Subcutaneous Injection of Testosterone Is an Effective and Preferred Alternative to Intramuscular Injection: Demonstration in Female-to-Male Transgender Patients

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Context: Testosterone (T) is commonly administered intramuscularly to treat hypogonadal males and female-to-male (FTM) transgender patients. However, these injections can involve significant discomfort and may require arrangements for administration by others.

Objective: We assessed whether T could be administered effectively and safely subcutaneously as an alternative to intramuscular (IM) injections.

Design: Retrospective cohort study.

Setting: Outpatient reproductive endocrinology clinic at an academic medical center.

Patients: Sixty-three FTM transgender patients aged >18 years electing to receive subcutaneous (SC) T therapy for sex transition were included. Fifty-three patients were premenopausal.

Intervention: Patients were administered T cypionate or enanthate weekly at an initial dose of 50 mg. Dose was adjusted if needed to achieve serum total T levels within the normal male range.

Main Outcome Measurements: Serum concentrations of free and total T and total estradiol (E2), masculinization, and surveillance for reactions at injection sites.

Results: Serum T levels within the normal male range were achieved in all 63 patients with doses of 50 to 150 mg (median, 75/80 mg). Therapy was effective across a wide range of body mass index (19.0 to 49.9 kg/m^2). Minor and transient local reactions were reported in 9 out of 63 patients. Among 53 premenopausal patients, 51 achieved amenorrhea and 35 achieved serum E2 concentrations <50 pg/mL. Twenty-two patients were originally receiving IM and switched to SC therapy. All 22 had a mild (n = 2) or marked (n = 20) preference for SC injections; none preferred IM injections.

Conclusions: Our observations indicate that SC T injections are an effective, safe, and well-accepted alternative to IM T injections. (***J Clin Endocrinol Metab*** **102: 2349–2355, 2017)**

Testosterone (T) therapy is commonly administered to hypogonadal men and female-to-male (FTM) transgender patients. Since its introduction in the 1930s, parenteral T has typically been administered intramuscularly (1, 2). However, intramuscular (IM) administration of T has drawbacks such as pain, bruising, and the frequent necessity to arrange injections by a medical provider or other person. T undeconoate provides an option for IM

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Abbreviations: ANOVA, analysis of variance; BMI, body mass index; E2, estradiol; FTM, female-to-male; IM, intramuscular; SC, subcutaneous; T, testosterone; WHO, World Health Organization.

injections at 10-week intervals but is available only through a risk evaluation and mitigation program because of the risk of pulmonary oil microembolism (3–5). Transdermal T formulations (patches and gels) can also have limitations such as local reactions, poor adhesion, fear of skin-to-skin transmission (6), unpleasant odor (7), lack of insurance coverage or high copays, and limited patient acceptance (8). Subcutaneous (SC) insertion of T pellets is available but has been limited by the need for surgery, the possibility of infection, fibrosis or pellet extrusion, limited data regarding efficacy, inflexibility of dosing, and limited acceptance (9).

Two preliminary reports (10, 11) and a pharmacokinetic study (12) of SC T administration suggest that the SC route may be a safe, convenient, and effective alternative to currently available options. The preliminary reports assessed short-term therapy in hypogonadal men (10) and FTM transgender patients (11) and did not universally attain serum levels of T within the normal range. The pharmacokinetic study used fixed doses from a potentially expensive autoinjector (12). To further characterize SC T as a practical and acceptable alternative to IM administration, we evaluated the efficacy, safety, and acceptability of manual SC injections of T cypionate to patients undergoing FTM sex transition in our clinic. Genetic females undergoing sex transition provide an ideal population with which to study efficacy because their low endogenous secretion of T contributes minimally to serum measurements of T. In addition, biological effects of T can be assessed by monitoring suppression of ovarian activity and masculinization. Previous studies in hypogonadal men either did not report pretreatment serum levels of T (10) or allowed pretreatment levels up to 300 ng/dL (12). FTM transgender patients also provide clear clinical indicators of the efficacy of SC T injection with the appearance of amenorrhea and masculinization. The primary aim of this study was to determine if SC administration of T could consistently achieve serum T concentrations within the normal adult male range at doses equivalent to or lower than those typically used for IM dosing with minimal or no reactions to the injections. In addition, we assessed patient preference for this option of T therapy. Biological effects of the SC administered T were evaluated by assessing ovarian suppression and masculinization.

Methods

Patients

Patients in the Maine Medical Center Division of Reproductive Endocrinology and Infertility undergoing FTM sex transition who were seen between September 2010 and September 2016 were offered the options of SC, IM, or transdermal T therapy and then routinely monitored. Ninety-one of 96 patients selected the option of SC T. Sixty-three of those 91 patients have completed the process of individualized dose adjustment with laboratory monitoring performed through LabCorp (Calabasas, CA) and were included in a retrospective cohort study. The other 28 patients have not completed dose adjustments or had monitoring performed through a different laboratory. All 63 patients met criteria for inclusion: (1) age >18 years, (2) good general health with normal hepatic and renal function, (3) serum total T concentrations <50 ng/dL prior to therapy (in patients not already receiving IM T), and (4) no concomitant administration of drugs known to affect the hypothalamic-pituitary-ovarian axis, including progestins or gonadotropin-releasing hormone agonists. The study was approved by the Maine Medical Center Institutional Review Board. Informed consent was not required.

Administration of T

Prior to beginning SC T, patients received teaching from a nurse who observed their first injections. Treatment was initiated with T cypionate in cottonseed oil (West-Ward®, Cherry Hill, NJ). A subset of patients was switched to T enanthate in sesame oil (West-Ward®) if T cypionate became unavailable through their pharmacy or if they had persistent local reactions to T cypionate injections. Patients were instructed to draw up T into a 1-mL syringe with a 20- or 25-gauge needle. Because of the solution's viscosity, a luer lock syringe was used to prevent the needle from disengaging from the syringe during injection. A 25-gauge, 5/8-inch needle was used to inject T into the SC tissue of the abdomen or thigh. Patients initially received weekly SC injections of 50 mg of T. Weekly SC T doses were increased sequentially to 75 or 80 mg, 100 mg, and 150 mg if needed to attain a serum concentration of total T within the adult normal male range (348 to 1197 ng/dL). Doses were further adjusted to achieve serum concentrations of 500 to 1197 ng/dL unless patients had a satisfactory clinical response at concentrations of 348 to 500 ng/dL. All patients self-administered their injections. More recent patients received a second level dose of 80 mg rather than 75 mg because of greater ease of measuring on the syringe. These patients are referred to as a single dosing group designated as 75/80 mg for the remainder of this paper.

Monitoring

Baseline serum T concentrations were measured prior to therapy in patients not already receiving T therapy at their initial visits in our clinic. While receiving therapy, serum concentrations of total and free T were measured 3 to 4 days after the fourth or subsequent SC injection of any given dose. Serum total T levels were measured every 6 to 12 months after the dose was optimized. Serum total estradiol (E2) was measured in premenopausal patients once dose adjustments were completed.

Patients were asked at each office visit if they had experienced any vaginal bleeding. Facial and body hair, lowering of the voice, and injection sites were assessed on physical exam.

Assessment of preference and safety

Patient preference for IM or SC T administration was assessed verbally among patients who had received both IM and SC T injections and was entered into the medical record; potential responses were a mild or marked preference for IM injection, no preference, or a mild or marked preference for SC injection. In addition, at each visit, patients who initiated therapy with SC T or

had switched to SC therapy were asked if they would prefer to change to IM injections or a transdermal preparation. Safety was assessed at each visit by recording adverse reactions at the site of injection by patient history and/or by physical exam. The appearance of acne was assessed at each visit. Chemistry panel, including hepatic enzymes and hepatic function parameters, and hematocrit were routinely monitored in all patients.

Assays

Serum total T and total E2 were measured by liquid chromatography/mass spectrometry, and free T was measured using equilibrium dialysis (LabCorp). Proficiency tests for these assays were concordant with the Centers for Disease Control and Prevention reference method assays. The normal adult male range for total T was 348 to 1197 ng/dL and for free T was 52 to 280 pg/mL. The normal range for adult males in the total E2 assay was 8.0 to 35.0 pg/mL. We accepted the Endocrine Society guideline for suppression of E2 in FTM transgender patients to <50 pg/mL (1). Interassay precision for low, medium, and high concentration quality control sera, respectively, expressed as percentage coefficient of variation, was: T, 9.9%, 7.9%, and 5.0%; free T, 8.5%, 9.1%, and 6.7%; and E2, 4.4%, 3.5%, and 3.3%. The lower limits of detection were total T 2.5 ng/dL, free T 0.2 pg/mL, and E2 1 pg/mL.

Data analysis

Because the 75- and 80-mg doses were essentially equivalent, they are included in a single dosing group designated as 75/80 mg. Clinical and demographic data were summarized as mean (standard deviation), median (range), and/or n (%), as appropriate. The relationship between body mass index (BMI) and T dose was evaluated by Spearman's correlation. Differences in continuous variables between subgroups were evaluated by Student *t* test or by analysis of variance (ANOVA) or Kruskal-Wallis test, as appropriate. Pairwise *post hoc* analyses were by Student *t* test with Bonferroni correction for multiple comparisons. World Health Organization (WHO) BMI categories were defined as 18 to 24.9 kg/m^2 (normal), 25.0 to 29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese).

Results

Patient characteristics

Patient characteristics are displayed in Table 1. For the 63 patients receiving SC T, mean age at the completion of dose titration was 27.6 (10.3) years (range, 18 to 69 years). Mean BMI was 28.7 (7.6) kg/m^2 (range, 19.0 to 49.9 kg/m^2), and 26 (41.3%), 14 (22.2%), and 23 (36.5%) patients were in the normal, overweight, and obese WHO BMI categories, respectively. Among 10 postmenopausal patients, 6 were aged >40 years, of whom 2 had prior bilateral oophorectomy with hysterectomy and 1 had prior hysterectomy alone; all 4 postmenopausal patients aged <40 years had had bilateral oophorectomy with hysterectomy. Eight of the 10 postmenopausal patients reported a past history of regular menses. Forty-seven of the 53 premenopausal patients reported a history of regular menses prior to initiating T therapy; none had undergone ovarian surgery. Two patients had a diagnosis of hypothalamic amenorrhea, and four had a diagnosis of polycystic ovary syndrome prior to treatment.

Serum T levels and dosing

All 63 patients achieved serum total T levels within or above the normal male range. At their most recent blood draw on optimized therapy, mean total serum T was 702 (212) ng/dL with a range between 357 and 1377 ng/dL (Fig. 1). These measurements were obtained after patients had been on the optimized T dose for 0.5 to 42.7 months. Two subjects had levels above the normal serum range, one at 1203 ng/dL (T dose: 50 mg) and one at 1377 ng/dL (T dose: 150 mg). In the first patient, a previous total T level on the same dose was 696 ng/mL with free T 90 pg/mL. In the second patient, a previous total T on the same dose was 987 ng/dL with free T 138 pg/mL. Free T data were available for 50 patients at their most recent follow-up visit, of whom 48 (96%) had values within the normal range (Fig. 1); two values were low at 42 and 47 pg/mL (with total T values of 342 and 589 ng/dL and suppressed total E2 levels of 13 and 27 pg/mL). Mean serum free T concentration was 129 (57) pg/mL with a range between 42 and 275 pg/mL.

The median T dose was 75/80 mg weekly (range, 50 to 150 mg). Twenty (31.7%) patients achieved normal serum total T concentrations at a weekly T dose of 50 mg, 34 (54.0%) at 75/80 mg, 7 (11.1%) at 100 mg, and 2

Table 1. Characteristics of the Patients

Variable	All Patients	Premenopausal	Postmenopausal
n	63	53	10
Age (y)	27.6 (10.3) [18–69]	24.8 (5.7) [18–40]	42.8 (15.5) [24–69]
BMI (kg/m^2)	28.7 (7.6) [19.0–49.9]	28.4 (7.6) [19.0–49.9]	30.1 (7.7) [20.3–44.5]
T dose	80 [25–150]	80 [25–150]	80 [50–100]
Time on dose (mo)	9.5 [0.5–42.7]	12.7 (11.3) [0.5–42.2]	9.0 (6.3) [1.1–17.4]
Serum total T (ng/dL)[a]	702 (212) [357–1377]	711 (211) [405–1377]	654 (220) [357–1077]
Serum free T (pg/mL)[a]	129 (57) [42–275]	131 (56) [47–275]	114 (66) [42–233]
Serum E2 (pg/mL)[a]	—	39.9 (21.7) [5–130]	—

Data are shown as n (%), mean (standard deviation) [range], or median [range].

[a]Most recent follow-up assay.

(3.2%) at 150 mg. No patient required a dose >150 mg per week.

Patients were followed with laboratory testing at the effective dose for a median of 9.5 months (range, 0.5 to 42.7 months). Repeat serum total T was measured at 6- to 12-month intervals in 35 patients who had received the optimized dose for ≥6 months (Fig. 2). At their most recent follow-up visit, all 35 patients maintained serum T within the normal range over 6.3 to 42.7 (median, 19.3) months. Total serum T data through LabCorp were available for 29 of these 35 patients at their penultimate follow-up visit (median, 10.9 months prior to the most recent visit). Twenty-eight (96.6%) had values in the normal range, and one had a slightly low total T value of 331 ng/dL (T dose, 80 mg; free T normal at 93 pg/mL). That patient's most recent follow-up total T value was within the normal range at 451 ng/dL.

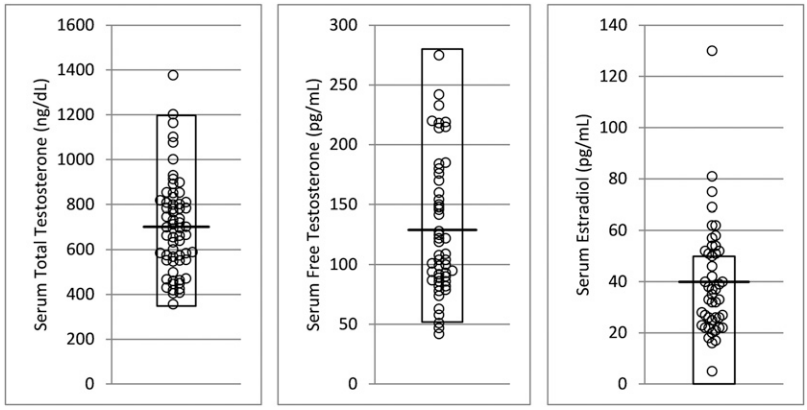

Figure 1. Serum hormone levels in FTM patients receiving SC T injections. Serum total T data were available for all 63 patients; free T data were available for 50 patients; and serum E2 concentrations measured by LabCorp were available for 47 of 53 premenopausal patients. Rectangles indicate normal ranges. Bars designate mean values. Note that the patient with an E2 level of 130 pg/mL had a previous serum E2 measurement of 37 pg/mL on the same dose (see text).

Ovarian function and masculinization

Of the 53 premenopausal patients, 51 (96.2%) achieved amenorrhea. Of the remaining two, one had minimal light bleeding (with serum E2 69 pg/mL and total T 1102 ng/dL) and was lost to long-term follow-up, and one had persistent bothersome bleeding (with E2 75 pg/mL and total T 768 ng/dL) leading to the addition of progestin therapy. Among premenopausal patients, serum total E2 concentrations were available through LabCorp in 46 patients. The most recent mean serum total E2 concentration on the optimized dose was 39.9 (21.7) pg/mL with a range between 5 and 130 pg/mL. Thirty patients (63.8%) had serum E2 levels <50 pg/mL, nine patients had levels from 50 to 54 pg/mL, and eight patients had levels >54 pg/mL (Fig. 1). The patient with the E2 value of 130 pg/mL had a simultaneous total T value of 854 ng/mL and a previous serum E2 concentration of 37 pg/mL on the same dose of T. All patients who received the optimized dose for at least 6 months reported deepening of the voice into the male range as well as the appearance of terminal facial hair growth to varying degrees.

BMI

Normal serum total T levels were attained in all patients in all BMI categories (Fig. 3). The median dose of SC T required to attain serum T levels within the normal range (75/80 mg) did not differ among patients with BMI in the normal, overweight, or obese WHO BMI categories (P = 0.69 by Kruskal-Wallis). Similarly, there was no relationship between BMI and T dose among patients at the dose giving normal male serum T levels (ρ = 0.20; P = 0.11; n = 63). Serum free T concentrations did not differ significantly between WHO BMI categories (P = 0.92 by ANOVA). Serum total T, however, differed across normal [754 (217) ng/dL, n = 26], overweight [765 (220) ng/dL, n = 14], and obese [606 (169) ng/dL, n = 23] BMI categories (P = 0.021 by ANOVA). In *post hoc* analysis, the difference in total serum T between normal and obese groups was statistically but not clinically significant (P = 0.04).

Preference, tolerability, local reactions, and safety

Surveys administered to patients who had previously received IM T prior to SC demonstrated that after

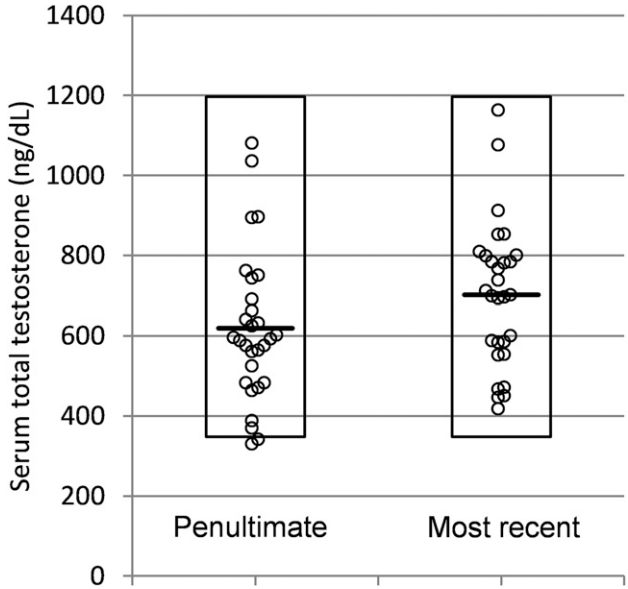

Figure 2. Serial serum total T concentrations in 29 FTM patients followed for ≥6 months on SC T injections. Serum total T levels within the normal range were sustained within the normal range with continued therapy. SC T doses were the same for both penultimate and most recent measurements. Rectangles designate normal ranges, and bars indicate mean values.

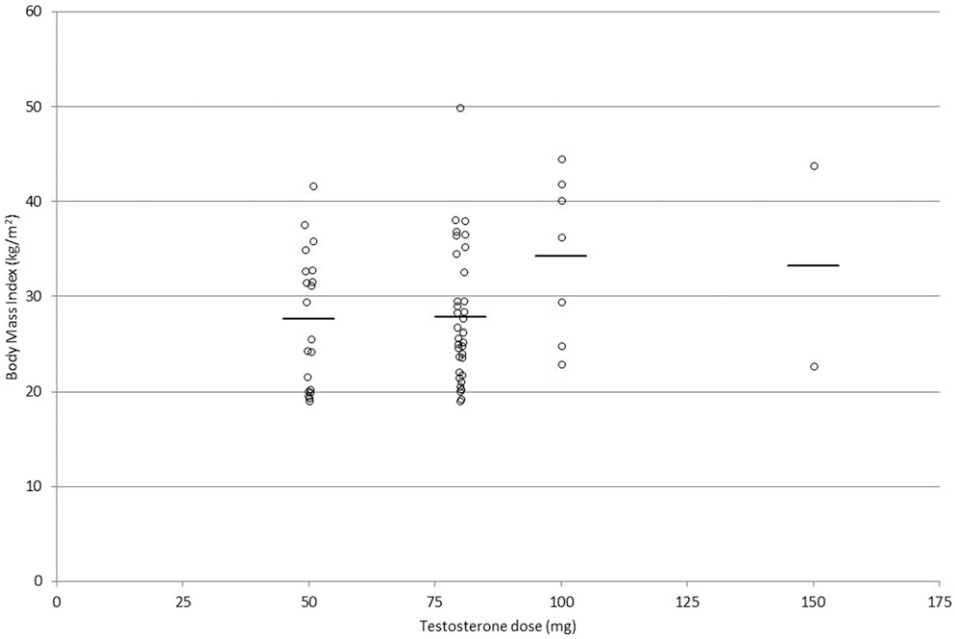

Figure 3. Optimized doses of SC T in patients according to BMI. SC T injections were effective across the broad range of BMI values encountered in our patients. No effect of BMI on dosing requirements was observed. The bars indicate mean values. Note that patients administered a dose of 75 mg were combined with patients administered a dose of 80 mg for this graph.

initiating SC therapy, all 22 preferred SC injections; two had a mild preference and 20 a marked preference for SC injections. No patients were neutral or expressed a preference for IM injections.

There were 10 site reactions reported by 9 patients. Four patients reported a small nodule at the site of injection that occurred intermittently or consistently, resolved in 1 to 2 days, and was not bothersome. Two patients reported that a small area of urticaria appeared at the injection site several hours after each injection and persisted for 2 to 3 days. Two patients reported some transient inflammation at the injection site, one of whom later experienced a single episode of cellulitis that resolved without therapy. There were no other local or systemic adverse effects.

Acne emerged in 37 of our 63 patients and was usually mild. In only two patients was the degree of acne sufficient to prompt referral to a dermatologist. No patients opted to decrease their T dose on the basis of the acne. None of our patients, including those who had undergone ovariectomy, experienced vasomotor symptoms while receiving T therapy.

Hematocrit values remained within the normal adult male range in all patients, and chemistry panel values including hepatic function parameters and enzymes remained normal throughout the course of therapy.

Discussion

Data from our patients indicate that long-term SC administration of T cypionate to FTM transgender patients is effective, safe, and well accepted. Because our patients were genetically female with low endogenous T secretion, the normal male levels of serum T necessarily resulted from absorption of the T that was administered subcutaneously. Sustained efficacy for more than 6 months of therapy was demonstrated. Our observations extend information reported in preliminary short-term studies in hypogonadal men (10) and young FTM transgender patients (11) as well as a pharmacokinetic study in hypogonadal men (12). In the initial report in hypogonadal men (10), 22 men with primary and secondary hypogonadism were administered SC T with doses ranging from 50 to 100 mg per week. Both peak and trough T values were within the normal adult male range, and no local reactions were reported. Pretreatment serum T concentrations were not reported. In 35 young FTM transgender patients with a mean age of 18.7 years, an average final dose of 46.4 mg once per week resulted in serum T levels within the normal adult male range in 91.4% of patients (11). The lowest total T level on therapy was 49 ng/dL (normal range: 250 to 1100 ng/dL). By adjusting doses to assure that serum T levels reached the normal range, we were able to provide more detailed dosing information than previously available.

Biological effects of SC T administration were apparent with the development of amenorrhea in our premenopausal patients and with deepening of voices and the appearance of facial hair. The development of amenorrhea in all but two patients who had regular menses prior to therapy and the suppression of serum E2 levels to <50 pg/mL in most of those patients (meeting the

Endocrine Society guidelines for suppression) (1) indicated that T that is injected subcutaneously has a similar biological effect to that reported with IM T. A previous report in transgender patients attained amenorrhea in only 85% of patients (11). With careful dose adjustment, we were able to demonstrate a broader efficacy of SC T therapy to suppress menstruation. The appearance of acne that also occurs with other forms of T administration (1, 2) was observed in a subset of our patients and was deemed tolerable by the patients.

In the previous report of SC T therapy in FTM transgender patients, normal serum T levels were not universally achieved in patients whose BMI ranged from 18 to 32 kg/m^2 (11). We demonstrated in our patient population that normal serum T levels could be attained across an even broader range of BMIs (19.0 to 49.9 kg/m^2). Because the SC route of injection was not less effective in patients with higher BMIs, obesity does not appear to be a limitation for SC administration of T.

Our patients expressed a marked preference for SC administration. When provided with options of IM, SC, topical, and transdermal T administration for initial therapy, almost all chose SC injections. Furthermore, all patients who experienced both IM and SC injections voiced a preference for SC injections, mostly a strong preference. This preference for SC injections is consistent with previous reports regarding factors determining patient preferences for mode of T administration (8), including factors such as the pain associated with IM injections (4, 13) and a patient preference for smaller needle size (14). Consistent with previous reports (10–12), no serious local reactions at the injection sites were observed, and the SC injections were well tolerated. These observations indicate that SC T therapy can be a widely accepted option for patients. The high level of acceptance by our patients of manual SC injections is clinically important because the manual injection is likely to be more economical than injections with an autoinjector (12).

The median SC dose used in our patients was 75/80 mg per week, which is lower than the typical dose of 100 mg per week (or 200 mg every 2 weeks) recommended for IM dosing (1). Previous studies also indicate that therapeutic serum concentrations of T can be attained with lower doses when T is administered subcutaneously rather than intramuscularly (10–12). This observation suggests that SC administration of T is at least as economical as IM injection, if not more, particularly with the decreased need for office visits for injections for many patients. SC administration of T is far more economical than transdermal options, with costs in excess of $400 per month.

In summary, we have provided information regarding efficacy, dosing, and safety of SC T injections in FTM transgender patients. Manual SC injection of T provides a practical and economic alternative to IM dosing across a broad range of ages and BMI values for patients who require T therapy. We have extended the previous initial reports of SC injection of T cypionate (10–12) to confirm its sustained efficacy in patients with very low endogenous T secretion for up to 42 months of therapy. It appears to be well tolerated and preferred by patients to IM dosing. Our observations that both total and free T concentrations were within the normal adult male range indicate that monitoring of dosing can be carried out with serum total T and E2 concentrations, with free T measurements not usually necessary. Although we measured serum levels of T 3 to 4 days after a dose, a pharmacologic study reported fairly stable levels between dosing, suggesting that serum T levels can be effectively monitored on other days as well (11). These observations simplify monitoring of T therapy. Additional pharmacologic studies of this route to evaluate longer intervals of dosing, similar to those on which IM dosing is based (15, 16), are probably not needed because of the convenience of the weekly administration by the SC route. Although this study was limited to FTM transgender patients, it is reasonable to believe that the same information can be applied to treatment of hypogonadal males, as indicated by the previous preliminary studies already cited (10, 12).

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