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Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men*

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ABSTRACT

Testosterone (T) therapy for hypogonadal men should correct the clinical abnormalities of T deficiency, including improvement of sexual function, increase in muscle mass and strength, and decrease in fat mass, with minimal adverse effects. We have shown that administration of a new transdermal T gel formulation to hypogonadal men provided dose proportional increases in serum T levels to the normal adult male range. We now report the effects of 180 days of treatment with this 1% T gel preparation (50 or 100 mg/day, contained in 5 or 10 g gel, respectively) compared to those of a permeation-enhanced T patch (5 mg/day) on defined efficacy parameters in 227 hypogonadal men. In the T gel groups, the T dose was adjusted up or down to 75 mg/day (contained in 7.5 g gel) on day 90 if serum T concentrations were below or above the normal male range. No dose adjustment was made with the T patch group. Sexual function and mood changes were monitored by questionnaire, body composition was determined by dual energy x-ray absorptiometry, and muscle strength was measured by the one repetitive maximum technique on bench and leg press exercises. Sexual function and mood improved maximally on day 30 of treatment, without differences across groups, and showed no further improvement with continuation of treatment. Mean muscle strength in the leg press exercise increased by 11 to 13 kg in all treatment groups by 90 days and did not improve further at 180 days of treatment. Moderate increases were also observed in arm/chest muscle strength. At 90 days of treatment, lean body mass increased more in the 100 mg/day T gel group (2.74 ± 0.28 kg; $P = 0.0002$) than in the 50 mg/day T gel (1.28 ± 0.32 kg) and T patch groups (1.20 ± 0.26 kg). Fat mass and percent fat were not significantly decreased in the T patch group, but showed decreases in the T gel groups (50 mg/day, −0.90 ± 0.32 kg; 100 mg/day, −1.05 ± 0.22 kg). The increase in lean mass and the decrease in fat mass were correlated with the changes in average serum T levels attained after transdermal T replacement. These beneficial effects of T replacement were accompanied by the anticipated increases in hematocrit and hemoglobin but without significant changes in the lipid profile. The increase in mean serum prostate-specific antigen levels (within the normal range) was correlated with serum levels of T. The greatest increases were noted in the 100 mg/day T gel group. Skin irritation was reported in 5.5% of subjects treated with T gel and in 66% of subjects in the permeation-enhanced T patch group.

We conclude that T gel replacement improved sexual function and mood, increased lean mass and muscle strength (principally in the legs), and decreased fat mass in hypogonadal men with less skin irritation and discontinuation compared with the recommended dose of the permeation-enhanced T patch. (*J Clin Endocrinol Metab* **85:** 2839–2853, 2000)

ANDROGEN REPLACEMENT therapy in hypogonadal men improves sexual function, decreases body fat, and increases lean muscle mass and function and bone mass (1–3). These beneficial effects of testosterone (T) replacement therapy are accompanied by slight lowering of high density lipoprotein (HDL) cholesterol levels, increase in hematocrit (Hct)/hemoglobin (Hgb), and increase in the size of the prostate gland to within the normal adult male range (2, 3). Recent developments in the delivery of adequate amounts of T to mimic the daily production rate use the skin as the route of administration. The transdermal T patches, including the scrotal patch (Testoderm), the nonscrotal permeation-enhanced patch with an alcohol-based reservoir (Andro-

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derm), and the nonscrotal patch without a reservoir (Testoderm TTS), deliver 5–6 mg/day T to the body and provide a relative steady state level of T at the low to midnormal range (4–13). Higher serum T levels can be achieved by using more than one transdermal patch. Long term use of these patches (3–10 yr) has been shown to be effective in maintaining sexual function and bone and muscle mass in young as well as elderly hypogonadal men (14–18). Nonetheless, one of the permeation-enhanced T patches is associated with skin irritation in about a third of the subjects and has a 10–15% discontinuation rate despite the use of local preapplication of corticosteroid cream (19–21). The scrotal patch requires a large surface of scrotal skin and clipping or shaving of the hair. The nonscrotal body patches do not adhere optimally in some patients.

We have reported that T when applied as a gel over a larger area of skin in an open system rarely produces problems of skin irritation (22). We have also shown that this new T gel (AndroGel) formulation can efficiently and rapidly increase serum T levels into the normal range in hypogonadal men.[1] About 9–14% of T applied to the skin as the gel is bioavailable. Pharmacokinetic analyses of T gel *vs.* T patch showed that the average serum T levels over the 180-day treatment period were highest in the 100 mg/day T gel group, and these levels were 1.4- and 1.9-fold higher than those achieved by the 50 mg/day T gel and the T patch (Androderm) groups, respectively. The daily application of the gel resulted in steady state serum T pharmacokinetics with dose proportional increases in serum estradiol and suppression of LH and FSH levels. Serum 5α-dihydrotestosterone concentrations were elevated, but 5α-dihydrotestosterone to T ratios increased slightly after T gel application. Daily T gel application provided more flexibility in dosing, dose proportionality in T gel pharmacokinetics, and less discontinuation rate than the permeation-enhanced patch (22; see Footnote 1). We now report the efficacy and safety of 2 doses of T gel (AndroGel, 50 and 100 mg T/day, contained in 5 and 10 g gel, respectively) *vs.* T patch (Androderm, 2 patches delivering 5 mg T/day) in 227 hypogonadal men. We monitored the effect of T replacement on sexual function, mood changes, body composition, muscle strength, red cell indexes, lipid profile, prostate dysfunction indexes, skin problems, and other potential side-effects.

Subjects and Methods

Subjects

Hypogonadal men were recruited and studied in 16 centers in the United States. The patients were between 19–68 yr old and had single morning serum T levels at screening of 10.4 nmol/L (300 ng/dL) or less. Previously treated hypogonadal men were withdrawn from T ester injection for at least 6 weeks and from oral or transdermal androgens for 4 weeks before the screening visit. Aside from the hypogonadism, the subjects were in good health, as evidenced by medical history, physical examination, complete blood count, urinalysis, and serum biochemistry. If the subjects were taking lipid-lowering agents or tranquilizers, the doses were stabilized for at least 3 months before enrollment. The subjects had no history of chronic medical illness or alcohol or drug abuse. They had normal rectal examination, prostate-specific antigen (PSA) level of less than 4 ng/mL, and urine flow rate of 12 mL/s or greater before enrollment in the study. They were excluded if they had a generalized skin disease that might affect the T absorption or prior history of skin irritability with Androderm patch. Subjects weighing less than 80% or more than 140% of their ideal body weight were also excluded.

A total of 227 patients were enrolled; 73, 78, and 76 were randomized to receive 50 mg/day T gel (contained in 5 g gel), 100 mg/day T gel (contained in 10 g of gel), or the T patch, respectively. There were no significant group-associated differences in the patients' characteristics at baseline (age, height, weight, cause of hypogonadism, and previous T treatment). About 3.9–11.0% of the subjects were less than 35 yr of age, 23.3–36.8% were between 35–49 yr of age, 55.1–57.5% were between 50–64 yr of age, and 3.9–8.2% were 65 yr or over in the 3 initial treatment groups. About 35–45% of the patients had primary hypogonadism (Klinefelter's syndrome, anorchia, or testicular failure), and 15–25% had secondary hypogonadism (Kallman's syndrome, hypothalamic pituitary disease, or pituitary tumor). Hypogonadism in the remaining men was attributed to aging or normogonadotropic hypogonadism (symptoms of hypogonadism with low serum T but normal LH). Forty-one percent of the subjects had not received prior T replacement.

Study design

The study was a randomized, multicenter (16 centers), parallel study comparing 2 doses of T gel with a T patch. The study was double blind with respect to the T gel dose and open label for the T patch group. For the first 3 months of the study (days 1–90), the subjects were randomized to receive 50 mg/day T gel in 5 g gel, 100 mg/day T gel in 10 g gel, or 2 nonscrotal patches delivering 5 mg/day (T patch). In the following 3 months (days 91–180), the subjects were administered 1 of the following treatments: 50 mg/day T gel, 100 mg/day T gel, 5.0 mg/day T patch, or 75 mg/day T gel in 7.5 g gel. Patients who were applying T gel had a single, preapplication serum T measurement on day 60, and if the levels were within the normal range of 10.4–34.7 nmol/L (300–1000 ng/dL) they remained on their original dose. Patients with T levels less than 10.4 nmol/L and who were originally assigned to apply 50 mg/day T gel and those with T levels more than 34.7 nmol/L who had received 100 mg/day T gel were then reassigned to administer 75 mg/day T gel for days 91–180.

Subjects returned to the study center on days 0 (baseline), 30, 60, 90, 120, 150, and 180 for a clinical examination and skin irritation and adverse event assessments. Fasting blood samples were drawn on all days. Hematology and clinical biochemistry, including electrolytes, glucose, renal and liver function tests, and lipid profile, were performed at all clinic visits.

T gel and patch

Testosterone gel (AndroGel) was manufactured by Besins Iscovesco (Paris, France) and supplied by Unimed Pharmaceuticals, Inc. (Buffalo Grove, IL). The formulation is a hydroalcoholic gel containing 1% (10 mg/g) T. Approximately 250 g gel were packaged in multidose glass bottles that delivered 2.25 g of the gel for each actuation of the pump. Patients assigned to apply 50 mg/day T were given one bottle of T gel and one bottle of placebo gel (vehicle only); those assigned to receive 100 mg/day T gel were dispensed two bottles of the active T gel. On the morning of day 1 of the study, the patients were instructed to depress the pump of one of the bottles once. The gel was applied to the right upper arm/shoulder. Then, using the same bottle, a second dose of gel was delivered and applied to the left upper arm/shoulder. The second bottle was then used, with gel from the actuation of the pump applied to the right abdomen and the second actuation to the left abdomen. Thus, each patient randomized to T gel applied gel to four application sites each day. On the following day, the application sites were reversed. Alternate application sites continued throughout the study. After application of the gel to the skin, the gel dried within a few minutes. Patients washed their hands thoroughly with soap and water immediately after gel application. After 90 days, for the subjects titrated to the 75 mg/day dose of T gel, the patients were supplied with three bottles, one containing placebo and the other two containing T gel. The subjects were instructed to apply one actuation from the placebo bottle and three actuations from a T gel bottle to four different sites of the body as

[1] Swerdloff, R. S., C. Wang, G. Cunningham, A. Dobs, A. Iranmanesh, A. Matsumoto, P. Snyder, T. Weber, N. Berman, and T-gel Study Group, submitted for publication.

described above. The sites were rotated each day, using the same sequence as that described above.

Testosterone patches (Androderm) delivering 2.5 mg/day T were provided. The patients were instructed to apply two T patches to a clean dry area of skin on the back, abdomen, upper arms, or thighs once per day. Application sites were rotated with approximately a 7-day interval between applications to the same site. T gel or patches were applied at approximately 0800 h each morning for 180 days.

Methods

Body composition (total body mass, lean body mass, fat mass, and percent fat) was measured by dual energy x-ray absorptiometry with Hologic, Inc., 2000 or 4500A series on days 0, 90 and 180. These assessments were performed in 168 of 227 subjects because the Hologic, Inc., dual energy x-ray absorptiometry equipment was not available at 3 of the 16 study centers. All body composition measurements were centrally analyzed and processed by Hologic, Inc. (Waltham, MA). The data for bone mineral density and bone markers will be reported in a subsequent report.

Muscle strength was assessed on days 0, 90, and 180 with the one-repetitive maximum technique in bench press and seated leg press exercises. The one-repetitive maximum technique assesses the maximal force-generating capacity of the muscles used to perform the test. Muscle strength was assessed in 167 of the 227 patients. Four of the 16 centers did not participate in the muscle strength testing because of lack of the required equipment.

Sexual function and mood were assessed by questionnaires the patients answered daily for 7 consecutive days before clinic visits on day 0 and on days 30, 60, 90, 120, 150, and 180 days during gel and patch application. The subjects recorded whether they had sexual day dreams, anticipation of sex, flirting, sexual interaction (sexual motivation parameters) and orgasm, erection, masturbation, ejaculation, and intercourse (sexual performance parameters) on each of 7 days. The value was recorded as 0 (none) or 1 (any) for analyses, and the numbers of days the subjects noted a parameter were summed for the 7-day period. The average of the four sexual motivation parameters was taken as the sexual motivation score, and that of the five sexual performance parameters was used as the sexual performance mean score (0–7). The subjects also assessed their level of sexual desire, sexual enjoyment, and satisfaction of erection using a seven-point Likert-type scale (0–7), and assessed the percentage of full erection from 0–100%. The subjects rated their mood using a 0–7 score. The parameters assessed included positive mood responses (alert, friendly, full of energy, well/good feelings) and negative mood responses (angry, irritable, sad, tired, nervous). Weekly average scores were calculated. The details of this questionnaire were described previously (24–26).

Skin irritation assessment were measured at every clinic visit using the following scale: 0 = no erythema, 1 = minimal erythema, 2 = moderate erythema with sharply defined borders, 3 = intense erythema with or without edema, and 4 = intense erythema with edema and blistering/erosion. When subjects developed skin irritation, pretreatment with corticosteroid cream was advised. The Prostate Symptom Score were assessed on days 0, 30, and 90 using the International Prostate Symptom Score (I-PSS) (27, 28). The maximum score for I-PSS is 35. Complete blood counts, serum clinical chemistry, and serum PSA levels were measured at each center's laboratory.

The study protocol was approved by the institutional review board of each study center. Written consent was obtained from each subject.

Statistical analyses

Descriptive statistics for each parameter were calculated. All data in the figures and tables show the treatment mean (±SEM) by day for each of the three groups of subjects based on the treatment pattern from days 0–90 (*left panels*) and for each of the five groups from days 91–180 (*right panels*). However, as the final treatment groups (five groups) for the subjects using T gel were no longer randomized, between-group comparisons were made only up to day 90 using the original treatment assignments, 50 or 100 mg T gel or T patch, as the independent groups. The primary model for analysis of the variables was a two-way ANOVA model, including all subjects as a group with one repeated measure effect (study day), one independent group effect (treatment), and their interaction. If none of the effects was statistically significant, then no further testing was performed. If the study day effect was significant, then it was tested using contrasts comparing the results at follow-up visits to baseline measurements. If the treatment effect was significant, then group means were compared using pairwise methods. If the interaction was significant, then both the more detailed evaluation of study day within treatment and treatment differences within study day was made. Changes in the sexual function variables were analyzed using equivalent repeated measures models for categorical variables. Analyses of change from days 0 to 180 within treatment groups were made within each of the five groups based on pattern using paired *t* tests or Wilcoxon's test. Comparisons resulting in a $P \leq 0.05$ were considered statistically significant. SAS version 6.12 (SAS Institute, Inc., Cary, NC) was used for all analyses.

Results

Subjects

Two hundred and twenty-seven subjects were initially randomized to 73 in the T gel 50 mg/day (in 5 g gel), 78 in the T gel 100 mg/day (in 10 g gel), and 76 in the T patch groups, respectively. At 90 days, dose adjustments were made in the T gel groups based on the preapplication serum T levels on day 60. Twenty subjects in the 50 mg/day T gel group had the T gel dose increased to 75 mg/day, and 20 in the T gel 100 mg/day group had the T gel dose reduced to 75 mg/day. There were 3 patients in the T patch group who were switched to 50 mg/day T gel because of patch intolerance, one 100 mg/day T gel subject was adjusted to receive 50 mg/day, and one 50 mg/day T gel subject had the dose adjusted to 25 mg/day. The number of subjects enrolled in days 91–180 of the study consisted of 51 continuing 50 mg/day T gel, 40 receiving 75 mg/day T gel, 52 receiving 100 mg/day T gel, and 52 continuing on the patch.

T patch compliance, assessed by counting returned patches, was 65% during days 1–90 and 74% during days 91–180 days. The T gel compliance rate, assessed by the weight of the T gel bottles, was over 93% and 96% for 50 and 100 mg T gel groups, respectively, during days 1–90 and remained at that level from days 91–180.

TABLE 1. Average serum T levels (during 24 h) after transdermal application of T gel or patch

	T patch	T gel (50 mg/day)		T gel (100 mg/day)	
Day 0	8.22 ± 0.55[a]	8.22 ± 0.53		8.60 ± 0.55	
Day 90	14.46 ± 0.68	19.17 ± 1.06		27.46 ± 1.12	
	T patch	T gel 50	T gel 50→75[b]	T gel 100→75[b]	T gel 100
Day 180	14.14 ± 0.88	19.24 ± 1.18	15.60 ± 3.68	25.79 ± 2.55	24.72 ± 1.05

[a] Mean ± SE.

[b] In subjects receiving T gel, if serum T on day 60 is higher or lower than the normal range, the dose is adjusted downward from 100 mg to 75 mg/day or upward from 50 to 75 mg/day on day 91, respectively.

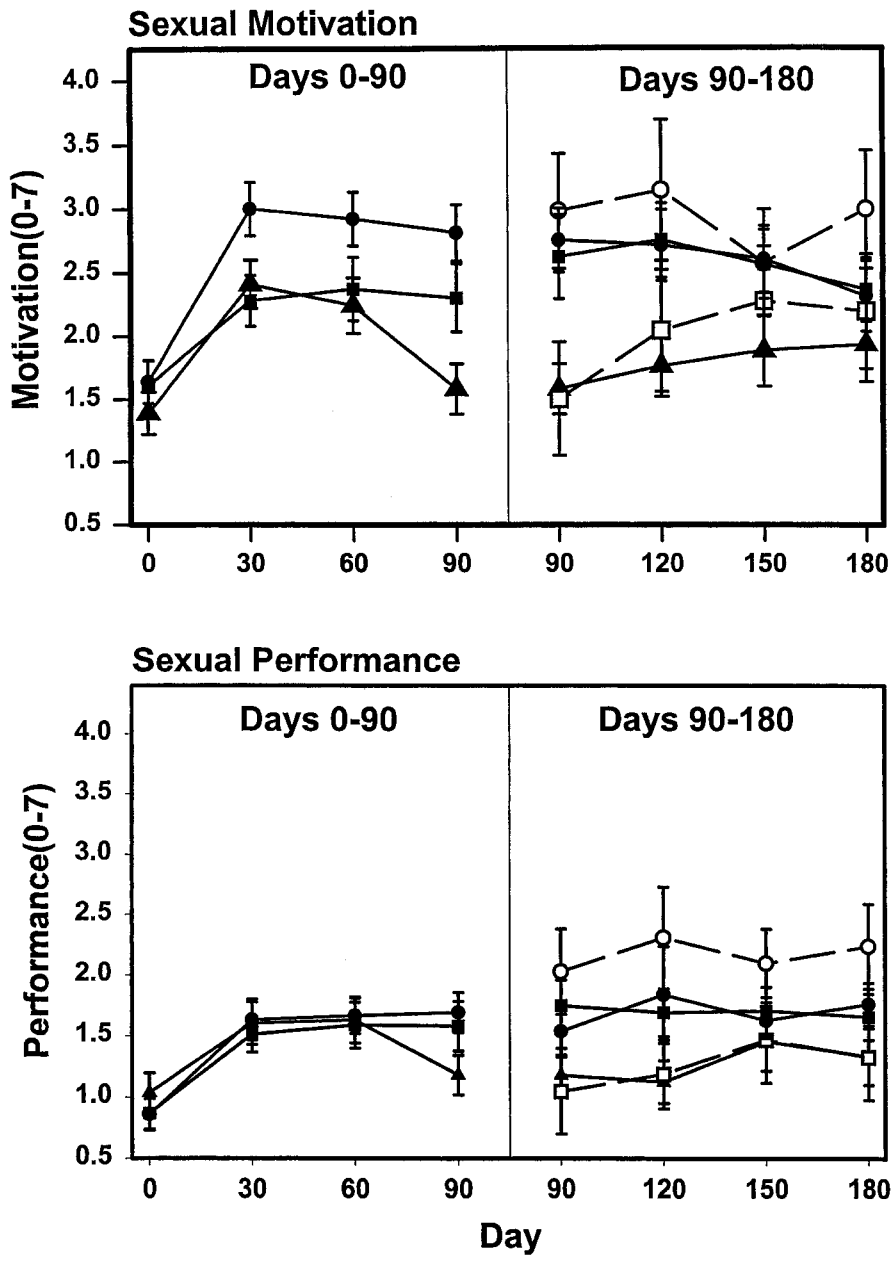

FIG. 1. Effects of transdermal T gel and T patch treatment on sexual motivation (*top*) and performance (*bottom*) summary scores in hypogonadal men. In this and subsequent figures, the *left panel* shows the subjects initially randomized to three treatment groups: T patch (▲), 50 mg/day T gel (■), and 100 mg/day T gel (●). Based on the serum T levels, the dose of T gel was adjusted up or down (from days 91–180) to 75 mg/day if the serum T level was below or above the adult male range, respectively. The *right panel* shows the subjects in the final five treatment groups (three original treatment groups plus the additional two groups of subjects whose T gel doses were adjusted): 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

Serum T concentrations

At the screening visit, mean serum T concentrations (single sample) were 5.9 ± 0.36, 4.1 ± 0.51, 7.7 ± 0.27, and 8.0 ± 0.51 nmol/L, respectively, in the subjects diagnosed with primary, secondary, normogonadotropic, and aging-related hypogonadism. At baseline (day 0) mean serum T concentrations (average values over 24 h) were 7.9 ± 0.52, 4.9 ± 0.55, 10.5 ± 0.43, and 10.7 ± 0.80 nmol/L in the subjects with primary, secondary, normogonadotropic, and aging-related hypogonadism. These differences in baseline serum T levels were observed in all three treatment groups. Although baseline serum T levels were different in the four hypogonadal subcategories, the responses of sexual function, muscle strength, and body composition to T treatment were independent of initial diagnostic classification. Average serum T concentrations over 24 h at baseline (day 0) and on days 90 and 180 after treatment are summarized in Table 1. These results have been previously reported as a detailed pharmacokinetic report (see Footnote 1). After transdermal application on day 90, the average serum T concentration in the 100 mg/day T gel group was 1.4-fold higher than that in the 50 mg/day T gel group and 1.9-fold higher than that in the T patch group. Dose adjustment from 50 to 75 mg/day did not increase the average serum T concentration, but decreasing the dose from 100 to 75 mg/day lowered the average serum T concentration (see Footnote 1).

Sexual function (Fig. 1)

At baseline, the sexual motivation and performance scores were similar across groups. After transdermal T treatment,

with all subjects as a group, sexual motivation showed significant improvement ($P = 0.0001$; Fig. 1, *top*). The change in the summary score from baseline, however, was not different among the three treatment groups. The mean improvement in sexual motivation was at a maximum by day 30. As a group, sexual desire (Fig. 2, *top*) increased after transdermal T treatment ($P = 0.0001$) without intergroup difference. Sexual enjoyment with a partner (Fig. 2, *bottom*) also increased as a group ($P = 0.007$). This increase was less in the T patch than in the T gel groups ($P = 0.0113$). Similarly, the sexual performance score improved significantly in all subjects as a group ($P = 0.0001$). The improvement in sexual performance from baseline values was not different between transdermal preparations. The maximum effects of T replacement on sexual performance were observed at the first assessment (day 30). As a group, the subjects' self-assessment of satisfaction of erection ($P = 0.0001$) and percentage of full erection ($P = 0.0001$) were also increased with T replacement without significant differences between groups (Fig. 3). T dose adjustment on day 90 did not alter the improvement in sexual function. Those adjusted to 75 mg/day T gel had responses very similar to those remaining on 50 or 100 mg/day T gel.

Mood

The positive and negative mood summary responses to T replacement therapy are shown in Fig. 4. All three treatment groups had similar scores at baseline, and all subjects as a group showed improvement in positive mood ($P = 0.0001$; Fig. 4, *top*). Similarly, the negative mood summary scores

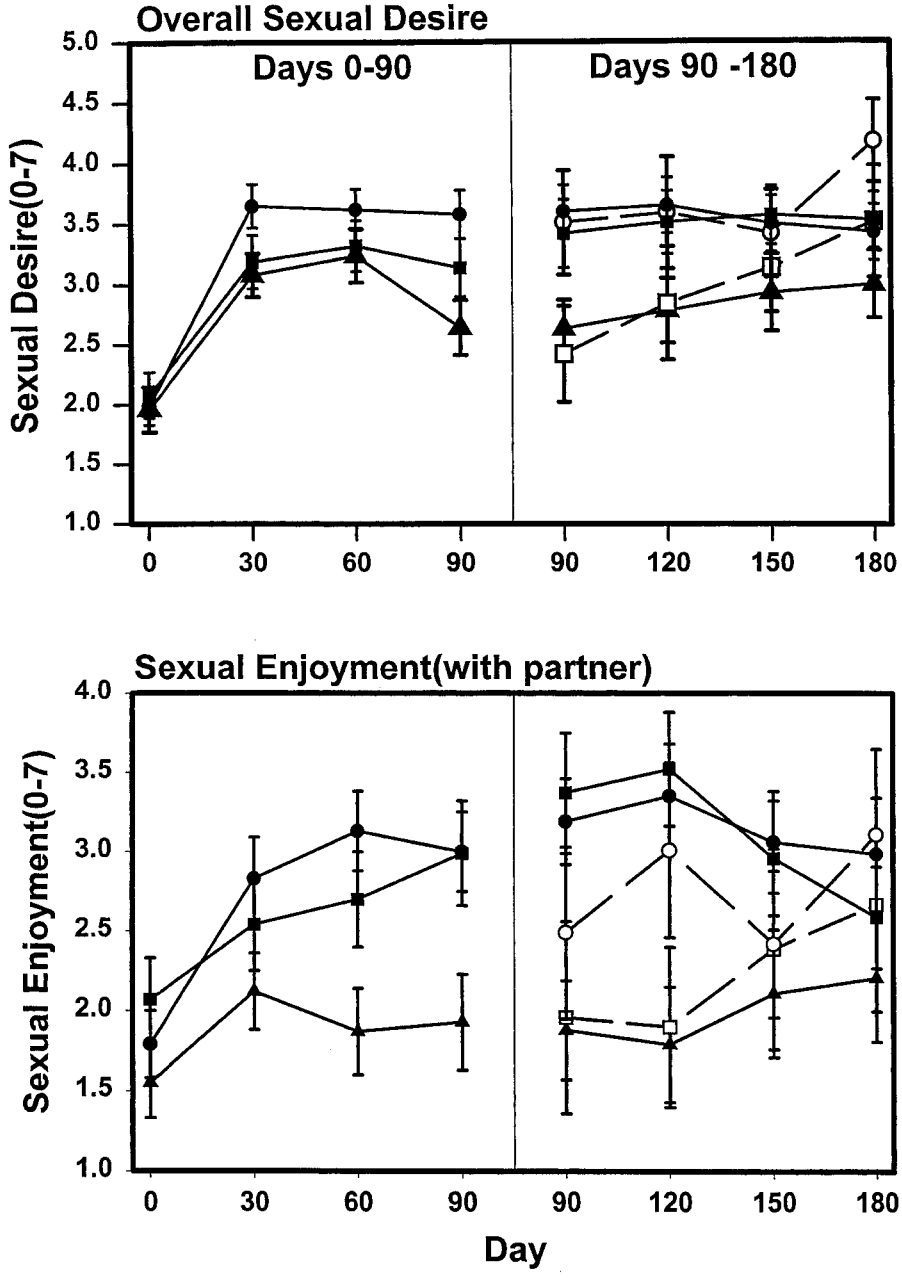

FIG. 2. Effect of transdermal T gel/patch on sexual desire (*top*) and sexual enjoyment with partner (*bottom*) in hypogonadal men. Days 0–90: T patch (▲), 50 mg/day T gel (■), and 100 mg/day T gel (●); days 90–180: 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

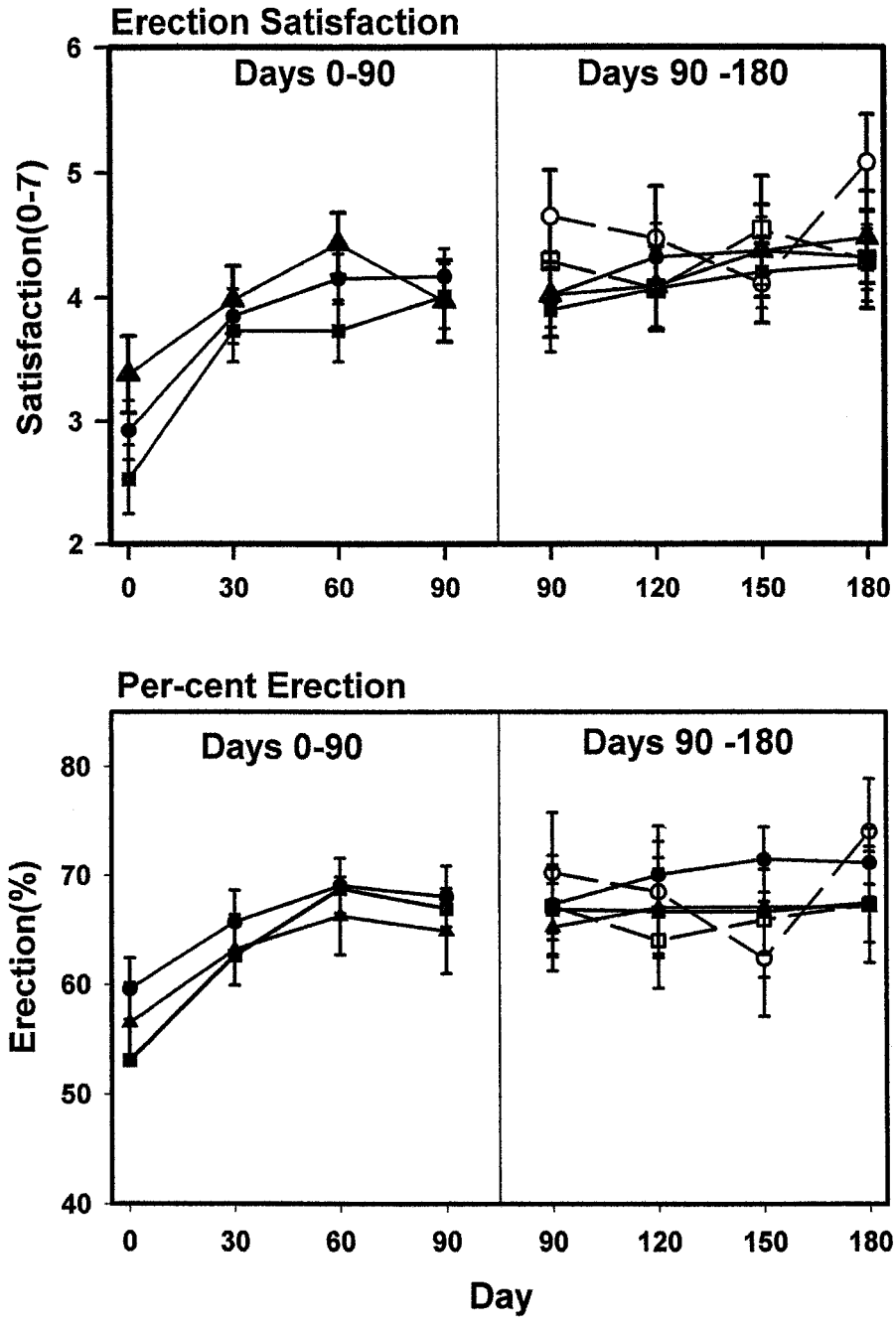

FIG. 3. Effect of transdermal T gel/patch treatment on erectile function assessed by questionnaire (*top*, satisfaction with erection; *bottom*, percentage of full erection). Days 0–90: T patch (▲), 50 mg/day T gel (■), and 100 mg/day T gel (●); days 90–180: 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

were similar in the three groups at baseline, and as a group the responses to transdermal T applications showed significant decreases ($P = 0.0001$) without showing between-group differences (Fig. 4, *bottom*).

Muscle strength

The responses of muscle strength testing by the arm/chest and leg press tests are shown in Fig. 5. There were no statistically significant differences in arm/chest or leg muscle strength among the three groups at baseline. In all treatment groups, the same proportion of subjects less than 45, between 45–65, and over 65 yr of age completed the muscle strength tests on days 0, 90, and 180. The increase in muscle mass was not affected by the cause of hypogonadism. In general, muscle strength improved in both arms and legs in all three treatment groups without intergroup differences on days 90 and 180. The muscle strength in the leg press exercises on day 90 increased by 11.6 ± 2.5 kg ($P = 0.0001$), 13.7 ± 3.4 kg ($P = 0.0003$), and 12.7 ± 2.7 kg ($P = 0.0001$) in the T patch, 50 mg T gel, and 100 mg T gel groups, respectively (Fig. 5, *top*). The muscle strength in the arm/chest muscles significantly increased to a much smaller extent than the legs in the T gel groups [T patch, 1.5 ± 0.8 kg ($P = 0.08$); 50 mg/day T gel, 2.6 ± 0.7 kg ($P = 0.0009$); 100 mg/day T gel, 2.9 ± 0.8 kg ($P =$

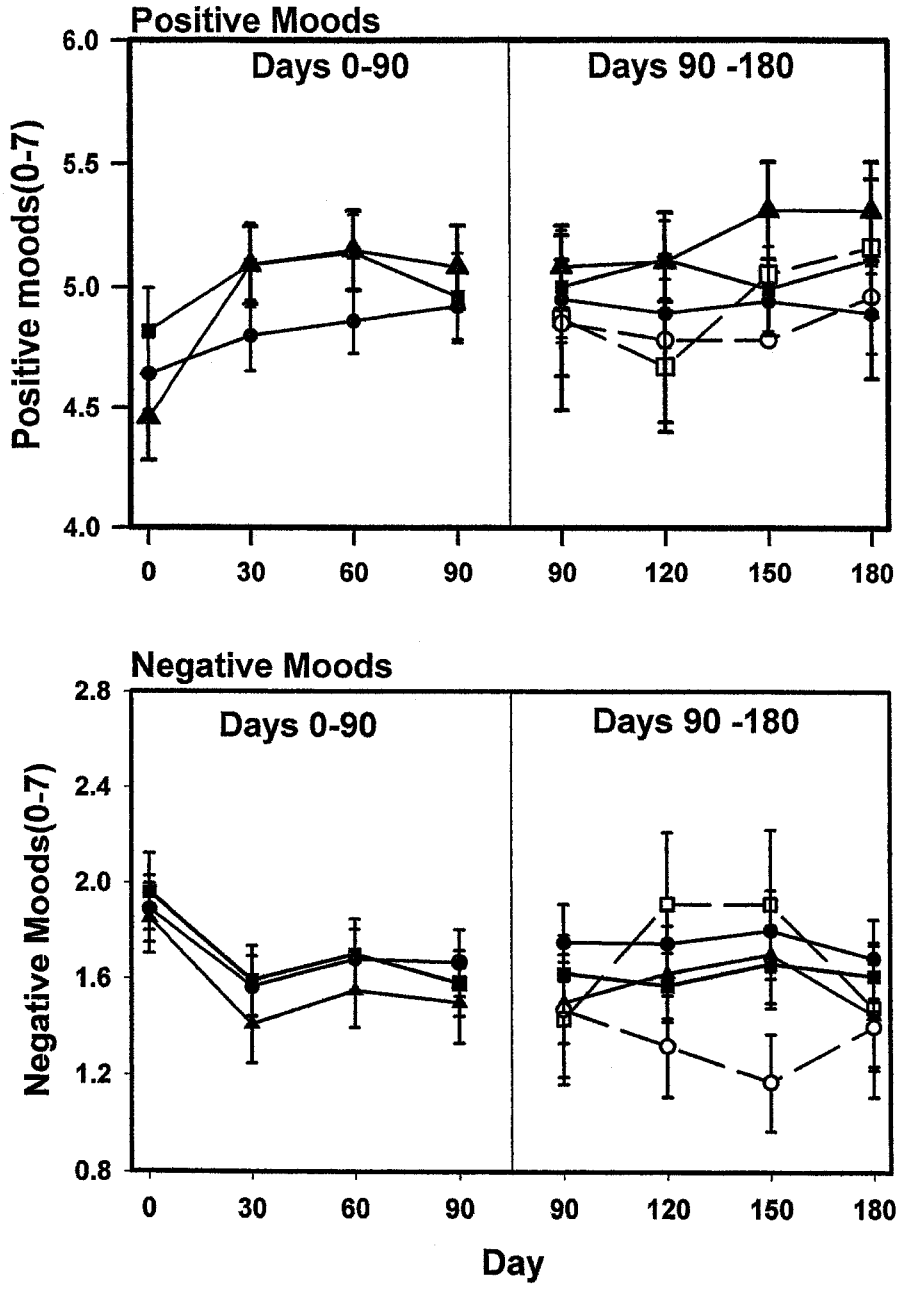

FIG. 4. Effect of transdermal T gel/patch treatment on positive (*top*) and negative (*bottom*) mood summary scores. Days 0–90: T patch (▲), 50 mg/day T gel (■), and 100 mg/day T gel(●); days 90–180: 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

0.0004); Fig. 5, *bottom*]. Adjustment of the dose on day 90 did not significantly affect the muscle strength responses to transdermal T preparations.

Body composition

At baseline, there were no significant differences in total body mass, lean mass, percent fat, and fat mass in the three treatment groups. On day 90, as a group the overall increase in total mass was significant ($P = 0.04$). The increase in total mass was higher in the 100 mg/day T gel group (1.69 ± 0.29 kg) and T patch group (1.22 ± 0.32 kg) than in the 50 mg/day T gel group (0.39 ± 0.32 kg; $P = 0.01$). The increase in total mass was not significantly different from day 0 in the 50 mg T gel group. On day 180, these small increases were maintained in all treatment groups (50, 75, and 100 mg/day T gel and T patch; Fig. 6, *top left*). The increase in body mass was mainly due to the increases in lean body mass. After 90 days of T replacement, the increase in lean body mass was significantly higher in the 100 mg/day T gel group (2.74 ± 0.28 kg; $P = 0.0002$) than in the 50 mg/day T gel (1.28 ± 0.32 kg) and T patch (1.20 ± 0.26 kg) groups. On day 180 the increases in lean body mass were further enhanced or maintained in all T gel-treated groups (50 mg/day T gel, 1.59 ± 0.39 kg; 50 to 75 mg/day T gel, 2.75 ± 0.97 kg; 100 to 75 mg/day T gel, 3.33 ± 0.43 kg; and 100 mg/day T gel, 3.03 ± 0.35, respectively) as well as in the T patch group (0.99 ± 0.38 kg; Fig. 6, *top right*).

The percent body fat and the fat mass decreased in all transdermal T gel treatment groups. At 90 days of treatment,

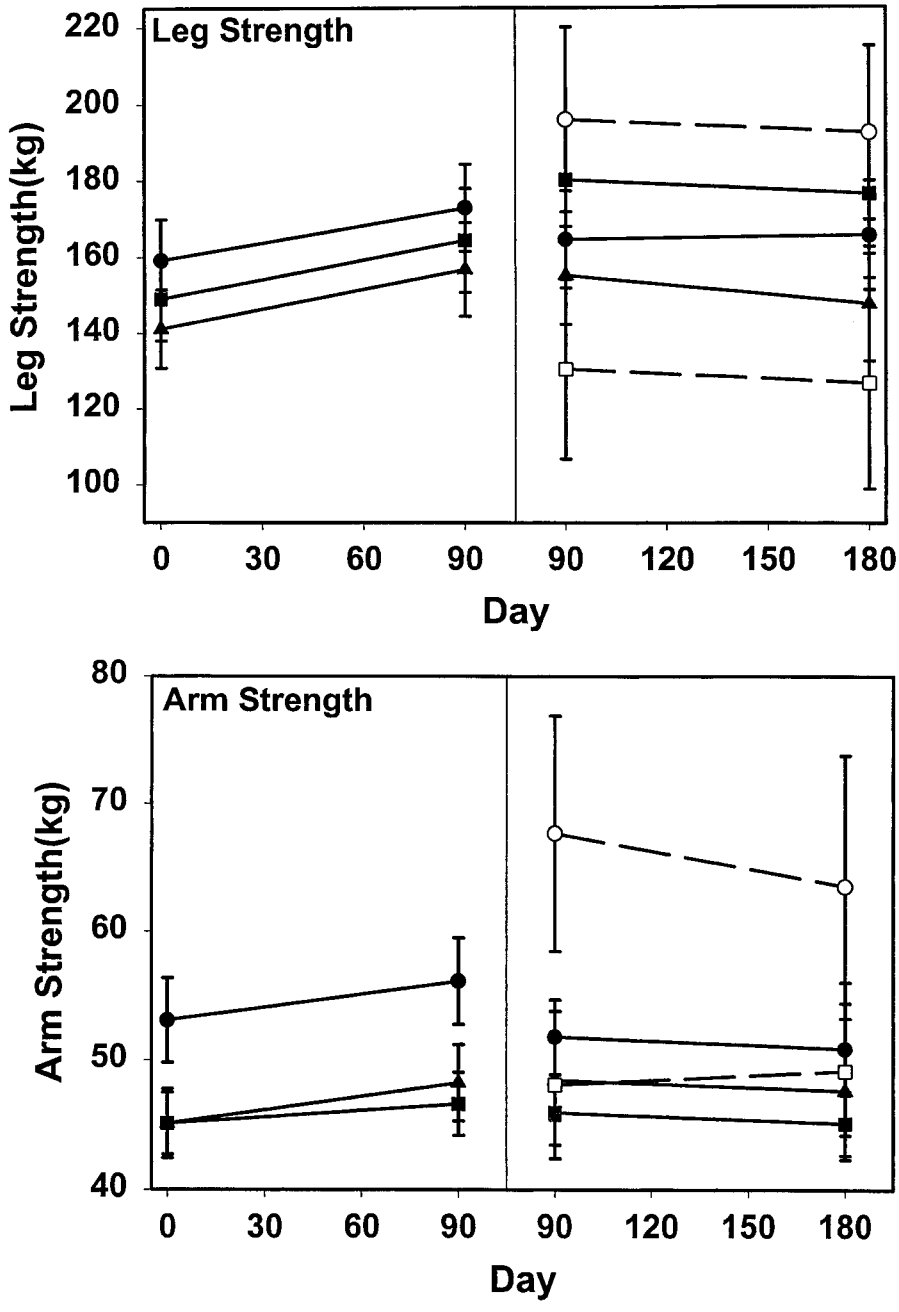

FIG. 5. Effect of transdermal T gel/patch treatment on leg (*top*) and arm (*bottom*) strength. The original treatment groups are on the *left*, and the final treatment groups are on the *right*. Days 0–90: T patch (▲), 50 mg/day T gel (■), and 100 mg/day T gel (●); days 90–180: 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

total fat mass was significantly reduced by −0.90 ± 0.32 kg ($P = 0.0065$) and −1.05 ± 0.22 kg ($P = 0.0001$) in the 50 and 100 mg/day T gel groups, respectively, but was not changed in the T patch group (0.01 ± 0.2 kg). At 180 days, the decrease in total fat mass was sustained in the 50 and 75 mg/day T gel groups. In the 100 mg/day T gel group, fat mass decreased further on day 180 compared with that on day 90 ($P = 0.0008$; Fig. 6, *bottom left*). Correspondingly, on day 90, the percent body fat was decreased significantly by −1.0 ± 0.3 and −1.8 ± 0.2 in the 50 and 100 mg/day T gel groups, respectively ($P = 0.0018$ and $P = 0.0001$), but not in the T patch group (−0.4 ± 0.2). At 180 days the decrease in percent fat remained significantly lower in all T gel groups, but was not significantly reduced in the T patch group (Fig. 6, *bottom right*).

Before treatment (on day 0), the total fat mass ($r = -0.21$; $P = 0.0038$) and percent body fat ($r = -0.26$; $P = 0.0002$) were negatively correlated with baseline serum T levels. At the end of 180 days of T replacement, the increase in lean body mass was positively correlated with the increase in serum T levels on day 180 from baseline 0 ($r = 0.25$; $P = 0.0027$). In contrast, decreases in total fat mass ($r = -0.18$; $P = 0.03$) and percent fat ($r = -0.25$; $P = 0.0035$) were correlated with the increase in the average serum T levels on day 180 from baseline. The cause of the hypogonadism did not affect the change in body composition.

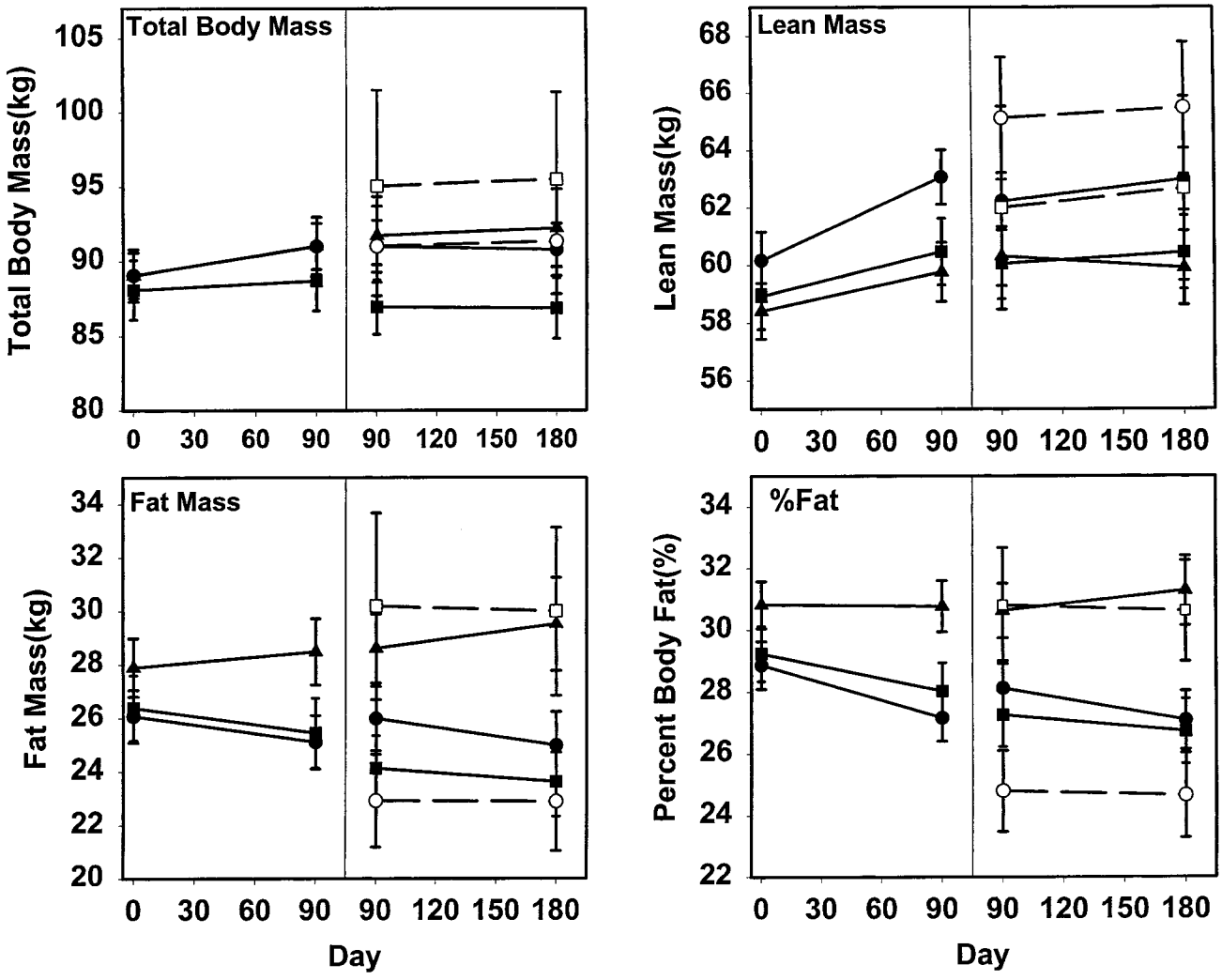

FIG. 6. Effect of transdermal T gel/patch treatment on total body mass, lean mass, fat mass, and percent fat after treatment with T gel or patch for 180 days. The original treatment groups are in the *left panels* of each graph (days 0–90), and the final treatment groups are in the *right panels* of each graph (days 91–180). Days 0–90: T patch (▲), 50 mg/day T gel (■), and 100 mg/day T gel (●); days 90–180: 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

Hgb and Hct

At baseline, there were no differences in the Hgb or Hct levels among the three groups (Fig. 7). As a group, both Hgb and Hct increased ($P = 0.0001$) with statistically significance across treatment groups ($P = 0.0001$). On day 90 the mean increase in Hgb and Hct was very small in the T patch (Hgb, 0.43 ± 0.11 g/dL; Hct, 1.35 ± 0.40%) and the 50 mg/day T gel (Hgb, 0.46 ± 0.12 g/dL; Hct, 1.38 ± 0.40%) groups. In the 100 mg/day T gel group, both Hct and Hgb increased significantly on day 90 (mean increase in Hgb, 1.09 ± 0.12 g/dL; in Hct, 3.54 ± 0.39%) and remained increased on day 180 (mean increase in Hgb, 1.27 ± 0.15 g/dL; in Hct, 4.14 ± 0.44%). Decreasing the dose of T gel from 100 to 75 mg/day did not significantly change this increase (Fig. 7, *top* and *bottom*).

The percentage of subjects who had normal Hct at baseline which rose to above the normal range (of each center's laboratory) on day 180 were dependent on the dose and type of T replacement, with 2.8%, 11.3%, and 17.9% for T patch, 50 mg/day T gel, and 100 mg/day T gel, respectively. The percentages of subjects who initially had low Hct that rose to normal with T treatment were 8.5%, 7.5%, and 14.3%, respectively, for the T patch, 50 mg/day T gel, and 100 mg/day T gel groups, respectively. Approximately 70–80% of the subjects had red cell parameters that remained in the normal range during T replacement. There were no significant changes in white cell or platelet counts.

Lipid profile and blood chemistry

The serum total, HDL, and low density lipoprotein (LDL) cholesterol levels at baseline were not significantly different in all treatment groups. With transdermal T replacement, there were no overall treatment effects or intergroup differences in serum concentrations of total, HDL, and LDL cholesterol (Fig. 8) or triglycerides (data not shown). There was a significant change in serum total cholesterol concentrations as a group with time ($P = 0.0001$); the concentrations on days 30, 90, and 180 were significantly lower than that on day 0.

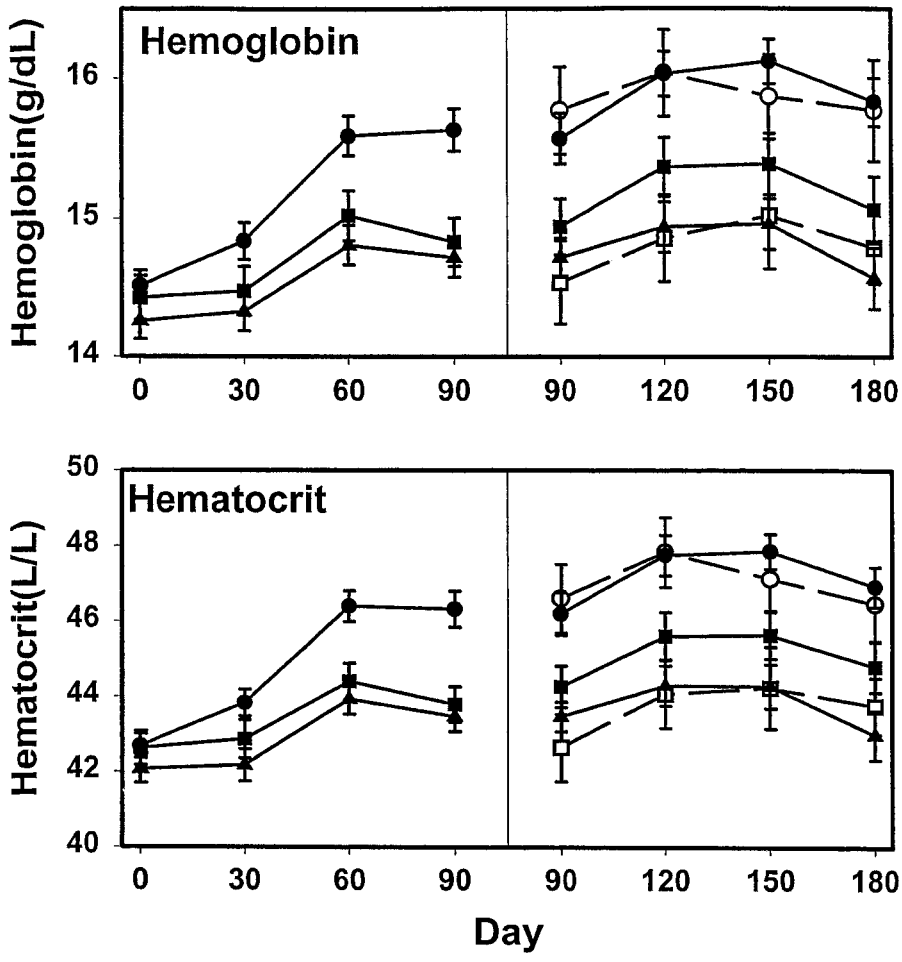

FIG. 7. Effect of transdermal T gel/patch treatment on Hgb (*top*) and Hct (*bottom*). Days 0–90: T patch (▲), 50 mg/day T gel (■), and 100 mg/day T gel (●); days 90–180: 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

Approximately 70–95% of the subjects had no significant change in their serum lipid profile during T replacement therapy. Total cholesterol levels that were initially high were lowered into the normal range (of each center's laboratory) on day 180 in 17.2%, 20.4%, and 12.2% of subjects using T patch, 50 mg/day T gel, and 100 mg/day T gel, respectively. Serum HDL cholesterol levels (initially normal) were reduced to below the normal range (of each center's laboratory) in 9.8%, 4.0%, 9.1%, and 12.5% of subjects on day 180 in the T patch and 50, 75, and 100 mg/day T gel groups, respectively. There were no clinically significant changes in renal or liver function tests in any treatment group.

Prostate dysfunction markers

The number of subjects who had urogenital adverse events that the investigators reported to be possibly or probably drug related included none in the T patch group, 7 (9.6%) in the 50 mg/day T gel group, and 4 (5.1%) in the 100 mg/day T gel group. These adverse events included enlarged prostate on digital rectal examination or elevated serum PSA in 8 subjects, penile/testis pain/sensitivity in 2, and varicocele in another. At baseline 9 of 76 subjects in the T patch group, 13 of 73 in the 50 mg T gel group, and 12 of 78 in the 100 mg T gel group had enlarged prostates on digital rectal examination. Of these 4, 8, and 9 subjects had prior testosterone injection (200 mg every 2–3 weeks) for a mean duration of 4.1, 3.2, and 2.7 yr in the T patch, 50 mg T gel, and 100 mg T gel groups, respectively. Mean serum PSA levels were similar in treatment groups at baseline and increased significantly in the 100 mg/day T gel (day 0, 0.89 ± 0.08 ng/mL; day 90, 1.19 ± 0.12 ng/mL; $P = 0.008$) and 50 mg/day T gel (day 0, 0.88 ± 0.08; day 90, 1.05 ± 0.14 ng/mL; $P = 0.05$) groups, respectively, without significant change in the T patch group (day 0, 0.89 ± 0.10; day 90, 0.88 ± 0.09 ng/mL) on day 90. The increases in serum PSA remained the same in the T gel groups at the end of treatment (50 mg/day, 1.06 ± 0.1; 100 mg/day, 1.19 ± 0.13 ng/mL). Serum PSA levels were positively correlated with serum T levels before treatment ($r = 0.29$; $P = 0.0001$) and 90 days ($r = 0.18$; $P = 0.023$) and 180 days ($r = 0.17$; $P = 0.034$) after transdermal T replacement.

Serum PSA levels were elevated to above the normal range in 0, 1, and 4 subjects in the T patch, 50 mg/day T gel, and 100 mg/day T gel groups, respectively (Table 2). One patient (no. 14–05) in the 100 mg T gel group had elevated PSA (5.3 ng/dL on day 150) and dropped out of the study. Ultrasound failed to detect a lesion, and sextant biopsy was negative for prostate cancer. Four patients (no. 11–02, 9–19, 3–07, and 4–17) had enlarged prostates on digital rectal examination, presumably due to benign prostate hyperplasia (PSA, 4.2, 6.0, 4.6, and 4.7 ng/mL). All four subjects (no. 11–02, 9–19, 3–07,

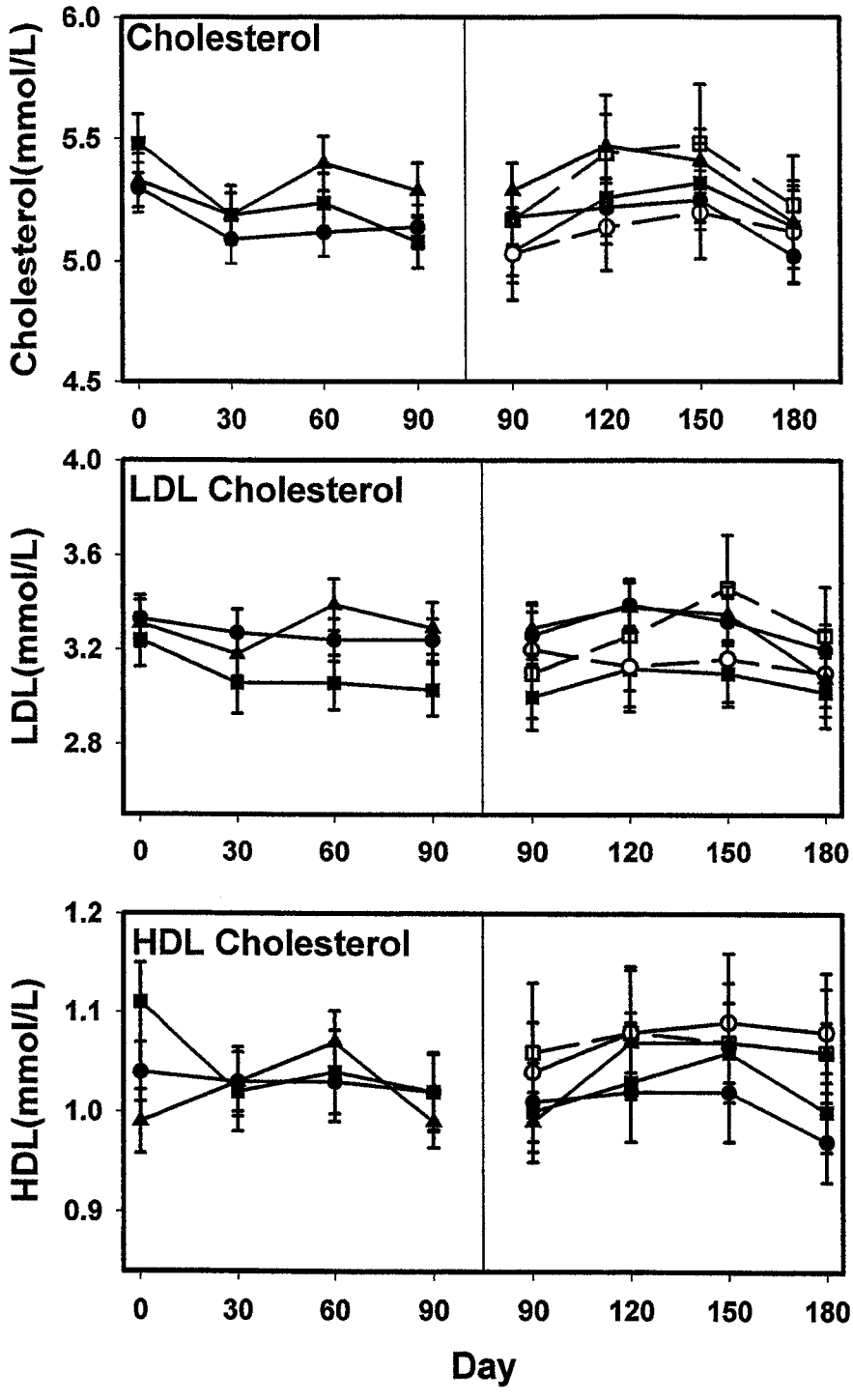

FIG. 8. Effect of transdermal T gel/patch treatment on serum total (*top*), LDL (*middle*), and HDL cholesterol (*bottom*) . Days 0–90: T patch (▲), 50 mg/day (■), and 100 mg/day T gel (●); days 90–180: 50 to 75 mg/day T gel (□) and 100 to 75 mg/day T gel (○).

and 4–17) were enrolled in an open label T gel extension study (total treatment duration, 24 months). Subjects 3–07 and 11–02 had persistent elevated PSA and were discontinued from the study at 6 and 12 months into the extension study, respectively. Subject 9–19 had a PSA level of 6.0 ng/dL on day 180, and he was without symptoms. This subject was referred to a urologist and discontinued 1 month after enrollment in the extension study. One month later his PSA level was 2.7 ng/mL. Subject 4–17 had a serum PSA level of 6.2 at 6 months into the extension study. T gel was discontinued, and prostate biopsy showed prostate cancer. These data suggested that elevated PSA to above the normal range and prostate-related adverse events occurred more frequently in the 100 mg/day T gel group than in the 50 mg/day T gel and T patch groups.

The mean I-PSS in the 3 groups was between 4.8–6.2 (maximum score, 35) throughout the treatment period, without significant changes or differences across the treatment

TABLE 2. Description of subjects whose serum PSA level rose to above the normal range during transdermal T therapy

Subject no.	Age (yr)	Treatment	Serum PSA levels (ng/mL)			Comments
			Day 0	Day 90	Day 180	
11–02	65	T gel (50 mg/day)	2.6	4.2	4.2	Enlarged prostate at baseline. Urine flow, 11.5 and 13.6 mL/s on days 90 and 180, respectively. No symptoms. Subject entered extension study.[a] Serum PSA was 5.2 ng/mL at 12 months and 5.8 ng/mL at 18 months (extension study). Patient was withdrawn from study and referred to urologist.
9–19	55	T gel (100 to 75 mg/day)	2.5	2.2	6.0	Prostate enlarged at baseline. Urine flow, >15 mL/s on days 90 and 180. No symptoms. Subject stopped T gel application 1 month after entering extension. Referred to urologist. PSA 1 month later was 2.7 ng/mL.
3–07	64	T gel (100 mg/day)	3.6	3.6	4.6	Prostate large at baseline. Urine flow, >15 mL/s on days 90 and 180. No symptoms. Patient entered extension study. Serum PSA was 5.7 ng/mL at 12 months (extension study). Patient discontinued from study because of elevated PSA.
4–17	62	T gel (100 mg/day)	3.2	4.0	4.7	Prostate large at baseline. Urine flow, 10.5 mL/on day 180. No symptoms. Patient entered extension study. PSA was 6.2 at 12 months (extension study). Subject was discontinued from study because of elevated PSA and referred for biopsy. Biopsy was positive for carcinoma of prostate.
14–05	53	T gel (100 mg/day)	0.7	4.3/3.5	5.3 (day 150)	Patient discontinued from study on day 150 because of rising PSA. Prostate ultrasound followed by biopsy showed no prostate cancer.

[a] Extension study referred to an on ongoing open label 24-month extension study for patients who were in this study.

groups for any individual symptom or total score. The I-PSS was above 15 in only 2 (2.7%) subjects. Both subjects were in the 50 mg/day group and had enlarged prostates on examination before treatment. Their maximum urine flow rate decreased to 9 and 8 mL/s, respectively, on day 30, but returned to 17/12.3 and 24/15.3 mL/s on days 90/180, respectively. The mean maximum urine flow rate was not significantly changed with T treatment. There were 6 (7.9%), 10 (13.7%), and 3 (3.8%) patients in the T patch, 50 mg/day T gel, and 100 mg/day T gel groups whose urine flow rate decreased transiently to less than 10 mL/s during T replacement. Urinary obstruction did not occur in any of the subjects. In the majority of these patients with low urine flow rate (14 of 19), the subjects had preexisting enlarged prostate on examination, diabetes mellitus, impotence, or penile prosthesis.

Skin irritations

Minimal skin irritation (erythema) at the application site was noted in three patients (5.7%) in the 50 mg/day T gel group and another 3 (5.3%) in the 100 mg/day T gel group. Skin irritation varying in intensity from minimal to severe (mild erythema to intense erythema with blisters) occurred in 65.8% of patients in the T gel group. Patients were not advised to use pretreatment with corticosteroid cream until skin irritation developed. Because of the skin irritation with the T patch, 16 subjects discontinued the study; 14 of these had moderate to severe skin reactions at the medication site(s).

Other adverse effects

Adverse events (other than prostate or skin problems described above) that were ascribed to be possibly or probably related to T replacement and led to discontinuation from the study included one subject in the 50 mg/day T gel group who had severe depression and was discontinued from the T gel treatment. This patient had prior episodes of depression that he failed to disclose at entry to the study. Another subject discontinued 100 mg/T gel treatment because of complaints of memory loss and sadness. Another patient using 100 mg/day T gel had high blood pressure and was discontinued from the study. One patient was discontinued from T patch because of Hct and Hgb rising progressively to 57.4% and 18.4 mg/dL on day 150 of treatment.

Gynecomastia was reported to occur in one patient receiving 50 mg/day T gel, three receiving 100 mg/day T gel, and none in the T patch group. Two of the patients had preexisting gynecomastia, and one of them underwent a cosmetic mastectomy 2 months after the start of T gel. After surgery, his gynecomastia was not increased with T gel treatment. The other patients had mild gynecomastia requiring no treatment.

The other adverse events considered by the investigators

to be possibly related to the T application were uncommon, usually occurring in less than 2% of subjects, and included transient abnormal laboratory tests (liver enzymes and electrolytes), headache, asthma, hypertension, dizziness, anxiety, and nervousness.

Discussion

We have shown in this study that T applied transdermally as a hydroalcoholic gel at 50, 75, and 100 mg/day (contained in 5, 7.,5 and 10 g gel, respectively) was effective in improving sexual function, mood, and muscle strength; increasing lean body mass; and decreasing body fat. These beneficial effects were associated with dose-related increases in Hct and Hgb. Serum PSA rose with treatment; but stabilized with continued administration. The increase in serum PSA was not associated with an increase in prostate symptom score or a decrease in urine flow rate. Serum HDL and LDL cholesterol levels were not changed with transdermal T application. In contrast to the permeation-enhanced T patch, which caused significant skin irritation in about a third of the patients and discontinuation in a fifth, the T gel preparation caused minimal skin erythema in only 6 of 151 subjects.

Sexual function, including sexual desire and motivation and sexual performance, increased in all treatment groups at 30 days after initiation of transdermal T and was maintained with continued replacement. These data are similar to those previously reported with T enanthate injections, sublingual/buccal T administration, transdermal patches, and T implants (13, 14, 24, 29–36). The improvement in sexual function was not related to the dose or the delivery method of T, nor was the improvement related to the serum T levels achieved by the various T preparations. The data suggest that once a threshold (serum T level probably at the low normal range) is achieved, normalization of sexual function occurs. Increasing serum T levels higher to the upper normal range does not further improve sexual motivation or performance.

In parallel with changes in sexual motivation and performance, administration of transdermal T, either patch or gel, improved mood. Positive mood parameters, such as sense of well-being and energy level, improved, and negative mood parameters, such as sadness and irritability, decreased. The improvement in mood was observed on day 30 and was maintained with continued treatment. Similar to our previous report and those of others, the improvement in mood parameters was not dependent on the magnitude of increase in the serum T levels (29, 36). Once the serum T increased into the low normal range, maximal improvement in mood parameters occurred. Thus, the responsiveness in sexual function and mood in hypogonadal men in response to T therapy appeared to be dependent on reaching a threshold of serum T at the low normal range. As this study was not designed as a placebo-controlled trial, the possibility of a placebo effect on sexual function and mood had not been excluded. Previously reported and unpublished data from our laboratory showed that sexual function and mood were not significantly changed when hypogonadal or normal men were administered placebo (37).

In this study muscle strength was measured by a one-repetitive maximum technique using chest and leg press exercises. The subjects did not participate in any exercise training. The results showed an improvement in muscle strength at 90 and 180 days, more in the legs than the arms, which was not different across treatment groups or on the different days of assessment. There were large variations between subjects and groups, and the possibility of a training effect could not be excluded. Our findings were similar to those reported previously with injectable T, transdermal patch, and sublingual T preparations in young hypogonadal men (25, 38–40). Improvement in grip strength as well as hamstring and quadriceps work was also reported in elderly men with low serum T levels administered T enanthate injections (41–44). In another report in which muscle strength was assessed by dynamometer, no change in the strength of knee extension or flexing occurred when transdermal T patches were administered for 36 months in elderly men (17). The increase in muscle strength after androgen replacement may be related to increased fractional muscle protein synthesis (37, 44). Available data, including those from this study, do not clearly support a dose-related response in muscle strength. However, different studies employed different methods of assessment, and the elderly might respond differently than young hypogonadal men (40).

In contrast, the increase in lean body mass and the decrease in fat mass associated with T replacement therapy showed significant correlations with the serum T level attained by the T patch and the different doses of T gel. T gel administered at 100 mg/day increased lean mass more than the T patch and 50 mg/day T gel. The changes in body composition were not affected by the initial diagnosis. The changes were apparent on day 90 after treatment and were maintained or enhanced on day 180. These changes were not due to fluid retention observed after T replacement, because accumulation of water occurs early within the first few weeks. Lean mass was not measured until 3 months and was sustained for 6 months. Changes in body composition were significant even though the subjects were withdrawn from prior T therapy for only 6 weeks. The increase in lean mass after T replacement was very similar to those previously reported in young and elderly hypogonadal men (17, 24, 38–43, 45). The decreases in fat mass and percent body fat were also related to the serum T level achieved and were different across the treatment groups. The T patch group did not show a decrease in percent body fat or fat mass after 180 days of treatment, which may be related to the lower mean serum T levels achieved. Treatment with T gel (50–100 mg/day) for 90 days reduced percent body fat and fat mass. This decrease was maintained in the 50 and 75 mg/day groups at 180 days, but was further lowered with continued treatment with the higher dose of the T gel (100 mg/day). In the prior studies of hypogonadal men, T replacement resulted in a decrease in fat mass in some studies using injectable or transdermal T (39, 45), but not in others administering injectable or sublingual T (25, 38). The differences in the results could be due to the less sensitive methodologies used in assessment of fat mass or to the lower average serum levels of T achieved by the sublingual preparation.

Monitoring of safety parameters showed an increase in Hct and Hgb levels in all treatment groups. The mean increases in Hct and Hgb levels were minimal with the T patch

and 50 mg/day T gel groups and were more marked in the T gel higher dose (100 mg/day) group. Analyses of the data from individual subjects showed that about 20% of the subjects in the higher dose T gel group had a Hct that was elevated to above the normal range on day 180 of treatment. Only one subject in the T patch group was discontinued from the study because of rising Hct. The other blood parameters, lipid profile, and liver or renal function tests showed no consistent changes with T replacement. The changes in red cell indexes were consistent with the anticipated effect of T replacement therapy (13, 24).

Serum PSA concentrations showed the anticipated small rises with both doses of T gel replacement, but not with T patch. These PSA levels plateaued after day 90. In 5 (4 in the 100 mg/day T gel group and 1 in the 50 mg/day T gel group) of the 227 subjects, PSA rose above the upper range of 4 ng/mL. Most of these subjects had enlarged prostates suggestive of benign prostate hyperplasia. All subjects were discontinued from the open label T gel extension study because of persistence of elevated serum PSA levels. In 1 of these subjects (100 mg/day group), prostate biopsy showed prostate cancer. Serum PSA was weakly related to the serum T levels before replacement and those achieved by the dose of T delivered to the body. As T has not been shown to induce prostate cancer, we presume that the elevation of PSA in the T treatment protocol either unmasked asymptomatic prostate cancer and led to biopsy due the increased PSA level or the cancer finding was coincidental to treatment. The prostate symptom scores and the uroflow rates were not significantly changed by T replacement in any treatment group.

Tolerability of the daily application of T gel at the tested dosages was much better than that of the permeation-enhanced T patch. Only 5.5% of subjects had minimal erythema after gel application. Skin irritation, some relatively severe, occurred in about 66% of the subjects using the permeation-enhanced T patch, which resulted in discontinuation of the study in 16 subjects. The open system and the lower concentration of alcohol in the T gel formulation markedly reduced skin irritation, resulting in better tolerability and continuation rate of T replacement therapy.

We have shown in this study that T gel is more effective in increasing lean body mass and decreasing body fat than the recommended T patch regimen, with comparable effects on sexual function, mood, and muscle strength. The differential effects of T gel compared to T patch on lean body mass and body fat may be related to the higher blood levels of T and dihydrotestosterone attained with T gel. Increasing the dose delivered by T patches from 5 to 10 mg/day might increase blood androgen levels and improve response, but perhaps at the risk of more skin irritation. The relative lack of skin irritation coupled with high compliance make T gel a more favorable transdermal androgen delivery method than T patch.

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