LGBT Health
Volume 1, Number 3, 2014

DOI: 10.1089/lgbt.2014.0018



# Subcutaneous Testosterone: An Effective Delivery Mechanism for Masculinizing Young Transgender Men

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## Abstract

***Purpose:*** Testosterone is the recommended treatment for transgender youth who desire the development of male secondary sexual characteristics. While intramuscular injection remains the most common means of delivering injectable testosterone, subcutaneous (SC) delivery has been used with clinical success. No data reporting serum levels and feasibility are available. We aimed to determine both if subcutaneous delivery of testosterone resulted in menstrual cessation, and the normal male ranges of serum testosterone in this subpopulation of female-to-male transgender youth.

***Methods:*** Within an urban hospital-affiliated Adolescent Medicine clinic, thirty-six youth aged 13 to 24 years transitioning from female to male received testosterone cypionate via subcutaneous injections for masculinization. Participants were a subpopulation of those enrolled in a longitudinal, prospective study examining the impact of treatment for transgender youth. A titrated dose of testosterone cypionate (average dose 46.4 mg per week) via subcutaneous injection was delivered over 6 months. The main outcomes included menstrual cessation as well as raised free and total testosterone levels.

***Results:*** Eighty-five percent of participants had ceased menstrual bleeding within 6 months after initiating testosterone. The average time to menstrual cessation was 2.9 months. Most participants (91.4%) reached total testosterone levels within the normal male range after 6 months of subcutaneous delivery (49–1138 ng/dL, 521.4 ng/dL total test). Few adverse effects were reported.

***Conclusion:*** Subcutaneous delivery of testosterone for masculinization of transgender youth seems to be effective and well tolerated over short treatment times. Additional studies are needed to determine whether long term use of subcutaneous testosterone delivery yield similar results.

**Key words:** masculinization, subcutaneous testosterone, transgender men, transgender youth.

## Introduction

Transgender is a term used to describe the experience of a discrepancy between one's internal gender identity and their assigned sex at birth.[1] Many transgender individuals choose to pursue medical, and often surgical, intervention in order to bring their bodies into closer alignment with their internal gender.[2] Experiencing a regular menstrual cycle, breast development and high voice pitch are three elements of female development that are extremely undesirable to many transgender men and may pose challenges to assimilation in the male role in society. Testosterone therapy has been used for decades in transgender men who desire menstrual cessation, deepening of voice pitch, and the development of male secondary sexual characteristics.[3]

Although there are several means of delivering testosterone, the most common and accessible are the testosterone esters (cypionate or enanthate) administered via intramuscular delivery.[3] While rare, side effects of intramuscular (IM) delivery of testosterone have been reported, including irritation at injection site, breakage of needles in the body of the muscle, and development of local infections from IM injections.[4] Additionally, intramuscular delivery of testosterone results in declining serum levels to subnormal just prior to the next delivery date. Patients may experience fatigue and mood changes with this decline.[5]

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An alternative method for delivering testosterone is subcutaneously (SC) in the form of long-acting pellets, used successfully in adolescent hypogonadal natal boys.[6] In the clinical setting, subcutaneous testosterone injections are tolerated much better, hurt less, and result in fewer complications (Personal communication, Norman Spack, MD, January 2010). Subcutaneous injection of testosterone has been used with clinical success within the transgender male population, but no data reporting serum levels and feasibility are available. One small pilot study has described successful achievement of normal male serum testosterone levels in 22 hypogonadal men receiving testosterone enanthate via subcutaneous delivery. In this study, all subjects achieved normal male ranges of free and total testosterone after subcutaneous delivery of testosterone enanthate.[7] This manuscript describes baseline and 6 month follow-up data collected for a subset of transgender youth undergoing phenotypic transition with testosterone delivered subcutaneously in order to masculinize their bodies.

## Methods

From 2011 through 2012, youth ages 12 to 24 years seeking treatment for gender transition with cross-sex hormones were recruited from those patients who self-referred to a large, transgender youth-specialized, multidisciplinary clinic. All youth were approached to participate in the study if they were between 12 and 24 years old, naïve to cross-sex hormones, and able to read English. Minors provided assent, and legal guardians provided required consent for participation in the study. Those over 18 years consented for themselves. Participants described here represent a subgroup of a larger, prospective, longitudinal study evaluating the psychosocial and physiologic impact of cross-sex hormones and mental health therapy in transgender youth. The study received approval from the Internal Review Board at Children's Hospital Los Angeles.

Thirty-six of the first cohort of participants between the ages of 13 and 24 reported male gender identities and were treated with testosterone cypionate, delivered subcutaneously. For cost savings, we used testosterone cypionate suspended in sesame oil prepared by a compounding pharmacy. Participants were initially given injections by a trained nurse in the clinic, but were taught to self-inject over several weeks. Patients needed to demonstrate satisfactory knowledge and skill in order to begin self-injections. Testosterone dosing was started at a biweekly dose of 25 mg for the first 8 weeks, then increased to 25 mg SC weekly for four weeks and, if tolerated, increased to 50 mg weekly. Dosing was adjusted after this based on clinical response. Most participants ended up on a final dose of 25 to 75 mg per week. The four participants who were 15 years of age or younger were on 25 mg weekly at six months. The average dose of weekly testosterone delivered was 46.4 mg. Injections were given via 25-gauge, 5/8 inch needles on alternating sides into subcutaneous fat tissue in the midsection of the torso.

Demographic data collected, including assigned sex at birth (male or female), age (years), country of birth (United States [not including Puerto Rico], or any other country), and race/ethnicity (African American/Black, Caucasian/White, Latino, Asian/Pacific Islander, or other) were collected via computer-assisted survey instrument prior to initiating hormone treatment. Untimed levels of serum free testosterone, total testosterone, and estradiol were collected at the end of the initial visit and six-month follow-up. Hormone levels, lab values, anthropometric measurements, and menstrual history were obtained via chart abstraction by the treating physician (also the study's Principal Investigator) at baseline and follow-up visits.

## Results

One subject was missing demographic survey data. Among the other 35, patients ranged in age from 13 to 24 years old (mean = 18.7 years, standard deviation [SD] = 2.6 years). Only one subject (3%) was born outside the US. Twenty-six subjects (76%) reported their race as Caucasian, three (9%) were Latino, three (9%) were Black, one (3%) Asian/Pacific Islander, and one indicated (3%) another race.

The average length of time participants received injections in the clinic was 3 months. Most (93%) participants were self-injecting by 6 months after initiation of testosterone therapy. Three participants had family members administering their injections.

Most participants reached total and free testosterone levels (91.4%) within the normal male range after 6 months of subcutaneous testosterone cypionate delivery (total: range 49–1138 ng/dL [normal male range 250–1100 ng/dL], mean = 521.4 ng/dL, SD = 211.6 ng/dL; free: range 10.9–292.6 pg/mL [normal male range 35–155 pg/mL] mean = 104.3 pg/mL, SD = 58 pg/mL). One participant was missing total and free testosterone levels at the 6 month follow-up, and is excluded from this analysis. Both total testosterone (paired $t[33] = 13.5$, $p < 0.001$) and free testosterone (paired $t[32] = 9.6$, $p < 0.001$) had significantly increased after 6 months of treatment. Estradiol levels decreased significantly from baseline to 6 months after treatment (mean baseline 94 pg/mL SD = 14.8 pg/mL; mean 6 months 43.9 pg/mL SD = 14.8 pg/mL; paired $t(32) = -3.0$ $p = 0.006$).

Two youth were not menstruating at initiation of therapy; one participant had a progesterone containing intrauterine device in place for the purpose of achieving menstrual cessation, and one participant had a contraceptive progesterone secreting implant in place. One additional youth did not have menstrual information recorded in the chart. Data from these youth were not included in the menstrual cessation analysis. Of the 33 remaining youth, menstrual bleeding had ceased in 28 (85%) participants within 6 months after initiating testosterone. The average number of months to menstrual cessation among these youth was 2.9 months (SD = 1.5 months).

As expected, hemoglobin increased after 6 months of treatment, but not to a clinically significant level (mean baseline 13.1 g/dL; mean 6 months 14.5 g/dL; paired $t[34] = 7.49$ $p < 0.001$). Systolic blood pressure, body mass index and alanine aminotransferase increased to statistically significant levels, but not to clinically significant or dangerous levels. Other physiologic parameters including non-fasting total cholesterol, diastolic blood pressure, and aspartate aminotransferase were not significantly changed after 6 months of treatment. (Table 1).

## Side Effects

Two participants reported localized reactions to subcutaneous injections (erythema, swelling, and pain at the injection site) that were alleviated by switching to testosterone cypionate suspended in cottonseed oil, rather than sesame oil. Several participants noted the development of small, subcutaneous nodules that resolved over a few days following injections.

Table 1. Physiologic/Anthropometric Parameters

| *Physiologic parameter* | *Baseline mean (SD)* | *6 month mean (SD)* | *paired t(df)* | p-*value* |
|---|---|---|---|---|
| Total testosterone (ng/dL) | 35.2 (15.4) | 521.4 (211.6) | t[33] = 13.5 | < .001 |
| Free testosterone (pg/mL) | 5.2 (7.5) | 104.3 (58.0) | t[32] = 9.6 | < .001 |
| Estradiol (pg/mL) | 94 (14.8) | 43.9 (31.8) | t(32) = −3.0 | 0.006 |
| Systolic Blood Pressure (mm HG) | 114.5 (13.6) | 119.5 (12.0) | t(34) = 2.13 | 0.041* |
| Diastolic Blood Pressure (mm HG) | 65.8 (10.8) | 65.3 (10.6) | t(34) = −.255 | 0.8 |
| Body Mass Index (kg/m2) | 25.3 (5.2) | 26.6 (5.6) | t(34) = 4.94 | < .001 |
| Total Cholesterol (mg/dL) | 167.1 (34.7) | 165.3 (41.8) | t(35) = −.45 | 0.653 |
| Aspartate Aminotransferase (U/L) normal range 15–46 U/L | 54.6 (29.9) | 69.5 (43.5) | t(33) = 1.46 | 0.154 |
| Alanine Aminotransferase (U/L) normal range 3–35 U/L | 22.4 (10.9) | 27.0 (29.9) | t(33) = 2.99 | 0.005* |
| Hemoglobin (g/dL) | 13.1 (.9) | 14.5 (1.3) | t(34) = 7.49 | < 0.001 |
| Serum Estradiol level (pg/dL) | 93.0 (96.3) | 43.9 (30.5) | t(33) = −3.0 | 0.006 |

*Not clinically significant

### Acceptability

No participants reported dissatisfaction with subcutaneous delivery or a desire to switch to another method of delivery during the first six months of therapy.

### Conclusion

Many transgender men will face a future of life-long testosterone treatment in order to maintain appropriate and desired masculinization. Current testosterone delivery mechanisms pose both benefits and challenges. While topical testosterone delivery via patches and gels may be less invasive, the side effects of irritation (patches) and potential to transfer to partners (gel) may make topical a less desirable form of delivery, particularly for adolescents. Intramuscular injections are painful, and are associated with rollercoaster levels of testosterone, supraphysiologic in the first few days after injection, and sub-physiologic toward the end of a 14-day cycle. Subcutaneous testosterone implants have been used for testosterone replacement for decades, but require surgical outpatient placement with the possibility for infection and pellet extrusion.[8]

In this first cohort of transgender youth treated with weekly testosterone injections, short-term follow up found that subcutaneous delivery may be an effective mechanism for achieving normal male ranges of testosterone, induce amenorrhea, and have little adverse impact on physiologic parameters over the first six months of therapy. This study is limited due to the short follow up period, and has limited generalizability to transgender men of all ages due to the young age group that was included. Additionally, this study was not undertaken nor designed as a pharmacokinetic investigation, and the testosterone levels in this study are untimed. Larger studies should consider peak and trough timing to assure adequate levels are achieved throughout the dosing interval. Impact on physiologic parameters, including body mass index, liver function, fasting lipid levels, and hemoglobin over longer periods of time would be useful. Of significant value would be a comparison study between intramuscular and subcutaneous testosterone delivery. Future studies and longer-term follow-up in this cohort are necessary to determine the impact of this delivery mechanism over time. In this cohort, subcutaneous testosterone cypionate was feasible and well tolerated, and perhaps offers insight into a new mechanism for testosterone delivery.

### Acknowledgment

Special thanks to Norman Spack, MD, Medical Director of the Gender Management Service at Boston Children's Hospital, for introducing our care team to the concept and details of subcutaneous testosterone delivery.

### Author Disclosure Statement

No competing financial interests exist.

### References

1. Grossman AH, D'Augelli AR: Transgender youth and life-threatening behaviors. Suicide Life Threat Behav 2007;37: 527–537.
2. Coolhart D, Baker A, Farmer S, Malaney M, Shipman D: Therapy with transsexual youth and their families: A clinical tool for assessing youth's readiness for gender transition. J Marital Fam Ther 2012;39:223–243.
3. Mueller A, Kiesewetter F, Binder H, Beckmann MW, Dittrich R: Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. J Clin Endocrinol Metab 2007;92:3470–3475.
4. Wright E: Hypogonadism: Treatment, side effects and monitoring. University of Tennessee Advanced Studies in Pharmacy 3;2007:149–156.
5. Jacobeit JW, Gooren LJ, Schulte HM: Long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. J Sex Med 2007;4:1479–1484.
6. Zacharin MR, Warne GL: Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets. Arch Dis Child 1997;76:495–499.
7. Al-Futaisi AM, Al-Zakwani IS, Almahrezi AM, Morris D: Subcutaneous administration of testosterone. A pilot study report. Saudi Med J 2006;27:1843–1846.
8. Seftel A: Testosterone replacement therapy for male hypogonadism: part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents. Int J Impot Res 2007;19:2–24.

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