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TOPIC PAPER

Peyronie's disease and testosterone deficiency: Is there a link?

Ishan Aditya[1] · **Ethan D. Grober**[2] · **Yonah Krakowsky**[2]

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Abstract

Introduction Peyronie's disease (PD) and testosterone deficiency (TD) impact men at the same stage of life and can ultimately contribute to erectile dysfunction. There is speculation that low levels of testosterone (T) may predispose men to penile fibrosis; however, there is no published, up-to-date review summarizing the current evidence. Therefore, we conducted a narrative review of the literature exploring the relationship between PD and TD.

Methods A comprehensive systematic search of existing literature of five online databases from June 1990 to June 2018 examining the relationship between PD and TD was conducted. The Cochrane risk-of-bias tool for randomized trials and the risk-of-bias assessment tool for cohort studies were used to evaluate the quality of studies.

Results Six studies were identified ($n=675$). Overall, five studies supported the link between PD and TD by demonstrating relationships in PD patients with low total T, free T, bioavailable T, greater penile curvature, and plaque development. However, one study demonstrated no connection between the conditions. The literature is restricted by small studies with methodological flaws.

Conclusion There are a number of mechanisms to support the link between TD and PD. The literature on the topic is limited by small studies which are overall conflicting. The findings of this work suggest the need for larger, prospective studies to clarify the role of TD in the development, evaluation, and treatment of PD. Establishing such a relationship could change management of PD as a diagnosis of PD may encourage clinicians to evaluate a patient's testosterone levels.

Keywords Peyronie's disease · Testosterone deficiency · Penile curvature · Penile fibrosis · Penile plaque · Andropause · Low testosterone · Androgens · Erectile dysfunction

Introduction

Peyronie's disease (PD) is a connective tissue disorder that involves scarring and plaque development in the tunica albuginea of the penis [1]. PD is associated with penile pain, curvature, shortening, and can contribute to erectile dysfunction (ED) [2]. Globally, PD is common, with a prevalence ranging from 0.7 to 11.8% [3].

Testosterone deficiency (TD) occurs in 40% of men over the age of 45 and is associated with erectile dysfunction, decreased libido, loss of lean muscle, fatigue, anemia, and depression [4]. TD may be caused by testicular, pituitary or hypothalamic abnormalities, and it is known that testosterone (T) levels decline with age [5]. TD contributes to many different forms of sexual dysfunction [6, 7]. A 2016 highly publicized randomized control trial demonstrated that testosterone therapy (TTh) in men with TD led to a significant improvement in sexuality when compared to placebo [8].

The relationship between TD and PD has not been fully elucidated. There is evidence that castration leads to significant changes within the tunica albuginea [9, 10]. This suggests the idea that low T levels may play a role in the pathogenesis of PD. Both TD and PD impact men at middle age even though men likely sustain more penile microtrauma at younger ages with higher sexual frequencies [11]. While

✉ Yonah Krakowsky
yonah.krakowsky@sinaihealthsystem.ca

Ishan Aditya
Ishan.aditya@mail.utoronto.ca

Ethan D. Grober
Ethan.grober@wchospital.ca

[1] Faculty of Medicine, University of Toronto, Toronto, ON, Canada

[2] Division of Urology, Department of Surgery, Women's College Hospital and Mount Sinai Hospital, University of Toronto, Box 19, 6th Floor 60 Murray St, Toronto, ON M5T 3L9, Canada

the higher prevalence of PD in middle-aged men may be a result of unique microtraumas due to less rigid erections [11], plaque formation may also be independently connected to the declining T levels in aging men.

Currently, there is little research exploring the relationship between TD and PD. Exploring this relationship will help clarify a potential mechanism underlying the pathogenesis of PD. We herein provide a narrative review of the published literature on this potential association to explore what is currently known regarding the relationship between these two common conditions.

Methods

A comprehensive literature search was conducted. We searched Medline, Embase, Central, CINAHL, and Web of Science to identify studies published between June 1990 and June 2018 examining the association between TD and PD. The following key terms were used: "Peyronie's Disease" OR "Penile Curvature," AND "Testosterone Deficiency," "Andropause," "Androgen Deficiency" OR "Low Testosterone." A total of five articles and one abstract were included. Review articles were excluded. The Cochrane risk-of-bias tool for randomized trials and the risk-of-bias assessment tool for cohort studies were used to evaluate the quality of studies (see Table 1) [12, 13]. Due to the weak and poor number of studies, a narrative review was performed.

Results

Five articles and one abstract have been published evaluating the relationship between TD and PD. Four were retrospective cohort studies, one was a prospective case–control study, and one was a randomized controlled trial. Overall, the study populations ranged from 24 to 205 individuals (see Table 1).

Studies supporting an association between TD and PD

A retrospective study conducted by Moreno et al. [14] investigated medical records of 121 patients with PD to explore the relationship between serum T concentrations and features of PD. Patients were being evaluated in a specialized sexual dysfunction clinic. The prevalence of TD in men with PD, along with total testosterone (TT) levels, free testosterone (FT), severity of curvature, and plaque size was studied. The authors reported that low T levels (< 300 ng/dL) were found in 74.4% of the PD patients, and that men with low free T had greater penile curvature compared to those with regular free T levels (55.9° vs. 37.5°, respectively, $P = 0.003$) [14]. Penile curvature was measured either with photographs, patient reports, or after in-office intracavernosal injections.

A 2011 retrospective study of 106 patients with PD compared serum total testosterone levels, PD duration, plaque size, plaque location, severity of penile curvature, presence of pain, and severity of ED between patients with PD and TD ($n = 30$) and PD patients with normal T levels ($n = 76$) [15]. Patients with both PD and TD demonstrated larger plaques (3.0 cm ± 1.2 vs. 2.0 cm ± 1.2; $P = 0.039$), worse curvature (32.0 ± 16.9° vs. 21.8 ± 15.4°), and a higher proportion of moderate-to-severe penile curvature (40° vs. 23.7°, respectively; $P = 0.015$) [15].

A retrospective chart review from a specialized sexual dysfunction clinic in 2009 looked at 34 patients with erectile dysfunction and studied the incidence of TD in patients with and without PD [16]. It was observed that 76.5% of patients with PD had TD (< 325 ng/dL) with a mean serum T of 306 ng/dL while patients without PD had a mean serum T of 373 ng/dL ($P < 0.0001$) [16]. This study has only been published as an abstract and limited data are available.

A case–control study of 24 patients (14 men with PD and 10 volunteer controls) sought to identify the relationship between androgens, collagen metabolism regulators, and PD [17]. It was observed that tissue inhibitor of metalloproteases-2 (TIMP-2) and dehydroepiandrosterone sulfate (DHEA-S) levels was significantly increased in PD ($P < 0.001$, $P = 0.04$, respectively; $R^2 = 0.63$). TIMP-1 and DHEA-S ($r = 0.55$, $P < 0.05$) were positively correlated in the PD group, while IGF-1 and testosterone ($r = -0.54$, $P < 0.05$), and IGF-BP3 and testosterone ($r = -0.68$, $P < 0.05$) were negatively correlated in PD patients [17]. These results suggest that decreased androgen levels may be associated with PD.

A multicenter, single-blinded, placebo-controlled, Italian study demonstrated that TT (9.6 nmol/L vs. 12.4 nmol/L; $P = 0.0093$), free T (28.4 nmol/L vs. 46.3 nmol/L; $P = 0.009$), and bioavailable T (4.6 nmol/L vs. 7.7 nmol/L; $P = 0.0054$) are significantly lower in PD patients seeking treatment than in a control population of healthy volunteers without PD [18]. In addition, plaque size was larger among patients with low free T/bioavailable T (4.9 cm^2 vs. 3.6 cm^2; $P = 0.0034$). It was found that adding TTh increased the efficacy of verapamil injections when comparing plaque size reduction and penile deformity ($P < 0.01$) [18].

Studies that do not support an association between PD and TD

A retrospective study evaluating 185 men presenting to a large urology clinic with PD or ED compared the prevalence of TD in these groups [19]. The authors also explored the relationship between TD and PD severity. The PD group

Table 1 Studies exploring the link between Peyronie's disease and testosterone deficiency

Study	Type of study	Sample size	Aim of study	Results	Risk-of-bias assessment
Moreno and Morgentaler [14]	Retrospective cohort	121	Review of medical records from a sexual dysfunction clinic to explore the relationship between TD and features of PD	Low T levels (< 300 ng/dL) present in 74.4% PD patients. Men with low free T had greater penile curvature than patients with regular free T levels (55.9° vs. 37.5°, respectively, $P = 0.003$). Penile curvature correlated significantly with free T ($r = -0.314$, $P = 0.016$) and estradiol ($r = 0.476$, $P = 0.0001$), but not TT ($r = -0.1999$, $P = 0.138$)	Sampling and representativeness of population: low; assessment of exposure: low; outcome present at start of the study: low; adjustment for confounding: high; assessment of outcome: low; follow-up of cohorts: high; co-interventions similar between groups: high
Sturm et al. [16]	Retrospective cohort (abstract only)	34	Review of medical records from a sexual dysfunction clinic to explore the relationship between TD and PD	76.5% of patients with PD had concomitant TD. Patients with PD demonstrated T levels of 306 ng/dL, and patients without PD had a serum testosterone of 373 ng/DL ($P < 0.0001$)	Sampling and representativeness of the population: low; assessment of exposure: low; outcome present at start of the study: low; adjustment for confounding: high; assessment of outcome: low; follow-up of cohorts: high; co-interventions similar between groups: high
Karavitakis et al. [17]	Prospective case–control	24	14 PD patients and 10 age-matched controls were studied to identify possible associations between androgens (T and DHEA-S), regulators of collagen metabolism (IGF-1 and MMP/TIMPs), and PD	Tissue inhibitor of metalloproteases-2 (TIMP-2) and dehydroepiandrosterone sulfate (DHEA-S) was significantly related to PD ($P < 0.001$, $P = 0.04$, respectively; $R^2 = 0.63$). TIMP-1 and DHEA-S ($r = 0.55$, $P < 0.05$) were positively correlated in the PD group, while IGF-1 and testosterone ($r = -0.54$, $P < 0.05$), and IGF-BP3 and testosterone ($r = -0.68$, $P < 0.05$) were negatively correlated in PD patients	Sampling and representativeness of the population: low; assessment of exposure: low; outcome present at start of the study: low; adjustment for confounding: high; assessment of outcome: low; follow-up of cohorts: high; co-interventions similar between groups: high
Nam et al. [15]	Retrospective cohort	106	PD patients with TD were compared with PD patients with normal T levels	In patients with PD and TD, plaque size was larger (3.0 ± 1.2 vs. 2.0 ± 1.2 cm; $P = 0.039$), degree of penile curvature was worse ($32.0 \pm 16.9°$ vs. $21.8 \pm 15.4°$) and the frequency of moderate-to-severe penile curvature was greater (40% vs. 23.7%; $P = 0.015$)	Sampling and representativeness of the population: low; assessment of exposure: low; outcome present at start of the study: low; adjustment for confounding: high; assessment of outcome: low; follow-up of cohorts: N/A; co-interventions similar between groups: N/A

Table 1 (continued)

Study	Type of study	Sample size	Aim of study	Results	Risk-of-bias assessment
Cavallini et al. [18]	Randomized controlled trial	205	T levels compared in patients with PD and controls. Results from verapamil administration between TD patients and eugonadal patients were compared	TT (9.6 nmol/L vs. 12.4 nmol/L; $P=0.0093$), free T (28.4 nmol/L vs. 46.3 nmol/L; $P=0.009$), and bioavailable testosterone (4.6 nmol/L vs. 7.7 nmol/L; $P=0.0054$) are significantly lower in PD patients than controls Plaque size was larger among patients with low free T/bioavailable T (4.9 cm^2 vs. 3.6 cm^2; $P=0.0034$). TTh increased the efficacy of verapamil injections when comparing plaque size and penile deformity ($P<0.01$)	Sequence generation: low; allocation concealment: low; blinding of participants and personnel: low; blinding of outcome assessment: low; incomplete outcome data: low; selective outcome reports: low; other issues: low
Kirby et al. [19]	Retrospective cohort	185	Chart review of men with PD or ED comparing the prevalence of TD	Average plaque size in the low T group was the same as the normal T group. TD was not associated with more severe penile curvature	Sampling and representativeness of the population: low; assessment of exposure: low; outcome present at start of the study: low; adjustment for confounding: low; assessment of outcome: low; follow-up of cohorts: high; co-interventions similar between groups: high

had a slightly higher incidence of low T (52.9% vs. 45.9%), but this difference was not statistically significant ($P=0.35$) [19]. No significant association between T levels and plaque size ($P=0.85$), direction of curvature ($P=0.11$), or degree of curvature (P value not significant, not reported) were demonstrated in the cohort.

Globally, the relationship between PD and TD is unclear and this is reflected by the conflicting evidence presented above in the available literature on this topic.

Discussion

The pathophysiology of PD has yet to be fully understood. Current evidence suggests that microtrauma to the penis followed by disordered wound healing may cause plaque development [3, 14]. Most men are exposed to some level of microtrauma during coitus; however, a small number will develop PD due to microtrauma [20]. Interestingly, while most postulate that PD is a result of microtrauma, the disease generally impacts men at midlife [11]. Other potential risk factors for PD include smoking, inflammatory genital disease in the partner, fibromatous lesions of the genital tract, and history of genital tract surgery [21]. PD has also been shown to be associated with both Dupuytren's contracture and plantar fibromatosis which involves fibrosis of the fascia underlying the palm and the feet, respectively [1, 3]. From a genetic perspective, PD scar formation is associated with the upregulation of genes associated with tissue remodeling, collagen synthesis, myofibroblast differentiation, inflammation, and proteolysis, while the genes which inhibit these processes, including those which code for collagenases, are downregulated [20].

There are no proven oral therapies for PD [22]. For patients experiencing pain during the active form of the disease, nonsteroidal anti-inflammatory drugs are recommended. Intralesional therapies involve the administration of collagenase clostridium histolyticum (Xiaflex®), interferon α-2β, or verapamil [22]. Collagenase clostridium histolyticum is the first FDA, and now Health Canada, approved therapy for PD [23]. Surgical treatments for PD involve tunica albuginea plication, plaque excision/incision and grafting, or penile prosthesis.

A comprehensive assessment of the literature suggests that it is unclear whether TD plays a significant and definitive role in the pathogenesis of PD and its treatment. While many studies do provide data supporting a possible relationship, there are substantial methodological limitations which warrant higher quality studies.

Many of the available studies are retrospective in nature and thus prone to bias [14–17]. Moreno et al. [14] lacked a control group and a rigorous approach for measuring erectile function and severity of penile curvature. Their results hinge on the degree of penile curvature; however, they did not employ a consistent method of measuring the angle of deformity and included patient-reported estimations.

The retrospective design of Sturm et al. [16] used a small sample size ($n=34$), and little data are available from the actual abstract. While they report a significant difference in total T levels between those with PD and those without PD, the difference is small (only 67 ng/dL) and unlikely to be clinically significant.

The case–control study by Karavitakis et al. [17] also utilized a small sample size (10 individuals with PD and 14 healthy controls). This small population has an age range of 20 years, which can interfere with the interpretation of DHEA and DHEA-S which are age-dependent values [17].

The retrospective chart review by Nam et al. [15] presented relationships between low total T and ED, penile deformity, and plaque size. However, this study lacked multivariate analyses, which may identify important covariates as risk factors for PD that also impact T levels [15].

The multicenter trial conducted by Cavallini et al. [18] lacked an arm treated with placebo alone or an arm treated only with testosterone alone, which prevented appropriate comparisons with the treatment groups. It is also interesting that individuals treated with verapamil alone showed no benefit despite a body of research suggested its modest efficacy [24].

The retrospective review conducted by Kirby et al. [19] showed there to be no relationship between TD and PD. However, serum T levels were not obtained at consistent times of day, and only total testosterone levels were analyzed. It is known that sex hormone-binding globulin can dramatically impact the level of biologically active T which is especially significant as men age [25]. Information on ED severity, libido, and sexual function were also not reported.

PD and TD may be connected through the theory that low T levels directly impact collagen metabolism and penile scar formation [18, 26, 27]. This theory is strengthened by the fact that TD and PD generally impact men at the same decade of life (middle age), despite the fact that the majority of penile microtraumas likely impact men at much younger ages when sexual frequency is the highest. Further, as mentioned above, there is evidence of significant tunica albuginea changes in those who have undergone castration suggesting low levels of T may predispose men to penile scar formation [9, 10]. Alternatively, it is also possible that TD and PD present at middle age due to the prevalence of less rigid erections predispose men to penile trauma and scar formation. Erectile dysfunction, and not TD, would therefore be the driving force behind penile scar formation and PD.

The implications of a meaningful association between TD and PD would have significant clinical implications. Firstly, a diagnosis of PD may encourage clinicians to check a patient's testosterone levels. TD is associated with low

bone mineral density, anemia, and metabolic syndrome, and treatment has been demonstrated to improve those parameters [28, 29]. Currently, both the AUA and CUA guidelines on PD do not recommend checking testosterone levels [30, 31]. Further, if normalizing testosterone levels improves the deformity associated with PD, treating with T could potentially improve the results of minimally invasive injection therapies.

This narrative review is limited by the weak published evidence available on the link between PD and TD. It is impossible to make any definitive conclusions based on the information available due to the methodological limitations stated above. The literature to date allows speculation, but does not provide any definitive link between PD and TD.

Conclusion

To date, there is insufficient evidence to conclude that a relationship exists between TD and PD. Establishing such a relationship could change the evaluation and treatment of men with PD. Current guidelines do not recommend obtaining T levels in men with PD [30, 31].

While the literature on the topic is weak and conflicting, larger and more robust studies could clarify the role of T levels in the development, evaluation and treatment of PD. Understanding the true relationship between TD and PD would have profound effects on the evaluation and treatment of PD.

Author contribution Aditya was involved in project development, data collection, data analysis, manuscript writing, and editing. Grober was involved in project development, data collection, data analysis, manuscript writing, and editing. Krakowsky was involved in project development, data collection, data analysis, manuscript writing, and editing.

Compliance with ethical standards

Conflict of interest There are no personal conflicts of interest.

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