm, 2 patches × 12.2 mg/d T). Approximately 5, 10, and 5 mg of the applied T dose is absorbed across skin of average permeability during a 24-hour period for the 50 and 100 mg/d T gel and the T patch treatments, respectively. The T gel and placebo gel were identical and applied as 2 tubes of 50 mg/d T (100 mg/d), 1 tube of 50 mg/d T and 1 tube of placebo (50 mg/d), or 2 tubes of placebo. Neither the subjects nor the investigators were aware of the contents of the tubes.

All study drug treatments were applied in the morning; repeat applications occurred at the same time of day for the duration of the study. Each day in the gel-treated group, subjects applied the contents of 2 tubes. Subjects allocated to receive the T patch applied 2 adhesive patches daily. Patches were to be worn for 24 hours and then replaced each morning at approximately the same time.

Study Design

The study was designed as a randomized, multidose, multicenter, active, placebo-controlled study. Subjects were randomized to 50 (99 subjects) or 100 mg/d (106 subjects) T gel and matching placebo gel (99 subjects) or T patch (102 subjects). Randomization was performed to ensure an equal distribution of treatments across study centers. The study was double-blinded for the T gel and placebo groups and open-label for the T patch group. Subjects randomized to 1 of the 2 T gel arms could be titrated at day 60 on the basis of their day 30 T pharmacokinetic profile. Subjects were titrated from 50 mg/d to 100 mg/d at day 60 if their day 30 mean serum T concentration (C_{avg}) was <300 ng/dL (10.4 nmol/L). Subjects were titrated from 100 to 50 mg/d at day 60 if their day 30 T C_{avg} was >1000 ng/dL (34.7 nmol/L). These titration decisions were undertaken by a third party physician who was unaware of any clinical aspects of the individual subjects.

Subjects had a baseline 24-hour profile for serum T consisting of serum samples taken at 8 and 10 AM and 12 and 4 PM on day −1 and 8 AM on day 1, immediately before the first dose of study drug. On days 30 and 90, subjects had another 24-hour profile for T consisting of serum samples at predose and 2, 4,

8, 12, and 24 hours after study drug administration. On day 60, a single 8 AM serum sample was taken.

Sexual function diaries were completed daily for 14 days before day 1 and daily for 7 days before days 30, 60, and 90. Data were collected centrally in real time via an interactive telephone voice response system.

Methods

Sexual functioning assessments were based on a self-report daily diary—one that has been validated for assessment of sexual function and mood and was used in a previous study to evaluate the effects of T gel on sexual function (Lee et al, 2003). The diary elicited information on sexual desire and the occurrence of nighttime erections and intercourse. Sexual desire was assessed on a Likert-type scale (score range 0–7) and was calculated as an average score. The evaluation of nighttime erections and intercourse was calculated as the average number of days in a 7-day week that the events occurred. Of note, the number of subjects evaluated for the frequency of intercourse differs from those evaluated for sexual desire and nighttime erections because the requirement for a steady, sexual partner was not a study entry criterion.

Serum T levels were measured and analyzed at ICON Laboratories (Farmingdale, NY) with validated radioimmunoassay kits obtained from Diagnostic Products Corporation (Los Angeles, Calif).

Statistical Analyses

The 24-hour pharmacokinetic profiles for T were summarized by C_{avg} (AUC_{0-24} divided by the 24-hour sampling period, where AUC is the area under the concentration curve calculated by the trapezoidal rule). The change from baseline to day 30 and day 90 in T C_{avg} was analyzed by analysis of covariance (ANCOVA) with the baseline value as the covariate and treatment group as the factor.

Number of days with nighttime erections and frequency of intercourse during a 7-day week were summarized at baseline, day 30, and day 90. Change in frequency relative to baseline for intercourse and nighttime erections for day 30 and day 90 were categorized as decrease, no change, or increase and analyzed for each pair of treatments with the Mantel-Haenszel analysis of variance statistic. Change in frequency was made on the basis of the actual number of days in which a subject reported nighttime erections or intercourse in a 7-day week. The change was noted as ''Decrease'' if fewer days were reported during the study than during baseline; the change was noted as ''No Change'' if the same number of days were reported on treatment as during baseline; the change was noted as ''Increase'' if more days were reported during treatment than during baseline.

The change from baseline to day 30 and day 90 in mean daily score for sexual desire was analyzed by ANCOVA with baseline value as the covariate and treatment group as the factor. Subjects randomized to T gel (50 or 100 mg/d) could have their dose changed at the day 60 visit. Those subjects with a dose change were analyzed at day 90 under the dose they received at the day 60 visit. SAS version 8.02 (SAS Institute, Cary, NC) was used for all analyses. For each comparison, an alpha of .05 was considered significant. All data in tables are presented as means ± SD.

Additionally, a post hoc examination of a potential threshold relationship between sexual function response and T levels, as measured by C_{avg}, was carried out for each parameter. For ease of display and analysis, T levels were divided into 3 categories: below normal (0–300 ng/dL), low normal (300 to the cut-off value [CV]) and above low normal (CV+). The CV for low normal was determined separately for each sexual function parameter. We hypothesized that as T levels were restored to the therapeutic range, each sexual function parameter would demonstrate a ''threshold'' C_{avg} T value below which there was no change and above which a change occurred. Analyses similar to those involving the treatment groups were carried out with the use of the T level categorization in place of the treatment group. All pairwise category comparisons were made to highlight the threshold effect. The analysis was based on first dividing the T levels into deciles, plotting the mean values for each decile group, and then collapsing the deciles as the data indicated.

Finally, although data on sexual function response was evaluated on the basis of change in T level from baseline (rather than as the final T level vs response), no differences in correlations, significance, or interpretation were noted. Considering these results and because the actual T level vs response analysis is consistent with the threshold concept, only the actual T level vs response analysis is discussed and presented.

Results

Subjects

A total of 406 subjects were randomized to the 50 mg/d T gel (99), 100 mg/d T gel (106), T patch (102), and placebo (99) treatment groups (Table). Baseline subject characteristics (age, height, weight, body mass index, serum T at screening) were comparable. Baseline mean C_{avg} serum T concentrations were 246 ± 81, 224 ± 79, 236 ± 81, and 219 ± 81 ng/dL in the 50 mg/d T gel (T gel 50, hereafter), 100 mg/d T gel (T gel 100), T patch, and placebo groups, respectively. A total of 15 subjects had morning serum total T levels of >300 ng/dL at screening. Specifically, 5.1%, 4.7%, 2.9%, and 2.0% in the respective groups had values of >300 ng/dL. These subjects were entered into the study as protocol exceptions or deviations. Fifty percent of the subjects were aged 58 years or older and approximately 26% were aged 65 and older, with a mean age of 58 years. Subject hypogonadism was primarily attributed to the secondary cause of aging and normogonadotrophic hypogonadism; these determinations were made by the study investigators and accounted for 91% of all causes in the overall population (Table). Titrations made at day 60 in the T gel groups were as follows: 52 subjects started on the 50 mg/d dose and remained on it for the entire study, 43 subjects who started on the 50 mg/d dose were titrated up to the 100 mg/d dose, 93 subjects who started on 100 mg/d dose remained

at that dose for the entire study, and 4 subjects who started on the 100 mg/d dose were titrated down to the 50 mg/d dose.

Sexual Desire

At baseline, the mean sexual desire scores were 2.1 ± 1.4, 2.6 ± 1.4, 2.2 ± 1.3, and 2.1 ± 1.4 in the T gel 50, T gel 100, T patch, and placebo groups, respectively (score range: 0–7). A significant increase from baseline in sexual desire was noted for the T gel 100 group (change = 1.2) compared with the T gel 50 (0.4, $P < .001$), T patch (0.7, $P < .0013$), and placebo groups (0.4, $P < .001$) on day 30; on day 90, change = 1.0 (T gel 100) vs 0.5 (T gel 50, $P = .0165$), 0.6 (T patch, $P = .0317$), and 0.5 (placebo, $P = .0035$) (Figure 1). At day 30, a significant increase ($P = .0269$) from baseline in sexual desire was noted for the T patch vs placebo group that was not maintained at day 90. Mean C_{avg} serum T concentrations were 213 ± 78, 377 ± 122, 346 ± 135, and 629 ± 287 ng/dL in the T gel 50, T gel 100, T patch, and placebo groups, respectively, at day 30, and 213 ± 79, 330 ± 127, 405 ± 248, and 506 ± 234 ng/dL in the same groups, respectively, at day 90 (Figure 1).

The change in desire correlated with the serum T levels achieved as measured by C_{avg} for day 30 ($r = .33$, $P < .0001$) and day 90 ($r = .28$, $P < .0001$). Similar results were seen at day 60, except that only 8 AM serum T levels were obtained for each subject, so results are therefore not reported here.

Nighttime Erections

At baseline, nighttime frequency distributions were similar across the 4 treatment groups, with 33%, 35%, 39%, and 33% in the T gel 50, T gel 100, T patch, and placebo groups, respectively, reporting no days on which nighttime erections occurred (Figure 2).

At day 30, a significant increase from baseline in the frequency of nighttime erections was noted for the T gel 100 dose compared with the T gel 50 dose (51% of subjects in the T gel 100 group had an increase in frequency vs 30% for the T gel 50 group, $P = .0028$) and placebo group (26%, $P = .0001$). At day 90, the T gel 100 group continued to demonstrate a significant increase from baseline compared with the placebo group ($P = .0354$) (Figure 2). At day 30, a significant ($P = .0278$) increase from baseline in frequency of nighttime erections was noted for the T patch vs placebo group that was not maintained at day 90.

The change in the number of days per week in which subjects reported nighttime erections was correlated with the serum T levels achieved as measured by C_{avg} for day 30 ($r = .27$, $P < .0001$) and day 90 ($r = .28$, $P < .0001$).

Intercourse

At baseline, intercourse frequency distributions were similar across the 4 treatment groups, with 45%, 47%, 49%, and 43% in the T gel 50, T gel 100, T patch, and placebo groups, respectively, reporting no days on which intercourse occurred (Figure 3).

At day 30, a significant increase from baseline in the frequency of intercourse was noted for the T gel 100 dose compared with the T patch and placebo groups (39% of subjects in T gel 100 dose group had an increase in frequency vs 21% in the T patch group ($P = .0356$) and 24% in the placebo group ($P = .0096$). At day 90, the T gel 100 group continued to evidence a significant increase from baseline compared with the T patch and T gel 50 groups (37% vs 13%, $P = .0027$, and 6% $P = .001$, respectively) (Figure 3). Mean C_{avg} serum T concentrations at day 30 for those subjects who also had a partner available were 209 ± 81, 386 ± 113, 338 ± 136, and 587 ± 216 ng/dL in the T gel 50, T gel 100, T patch, and placebo groups, respectively, and 218 ± 74, 315 ± 112, 373 ± 145, and 487 ± 213 ng/dL in the T gel 50, T gel 100, T patch, and placebo groups, respectively, at day 90 (Figure 3).

The change in the number of days per week in which subjects reported intercourse was correlated with the serum T levels achieved as measured by C_{avg} ($r = .20$, $P = .0027$ for day 30; $r = .16$, $P < .0202$ for day 90).

Sexual Function and Serum T Levels

We explored the possibility that there might be a threshold average daily serum T level for sexual response, meaning a T level at which the sexual response was no different from that of the group of subjects with the lowest serum T level (0–300 ng/dL) and above which there was a significant change compared with that of the group of subjects with the lowest serum T level. This threshold level appeared to be approximately 400 ng/dL for nighttime erections, 500 ng/dL for sexual intercourse, and 600 ng/dL for sexual desire. In all 3 parameters, there was no significant difference in sexual function between the group of subjects with the lowest serum T levels (0–300 ng/dL) and the group of subjects with the next highest serum T level (300–400 ng/dL for nighttime erections, 300–500 ng/dL for sexual intercourse, and 300–600 ng/dL for sexual desire, $P \geq .16$). However, there were significant differences between the group of subjects above the threshold serum T value and the group with the lowest serum T levels (0–300 ng/dL, $P \leq .0028$). In addition, there were significant differences between the group of subjects above the threshold serum T value and the group of subjects with serum T levels between 300 ng/dL and the threshold for sexual desire and intercourse ($P \leq .0098$) (Figure 4). These results indicate that the response

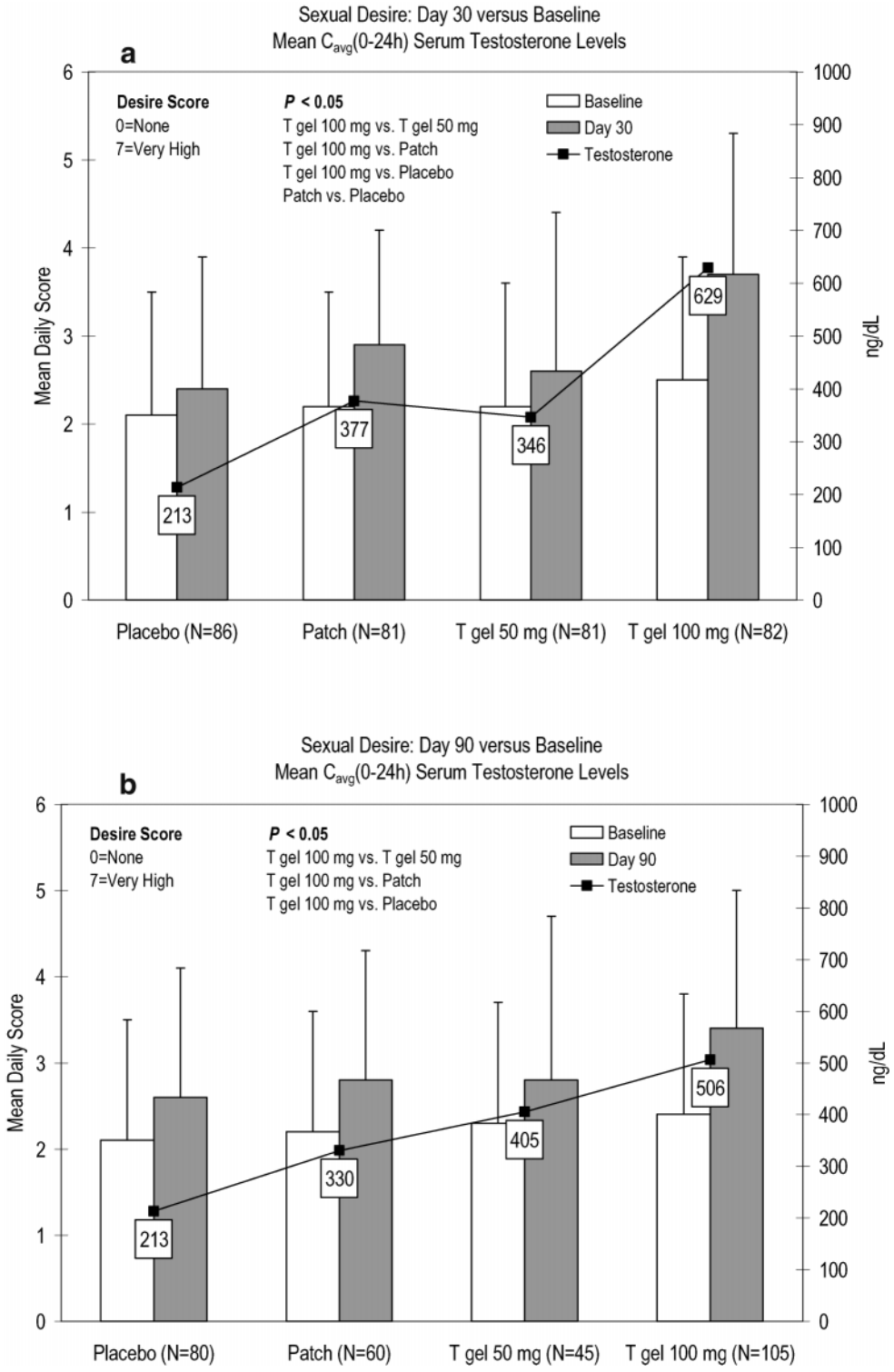

Figure 1. Mean daily sexual desire scores (range: 0–7) at baseline, day 30, and day 90, and mean (SD) C_{avg} (0–24 hours) serum testosterone levels (ng/dL) for all treatment groups.

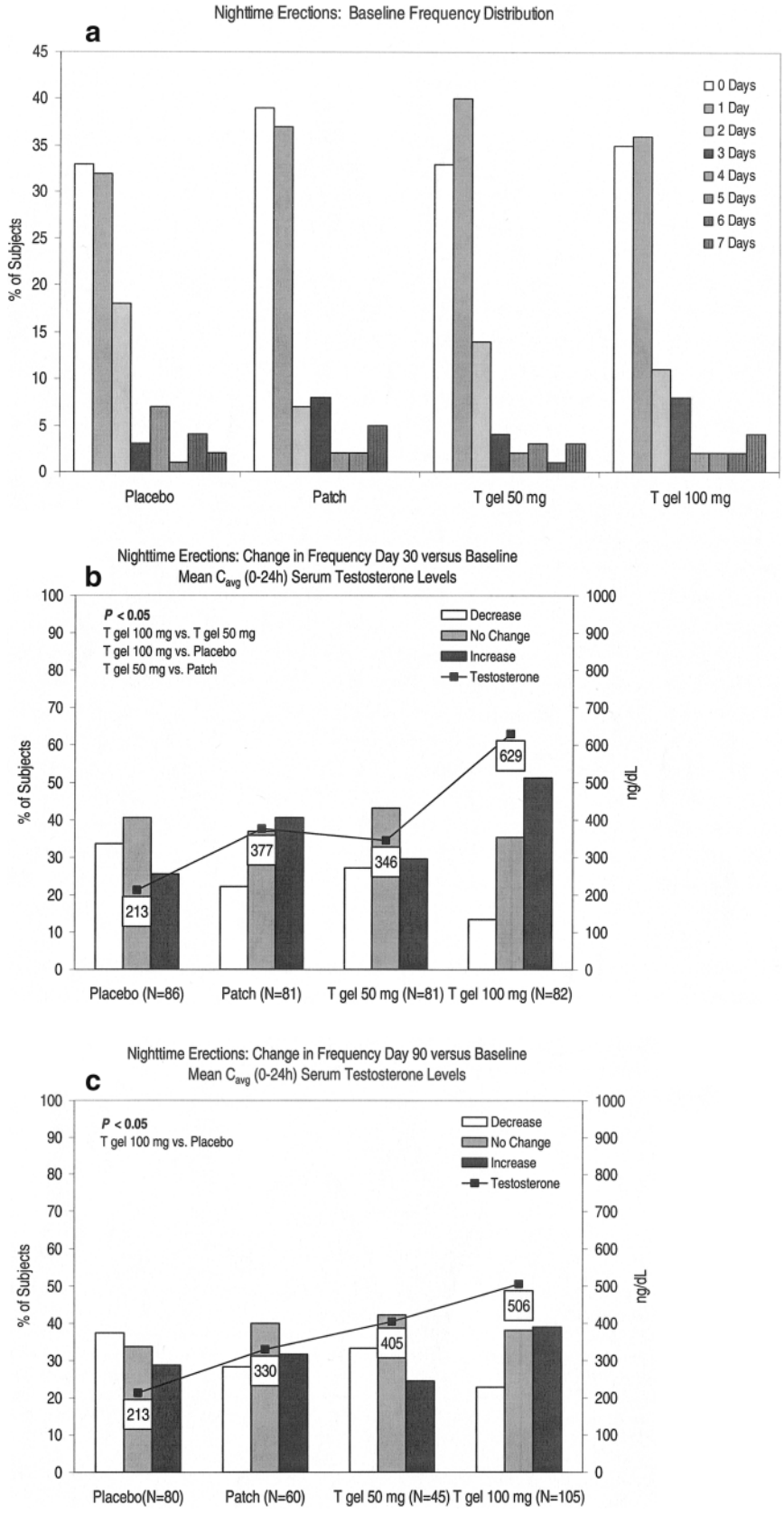

Figure 2. Percentage of subjects reporting days (range: 0–7) in which nighttime erections occurred at baseline; percentage of subjects reporting a decrease, no change, or increase at day 30 and day 90; and mean (SD) C_{avg} (0–24 hours) serum testosterone levels (ng/dL) for all treatment groups.

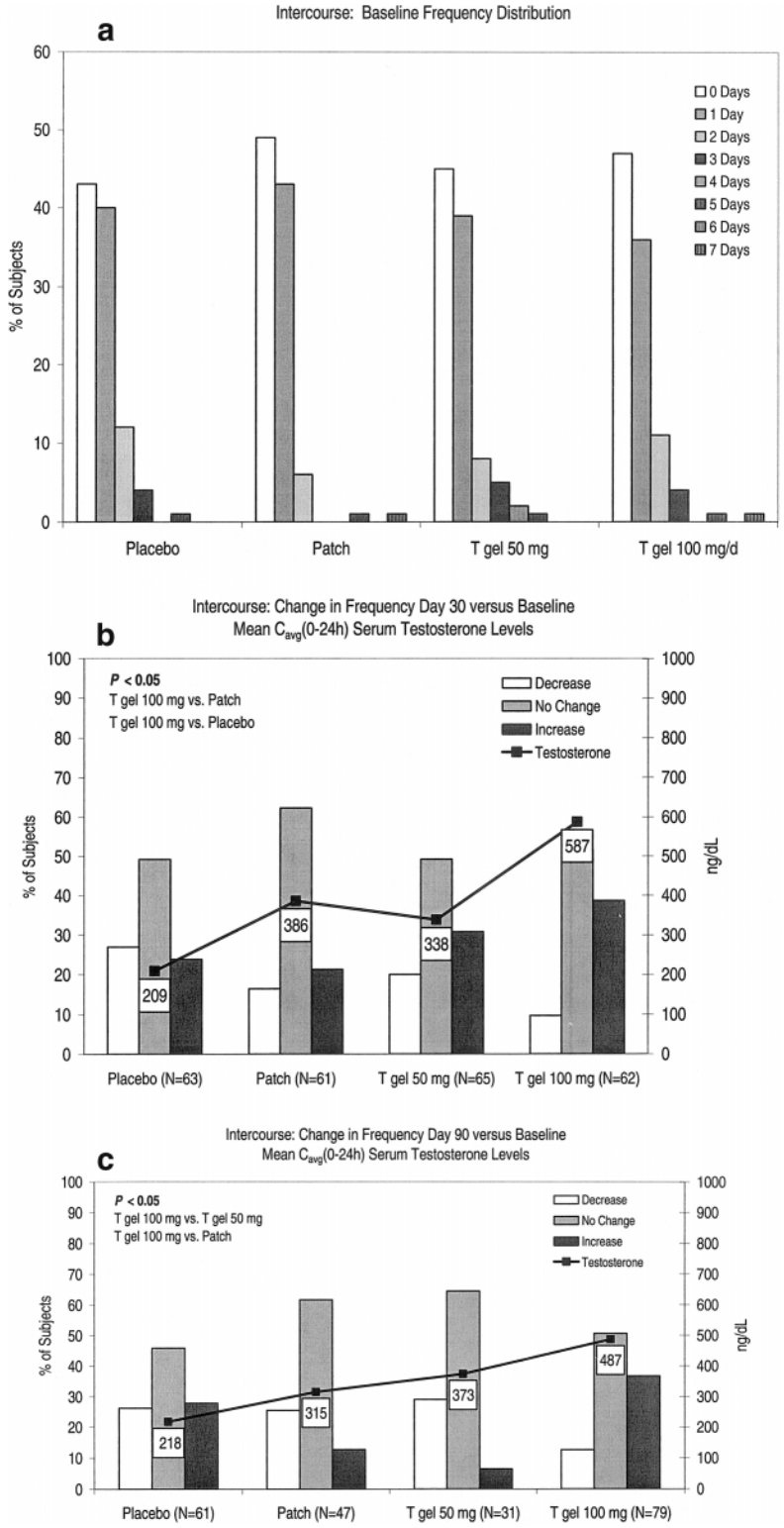

Figure 3. Percentage of subjects reporting days (range: 0–7) in which intercourse occurred at baseline; percentage of subjects reporting a decrease, no change, or increase at day 30 and day 90; and mean (SD) C_{avg} (0–24 hours) serum testosterone levels (ng/dL) for all treatment groups.

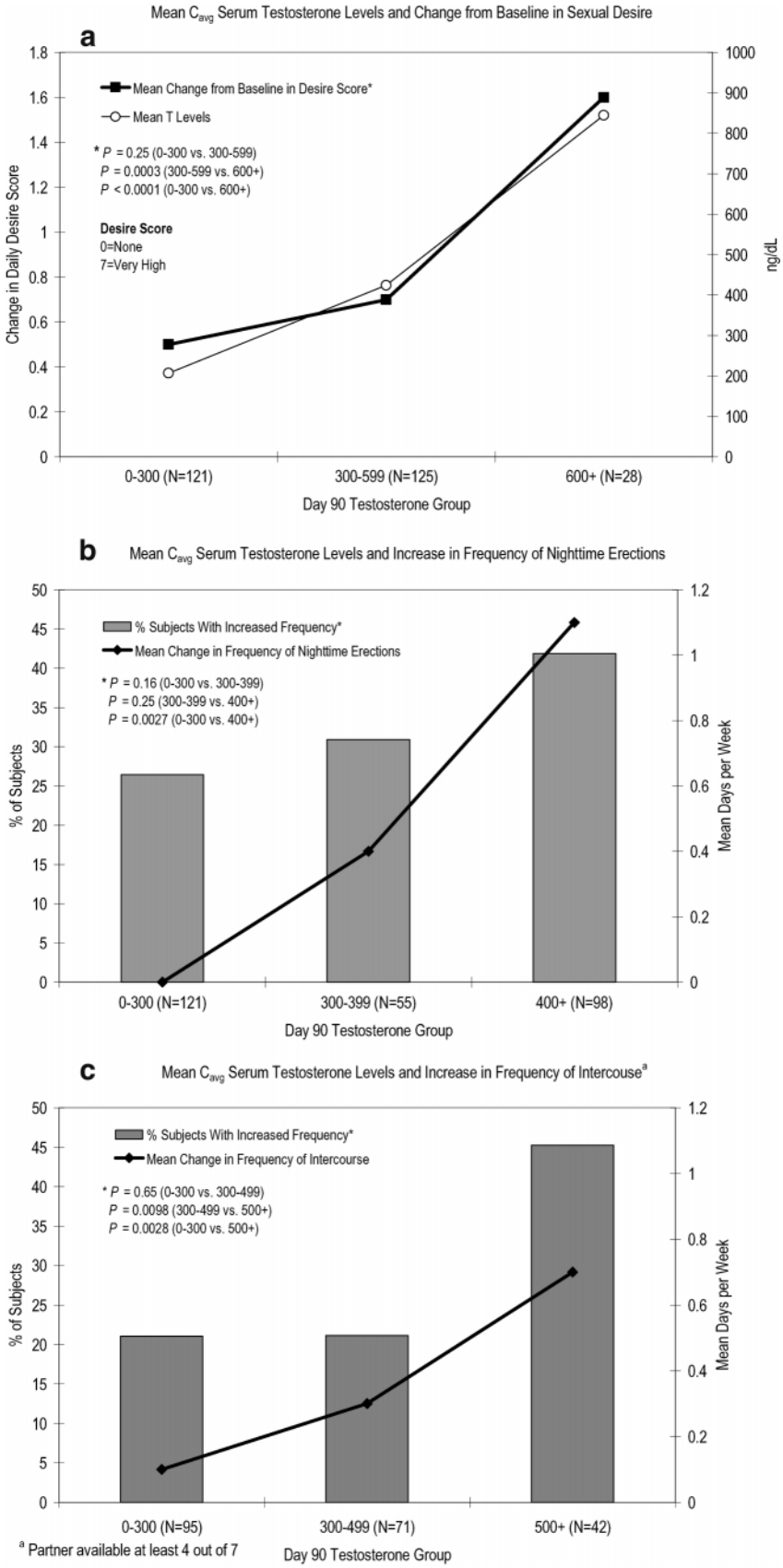

Figure 4. Mean change from baseline for daily sexual desire score and mean C_{avg} (0–24 hours) serum testosterone levels (ng/dL); percentage of subjects with increased frequency and mean change in frequency for nighttime erections and intercourse.

functions for sexual desire and intercourse were relatively flat until the serum T levels were restored to levels above the threshold value, whereas the response function for nighttime erections gave an indication of an increased response even with restoration of serum T levels into the low-normal range (300–400 ng/dL).

Discussion

The data in this placebo-controlled study demonstrate that restoration of T to eugonadal levels improves the level of sexual desire, the frequency of intercourse, and the frequency of nocturnal erections. An additional novel finding is that there might be threshold levels for each of these sexual parameters, thus providing treatment guidance to the clinician.

Signs and symptoms of low T in adult males include loss of libido and erectile dysfunction (Tenover, 1998; Petak et al, 2002). Men affected by this condition report irritability, loss of concentration, declining libido, erectile dysfunction, and a decreased sense of well-being (Tenover, 1998). Mood disorders such as depression and behavioral symptoms such as irritability and lethargy also occur. Some regression of secondary sexual characteristics such as reduced auxiliary and pubic hair might be observed, but voice, penis length, and prostate size often remain unchanged (Braunstein 1997; Tenover, 1998; Petak et al, 2002).

How does testosterone affect sexual function? In hypogonadal men, spontaneous erections have been shown to be androgen dependent (Davidson et al, 1979; Shakkebaek et al, 1981; O'Carroll et al, 1985) and erections in response to erotic stimuli have been shown to be androgen independent (Bancroft and Wu, 1983; Kwan et al, 1983). In terms of the relationship between mood and androgens, several studies have demonstrated a positive effect (O'Carroll et al, 1985; Wang et al, 1996b; Anderson et al, 1999; Wang et al, 2000), whereas other studies have not (Davidson et al, 1979). Thus, many relationships between hypogonadism and sexual function have not been fully elucidated. This placebo-controlled study attempts to address these deficient areas. The study reported here includes comparisons among 4 parallel treatment groups in a population of aging, hypogonadal men reporting at least one or more symptoms of hypogonadism, with a specific focus on desire and erectile function reported in this data set. Active treatments consisted of either 50 or 100 mg/d T gel or a T patch (2 patches, each delivering 2.5 mg/d T), doses that have been shown to produce clinically relevant increases in serum T levels (Dobs et al, 1999). A fourth group of matching placebo gel was also included to provide a valid and definitive assessment of clinical and subjective symptom improvements. The sexual function response was based on daily logs, which were part of a self-report diary that had been used previously in the development of other T preparations (Wang et al, 1996; Swerdloff et al, 2000).

Sexual desire increased in all treatment groups, including the placebo group, confirming the partially subjective nature of the entity termed ''desire.'' Because of the notable placebo effect, the data suggest that average daily serum T levels need to be in excess of a threshold of 600 ng/dL in order to detect a significant treatment effect over and above the placebo effect.

Intercourse was recorded daily for 14 days before the end of the baseline period and daily for 7 days before the end of the first, second, and third 30-day treatment periods; hence, the total occurrences of intercourse during a 30-day period was not captured as were other measurement instruments based on a 1-month recall methodology. Notwithstanding this methodological difference, a clear treatment effect of T gel 100 was seen at day 30 compared with T gel 50, T patch, and placebo. At day 90, there were still no differences seen among the T gel 50, T patch, and placebo groups. However, the T gel 100 group was significantly different from T patch and T gel 50 and marginally significantly different from the placebo group ($P = .06$) at day 90. Because subjects were included in this analysis only if they had a partner available at least 4 days out of each questionnaire period, there were fewer subjects in this analysis, resulting in some loss of power. A sexual partner was not mandatory for entry into this study; however, approximately 80% of all men had a partner available. Even though there were fewer subjects, it still followed that the percentage of subjects who experienced an increase in frequency of intercourse was significantly higher in those subjects whose average daily serum T levels were above 500 ng/dL than in those whose serum T levels were less than 500 ng/dL, regardless of how much less.

Nighttime erections occurred at a higher rate in the T gel 100 compared with the placebo group at both day 30 and day 90. The increase in nighttime erections seemed to start at a lower average daily serum T level than seen in the other 2 sexual parameters (400 ng/dL), suggesting that this androgenic effect is among the first to be restored or affected as the serum T levels are raised with T replacement therapy

Notwithstanding the fact that this study was not designed to measure explicitly a threshold effect, especially whether the threshold is strongly subject dependent, these exploratory analyses demonstrated a clear relationship between the restoration of T levels and significant improvements in basic aspects of sexual function (eg, sexual desire, frequency of nighttime erections, and frequency of intercourse). The results also indicate that there might be threshold serum T levels associated with improvements

in sexual function that are higher than the levels required to affect changes in other areas negatively affected by the hypogonadal state (eg, body composition) and that additional studies should be conducted to further investigate this correlation. Furthermore, these findings are consistent with studies conducted in eugonadal young men in which hypogonadism was induced with a GnRH antagonist.

The data from this study demonstrate that T replacement in hypogonadal men has an effect on sexual desire, frequency of nocturnal erections, and frequency of sexual intercourse. The novel concept explored herein—specifically, that a threshold value exists above which a demonstrable effect is evidenced—provides further guidance to clinicians regarding T replacement therapy.

References

Anderson RA, Martin CW, Kung AW, et al. 7 Alpha-methyl-19-nortestosterone maintains sexual behavior and mood in hypogonadal men. *J Clin Endocrinol Metab.* 1999;84:3556–3562.

Arver S, Dobs AS, Meikle AW, Allen RP, Sanders SW, Mazer NA. Improvement of sexual function in testosterone deficient men treated for 1 year with a permeation enhanced testosterone transdermal system. *J Urol.* 1996;155:1604–1608.

Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ. Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. *J Clin Endocrinol Metab.* 1994;78:711–716.

Bancroft J, Wu FC. Changes in erectile responsiveness during androgen replacement therapy. *Arch Sex Behav.* 1983;12:59–66.

Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab.* 2001;281:E1172–E1181.

Braunstein GD. Testes. In: Greenspan FS, Strewler GJ, eds. *Basic and Clinical Endocrinology.* 5th ed. Stamford, Conn: Appleton & Lange; 1997:403–433.

Buena F, Swerdloff RS, Steiner BS, Lutchmansingh P, Peterson MA, Pandian MR, Galmarini M, Bhasin S. Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. *Fertil Steril.* 1993;59:1118–1123.

Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *J Androl.* 1992;13: 297–304.

Davidson JM, Camargo CA, Smith ER. Effects of androgen on sexual behavior in hypogonadal men. *J Clin Endocrinol Metab.* 1979;48: 955–958.

Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison to bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab.* 1999;84:3469–3478.

Fielder TJ, Peacock NR, McGivern RF, Swerdloff RS, Bhasin S. Testosterone dose-dependency of sexual and nonsexual behaviors in the gonadotropin-releasing hormone antagonist-treated male rat. *J Androl.* 1989;10:167–173.

Kwan M, Greenleaf WJ, Mann J, Crapo L, Davidson JM. The nature of androgen action on male sexuality: a combined laboratory-self-report study on hypogonadal men. *J Clin Endocrinol Metab.* 1983;57:557–562.

Lee KK, Berman N, Alexander GM, Hull L, Swerdloff RS, Wang C. A simple self-report diary for assessing psychosexual function in hypogonadal men. *J Androl.* 2003;24:688–698.

Liverman CT, Blazer DG, eds. *Testosterone and Aging: Clinical Research Directions.* Washington, DC: The National Academies Press; 2004.

O'Carroll R, Shapiro C, Bancroft J. Androgens, behavior and nocturnal erection in hypogonadal men: the effects of varying the replacement dose. *Clin Endocrinol (Oxf).* 1985;23:527–538.

Petak SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Rigau LJ (for the AACE Hypogonadism Task Force). American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of low testosterone in adult male patients—2002 update. *Endocr Pract.* 2002;8:439–456.

Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol (Oxf).* 1981;14:49–61.

Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand R. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab.* 2003;88:2673–2681.

Swerdloff RS, Wang C, Cunningham G, et al. The Testosterone Gel Study Group. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab.* 2000;85:4500–4510.

Tenover JL. Male hormone replacement therapy including ''andropause.'' *Endocrinol Metab Clin North Am.* 1998;27:969–987.

Wang C, Alexander G, Berman N, et al. Testosterone replacement therapy improves mood in hypogonadal men—a clinical research center study. *J Clin Endocrinol Metab.* 1996a;81:3578–3583.

Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab.* 2000;85:2839–2853.