ORIGINAL RESEARCH—ENDOCRINOLOGY

Subcutaneous Testosterone Pellet Implant (Testopel®) Therapy for Men with Testosterone Deficiency Syndrome: A Single-Site Retrospective Safety Analysis

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ABSTRACT

Introduction. Long-acting subcutaneous testosterone pellets provide sustained and steady testosterone levels for 3 to 6 months. Testopel® subcutaneous crystalline testosterone pellets are U.S.-approved for the treatment of men with testosterone deficiency syndrome. Published experience with testosterone pellets manufactured by Organon has noted relatively high rates of pellet extrusion and infection.

Aim. To report safety and limited efficacy data from our patients treated for testosterone deficiency syndrome with Testopel® subcutaneous testosterone pellets.

Main Outcome Measures. Infection with or without pellet extrusion, as determined by longitudinal follow-up.

Methods. Single-site, retrospective analysis of medical records from December 2003 through April 2008.

Results. A total of 80 men met inclusion and exclusion criteria. In the 292 implant procedures performed, four adverse events were reported including one implantation site infection. No spontaneous pellet extrusions were reported. Total and free testosterone concentrations were significantly higher at follow-up than at baseline for all patients. Eighty-six percent of patients were satisfied with this treatment modality based on symptom improvement or having subsequent implant procedures.

Conclusions. Testosterone replacement with long-acting Testopel pellets had a lower rate of infection (0.3%, 1/292 procedures) as compared with historical data from the Organon testosterone pellet (1.4–6.8%). Additionally, the rate of pellet extrusion was substantially lower (0.3%, 1/292 procedures) as compared with historical data (8.5–12%). None of the patients who complied with post-implant procedure instructions experienced infection or pellet extrusion. Patient satisfaction was high and serum hormone values were improved. The low infection and extrusion rates observed may have been the result of the manufacturing process, which results in small, smooth-surfaced pellets; the absence of foreign material within the pellet packaging; and/or differences in the surgical implantation technique used. Though Testopel pellets have been used in the United States for several decades, more research is needed to document their safety and efficacy. **Cavender RK, and Fairall M. Subcutaneous testosterone pellet implant (Testopel®) therapy for men with testosterone deficiency syndrome: A single-site retrospective safety analysis. J Sex Med 2009;6:3177–3192.**

Key Words. Testosterone; Subcutaneous Testosterone Pellet Implant; Hypogonadism; Testosterone Deficiency Syndrome

Introduction

When an adult male patient is diagnosed with testosterone deficiency syndrome based on clinical symptoms and serum testosterone values [1–4], various testosterone delivery systems such as oral, intramuscular, topical patch, gel, or subcutaneous pellet implants may be considered [5–12]. Each has important benefits and limitations.

Most practitioners are unaware that testosterone replacement therapy via subcutaneous testosterone pellets has been utilized clinically for

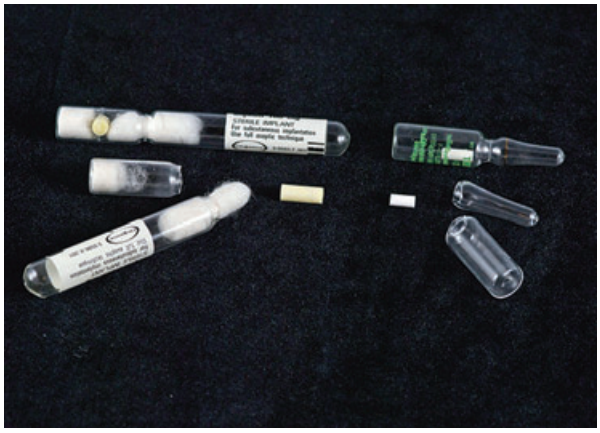

Figure 1 Testosterone pellets for subcutaneous implantation marketed by Organon Laboratories Ltd., Milton Road, Cambridge, United Kingdom (left) and Slate Pharmaceuticals, Durham, North Carolina (Testopel® pellets). Products are shown in and with their commercial packaging. See text for details.

more than 65 years [13]. Testosterone pellets have the advantage of 100% patient compliance once they are inserted subcutaneously, as long as no subsequent pellet extrusion occurs [14–22]. Subcutaneous testosterone pellets can achieve sustained and steady testosterone levels for 3 to 6 months with relatively low testosterone metabolite formation [15].

Worldwide, two different subcutaneous testosterone pellets are currently government-approved. One is marketed by Organon Laboratories Ltd., Milton Road, Cambridge, United Kingdom, and formulated as a cylindrical 5×15-mm pellet (diameter $\times$ length) containing 200 mg testosterone (Testosterone Implant). Each pellet is surrounded by wool or cotton for pellet protection, and stored in a sterile glass ampule (Figure 1, left). Historically, this product has been available in Europe and Australia. The second product is marketed by Slate Pharmaceuticals, Durham, North Carolina, USA, and formulated as a cylindrical 3×8-mm pellet containing 75 mg crystalline testosterone (Testopel®). Approved in the United States since 1972 for the treatment of men with testosterone deficiency syndrome, Testopel pellets have reportedly been manufactured in a manner that ensures prolonged stability. For sterility, these pellets are packaged in individual sterile glass ampules without any additional protective material (Figure 1, right).

The Testopel pellet is considerably smaller in size than the Organon pellet (Figure 1) and, under magnification, the Testopel pellet surface is regular and smooth, in contrast to the markedly irregular surface of the Organon product (Figure 2). Each subcutaneous testosterone pellet is inserted during an outpatient sterile surgical procedure via a trocar: 16 gauge for Testopel pellets, and a slightly larger one for the Organon pellets to accommodate their larger size.

Adverse experiences associated with use of the Organon testosterone pellets include bruising, local pain and tenderness, minor bleeding, local infection, and pellet extrusion [16–19]. The reported prevalence of pellet extrusion is 8.5% to 12%, and maneuvers such as washing the pellets with alcohol or soaking them in antibiotic have not reduced the prevalence of this adverse event.

There are limited studies reporting adverse effects associated with use of the Testopel pellets, and the primary goal of this retrospective research was to report preliminary safety data from patients who had utilized Testopel subcutaneous testosterone pellets for treatment of testosterone deficiency syndrome. Because the Testopel pellets are reportedly manufactured in a different manner than the Organon pellets, are smaller, and are stored without foreign protective material, the primary focus of this analysis was to see if the rate of infection with Testopel pellets was lower than the rate historically reported for the Organon product.

To avoid confusion in this report about which testosterone product is being discussed, the testosterone pellet approved by the U.S. Food and Drug Administration (FDA) has been referred to by its brand name, Testopel. The only known name for the Organon product, Testosterone

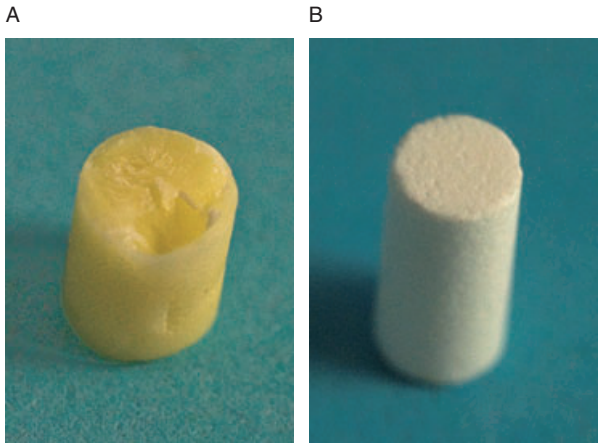

Figure 2 Magnified photograph of testosterone pellets manufactured by Organon (2A) and Slate (Testopel®, 2B). The surface of the Testopel® pellet is smooth, regular, and without defects compared to the Organon pellet.

Implant, was not used because it could readily be mistaken for the other testosterone product discussed herein.

Methods

Medical records including clinical follow-up at this practice site have been maintained for each subcutaneous testosterone pellet implantation procedure since 2002. Data were retrospectively collected to characterize patient experience with Testopel pellets, including clinical and laboratory responses. This was an anonymous and retrospective review of our own patient records. This study was reviewed by Independent Investigational Review Board, Inc., in Plantation, FL, and a Health Insurance Portability and Accountability Act-informed consent waiver was granted for 1 year.

Adult males at least 21 years of age with testosterone deficiency syndrome were eligible for inclusion in the analysis if they received at least one insertion procedure of Testopel subcutaneous testosterone pellets.

The diagnosis of testosterone deficiency syndrome was made following assessment of patient symptoms and laboratory testing of testosterone and metabolite levels [1–4]. No single blood test value was used to define hypogonadism. Total testosterone levels <350 ng/dL were consistent with the biochemical diagnosis of hypogonadism, whereas patients with clinical symptoms suggestive of hypogonadism who also had comorbid disease and testosterone levels >350 ng/dL yet in the lower quartile of the reference range were offered a trial of testosterone therapy. In addition to any pharmacological therapy, all patients with testosterone deficiency syndrome received patient counseling relative to lifestyle modification with clinical nutrition and exercise prescriptions. In addition, concomitant metabolic syndrome conditions (e.g., central obesity, insulin resistance diabetes, dyslipidemia, hypertension) and aging-related endocrinopathies (e.g., hypothyroidism) were diagnosed and simultaneously treated [1–4,23]. All physical examinations and symptom assessments were performed by the same physician.

Each patient who considered testosterone replacement therapy received detailed counseling on the potential risks and benefits related to their disease state(s) and treatment options, and provided informed consent for their choice of treatment. Those who elected to undergo subcutaneous testosterone pellet implant therapy received detailed information on the potential risks and benefits of the Testopel pellet implantation procedure (including the signs and symptoms of implant site infection, and instructions to avoid implant site exposure or use of a sauna or hot tub for 1 week following pellet implantation; see Appendix 1) and signed an additional, separate surgical consent.

Patients were excluded from the analysis if: (i) they were on testosterone treatment at the time of the initial evaluation and therefore had no pretreatment baseline data; (ii) they were lost to follow-up within 120 days after pellet insertion; or (iii) following subcutaneous pellet insertion, they were coadministered other testosterone therapies such as oral, topical, or injectable testosterone, or received concomitant human chorionic gonadotropin (HCG), as these therapies would have biased the follow-up laboratory data. Patients who required concomitant treatment with finasteride or anastrozole because of elevations in dihydrotestosterone, estrone, or estradiol, or secondary to the treatment of other clinical conditions, were not excluded from this study.

Dose and Pellet Implantation

The testosterone dose for each implant procedure was based on the individual patient's symptoms, baseline laboratory data, age, body weight, percent body fat, and activity level. In general, these parameters were chosen because they were felt to clinically predict the testosterone pellet metabolism. In general, higher doses were utilized in men with testosterone deficiency syndrome who were more clinically symptomatic, were younger in age, had a higher body weight with lower percent body fat, and/or had a more active lifestyle. In contrast, lower doses were utilized in men with testosterone deficiency syndrome who were less clinically symptomatic, were older in age, had a lower body weight with higher percent body fat, and/or had a less active lifestyle. For example, a dose of 10 pellets (750 mg) was selected in cases of 3 or more symptoms consistent with testosterone deficiency syndrome, 45 to 50 years of age, weight 175 to 199 lbs with body fat 30 to 34.9%, and/or a moderately active lifestyle. A dose of 12 pellets (900 mg) was selected in cases of four or more symptoms consistent with testosterone deficiency syndrome, 40 to 44 years of age, weight 200 to 224.9 lbs with body fat 25 to 29.9%, and/or high activity level. In each case, determination of the dosage was based on the presence of comorbid disease, response to previous treatment, and the

clinical experience of the physician (RKC). Subsequent Testopel pellet dosing was based on symptomatic improvement and the achievement of serum testosterone target levels at approximately 8 weeks following pellet implantation.

The testosterone pellet implantation procedure was usually completed in approximately 20 minutes and was performed under sterile conditions in an office setting. The implant procedure utilized was a modification of the procedures previously described by Handelsman and Cavender [16,24]. The patient was placed in the lateral jackknife or fetal position for implantation in the upper outer posterior gluteal region (Figure 3). The implant area was prepped with povidone-iodine and draped in the normal sterile fashion. Local anesthesia was utilized without any concomitant sedation. Lidocaine with epinephrine for local vasoconstriction was administered using a 1.5-in. 25 gauge needle. First, a skin wheal was developed at the site of the intended skin incision, and then the local anesthesia was administered to a depth of 1 to 2 cm below the skin surface in a large fan-shaped area over the 10 cm length of the projected trocar tract.

Following adequate anesthesia, a #11 blade scalpel was used to make a 3- to 4-mm stab incision into the subcutaneous region of the skin (Figure 4). The #16 trocar with sharp stylet was then introduced at a 30-degree angle to the skin surface and advanced approximately 1 to 2 cm deep into the subcutaneous tissue. The trocar and sharp stylet were then angled horizontal to the skin surface and advanced in the trajectory of the femur for the length of the 10-cm trocar. The sharp stylet was removed and replaced with a blunt stylet (not shown in the figures; see Discussion), then the trocar was moved laterally to create a subcutaneous pocket by blunt dissection. The blunt stylet was removed, and the pellets were individually loaded into the trocar lumen (Figure 5), advanced with the blunt stylet, and then launched via advancement and lateral trocar movement. Each pellet was positioned 90 degrees to the trocar tract and side-to-side within the subcutaneous pocket. Following placement of each pellet, the trocar was withdrawn approximately 4 mm (the pellet diameter). This process was repeated until all pellets were properly positioned. After all pellets were placed within the subcutaneous pocket, the trocar was removed (Figure 6). The incision was closed with the application of tincture of benzoin and sterile adhesive strips, and covered by a sterile bandage to protect the area. To minimize bruising and prevent subcutaneous hematoma formation, external cold compression was then applied over the region of the subcutaneous pocket by placing the patient in the opposite lateral jackknife position on an ice pack for approximately 10 minutes.

Data Procedures

Baseline data were identified in the patient's medical record as data obtained prior to subcutaneous testosterone pellet implantation. Baseline information included both clinical symptoms and biochemical assessments of serum hormones. Several laboratories were used by our practice during the study period and all were accredited clinical laboratories that utilized standard procedures for performing laboratory tests including sex steroid hormones. Although the laboratories used similar reference ranges for total testosterone, the reference ranges for other laboratory tests were not as consistent. The largest difference in reference ranges was for free testosterone, because of the different test methods utilized (e.g., equilibrium dialysis and liquid chromatography-tandem mass spectrometry vs. direct radioimmunoassay).

The primary outcome measure was the prevalence of local infection, with or without pellet extrusion. Additional outcome measures included adverse events (other than infection), patient satisfaction, and the results of clinical laboratory tests related to testosterone therapy. Adverse event and clinical laboratory result data were taken directly from the medical records. Determining patient satisfaction was less direct and patients were considered "satisfied" with treatment if they either reported improved symptoms or scheduled an additional pellet insertion procedure. Patients were considered "not satisfied" with treatment if their symptoms did not improve, therapy did not meet their expectations, they did not schedule a subsequent pellet insertion procedure, or therapy was started with another form of testosterone.

Statistical Analyses

Data were summarized and analyzed using Microsoft Office Excel (Microsoft, Redmond, WA, USA) and SAS (SAS Institute, Inc., Cary, NC, USA). As the hormone data were not log-normally distributed, continuous variables were summarized by arithmetic mean, standard deviation, median, minimum, and maximum. Statistical significance was determined by *t*-test on the

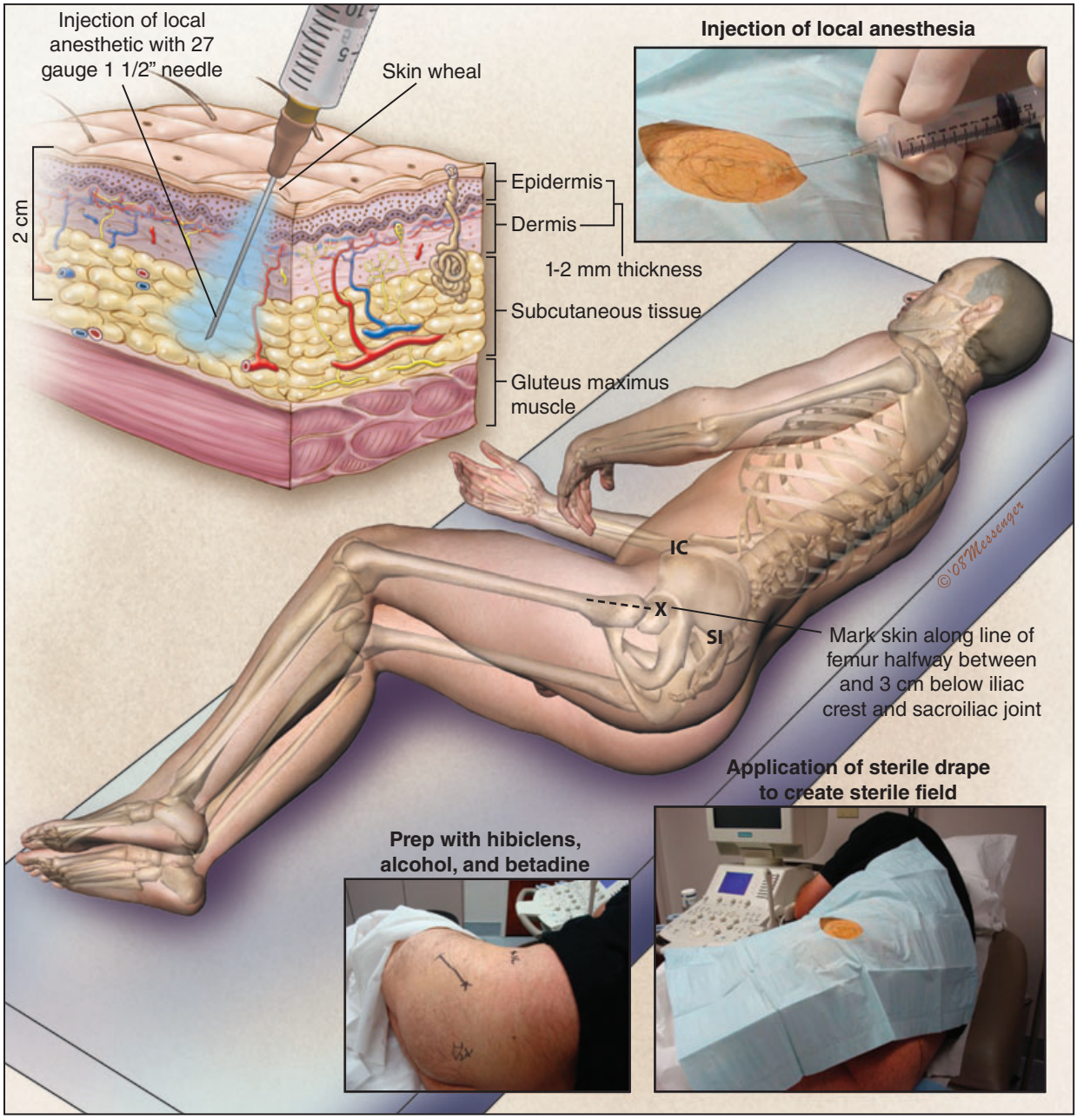

Figure 3 The patient is placed in the lateral jackknife or fetal position. Implantation occurs in the upper outer quadrant of the posterior gluteal region. The skin is marked 3 cm below the halfway mark between the iliac crest and sacroiliac joint in a 10-cm line parallel to the femur. Hibiclens®, alcohol, and povidone-iodine solution are used sequentially to prep. A sterile skin drape is used. For local vasoconstriction, 2% lidocaine (10 mL) with epinephrine (1:100,000) is administered first by skin wheal and then to a depth of 1 to 2 cm below the skin using a 1.5-inch 25 to 27 gauge needle. Repeated subcutaneous injection results in a large fan-shaped anesthetized area. Image used with permission, copyright Lori A. Messenger, CMI.

change from baseline to follow-up, with significance defined as $P < 0.05$. Data were initially analyzed for all patients combined. After review of the data (including clinical laboratory issues and concomitant use of potentially confounding medications), subgroups of patients were analyzed based on the laboratory performing the baseline and follow-up tests, and on the concomitant use of anastrozole or finasteride.

Results

Between December 2003 and April 2008, 166 men presented with testosterone deficiency syndrome.

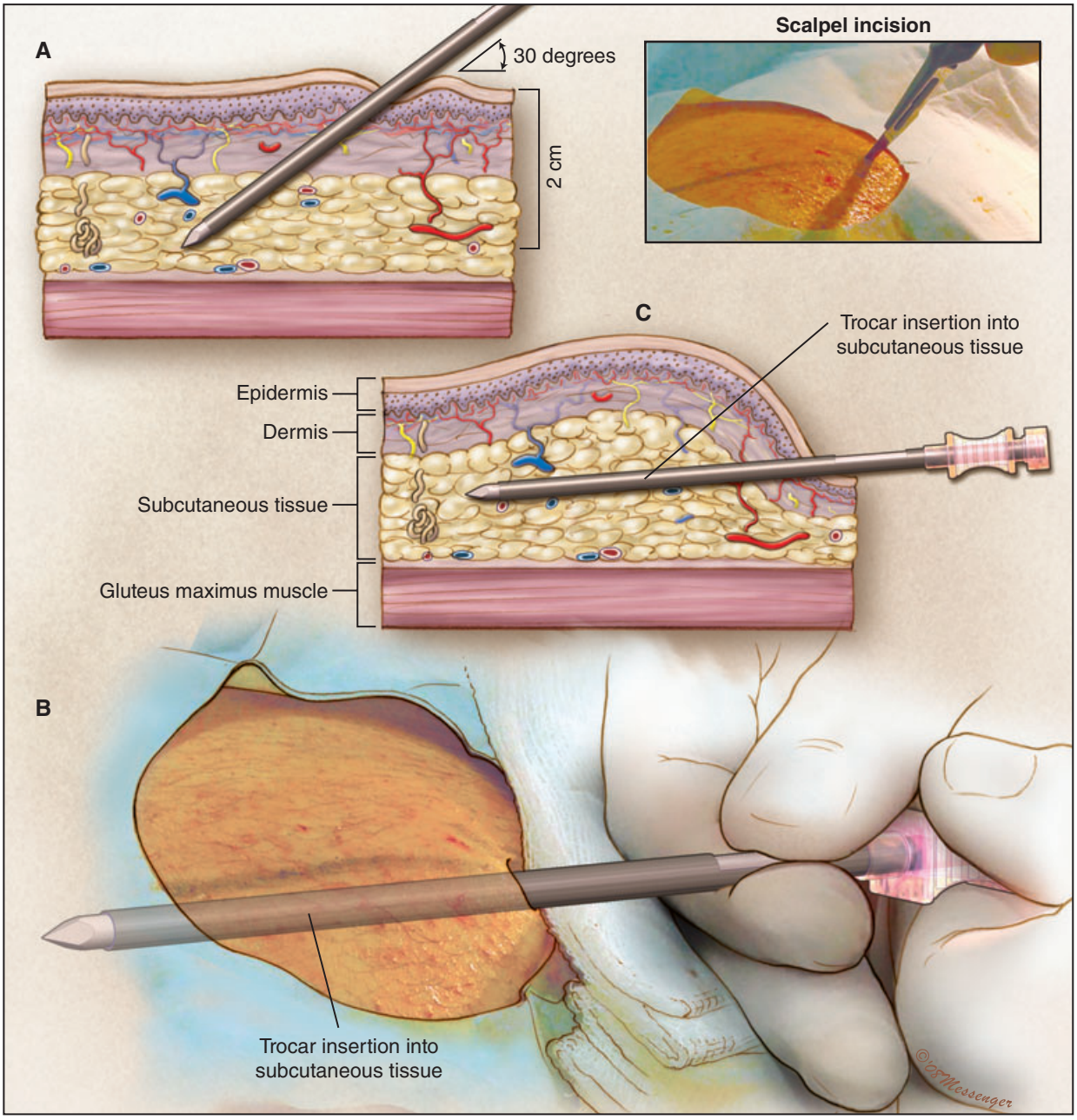

Figure 4 Following adequate local anesthesia, a #11 blade scalpel is used to make a 3- to 4-mm stab incision. The trocar with sharp stylet is then introduced at a 30-degree angle to the skin surface and then advanced to a depth of 1 to 2 cm within the subcutaneous tissue. The trocar and stylet are then angled horizontally to the skin surface and advanced in the trajectory of the femur at a 1 to 2 cm depth. The trocar and stylet are advanced to their complete 10 cm length. Image used with permission, copyright Lori A. Messenger, CMI.

Medical records for 80 patients (48%) met inclusion and exclusion criteria. Patients were eliminated from the analysis for one or more of the following reasons: did not return to clinic for post-implant follow-up (N = 45), were receiving androgen therapy at initial assessment (i.e., no true baseline, N = 12), had hypogonadal symptoms with significant comorbid disease and borderline normal testosterone levels (N = 12), had concomitant therapy with HCG (N = 17), or had concomitant therapy with another form of androgen (N = 13). Patient characteristics at baseline (before the first implant procedure that met study criteria) are shown in Table 1.

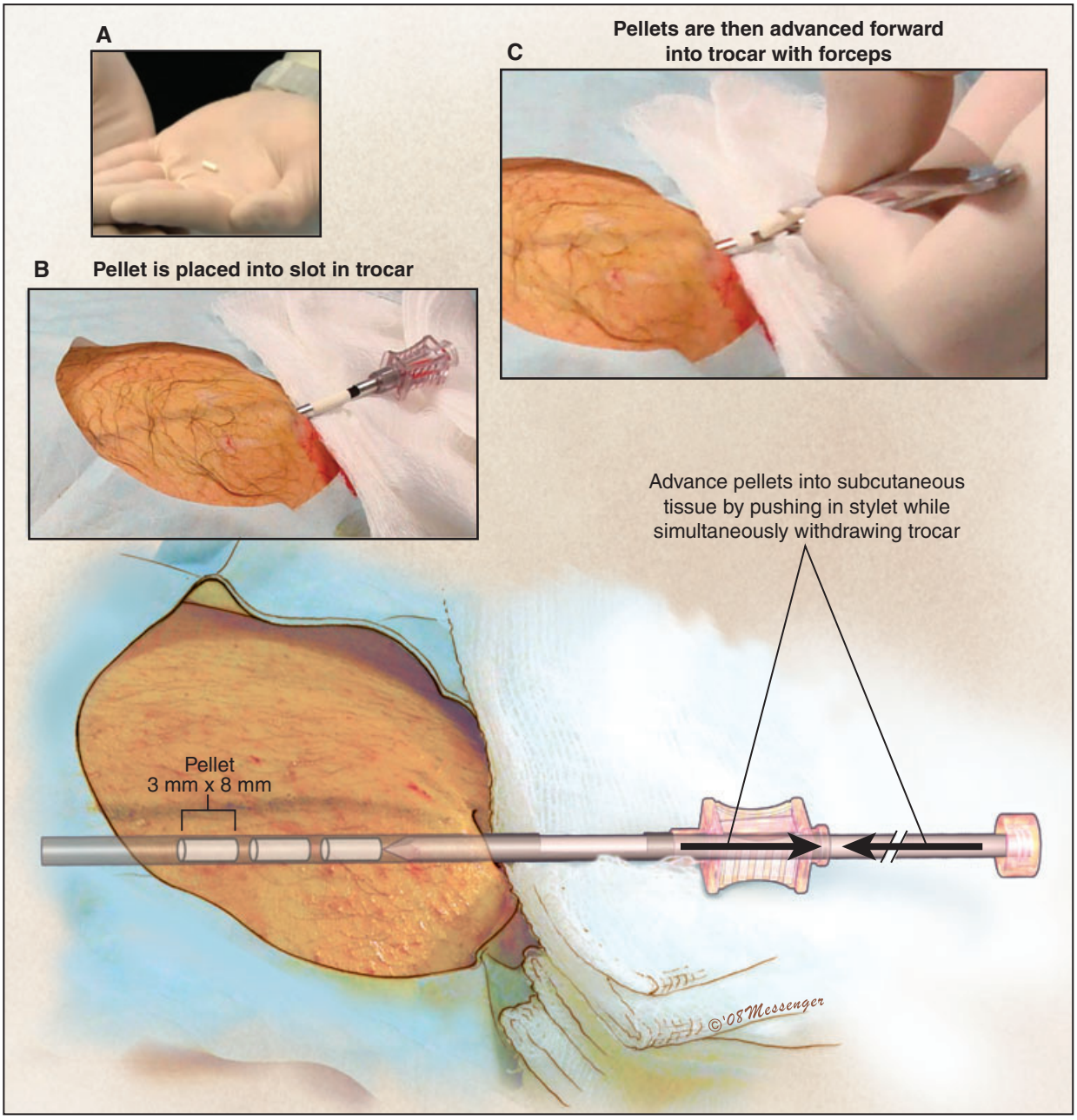

Figure 5 Once the trocar has been advanced to its maximum length (10 cm), the stylet is removed and the testosterone pellets are individually placed through the trocar slot and into the hollow sheath. Following the positioning of all the pellets into the trocar, the stylet is advanced inward as the trocar is simultaneously withdrawn, launching the pellets end-on-end within the tract formed by the trocar within the subcutaneous tissue. See Discussion for a modification of this procedure to minimize the potential for pellet extrusion. Image used with permission, copyright Lori A. Messenger, CMI.

Safety

The safety evaluation included all 292 Testopel pellet implantation procedures performed during the study period for the 80 patients meeting the inclusion and exclusion criteria. Individual patients received one (N = 22) to 13 (N = 1) procedures in that time period, and 41% (33/80) had at least four consecutive implantations. The mean dose was 13 pellets or 975 mg testosterone, with a range of 6 to 20 pellets (450 to 1,500 mg testosterone).

Testopel pellets and the implantation procedure were well tolerated, with only four adverse events reported: a self-limiting contact dermatitis secondary to the sterile adhesive strips (N = 1);

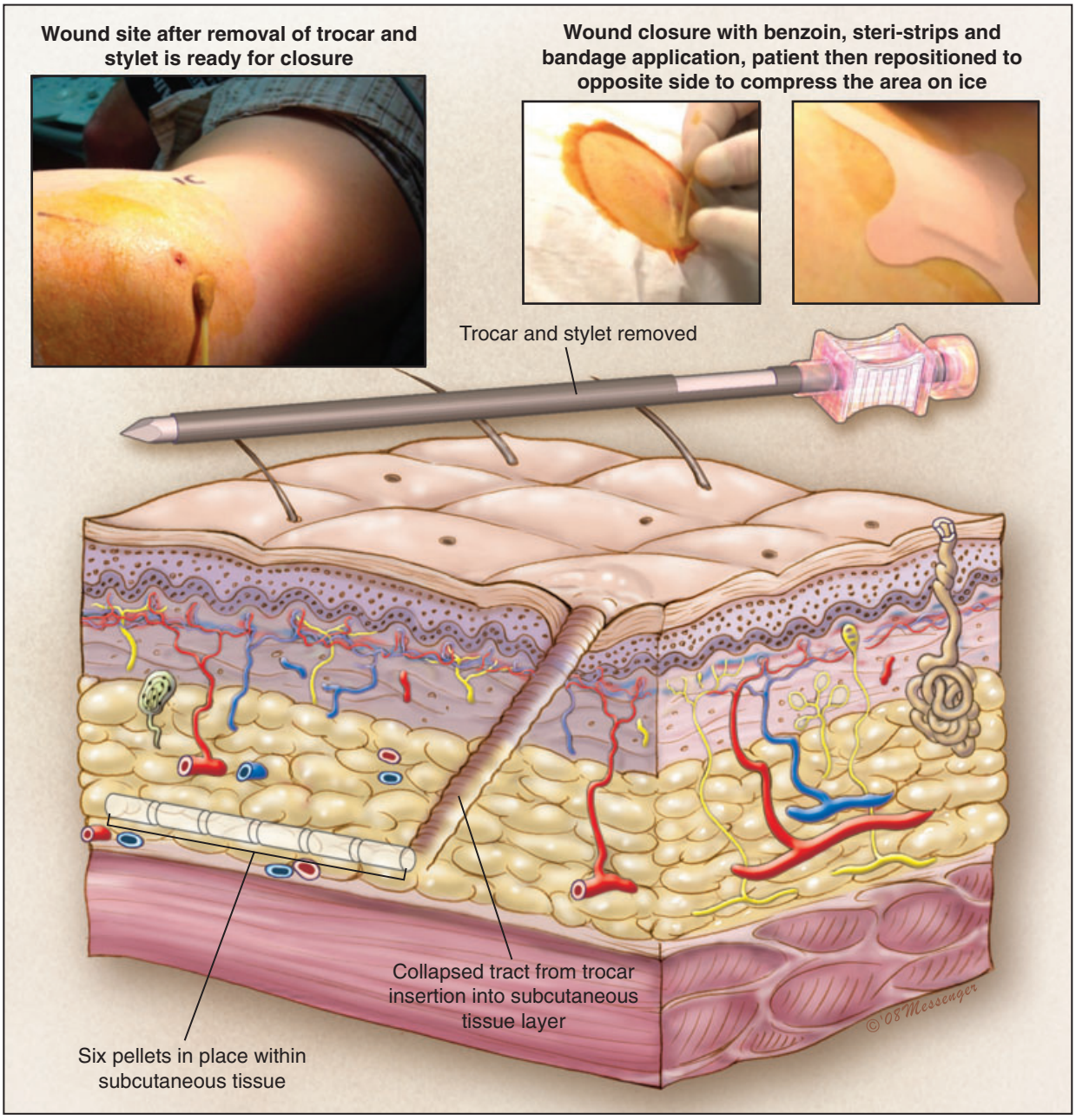

Figure 6 After all pellets are placed and the trocar has been removed, tincture of benzoin is placed on the skin. Sterile adhesive strips are then used to close the skin and a sterile bandage is placed to protect the area. The patient is then placed in the opposite jackknife position and the implant site is subjected to cold compression by utilizing body weight on an ice pack for approximately 10 minutes. Image used with permission, copyright Lori A. Messenger, CMI.

a self-limiting local reaction consisting of erythema, pruritus, and edema at the implantation site (N = 1, reported 2 months after pellet insertion); an immunologic foreign body reaction (N = 1); and a local infection of the pellet insertion tract (N = 1). None of the events was considered serious. The 39-year old man who experienced an immunologic foreign body reaction had experienced similar immunologic reactions and subsequent therapeutic failure with testosterone injections, testosterone topical gel, and HCG injections before receiving testosterone pellets. Although the pellet implantation procedure was uneventful, approximately 6 months post implantation the patient reported sharp pain upon palpation of the implantation site. The

Table 1 Patient characteristics at baseline

Units	N†	Mean ± standard deviation	Median (range)
Age (year)	80	46.6 ± 9.7	46 (28–72)
Height (m)	72	1.80 ± 0.06	1.79 (1.68–1.96)
Weight (kg)	71	96.37 ± 15.55	94.8 (71.3–143.7)
BMI (kg/m^2)	70	29.9 ± 4.8	29 (22–45)
Waist/hip ratio	45	0.95 ± 0.05	0.94 (0.84–1.08)
Body fat (%)	49	26.57 ± 7.41	26.5 (8.5–46.1)

†Indicates the number of patients for whom data were available.
BMI = body mass index.

pellets were subsequently excised via a 2-cm incision. Gross inspection revealed fibrous connective tissue encapsulating minimally-absorbed testosterone pellets. Pathologic evaluation confirmed the above findings with the addition of a neuroma as the etiology for the symptoms. Following the surgical excision, the patient's symptoms resolved with no further incident. The adverse reaction of significance was the local infection reported by a 70-year-old man who bathed in a hot tub several days following his fourth pellet implantation procedure, despite instructions to avoid hot tub use. The purulent material was evacuated via ultrasound-assisted manual manipulation, during which four pellets were extruded. The patient was treated with systemic antibiotics and the site healed without further incident. This patient had undergone three previous pellet insertion procedures with no adverse reactions.

Other Evaluations

Evaluations other than safety were based on only the first Testopel pellet implantation procedure that met the inclusion and exclusion criteria, which was generally the patient's first procedure.

Most patients were considered satisfied with Testopel treatment (86%, 69/80) based on a report of improved symptoms or scheduling a subsequent Testopel pellet insertion procedure. About one-third of the patients had previously received other androgen replacement therapy, and most of these (63%, 15/24) indicated a preference for testosterone pellets.

Sex hormone, prostate-specific antigen (PSA), and hematocrit laboratory results from baseline and follow-up are shown in Table 2. Total and free testosterone concentrations were significantly higher at follow-up than at baseline for all patients. The change in mean sex hormone binding globulin concentration was small and not clinically relevant. Mean PSA concentration was slightly increased at follow-up ($P = 0.003$); however, no single value was above the upper limit of normal and the mean change was not clinically relevant. Similarly, although mean hematocrit was slightly increased at follow-up ($P = 0.002$), the observed changes were not clinically relevant (e.g., no exces-

Table 2 Hormonal, PSA, and hematocrit levels at baseline and follow-up

Test	Statistic	Baseline	Follow-up†	*P**
Total testosterone (ng/dL)	Mean ± SD Median (range) N	317.5 ± 108.0 332 (57–492) 80	618.9 ± 183.2 620 (207–974) 80	<0.001
Free testosterone (pg/mL)	Mean ± SD Median (range) N	41.94 ± 30.06 41.7 (1.70–116.9) 80	100.8 ± 70.57 95.3 (10.2–294.8) 79	<0.001
Sex hormone binding globulin (nmol/L)	Mean ± SD Median (range) N	24.20 ± 10.66 25.0 (4.0–58) 74	24.93 ± 11.25 24.5 (6–69) 72	0.544
Prostate-specific antigen (ng/mL)	Mean ± SD Median (range) N	0.78 ± 0.52 0.7 (0.04–2.7) 78	0.96 ± 0.66 0.7 (0.2–3.5) 68	0.003
Hematocrit (%)	Mean ± SD Median (range) N	45.11 ± 2.97 45.2 (34.9–51.4) 77	46.72 ± 3.35 47.0 (36.6–52.8) 49	0.002

*For mean change from baseline to follow-up.
†The follow-up visit occurred 58 ± 21 days (mean ± standard deviation [SD]) after pellet implantation (range 13–120 days; N = 80 patients). More than one pellet implantation procedure may have occurred between baseline and follow-up assessments.

sively elevated hematocrit levels or hematocrit levels requiring phlebotomy based on adverse hemodynamic effects).

Most patients had both baseline and follow-up tests performed by the same laboratory, using either Quest Diagnostics (N = 47) or LabCorp (N = 20). When laboratory data were analyzed for these laboratory subgroups, results were similar to those from all patients, with total and free testosterone significantly increased at follow-up in each laboratory subgroup (data not shown). Thirteen patients were excluded from this subgroup analysis because baseline and follow-up tests were performed at different laboratories (e.g., baseline from Quest Diagnostics and follow-up from LabCorp).

In the subgroup of patients with both baseline and follow-up test results from the same laboratory, 60% (40/67) received Testopel alone and 31% (21/67) received Testopel and anastrozole (Table 3). Only three patients (4.5%) each received Testopel and finasteride or Testopel, anastrozole, and finasteride, and data from these two subgroups are not shown because of the small sample size. As expected, the mean total and free testosterone concentrations at follow-up were increased more in patients who received Testopel with anastrozole than in patients who received Testopel alone. Mean estrone and estradiol levels at follow-up were slightly increased in patients who received Testopel alone, whereas these levels decreased in patients who received Testopel with anastrozole.

Serum testosterone data were available from a second follow-up visit for seven patients in this analysis who had all test results from the same laboratory and received Testopel alone. Median total testosterone levels were 397 ng/dL at baseline and 600 and 487 ng/dL at 56 and 132 days, respectively, post pellet implantation (median time to follow-up visit). Median free testosterone levels were 57 pg/dL at baseline and 116 and 74 pg/dL at the follow-up visits. These patients received an average testosterone dose of 10 pellets or 750 mg (range 8–15 pellets or 600–1,125 mg). The profile of sustained testosterone levels was similar when data from these patients were analyzed in combination with data from an additional seven patients who had all test results from the same laboratory and received Testopel with anastrozole (N = 5) or with anastrozole and finasteride (N = 2). In these 14 patients, median total testosterone was 334 ng/dL at baseline and 635 and 482 ng/dL at 48 and 127 days after pellet implantation. Median free testosterone levels were 47 pg/dL at baseline and 92 and 53 pg/dL at the follow-up visits. The testosterone dose (median and range) for this subgroup was also 10 pellets (750 mg) and 8 to 15 pellets (600–1,125 mg).

Discussion

For patients with testosterone deficiency syndrome who are considering long-term testosterone replacement therapy, treatment with subcutaneous testosterone pellet implants have several theoretical advantages over short-acting testosterone products such as gels, injections, and patches [6–12]. With subcutaneous testosterone pellet insertion, compliance with the treatment is 100% for the following 3 to 6 months unless the pellets are removed or extruded. In contrast, topical gels need to be administered daily and deep intramuscular injections are administered every 1 to 4 weeks. Thus, over a 1-year treatment period, eugonadal testosterone values in a patient with testosterone deficiency syndrome would require administration of subcutaneous testosterone pellet implants 2 to 4 times per year, vs. 365 daily administrations of a gel or 13 to 52 dep intramuscular injections. The prolonged testosterone release from subcutaneous pellets over a period of 3 to 6 months also avoids the peaks and troughs of symptoms and circulating testosterone levels characteristic of intramuscular preparations or missed daily gel administrations [6,11,12]. Concern over patient abuse with testosterone administration is lessened based on the inability of the patient to self-administer the subcutaneous testosterone pellets. Furthermore, the lack of excess testosterone metabolite production, dermal transference, and scent clearly differentiate the topical gels from subcutaneous pellets.

The only long-acting subcutaneous testosterone pellet currently approved in the United States is the Testopel® product. In this single-site retrospective analysis, adverse events with the Testopel subcutaneous testosterone pellet were few (1.4% of procedures, 4/292) and not serious. Although erythrocytosis and gynecomastia can develop during testosterone treatment and are considered significant adverse events, we have not seen clinically significant cases in our patients receiving subcutaneously implanted pellet therapy.

Local infection with or without pellet extrusion is a concern with subcutaneously implanted pellets based on publications referencing the Organon product (infection rates 1.4–6.8%) [17–19]. However, none of our patients who complied with the post-procedure instructions to avoid exertion,

Table 3 Characteristics of patients who had baseline and follow-up results from the same laboratory and received Testopel alone and Testopel with anastrozole

		Testopel alone			Testopel with anastrozole		
Test	Statistic	Baseline	Follow-up*	Change from baseline	Baseline	Follow-up†	Change from baseline
Testosterone							
Total	Mean ± SD	336.9 ± 101.0	577.2 ± 173.0	240.3 ± 192.6	287.0 ± 111.4	656.0 ± 168.3	369.0 ± 138.5
(ng/dL)	Median (range)	340 (79–492)	579 (309–959)	226 (–111–880)	286 (70–473)	645 (383–974)	373 (161–585)
	N	40	40	40	21	21	21
Free	Mean ± SD	48.60 ± 28.98	92.12 ± 59.34	43.53 ± 48.36	40.89 ± 31.73	101.32 ± 65.98	60.43 ± 46.89
(pg/mL)	Median (range)	53.4 (7.7–99.4)	95.3 (10.2–266)	34.0 (–4.3–255)	39.4 (1.7–117)	107.5 (11.8–225)	49.9 (10.1–162)
	N	40	40	40	21	21	21
DHT	Mean ± SD	45.7 ± 55.5	39.9 ± 22.1	–2.26 ± 46.9	30.1 ± 19.5	40.3 ± 19.0	9.2 ± 21.0
(ng/mL)	Median (range)	30 (5.3–285)	38 (16–115)	3.0 (–211.3–71)	29 (7.8–95)	40 (6–76)	11 (–56–49)
	N	39	34	33	21	19	19
SHBG (nmol/L)	Mean ± SD	26.6 ± 10.5	27.0 ± 12.2	–0.8 ± 4.4	23.0 ± 11.2	23.3 ± 11.4	–0.1 ± 8.8
	Median (range)	27 (8–58)	26 (6–69)	0.0 (–15–8)	21 (8–48)	23 (7–52)	–0.5 (–29–18)
	N	36	36	33	21	20	20
Estradiol	Mean ± SD	22.0 ± 10.5	24.5 ± 11.7	2.3 ± 16.5	26.0 ± 14.6	16.6 ± 20.4	–9.0 ± 25.7
(pg/mL)	Median (range)	20 (9–54)	21 (8–57)	5 (–34–42)	21 (3–55)	13 (3–98)	–13 (–51–80)
	N	40	39	39	21	20	20
Estrone	Mean ± SD	48.3 ± 42.0	50.5 ± 33.4	–3.8 ± 40.9	68.8 ± 67.7	52.7 ± 30.4	–11.4 ± 76.8
(pg/mL)	Median (range)	38 (10–196)	44 (10–150)	7 (–141–29)	50 (19–309)	47 (10–137)	–3.0 (–268–77)
	N	17	22	16	17	17	16
PSA	Mean ± SD	0.74 ± 0.41	0.86 ± 0.45	0.12 ± 0.36	0.94 ± 0.62	1.27 ± 0.95	0.29 ± 0.68
(ng/mL)	Median (range)	0.7 (0.2–2.2)	0.7 (0.3–2.1)	0.1 (–0.8–1.2)	0.9 (0.2–2.7)	1.1 (0.3–3.5)	0.1 (–0.7–2.7)
	N	39	34	33	21	18	18
Hematocrit (%)	Mean ± SD	45.12 ± 2.34	46.38 ± 2.89	1.54 ± 3.26	45.38 ± 4.49	46.83 ± 3.79	0.86 ± 2.28
	Median (range)	45.5 (39.7–49.3)	46.3 (40.5–52.8)	1.3 (–3.9–10.5)	45.9 (34.9–51.4)	47.5 (36.6–51.5)	1.25 (–3.7–4.2)
	N	40	24	24	21	14	14

*In this subgroup, the follow-up visit occurred an average of 64 days after pellet implantation (SD = 22 days; range 26–120 days). More than one pellet implantation procedure may have occurred between baseline and follow-up assessments.
†In this subgroup, the follow-up visit occurred an average of 52 days after pellet implantation (SD = 14 days; range 23–84 days). More than one pellet implantation procedure may have occurred between baseline and follow-up assessments.
DHT = dihydrotestosterone; SD = standard deviation; SHBG = sex hormone binding globulin; PSA = prostate-specific antigen.

hot tubs, and saunas in the week following pellet implantation has reported an infection, including those who did not meet the criteria for inclusion in this retrospective study. The one subject in the study population who reported an infection (0.3%, 1/292 procedures) is also the only patient in our experience with Testopel to report an infection, and he acknowledged noncompliance and that he exposed the implant area to hot tub water 2 days after the implant procedure.

Infection is theoretically more likely to occur under the following circumstances: (i) inadvertent bacterial contamination of pellets during the implantation procedure; (ii) inadvertent bacterial contamination of the trocar tract, which results in delayed or failed tract closure (such as from a contaminated trocar); and/or (iii) patient failure to follow post-procedure instructions in the week following pellet implantation (such as refraining from wound exposure, and hot tub/sauna use), resulting in a secondary tract infection. In addition, factors that may contribute to extrusion include: (i) the surgical technique employed by the physician, (ii) inadvertent insertion of foreign material, such as that used in pellet packaging, and (iii) implantation at a site close to scar tissue from previous pellet implantation. The lower infection rate seen in our analysis with Testopel subcutaneous testosterone pellets may be caused by the differences in pellet size, manufacturing processes, product packaging, implantation technique, and/or the experience of the physician performing the implant.

Handelsman reported adverse events from 13 years of experience with the Organon testosterone pellet, during which pellet extrusion was reported in 83 of 973 (8.5%) pellet implant procedures [16]. Subsequent prospective randomized clinical trials demonstrated that neither washing the Organon pellets in filtered sterile alcohol nor soaking them in antibiotic solution prior to implantation significantly reduced the likelihood of pellet extrusion [17–19]. When pellets were alcohol-washed, 15 men (12%) experienced pellet extrusions among 125 procedures whereas, in the control group, 14 men (11%) experienced pellet extrusions among 126 procedures. Similarly, when pellets were antibiotic-soaked, 18 pellet extrusions were reported among 195 procedures (9%) whereas the control group reported 23 pellet extrusions among 205 procedures (11%, $P = 0.31$).

Pellet extrusion (with or without infection) is a valid concern with subcutaneously implanted pellets, yet can be modified by the technique used for pellet insertion. Prior to using the commercially available Testopel pellets, one of the authors (RKC) gained extensive experience with the use of hormone pellets from another manufacturer. The insertion technique used was similar to that described by Handelsman, which oriented the pellets end-to-end in the trocar tract as illustrated in Figures 5 and 6. Although this technique was successful for most patients, some patients experienced extrusion of one or more pellets. Once the implantation technique was modified by placing the pellets side-to-side within the subcutaneous pocket, and perpendicular to the trocar tract, patients no longer experienced pellet extrusion. This pellet orientation was designed to impede pellet migration and extrusion. All implantations of Testopel pellets in our practice, from December 2003 to the present, have been performed using this modified procedure and we believe that the modified procedure may represent the primary reason we have seen no pellet extrusions in patients who followed post-procedure care instructions.

The Testopel pellets may also have physical differences that contribute to the lower rate of infections and extrusions that we have experienced. As already mentioned, Testopel pellets are smaller and have a smoother surface than the Organon pellets, and may therefore be more dense or less likely to fracture. Testopel pellets also exhibit fewer irregular spaces where the pellet can inadvertently be contaminated during the implantation procedure. Tests of the physical characteristics such as density and friability for the two pellets should be considered by researchers with the appropriate knowledge and equipment.

Individualizing the dosing regimen to the patient's therapeutic response was important in maximizing clinical success (i.e., achieving treatment objectives), controlling adverse reactions, and resolving the symptoms of testosterone deficiency syndrome. Although we have observed that one 75 mg Testopel pellet raises the total testosterone level by an average of approximately 25 ng/dL, testosterone pellet metabolism is highly variable. Patients in this analysis received doses of 450 to 1500 mg, which is somewhat greater than the 150 to 450 mg dose range stated in the Testopel prescribing information. The average testosterone dosage regimen for implantation in our patients, 975 mg every 5 to 6 months, was consistent with the dosage regimen of 600 to 1,200 mg every 4 to 6 months reported with the Organon pellets [14–16,18,20]. The timing for subsequent testosterone implant procedures in our patients was

based on clinical and laboratory assessments, and consideration of patient preference. The testosterone levels from two post-implantation follow-up visits for a small number of our patients are, to our knowledge, the first biochemical data to document the long-acting nature of Testopel pellets.

A total of 63% of the study patients who had previous exposure to other androgen therapies preferred subcutaneous testosterone pellet therapy. Treatment preference was based on both therapeutic and practical factors, and some patients who were quite satisfied with testosterone implants chose not to continue using them for other reasons (e.g., out-of-pocket costs). Though the subject numbers in our analysis were small, the preference for testosterone implants over other forms of testosterone therapy was similar to previous reports [15,16].

Aromatase inhibitors such as anastrozole and letrozole are commonly employed, off-label and in modest doses, in the management of androgen deficiency syndrome. Their pharmacologic action is to inhibit the aromatization of testosterone to the undesirable metabolites estrone and estradiol, both of which exhibit negative feedback on the hypothalamus and anterior pituitary gland. Inhibiting testosterone aromatization results in increased testosterone levels and an increased testosterone-to-estrogen ratio. Anastrozole has been shown, even at low doses, to increase serum leutinizing hormone and testosterone levels while decreasing serum estrogen levels in both young and elderly men with hypogonadism, without adverse sequelae [25,26]. In this study population, men with excess aromatization who presented with borderline-high or supraphysiologic levels of estrone or estradiol received anastrozole orally at doses of 0.5 mg once weekly to 0.5 mg every other day in addition to subcutaneous testosterone replacement.

There were several limitations with this analysis, including all those associated with a single-site, retrospective study design (e.g., the potential for patient selection bias, investigator bias, and inconsistent evaluation and follow-up). More than half of the men (52%, 86/166) who presented during the 4.5-year study period did not meet eligibility criteria, which resulted in loss of important clinical data. In addition, 45 patients did not return for follow-up and it is possible that some of these could have had an adverse event that was not reported. Our analysis focused on patient safety, and did not rigorously investigate pharmacokinetic or pharmacodynamic relationships between hormone levels and time, dose, or patient satisfaction. This analysis also did not include medium or long-term patient satisfaction and discontinuation rates, as our records did not contain these data.

Patient satisfaction was crudely estimated in our analysis by answers to clinical questions at follow-up and by the number of subjects returning for subsequent treatment. No specific or questionnaire data were available in the medical records to explain why a patient discontinued treatment with testosterone pellets or preferred one therapy over another. In our experience, patients discontinue using testosterone pellets for a variety of reasons, including the occurrence of an adverse event, dissatisfaction with the clinical results, and the out-of-pocket expense associated with subcutaneous implants when the treatment and procedure aren't covered by the patient's insurance provider. A standardized and validated questionnaire for clinical symptoms and patient satisfaction data would have been preferred for this analysis. However, if one existed in 2003 when we started using Testopel, we were not aware of it. Prospective studies of any treatment for testosterone deficiency syndrome should include a validated questionnaire, such as the Aging Males' Symptoms scale or the European Male Aging Study—Sexual Function Questionnaire, which reliably assesses male sexual health [27–29].

Interpretation of changes in sex steroid hormones and other laboratory tests was somewhat difficult in this analysis as testing services were provided by multiple clinical laboratories. Because these laboratory data were obtained for clinical use, a reference range was reported for each test but the analytical method used was not documented. Although the reference ranges were sufficiently similar at the different laboratories and over time that we could summarize some laboratory data for all study patients (i.e., Table 2), there were substantial differences in the reference ranges for free testosterone. These data are included in Table 2 because of the statistically significant change from baseline despite the variability in the data. LabCorp and Quest Diagnostics were unable to identify the methodology used for the sex hormone tests between 2003 and the current method. Currently, Quest Diagnostics uses equilibrium dialysis with liquid chromatography-tandem mass spectrometry to measure free testosterone (reference range 35–155 mg/mL for men 18–69 years of age), whereas LabCorp uses direct radioimmunoassay (reference range 8.7–25.1 pg/mL), and these methods have very different reference ranges. To

provide a more accurate picture of the change from baseline, the laboratory data were analyzed for each lab separately to limit the variability in the data. These results were similar to those from the overall analysis; therefore these data were not presented. The variability in test methods and reference ranges also complicated patient care, especially when the choice of clinical laboratory was based on the patient's insurance provider rather than physician preference.

The primary goal of this analysis was to report our clinical experience with subcutaneously-implanted testosterone pellets (Testopel), with a focus on safety concerns, particularly local infection and pellet extrusion. Although the Testopel product has been in clinical use for over 35 years in the United States, there are few published studies describing the safety, pharmacokinetics, pharmacodynamics, or efficacy associated with its use. To gain more experience with this product, it will be important to perform prospective clinical trials engaging a larger patient population from multiple sites and from both academic- and community-based practices. A placebo-controlled arm in these studies would be ideal but may not be allowed by Institutional Review Boards because of the invasive nature of the drug delivery system. Therapy with subcutaneous testosterone pellets may be more effective for the restoration of metabolic health compared with other methods of shorter-acting testosterone therapy that have less patient compliance (oral, injectable, topical), but more data are needed. In summary there are several limitations with this study including no analyses of long-term patient satisfaction and discontinuation and validated questionnaires concerning hypogonadism diagnosis.

In the end, however, Testopel is a long-acting subcutaneous testosterone delivery system alternative to the patient with hypogonadism. The subcutaneous testosterone pellet choice offers several advantages to the patient with hypogonadism. In particular, the FDA recently emphasized the danger of short-acting testosterone drug transfer causing harm to partners and children. Use of Testopel is not associated with drug transfer concerns. In terms of cost, use of Testopel is half the cost of using short-acting testosterone gels when amortized over a year. The estimated annual cost of 5 g of testosterone gel once daily, which represents 75% of the U.S. market, is over $3,300, whereas 10 g testosterone gel once daily is over $6,600. The estimated annual cost of inserting eight pellets two to three times per year is around $1,500.

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Appendix 1

TESTOPEL Implant Procedure Discharge Instructions

1. You may apply ice locally to site as needed for discomfort/pain/swelling intermittently for 20–30 minutes every hour. If discomfort continues, take ibuprofen 600 mg orally every 6–8 hrs as needed. You may experience pellet site tenderness for several days post procedure.
2. You may experience redness and swelling at the implant site for several days following the procedure. This localized swelling and redness is generally secondary to the release of the medication and bruising from the procedure.
3. Please call the office if you experience the following: discharge from the procedure site, excessive redness or swelling, chills and/or fever of greater than 101.5°F, nausea or vomiting, dizziness or lightheadness, excessive tenderness, or any other symptoms.
4. Avoid hot tubs, swimming, or full water immersion of implant site for one week post-procedure. Showering is permissible the same day of the procedure. Keep bandage away from direct shower stream.
5. The bandage may be removed after one day, but the adhesive strips should be left in place for one week.
6. You may resume normal activity level as tolerated.

I have read, reviewed, discussed and fully understand the discharge instruction for the Testopel Implant procedure. I have no further questions or concerns at present. I understand I am to call the office with further questions or concerns.

Patient Signature: _____Date:_____

Witness:_____Date:_____