Pharmacokinetic Evaluation and Dosing of Subcutaneous Testosterone Pellets

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Abstract

Abstract: Subcutaneous testosterone (T) pellets are a viable treatment modality for hypogonadism. Optimal dosing, frequency of reimplantation, and long-term safety of T pellets remain incompletely elucidated parameters. A retrospective review of 273 patients treated for hypogonadism using subcutaneous T pellets was performed. Serum total T (TT), free T (FT), and estradiol (E2) levels were analyzed as a function of time from implantation, number of pellets implanted (6–9 or 10–12), body mass index (BMI; <25 or ≥25 kg/m^2), number of implantations (≤4 rounds, 501 insertions), and preimplantation T levels (<300 or ≥300 ng/dL). T decay was determined using linear regression and TT levels immediately postimplantation and the time for TT levels to reach 300 ng/dL extrapolated for all variables. Mean patient age ± SD was 56 ± 12.6 years. Baseline TT level was 328 ± 202 ng/dL, FT 9.49 ± 27.8 pg/mL, and E2 25.1 ± 17.3 pg/mL. Extrapolated TT and FT peaks were lower in men receiving 6 to 9 pellets than men receiving 10 to 12, although decay rates differed insignificantly. E2 levels rose significantly in men receiving 10 to 12 but not 6 to 9 pellets. Men with BMI ≥25 kg/m^2 attained lower TT peaks with slower decay than men with BMI <25 kg/m^2 receiving 10 to 12 pellets, although 300 ng/dL TT levels were reached at approximately 100 days in both groups. No differences were seen in decay rates for men with multiple implant rounds, and no differences in T peaks or decay rates were seen in men with preimplant T level <300 or ≥300 ng/dL. One patient developed erythrocytosis, and no prostate-specific antigen recurrences were observed in men with prostate cancer treated with T pellets. Men with BMI <25 kg/m^2 should receive fewer pellets, and reimplantation for all men should occur 100 to 120 days after prior implantation. Men receiving 10 to 12 pellets have higher E2 levels, potentially reflecting increased aromatization of T. Reimplantation and preimplantation TT levels do not affect pellet decay kinetics.

Late-onset hypogonadism (LOH) is characterized by low serum testosterone (T) levels and symptoms of androgen deficiency, including low libido, decreased muscle mass and bone density, impaired cognition, impaired sexual function, and depression (**Wang et al, 2009**). Although the true prevalence of LOH remains unknown because of variable biochemical and clinical criteria used for diagnosis, under the conditions of total T (TT) level <300 ng/dL and symptomatic hypogonadism, LOH is present in 3.1% to 7.0% of men aged <70 years and in ≤18.4% of men older than 70 (**Araujo et al, 2007**). Androgen replacement in the form of T replacement therapy (TRT) can help mitigate the negative sequelae of this condition.

There are numerous T delivery systems available for treating hypogonadism, including topical gels and patches for transdermal delivery, intramuscular injections, and subcutaneous pellets. Each T delivery modality has a distinct pharmacokinetic profile that impacts dosage and frequency of administration, and all formulations can have side effects, which include erythrocytosis, alterations in lipid profiles, gynecomastia, obstructive sleep apnea, testicular atrophy, and infertility. Intramuscular T injections and transdermal T, the 2 most commonly used formulations, differ significantly in rates of T delivery and decay. Injections have the most variable pharmacokinetics of the various forms of TRT, with peak serum T levels occurring 2 to 5 days after injection and return to baseline after 10 to 14 days, requiring redosingevery 2 to 3 weeks (**Bhasin et al, 1998**; **Rhoden and Morgentaler, 2004**). Long-lasting forms of injectable T such as T undecanoate are also available and are effective for ≤12 weeks between injections with maintenance of serum T levels in the normal range (**Yassin et al, 2006**). Transdermal T formulations also maintain more constant serum levels after an initial accumulation period of 48 to 72 hours but require daily administration to maintain physiologic serum T levels (**Swerdloff et al, 2000**).

Subcutaneous T pellet implants have been available in the United States since 1972 and offer several advantages over other T formulations, including 100% patient compliance, avoidance of the peaks and troughs found with injectable treatments, lower risk of drug transfer from patient to others, and maintenance of a stably elevated serum T level. Although T pellets are used to treat androgen deficiency, limited data exist regarding their pharmacokinetics and side effect profiles (**Cavender and Fairall, 2009**). Furthermore, the incidence of erythrocytosis and effects on lipid profiles are relatively unknown for T pellets.

Determining optimal dosing of T pellets can be challenging because individual rates of T metabolism must be considered, and these likely reflect patient weight and body mass index (BMI), as well as volume of distribution and sex hormone—binding globulin (SHBG) concentration. Thus, further evaluation of the pharmacokinetics of T pellets is merited to determine optimal dosing and to establish side effect profiles. In this study, we evaluated the pharmacokinetics of T pellets in a cohort of men with hypogonadism, permitting an objective evaluation of serum T metabolism and leading to dosing parameters for these pellets. We also assessed symptomatic benefits of T pellets and adverse events, including erythrocytosis and impact on prostate-specific antigen (PSA) levels.

Materials and Methods

Patient Selection and Pellet Implantation

A retrospective chart review, approved by the institutional review board of Baylor College of Medicine, was performed for 273 men with hypogonadism treated with subcutaneous T pellets (Testopel; Slate Pharmaceuticals, Durham, North Carolina), with follow up between 2008 and 2011. Of note, 65 men with prostate cancer (CaP) were included in this cohort, allowing the opportunity to evaluate the effects of T pellets in this setting. Clinical symptoms of hypogonadism included changes in energy, libido, erectile function, sleep, and strength and were evaluated before pellet implantation using direct questioning of patients. Serum free T (FT), TT, estradiol (E2), hemoglobin (Hgb), hematocrit (Hct), SHBG, and PSA levels were assessed before pellet implantation and within 1 to 3 months of implantation. Subsequent follow-up visits and hormonal evaluations occurred every 3 to 6 months thereafter, or sooner if patients experienced a return of hypogonadal symptoms. Additional pellet implantations occurred either with a return of hypogonadal symptoms or with a drop in serum TT to <300 ng/dL. Each patient analyzed had at least one T data point—a postimplantation T level—and all but 3 patients had preimplantation T levels. The number of additional T data points per patient were dependent on the number of follow-up appointments and reimplantations for each patient. Patient characteristics are summarized in Tables **1** and **2**. Patients were implanted with T pellets for hypogonadism based on symptoms, serum T levels, and efficacy of prior TRT, if applicable. Pellets were implanted according to published methods (**Cavender and Fairall, 2009**).

Table 1. *Patient demographics*[a]

Characteristic	Patient Group (n = 273)
Age, y	56 ± 12.6
Baseline TT, ng/dL	328 ± 201.6
Baseline FT, pg/mL	9.49 ± 27.8
Baseline E2, pg/mL	25.1 ± 17.3
BMI, kg/m^2 (n = 164)	30.3 ± 5.2

Characteristic	Patient Group (n = 273)
BMI category (n = 164)	
<25 kg/m^2 (18.5–24.9)	24 (14.6)
≥25.0 kg/m^2	140 (86.4)
Race	
White	209 (76.5)
Hispanic	10 (3.7)
African American	20 (7.3)
Other	7 (2.6)
Unknown	27 (9.9)
History of prior TRT	182 (66.7)
History of prostate cancer	68 (24.9)
Gleason grade (n = 32)	
3 + 3	14 (43.8)
3 + 4	15 (46.9)
4+3	2 (6.2)
4+4	1 (3.1)
Comorbidities	
Diabetes mellitus	36 (13.2)
Hypertension	87 (31.9)
Hyperlipidemia	50 (18.3)
Coronary artery disease	20 (7.3)

Characteristic	Patient Group (n = 273)
Depression	19 (7.0)
Smoking (previous or current)	62 (22.7)
Alcohol use	132 (48.4)
Erectile dysfunction	200 (73.3)

- Abbreviations: BMI, body mass index; E2, estradiol; FT, free testosterone; TRT, testosterone replacement therapy; TT, total testosterone.
- a Data are expressed as n (%) or $\bar{x} \pm$ SD.

Table 2. Summary of serum hormone data[a]

Table 2. *Summary of serum hormone data*[a]

	First Baseline	n	After First Implantation	Days After First Implantation	n	P^b	Second Baseline
6–9 Pellets							
TT, ng/dL	297.0 ± 143.9	14	473.0 ± 232.0	46.0 ± 26.0	12	.09713	. . .
FT, pg/mL	7.3 ± 4.9	9	9.6 ± 2.6	47.5 ± 27.9	10	.30987	. . .
E2, pg/mL	11.0 ± 9.0	10	19.0 ± 18.4	47.0 ± 25.0	13	.26755	. . .
Hgb, g/dL	14.9 ± 2.2	15	15.2 ± 1.3	59.1 ± 37.6	12	.87352	. . .
Hct, %	43.9 ± 5.0	15	46.4 ± 3.5	59.1 ± 37.6	12	.02443	. . .
10–12 Pellets							
TT, ng/dL	329.7 ± 203.6	253	659.0 ± 212.2	38.1 ± 24.2	216	<.0001	376.4 ± 250.7
FT, pg/mL	7.8 ± 5.5	236	16.4 ± 6.0	38.4 ± 24.2	213	<.0001	8.7 ± 6.9
E2, pg/mL	26.0 ± 17.4	236	37.4 ± 24.3	46.3 ± 34.5	222	<.0001	25.6 ± 14.3
Hgb, g/dL	14.9 ± 1.1	146	15.4 ± 1.4	43.8 ± 29.6	153	<.0001	15.2 ± 1.1
Hct, %	44.1 ± 3.0	147	46.0 ± 3.7	43.8 ± 29.6	152	<.0001	45.1 ± 3.1

	Third Baseline	n	After Third Implantation	Days After Third Implantation	Days After First Implantation	n	P^b	F Ba
10–12 Pellets								
TT, ng/dL	344.0 ± 189.6	55	407.2 ± 190.8	99.1 ± 29.1	392.7 ± 85.1	40	.00042	334.6
FT, pg/mL	8.0 ± 5.8	55	9.0 ± 4.9	99.6 ± 29.9	396.1 ± 84.9	40	.00214	8.6
E2, pg/mL	26.5 ± 17.4	51	28.2 ± 17.5	99.4 ± 29.5	394.9 ± 85.7	40	.324	24.8
Hgb, g/dL	15.5 ± 1.1	42	15.7 ± 1.2	103.9 ± 26.4	400.1 ± 88.6	37	.11561	15.6
Hct, %	45.9 ± 3.2	42	46.3 ± 3.6	103.9 ± 26.4	400.1 ± 88.6	37	.05464	46.2

Abbreviations: E2, estradiol; FT, free testosterone; Hct, hematocrit; Hgb, hemoglobin; TT, total testoste

[a] Data are expressed as $\bar{x} \pm$ SD, unless otherwise indicated.

[b] *P* values evaluate significance between preimplantation and postimplantation hormone levels for each

Data Analysis

The primary outcome of this study was the effect of T pellets on serum T levels as a function of the number of pellets implanted. Secondary outcomes included evaluation of serum T levels as a function of BMI, preimplantation T levels, and sequential order of implantations. The effects of T pellets on E2, Hgb, Hct, SHBG, and PSA levels, particularly in a cohort of men who had been treated for CaP, were also evaluated. Serum hormone levels were analyzed as a function of time from implantation, the number of pellets implanted, BMI, and preimplantation T levels. Patients were grouped into categories based on BMI (<25 and ≥25 kg/m^2) and number of pellets implanted (6–9 or 10–12) for analysis. Data were analyzed using Microsoft Office Excel (Microsoft, Redmond, Washington) and SPSS (IBM Corp, Somers, New York). A formula for T decay based on a linear regression of the log of postimplantation TT levels for all patients in a given category and time from implantation was determined and used to extrapolate serum TT

levels at day 0 postimplantation and the time for TT levels to reach 300 ng/dL. With this formula, decay curves were initially calculated for all TT and FT data points, and subsequently for BMI and pellet categories, and were plotted as a function of time after pellet implantation. Hgb, Hct, and PSA values were assessed before and after implantation. PSA velocities were calculated using ≥3PSA values per patient over ≥12 months. Comparisons between groups were performed using analysis of variance, with $P \leq .05$ considered statistically significant.

Results

Mean patient age ± SD was 56 ± 12.6 years (**Table 1**). Men were grouped by BMI into <25 and ≥25 kg/m^2 categories, with a mean BMI of 30.3 ± 5.7 kg/m^2, independent of group, and the distribution of BMI in the 164 patients with BMI measurements of 14.6% and 85.4% for BMI <25 and ≥25 kg/m^2, respectively. Patients were also grouped into 6 to 9 and 10 to 12 pellet categories based on the number of pellets implanted. The preimplantation mean TT level for all patients was 328 ± 202 ng/dL, FT was 9.49 ± 27.8 pg/mL, and E2 was 25.1 ± 17.3 pg/mL. A total of 833 serum TT measurements were assessed. Postimplantation TT, FT, and E2 levels were assessed during follow-up visits, from 1 to 393 days after pellet implantation and ≤969 days after initial implantation (**Table 2**). The natural logarithms of postimplantation serum TT, FT, and E2 levels were then plotted as a function of time and linear regression analysis performed. The resulting curve fit equations (**Table 3**) were used to extrapolate serum TT, FT, and E2 levels as a function of time, starting on postimplantation day 0, to estimate the rate of decay of TT, FT, and E2. Initially, we assessed hormonal decay as a function of time for all data points to provide the largest data aggregate. Subsequently, we performed subgroup analysis based on BMI, the number of pellets implanted, and preimplantation TT levels.

Table 3. *Curve fitting and decay data*

Pellet Group	Fit Equation[a]	*R*[b]	No. of Values[c]	Extrapolated Peak TT, ng/dL[d]	Days to 300 ng/dL[e]	Average TT Decay Rate, ng/dL/d[f]
Total testosterone						
All data	ln post-TT = 6.6982 — (0.0075 × days after implantation)	.45	228	811	90	5.68
6–9 Pellets	ln post-TT = 6.4206 — (0.0077 × days after implantation)	.45	12	614	135	2.33
10–12 Pellets	ln post-TT = 6.6991 — (0.0072 × days after implantation)	.45	216	812	130	3.94
BMI Group						
BMI <25 kg/m^2	ln post-TT = 7.2266 — (0.0159 × days after implantation)	.29	21	1376	100	10.76

BMI ≥25 kg/m^2	ln post-TT = 6.8073 — (0.0112 × days after implantation)	.49	122	904	100	6.04
Preimplantation TT						
<300 ng/dL	ln post-TT = 6.6588 — (0.0077 × days after implantation)	.46	136	779	120	3.99
≥300 ng/dL	ln post-TT = 6.7510 — (0.0072 × days after implantation)	.45	92	855	145	3.83
Serial implantations						
First implantation	ln post-TT = 6.6922 — (0.0074 × days after implantation)	.45	228	807	130	3.90
Second implantation	ln post-TT = 6.3741 — (0.0041 × days after implantation)	.43	90	586	155	1.85
Third implantation	ln post-TT = 6.8481 — (0.0095 × days after implantation)	.61	40	942	120	3.94
Fourth implantation	ln post-TT = 6.8468 — (0.0088 × days after implantation)	.70	19	941	130	3.94

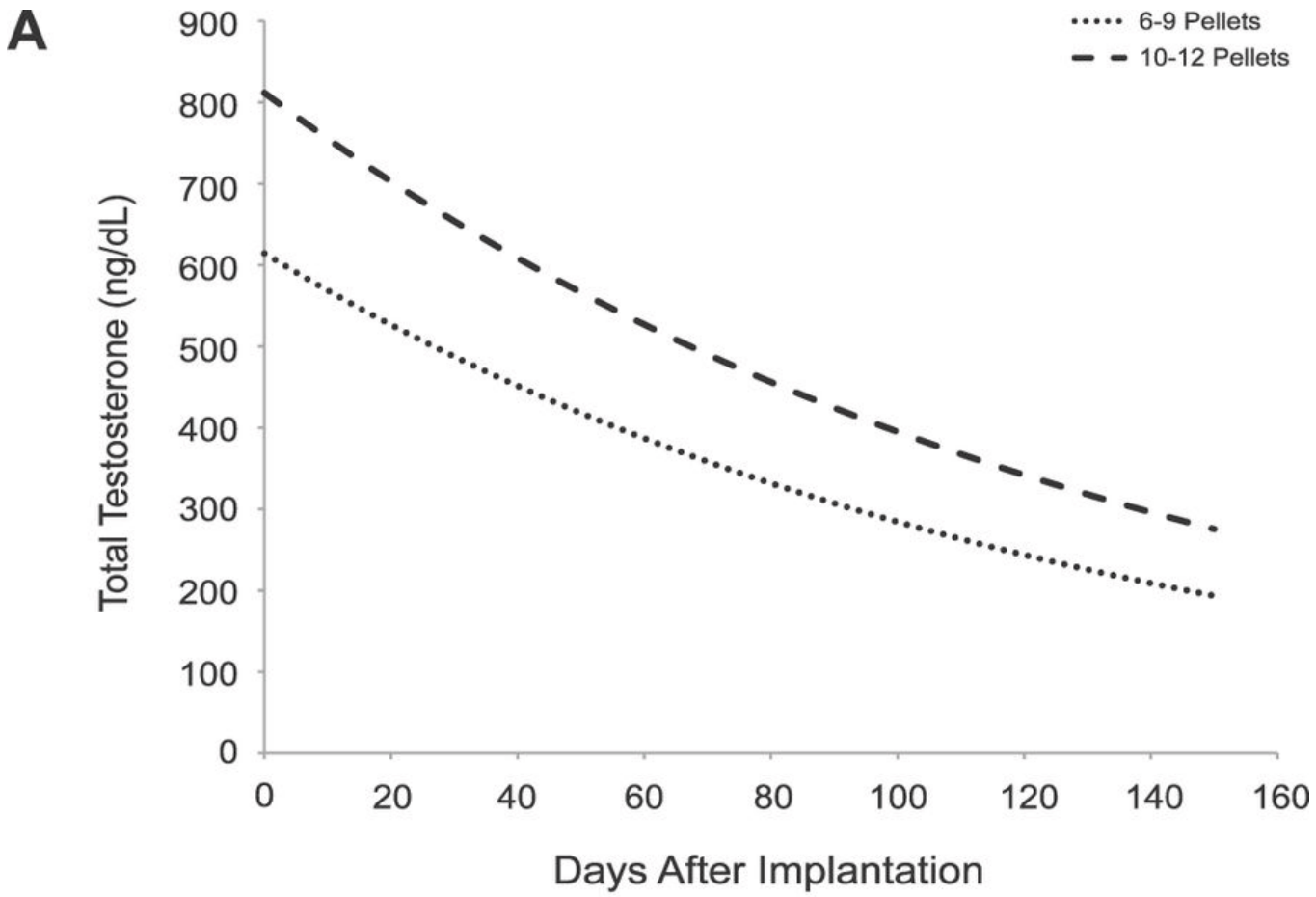
Group	Fit Equation[a]	*R*[b]	No. of Values[c]	Peak FT, pg/mL[d]
FT				
All data	ln post-FT = 3.0286 — (0.0086 × days after implantation)	.48	223	20.7
6–9 Pellets	ln post-FT = 2.4093 — (0.0038 × days after implantation)	.39	10	11.1
10–12 Pellets	ln post-FT = 3.0467 — (0.0086 × days after implantation)	.48	213	21.1

Group		Fit Equation[a]	R[b]	No. of Values[c]	Peak E2, pg/mL[d]
E2					
	All data	ln post-E2 = 3.4654 — (0.0029 × days after implantation)	.12	229	32.0
	6–9 Pellets	ln post-E2 = 4.1214 — (0.0260 × days after implantation)	.37	16	61.7
	10–12 Pellets	ln post-E2 = 3.3648 — (0.0002 × days after implantation)	.03	213	28.9

- Abbreviations: BMI, body mass index; E2, estradiol; FT, free testosterone; TT, total testosterone.
- a Fit equation represents the formula for testosterone decay derived as described in "Materials and Methods."
- b *R* represents the correlation coefficient for each curve fit equation.
- c No. of values represents the number of values analyzed per group.
- d Peak TT, FT, and E2 represent the peak TT, FT, and E2 values extrapolated on day 1 postimplantation using the fit equations.
- e Time to 300 ng/dL represents the number of days required for TT to decay to 300 ng/dL.
- f Average rate of TT decay represents the calculated average rate of decay of TT.

Implantation of T pellets results in an increase in serum TT levels followed by exponential decay, consistent with previously observed zero-order kinetics for T decay with subcutaneous pellets (**Figure 1A**). Extrapolated TT peaks in men receiving 6 to 9 pellets (614 ng/dL) were significantly lower than those from men receiving 10 to 12 pellets (811 ng/dL; P = .0006) for all implanted patients (**Table 3**); decay was also slower for the 6 to 9 pellets group. The correlation coefficient for ln TT vs time from implantation was 0.45 for both groups. Similarly, significantly higher extrapolated FT peaks were observed in men receiving 10 to 12 pellets, in contrast to men receiving 6 to 9 pellets (P = .0002) (**Table 2**; **Figure 1B**). Of note, by virtue of the analysis used, our extrapolated peak TT levels were modeled to occur on day 0 postimplantation. In reality, peak TT levels after T pellet implantation likely occur several days to weeks after pellet implantation (**Handelsman et al, 1990**; **Jockenhovel et al, 1996**; **Kaminetsky et al, 2011**). Given the variable timing of follow-up for our patients, we examined the mean differences in T levels after pellet implantation in all patients as a function of time. We found that the mean increase in TT levels, when compared with preimplantation TT levels, trended toward a smaller change during the first week after implantation (mean difference ± SD, 244.2 ± 205.6 ng/dL) than during the 2 to 4 weeks after implantation (409.6 ± 250.8 ng/dL; P = .184) and was significantly larger during the 2 to 4 weeks after implantation than 5 to 8 weeks after implantation (328.2 ± 282.7 ng/dL; P = .027). These data suggested that peak TT levels occurred 2 to 4 weeks after pellet implantation. In contrast to TT peaks, E2 peaks were extrapolated to be higher in men receiving 6 to 9 pellets, although this increase was not statistically significant (P = .537). Curve fits were suboptimal for men receiving 10 to 12 pellets (R = .03) in contrast to those receiving 6 to 9 pellets (R = .37), and a statistically significant increase in E2 levels was only observed for men receiving 10 to 12 pellets (P < .0001) (**Table 3**; data not shown). The approximate time for serum TT levels to decay to 300 ng/dL, the lower end of the normal range of serum TT, was 135 days for men receiving 6 to 9 pellets and 130 days for men receiving 10 to 12 pellets (**Table 3**). Four months after

implantation, extrapolated serum TT and FT levels were both significantly lower than those at 1 month after implantation ($P < .0001$).


A
6-9 Pellets
10-12 Pellets
Total Testosterone (ng/dL)
900
800
700
600
500
400
300
200
100
0
0
20
40
60
80
100
120
140
160
Days After Implantation

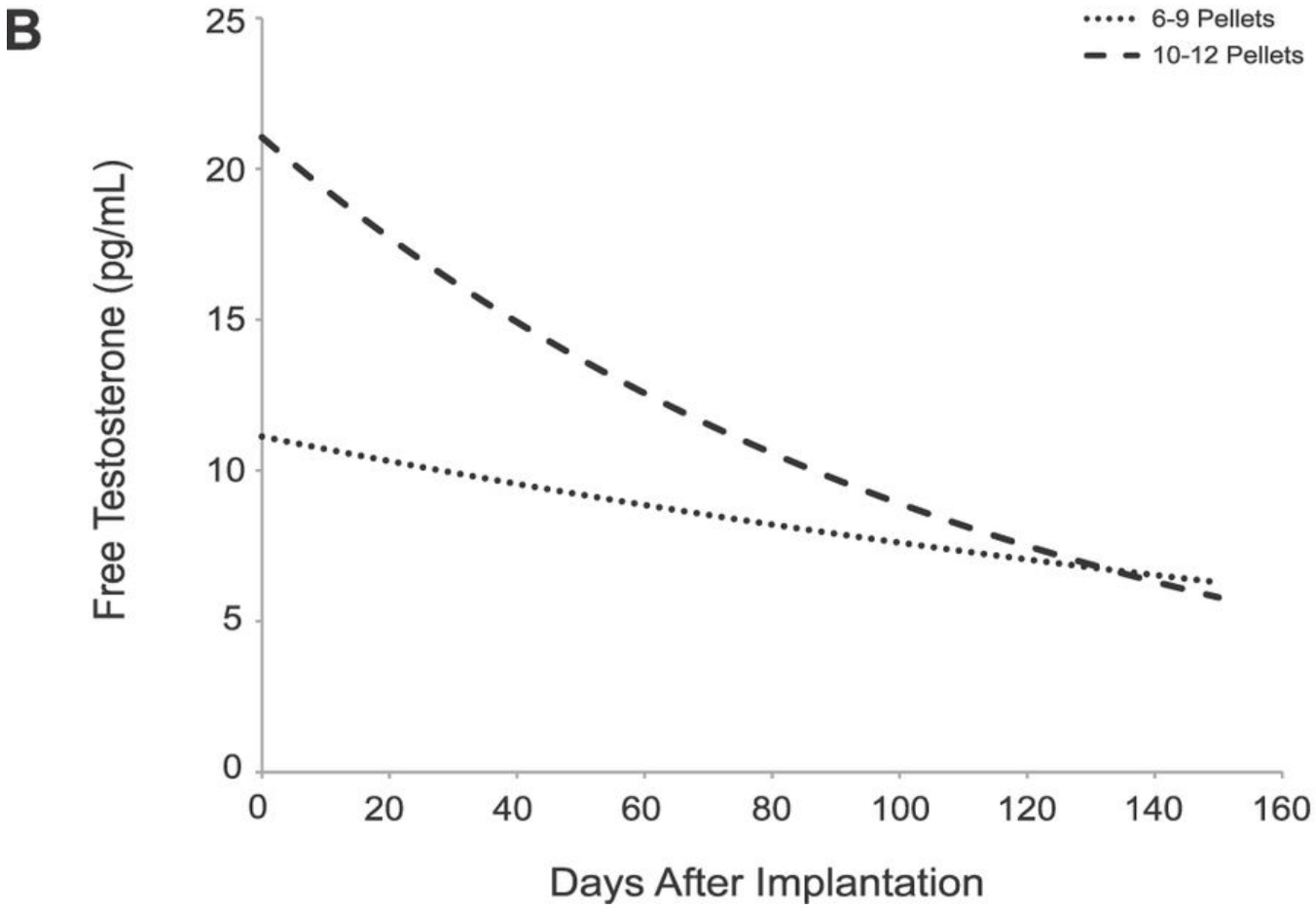

B
6-9 Pellets
10-12 Pellets
Free Testosterone (pg/mL)
25
20
15
10
5
0
0
20
40
60
80
100
120
140
160
Days After Implantation

Figure 1

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Total testosterone decay curves. **(A)** Plot of extrapolated total testosterone vs days after implantation for all patients and patients receiving 6 to 9 and 10 to 12 pellets using the curve fit equations in **Table 2**. **(B)** Plot of extrapolated free testosterone vs days after implantation for all patients and patients receiving 6 to 9 and 10 to 12 pellets.

Serum hormone levels as a function of preimplantation serum TT levels were assessed, and men receiving 10 to 12 pellets were separated into preimplantation TT levels <300 ng/dL and ≥300 ng/dL. No significant differences were observed between extrapolated TT peaks between groups (780 ng/dL for preimplantation TT <300 ng/dL and 855 ng/dL for preimplantation TT ≥300 ng/dL; $P = .155$) or between TT decay rates (**Table 3**; **Figure 2A**). Notably, when patients receiving 10 to 12 pellets were separated by BMI, we observed significantly higher extrapolated TT peaks and faster decay in men with BMI <25 kg/m^2 (1376 ng/dL, 10.76 ng/dL/d) than those with BMI ≥25 kg/m^2 (904 ng/dL, 6.04 ng/dL/d; $P = .006$) (**Table 3**; **Figure 2B**), suggesting that men with lower BMI should receive fewer pellets per implantation. The possibility of alterations in T decay kinetics as a function of persistent TRT exists, and we examined TT decay kinetics as a function of ≤4 sequential implantations in our cohort and found no significant difference in TT decay or extrapolated peaks as a function of implantation round ($P = .13$, $P = .74$, and $P = .45$ between first and second, second and third, and third and fourth implantations, respectively) (**Table 3**; **Figure 2C**). No significant difference in serum SHBG levels before and after pellet implantation was observed, which is consistent with prior studies.

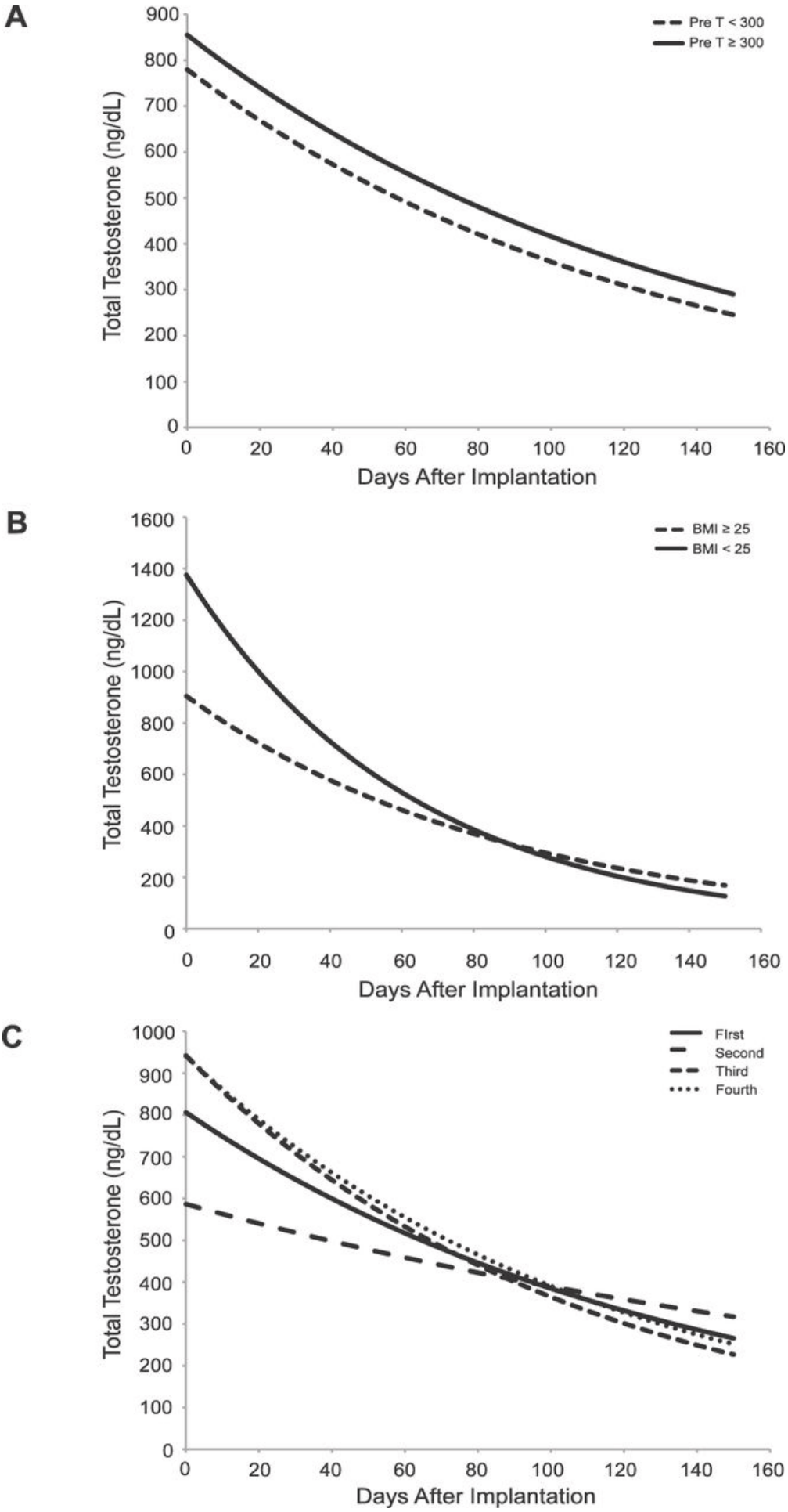
A
Pre T < 300
Pre T ≥ 300
Total Testosterone (ng/dL)
Days After Implantation
B
BMI ≥ 25
BMI < 25
Total Testosterone (ng/dL)
Days After Implantation
C
FIrst
Second
Third
Fourth
Total Testosterone (ng/dL)
Days After Implantation

Figure 2

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Testosterone (T) decay as a function of preimplantation T, body mass index (BMI), and sequential implantations. **(A)** Plot of extrapolated total T vs days after implantation for patients receiving 10 to 12 pellets, separated by men with preimplantation T <300 and ≥300 ng/dL. **(B)** Plot of extrapolated total T vs days after implantation for patients receiving 10 to 12 pellets, separated by BMI group. **(C)** Plot of extrapolated total T vs days after implantation for patients receiving 10 to 12 pellets based on sequential implantations.

One of the most common side effects of TRT is erythrocytosis, and we observed small but significant increases in both Hgb (mean difference ± SD, 0.42 ± 0.94 g/dL, 70.2% of patients; $P < .0001$) and Hct (1.97 ± 2.97 g/dL, 81.9% of patients; $P < .0001$) levels after first pellet implantation, irrespective of BMI group. Only 1 patient in our cohort, who incidentally had BMI <25 kg/m^2 and was implanted with 12 pellets, developed significant enough erythrocytosis to require phlebotomy as treatment (**Table 4**). No data on lipid parameters were available in our cohort of men.

Table 4. *Absolute numbers and percentages of all patient-reported adverse events*

Adverse Events	Patient Group, n (%)
Physical	19 (6.9)
Discomfort/pain at insertion site	7 (2.6)
Swelling or hematoma at insertion site	2 (0.7)
Nonhealing wound	1 (0.4)
Infection at insertion site	1 (0.4)
Fluid retention	2 (0.7)
Skin rash	1 (0.4)
Breast tenderness	1 (0.4)
Elevated Hct/Hgb (requiring phlebotomy)	1 (0.4)
Pellet extrusion	3 (1.1)
Prefer other form of TRT	3 (1.1)
Insurance or cost difficulties	10 (3.7)

PSA was monitored before and after pellet implantations, and no significant increases were observed after first and second implantations across the cohort ($P = .54$ and $P = .06$, respectively). However, a mean increase in PSA of 0.096 ± 0.636 ng/mL (range, 22.5 to 5.0 ng/mL; $P = .044$) was observed only after the first implantation for all men. We

then separated men with and without CaP and found no significant differences in PSA levels or PSA velocities between these groups at any point (**Table 5**). Notably, 5 men in our cohort had a sudden increase in PSA level to <4 ng/mL, which stabilized after the initial rise, and none of these men were diagnosed with CaP before or during their TRT. Of the 65 patients with known history of CaP in our cohort, no biochemical recurrences were observed during TRT with T pellets.

Table 5. *PSA Parameters*[a]

	n	Baseline PSA	n	PSA After First Implant	Days After First Implant	*P*[b]	n	PSA After Second Implant	Days After Second Implant	Days After First Implant	*P*[b]	n	PSA Aft Third Implan
All	179	1.071 (1.785)	179	1.168 (1.929)	76.0 (60.8)	.04	46	1.057 (1.452)	102.3 (48.0)	262.8 (88.1)	.82	26	1.211 (1.977)
CaP	60	0.129 (0.452)	60	0.158 (0.563)	70.8 (65.7)	.20	20	0.177 (0.537)	115 (42.5)	292.3 (101.2)	.18	12	0.099 (0.259)
No CaP	119	1.546 (2.006)	119	1.677 (2.163)	78.6 (58.2)	.07	26	1.700 (1.576)	92.5 (50.4)	240.9 (71.3)	.64	14	2.164 (2.310)

- Abbreviations: CaP, prostate cancer; PSA, prostate-specific antigen; PSAV, PSA velocity.
- a Data are expressed as $\bar{x}$ (SD), unless otherwise indicated. All PSA values are in ng/mL.
- b *P* represents comparison between baseline and sequential implantations.

Implantation site infections and pellet extrusion are 2 potential adverse events with T pellets. In our experience, only 3 patients (1.1%) experienced pellet extrusion, and 1 (0.4%) implantation site infection was observed (**Table 4**). These findings are in line with the previously published pellet extrusion rate of 1% to 4% (**Kelleher et al, 2004**; **Cavender and Fairall, 2009**). Additional adverse events are listed in **Table 4**.

In summary, we found that subcutaneous T pellets resulted in a rise and decay in serum T levels and that peak T levels were a function of the number of pellets implanted and patient BMI but not of the preimplantation serum T level or the order of implantations. Furthermore, we observed predictable effects of T pellets on FT, SHBG, E2, and Hgb and Hct levels, with few adverse events. Importantly, we observed no clinical evidence of CaP progression or recurrence in men who had undergone treatment of CaP.

Discussion

Treatment of hypogonadism with TRT results in a rise in serum T levels. To date, limited assessment of the efficacy and pharmacokinetics of T pellets has been available in the peer-reviewed literature. In this study, which represents the largest cohort of hypogonadal men treated with subcutaneous T pellets to date, we found that T pellets provided a reliable and predictable rise in serum T levels and that the magnitude of this rise was a function of patient BMI and the number of pellets implanted. The most recent studies to examine subcutaneous T pellets evaluated their efficacy and safety in 80 and 30 men, respectively (**Cavender and Fairall, 2009**; **Kaminetsky et al, 2011**). The authors observed sustained increases in serum T levels and satisfaction in both studies with this treatment modality in <80% of patients. However, neither study assessed the effect that the number of pellets or BMI had on serum T levels.

Prior studies have found serum TT levels in men treated with T pellets to be independent of height, weight, and BMI (**Kelleher et al, 2004**). However, we observed a difference in extrapolated peak serum TT levels as a function of BMI and the number of pellets implanted. Most notably, for men with BMI <25 kg/m^2, implantation of ≥10 pellets resulted in initial extrapolated supraphysiologic peak TT levels, suggesting that these men may benefit from fewer implanted pellets. In contrast, extrapolated peak TT levels in men with BMI ≥25 kg/m^2 were predicted to remain <1000 ng/dL regardless of the number of pellets implanted. In addition to increases in serum TT levels, our data supported improvement in hypogonadal symptoms as a result of TRT and suggested more significant improvement in men treated with 10 to 12 pellets. Prior work has demonstrated that T levels can remain elevated for 3 to 6 months after pellet implantation. Our data indicated that, regardless of BMI and the number of pellets implanted, TT levels decayed to hypogonadal levels within 3 to 4 months after implantation, indicating that reimplantation should be performed at this time. We also observed no differences in extrapolated peak T levels or decay kinetics in men who were sequentially reimplanted with pellets. However, our current data set did not indicate whether these men were reimplanted based solely on serum T levels or whether return of hypogonadal symptoms prompted reimplantation. If symptomatic recrudescence, independent of low serum T levels, resulted in pellet reimplantation, this could result in T levels higher than those expected due to reimplantation for hypogonadal T levels and thus could affect extrapolated peak T levels and decay.

We observed a significant increase in E2 levels in men treated with 10 to 12 pellets ($P < .0001$), which is consistent with other studies examining T pellets (**Jockenhovel et al, 1996**; **Cavender and Fairall, 2009**). In our study cohort, only 1 patient was treated with an aromatase inhibitor for elevated E2, which resulted in normalization of serum E2 levels, although no symptomatic effects of this intervention were noted. In addition, the lack of change in serum SHBG levels in our study is also consistent with the results of prior studies (**Handelsman et al, 1990**; **Kelleher et al, 2004**; **Cavender and Fairall, 2009**), although 1 study did find a decrease in SHBG levels in men with primary hypogonadism (**Jockenhovel et al, 1996**).

Administration of exogenous T increases the risk of erythrocytosis, as defined by an increase in Hgb of <3 g/dL or Hct <54%, and the incidence of erythrocytosis varies between T preparations, with ≤18% of patients on gels and ≤44% of patients using injections developing erythrocytosis (**Dobs et al, 1999**; **Snyder et al, 2000**; **Wang et al, 2000**). In our study, small but significant average increases in both Hgb and Hct levels were observed, although no men had an increase in Hgb of <3 g/dL and only 1 patient's Hct increased to <54%, requiring phlebotomy. Of note, the patient who developed erythrocytosis had BMI <25 kg/m^2 and had been implanted with 12 pellets. This suggested an overall low rate of erythrocytosis in the setting of T pellets, with an increased risk in men with BMI <25 kg/m^2 receiving <10 pellets. Cavender and Fairall (**2009**) in a retrospective analysis of 80 patients found a small, clinically insignificant increase in Hct in patients treated with T pellets.

No data on lipid parameters were available for our analysis, although alterations in lipid profiles have been demonstrated in men treated with transdermal gels and intramuscular injections. Notably, no significant differences were demonstrated in these studies, and the effects on high-density lipoprotein, low-density lipoprotein, and total cholesterol appeared to depend on the T preparation (**Dobs et al, 1999**; **Snyder et al, 2001**; **Whitsel et al, 2001**). Currently, no data are available in the literature examining the effects of T pellets on lipid profiles.

Given that CaP cells are androgen responsive, monitoring of PSA in men receiving TRT should be considered. In our cohort, we found a small but significant overall increase in PSA levels in men treated with T pellets but only after the first implantation, with few men having a PSA rise to <4 ng/mL. Furthermore, when men with and without CaP were separated, we found no differences between PSA levels or PSA velocities between the groups, further supporting no measurable effect of T pellets on the development or progression of CaP. We acknowledge that no control group was available to contrast our findings, particularly in the men with a history of CaP, but we also noted that men with PSA increasing to <4 ng/mL were not diagnosed with CaP and that no men with CaP had a rise in PSA to <4 ng/mL during their follow-up course. These findings are in line with those of a recent study that found a small increase in PSA level in men treated with T pellets but with no PSA levels above the upper limit of normal (**Cavender and Fairall, 2009**).

Our study is limited by several factors. First, it is unclear in our study how rapidly serum TT levels reach their peak after pellet implantation, given that we extrapolated peak TT levels and by virtue of our analysis, assumed that peak levels occurred on day 0 postimplantation. The most detailed pharmacokinetic study involving T pellets evaluated 14 patients implanted with six 200-mg pellets and found that peak TT levels were achieved within half a day with a plateau lasting approximately 2 months, followed by a decline in TT levels (**Jockenhovel et al, 1996**). A recent open-label study examining the effects of T pellets in 30 men demonstrated peak T levels within 4 weeks of implantation, which echoes other studies demonstrating peak TT levels within the first month postimplantation, regardless of pellet size (**Handelsman et al, 1990**; **Kaminetsky et al, 2011**). Given the variable time to follow-up within our cohort of men, we reviewed our T data as a function of time from pellet implantation and found that the greatest change in serum T levels occurred within 2 to 4 weeks of pellet implantation, supporting the findings of Kaminetsky et al (**2011**). Regarding T release rates, a prior study indicated that T pellets released hormone at a rate of approximately 1.3 mg/pellet/d in men treated using four 200-mg pellets (5.2 mg/d), although peak TT levels were not assessed (**Kelleher et al, 2004**). The T release rate in our study was approximately 0.6 mg/pellet/d (6.6 mg/d) when 11 pellets of 75 mg each were considered, which translates into an approximate increase of 60 ng/dL in serum T per pellet implanted and is essentially identical to the release rate derived by Kaminetsky et al (**2011**) in their recent work.

Further limitations of our work include the lack of a placebo group as well as validated questionnaires to assess improvement in hypogonadal symptoms. Thus, although improvements in serum T levels were reported by patients, the effects of T pellets on symptoms of hypogonadism remain less clear. Furthermore, given the diurnal variation in T levels in men, the true effects of T pellets on serum hormone levels cannot be evaluated in the absence of a control. However, given the doseresponse effect observed using pellets, it is likely that an increase in serum TT levels does occur as a direct result of pellet implantation. Third, we lack data to assess changes in serum lipids, as well other components of the metabolic syndrome, upon which the effects of T remain unclear. Fourth, the effects of T pellets on BMI over the longer term were not evaluated in this study. T supplementation has been found to increase lean body mass and thus over the long term may result in a reduction in BMI (**Sattler et al, 2009**). Fifth, the long-term effects of TRT using T pellets in the setting of CaP is unknown. Although data continue to accumulate indicating that TRT in the setting of CaP is safe, the effects of T pellets on CaP recurrence and progression remain to be determined. This information will be addressed in future work.

We found that subcutaneous T pellets represent a safe, efficacious mode of TRT and that the effects on serum hormone levels and hypogonadal symptoms of these pellets are a function of the number of pellets implanted and patient BMI. Men with BMI <25 kg/m^2 achieved therapeutic TT levels with <10 pellets, whereas men with BMI ≥ 25 kg/m^2 required ≥ 10 pellets to achieve therapeutic TT levels. Most men demonstrated improvement in hypogonadal symptoms after pellet implantation. Regardless of the number of pellets implanted, roughly equal serum TT levels were observed at 100 to 120 days, indicating that reimplantation should be performed at this time. Furthermore, multiple sequential implantations did not appear to affect TT decay kinetics nor did preimplantation TT levels. Finally, minimal effects on Hgb and Hct parameters, and no effects on PSA, particularly in men with CaP, were observed.