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TESTOSTERONE THERAPY IN MEN WITH SEXUAL DYSFUNCTION: REVIEW

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Peyronie's Disease and Testosterone: A Narrative Review

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Abstract

The pathophysiology of Peyronie's disease (PD) remains incompletely understood; current hypotheses point to a combination of predetermined genetic factors and tissue ischemia. Testosterone has been shown in pre-clinical studies to have anti-inflammatory properties and influence collagen metabolism, prompting various clinical studies examining its effect on disease development and impact on the severity of PD. We seek to review these studies to determine if testosterone levels are associated with PD. A comprehensive literature search of PubMed, Scopus, CENTRAL, Embase, and Web of Science was conducted with the search terms "Testosterone AND (Peyronie OR Peyronie's OR Peyronies)." Titles and abstracts were screened for relevance, and included studies were then manually reviewed. A narrative review was chosen due to the low number of available studies. A total of 381 studies were identified, of which 202 were duplicates, leaving 179 that underwent title and abstract screen. Full-text review was conducted for 52 studies, and a total of 15 studies were identified that examined or compared the relationship between testosterone levels and either the prevalence or severity of PD; some studies examined both. Three of the 12 studies examining the development of PD with relation to testosterone support an association between hypogonadism and PD, while another four possibly support an association and five do not support such an association. Of the nine studies that examine the severity of PD, three studies support a statistically significant association between PD severity and hypogonadism, while six do not support such an association. After a comprehensive review of the literature, no definitive statement can be made regarding a relationship between PD and testosterone deficiency. Studies examining such a link suffer from significant heterogeneity and retrospective bias. There is a need for more prospective randomized studies to further elucidate a possible relationship.

Keywords: Peyronie's disease; testosterone; hypogonadism; male hypogonadism; androgens

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Introduction

Historically, Peyronie's disease (PD) was often misconceived by urologists as being a rare condition. Reports published between 1991 and 2005 initially stated its prevalence to be <1% in the older adult male U.S. population.^{1,2} However, contemporary studies state rates ranging from 3% in asymptomatic males up to 16% for males seeking evaluation for erectile dysfunction (ED).^{3–5}

PD is a localized connective tissue disorder of the penis defined by penile plaques and deformities.⁶ In addition, PD is associated with the onset of ED in roughly 20–50% of men, and penile deformities and compromised rigidity can make penetrative intercourse a difficult if not impossible task. These set of symptoms can severely impact the quality of life, mental health, and relationship status of patients and their partners.⁷

The pathogenesis of PD is hypothesized to be based on an intersection of genetic factors and tissue ischemia, either traumatic or during the course of normal sexual intercourse.^{8,9} Fibrous collagenous plaques are deposited within the tunica albuginea that may hinder the expansion of the tunica during penile erection. This may lead to penile shortening, bending, and indentation.

At present, the mainstays of PD management are intralesional injection of collagenase clostridium histolyticum (CCH), the only Food and Drug Administration-approved drug for the management of PD, as well as surgical therapy for patients in the chronic phase of the disease. In patients with adequate erectile function, plication of the tunica albuginea, incision and/or partial excision, and grafting can be offered, depending on the degree of curvature and the nature of the initial destabilizing deformity.¹⁰ In patients with ED not responsive to oral therapy, insertion of an inflatable penile prosthesis with or without straightening procedures is at present offered.¹¹

Numerous other oral and intralesional treatments have been described in the literature, but the evidence supporting their use is equivocal at best, as reflected by the current American Urological Association (AUA) guidelines solely recommending oral nonsteroidal anti-inflammatory drugs for acute pain management.^{12–19} As the current options for PD management are limited, further research into the pathophysiology of PD is a promising avenue for the development of future medical therapies.

One such promising avenue for investigation of PD pathogenesis involves better understanding of the role androgens play in PD. Traditionally, androgens, such

as testosterone, are known to affect collagen metabolism and wound healing in the body, a target that is well suited to the collagenous and fibrous nature of PD plaques.²⁰ Testosterone has anti-inflammatory properties and influences collagen metabolism and there have been a small subset of studies in the past few years that have examined the relationship between low testosterone levels and keloid development.^{20,21} It has also been shown that androgens, such as testosterone, prevent transforming growth factor-beta 1 (TGF- β 1) expression, which is a modulator of fibrosis.

We seek to review the current clinical literature regarding the relationship between androgens and both the prevalence and severity of PD.

Methods

A comprehensive literature search of PubMed, Scopus, CENTRAL, Embase, and Web of Science was conducted with the search terms “Testosterone AND (Peyronie OR Peyronie's OR Peyronies).” Titles and abstracts were screened for relevance, and included studies were then manually reviewed. A narrative review was chosen due to the low number of available studies.

Results

Literature search results

A total of 381 studies were identified, of which 202 were duplicates, leaving 179 that underwent title and abstract screen. Full-text review was conducted for 52 studies, and a total of 15 studies were identified that examined or compared the relationship between testosterone levels and either the prevalence or severity of PD. Twelve of these studies examined prevalence, while nine examined severity.

Studies assessing the prevalence of PD

Of the 15 studies we found that examined the relationship between testosterone and PD pathophysiology, 12 unique studies were identified that examined the prevalence of PD in relation to testosterone levels, nine of which included statistical comparisons and two of which were descriptive studies.

In the first study to comment on a possible association between PD and testosterone, El-Sakka in 2006 investigated the prevalence of PD among men with ED, and also conducted a laboratory assessment that included testosterone. They did not find a significant association between PD and testosterone levels.²²

In 2009, however, an abstract by Sturm et al. described an association between hypogonadism and PD.



Seventeen men with PD and 17 men with organic ED were assessed for hypogonadism, defined as having a total testosterone (tT) <325 ng/dL. Among patients with PD, 76.5% were hypogonadal with a mean tT of 306 ng/dL compared with 41.2% of men with organic ED, whose mean tT was 372 ng/dL ($p < 0.01$). Among men with PD, 59% experienced ED, and among those with both, 80% were hypogonadal.²³ Moreno and Morgentaler in 2009 similarly described a prevalence of hypogonadism of 29.5% (tT <300 ng/dL) or 74.4% (free testosterone [fT] <1.5 ng/dL) in 121 men with PD.²⁴

On the contrary, Rhoden et al. in 2010 failed to show an association between PD and testosterone. In their case/control study of 83 men with PD and 252 control patients seen in a urology clinic, men with PD had a mean tT of 476.9 ng/dL, while men without PD had a mean tT of 446.4 ($p = 0.12$).²⁵

These findings were echoed by Karavitakis et al. in 2010, who conducted laboratory evaluations of 14 men with PD and 10 age-matched healthy controls. There was no statistically significant association between PD and testosterone, with men with PD showing a mean tT of 368 and control men showing a mean tT of 436.8 ($p = 0.1$). Interestingly, however, this study did demonstrate some associations between PD and androgens, as dehydroepiandrosterone sulfate (DHEA-S) was noted to be significantly lower in men with PD compared with controls ($p = 0.03$); this finding held on regression analysis ($p = 0.04$).

On bivariate analysis, negative correlations were found between insulin-like growth factor binding protein 3 and insulin-like growth factor 1 and testosterone, as well as a positive correlation between tissue inhibitors of metalloproteases 1 and DHEA-S was seen in the PD group, but not in the control group, suggesting a role of androgens in the fibrotic process in PD patients.²⁶

In a 2012 abstract, Cristallo et al. conducted a cross-sectional study of 42 patients with PD, of whom 12.9% were hypogonadal. The authors did not specify what was used as a tT cutoff for a patient to be considered hypogonadal.²⁷ Similarly, a separate 2017 abstract by Krakowsky et al. retrospectively reviewed 50 patients undergoing CCH treatment for PD. Mean tT was 357 ng/dL and fT was 0.74 ng/dL. Using a tT cutoff of <350 ng/dL, 62% of patients were hypogonadal and, using a fT cutoff of <1.0 ng/dL, 86% were hypogonadal.²⁸

However, a prospective study from 2012 by Cavallini et al. examined 106 men with PD and compared them with 99 controls without PD. Hormonal panels were collected, and men with PD were found to have sig-

nificantly higher luteinizing hormone ($p < 0.01$) and sex hormone binding globulin ($p < 0.01$), as well as significantly lower tT ($p < 0.01$), bound testosterone (bT; $p < 0.01$), and fT ($p < 0.01$). Among men with PD, the mean tT was 9.6 nmol/L, bT was 4.6 nmol/L, and fT was 28.4 pmol/L, compared with 12.4 nmol/L, 7.7 nmol/L, and 46.3 pmol/L, respectively, among controls.²⁹

Shamloul et al. in a brief 2012 abstract compared 120 patients with PD and 30 healthy controls by obtaining laboratory studies. Although there are no values or statistical analyses noted, the authors did find that “serum tT and fT were significantly lower” in the PD group compared with the control group.³⁰

In 2015, Kirby et al. retrospectively assessed 87 men with PD and 98 with organic ED, notably excluding those with concomitant PD and ED. Among men with PD, 52.9% were hypogonadal with an average tT of 328 ng/dL and fT of 11.5 ng/dL, while among men with organic ED, 45.9% were hypogonadal (tT <300 ng/dL; $p = 0.35$), average tT was 332 ng/dL ($p = 0.98$), and average fT was 12.1 ng/dL ($p = 0.79$). As men with concomitant PD and ED were excluded, this possibly suggests that previously observed associations are rather due to a common pathophysiologic factor in erectile function, not plaque formation.³¹

Finally, in 2020, Can et al. prospectively assessed 147 patients with PD and 137 healthy volunteers. The mean tT among men with PD was 3.9 ng/mL compared with 4.2 ng/mL among healthy controls ($p = 0.06$). Thus, while there was an observed difference, it failed to reach statistical significance.²⁰ Many of the same authors reported in 2019 similar findings. In a prospective analysis of 103 men with PD and 162 controls, mean tT was 3.9 ng/mL among men with PD compared with 4.2 ng/mL among controls ($p = 0.20$).³²

In summary, 3 of the 12 studies support an association between PD and hypogonadism, four possibly support such an association, and five do not support an association (Table 1).

Studies assessing the severity of PD

Nine studies were identified that assessed the severity of PD in relation to testosterone levels, including examining the degree of penile curvature, plaque size, or symptoms (Table 2).

In the first study examining PD severity in relation to testosterone, Moreno and Morgentaler in 2009 compared 121 men with PD, 90 hypogonadal (tT <300 ng/dL or fT <1.5 ng/dL), and 31 eugonadal men.



Table 1. Studies Examining Prevalence of Hypogonadism in Peyronie's Disease

Study	Peyronie's patients	Control patients	Peyronie's testosterone	Control testosterone	p	Notes
Can et al. ²⁰	147	137	3.9 ± 1.1	4.2 ± 1.7	0.62	N/A
Canat et al. ³²	103	162	3.9 ± 1.1	4.2 ± 1.5	0.198	N/A
Krakowsky et al. ²⁸	50	N/A	357 ± 157.3	N/A	N/A	62% hypogonadal at <350 ng/dL cutoff
Kirby et al. ³¹	87	98	328	332	0.98	52.9% vs. 45.9% hypogonadal p=0.35
Shamloul et al. ³⁰	120	30	N/A	N/A	N/A	Serum tT and fT were significantly lower in the Peyronie's group. No values or p-values were provided
Cavallini et al. ²⁹	106	99	9.6 ± 5.6	12.4 ± 6.6	0.0093	
Cristallo et al. ²⁷	42	N/A	N/A	N/A	N/A	12.9% hypogonadal, "no relationship"
Karavitakis et al. ²⁶	14	10	368 ± 105.6	436.8 ± 128.8	0.1	N/A
Moreno and Morgentaler ²⁴	121	N/A	411.6 ± 203.6	N/A	N/A	Low tT 29.5%, low fT 74.4%
Rhoden et al. ²⁵	83	252	476.9 ± 191.8	446.4 ± 207.8	0.12	19.3% vs. 25.4% were hypogonadal, p=0.3
Sturm et al. ²³	17	17	306	372	<0.0001	76.5% hypogonadal, 80% of those with ED hypogonadal
El-Sakka ²²	114	1326	N/A	N/A	N/A	11.3% hypogonadal, hyperprolactinemia 9.2%, not significant, no p-values given

ED, erectile dysfunction; fT, free testosterone; N/A, not applicable; tT, total testosterone.

Hypogonadal men experienced a significantly higher degree of curvature, 54.3°, compared with eugonadal men, 37.1° ($p < 0.01$). Interestingly, this association was only significant with fT as the measurement. Low fT was significantly associated with more severe curvature ($p < 0.01$), while low tT approached but did not reach significance ($p = 0.06$).

On univariate analysis, fT showed a similar significant correlation with the degree of curvature ($r = -0.314$, $p = 0.02$), while tT did not show a significant association ($r = -0.199$, $p = 0.14$). In addition, plaque size did not differ significantly between the groups, as hypogonadal men had a mean plaque size of 2.05 cm compared with eugonadal men with a mean plaque size of 1.88 cm (0.45).

In addition, in the previously discussed 2009 abstract by Sturm et al., no significant correlation between plaque size or volume and testosterone was seen.²³

In a 2011 abstract, Matsushita et al. examined the degree of penile curvature among 138 men with PD and a tT measurement within 12 months of presentation. A total of 33 hypogonadal men (tT <300 ng/dL) experienced a mean curvature of 35.6°, compared with 105 eugonadal men with a mean curvature of 36.0° ($p = 0.92$); in addition, there was no univariate association between testosterone and degree of curvature ($r = -0.06$, $p = 0.46$). Finally, patients were divided into tT quartiles (tT <300 ng/dL, 300–450, 450–600, >600), and no significant difference in degree of curvature was found ($p = 0.74$).³³

Nam et al.⁴² in 2011 retrospectively reviewed the records of 106 men, 30 hypogonadal (tT <350 ng/mL) and 76 eugonadal. They found that hypogonadal men had significantly more severe curvature at 32.0°, compared with eugonadal men at 21.8° ($p = 0.03$). Similarly, penile plaques were significantly larger in men

Table 2. Studies Examining the Relationship Between Testosterone and Curvature

Study	Low T #	Normal T #	Low T curvature	Normal T curvature	p	Notes
Can et al. ²⁰	Unknown	Unknown	Unknown	Unknown	0.06	147 PD patients, based on photographs after vasodilator or natural erection
Candela et al. ³⁵	21	128	40	45	0.7	Based on examination after vasodilator
Mulhall et al. ³⁴	33	151	35 ± 17	34 ± 20	0.84	Based on examination after vasodilator
Kirby et al. ³¹	46	41	30% <30, 42% 30–60, 24% > 60	29% <30, 49% 30–60, 22% > 60	0.74	Based on exam after vasodilator
Cavallini et al. ²⁹	54	52	18.4 ± 13.1	16.2 ± 13.2	0.234	Based on photograph by Kelami method after vasodilator
Matsushita et al. ³³	33	105	35.6 ± 17	36 ± 20	0.92	Unknown methods
Nam et al. ⁴²	30	76	32 ± 15.9	21.8 ± 15.4	0.033	Based on photograph after vasodilator
Moreno and Morgentaler ²⁴	90	31	54.3 ± 24.9	37.1 ± 12.2	0.006	Based on photographs, examination after vasodilator, or self-reports
Sturm et al. ²³	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown methods

PD, Peyronie's disease.



with low testosterone, 3.0 cm, compared with men with normal testosterone, 2.0 cm ($p=0.04$). Pain with erection, however, did not differ based on gonadal status ($p=0.44$).

Cavallini et al. in 2012 also investigated curvature, plaque size, and pain. In a total of 106 men with PD, 54 hypogonadal (bioavailable testosterone under 3.8 nmol/L or fT under 25 pmol/L) and 52 eugonadal, no significant difference in curvature was found, 18.4° in hypogonadal men compared with 16.2° in eugonadal men ($p=0.23$); similarly, hypogonadal and eugonadal men experienced the same amount of pain ($p=0.34$). However, plaques in men with low testosterone were significantly larger, 4.9 cm², compared with men with normal testosterone, 3.6 cm² ($p<0.01$). In addition, 43 hypogonadal men received intralesional verapamil, 20 with testosterone supplementation and 23 with placebo. Pain significantly improved in both groups ($p<0.01$), however plaque area and penile curvature significantly improved ($p<0.01$) only in the testosterone supplementation group.²⁹

The previously discussed retrospective study of 300 men with either PD or ED by Kirby et al. in 2019 also assessed the degree of curvature and plaque size. Degree of curvature was found to not differ significantly between hypogonadal (tT <300 ng/dL) and eugonadal men ($p=0.74$). Similarly, mean plaque size was measured at 3.5 cm for both groups ($p=0.85$).³¹

In another retrospective analysis from 2019, Mulhall et al. examined 184 men with stable chronic disease and compared penile curvature between hypogonadal ($n=33$, defined as tT <300 ng/dL) and eugonadal ($n=151$) men. Men with low testosterone had a mean curvature of 35° compared with 34° in eugonadal men ($p=0.70$). When analyzed as continuous variables, there were no associations found between either tT ($r=-0.01$, $p=0.95$) or fT ($r=-0.003$, $p=0.95$) and degree of curvature. These findings were echoed on multivariate analysis, as both tT ($\beta=-0.01$, $p=0.95$) and fT ($\beta=-0.01$, $p=0.95$) were not predictive of degree of curvature. Finally, there was no observed

difference between tT z-scores ($r=-0.003$, $p=0.95$) or fT z-scores ($r=-0.08$, $p=0.43$) and degree of curvature.³⁴

Can et al. in 2020 in an analysis of 147 men with PD found an interestingly positive association between tT and curvature degree that did not reach statistical significance ($r=0.207$, $p=0.057$). Penile plaque size also did not differ based on tT ($r=0.038$, $p=0.731$).²⁰

In a retrospective analysis of 149 men presenting with chronic phase PD, Candela et al. compared penile curvature, plaque size, and pain between hypogonadal men ($n=21$, defined as tT <10.4 nmol/L) and eugonadal men ($n=128$). Among hypogonadal men, median curvature as measured by a goniometer during maximal rigidity was 40°, compared with 45° in eugonadal men ($p=0.7$). Similarly, median plaque size did not differ between hypogonadal or eugonadal men, 1.5 and 1.3 cm, respectively ($p=0.4$). Finally, based on the standardized PD questionnaire, hypogonadal and eugonadal men experienced similar levels of subjective symptoms ($p=0.6$), pain ($p=0.3$), and bother ($p=0.5$).³⁵

In summary, three of the nine studies support a statistically significant association between PD severity and hypogonadism, while six of nine do not support such an association (Tables 2 and 3).

Discussion

The true etiology of PD remains unclear, but the pathophysiology is believed to be a form of abnormal wound healing, due to the formation of fibrous collagenous plaques within a previously traumatized tunica albuginea.^{1–10} It has been well established that testosterone is an anabolic endogenous hormone that has a positive effect on wound healing. Furthermore, testosterone has anti-inflammatory properties by means of sequestering the circulation of inflammatory cytokines and plays a significant role in regulating collagen metabolism.

With regard to PD, it has been shown that TGF- β 1 is one of the most potent fibrogenic cytokines and upregulated in Peyronie plaques. It has also been

Table 3. Studies Examining the Relationship Between Testosterone and Plaque Size

Study	Low T #	Normal T #	Low T size	Normal T size	<i>p</i>	Notes
Can et al. ²⁰	Unknown	Unknown	Unknown	Unknown	0.731	147 PD patients, based on length
Candela et al. ³⁵	21	128	1.5 cm	1.3 cm	0.4	Based on length
Kirby et al. ³¹	46	41	3.5 cm	3.5 cm	0.85	Based on length
Cavallini et al. ²⁹	54	52	4.9 ± 2.2 cm ²	3.6 ± 1.8 cm ²	0.0034	Based on area
Nam et al. ⁴²	30	76	3.0 ± 1.2 cm	2.0 ± 1.2 cm	0.039	Based on length
Moreno and Morgentaler ²⁴	90	31	2.05 ± 0.71 cm	1.88 ± 0.58 cm	0.446	Based on length



demonstrated that androgens, such as testosterone, prevent TGF- β 1 expression, which has an active role on fibrosis.³⁶ Furthermore, regulators of collagen metabolism such as matrix metalloproteinases and tissue inhibitors of metalloproteinase-2 have been shown to be affected by androgens.^{26,37,38} This basic science evidence has prompted clinical studies to evaluate the role of hypogonadism in the development of PD. In addition, the associations seen with testosterone and libido, erectile, and sexual function, as well as the high rate of hypogonadism in older men, the same population who typically develop PD, have provided clinical rationale for these investigations.^{24,39}

While androgens' effect on collagen formation discovered in the basic science laboratory makes a potential case for clinical relationship between testosterone and PD, this is not borne out in the literature. Unfortunately, the current studies are plagued by significant heterogeneity, confounding variables, and conflicting conclusions. First, the published studies use varying cutoffs to define hypogonadism, ranging from a tT of 300 ng/dL suggested by the AUA to 350 ng/dL; others use fT cutoffs of 1.0 ng/dL or 1.5 ng/dL.⁴⁰ These definitions are especially critical when examining the severity of PD symptoms, as an effective study design necessitates comparing a hypogonadal group with a eugonadal control group.

Studies examining mean T values, rather than reference range cutoffs, mitigate this issue. In addition, in the light of evidence that fT may be a more accurate indicator of gonadal status than tT, many studies are significantly limited by excluding fT from their analysis.⁴¹ Second, conclusions may be driven by known associations between hypogonadism, ED, and sexual function generally, rather than hypogonadism and PD.³⁹

Two of the 12 studies that describe the prevalence of hypogonadism in men with PD are descriptive studies and thus highly challenging to contextualize.^{27,28} Of those with statistical comparisons, two lack rigorous information, including *p*-values.^{23,30} Thus, there are only six studies that directly and rigorously assess the prevalence of hypogonadism in relation to PD. Of those, two studies showed a statistically significant association between hypogonadism and PD.^{23,29} The study by Cavallini et al. was the only prospective study included, and was one of the largest with a total of 205 patients.²⁹ Sturm et al.'s, however, was a retrospective analysis that only included a total of 34 patients.²³

All four of the other studies with rigorous statistical analysis failed to show a direct and significant relation-

ship between testosterone and PD.^{20,25,26,31} Karavitakis et al. did demonstrate clinical evidence of androgen effects on wound healing proteins, as well as an association between DHEA-S levels and PD; however, this study was also limited by a small sample size and its retrospective nature.²⁶ It also must be noted that Can et al. in 2020 found an association that narrowly did not reach statistical significance.²⁰ In summary, while the more robust studies do not seem to suggest a link between hypogonadism and PD, the data are ultimately mixed and not of sufficient quantity to make a determination.

Studies examining the severity of PD in relation to androgens show similarly mixed data, with three of nine supporting a statistically significant association, and six of nine not supporting one. Moreno and Morgentaler showed an association between more severe curvature and hypogonadism, however, this was only statistically significant based on fT levels (using a cutoff of 1.5 ng/dL), not tT levels. Curvature was measured using photographs, office examination, or patient self-reports.⁴² Nam et al.'s investigation, on the contrary, showed more severe curvature and plaque size in hypogonadal men; however, the tT cutoff used was a nonstandard 350 ng/dL. Similarly, measurement was performed using photographs after injection of vasodilators.⁴²

Finally, while Cavallini et al. did not find an association between hypogonadism and curvature, plaque area was significantly larger among hypogonadal men than eugonadal men. This study again used nonstandard measurements to define hypogonadism, bioavailable testosterone of 3.8 nmol/L, or fT under 2.5 pmol/L, and measured plaque size in area, not length as in the other investigations.²⁹ It should also be noted again that Can et al. in 2020 found an association between testosterone and curvature that narrowly did not reach significance.

Thus, in all three studies that showed an association between PD severity and hypogonadism, inaccurate or nonstandard methods to measure curvature or plaque size. In contrast, in all three studies that strictly used physical examination by a urologist after injection of vasodilating agents, no association between hypogonadism and curvature was found.^{29,31,34} However, 37% of men studied by Mulhall et al. had undergone radical prostatectomy. While radical prostatectomy was distributed evenly across testosterone quartiles (*p* = 0.22), the higher incidence of PD in these patients brings into question the representativeness of the population.^{34,43}



Two of the studies that examined disease severity were only published as abstracts; therefore, limited methodological information was available, further limiting external validity and evidence strength.^{23,33} In addition, the abstract by Sturm et al. lacked rigorous statistical information, including *p*-values.²³ In summary, while data are mixed regarding an association between PD severity and hypogonadism, especially with regard to curvature, studies with stronger and more consistent methods do not seem to show any association.

There appears to be a convincing basic science rationale for an association between hypogonadism and PD; however, the literature does not necessarily confirm this. Significantly, more standardized, prospective, and well-controlled studies are necessary to determine the presence of any potential association. Heterogenous definitions and cutoffs should be avoided in favor of standard definitions endorsed by specialty associations, and every effort should be made to standardize how measurements are made, including consistent timing of laboratory studies and more objective determination of severity measurements.

In addition, further investigation is warranted into the potential role of testosterone replacement in hypogonadal men undergoing treatment for PD, especially in the era of CCH. Cavallini et al. found a potentially greater improvement in hypogonadal men undergoing intralesional verapamil who concurrently received testosterone supplementation; however, the sample size was notably small.²⁹ Similarly, Shlykova and Morgantaler found a greater degree of improvement following CCH treatment in men receiving testosterone replacement therapy; however, the degree of improvement was measured using subjective patient-reported metrics.⁴⁴

This review is significantly limited by its narrative nature; the quantity and quality of available studies were not sufficient for a systematic review or meta-analysis. Similarly, all, but one, of the included studies were retrospective, and many were only available as abstracts, increasing the overall bias and limiting generalizability.

Conclusion

After a comprehensive review of the literature, no definitive statement can be made regarding a relationship between PD and testosterone deficiency. Studies examining such a link suffer from significant heterogeneity and retrospective bias; further prospec-

tive standardized research should be pursued to truly determine if there is a link between hypogonadism and PD.

Authors' Contributions

D.S.: Study conception and design, data collection, analysis and interpretation of results, and article preparation. A.S.A.: Analysis and interpretation of results, and article preparation. F.A.Y.: Study conception and design, analysis and interpretation of results, and article preparation.

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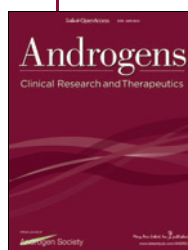
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Abbreviations Used

AUA = American Urological Association
bT = bound testosterone
CCH = collagenase clostridium histolyticum
DHEA-S = dehydroepiandrosterone sulfate
ED = erectile dysfunction
fT = free testosterone
PD = Peyronie's disease
TGF- β 1 = transforming growth factor-beta 1
tT = total testosterone

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