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Long-Term Testosterone Gel (AndroGel) Treatment Maintains Beneficial Effects on Sexual Function and Mood, Lean and Fat Mass, and Bone Mineral Density in Hypogonadal Men

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Transdermal testosterone (T) delivery represents an effective alternative to injectable androgens. We studied 163 hypogonadal men who applied 5, 7.5, or 10 g AndroGel (T gel) 1% CIII per day for up to 42 months. Efficacy data were presented in 123 subjects considered evaluable. Continuous AndroGel treatment normalized mean serum T and free T levels. Mean serum 5α-dihydrotestosterone concentrations and 5α-dihydrotestosterone/T ratio slightly increased, mean serum estradiol/T ratio doubled, and mean serum FSH and LH levels were suppressed by T replacement. Sexual function and mood parameters improved rapidly and were maintained throughout T treatment. Lean body mass increased ($P = 0.0001$) and fat mass decreased ($P = 0.0001$), and these changes were maintained with treatment but were not accompanied by significant increases in muscle strength. Increases in serum bone markers suggestive of increased bone formation were followed by gradual and progressive increases in bone mineral density more in the spine ($P = 0.0001$) than the hip ($P = 0.0004$). Mild local skin irritation occurred in 12 subjects, resulting in discontinuation in only one subject. Except for the anticipated increase in hematocrit and hemoglobin, there were no clinically significant changes in blood counts or biochemistry. In three subjects with elevated serum prostate-specific antigen, prostate biopsies showed cancer. We conclude that continued application of AndroGel resulted in beneficial effects similar to those with injectables and other transdermal preparations. This study was neither placebo controlled nor powered to determine the effects of T treatment on prostate cancer risk. Thus, monitoring for prostatic disease and assessment for erythrocytosis are strongly advised to reduce the risk of adverse events with T treatment of hypogonadal men. (*J Clin Endocrinol Metab* 89: 2085–2098, 2004)

WE PREVIOUSLY DEMONSTRATED that testosterone (T) gel (AndroGel T gel 1% CIII, Solvay Pharmaceuticals, Marietta, GA) provided steady serum T concentrations within the physiological range with proportional increases in serum free T, 5α-dihydrotestosterone (DHT), and estradiol (E_2) concentrations (1, 2). For simplicity, AndroGel will be used throughout this manuscript. Over 150 hypogonadal men who received the AndroGel replacement for 6 months showed significant improvement in sexual function, mood, lean mass, and muscle strength and decreases in fat mass and percent body fat (3). Furthermore, assessment of bone turnover markers indicated an initial, transient increase in bone formation markers and more sustained decreases in bone resorption markers. In subjects receiving AndroGel, 10 g/d, bone mineral density (BMD) increased by about 2% in the vertebrae by 6 months (4). The adverse effects were those anticipated from T replacement in hypogonadal men with minimal skin irritation. The compliance rate was good and the patient acceptance rate of this route of T delivery was high.

All 163 subjects in this report participated in the prior 6-month study comparing the efficacy of AndroGel with a T patch with enhancers (1, 3, 4). After the initial 6-month randomized study, the study was extended for up to another 36 months (42 months of total T gel exposure). We report the results from 123 evaluable subjects who were treated with AndroGel (5, 7.5, or 10 g/d) in which 70% of the subjects had at least 30 months of total T gel exposure. Safety data were reported for all 163 subjects enrolled in this study. Our goal was to determine whether serum T levels, efficacy, and safety were maintained during the long-term administration of AndroGel in hypogonadal men.

Abbreviations: BCE, Bone collagen equivalent; BMD, bone mineral density; Ca, calcium; Cr, creatinine; CV, coefficient of variation; DHT, 5α-dihydrotestosterone; E_2, estradiol; HDL, high-density lipoprotein; IPSS, International Prostate Symptom Score; IRMA, immunoradiometric assay; LDL, low-density lipoprotein; LOQ, limit of quantitation; *N*-telopeptide, urine type I collagen cross-linked *N*-telopeptide; PSA, prostatic-specific antigen; SALP, skeletal-specific alkaline phosphatase; T, testosterone.

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Subjects and Methods

Study design

Initially the study was a randomized, multicenter, parallel study including two doses of T gel [AndroGel (T gel)1% CIII, 5 and 10 g gel per day] and a single dose of two T patches (Androderm) delivering 5 mg T per day. Patients who were applying T gel had a single, preapplication serum T measured on d 60; if the levels were within the normal range (10.4–34.7 nmol/liter; 300-1000 ng/dl), they remained on their original dose. Men with T levels at 60 d of treatment less than 10.4 nmol/liter and who were applying T gel 5 g and those with T levels greater than 34.7 nmol/liter who had received T gel 10 g were then assigned to the T gel 7.5 g/d group for d 91–180. No changes in dose were made to subjects randomized to T patch.

At the end of the 6-month study, the subjects who elected to continue participation were then enrolled in a long-term AndroGel efficacy study of 24 months (total exposure 30 months). This protocol was further amended to extend treatment for up to 36 months (total exposure 42 months). All subjects receiving Androderm patch were assigned to the AndroGel 5 g group for this long-term study. During the long-term study, each subject's dose could be adjusted by the investigator at each study center, depending on the patient's clinical symptoms and serum T levels measured at each site. The investigator could increase the dose for the subjects whose serum T levels were less than 34.7 nmol/liter (1000 ng/dl). The daily dose of T gel was increased by increments of 2.5 g/d up to 10 g/d. Similarly the daily dose of T could be decreased by 2.5 g for safety-related issues.

Subjects

The patients were between 19 and 68 yr of age, diagnosed with hypogonadism by their physician and included in the study if they had a single morning serum T level at screening of 10.4 nmol/liter (300 ng/dl) or less. The screening serum T concentrations were measured at each center's clinical laboratory. Forty-nine of the evaluable subjects had primary hypogonadism (nine with Klinefelter's syndrome, four had anorchia or prior orchidectomy, and the remaining 36 were diagnosed as primary testicular failure); 27 of the subjects had secondary hypogonadism (16 had pituitary tumor and 11 were diagnosed with nonpituitary tumor hypothalamic pituitary disease including Kallman's syndrome). Hypogonadism in the remaining men was attributed to symptomatic age-related (>60 yr) decrease in serum T in 32 or as adult-onset normogonadotropic hypogonadism in the remaining 15 (symptoms of hypogonadism with low serum T but normal LH and FSH and no other cause of hypogonadism) (1, 3, 4). Previously treated hypogonadal men were withdrawn from T ester injection for at least 6 wk and from oral or transdermal androgens for 4 wk 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 on 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 a normal rectal examination, a prostatic-specific antigen (PSA) level of less than 4 ng/ml and a urine flow rate of more than 12 ml/sec using a urine flow meter before enrollment in the study. They were excluded if they had a generalized skin disease that might affect the T absorption. Subjects with body weight of less than 80% or more than 140% of ideal body weight and subjects taking medications known to alter the cytochrome P450 enzyme systems were also excluded from this study.

There were 163 subjects who participated in the long-term study. Safety data are presented for all the subjects. Data analyses for efficacy included 123 evaluable subjects. The subjects were excluded if: 1) there was an interval of 90 d or more between the end of the 6-month study and the long-term efficacy study in which the subjects could have received some other treatment (20 subjects); 2) the subjects participated for less than 3 months in the current long-term study (nine subjects); or 3) the subjects were enrolled in this study without completing the 6-month study (11 subjects). Of the 123 subjects, there were 45 in the 5-g group, 16 in the 7.5-g group and 36 in the 10-g group (total 97 of 123 or 79%) whose dose of AndroGel was not adjusted and remained constant from 6 months to the end of study.

Testosterone gel (AndroGel)

Testosterone gel (AndroGel T gel 1% CIII) was manufactured by Besins Iscovesco (Paris, France) and supplied by Solvay Pharmaceuticals. The formulation is a hydroalcoholic gel containing 1% T (10 mg/g). We have previously shown that about 9–14% of the steroid in the gel applied is available to the body. Thus 10 g of gel applied to the skin contains 100 mg T and delivers approximately 10 mg T to the body per day (1, 2). For this long-term study, the Androgel was packaged in polyethylene-lined foil sachets containing 2.5 or 5 g of the gel. The gel was applied in the morning after a shower and subjects were instructed to avoid showering until 5 h after application. All patients applied T gel at separate sites each day (right and left upper arms/shoulders or right and left abdomen). Alternate application sites continued throughout the study. After application of the gel to the skin, the gel dried within a few minutes. The patients washed their hands with soap and water thoroughly after gel application. Treatment compliance was estimated by counting at each study visit the number of packets of T gel dispensed minus those returned. An overall compliance (percent) was derived by the amount of medication used by each subject divided by the amount the subject should have taken by his prescribed dose during the study period expressed as a percentage.

Hormone assays

Serum T concentrations at screening and those used for dose adjustments during treatment in subjects who had clinical symptoms were measured at each site. All other hormone assays were measured at the Endocrine Research Laboratory of the Harbor-UCLA Medical Center (1–4). Serum T levels were measured after extraction with ethyl acetate and hexane by a specific RIA using reagents from ICN Pharmaceuticals (Costa Mesa, CA). The cross-reactivities of the antiserum used in the T RIA were 2.0% for DHT, 2.3% for androstenedione, 0.8% for 3β-androstanediol, 0.6% for etiocholanolone, and less than 0.01% for all other steroids tested. The lower limit of quantitation of serum T measured by this assay was 0.87 nmol/liter (25 ng/dl). The mean accuracy (recovery) of the T assay, determined by spiking steroid free serum with varying amounts of T (0.9–52 nmol/liter), was 104% (range 92–117%). The intraassay and interassay coefficients of the T assay were 7.3 and 11.1% at the normal adult male range, which in our laboratory was 10.33–36.17 nmol/liter (298–1043 ng/dl). Serum free T level was measured by RIA of the dialysate after an overnight equilibrium dialysis, using the same RIA reagents as the T assay. The lower limit of quantitation of serum free T, using this equilibrium dialysis method, was estimated to be 22 pmol/liter. When steroid free serum was spiked with increasing doses of T in the adult male range, increasing amounts of free T were recovered with a coefficient of variation (CV) that ranged from 11 to 18.5%. The intra- and interassay precisions of free T were 15 and 16.8% for adult normal male values (121–620 pmol/liter, 3.48–17.9 ng/dl).

Serum DHT was measured by RIA after potassium permanganate treatment of the sample followed by extraction. The methods and reagents of the DHT assay were provided by Diagnostic Systems Laboratories (Webster, TX). The cross-reactivities of the antiserum used in the RIA for DHT were 6.5% for 3β-androstanediol, 1.2% for 3α-androstanediol, 0.4% for 3α-androstanediol glucuronide, 0.4% for T (after potassium permanganate treatment and extraction), and less than 0.01 for other steroids tested. This low cross-reactivity against T was further confirmed by spiking steroid free serum with 35 nmol/liter (1000 ng/dl) of T and taking the samples through the DHT assay. The results even on spiking with more than 35 nmol/liter of T were measured as less than 0.1 nmol/liter of DHT. The lower limit of quantitation of serum DHT in this assay was 0.43 nmol/liter. All values below this value were reported as 0.43 nmol/liter. The mean accuracy (recovery) of the DHT assay determined by spiking steroid free serum with varying amounts of DHT from 0.43–9 nmol/liter was 101% (range 83–114%). The intraassay and interassay CVs for the DHT assay were 7.8 and 16.6%, respectively, for the adult male range, which in our laboratory was 1.06–6.66 nmol/liter (30.7–193.2 ng/dl).

Serum E_2 levels were measured by a direct assay without extraction with a kit from Diagnostic System Laboratories. The intraassay and interassay CVs of E_2 were 6.3 and 8.2%, respectively, for normal adult male range (E_2, 57–175 pmol/liter, 15.5–47.6 pg/ml). The lower limit of quantitation of the E_2 was 18 pmol/liter. All values below this value

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were reported as 18 pmol/liter. The cross-reactivities of the E_2 antibody were 6.9% for estrone, 0.4% for equilenin, and less than 0.01% for all other steroids tested. The accuracy of the E_2 assay was assessed by spiking steroid free serum with increasing amounts of E_2 (18–275 pmol/liter). The mean recovery of E_2, compared with the amount added, was 99.1% (range 95–101%).

Serum SHBG levels were measured by assay kits obtained from Delfia (Wallac, Gaithersburg, MD). The intra- and interassay precisions were 5 and 12%, respectively, for adult normal male range (10.8–46.6 nmol/liter). Serum FSH and LH were measured by highly sensitive and specific fluoroimmunometric assays with reagents provided by Delfia. The intraassay CVs for LH and FSH fluoroimmunometric assays were 4.3 and 5.2%, respectively; and the interassay CVs for LH and FSH were 11.0 and 12.0%, respectively (adult normal male range: LH, 1.0–8.1 U/liter; FSH 1.0–6.9 U/liter). For both LH and FSH assays, the lower limit of quantitation was determined to be 0.2 IU/liter. All samples obtained from the same subject were measured in the same assay.

Muscle strength

Muscle strength was assessed at baseline and then at six monthly intervals 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 66% of the subjects because some centers did not participate in the muscle strength testing because of lack of the required equipment.

Bone turnover markers

All serum/urine bone turnover markers were measured at the Endocrine Research Laboratory at Harbor-UCLA Medical Center. Serum intact PTH was measured by two-site immunoradiometric assay (IRMA) kits from Nichols Institute (San Juan Capistrano, CA). The lower limit of quantitation (LOQ) for the PTH assay was 12.5 ng/liter, the intra- and interassay CVs were 6.9 and 9.6%, respectively, and the normal male adult range was from less than 12.5 to 66.4 ng/liter. Serum osteocalcin was measured by an IRMA from Immutopics (San Clemente, CA) with the following characteristics: LOQ 0.45 μg/liter, intra- and interassay CV of 5.6 and 4.4%, respectively; the normal male adult range was from 2.9 to 12.7 μg/liter. Serum skeletal-specific alkaline phosphatase (SALP) was quantitated by a two-site IRMA using reagents supplied by Hybritech (San Diego, CA). The LOQ for the SALP assay was 3.8 μg/liter; the adult normal range was from less than 3.8 to 16.6 μg/liter; and the intra- and interassay CVs were 2.9 and 6.5%, respectively. Serum type I procollagen was measured using a RIA kit from Incstar Corp. (Stillwater, MN). The LOQ of the procollagen assay was 5 μg/liter; the normal adult male range from 56 to 310 μg/liter; and the intra- and interassay CVs were 6.6 and 3.6%, respectively. Urine calcium (Ca) and creatinine (Cr) were estimated by an autoanalyzer. The normal range for Ca/Cr ratio was 0.022 ± 0.74 mmol/mmol. Urine type I collagen cross-linked *N*-telopeptides (*N*-telopeptides) were measured by an ELISA from Ostex (Seattle, WA). The LOQ for the *N*-telopeptide assay was 5 nM bone collagen equivalent (BCE), and the normal range was from 47 to 2529 nM BCE with intra- and interassay CVs of 4.6 and 8.9%, respectively. The normal range for *N*-telopeptide/Cr ratio was 13–119 nM BCE/nM Cr. Samples containing low or high serum/urine bone marker levels were reassayed after adjusting sample volume or dilution to ensure all samples would be assayed within acceptable precision and accuracy. All hormone and biochemical data generated at Harbor-UCLA Medical Center were verified and audited by comparison with original laboratory data before transmitting to the data collection center of the sponsor.

Body composition and BMD

Body composition (total body mass, lean body mass, fat mass, and percent fat) and BMD at the hip and spine were measured by dual energy x-ray absorptiometry with 2000 or 4500A series (Hologic, Waltham, MA) at baseline, 6, 18, and 30 months after the start of T replacement therapy. These assessments were done in about 90% of the subjects because the Hologic dual energy x-ray absorptiometry equipment was not available in some centers. BMD of spine was calculated as the sum of measured bone mineral content at L1-L4 and divided by the total area of L1-L4 and that of left hip, calculated by the bone mineral content of the proximal femur divided by the area of the region measured. The scans were centrally analyzed and processed at Synarc (Maynard, MA). The between-center CV using the spine phantom was 0.15, and 0.37%, and the block phantom was 0.26, and 0.21%, for the Hologic QDR 2000 and 4500 A, respectively.

Sexual function and mood changes

The subjects were asked to complete the questionnaire daily for 7 consecutive days before each clinic visit (2, 5, 6). At each clinic visit when the diaries were collected, the study coordinator reviewed the questionnaires for completeness and clarified all missing data. The questionnaire covered three different domains: 1) sexual desire, enjoyment, and performance; 2) sexual activity score; and 3) mood. Sexual desire and sexual enjoyment with and without partners were rated on a 7-point Likert-type scale from 0 to 7, with 0 indicating none and 7 indicating very high. Sexual performance included self-assessment of satisfaction of erection that was rated using the 7-point Likert-type scale described above, and percentage of self-perceived full erection (10–100%). The latter two items were left blank if the subject did not have an erection allowing the determination of the percent of men without erections. The weekly value for these items was the simple average of the score for the 7 d. Sexual activity was assessed using a checklist format. The subjects recorded whether they had sexual daydreams, anticipation of sex, flirting (by themselves or others), sexual interactions with partner, erection, masturbation, intercourse, orgasm, and ejaculation on each of the 7 d. The value was recorded as 0 (none) or 1 (any) for analysis. The weekly value for the sexual activity items was the sum of the number of any responses for the week. The sexual activity score was then calculated as the average of the weekly values for all of the items. The mood parameters were assessed on the 7-point Likert scale. They included: alert, full of pep/energetic, friendly, and well/good (positive mood parameters) and angry, irritable, sad or blue, tired, and nervous (negative mood parameters). The weekly value of each of these items was the average of the 7 d. Positive mood was the average of the four positive mood parameters (alert, full of pep, friendly, well). Negative mood was the average of the five negative mood parameters (angry, irritable, sad or blue, tired, and nervous).

Skin irritation and safety parameters

Safety parameters were reported for all the subjects in the study (n = 163). Skin irritation assessments were made at every clinic visit using the following scale: 0 = no erythema, 1 = minimal erythema; 2 = moderate erythema with sharply defined borders; 3 = intense erythema and edema; and 4 = intense erythema with edema and blistering/erosion. When subjects developed skin irritation, pretreatment with corticosteroid cream was advised. Prostate Symptom Score was assessed every 6 months using the International Prostate Symptom Score (IPSS). The maximum score for IPSS 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 of the study centers. Written consent was obtained from each subject.

Statistical analyses

Descriptive statistics for each of the hormone levels were calculated. Before analysis, each variable was examined for its distributional characteristics and, if necessary, transformed to meet the requirements of a normal distribution. There were no significant differences among the study sites on any of the parameters; therefore, the data have been pooled for all the centers.

All data in the figures (up to 36 months of treatment) and tables show mean (± SEM). All parameters during AndroGel treatment were compared with the values at 0 (baseline) and 6 months corresponding to the start and end of the initial 6-month randomized study. Efficacy parameters were also compared between subjects who were under the age of 60 yr (younger, n = 124) and those over 60 yr (older, n = 39). Comparisons of change in serum T and free T concentrations between dosage

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groups at each treatment time were done using ANOVA after log transformations of the values, followed by Student-Newman-Keuls test for pairwise comparisons. *t* tests were used to compare total and free T levels between older and younger subjects. Analysis of the changes was done over the 30 months total time in treatment using repeated-measures ANOVA with all subjects included as a single group. If the overall ANOVA was significant, then values for each treatment time were compared with baseline. The model was repeated within diagnosis groups to compare suppression of FSH and LH in subjects with primary hypogonadism with those with normal or low serum gonadotropins. The analyses were also repeated within age groups to compare changes in efficacy parameters between older and younger subjects. The *P* values reported for the repeated-measures analyses are the overall *P* values for the time effect. Comparisons resulting in $P \leq 0.05$ were considered statistically significant. SAS version 6.12 (SAS Institute, Cary, NC) was used for all analyses.

Results

Patient characteristics

The characteristics of the subjects who participated in the long-term study are shown in Table 1. The mean age of the subjects was 51.4 ± 0.91 yr. The age, height, weight, diagnosis, and racial distribution were similar in the 62, 22, and 39 subjects who were receiving 5, 7.5, and 10 g gel at the end of 6 months of treatment when they were enrolled in the long-term study. Of these, 72.6, 72.7, and 92.3% of subjects remained at their original assigned 5-, 7.5-, and 10-g gel dose throughout this study. The number of evaluable subjects at each time point up to 36 months is shown in Fig. 1. Data were not shown for the 35 subjects who were evaluated at 42 months.

Serum T and free T concentrations

Serum T and free T concentrations in the three dose groups are shown in Fig. 1. Note that after the initial 6 months of the randomized trial, dose adjustments were allowed at each visit, depending on symptoms of the subjects. Compared with baseline, mean serum T and free T concentrations of all three dose groups remained within the reference range of adult males and were significantly different from baseline ($P < 0.0001$). At 6 months, which is the beginning of the long-term study, mean serum T levels were at 14.1 ± 1.3, 22.4 ± 2.7, and 25.6 ± 2.4 nmol/liter for the 5-, 7.5-, and 10-g T gel dose groups, respectively, which was significantly different between the groups ($P = 0.012$). At 12 months the differences in serum T concentrations among the different dose groups became smaller but remained significant ($P =$

TABLE 1. Subject characteristics at month 6

Parameter	All	5 g	7.5 g	10 g
Count	123	62[a]	22	39
Age (yr)	51.5 ± 0.9	51.1 ± 1.29	49.0 ± 2.35	53.4 ± 1.42
Height (m)	1.8 ± 0.01	1.8 ± 0.01	1.8 ± 0.02	1.8 ± 0.01
Weight (kg)	92.3 ± 1.3	91.8 ± 1.9	96.8 ± 3.9	90.5 ± 1.6
BMI (kg/m^2)	29.0 ± 0.34	29.0 ± 0.48	29.5 ± 1.00	28.8 ± 0.52
Diagnosis				
Primary	49	22	14	13
Secondary	27	15	4	8
Normogonadotropic hypogonadism	15	9	1	5
Aging	32	16	3	13
Race				
White	104	54	18	32
Black	10	4	4	2
Asian	5	1	0	4
Hispanic	3	2	0	1
Other	1	1	0	0
No medication change[b]	97	45	16	36

BMI, Body mass index.
[a] Includes 26 patch subjects who were previously applying T patches.
[b] Subjects who did not change medication dose from month 6 until leaving the study.

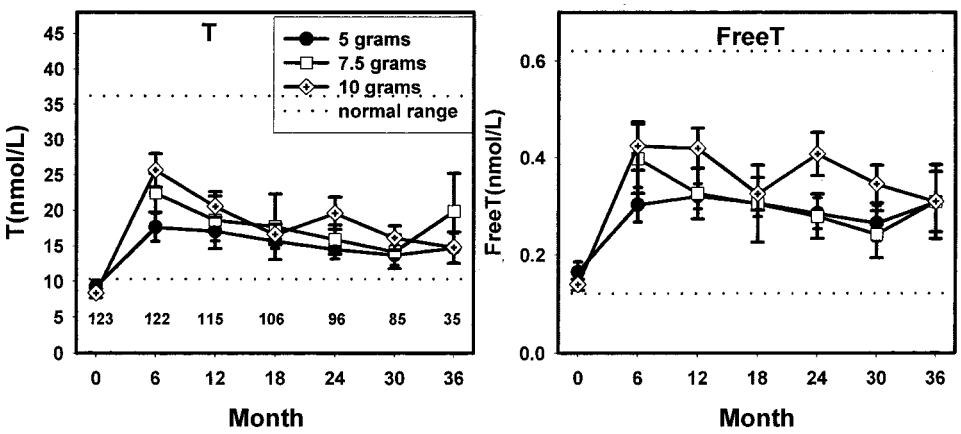

FIG. 1. Serum T and free T concentrations in patients receiving AndroGel 5 (*closed circles*), 7.5 (*open squares*), and 10 g/d (*diamonds*). The number of subjects in the study at each time point is shown at the *bottom of the graph*. In this and subsequent figures, the *dotted lines* when shown represent the adult male reference range.

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0.042: T gel 5 g/d, 16.9 ± 1.9 nmol/liter; 7.5 g/d, 17.9 ± 3.9 nmol/liter; and 10 g/d, 20.5 ± 1.5 nmol/liter). Thereafter with dose adjustment for the subjects, serum T levels were not different among the three groups. Serum free T followed the same pattern as serum T and also showed no significant differences among the dose groups after 12 months. The percent free T showed no significant change during the study. Mean serum T and free T levels throughout the study were not different among the groups of subjects who were younger than or older than 60 yr. Because the mean serum T and free T differences among the dose groups were small and became not significant with dose adjustments by each physician to maintain serum T concentrations within the adult male reference change, all other serum hormone and efficacy data are presented for all subjects as a group. Significant differences among the dose groups are discussed with each parameter.

Serum DHT, E_2, SHBG, FSH, and LH

Mean serum DHT concentrations were significantly higher after treatment ($P = 0.0001$) and were maintained within the adult male range for the treatment period with no further significant changes after 6 months (Fig. 2). Mean serum DHT was different in the three dose groups at 12 ($P = 0.0031$) and 24 ($P = 0.018$) months, with the levels in the 10-g group higher than the other two. Serum DHT/T ratio was 0.21 at baseline and remained between 0.26 and 0.30 throughout the treatment period without any time effect.

Mean serum E_2 levels were significantly higher during treatment with T, compared with baseline ($P = 0.0001$), and increased progressively from 6 ($P = 0.0001$) until 24 months of treatment, remaining at the upper limit of the male reference range (Fig. 2). Serum E_2/T ratio increased during treatment from 0.009 at 6 months to 0.013 and 0.014 at 18 and 24 months ($P = 0.0001$). Mean serum E_2 concentrations were also significantly different among the three groups at 12 ($P = 0.009$) and 24 ($P = 0.005$) months, with the levels highest in the 10-g dose group.

Serum SHBG showed no significant change with treatment and remained within the adult male reference range. Compared with baseline, mean serum LH and FSH concentrations were suppressed significantly with T gel treatment in subjects with primary and secondary hypogonadism as well as in those with low baseline serum T and normal serum gonadotropins ($P < 0.0001$). This suppression of LH and FSH was maintained throughout the treatment period without further significant

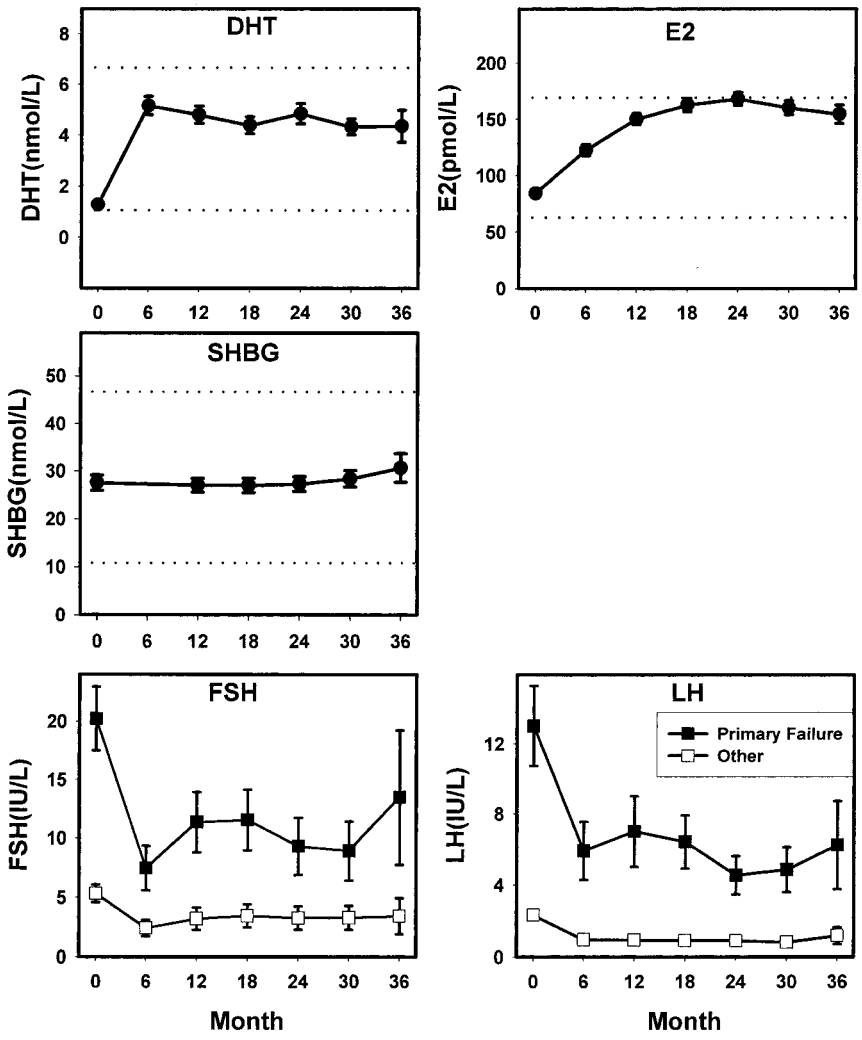

FIG. 2. Serum DHT, E_2, SHBG, FSH, and LH concentrations during treatment with AndroGel. Note that in the *upper* and *middle panels*, the *closed circles* represent all the subjects, whereas in the *lower panel* showing the gonadotropin levels, the *closed squares* represent the subjects with primary hypogonadism and the *open squares* represent those with secondary hypogonadism, aging-related hypogonadism, and normogonadotropic hypogonadism.

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changes after 6 months (Fig. 2). The suppression was more pronounced in the 10-g group than the lower doses.

Sexual function and mood scores

After treatment with T gel, as a group sexual desire ($P = 0.0001$), enjoyment without partner ($P = 0.0001$), enjoyment with partner ($P = 0.0022$), percent full erection ($P = 0.0001$), and self-assessment of satisfaction with erections ($P = 0.0001$) improved, compared with baseline, and were maintained at the same level from 6 months until the end of the treatment period (Fig. 3). Sexual activity scores were also significantly increased and maintained at the same level from 6 months throughout the treatment period ($P = 0.0001$). The proportion of subjects with erections increased from a baseline of 64.8% to 81.7% at 6 months without subsequent further significant increases. Positive mood scores improved with treatment and were sustained ($P = 0.0022$), whereas negative mood parameters were decreased and remained significantly lower ($P = 0.0013$) than baseline without further changes after 6 months of T gel replacement. There was overall improvement in psychosexual function in men over 60 yr, but the changes were smaller, compared with those younger than 60 yr of age (*e.g.* sexual activity $P = 0.0129$ in older men and $P = 0.0001$ in younger men).

Body composition

Average total body mass increased by 1.2 ± 0.3 kg at 6 months ($P = 0.0157$) and did not significantly change with continued T gel therapy (Fig. 4A). Lean body mass increased significantly ($P = 0.0001$) from baseline and remained increased throughout the study period. The change in lean body mass was 1.97 ± 0.24 kg at 6 months and was further increased to 2.93 ± 0.32 kg at 18 months and 2.89 ± 0.41 kg at 30 months ($P = 0.0065$). The differences in the lean body mass between the dose groups and those over and under age 60 yr were not significant. Fat mass decreased significantly as a group with T gel replacement ($P = 0.0058$). The decrease in fat mass was −0.8 ± 0.3 kg at 6 months and −1.57 ± 0.38 and −1.30 ± 0.51 kg at 18 and 30 months ($P = 0.088$ when compared with 6 months), respectively, without significant differences among the different dose groups. The decreases in fat mass ($P = 0.032$) and percent fat ($P = 0.0001$) were observed only in the younger subjects but not in older

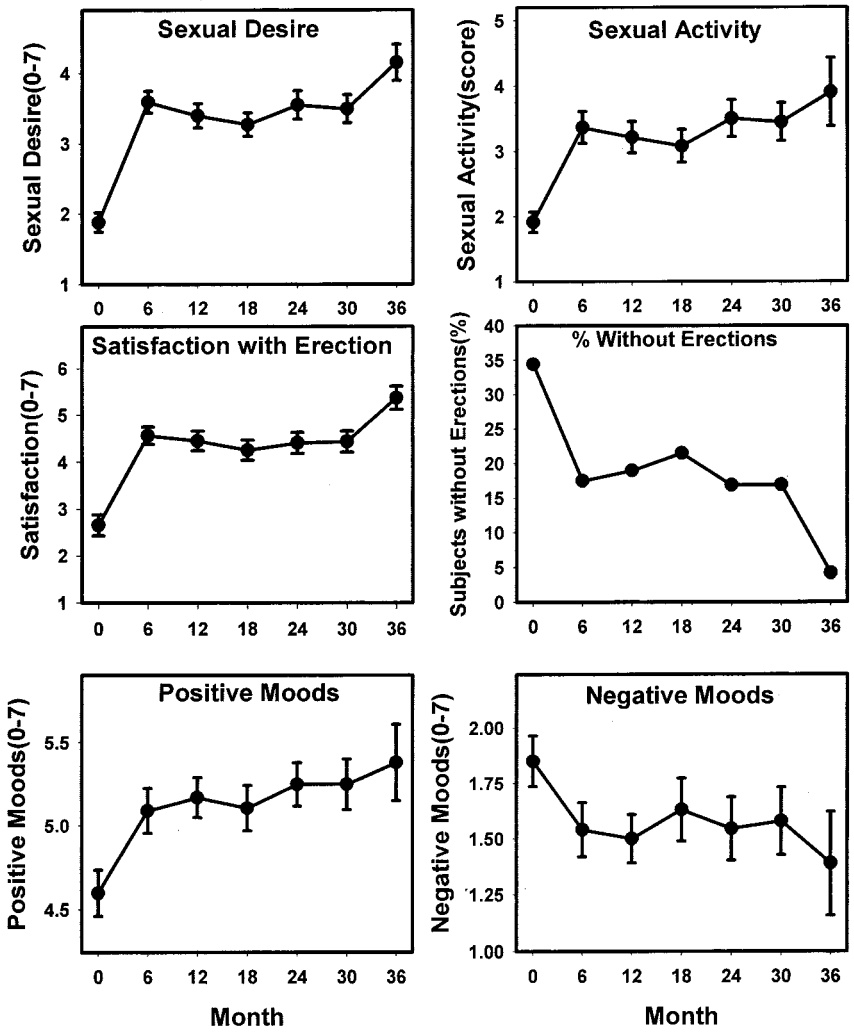

FIG. 3. Changes in sexual function and mood parameters as assessed by a self-report questionnaire during AndroGel treatment.

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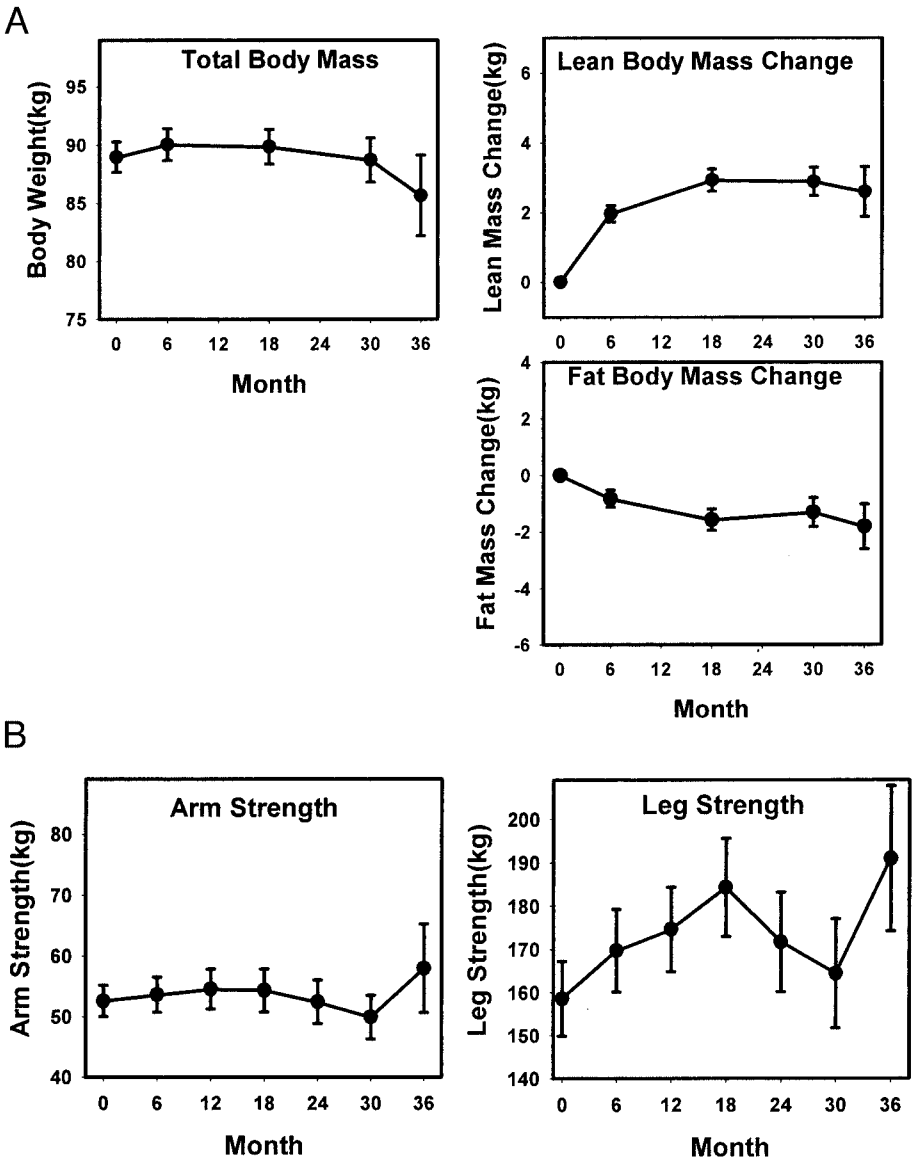

FIG. 4. Changes in body composition (A) and muscle strength (B) during treatment with AndroGel.

men. The changes in body composition parameters were not related to the change in serum T concentrations during replacement therapy.

Muscle strength testing of the upper and lower extremities by the chest and leg press increased, but this did not reach statistical significance over time (Fig. 4B) because of the large variations within and between subjects. The mean chest press increased by 1.7 to 4.1 kg and the leg press by 8.7 to 14.5 kg over the treatment period of up to 36 months. There were no sustained differences among the different dose groups or between subjects who were younger or older than 60 yr.

Bone turnover markers

Serum PTH, osteocalcin, SALP, procollagen, and urine Ca/Cr and *N*-telopeptide/Cr ratios during T gel replacement treatment are shown in Fig. 5. Serum PTH levels showed significant increases when compared with baseline ($P = 0.0001$) and continued to increase from 6 ($P = 0.0002$) until 12 months of treatment and then became stable throughout the treatment period (16.8 ± 0.7, 23.2 ± 1.29, 26.8 ± 1.3, 26.9 ± 1.4, and 27.5 ± 2.1 ng/liter at 0, 6, 12, 24, and 36 months, respectively). Serum SALP showed the same pattern, increasing from a baseline of 73.6 ± 2.4 pmol/liter to 77.6 ± 3.4 and 86.3 ± 3.2 at 6 and 12 months, respectively, and then plateaued ($P = 0.001$). Serum osteocalcin levels increased transiently during the initial few months of treatment (baseline 4.47 ± 0.15 μg/liter; 3 months 4.89 ± 0.18 μg/liter, data not shown; and returned baseline at month 6, 4.36 ± 0.17 μg/liter). At month 12 serum osteocalcin was significantly elevated, again compared with values at 6 months (5.23 ± 0.21 μg/liter), and stayed at the same level until the end of treatment (month 36, 5.18 ± 0.32 μg/liter) ($P = 0.0001$). Similarly, serum procollagen levels transiently increased during the initial treatment (baseline 118 ± 4, 3 months 133 ± 5 μg/liter, data not shown) but were back to

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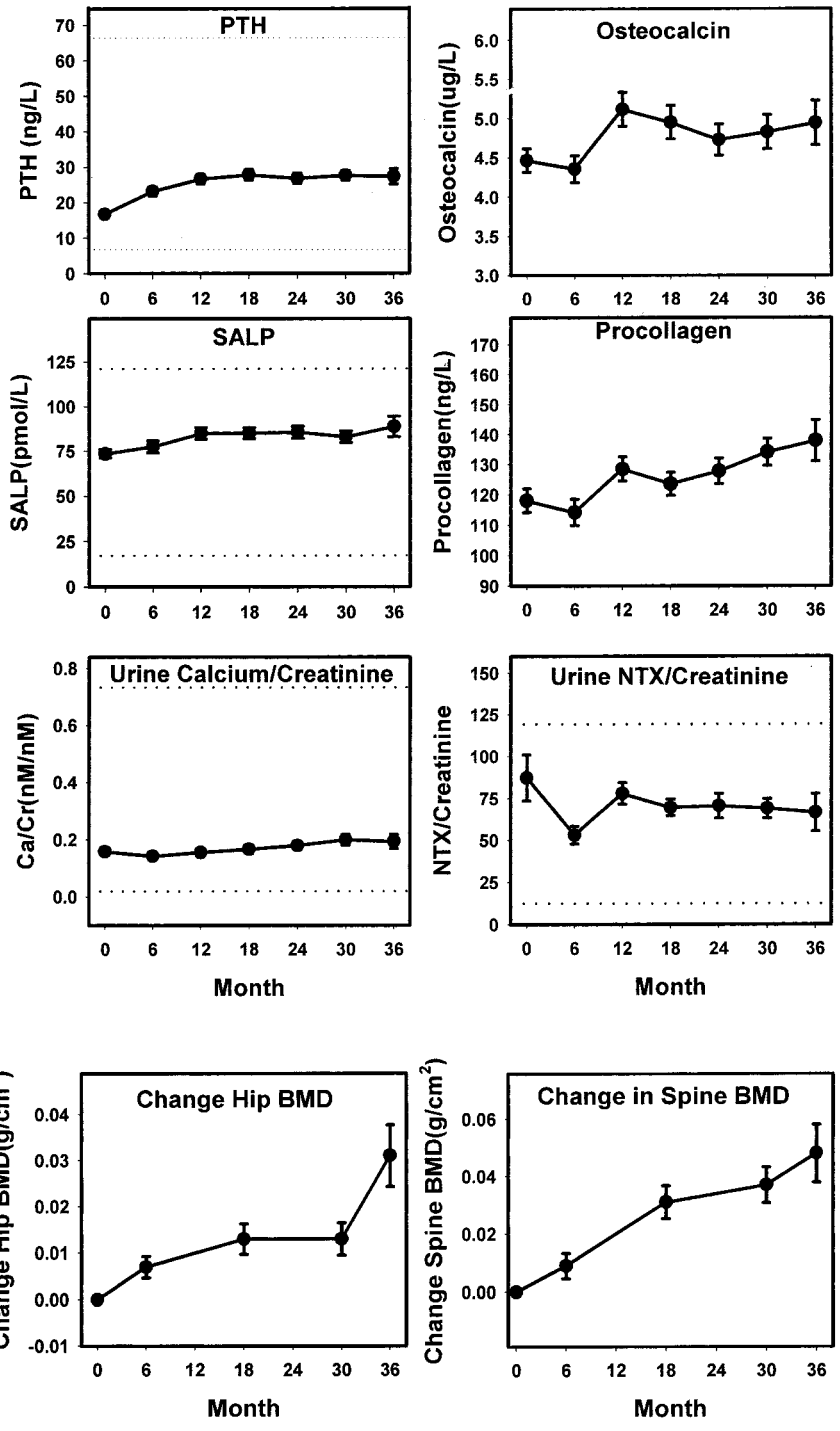

FIG. 5. Serum and urine bone turnover markers in hypogonadal men during AndroGel treatment. NTX, *N*-telopeptide.

FIG. 6. Changes in hip and spine BMD in hypogonadal men treated with AndroGel.

the baseline levels by 6 months (114 ± 4 μg/liter). Serum procollagen levels then rose steadily from 6 months to reach 142 ± 7 μg/liter at 36 months ($P = 0.0001$). Overall analyses of urine Ca/Cr ratio and urine *N*-telopeptide/Cr ratio did not show significant changes throughout the treatment period. However, urine *N*-telopeptide/Cr ratio decreased from 87.4 ± 13.6 to a trough at 53.2 ± 5.3 at 6 months of treatment ($P = 0.0069$); subsequently the ratios fluctuated with wide variation but were significantly higher when compared with the trough value at 6 months ($P = 0.0003$).

BMD

BMD of the hip ($P = 0.0004$) and spine ($P = 0.0001$) showed a gradual and progressive increase with treatment (Fig. 6). The increase in the BMD was more marked in the spine than the hip. Spine BMD increased by 0.031 ± 0.006 (3.1%) and 0.037 ± 0.006 g/cm^2 (3.8%) at 18 and 30 months of treatment, respectively, and was significantly higher than that at 6 months ($P = 0.0001$). There were no significant differences in the improvement in BMD among the

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three dose groups or between the younger and older age groups. The absolute increase in BMD in the hip and spine was not related to the baseline serum T or the change in serum T levels but was significantly related to baseline BMD ($P = 0.0001$).

Hemoglobin, hematocrit, clinical chemistry

Serum hemoglobin and hematocrit concentrations increased with T gel replacement, compared with month 0 ($P = 0.0001$) and month 6 ($P = 0.001$) and then plateaued at 12 months after initiation of treatment (Fig. 7). The increases in hematocrit and hemoglobin were statistically significant in both younger and older subjects ($P = 0.0001$). At 12 and 18 months after treatment, the increase in hemoglobin and hematocrit concentrations was higher in the group applying 10 g T gel per day ($P < 0.03$), compared with those applying less T gel. The increases were not different between the groups at months 30 and 36. Fourteen patients (of 153, 9%) had hemoglobin over 18 g/dl or hematocrit greater than 56% at some time during the study. The T gel dose was reduced or temporarily discontinued in these patients. Serum total and low-density lipoprotein (LDL) cholesterol levels did not change significantly throughout the T gel treatment period. Serum high-density lipoprotein (HDL) showed a very small but statistically significant increase ($P < 0.001$) across time with T gel. The increase was not clinically relevant. Mean serum creatinine was statistically increased ($P < 0.001$) across the treatment period. The mean increase varied from 0.08 to 0.20 mg/dl. Serum total bilirubin also showed a small (0.02 to 0.09 mg/dl) but significant ($P = 0.001$) increase with T gel treatment that was not considered to be clinically significant. There were no significant changes in serum liver enzymes or other clinical chemistry parameters.

Serum PSA levels and prostate disease

Mean IPSS score did not change significantly across time with T gel replacement. None of the individual scores showed any clinically meaningful changes. Prostate size was

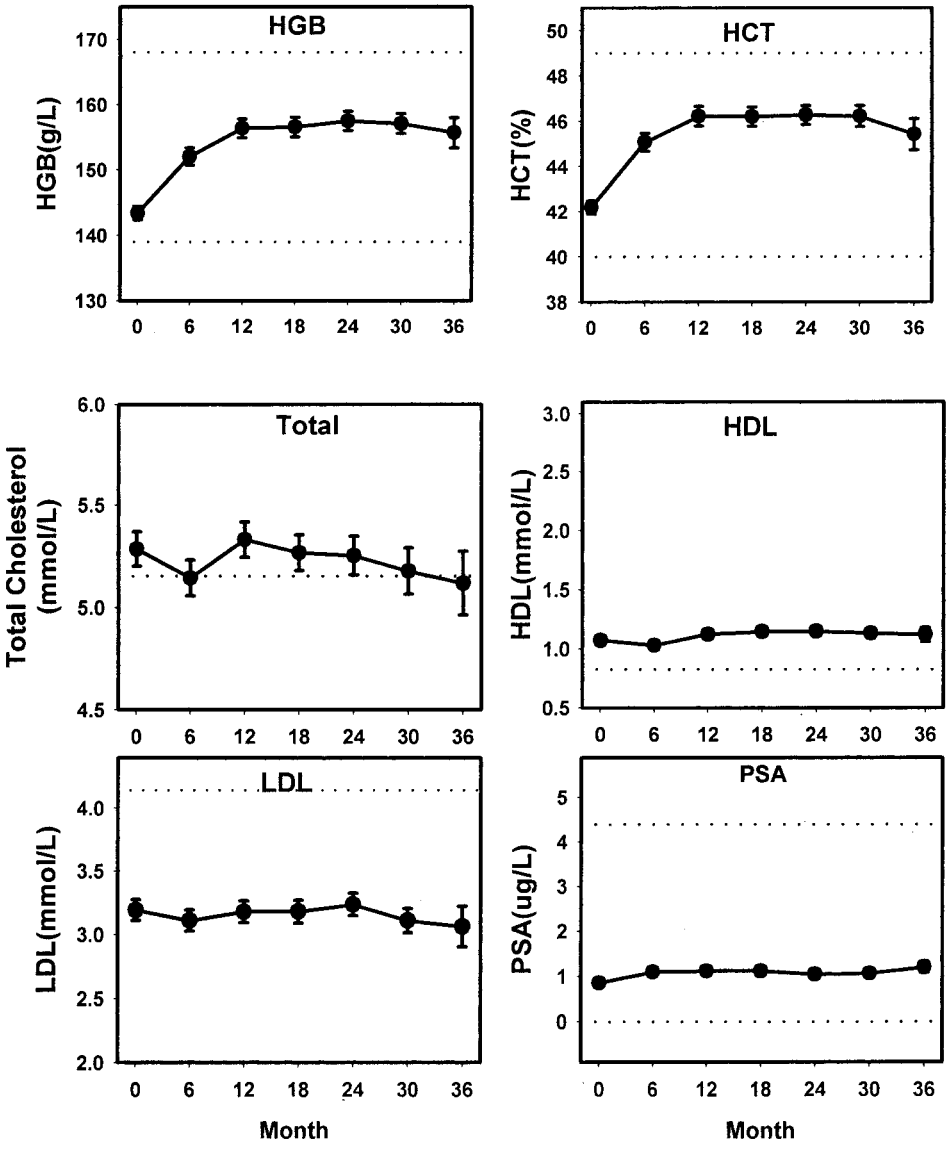

FIG. 7. Hemoglobin (HGB), hematocrit (HCT), serum total, HDL and LDL cholesterol, and PSA concentrations during AndroGel replacement therapy in hypogonadal men.

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not assessed by ultrasound but was assessed during digital rectal examinations and found to be enlarged in 23 subjects (14%) at any time in the study. Most of these patients had enlarged prostate at baseline assessment. Mean urine flow was not increased in the subjects as a group. Urine flow rate was less than 10 ml/sec in 24 subjects (15%). Except in one subject, there were no lower urinary tract obstructive symptoms in any subject that resulted in a serious adverse event or discontinuation from the study. Except for those subjects reported in Table 2, these subjects continued on T gel treatment.

Mean serum PSA concentrations are shown in Fig 7. The baseline PSA level was 0.85 ± 0.06 ng/ml. With T replacement there were significant increases in PSA levels over time ($P < 0.001$ in the whole group, $P = 0.0002$ in subjects > 60 yr, and $P = 0.0160$ in those < 60 yr). Mean serum PSA was 1.11 ± 0.08 ng/ml at month 6 and showed no further significant increases with continued T treatment ($P = 0.150$). There was no difference in serum PSA levels among the three T gel dose groups. Two subjects (603, 608) had transient elevations of PSA without any symptoms, and on repeat analysis on a subsequent sample, the serum PSA returned to within the normal range. These were ascribed to laboratory errors by the investigators. In addition, there were seven subjects whose serum PSA rose above the predetermined critical value of 5.5 ng/dl any time during the study (Table 2). One subject (919) had an elevated PSA to 6.0 ng/ml, his T gel was stopped, and his serum PSA returned to normal; no prostate biopsy was done. Subject 403 was discontinued from the study, referred to a urologist, diagnosed to have prostatitis, and treated with antibiotics. Subject 307 had elevated serum PSA during treatment, and prostate biopsy showed adenocarcinoma. Subject 417 had normal serum PSA at screening which rose to 6.2 ng/ml at 12 months, and prostate biopsy showed cancer. Subject 1102 had normal PSA on screening, which rose to 5.8 ng/ml at 18 months; prostate biopsy was negative. At 24 months repeat biopsy showed prostate cancer. Subject 514 was treated with 10 g T gel for over 36 months when a transurethral resection was performed for lower urinary tract symptoms.

Adverse events

In addition to the prostate disease described above, there were two serious adverse events possibly related to treatment. One was the subject who had transurethral resection as described above and another with normogonadotropin hypogonadism who had deep vein thrombosis deemed to be possibly related to T replacement. Application site skin reaction occurred in 12 of 163 subjects (five, three, and four subjects were receiving 5, 7.5, and 10 g T gel/d), 11 had minimal or mild erythema, and one was classified as moderate. Only one subject discontinued from the study after 12 months of 5 g T treatment because of worsening of minimal erythema and punctate rash. Gynecomastia was observed only in eight more subjects during treatment (4.9%). Breast enlargement was rated as mild in five and moderate in three subjects; all resolved without treatment. Of the eight with breast enlargement with treatment, only one had the diagnosis of Klinefelter's syndrome. Acne was noted in 12 subjects (7.4%). None of these subjects was discontinued because of acne.

Compliance

Overall compliance was 117, 88.2, and 71.4% of the prescribed dose in the 5-, 7.5-, and 10-g groups, respectively. The proportions of patients who were taking less than 80% of their prescribed dose were higher in the 7.5- and 10-g groups, whereas those who were taking more than 120% of their prescribed dose were higher in the 5-g group.

Discussion

In this study we reported long-term efficacy and safety data of continuous application of T gel (AndroGel) on the skin for more than 2 yr in 77% of 123 hypogonadal men. Because of the long duration of the study, the study design allowed dose adjustment throughout the study that occurred in about 20% of the subjects. The compliance was relatively good, considering the long duration of the study. We also recognized that about 90% of the subjects had body compo-

TABLE 2. Subjects with possible prostate dysfunction

Subject (no.)	Age (yr)	Dose (g)	Prostate problem	Outcome
919	55	7.5	Serum PSA rose to 6.0 ng/ml at 6 months of treatment from 2.5 ng/ml at baseline	AndroGel discontinued. PSA returned to 1.4 ng/ml; no biopsy
403	60	5	Serum PSA rose from 4.8 ng/ml at 6 months to 5.4 and 10.7 ng/ml at 12 and 18 months	AndroGel discontinued. Patient referred to urologist. Diagnosis prostatitis. PSA decreased to 5.1 ng/ml; no biopsy
307	63	10	Serum PSA rose from 3.6 ng/ml at baseline to 5.7 ng/ml at month 12. Rectal examination showed enlarged prostate with hard area in right upper pole.	AndroGel discontinued. Prostate biopsy showed adenocarcinoma.
417	62	10	Baseline PSA of 3.2 ng/ml rose to 6.2 ng/ml at 12 months.	AndroGel discontinued. Biopsy Ca prostate.
1102	65	7.5	Baseline PSA was 2.6 ng/ml. PSA increased to 5.8 ng/ml at 18 months and 6.6 ng/ml at 24 months.	AndroGel discontinued at 18 months; biopsy negative, AndroGel restarted. Repeat biopsy at 24 months showed Ca prostate.
514	65	10	Patient had normal PSA, diagnosed with lower urinary tract symptoms at 30 months of treatment.	Transurethral resection. AndroGel discontinued after surgery.

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sition and BMD studies and only 66% had muscle strength testing. Because the subjects were not preselected for these tests, the data presented were unbiased results that would be representative of the study population. Moreover, the data from the subjects demonstrated sustained improvements that were consistent within each subject and each parameter assessed. Because this was a long-term, open-label, follow-up study, subject attrition, allowance for dose adjustment, incomplete assessment of measures in all subjects, and noncompliance in some subjects were unavoidable. Although the present study departs from the idealized follow-up study, we believe that the data presented from this 3-yr followup study are relevant to the clinical practice of androgen replacement in hypogonadal men demonstrating the maintenance of the responses to T treatment.

In our prior reports, serum T and free T concentrations were proportional to the dose of T gel (5 or 10 g gel per day) administered in hypogonadal men (1). Recently other T gels have been studied (6–9), but none had reported long-term efficacy and safety data for up to 42 months of T gel exposure. In this report except for the first 12 months, serum T and free T concentrations were not different among the three dose groups during the T gel replacement period. The loss of dose proportionality could be ascribed to the dose adjustment performed by the investigators when the subjects had symptoms or when serum T levels were outside of the adult male reference range. The total number of subjects participating in the study was reduced with time, especially at 36 months of drug exposure. The mean serum T and free T concentrations in all dose groups were at the mid reference range from 12 months of treatment onward.

As we and others have reported, serum DHT concentrations followed those of serum T; however, because the gel was applied to the skin, a small increase in DHT/T ratio occurred early after 1 to 2 months of application and showed no progressive increase over time. Although serum DHT increased more from baseline than T, the actual levels of serum DHT are small relative to T. Despite the fact that DHT has been reported *in vitro* to have higher relative binding activity to the androgen receptor and *in vivo* in experimental animals more androgenic activity (10), it remains unclear whether circulating DHT has higher *in vivo* androgenic activity on multiple target organs in men. Whereas it is clear that intraprostatic conversion of T to DHT is critical for androgenic effects on prostate tissue, most of the DHT in the prostate is derived from conversion of T to DHT within the prostate cells. It is also not known what the relative contribution of equal amounts circulating T and DHT would be on the concentration of intraprostatic DHT (11). Serum E_2 levels increased progressively with time with AndroGel treatment until 24 months and thereafter plateaued. The mean serum E_2 remained at the upper limit of the male reference range. This resulted in a doubling of the E_2/T ratio. This gradual increase in E_2 was not reported in our prior shorter-term study (1). The cause of this increase in E_2 is not known and could be due to the increased aromatization of T to E_2 in the skin or adipose tissues (12, 13). Serum SHBG levels were not changed in this study, similar to our prior findings (1), suggesting that steady and physiological concentrations achieved by AndroGel treatment does not cause decreases in SHBG production by the liver. As anticipated, serum LH and FSH concentrations were suppressed to low levels, and this suppression was sustained throughout the T gel treatment period.

Sexual function improved rapidly after T replacement in hypogonadal men, and this improvement was sustained throughout the study without significant differences among the different dose groups. The improvements assessed by a validated self-reporting questionnaire (6) affected all aspects of sexual function including motivation, performance, and activity. This improvement in sexual function has been reported in prior reports (3, 5, 7, 8, 14, 15). Sexual activity improvement after T replacement in hypogonadal men is not dose dependent, and as soon as serum T is restored to the lower adult male concentrations, sexual function is returned to normal (16). As a group, mood changes improved early after institution of replacement, and this improvement was maintained in the study period. Overall the improvement in psychosexual function was greater in the younger men. As previously reported by other investigators and by our earlier studies on shorter duration of T treatment, enhancement of positive mood was more prominent than the decrease in negative mood parameters (3, 5, 17). Because there was no placebo group, some of the initial effect of T gel could have been due to a placebo effect, but sustained behavioral changes argued against this. With the improvement in sexual function and mood, it is likely that the quality of life in these hypogonadal men would be improved. This was not specifically assessed in this study, and instruments for hypogonadal men that may be more sensitive to the effects of T treatment may have to be developed.

Increases in lean body mass (average of about 3 kg) occurred in the hypogonadal men as early as 3 months and were sustained with continuous T replacement both in younger and older men. This increase was associated with a very small increase in total weight and loss of fat mass. The decrease in fat mass and percent body fat failed to reach statistical significance in older men in this study possibly because of the small number of older subjects. Such changes in body composition with T replacement had been shown previously in young and older men (3, 5, 7, 15, 16, 18–21). The increase in lean mass is likely due to muscle fiber hypertrophy that is increased with T treatment (22). It should be noted that in this long-term T replacement study, the changes in body composition plateaued after 12 months treatment. The changes in fat mass and lean mass have been shown to be dependent on the serum T achieved after exogenous T replacement (16). Overall, the changes in muscle and fat mass were not different in the different dose groups, most likely because of the dose adjustment that occurred in some subjects to maintain the serum T concentrations within the adult male range. Increases in muscle strength associated with increases in lean mass after T replacement have been reported by us and others (3, 14, 21). In this longer-term study, the mean strength in both upper and lower extremities increased as a group, but because of the marked variability, this failed to reach statistical significance over time. This finding is similar to that reported by Snyder *et al.* (23) in which hypogonadal men were treated with a scrotal patch in which

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knee flexion and extension and hand grip did not change during the 36 months of treatment.

Assessment of bone markers showed that serum PTH and SALP showed a steady increase over the first 12 months and then remained at the same level during the treatment period. Such increases in serum PTH have been reported by us (3, 5, 18) and could be related to the early decreases in serum calcium (3). The clinical significance of this rise of serum PTH and SALP within the normal range is not known. Others reported no change or decrease in SALP with T replacement (18, 24–26). The other markers of bone formation, osteocalcin and procollagen, followed the same pattern. The early rise and subsequent decrease after T replacement therapy of serum osteocalcin have been previously reported (3, 5, 24). In this study we showed that both serum osteocalcin and procollagen rose further at 6 months and then plateaued at a higher level at 12 months of T treatment than at baseline. Urinary bone resorption markers decreased to reach a trough in the first 6 months of treatment and then became very variable. Similar decreases in urine bone resorption markers within 6 and 12 months of T replacement followed by no further decreases in hypogonadal men were reported by Katznelson *et al.* (18) using T injectables and Snyder *et al.* (23) using scrotal T patches. Taken together in our long-term study of AndroGel replacement of hypogonadal men, the bone markers indicated that there was an early phase in which there was decreased bone resorption and increased bone formation and a later phase in which there is no apparent further decrease in bone resorption but a suggestion of a second phase of continued increase in bone formation.

BMD increased with T replacement therapy in hypogonadal younger men (5, 18, 23, 27) but not in some older men (25, 26). In our study BMD continued to increase by 0.76, 1.47, and 1.60% at the hip and 0.99, 3.10, and 3.80% at the spine after 6, 18, and 30 months of treatment. BMD in the spine increased both in older and younger men. The increases in BMD in the vertebrae of our subjects appeared to be similar to the 5% reported after 18 months of T enanthate (18) injections and less than the 7.7% after 36 months of scrotal transdermal T patch (23) as replacement therapy. In the subjects treated by Snyder *et al.* (23), the 14 hypogonadal men were never treated with prior T treatment; thus, the greater increase could be related to their previously untreated hypogonadism at baseline. Most of the subjects in our study had been previously on T replacement, which could have improved baseline BMD status, and therefore the full benefit of testosterone was underappreciated. The absolute change in BMD in response to T treatment in hypogonadal young and older men is highest when the initial serum T and BMD are the lowest (3, 24).

The few case reports of estrogen receptor mutations and aromatase deficiency in males were all associated with severe osteoporosis (28–30). In addition, there is strong evidence that estrogen is also important in maintaining BMD in adult men (31, 32). Epidemiological studies also demonstrate that BMD is related to serum E_2 and bioavailable E_2 concentrations and experimental studies in men showed that estrogens are important in maintaining bone mass (32). Thus, the current hypothesis is that the presence of adequate estrogen levels is required for achievement and maintenance of peak BMD in men. The concentration of serum E_2 or the level of estrogen activity in the target tissues required to maintain BMD is not known, although recent work would suggest that there indeed may be a critical level of bioavailable E_2 that is required to maintain bone resorption in check (32, 33). Whereas it is apparent that some estrogenic action is required for normal BMD, it is probable that T has positive effects on BMD through both estrogen and androgen receptor-related mechanisms. In our study serum E_2 rose with continued T replacement to reach the upper limit of the normal range. It is unclear whether the resultant increase in the relative E_2/T ratio may be partially responsible for this apparent continued increase in BMD observed in our subjects.

As in prior reports on AndroGel (3), skin irritability is minimal and caused discontinuation in only one subject. The anticipated appearance of acne occurred in a very small number of subjects. Gynecomastia occurred in eight subjects, and the incidence was not increased, despite the higher E_2/T ratio. The hemoglobin and hematocrit levels increased as anticipated with androgen replacement, but the increase reached the maximum level at 6–12 months with no further increases with continued T gel replacement. The number of subjects with high hemoglobin or hematocrit that required discontinuation was similar to other reports (23, 34, 35). There were small and clinically nonsignificant increases in creatinine and bilirubin in the subjects without any significant changes in liver enzymes or electrolytes. The serum total, HDL and LDL cholesterol, and triglycerides also did not show clinically significant changes.

Mean I-PPS scores were not increased in subjects as a group. One subject had transurethral resection of the prostate for lower urinary tract symptoms. Of the subjects who had elevated PSA during the study, three had confirmed prostate cancer on biopsy. All three subjects were over 63 yr old at enrollment in the study. In prior T replacement treatment of smaller numbers of hypogonadal men, no cancer of the prostate was reported (18, 23). The incidence of prostate cancer in three of 163 (1.8%) subjects who were enrolled in this study was similar to that reported in older men by Snyder *et al.* (26) who were treated with scrotal transdermal patches for 3 yr (one of 54, 1.8%). However, if only men over 60 yr enrolled in this study were considered, the incidence would be higher: three of 39 (7.7% over a 3-yr period). Based on the data from the Surveillance, Epidemiology, and End Result Program of the National Cancer Institute, the anticipated incidence of prostate cancer in the population of men between the ages of 65 and 74 yr is between 973 and 994 cases per 100,000 men [National Cancer Institute, Surveillance, Epidemiology, and End Result (SEER) Program 2002, www.seer.cancer.gov]. However, with the close monitoring of PSA in this study, the heightened awareness of the investigators, and the rate of referral to a urologist for prostate biopsy could cause the incidence to be increased. One could postulate, however, that during intervention studies such as the present study, the increased surveillance as shown by other studies (36) would result in higher prostate biopsy and higher cancer detection rate (24.4% in men aged 55 yr and during a 7-yr period). The cancers might therefore be detected earlier, leading to a higher cure rate. It is not clear whether androgen replacement in hypogonadal men will result in growth or devel-

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opment of a prostate cancer. In the recent evidence-based report by the Institute of Medicine, the issue of T replacement in androgen deficiency associated with aging in men remains controversial, and more controlled studies are required (37). In each subject with adult-onset hypogonadism associated with aging, the benefits must be balanced and carefully assessed against the potential risks for the patient. In older subjects, it is prudent to monitor serum PSA and conduct digital rectal examinations very early after the initiation of treatment (1–3 months) and then follow up the subjects periodically as recommended by practice guidelines (38).

We conclude that AndroGel replacement in hypogonadal men led to restoration of serum T and free T into the adult male range. Serum DHT/T and E_2/T ratios were increased during treatment but remained within the reference range. The improvements in sexual function and mood were sustained with long-term treatment. The decrease in fat mass and increase in lean mass were persistent with T replacement. Serum bone markers showed changes suggestive of an increase in bone formation and BMD increase both in the hip and spine. The safety parameters were comparable with other delivery systems. However, the benefits of androgen replacement must be weighed against potential risks. As with all androgen replacement, continuous vigilance is required for the monitoring of hemoglobin and hematocrit and serum PSA for values that are above the critical range that intervention may be necessary. In addition to the ease of administration and the lack of skin irritation, we conclude that AndroGel is also safe and effective when used in the long-term treatment of hypogonadal men.

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