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Augmenting Intralesional Collagenase Treatment with Testosterone Therapy Provides Greater Self-Assessed Improvement in Penile Curvature due to Peyronie's Disease

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Abstract

Introduction: Testosterone (T) deficiency has been reported to be associated with Peyronie's disease (PD). This study investigated response rates to intralesional injections of collagenase clostridium histolyticum (Xiaflex™) (CCx) for penile curvature in men who simultaneously received T therapy (TTh) and in men who received CCx without TTh.

Methods: Search of electronic records identified all men treated with CCx from 2013 to 2018, and whether they also received TTh during that time. Laboratory results for baseline serum T, free T, and luteinizing hormone were available for all men. Response to CCx was categorized as no change, mild change, substantial change, or complete resolution based on subjective reports by patients.

Results: A total of 117 men received treatment with CCx. Of these, 72 received CCx alone (henceforth referred to as XA group) and 45 received CCx plus TTh (referred to as XT group). Mean baseline serum T was 458 ng/dL for the XA group and 384 ng/dL for the XT group ($p = 0.10$). Mean age was 60.4 years for the XT group and 56.5 years for the XA group ($p = 0.028$). Baseline mean curvature was 46° for the XA group and 45° for the XT group. Mean number of treatment cycles (two injections per cycle) was 2.7 for both groups. Overall, 67.5% reported some improvement in curve with CCx. Reports of any improvement were 84.4% for the XT group and 56.9% for the XA group ($p < 0.001$). Conversely, rates of no improvement were 15.6% for the XT group and 43.1% for the XA group. Substantial improvement or complete resolution of curve was noted by 48.8% of the XT group and 20.8% of the XA group ($p = 0.001$).

Conclusions: These pilot observational results suggest that TTh may improve the response to intralesional CCx treatment of PD. A prospective study is warranted to investigate this further.

Keywords: Peyronie's disease; testosterone; testosterone deficiency; hypogonadism; collagenase; Xiaflex

Introduction

Peyronie's disease (PD) is an inflammatory disorder of the tunica albuginea (TA) of the penis that results in collagen deposition and alterations in the elastin framework that lead to creation of fibrous plaques.[1] These inelastic plaques limit expansion of the TA during erection, leading to curvature, reduced length, and girth. Penile trauma or microtrauma is believed to be the inciting event. Significant curvature may result in pain and inability to successfully engage in sexual intercourse. The prevalence of PD is estimated to be 0.5–13%.[2]

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Collagenase clostridium histolyticum (CCx) (Xiaflex™) is an FDA-approved intralesional injection used to treat penile curvature due to PD.[3] Treatment consists of up to four cycles, with each cycle comprising two injection procedures on separate days and a penile modeling procedure to stretch the plaque.[3] In combined data from two large double-blind randomized studies, the average improvement in penile curvature with CCx was 34%, or 17°, compared with 18% improvement and 9° in men receiving placebo.[4] A recently published phase 4 study in 204 men reported mean improvement of 20.9° or 39.5% with a further 9.1% improvement with an additional 5 years of follow-up.[5] There is little published information on how various ethnic, biological, or genetic factors may influence response to CCx in men with PD.

In 2009, Moreno and Morgentaler reported in a series of 121 consecutive men presenting with PD that 74% had low baseline concentrations of total or free testosterone (T), and that the severity of T deficiency (TD) was correlated with degree of curvature.[6] Other studies have similarly reported associations between increased plaque size or magnitude of curvature with TD,[7,8] but not all.[9]

This study is a retrospective investigation of subjective self-assessment of change in curvature with CCx in men who simultaneously received TTh during CCx compared with men who received CCx alone. We aimed to test the hypothesis that treatment of TD would improve response to CCx.

Methods

Study population

A search of in-office electronic records identified 117 men who had undergone at least one completed cycle of treatment with CCx at our center during 2013–2018. Chart review was performed for baseline and follow-up information, including number of CCx injections, degree of baseline curvature, laboratory results, and use and type of TTh. There were no cases of ventral curvature treated with CCx. Forty-five men received TTh during CCx treatment (XT group), and 72 men received CCx alone (XA group). Initiation of TTh was within several weeks of first CCx injection in all patients. Forms of TTh included pellets, injections, or topical gels, depending on patient preference and insurance coverage. Chart review was done under Beth Israel Deaconess Medical Center IRB protocol no. 2010P000241.

Hormone testing

All patients underwent routine laboratory testing for total T (TT), free T (FT), estradiol (E), and sex hormone binding globulin (SHBG). Blood tests were obtained during clinic hours between 8 am and 4:30 pm. Although morning determination of T is usually recommended, current evidence indicates that diurnal variation appears to be greatly reduced in men >40 years[10] and absent in men with TD.[11] Immunoassays were used for measurement of all laboratory blood draws (Tosoh Bioscience, San Francisco, Los Angeles, CA) except FT, which was performed through analog assay (Quest Diagnostics Nichols Institute, Valencia, CA). Men were considered candidates for TTh if TT was <300 ng/dL or FT <1.5 ng/dL.

Assessment of change in curvature

The degree of baseline curvature was based on direct measurement after in-office intracavernosal injection of vasoactive medications, photographs brought in by the patient, or patient description. Patients were then placed into one of four categories based on documented self-assessed response to treatment: no change, mild change, substantial change, and complete resolution of the curve.

Statistical analysis

Statistical analysis of the two groups was done with simple *t*-test focusing on analyzing differences in response to CCx treatment between the two groups. Hypothesis testing was performed with R software 3.3.2 (R Project for Statistical Computing). Demographic data were analyzed to determine baseline differences between treatment groups.

Results

The study population (Table 1) consisted of 117 subjects, with 45 treated with collagenase and T (XT) and 72 who

Table 1. Baseline Patient Characteristics

		Xiaflex+T therapy *n* = 45	Xiaflex *n* = 72	*p*
Age (years)	Mean (SD)	60.4 (7.80)	56.5 (11.57)	0.03*
Baseline total T	Mean (SD)	384 (247)	458 (198)	0.10
Baseline free T	Mean (SD)	0.74 (0.30)	0.88 (0.37)	0.03*
Baseline angle (°)	Mean (SD)	45 (15)	46 (16)	0.74
SHBG	Mean (SD)	36 (15)	52 (14)	0.43
Estradiol	Mean (SD)	52 (16)	38 (14)	0.83
Diabetes	*N* (%)	0 (0)	2 (2.90)	0.17
Hypertension	*N* (%)	16 (7.54)	15 (22.10)	0.04*

*$p < 0.05$.
SD, standard deviation; SHBG, sex hormone binding globulin.

were treated with collagenase alone (XA). Mean age for the entire population was 58.5 years.

In the XT group, 44.4% had TT of 300 ng/dL or below and 60% had TT of 350 ng/dL or below. In the XA group, 13.9% had TT of 300 ng/dL or below and 25% had TT of 350 ng/dL or below. FT at base line was <1.5 ng/dL in 97.7% of the XT group and 97.2% of the XA group.

The XT group was older than the XA group, at 60.4 ± 7.8 years versus 56.5 ± 11.6 years ($p = 0.03$). Baseline curvature was similar for both groups at 45°, and both groups completed 2.7 cycles of CCx. TTh consisted of T undecanoate injections in 7 subjects, T cypionate injections in 3 subjects, T pellets in 31 subjects, and 4 subjects received a mix of T formulations.

Hormones

Baseline concentrations of serum TT were 384 ng/dL ±247 for the XT group and 458 ng/dL ±198 for the XA group ($p = 0.1$). FT was slightly lower for the XT group than for the XA group (0.74 ± 0.30 vs. 0.88 ± 0.37, respectively; $p = 0.03$). Differences in SHBG and E were not significantly different between groups. Follow-up TT concentrations rose in the XT group to 616 ng/dL ±299. Follow-up T levels were not obtained in the XA group.

Response to treatment

For the entire study population, 14.5% of subjects reported complete resolution of penile curvature, 35.9% reported mild change, 17.1% reported seeing substantial change, and 32.5% reported no change.

When examined by groups (Table 2), 15.6% of the XT group reported no change in curvature, mild improvement was noted in 35.6%, substantial change was reported by 28.8%, and complete resolution was reported by 20%. In the XA group, no change was reported by 43.1%, mild change was reported by 36.1%, substantial change was reported by 9.7%, and 11.1% claimed complete resolution of curvature. In the XT group, 48.8% reported substantial improvement or complete resolution, compared with 20.8% for the XA group ($p = 0.001$). Overall (Table 3) 84.4% of the XT group reported at least some improvement in curvature compared with 56.9% of the XA group ($p = 0.002$). Conversely, 15.6% of the XT group reported no change compared with 43.1% of the XA group ($p = 0.002$).

Table 2. Curvature Response to Treatment

Improvement in curvature	Xiaflex+T therapy $n = 45$	Xiaflex $n = 72$	p
No change	7 (15.6)	31 (43.1)	0.002
Mild change	16 (35.6)	26 (36.1)	0.95
Substantial change	13 (28.8)	7 (9.7)	<0.01
Complete resolution	9 (20)	8 (11.1)	0.18
Substantial and complete resolution	22 (48.8)	15 (20.8)	<0.001

Table 3. Response to Treatment

Improvement in curvature	Xiaflex+T therapy, $n = 45$	Xiaflex, $n = 72$	p
Any change	38 (84.4)	41 (56.9)	
No change	7 (15.6)	31 (43.1)	
			0.00085

Adverse events

Bruising and swelling consistent with some degree of subcutaneous bleeding were routinely noted. No patient required drainage, surgery, or hospitalization. There were no penile ruptures.

Discussion

PD is a difficult-to-treat condition that causes considerable distress for affected men. The pathophysiology is believed to be related to mechanical stress and microvascular trauma to the TA of the erect penis that results in bleeding into the subtunical space or tunical delamination. Subsequent fibrin deposition initiates an exaggerated wound healing and inflammatory response, including recruitment of macrophages and neutrophils, which, in turn, release cytokines, vasoactive factors, and growth factors, including transforming growth factor (TGF)-β1.[1] Fibroblasts migrate into the area, proliferate, and under the influence of TGF-β1 synthesize collagen, proteoglycans, and fibronectin, while increasing synthesis of tissue inhibitors of collagenase, thus preventing connective tissue scarring during remodeling.[1] The resulting fibrotic area, or plaque, lacks the normal elasticity of adjacent undamaged TA, and in this way impedes tissue compliance and causes curvature and other deformities when the penis engorges during erection.

The evidence suggests an important role for androgens in regulating the fibrotic process of the penis during injury. Wang et al. showed that castration of adult male Sprague-Dawley rats resulted in greater fibrosis, decreased smooth muscle/collagen ratio, and higher expression of TGF-β1, all of which were partly restored with T administration.[12] A review of cavernosal fibrosis

by Cho et al. indicated that a number of TGF-β1–driven mechanisms promote fibrosis in the rat model, including RhoA-ROCK1-LIMK2-cofilin and p42-44.[13] The authors proposed that strategies to minimize the impact of TGF-β1–signaling pathways might, therefore, be beneficial for attenuating fibrotic conditions of the penis, such as PD. The gene for TGF-β1 has been found to be overexpressed in PD.[14] Indeed, injection of microspheres containing TGF-β1 into the corpus cavernosum of the rabbit was sufficient to increase connective tissue and reduce smooth muscle content within 3 days.[15] Another possible mechanism by which TD may predispose to PD comes from the work of Shen et al., who showed that TA thickness is reduced to 25% of normal, from 0.16 to 0.04 mm, and with loss of elastic fibers.[16] This suggests a structural vulnerability to tunical injury in men with TD.

Androgens appear to play a critical role in the health of penile tissue, particularly with regard to fibrosis and PD. Inhibition of conversion of T into 5α-dihydrotestosterone with finasteride has been shown to upregulate TGF-β1 in association with deposition of increased collagen fibers in the prostate of adult Wistar rats.[17] T itself has been shown to inhibit TGF-β1 signaling.[18] Thus, the known anti-inflammatory effects of androgens,[19] particularly the suppression of TGF-β1 and its downstream pathways, provide a plausible biochemical mechanism by which TTh may potentially aid men with PD undergoing treatment with intralesional collagenase.

Mechanistically, androgens are thought to regulate the expression and function of inflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-1β, IL-6, C-reactive protein, and TGF-β1. TTh in men with TD and chronic inflammatory conditions appears to attenuate the inflammatory process.[19] Furthermore, in experimental model, it was shown that T treatment suppresses TGF-β1 signaling that plays a key role in fibrocalcification of the plaques in PD.[20] Furthermore, there is increasing evidence that TGF-β1 may activate lysyl oxidase, the enzyme that plays a key role in cross-linking of collagen and elastin fibers and facilitates the fibrotic process in the penile tissues.[21–23] It remains to be determined whether T treatment regulates TGF-β1 expression and signaling in a way that translates into attenuation of the expression and activity of lysyl oxidase, and reduced fibrosis.

The introduction of an FDA-approved intralesional injection in the form of CCx in 2013 has provided an important new treatment option for men with PD. In the United States, current recommendations are to perform up to four cycles of treatment at 6-week intervals, with each cycle comprising two injections 1–3 days apart, followed by a third visit for in-office modeling, in which the flaccid penis is stretched by the treating health care provider as a form of manual traction. Published results for curvature improvement with CCx have generally been reported with mean of 31–34%, with either standard four cycles of two injections per cycle,[24] or a shortened protocol of three injections at monthly intervals.[25]

In this study, we compared the curvature response with treatment with CCx in 117 men with PD, of whom 45 also received TTh (XT) and 72 who received CCx alone (XA). Baseline curvature was similar at 45° and 46°, respectively. The number of completed treatment cycles for each group was also similar at 2.7; however, the XT group was slightly older. Overall, 67.5% of men observed some improvement in curvature, and 32.5% reported no change.

The primary results of this study revealed that men who received TTh in combination with CCx treatments reported a substantially greater improvement in curvature than men treated with CCx alone. A response categorized as substantial or complete improvement occurred more than twice as often in men who received TTh with CCx (48.9%) than in men who were treated with CCx alone (20.8%). Conversely, failure to observe any change in curvature was reported by only 15.6% of the TTh group compared with 43.1% in the CCx alone group. Although one must interpret observational data such as this with caution, these results suggest the possibility that correction of TD may enhance the response to CCx treatment in men with PD. It also indirectly supports the hypothesis that serum T has some role in development or progression of PD.

A number of studies support the concept that T may be involved in PD. In the original 2009 series by Moreno and Morgentaler involving 121 U.S. men presenting with PD, 74% had low levels of total and/or FT, and the degree of curvature correlated with severity of TD.[6] Nam et al. investigated the impact of TD in 106 men with PD, reporting that men with TD had larger plaque size, greater curvature, and lower erectile function scores.[7]

In a multicenter single-blind study in 2012, Cavallini et al. investigated 106 men with PD and 99 controls, including intralesional verapamil injections in 43 T-deficient men randomized to concurrent treatment

with either buccal T or placebo.[8] At baseline, plaque size was greater in men with low bioavailable or FT, however degree of curvature was similar. Response to verapamil injections for reduction in plaque area and curve was improved for men treated with T, but there was no significant change in these parameters for men who received placebo. Those results with verapamil injections are similar to those observed in this study with CCx.

Not all studies demonstrate a relationship between TD and PD. Tal et al. found no association with serum T levels in a specific population of men who developed PD after radical prostatectomy (RP),[26] and more recently, authors from the same institution found no association between serum T concentrations and magnitude of penile deformity in a more general population of 184 men with PD.[9] However, the latter population still comprised greater than one-third (37%) who had undergone RP. Since the etiology of PD is likely to differ in men after RP, these results do not necessarily argue against TD as a contributing factor in non-RP cases of PD. Kirby et al. reported that 52.9% of men with PD had low T concentrations, compared with 45.9% in men with erectile dysfunction (ED).[27] Although no correlation was noted in that study for T levels and plaque size or degree of curvature, there was clearly a high prevalence of TD in the PD population.

There are several important limitations to this study, including its retrospective nature, limited population size, nonuniform assessment of baseline curvature, and subjective response to treatment. The retrospective nature of this study makes it impossible to draw conclusions regarding causality. In addition, we note that the two groups differed with regard to age and baseline T, which, in turn, may have influenced the results. It is also possible that the self-reported improvement among men who received TTh may relate in some way to improved psychological status from correction of TD. Nonetheless, we believe these results are provocative and merit further investigation through a rigorous prospective clinical trial.

Conclusions

Men who received TTh during treatment with CCx for PD demonstrated greater improvement in curvature than men who did not receive TTh. These results argue for a prospective trial to determine whether TTh may provide an optimized response to CCx treatment in men with PD.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

E = estradiol
FT = free T
IL = interleukin
PD = Peyronie's disease
RP = radical prostatectomy
SHBG = sex hormone binding globulin
T = testosterone
TA = tunica albuginea
TD = T deficiency
TGF = transforming growth factor
TT = total T