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Comparison of Outcomes for Hypogonadal Men Treated with Intramuscular Testosterone Cypionate versus Subcutaneous Testosterone Enanthate

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Study Need and Importance: The incidence of hypogonadism is rising in the United States due to the aging population as well as the worsening prevalence of metabolic disorders. A multifaceted approach to therapy is required, which includes behavioral changes as well as pharmacological interventions. Intramuscular testosterone cypionate (IM-TC) is the most commonly prescribed modality. A novel subcutaneous testosterone enanthate autoinjector (SCTE-AI) recently approved by the U.S. Food and Drug Administration has a lower testosterone peak-to-trough ratio. We compare the total testosterone (TT), estradiol (E2), hematocrit (HCT) and prostate specific antigen (PSA) response to treatment with IM-TC versus SCTE-AI.

What We Found: Post-testosterone replacement therapy (TRT), both cohorts had significant increases in trough TT compared to their baseline levels (IM-TC: 313.6 ng/dL to 536.4 ng/dL, $p < 0.001$; SCTE-AI: 246.6 ng/dL to 552.8 ng/dL, $p < 0.001$). After linear regression of log-transformed variables, type of TRT modality was not found to be associated with TT levels ($p = 0.057$). SCTE-AI was independently associated with lower post-therapy E2 ($p < 0.001$) and HCT ($p < 0.001$). Neither TRT modality was associated with significant post-therapy elevation of PSA ($p = 0.965$; see figure).

Limitations: A portion of participants in this study was treated with both TRT modalities due to constraints with our small sample size. While testosterone enanthate and testosterone cypionate are both short-acting testosterone esters, analysis of SCTE-AI and IM-TC compare 2 different formulations of injectable testosterone. Lastly, the SCTE-AI is a newer delivery option, limiting the duration of followup.

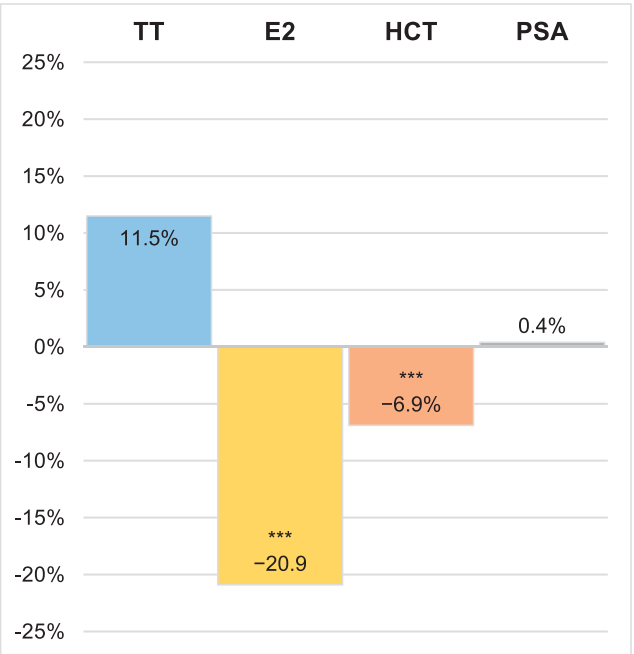

Figure. Treatment outcomes with SCTE-AI in comparison to IM-TC after adjusting with log-transformed linear regression models. Triple asterisks indicate statistically significant ($p < 0.001$).

Interpretation for Patient Care: This is the first investigation comparing the novel SCTE-AI to intramuscular testosterone for the treatment of hypogonadism in men. At a mean followup of 14.2 weeks, both TRT modalities significantly improved trough TT levels to eugonadal ranges, but there were significantly fewer increases in E2 and HCT with SCTE-AI.

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Comparison of Outcomes for Hypogonadal Men Treated with Intramuscular Testosterone Cypionate versus Subcutaneous Testosterone Enanthate

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Abbreviations and Acronyms

E2 = estradiol
HCT = hematocrit
IM = intramuscular
IM-TC = intramuscular testosterone cypionate
PSA = prostate specific antigen
SCTE-AI = subcutaneous testosterone enanthate autoinjector
TRT = testosterone replacement therapy
TT = total testosterone

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Purpose: Intramuscular testosterone cypionate (IM-TC) is known to cause significant rises in estradiol (E2), hematocrit (HCT), and prostate specific antigen (PSA) due to its supraphysiological testosterone peaks, whereas a novel subcutaneous testosterone enanthate autoinjector (SCTE-AI) was designed with a lower testosterone peak-to-trough ratio to mitigate these reactions. We compare the total testosterone (TT), E2, HCT and PSA response to treatment with IM-TC versus SCTE-AI.

Materials and Methods: A total of 234 hypogonadal men were treated with testosterone replacement therapy (TRT) via IM-TC 100 mg weekly or SCTE-AI 100 mg weekly. TT, E2, HCT and PSA levels were obtained at baseline and 12 weeks post-treatment. Significant differences in baseline and post-treatment levels were identified by univariate analysis. Linear regression models determined whether treatment modality was independently associated with post-TRT levels of TT, E2, HCT and PSA.

Results: Post-TRT, both cohorts had significant increases in trough TT compared to their baseline levels (IM-TC: 313.6 ng/dL to 536.4 ng/dL, $p < 0.001$; SCTE-AI: 246.6 ng/dL to 552.8 ng/dL, $p < 0.001$). After linear regression, type of TRT modality was not found to be associated with TT levels ($p = 0.057$). SCTE-AI was independently associated with lower post-therapy E2 ($p < 0.001$) and HCT ($p < 0.001$). Neither TRT modality was associated with significant post-therapy elevation of PSA ($p = 0.965$).

Conclusions: While IM-TC and SCTE-AI provide a significant increase in TT levels, SCTE-AI is associated with lower levels of post-therapy HCT and E2 compared to IM-TC after adjusting for significant covariates. SCTE-AI is an effective testosterone delivery system with a potentially preferable safety profile over IM-TC.

Key Words: hypogonadism; testosterone; injections, subcutaneous; injections, intramuscular; drug delivery systems

Hypogonadism in men is characterized by diminished serum testosterone levels clinically manifesting as depressed libido and sexual dysfunction in addition to fatigue, decreased muscle mass, poor bone mineralization, increased body fat, gynecomastia and hot flashes.[1,2] Hypogonadism also has complex associations with chronic conditions such as type 2 diabetes mellitus, obesity and metabolic syndrome that require a multifaceted approach to therapy including behavioral changes as well as pharmacological interventions.[3,4]

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The estimated incidence of hypogonadism in the United States is approximately 481,000 cases per year.[5] However, this rate will likely rise due to the increasing proportion of aging males as well as the worsening prevalence of metabolic disorders.[6,7]

While intramuscular (IM) testosterone injections are a conventional method for testosterone replacement therapy (TRT), patient compliance to treatment can be deterred by pain associated with the large needle bore required as well as some of the problematic associated side effects.[8] Injectable testosterone is esterified to decrease polarity, increase solubility in oils, slow release into the bloodstream and increase half-life.[9] Testosterone cypionate and testosterone enanthate are the most common esters for TRT with studies demonstrating that both formulations have similar pharmacokinetic profiles.[9–11] A novel subcutaneous testosterone enanthate autoinjector (SCTE-AI) gained approval by the U.S. Food and Drug Administration for clinical use and is available as a self-administered, once-weekly dose with a small $^{5}/_{8}$ inch 27-gauge needle.[12,13] The SCTE-AI has been shown to safely elevate testosterone levels to eugonadal ranges and offers a reduced peak-to-trough ratio compared to IM testosterone, resulting in a more steady state of available testosterone within normal physiological ranges.[8,12,14] This is especially important to consider as supraphysiological levels of testosterone have been associated with undesirable rises in estradiol (E2), hematocrit (HCT) and prostate specific antigen (PSA).[15–17] In this study, we aim to compare the novel SCTE-AI to IM testosterone cypionate (IM-TC) in their ability to effectively increase total testosterone (TT) levels as well as evaluating safety profiles by measuring E2, HCT and PSA responses.

METHODS

Institutional review board approval was obtained, and data collection and storage were performed in a de-identified fashion in compliance with the Health Insurance Portability and Accountability Act (IRB No. 2017-3746). This was a retrospective study on prospectively managed databases between 2 high-volume practices. Between October 2016 and October 2019, 234 hypogonadal men were treated with injectable forms of TRT. Men with a history of prostate cancer were excluded from this study. Men were either treated with IM-TC alone, SCTE-AI alone or started with IM-TC and crossed over to SCTE-AI with at least 6 weeks of washout between the 2 treatment modalities. Dosing for IM-TC and SCTE-AI was 100 mg weekly. Serum values of TT (280 to 1,100 ng/dL), E2 (10 to 50 pg/mL), HCT (38.8% to 50.0%) and PSA (<2.5 ng/mL) were drawn prior to initiation of TRT and at 12-week followup. Baseline laboratory blood draws were specified to occur in the morning prior to 10:00 a.m. and 5–6 days after their last injection to observe trough TT values. If HCT levels rose beyond a threshold of 54%, TRT was immediately discontinued and therapeutic phlebotomy ordered. TRT was also terminated if E2 levels were elevated ≥50 pg/mL. TRT was finally discontinued when the PSA increased by more than 0.75 ng/mL or surpassed 4 ng/mL, which also prompted a prostate cancer evaluation.

Statistical analyses were performed on the IBM® SPSS® Statistics program (IBM, Armonk, New York). Pre and post-therapy levels of TT, E2, HCT and PSA were natural-log transformed to improve normality in distributions. Paired t-tests determined whether pre and post-therapy levels were significantly different within cohorts and independent-samples t-tests determined whether baseline and post-therapy levels were different between the cohorts. Four linear regression models were created to assess whether TRT modality was an independent predictor of post-therapy TT, E2, HCT or PSA. Fisher's exact tests compared the incidence of significantly elevated levels of post-therapy E2 and HCT, which were defined as ≥50 pg/mL and ≥54%, respectively. Significant adverse events, such as major adverse cardiac events, as well as aberrant elevations in E2, HCT and PSA were carefully monitored.

Table 1. *Clinical demographics and treatment outcomes of IM-TC compared to SCTE-AI*

	Mean IM-TC (SD)(188 pts)	Mean SCTE-AI (SD)(110 pts)	p Value
Age	54.4 (13.4)	49.7 (10.5)	**<0.001**
Pre-therapy:			
TT*	5.56 (0.60)	5.42 (0.43)	**0.022**
E2*	3.31 (0.45)	3.18 (0.35)	**0.017**
HCT*	3.81 (0.10)	3.80 (0.08)	0.446
PSA*	−0.11 (0.95)	−0.17 (0.67)	0.560
Post-therapy:			
TT*	6.16 (0.50)	6.24 (0.39)	0.170
E2*	3.71 (0.51)	3.41 (0.41)	**<0.001**
HCT*	3.88 (0.09)	3.83 (0.09)	**<0.001**
PSA*	−0.09 (0.81)	−0.08 (0.69)	0.931

Entries set in bold indicate statistical significance at $p < 0.05$.
* Log-transformed.

RESULTS

A total of 234 hypogonadal men were treated with TRT of whom 124 were treated with IM-TC alone, 46 treated with SCTE-AI alone and 64 treated with both modalities. Overall, the mean age of every participant in this study was 54.2 years (SD: 12.7). The 188 men who received IM-TC had a mean age of 54.4 years (SD: 13.4) and the 110 who received SCTE-AI had a mean age of 49.7 years (SD: 10.5; table 1). The IM-TC cohort had significantly higher levels of baseline TT (313.6 ng/dL vs 246.6 ng/dL, $p=0.004$) and E2 (30.4 pg/mL vs 25.5 pg/mL, $p=0.005$) whereas the 2 cohorts had similar pre-therapy levels of HCT (45.2% vs 44.7%, $p=0.365$) and PSA (1.41 ng/dL vs 1.07 ng/dL, $p=0.070$). These baseline differences remained statistically significant after natural-log transformation (table 1). Of note, not all secondary lab values were available at time of analysis as they were drawn significantly

Table 2. *Independent factors associated with post-therapy TT*

	Unstandardized		Standardized			95% CI for B	
	B	SE	β	t	Significance	Lower	Upper
Constant	5.116	0.349		14.677	<0.001	4.428	5.804
TRT modality (IM-TC [reference] vs SCTE-AI)	0.109	0.057	0.137	1.919	0.057	−0.003	0.221
Age (continuous)	0.009	0.003	0.243	3.387	**<0.001**	0.004	0.014
Pre-therapy TT*	0.090	0.058	0.114	1.539	0.126	−0.025	0.205
Pre-therapy E2*	0.177	0.078	0.170	2.279	**0.024**	0.024	0.331

Entries set in bold indicate statistical significance at p <0.05.
* Log-transformed.

beyond the 12-week followup period. Among the IM-TC group, there were 100 men with E2 levels, 114 with HCT and 99 with PSA values. In the SCTE-AI group, 106 had E2 levels, 107 had HCT and 105 had PSA values for analysis.

After an average followup of 14.2 weeks after initiating TRT, both cohorts had significant increases in trough TT compared to their respective baseline levels (IM-TC: 313.6 ng/dL to 536.4 ng/dL, p <0.001; SCTE-AI: 246.6 ng/dL to 552.8 ng/dL, p <0.001). Both cohorts also experienced post-therapy rises in E2 (IM-TC: 30.4 pg/mL to 46.6 pg/mL, p <0.001; SCTE-AI: 25.5 pg/mL to 33.1 pg/mL, p <0.001) and HCT (IM-TC: 45.2% to 48.4%, p <0.001; SCTE-AI: 44.7% to 46.2%, p <0.001). Post-therapy PSA levels were equivalent to baseline for both the IM-TC (1.41 ng/dL to 1.26 ng/dL, p=0.179) and SCTE-AI cohorts (1.07 ng/dL to 1.17 ng/dL, p=0.390). The IM-TC cohort had a significantly greater proportion of men with post-therapy E2 elevations ≥50 pg/mL with 31 (31%) men in this group passing the threshold compared to only 11 (10.4%) men in the SCTE-AI group (p <0.001). The IM-TC cohort also had a greater proportion of patients experiencing polycythemia with 12 (10.5%) in the IM-TC group compared to only 1 (0.9%) participant in the SCTE-AI group with post-therapy HCT ≥54% (p=0.003).

After adjusting for age, baseline TT and baseline E2, the type of TRT received was not significantly associated with post-therapy TT levels (B: 0.109, SE: 0.057, p=0.057; table 2). Age (p <0.001) and baseline E2 (p=0.024) were significantly associated with higher levels of post-therapy TT (table 2). SCTE-AI was found to be independently associated with lower post-therapy E2 (B: −0.235, SE: 0.068, p <0.001) and HCT (B: −0.072, SE: 0.012, p <0.001; tables 3 and 4). Baseline E2 (B: 0.274, SE: 0.092, p=0.004) was significantly associated with post-therapy E2 (table 3). While age was a significant predictor of post-therapy PSA (B: 0.013, SE: 0.005, p=0.005), type of TRT modality was not significantly associated with post-therapy elevation of PSA (B: 0.004, SE: 0.102, p=0.965; table 5). In the SCTE-AI group, 1 patient saw an aberrant rise in PSA and was diagnosed with prostate cancer. TRT was immediately terminated. No significant adverse events, including major adverse cardiac event, were reported.

DISCUSSION

This is the first investigation comparing the novel SCTE-AI to IM testosterone for the treatment of hypogonadism in men. At a mean followup of 14.2 weeks, both TRT modalities significantly improved trough TT levels to eugonadal ranges. While both modalities appropriately raise TT, IM testosterone is known to produce wide fluctuations that have been linked to variability in libido, mood and energy.[18,19] Investigations into subcutaneous administration, on the other hand, have achieved therapeutic levels of testosterone without such variability.[8,18] Manual subcutaneous injections should theoretically provide similar benefits to the SCTE-AI, though this would require thorough patient training and/or repeated clinic visits for drug administration which would likely negatively impact patient compliance as it does for IM testosterone. The autoinjector mechanism also decreases anxiety for men with needle phobia.

Table 3. *Independent factors associated with post-therapy E2*

	Unstandardized		Standardized			95% CI for B	
	B	SE	β	t	Significance	Lower	Upper
Constant	3.290	0.428		7.689	<0.001	2.445	4.135
TRT modality (IM-TC [reference] vs SCTE-AI)	−0.235	0.068	−0.249	−3.456	**<0.001**	−0.370	−0.101
Age (continuous)	0.005	0.003	0.123	1.699	0.091	−0.001	0.011
Pre-therapy TT*	−0.095	0.070	−0.100	−1.364	0.174	−0.232	0.042
Pre-therapy E2*	0.274	0.092	0.220	2.962	**0.004**	0.091	0.456

Entries set in bold indicate statistical significance at p <0.05.
*Log-transformed.

Table 4. *Independent factors associated with post-therapy HCT*

	Unstandardized		Standardized			95% CI for B	
	B	SE	β	t	Significance	B	SE
Constant	3.929	0.075		52.669	<0.001	3.782	4.076
TRT modality (IM-TC [reference] vs SCTE-AI)	−0.072	0.012	−0.406	−5.867	**<0.001**	−0.096	−0.048
Age (continuous)	−0.001	0.001	−0.066	−0.955	0.341	−0.002	0.001
Pre-therapy TT*	0.009	0.012	0.051	0.707	0.480	−0.016	0.033
Pre-therapy E2*	−0.024	0.016	−0.108	−1.494	0.137	−0.057	0.008

Entries set in bold indicate statistical significance at p <0.05.
*Log-transformed.

While both cohorts in our study experienced rises in E2 after TRT, men treated with SCTE-AI had significantly lower post-therapy E2 levels, approximately 20% less compared to the IM-TC cohort (B: −0.235, SE: 0.068, p <0.001; table 3). We found that those treated with IM-TC experienced elevated E2 ≥50 pg/mL more often with 31% surpassing this threshold compared to only 10% in the SCTE-AI cohort (p=0.003). Prior investigations have shown that short-acting IM testosterone may induce higher levels of E2 compared to other TRT modalities, including transdermal gels and pellets.[15,17] This may be due to supraphysiological peaks of testosterone, which drastically increases bioavailable testosterone for aromatization into E2.[17,20] While uncommon, clinical manifestations of hyperestrogenism, such as gynecomastia, have been reported in men treated with TRT.[21] No one in this study experienced such symptoms. If a patient develops supraphysiological estrogen levels, aromatase inhibitors can be utilized, though this is considered an off-label use.[22]

Major guidelines define erythrocytosis to be ≥54% HCT and require interruption of TRT and/or therapeutic phlebotomy.[1,23] While HCT significantly rose for both TRT modalities, only 1% in the SCTE-AI group reached the ≥54% threshold compared to the 10.5% in the IM-TC cohort (p <0.001). Men who received SCTE-AI experienced 7% lower post-therapy HCT levels compared to those treated with IM-TC (B: −0.072, SE: 0.012, p <0.001; table 4). Erythrocytosis has been associated with supraphysiological peaks of testosterone and E2, phenomena anticipated with short-acting IM testosterone.[24,25] One study found that IM testosterone significantly elevated HCT higher than transdermal gel or pellets.[15] Furthermore, short-acting IM testosterone has been reported to induce erythrocytosis in up to 40% of patients who receive this form of TRT.[24] While brief episodes of mild erythrocytosis secondary to TRT have not been linked to thromboembolic events, HCT should be closely monitored to minimize this potential risk.[2,24]

Neither group in this study experienced significant rises in PSA after TRT, which is consistent with other prospective studies (table 5).[17,24,26] While elevations in PSA can be expected after TRT initiation, these increases have not been shown to be related to greater risk of developing prostate cancer.[24,27,28] The 2018 American Urological Association guidelines on testosterone deficiency report a lack of evidence in the link between TRT and risk for prostate cancer.[2] Modern understanding of testosterone and prostate cancer has greatly advanced since the introduction of the "saturation model" by Rhoden and Morgentaler, which sought to explain the lack of increased prostate cancer risk in men receiving TRT.[24] One such study was an analysis on the National Prostate Cancer Register of Sweden database, which did not find an association between TRT and prostate cancer risk.[29] The majority of studies on this topic have been either retrospective, population analyses or prospective with small sample sizes. Currently, the Study to Evaluate the Effect of Testosterone Replacement Therapy on the Incidence of Major Adverse Cardiovascular Events and Efficacy Measures in Hypogonadal Men (TRAVERSE) is ongoing and is designed as a prospective analysis on how TRT

Table 5. *Independent factors associated with post-therapy PSA*

	Unstandardized		Standardized			95% CI for B	
	B	SE	β	t	Significance	B	SE
Constant	0.741	0.619		1.196	0.233	−0.482	1.964
TRT modality (IM-TC [reference] vs SCTE-AI)	0.004	0.102	0.003	0.044	0.965	−0.198	0.206
Age (continuous)	0.013	0.005	0.218	2.858	**0.005**	0.004	0.023
Pre-therapy TT*	−0.078	0.102	−0.059	−0.761	0.448	−0.280	0.124
Pre-therapy E2*	−0.115	0.135	−0.067	−0.858	0.392	−0.381	0.150

Entries set in bold indicate statistical significance at p <0.05.
*Log-transformed.

affects multiple safety concerns including prostate cancer risk.[30]

This is the first study of the novel SCTE-AI in direct comparison to another TRT modality for the treatment of hypogonadism in men. Limitations to this study include its retrospective nature preventing randomization of patients. We also acknowledge the limitations associated with the portion of participants who had been treated with both TRT modalities, of whom all had received IM-TC prior to switching to SCTE-AI. This was performed due to constraints with our relatively small sample size. A washout period was utilized prior to SCTE-AI initiation, though a more robust study in the future would compare independent patient pools who receive only 1 TRT modality. While testosterone enanthate and testosterone cypionate are both short-acting testosterone esters, our analysis of the SCTE-AI and IM-TC compares 2 different formulations of injectable testosterone. Furthermore, our databases lacked depth in clinical information, such as body mass index, or relevant medication use, such as aromatase inhibitors, which is rarely used in tandem with TRT in our practices. We acknowledge these factors may act as unknown confounders. Lastly, as the SCTE-AI is a newer device, future studies will benefit from larger sample sizes and longer followup as the SCTE-AI becomes more widely used.

CONCLUSION

This is the first study to compare the SCTE-AI to another form of TRT. While IM-TC and SCTE-AI both provided significant increases in TT levels, the SCTE-AI was associated with lower levels of E2 and HCT compared to IM-TC after adjusting for baseline differences in the cohorts. With its improved peak-to-trough ratio that reduces supraphysiological testosterone exposure, the SCTE-AI has been shown to be an effective testosterone delivery system with a potentially preferable safety profile over short-acting IM testosterone.

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