

New Testosterone Buccal System (Striant) Delivers Physiological Testosterone Levels: Pharmacokinetics Study in Hypogonadal Men

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A new mucoadhesive testosterone buccal system (Striant), 30 mg testosterone (T), was applied twice daily in 82 hypogonadal men for 3 months. Serum T, free T, and 5 α -dihydrotestosterone were measured during this period. T pharmacokinetics were determined from the data obtained during a 24-h sampling at wk 12. Physiological mean serum T concentrations were steady and consistently maintained. The mean percentage of time over a 24-h period that total serum T concentrations were above the lower limit of adult male range was 80.1%. During treatment, mean serum 5 α -dihydrotestosterone, free T, and estradiol concentrations paralleled serum T.

T pharmacokinetics were not significantly affected by body mass index, age, food or beverage, gum abnormalities, or medications known to cause dry mouth. Gum-related adverse events occurred in 16.3% of subjects. Except for three subjects, the gum adverse effects occurred early during treatment, did not cause interruption of treatment, and resolved rapidly and completely. The T buccal system is a novel T formulation that offers a safe, effective, and convenient alternative to existing formulations for physiological T replacement therapy in hypogonadal men. (*J Clin Endocrinol Metab* 89: 3821–3829, 2004)

TESTOSTERONE (T) SECRETION in healthy young men typically exhibits a circadian variation with maximum concentrations achieved at approximately 0800 h and minimum concentrations achieved at approximately 2200 h, with a range of 10.4–36.4 nmol/liter (3.0–10.5 ng/ml) (1). These concentrations decrease with age and are associated with a loss of circadian rhythm (2, 3). Subnormal serum T concentrations as a consequence of testicular disease (primary hypogonadism) or hypothalamic-pituitary disease (secondary hypogonadism) have significant effects on patient well-being, including loss of muscle and bone mass and decreased libido (4–9).

T replacement therapy has been shown to be effective in reversing the consequences of hypogonadism. The goal of therapy is to replace T in as physiological a fashion as possible (1, 4–9). Due to rapid hepatic catabolism after oral

ingestion, replacement of native T is ineffective in treating hypogonadism (4–10). Older forms of replacement, by 17-alkylated androgens and T esters, have been used less frequently because of hepatotoxicity (11, 12) and the necessity of injections (13, 14), respectively. Newer forms of administration include patches and gels (15–21), which are generally well tolerated. Skin irritation may occur with patch use (22, 23), and the possibility that skin transfer may occur with gel use has been raised, which can be prevented by showering or wearing protective clothing. T undecanoate administered orally, which is available in Europe and Asia, is not associated with hepatotoxicity but shows large intra- and intersubject absorption variation, depending on food intake (4, 8, 9, 24). The availability of alternative forms of effective T replacement therapy would be welcome.

A new sustained and controlled-release T buccal system (TBS) (Striant), contains 30 mg T and mucoadhesive excipients. Because venous drainage from the oral cavity flows directly to the superior vena cava, transbuccal delivery of T substantially circumvents hepatic first-pass catabolism. Buccal administration, therefore, is a rational method of T delivery. The TBS was designed to rapidly adhere to the buccal mucosa and slowly form a gel. As the tablet hydrates, T is released and absorbed across the buccal mucosa. This new

Abbreviations: AUC, Area under the curve; BMI, body mass index; C_{avg} , average serum T levels over a 24-h period; CV, coefficient of variation; DHT, dihydrotestosterone; E₂, estradiol; PK, pharmacokinetics; T, testosterone; TBS, T buccal system.

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formulation was investigated for its ability to provide T replacement therapy in hypogonadal men.

Subjects and Methods

Subjects

The baseline characteristics of the 98 subjects are shown in Table 1. Subjects were between 20 and 74 yr of age (mean 53.9 ± 13.6 yr) and were otherwise healthy. Thirty-six had primary hypogonadism (Klinefelter's syndrome, postorchidectomy, primary testicular failure), 45 had secondary hypogonadism (pituitary tumor, Kallmann syndrome, hypothalamic-pituitary dysfunction), and 17 had adult-onset T deficiency associated with aging. The mean serum FSH/LH concentrations were elevated in the subjects with primary testicular disease, low in subjects with secondary hypogonadism, and normal in subjects with age-related hypogonadism. The serum total T levels at baseline were lowest in the secondary hypogonadism group. Sixty-eight subjects were white, 15 Hispanic, nine black, four Asian, and two others. Approximately 10% of subjects were current users of oral tobacco products and approximately 42% currently drank alcohol socially. The subjects' body mass index (BMI) was 35 kg/m² or less to qualify for enrollment, and the height, weight, and BMI are shown in Table 1. All subjects were either treatment naïve ($n = 31$) or had a wash-out period of at least 1 wk for prior transdermal replacement or at least 4 wk for prior im replacement therapy ($n = 67$). The duration of prior T therapy varied between 1 month and 18 yr (average 3 yr) before entering the study. Respectively, 69.7, 75.6, and 47.1% of the subjects with primary, secondary, and age-related hypogonadism had received prior T treatment. Of a total of 98 subjects enrolled, 82 hypogonadal subjects at nine centers in the United States completed the study with pharmacokinetics (PK) data on wk 12.

Subjects had fasting blood specimens for baseline chemistry, hematology, prostate-specific antigen, T, free T, dihydrotestosterone (DHT), estradiol (E₂), LH, and FSH, collected 1 wk before receiving their first application TBS. Baseline blood counts, clinical chemistry, and serum prostate-specific antigen levels were all within normal limits. To be eligible, the serum T level had to be below the lower limit of the adult male reference range of 2.5 ng/ml (8.7 nmol/liter). The mean baseline serum T for these subjects was 1.49 ± 0.88 ng/ml (5.2 ± 3.3 nmol/liter, mean \pm sd). All subjects signed an informed consent as approved by the institutional review board at each center.

TBS

The TBS (Striant) containing 30 mg T was provided by Columbia Laboratories, Inc. (Livingston, NJ). The mucoadhesive polymers, polycarbophil and Carbopol 974P, were among the inactive ingredients. The TBS was provided in blister-pack units. The TBS was designed to quickly adhere to the buccal mucosa and remain in place for up to 16 h after application. As the TBS absorbs water from the oral cavity, it slowly hydrates and become soft and gelatinous. The slow and continuous hydration of the formulation allows the T in the system to be constantly released and immediately absorbed through the buccal mucosa. The dry portion of the system protects the active ingredient from moisture and the environment until it is hydrated and released. TBS is the first product to use this novel buccal delivery system.

Study design

A multicenter, single-arm, open-label design was used for this phase III study. Each subject made seven clinic visits and received TBS for 12 wk. Screening and baseline assessments were performed up to 8 wk before subjects receiving the first dose of TBS. Safety assessments, including complete blood counts and clinical chemistry, were performed at 4, 8, and 12 wk after the first dose of TBS, and at the follow-up visit 4–14 d after completion of the 12-wk treatment period.

TBS was applied twice daily (at ~0800 and 2000 h) to the gum at alternating sites above the upper incisors on the left or right side of the mouth. Once the TBS was positioned on the gum, the subject held the TBS in place with a finger above the lip for approximately 30 sec to achieve adhesion. Before applying a new TBS, the previous TBS was removed manually by sliding the TBS downward from the gum toward the tooth. There was no dose adjustment allowed for this study.

At 4 and 8 wk, blood samples were drawn before the change of TBS for T, free T, DHT, SHBG, LH, FSH, and E₂ levels. At wk 12, subjects were admitted to the Clinical Research Center at each center for the 24-h PK assessments. TBS was administered at 800 and 2000 h on the day of the PK study. Blood was drawn at 0.25 h before change of TBS and at 0.5, 1, 2, 4, 6, 8, 10, 12, 12.5, 13, 14, 16, 18, 20, and 24 h post dose for T and 0.25, 4, 8, 12, and 24 h for free T and DHT. Serum LH, FSH, and E₂ were analyzed at 0.25 h before the change of TBS only. SHBG was assessed at multiple time points during the 24-h PK assessments. Meal times were recorded to assess food effect on T absorption. Conditions that could affect T absorption were also recorded. These included food and beverage effects, the effects of gum abnormalities, concomitant medications causing dry mouth, age, and BMI. Gum abnormalities were assessed by the investigator as normal or abnormal, and if abnormal the investigator recorded whether gingivitis, edema, ulcerations, lesions, and/or leukoplakia was present and the intensity of the gum abnormalities.

Hormone assays

All hormone assays were performed by the Esoterix Center for Clinical Trials (Calabasas, CA). Table 2 provides assay characteristics for all methods used in this study.

Serum T levels were measured by RIA after hexane ethyl acetate extraction and aluminum oxide microcolumn chromatography. Recovery was 97%. The cross-reactivities of the antiserum used in the T and free T RIA were 22% for DHT; 5.5% for 4-androsten-3 β , 17 β -diol; 2.3% for 5 α -androstan-3 β , 17 β -diol; 1.4% for androstenedione; and less than 1% for all other steroids tested. Serum free T was determined using equilibrium dialysis. A serum sample volume of 300 μ l containing tritium-labeled T was placed inside a semipermeable dialysis cell and dialyzed against a buffer at 37 C for 16–18 h. The percentage of free T was calculated from the ratio of radioactivity outside the cell *vs.* inside the cell and calculated from the total T in serum. Serum DHT levels were measured by RIA after hexane ethyl acetate extraction followed by a proprietary oxidation step that removed greater than 99% of T from the sample. Steroid-free serum samples spiked with 30 nm T when assayed were not significantly different from steroid-free serum. DHT recovery, performed by analyzing samples spiked with known quantities of DHT, was approximately 96%. DHT antiserum cross-reactivity was 40% with T, 2.7% with 4-androsten-3 β , 17 β -diol, 4.8% with 5 α -androstan-3 β , 17 β -

TABLE 1. Subject baseline characteristics

	All subjects	Primary	Secondary	Age related
Count	98	36	45	17
Age (yr)	53.6 [13.6]	51.5 [15.5]	50.7 [12.0]	65.5 [4.9]
Height (cm)	177.8 [7.8]	178.4 [8.1]	177.1 [8.2]	178.1 [5.9]
Weight (kg)	92.2 [14.0]	89.7 [15.0]	92.6 [14.2]	96.4 [10.6]
BMI (kg/m ²)	29.1 [3.7]	28.0 [3.9]	29.5 [3.4]	30.4 [3.4]
Baseline LH (IU/liter)	7.7 [10.3]	17.1 [11.9]	1.6 [1.5]	3.8 [1.7]
Baseline FSH (IU/liter)	14.5 [17.8]	32.8 [17.8]	2.9 [2.4]	6.3 [3.8]
Baseline T (nmol/liter)	5.2 [3.3]	5.7 [3.4]	4.3 [3.4]	6.6 [2.1]
Previous treatment subject no. (%)	67 (68.4%)	25 (69.4%)	34 (75.6%)	8 (47.1%)
Duration (yr)	3.0 [3.0]	3.3 [3.2]	2.9 [2.87]	2.9 [2.93]

Numbers in brackets represent SD and numbers in parentheses represent percentage.

diol; and less than 0.5% with other steroids tested. Serum SHBG was measured using an immunoradiometric assay developed at Esoterix. SHBG recovery performed by analyzing samples spiked with known quantities of SHBG was approximately 92%. Serum E_2 levels were measured by RIA after extraction with hexane ethyl acetate and column chromatography. E_2 recovery performed by analyzing samples spiked with known quantities of E_2 was approximately 116% indicating that the amount of E_2 measured in the serum might be higher than the actual mass of steroid. Antiserum cross-reactivity was 1.3% with estrone and less than 1% with all other steroids tested. Serum LH and FSH levels were measured using an immunochemiluminometric assay, using paired monoclonal antibodies. LH and FSH recovery performed by analyzing samples spiked with known quantities of LH or FSH was approximately 82–100% for each assay. The antisera used in each assay exhibited minimal cross-reactivity with TSH, α -subunit, or FSH or LH.

Statistical analyses

The PK parameters and their definitions are shown in Table 3. These include area under the curve (AUC) and average serum T levels over a 24-h period (C_{avg}) and other commonly used parameters.

Descriptive statistics were used to report the majority of results of this study. The relationship between BMI and the area under the total T serum concentration-time curve for the time period of 0–24 h [C_{avg} (0–24)] was investigated using correlation analysis. Normality testing was performed on this comparison, which found a nonnormal distribution and was transformed and analyzed accordingly. The data for serum total T concentration *vs.* time were summarized by noncompartmental estimation techniques using the PK software program WinNonlin Professional (versions 3.1 and 3.2; Pharsight Corp., Mountain View, CA).

Statistical analyses were performed only on the data from subjects who completed the PK analysis at wk 12 ($n = 82$). Descriptive statistics for safety and serum hormone parameters were means, SD, medians, minimum, and maximum values for continuous data and frequencies (percentage) for categorical data. Descriptive statistics for serum hormone concentrations, PK-calculated parameters, and serum hormone end points were performed using means, SD, and percentage of coefficient of variation (CV). A subsection of these parameters were further examined for effects potentially caused by food and beverages, gum abnormalities, concomitant medications causing dry mouth, and age. All

data are presented as mean \pm SD. Safety data were presented for all 98 subjects enrolled into the study.

Results

Serum T levels and PK

A total of 98 subjects enrolled in the study; 16 (16.3%) subjects discontinued from the study for reasons including subject request ($n = 10$), withdrawal by the investigator ($n = 1$), death in a motor vehicle accident ($n = 1$), and serious protocol violation that required the data to be excluded from analysis ($n = 4$). Most subjects ($n = 10$) discontinued during the first weeks of treatment, most likely due to problems associated with the application of the TBS or the inability to tolerate the TBS on the gums 24 h/d. These 10 subjects did not have abnormal gums on examination. This resulted in data for 82 subjects available for analysis.

Serum T concentrations (mean \pm SD) determined at baseline (*i.e.* before the first dose of study drug) through the 12-wk treatment and the follow-up period are shown in Fig. 1. At baseline the mean serum T concentration of 5.17 ± 3.05 nmol/liter (1.49 ± 0.88 ng/ml) was below the lower limit of the reference range (10.4–36.4 nmol/liter; 3.0–10.5 ng/ml). As a group the mean serum T concentrations within the adult male range were attained by the predose blood sampling at wk 4 and were consistently sustained within the physiological range at 20.1–24.9 nmol/liter (5.8–7.0 ng/ml) at wk 4, 8, and 12, respectively. At follow-up 14 d after stopping the TBS, the mean concentration returned to approximate baseline values of 6.1 ± 9.9 nmol/liter (1.7 ± 2.9 ng/ml).

Mean serum concentrations for T were within the adult male range over the two consecutive 12-h sampling periods after each dose of TBS at wk 12 (Fig. 2). Mean T values during

TABLE 2. Characteristics of the hormone assays used for this study

Hormone	LLOQ	Intraassay %CV	Interassay %CV	Normal male reference range
Total T (nmol/liter)	0.08	<3.9	<8.0	10.4–36.4
Free T (%)	0.53%	<8.9	<8.9	1.5–3.2
DHT (nmol/liter)	0.089	<2.2	<11.9	1.03–2.92
E_2 (pmol/liter)	23.9	<5.5	<12.0	29.5–129
SHBG (nmol/liter)	2.0	<2.4	<7.8	24–78
LH (IU/liter)	0.02	<4.5	<4.2	1.5–9.0
FSH (IU/liter)	0.02	<3.2	<6.7	2.0–9.2

Intraassay CV, The CV observed on the same specimen within individual assays; intraassay CV, the CV observed on the same specimen between individual assays; LLOQ, lower limit of quantitation.

TABLE 3. Definitions of PK parameters

PK parameter	Definition
$AUC_{(0-12)}$; $AUC_{(12-24)}$	AUC calculated from time 0–12 h and 12–24 h
AUC_{last}	AUC calculated to the time of last measurable concentration
AUC_{12-24}/AUC_{0-12}	Ratio of AUC of serum hormone for 12–24 h/0–12 h
C_{avg} (0–t)	$\frac{AUC_{(0-t)}}{t}$ where $t = 0-12, 12-24$, or $0-24$ h
C_{max} (0–24)	Maximum serum hormone concentration over 24 h
T/DHT AUC_{last} ratio	$T-AUC_{last}/DHT-AUC_{last}$
T_{max}	Time to maximum observed total T serum concentration
T_{min}	Time to minimum observed total T serum concentration
% Fluctuation (0–24)	$\% 100 \times \frac{(C_{max(0-24)} - C_{min(0-24)})}{C_{avg(0-24)}}$
% P_{24} (dur)	% T concentrations over 24 h that were within 10.4–36.4 nmol/liter (3.0–10.5 ng/ml)
% T_{24} (above)	% Time that serum concentrations were above 10.4 nmol/liter (3.0 ng/ml) over the 24-h sampling period

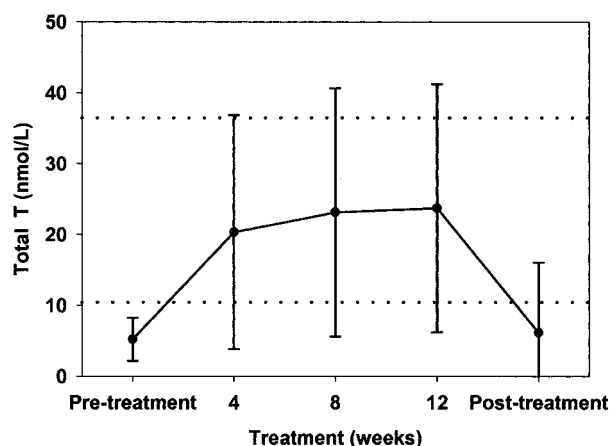


FIG. 1. Predose serum T concentration (mean \pm SD) during administration of TBS twice daily for 12 wk. Baseline (n = 80), wk 4 (n = 82), wk 8 (n = 81), wk 12 (n = 81), and follow-up (n = 64).

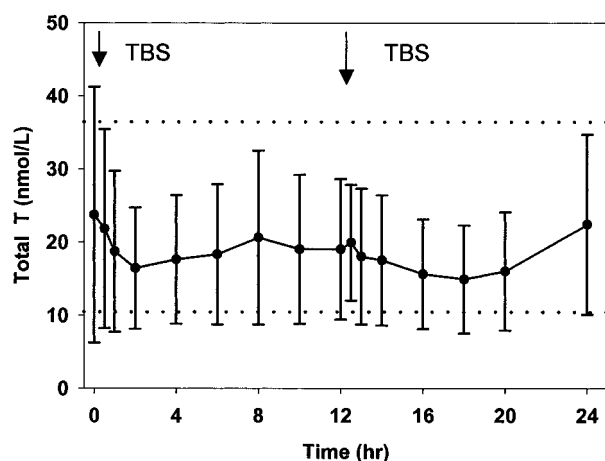


FIG. 2. Serum T concentration by 12-h dosing interval of TBS (0–12 h; 12–24 h) at wk 12 (n = 82).

the 24-h period ranged from 14.9 to 22.6 nmol/liter (4.3–6.5 ng/ml). As shown in Table 4 and Fig. 2, the mean $C_{avg(0-12)}$, $C_{avg(12-24)}$, $C_{avg(0-24)}$, and $C_{max(0-24)}$ concentrations over the 24-h sampling period at wk 12 for all subjects were within the adult male range. The mean degree of fluctuation of concentrations was minimal but variable. The mean T levels over 24 h that were above the lower limit and within the adult male range were 80.1 and 72.6%, respectively. Mean serum T levels were above or below the physiological range for 4.6 and 19.1% of the time, respectively. Two subjects had mean $C_{avg(0-24)}$ just above the upper limit of the normal range, whereas nine were slightly below the lower limit. At wk 12, 11.9, 84.5, and 3.6% of all the samples were below, within, and above the adult male range, respectively. There was good agreement between AUC parameters and between C_{max} parameters of the morning and evening dosing intervals at wk 12 (Table 4). The mean AUC_{12-24}/AUC_{0-12} ratio was 0.97 (CV = 31%) and the mean $C_{max(12-24)}/C_{max(0-12)}$ ratio was 0.96 (CV = 43%), indicating that the extent of systemic exposure of T was similar during the morning and evening dosing intervals.

Seventy-one of 82 subjects [86.6% (95% confidence interval

TABLE 4. Mean serum total T PK parameters in hypogonadal men at wk 12 after application of TBS twice per day (n = 82)

PK parameter	Value
AUC_{0-12} (h·nmol/liter)	224.40 \pm 98.2
AUC_{12-24} (h·nmol/liter)	207.78 \pm 87.6
AUC_{12-24}/AUC_{0-12} (CV)	0.97 (0.31)
$C_{avg(0-12)}$ (nmol/liter)	18.77 \pm 8.1
$C_{avg(12-24)}$ (nmol/liter)	17.32 \pm 7.3
$C_{avg(0-24)}$ (nmol/liter)	18.04 \pm 7.1
$C_{min(0-24)}$ (nmol/liter)	10.10 \pm 4.5
$C_{max(0-12)}$ (nmol/liter)	30.67 \pm 15.5
$C_{max(12-24)}$ (nmol/liter)	26.72 \pm 11.9
$C_{max(0-24)}$ (nmol/liter)	33.62 \pm 15.3
$C_{max(12-24)}/C_{max(0-24)}$ (CV)	0.96 (0.43)
% Fluctuation ($_{(0-24)}$ (CV)	134 (51.7)
$T_{min(0-24)}$ (h)	10.3 \pm 8.0
$T_{max(0-24)}$ (h)	10.5 \pm 9.3
% T_{24} (dur)	75.5 \pm 27.7
% T_{24} (above)	80.1 \pm 27.8
% P_{24} (dur)	72.6 \pm 25.9

77.3–93.1%)] had a time-averaged steady-state T concentration over the two consecutive 12-h dosing intervals [$C_{avg(0-24)}$] within the normal adult male range. Mean $C_{avg(0-24)}$ for these 71 patients was 18.7 \pm 9.3 nmol/liter (5.4 \pm 1.7 ng/ml), with $C_{max(0-24)}$ of 34.4 \pm 12.7 nmol/liter (9.9 \pm 3.6 ng/ml) and $C_{min(0-24)}$ of 10.4 \pm 4.3 nmol/liter (3.0 \pm 1.2 ng/ml). The remaining 11 subjects had a mean $C_{avg(0-24)}$ of 14.2 \pm 12.5 nmol/liter (4.1 \pm 3.6 ng/ml) with $C_{max(0-24)}$ of 28.8 \pm 27.4 nmol/liter (8.3 \pm 7.9 ng/ml) and $C_{min(0-24)}$ of 8.0 \pm 5.2 nmol/liter (2.3 \pm 1.5 ng/ml).

Free T

At baseline, the mean free T concentration of 126 \pm 98 pmol/liter (36.2 \pm 28.2 pg/ml) was below the lower adult male reference range. After the start of therapy, predose mean free T concentrations increased to within the expected range by the first predose blood collection at wk 4 and remained constant between 590 and 684 pmol/liter (170–197 pg/ml) for a further 8 wk until the study drug was discontinued at wk 12. At follow-up, the mean concentration was 135.0 \pm 185.0 pmol/liter (38.9 \pm 53.3 pg/ml) approximating the baseline mean (Fig. 3A).

All mean serum free T concentrations were within the adult male reference range over the two consecutive 12-h dosing intervals at wk 12 (Fig. 3B). The mean free T concentration averaged over the four time points at wk 12 was 569 \pm 409 pmol/liter (164 \pm 118 pg/ml). There was little fluctuation in levels over the 12 wk of T therapy or during the 24-h sampling period at wk 12 (Fig. 3B). At wk 12, 8.3, 81.0, and 10.7% of the samples had serum free T levels below, within, and above the male reference range.

The mean percentage of free T averaged over the treatment period for each subject was 2.8 \pm 0.7%. At the wk 12 predose sampling, the mean percentage of free T was 2.9 \pm 0.7%. The percentage of free T was also stable over the duration of the study (baseline: 2.4 \pm 0.6%; wk 4: 2.9 \pm 0.7%; wk 8: 2.9 \pm 0.7%), indicating that free T and T levels increased proportionally during treatment with TBS.

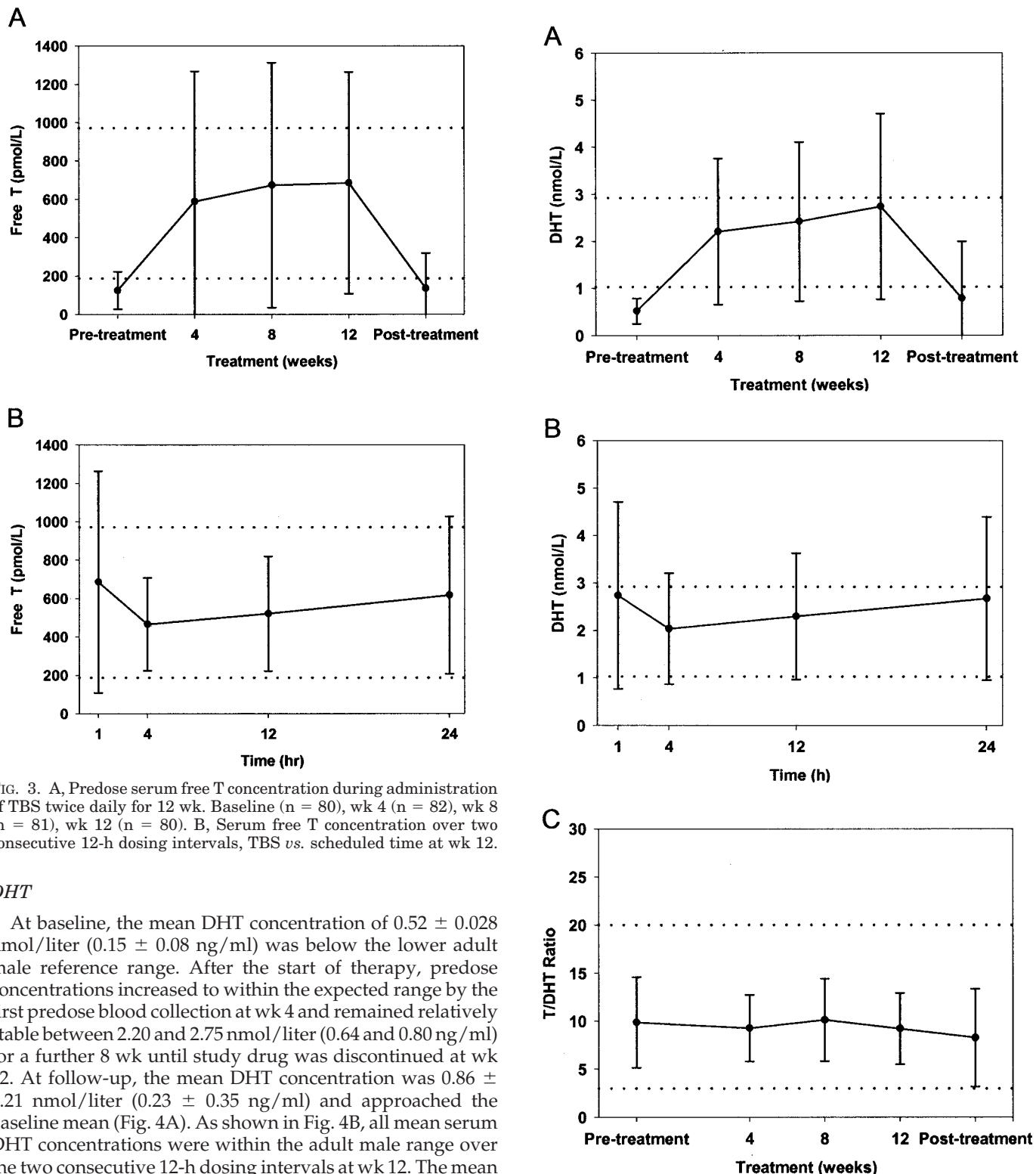


FIG. 3. A, Predose serum free T concentration during administration of TBS twice daily for 12 wk. Baseline ($n = 80$), wk 4 ($n = 82$), wk 8 ($n = 81$), wk 12 ($n = 80$). B, Serum free T concentration over two consecutive 12-h dosing intervals, TBS vs. scheduled time at wk 12.

DHT

At baseline, the mean DHT concentration of 0.52 ± 0.028 nmol/liter (0.15 ± 0.08 ng/ml) was below the lower adult male reference range. After the start of therapy, predose concentrations increased to within the expected range by the first predose blood collection at wk 4 and remained relatively stable between 2.20 and 2.75 nmol/liter (0.64 and 0.80 ng/ml) for a further 8 wk until study drug was discontinued at wk 12. At follow-up, the mean DHT concentration was 0.86 ± 1.21 nmol/liter (0.23 ± 0.35 ng/ml) and approached the baseline mean (Fig. 4A). As shown in Fig. 4B, all mean serum DHT concentrations were within the adult male range over the two consecutive 12-h dosing intervals at wk 12. The mean DHT concentration averaged over the four time points at wk 12 was 2.44 ± 1.62 nmol/liter (0.71 ± 0.47 ng/ml). There was little fluctuation in levels over the 12 wk of study drug therapy or during the 24-h sampling period at wk 12. At wk 12, 15.5, 56.0, and 28.5% of the samples had serum DHT levels below, within, and above the adult male range, respectively. The T/DHT AUC_{last} ratio (9.35) and the mean concentration

FIG. 4. A, Predose serum DHT concentration during administration of TBS twice daily for 12 wk; baseline ($n = 80$), wk 4 ($n = 82$), wk 8 ($n = 81$), wk 12 ($n = 80$), and follow-up ($n = 63$). B, Serum DHT concentration over two consecutive 12-h dosing intervals, TBS vs. scheduled time at wk 12. C, Serum T/DHT ratio during administration of TBS twice daily for 12 wk. Baseline ($n = 80$), wk 4 ($n = 82$), wk 8 ($n = 81$), wk 12 ($n = 80$), and follow-up ($n = 63$).

ratio of T/DHT (9.29) were similar and close to the expected value of about 10 (1). The concentration ratio was relatively constant over the duration of the study from baseline to wk 12, as shown in Fig. 4C. The small change (<11%) in the ratio from baseline to wk 12 indicates that DHT concentrations increased in parallel with T concentrations during treatment with TBS.

E_2

The E_2 response to T administration showed an increase from baseline values of 62.4 ± 28.3 pmol/liter (17.0 ± 7.7 pg/ml) to 105 ± 57.3 pmol/liter (28.7 ± 15.6 pg/ml) at wk 4, 118 ± 71.9 pmol/liter (32.1 ± 19.6 pg/ml) at wk 8, and 132 ± 85.5 pmol/liter (36.0 ± 23.3 pg/ml) at wk 12 (Fig. 5). At wk 12, 61.8% all samples were within and 38.2% of the samples were above the adult male reference range. The increase in circulating E_2 concentrations during the study reflects the peripheral aromatization of the serum T provided by the buccal T application. All samples were obtained just before the change of TBS on each visit day. Mean E_2 levels at the follow-up visit were 55.1 ± 34.9 pmol/liter (15.0 ± 9.5 pg/ml), returning to the baseline mean.

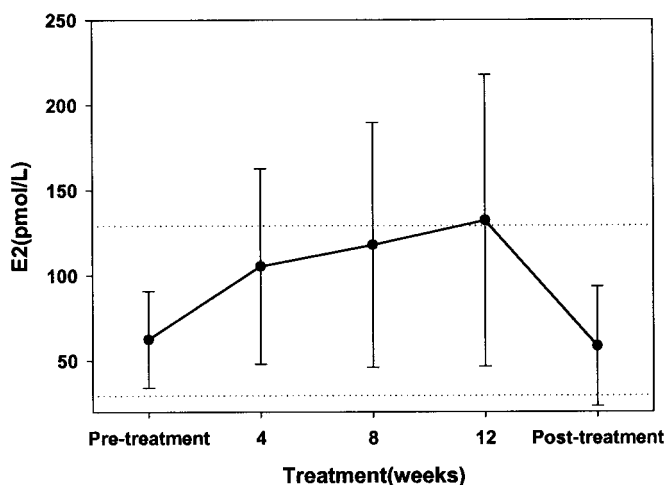
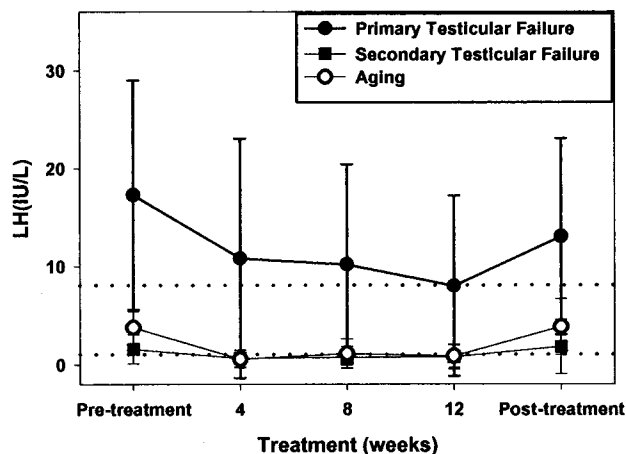


FIG. 5. Predose serum E_2 concentration during administration of TBS twice daily for 12 wk.



Serum LH and FSH levels

FSH and LH decreased in the hypogonadal subjects during the treatment period, which represents the normal physiological response to raising the T concentration (Fig. 6; because of the scales of the y-axis, the suppression of FSH/LH is not as apparent in the secondary and age-related hypogonadism groups, compared with the primary hypogonadal group). There was a steady decrease in FSH levels over time reaching a nadir of 50, 59, and 27% of baseline values by wk 12 in subjects with primary, secondary, and age-related hypogonadism, respectively. LH levels responded in a similar manner reaching 46, 40, and 21% of baseline values by wk 12 in subjects with primary, secondary, and age-related hypogonadism, respectively. FSH and LH returned to 89 and 85% of baseline levels, respectively, at the follow-up visit.

SHBG

SHBG concentrations varied slightly over the course of the study. At baseline SHBG was 41.2 ± 24.71 nmol/liter and at 14 d after treatment, 39.8 ± 21.7 nmol/liter. During treatment SHBG at wk 4 was 37.3 ± 20.8 nmol/liter, wk 8, 35.6 ± 21.2 nmol/liter, and wk 12, 38.5 ± 22.3 nmol/liter; these changes were not statistically significant.

Factors that may affect PK of TBS

A less than 6% relative difference was seen between average serum T values over the morning and evening dosing intervals. There were no statistical differences between T PK parameters during the 1- and 2-h time periods before (no food/beverages were taken) and after each meal in the morning dosing interval. There was no statistical difference in the PK profiles of the subject groups defined according to whether the subject had received concomitant medications that could cause dry mouth. Differences in mean T C_{avg} (0–24) and mean T/DHT AUC_{last} ratio were less than 6% between these subject groups. There were no statistical differences in the PK profiles of the subject groups defined according to whether the subject had any gum abnormalities at wk 12. Differences in mean T C_{avg} (0–24) values and mean T/DHT

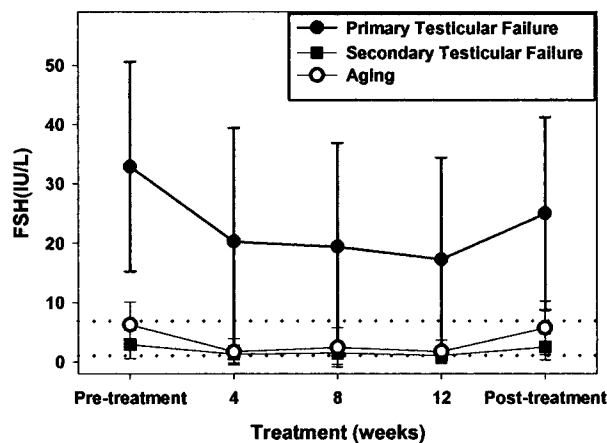


FIG. 6. Predose serum LH and FSH concentrations during administration of TBS twice daily for 12 wk in subjects with primary or secondary hypogonadism or age-related androgen deficiency.

AUC_{last} ratio between these subject groups were less than 12%.

Effects of age and BMI

Qualitative differences were observed in the PK profiles of two subject groups defined according to whether the subject was 65 yr of age or older at baseline. In the group of subjects 65 yr of age or older ($n = 20$), the serum T $C_{avg(0-24)}$ was 19.7 ± 8.4 nmol/liter (5.7 ± 2.5 ng/ml), which was 12.7% higher than in subjects younger than 65 yr ($n = 62$; 17.5 ± 6.6 nmol/liter; 5.0 ± 1.9 ng/ml), but this did not achieve statistical significance ($P > 0.05$). The total T/DHT AUC_{last} ratio was lower by 15.6% in subjects 65 yr or older (8.2 ± 2.2), compared with values observed in subjects younger than 65 yr of age (9.2 ± 3.3 , $P > 0.05$). There was a negative but not significant correlation between BMI and $C_{avg(0-24)}$ values ($r = -0.166$).

Clinical observations

All 98 subjects were included in the safety assessment. Two subjects dropped out of the study due to severe gum irritation and another because of mild mouth irritation (3.1%). A total of 19 gum-related adverse events (including edema, gingivitis, inflammation, and blister) were reported in 16 subjects (16.3%) during the study. The onset of most gum-related adverse effects occurred during the first month of treatment. With the exception of two events, all were of mild (12) or moderate (5) intensity and resolved in 11 d or less. In addition to gum abnormalities reported as adverse events, abnormal gum examination were also noted. These gum abnormalities (edema or gingivitis) occurred more commonly at baseline and follow-up visits when the subjects were not taking drug than during the treatment period. There were no treatment-related serious adverse events. Except for the gum irritation and bitter taste (reported by three subjects), all other treatment-related adverse events occurred in two or fewer subjects. Other than gum-related adverse events, the most common events reported by two or more subjects were headache ($n = 4$) and fatigue ($n = 3$).

Hematology parameters remained stable throughout the study. Mean baseline hemoglobin was 14.5 g/dl and hematocrit was 43%. Over the 12-wk TBS treatment period, mean hemoglobin ranged from 14.2 to 14.4 g/dl and hematocrit ranged from 0.43 to 0.44 (43–44%). Other mean hematological parameters also remained normal throughout the study. Two subjects had hematocrit/hemoglobin levels that increased to the polycythemia range with hematocrit values of 55 and 60% at wk 12 that were attributed to treatment with TBS. The subjects were discontinued from TBS per protocol, and no other intervention was considered necessary. At the follow-up visit, hemoglobin and/or hematocrit values had returned to normal in one or had decreased in the other.

Mean clinical chemistry parameters remained within reference intervals of the laboratory throughout the study, although the only fasting observations were made at baseline, making inferences about the data difficult. There were no clinically significant changes in vital signs, electrocardiogram, or physical examination including gynecomastia or

prostate enlargement as determined by digital rectal examination.

Treatment compliance and problems

Treatment compliance was assessed by TBS counting. Fifty subjects had 100–120% compliance, 16 had 90–100%, and six had 80–90%. Compliance could be calculated to be greater than 100% because the extra TBSs that were used in case of nonadhesiveness were counted in compliance calculations. Nonadhesiveness was closely monitored throughout the study and was low overall and improved over time. This is evidenced by a recorded swallowed TBS rate of 0.49% (78 of 15,890 tablets) and a recorded rate of dislodged or nonadhering TBS of 2.3% (362 of 15,890). The number of replaced TBSs in all subjects decreased from 160 at wk 1 to 73 at wk 3 and 33 at wk 12, demonstrating better subject familiarity with TBS application over time. Even when assuming that all tablet replacement was due to adhesion problems, the incidence over the course of the study remained low at 4.8% (766 of 15,890).

TBS acceptability

Within the first few weeks of the study, 10 of the 98 subjects withdrew from the study because of application problems or intolerance to the TBS. Once the subjects became accustomed to the buccal tablet and the application, the majority of subjects and investigators rated the study drug positively. Overall, 55 of the 82 subjects (67.1%) who completed the study said TBS was acceptable or very acceptable. Forty-five percent of subjects said they preferred TBS, 37% said they preferred their previous treatment, and 18.9% had no preference. Seventy-five percent of investigators rated TBS as acceptable or very acceptable. About 31% of investigators preferred TBS, 29% preferred the previous treatment, and about 40% had no preference.

Discussion

This study demonstrates that the TBS (Striant) is an effective treatment for physiological T replacement in hypogonadal men. There was no dose adjustment in this study, and all subjects applied one TBS twice per day. About 80% of subjects maintained mean serum T concentrations above the lower normal limit for adult men during the 24-h PK assessment at wk 12. A total of 71 subjects (86.6%) had time-averaged steady-state serum total T concentration over the two consecutive 12-h dosing intervals [$C_{avg(0-24)}$] within the adult male range. Of the remaining 11 subjects, the time-averaged steady-state serum T concentrations were above and below the reference range in two and nine subjects, respectively. TBS resulted in steady levels of serum T and eliminated the excessive peak and trough fluctuations seen by T administered after im injection (13, 14). TBS also maintained serum T and DHT levels within the normal range in most patients. TBS has the added benefit of being absorbed directly into the circulation through the buccal mucosa, avoiding first-pass hepatic metabolism.

Serum free T, DHT, and E_2 closely paralleled the rise in serum T. Mean serum free T were consistently maintained in

the midphysiological range, whereas mean serum DHT and E_2 were at the upper limit of the normal range. The percentage of free serum T increased slightly during the treatment period but remained within expected ranges. This may be related to the suppressed SHBG observed after T replacement treatment. Gonadotrophins decreased as expected with increased serum T concentration.

When transdermal T gels are applied to a large area of skin, higher serum DHT/T ratios have been reported, although the increase is considered not to be clinically significant (20, 21). This may be due to the presence of 5- α -reductase in the skin that may result in greater conversion of T to DHT and the larger skin area that is exposed to the gel on administration, compared with other topical formulations, or to TBS (18, 19). No dose titration was performed in the current study, but the one dose provided physiologic replacement in 86.6% of subjects. There were nine (11%) patients whose serum T C_{avg} (0–24) was below the adult lower reference limit. There were no patients with serum T C_{avg} (0–24) above the upper reference limit during the 24-h collection period at wk 12.

Our study also showed that the PK of TBS was not affected by gum abnormalities or medications that can potentially cause dry mouth. The lack of significant influence of BMI on serum T PK may be related to the exclusion of subjects with BMI greater than 35 enrolling in the study. It is possible that the standard dose of 30 mg twice a day may not achieve adequate serum T levels within the adult range in very obese men. It is also likely that one dose may not provide serum T levels within the adult male reference range for all hypogonadal men. Although no cross-over studies were done and the subjects were not controlled for posture or activity, the PK parameters of serum T do not appear to be significantly affected by food or beverages. In subjects 65 yr or older, the mean serum T levels were 12% higher than in subjects younger than 65 yr old, but this did not reach statistical significance; higher T levels in older men may be due to lower metabolic clearance rates of T with aging (25–28).

With appropriate dose titration, transdermal patches can provide physiologic T levels with circadian-like fluctuations, but one patch has a high incidence of site administration irritation, with pruritus in about 37–60% of patients and blistering in 12% (22, 23). By comparison, topical reactions to the TBS were usually mild. At the start of the study 10 of 98 subjects (10.2%) discontinued because of application problems or inability to tolerate the buccal system on their gums. None of these 10 subjects had gum abnormality. Sixteen of the 98 evaluable subjects (16.3%) in the study reported 19 gum-related adverse events that were transient with severity assessed as mild in 12, moderate in five, and severe in two. Generally these adverse events did not cause interruption of treatment and resolved completely within a short period of time. Only two subjects (2.4%) discontinued because of severe gum irritation and one because of mild mouth irritation. The rates of swallowing the TBS (0.49%) and adhesion problems (recorded nonadhesion 2.3%, tablet replacement 4.8%) were small. The adhesion problem decreased substantially when the subjects became familiar with the use of the TBS.

No changes were observed for the overall study population in routine hematology parameters; in particular, there

was no overall change from baseline to wk 12 for hemoglobin and hematocrit. There were two patients (2%) who experienced an elevated hematocrit above 55% and/or hemoglobin levels above 16 g/dl at wk 12 that decreased or became normal at the follow-up visit. A majority of subjects (67.1%) and investigators (75%) stated that the TBS was acceptable or very acceptable. About 80% of the subjects were offered the ability to continue in an extension study to assess safety; 41 subjects (60%) who completed the study chose to continue in a long-term treatment follow-up study. This follow-up study that is continuing will generate some data on long-term acceptability.

In conclusion, administration of T by buccal administration consistently maintained the mean serum T concentration within the physiologic range in most hypogonadal men. Because there is no dose adjustment, the one dose of 30 mg twice per day may provide insufficient or alternatively elevated serum T levels for some hypogonadal men. The application of the TBS caused mild to moderate gum irritation in some men that resulted in discontinuation in only 3% of subjects. The new dosage form was well accepted by the subject population. This novel T delivery system offers a viable alternative to the currently available methods for physiological replacement in hypogonadal men.

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References

- Griffin JE, Wilson JD 2002 Disorders of the male reproductive tract. In: Larson PR, Kronenberg HM, Melmed S, Polonsky KS, eds. William's textbook of endocrinology. 10th ed. Philadelphia: WB Saunders; 709–770
- Bremner WJ, Vitiello MV, Prinz PN 1983 Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab* 56:1278–1281
- Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD 2003 Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. *Clin Endocrinol (Oxf)* 58:710–717
- Nieschlag E, Behre HM 1998 Testosterone: action, deficiency, substitution. 2nd ed. Berlin: Springer
- Wang C, Swerdloff RS 1999 Androgen replacement therapy, risks and benefits. In: Wang C, ed. Male reproductive function. Boston: Kluwer Academic Publishers; 157–172
- Bagatell CJ, Bremner WJ 2003 Androgens in health and disease. Totowa, NJ: Humana Press
- Meikle WA 2003 Androgen replacement therapy for hypogonadal men. In: Meikle WA, ed. Endocrine replacement therapy in clinical practice. Totowa, NJ: Humana Press; 333–368
- Vermeulen A 2001 Androgen replacement therapy in the aging male—a critical evaluation. *J Clin Endocrinol Metab* 86:2380–2390
- van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW 2000 Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab* 85:3276–3282

10. Bhasin S, Bremner WJ 1997 Clinical review 85: emerging issues in androgen replacement therapy. *J Clin Endocrinol Metab* 82:3–8
11. Delorimier AA, Gordan GS, Lowe RC, Carbone JV 1965 Methyltestosterone, related steroids, and liver function. *Arch Intern Med* 116:289–294
12. Nadell J, Kosek J 1977 Peliosis hepatis. Twelve cases associated with oral androgen therapy. *Arch Pathol Lab Med* 101:405–410
13. Snyder PJ, Lawrence DA 1980 Treatment of male hypogonadism with testosterone enanthate. *J Clin Endocrinol Metab* 51:1335–1339
14. Sokol RZ, Palacios A, Campfield LA, Saul C, Swerdloff RS 1982 Comparison of the kinetics of injectable testosterone in eugonadal and hypogonadal men. *Fertil Steril* 37:425–430
15. Findlay JC, Place V, Snyder PJ 1989 Treatment of primary hypogonadism in men by the transdermal administration of testosterone. *J Clin Endocrinol Metab* 68:369–373
16. Cunningham GR, Cordero E, Thornby JI 1989 Testosterone replacement with transdermal therapeutic systems. Physiological serum testosterone and elevated dihydrotestosterone levels. *JAMA* 261:2525–2530
17. Meikle AW, Mazer NA, Moellmer JF, Stringham JD, Tolman KG, Sanders SW, Odell WD 1992 Enhanced transdermal delivery of testosterone across nonscrotal skin produces physiological concentrations of testosterone and its metabolites in hypogonadal men. *J Clin Endocrinol Metab* 74:623–628
18. Meikle AW, Arver S, Dobs AS, Sanders SW, Rajaram L, Mazer NA 1996 Pharmacokinetics and metabolism of a permeation-enhanced testosterone transdermal system in hypogonadal men: influence of application site—a clinical research center study. *J Clin Endocrinol Metab* 81:1832–1840
19. Yu Z, Gupta SK, Hwang SS, Kipnes MS, Mooradian AD, Synder PJ, Atkinson LE 1997 Testosterone pharmacokinetics after application of an investigational transdermal system in hypogonadal men. *J Clin Pharmacol* 37:1139–1145
20. Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Longstreth J, Berman N, and the Testosterone Gel Study Group 2000 Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab* 85:4500–4510
21. Steidle C, Schwartz S, Jacoby K, Seebree T, Smith T, Bachand R 2003 AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab* 88:2673–2681
22. Jordan Jr WP 1997 Allergy and topical irritation associated with transdermal testosterone administration: a comparison of scrotal and nonscrotal transdermal systems. *Am J Contact Dermat* 8:108–113
23. Jordan Jr WP, Atkinson LE, Lai C 1998 Comparison of the skin irritation potential of two testosterone transdermal systems: an investigational system and a marketed product. *Clin Ther* 20:80–87
24. Gooren LJ 1994 A ten-year safety study of the oral androgen testosterone undecanoate. *J Androl* 15:212–215
25. Meikle AW, Smith JA, Stringham JD 1989 Estradiol and testosterone metabolism and production in men with prostatic cancer. *J Steroid Biochem* 33:19–24
26. Baker HW, Burger HG, de Kretser DM, Hudson B, O'Connor S, Wang C, Mirovics A, Court J, Dumlop M, Rennie GC 1976 Changes in the pituitary-testicular system with age. *Clin Endocrinol (Oxf)* 5:349–372
27. Morimoto I, Edmiston A, Hawks D, Horton R 1981 Studies on the origin of androstenediol and androstenediol glucuronide in young and elderly men. *J Clin Endocrinol Metab* 52:772–778
28. Ishimaru T, Pages L, Horton R 1977 Altered metabolism of androgens in elderly men with benign prostatic hyperplasia. *J Clin Endocrinol Metab* 45:695–701

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