ORIGINAL RESEARCH—PEYRONIE'S DISEASE

Testosterone Deficiency and Peyronie's Disease: Pilot Data Suggesting a Significant Relationship

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ABSTRACT

Introduction. As testosterone (T) has been shown to influence wound healing, and serum T declines in the age group at risk for Peyronie's disease (PD), we explored the possibility that low serum T may be associated with PD.
Aim. The purpose of this study was to evaluate the relationship between serum T concentrations and features of PD.
Methods. Medical records were reviewed for 121 consecutive patients with PD seen over a 2-year period. All patients were assessed for sociodemographic data, medical history, comorbid medical conditions, findings on physical examination, and severity of curvature. Laboratory testing included serum concentrations of total testosterone (TT) and free testosterone (FT). Testosterone deficiency (TD) was defined as TT values less than 300 ng/dL and/or FT less than 1.5 ng/dL.
Main Outcome Measures. Prevalence of TD in men with PD and correlation of TT and FT with severity of curvature and plaque size.
Results. Mean patient age was 53.9 ± 10.6 years (range 28–77). Penile curvature was 50.2 ± 23.6 degrees (range 10–120). Mean TT was 411.6 ± 203.6 ng/dL (range 69–877), and mean FT was 1.12 ± 0.58 ng/dL (range 0.13–5.06). Low T was identified in 29.5% by TT alone and in 74.4% overall. Severity of curvature was greater for men with TD compared with men with normal T (54.3 vs. 37.1 degrees, $P = 0.006$). Men with low FT had greater penile curvature than men with normal FT (37.5 vs. 55.9 degrees, respectively, $P = 0.003$). Severity of penile curvature correlated significantly with FT ($r = -0.314$, $P = 0.016$) and estradiol/T ($r = 0.476$, $P = 0.0001$) but not TT ($r = -0.199$, $P = 0.138$).
Conclusions. This pilot study suggests a possibly important relationship between low T and PD. Further prospective studies are needed to confirm this relationship. **Moreno SA, and Morgentaler A. Testosterone deficiency and Peyronie's disease: Pilot data suggesting a significant relationship. J Sex Med 2009;6:1729–1735.**

Key Words. Peyronie's Disease; Testosterone; Penile Curvature; Hypogonadism

Introduction

Peyronie's disease (PD) is a common medical condition that causes penile curvature, erectile dysfunction (ED), and penile shortening, and can produce significant psychologic and sexual distress [1]. Recent data suggest that the prevalence of PD is increasing [2–4]. Yet despite ongoing and active scientific research, the pathophysiology of PD remains uncertain [1,5].

There is a general consensus that certain events are required to develop a Peyronie's plaque. Trauma or microtrauma represents the first step, followed by disordered local wound healing. The evidence suggests that genetic and immunologic factors may contribute to this pathologic wound healing [6–18].

As the frequency and vigor of sexual intercourse tend to be greatest in young men, it is unclear why the peak onset of PD would occur among men in their 50s if trauma is the precipitating event. One possibility is a cumulative effect of repetitive minor injuries to the tunica albuginea over time. Another is increased vulnerability

of the tunica albuginea as a result of age-related changes [19,20].

Since testosterone (T) has been implicated in wound healing [21–23] and is known to decline with age [24,25], we explored the possibility that low serum T may be associated with the development and severity of PD.

Methods

We retrospectively reviewed the medical records of all men seen with PD between January 2006 and January 2008. Sociodemographic data and medical history were obtained, including symptoms such as pain with erection, ability to intromit, duration of symptoms, penile trauma history, type and degree of penile curvature, medications, comorbidities, and other fibrotic conditions. ED was defined by patient report of diminished rigidity.

The diagnosis of PD was made based on the presence of characteristic symptoms and palpable penile plaque on physical examination. Size of plaque was determined by physical examination. Degree of curvature was determined by photographs, by assessment following intracavernosal injection of alprostadil 10–20 mcg, or by patient report. All patients underwent routine laboratory testing for total testosterone (TT) (reference range: 300–1,000 ng/dL), free testosterone (FT) (reference range: 1.5–3.5 ng/dL), sex hormone binding globulin (reference range: 9–45 nmol/L), luteinizing hormone (reference range: 1.5–9.3 mIU/mL), follicle-stimulating hormone (reference range: 1.6–8.0 IU/L), prolactin (reference range: 2.0–18.0 ng/mL), and estradiol (reference range: 20–75 pg/mL). Blood tests were obtained during normal clinic hours, between 8:30 AM and 5:30 PM. Immunoassays were used for the measurement of TT (Tosoh Bioscience, San Francisco, CA, USA) and FT (Diagnostic Products Corp., Los Angeles, CA, USA).

Low T was defined as TT less than 300 ng/dL [26] and/or FT less than 1.5 ng/dL [27].

Statistical analyses were performed with Minitab statistical program version 15 (Minitab Inc., State College, PA, USA). Analysis of variance was used to compare categorical and continuous variables. Comparisons between categorical variables were performed using χ^2 test. Pearson's rank correlation coefficients were used to evaluate possible relationships between continuous variables. Univariate and multivariate binary logistic regression analysis was performed to examine the relationship among the ability to intromit and associated factors. All results are expressed as means ± standard deviation. A P value of <0.05 was considered significant.

Table 1 Age range of patients with Peyronie's disease (N = 121)

Age (years)	Number (%)
<30	3 (2.48)
30–40	12 (9.92)
41–50	27 (22.31)
51–60	44 (36.36)
61–70	31 (25.62)
>70	4 (3.31)

Results

A total of 121 medical records were reviewed retrospectively. Mean patient age was 53.9 ± 10.6 years (range 28–77), with the highest prevalence noted among men in the sixth decade of life (Table 1). The mean duration of symptoms was 16.8 ± 19.1 months (range 1–120). Penile trauma was reported by 10.6% of the patients, and 25.7% reported pain during the evolution of the disease. ED was reported by 54.5% of the patients including 31.4% of the study population who were unable to intromit. Only 4.9% of the patients smoked. The most commonly associated comorbidity was hypertension (26.5%). Diabetes mellitus (DM) was reported by 7.4% of the patients. In addition, two patients (1.7%) had a diagnosis of Dupuytren's contracture.

The characteristics of the study population are presented in Table 2. The direction of primary curvature was dorsal in 66.9%, ventral in 12.4%, and lateral in 8.3% of cases. In 12.4% of the patients, no curvature was present. Mean plaque length was 2.0 ± 0.68 cm (range 1–4). Mean degree of penile curvature was 50.2 ± 23.6 degrees (range 10–120).

Mean TT was 411.6 ± 203.6 ng/dL (range 69–877), and mean FT was 1.12 ± 0.58 ng/dL (range 0.13–5.06). In total, 74.4% of the patients had low levels of T. FT was low in 71.1% of cases, and 29.5% were low by TT alone.

Comparison of men with low T vs. normal T (Table 3) revealed the following. Men with low T had a mean age of 54.8 years compared with 51.1 years for the normal T group. The duration of symptoms was shorter in the group with normal T but was not statistically significant (13.05 vs. 18.47 months, $P = 0.270$). ED was noted in 58.9% of men with low T and 41.9% with normal T ($P = 0.102$). No significant differences were noted

Table 2 General characteristics of Peyronie's population sample

Characteristics	Value*
Subjects	121
Age (years)	53.9 ± 10.6 (28–77)
Duration of symptoms (months)	16.8 ± 19.1 (1–120)
History of penile trauma	11 (10.6)
Erectile dysfunction	66 (54.5)
Smoke habit	6 (4.9)
High blood pressure	32 (26.5)
Diabetes mellitus	9 (7.4)
Dupuytren's disease	2 (1.7)
Peyronie's plaque	
Location	
Dorsal	81 (66.9)
Ventral	15 (12.4)
Lateral	10 (8.3)
No curvature	15 (12.4)
Curvature (degrees)	50.2 ± 23.6 (10–120)
Size (cm)	2.0 ± 0.68 (1–4)
Total testosterone (ng/dL)	411.6 ± 203.6 (69–877)
Free testosterone (ng/dL)	1.2 ± 0.58 (0.13–5.06)
Sex hormone binding globulin (nmol/L)	32.73 ± 16.2 (5–100)
Luteinizing hormone (mIU/mL)	3.8 ± 2.8 (0.2–19.3)
Follicle-stimulating hormone (mIU/mL)	7.8 ± 8.4 (5.8–67.8)
Estradiol (pg/mL)	41.4 ± 20.0 (2–85.2)
Prolactin (ng/mL)	6.9 ± 4.1 (2.4–25.3)
Estradiol (pg/mL)/testosterone (ng/dL)	0.121 ± 0.082 (0.005–0.548)

*Values expressed as means ± standard deviation (range), frequency (%).

between groups with regard to comorbidities or direction of curve. However, men with low T had a significantly greater degree of penile curvature than men with normal T (54.3 vs. 37.1 degrees, respectively, $P = 0.006$).

Men with low FT had greater penile curvature than men with normal FT (37.5 vs. 55.9 degrees, respectively, $P = 0.003$). Severity of penile curvature correlated significantly with FT ($r = -0.314$, $P = 0.016$) but not TT ($r = -0.199$, $P = 0.138$). A numerically greater degree of curvature for men with low TT compared with normal T approached but did not reach statistical significance (64.37 vs. 50.78, respectively, $P = 0.058$). No significant associations were found between either TT or FT and plaque size. A significant correlation was noted for the ratio of estradiol to testosterone (E/T) with severity of penile curvature ($r = 0.476$, $P = 0.0001$).

Univariate analysis revealed significant associations between the ability to intromit and age (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.88–0.97; $P = 0.001$), diminished penile rigidity (OR, 0.1; 95% CI, 0.04–0.28; $P = 0.0001$), and low T (OR, 0.33; 95% CI, 0.12–0.95; $P = 0.039$). No significant relationship with ability to intromit was noted for severity of penile curvature ($P = 0.158$) or plaque size ($P = 0.321$) (Table 4). Age and diminished penile rigidity maintained their significance in a multivariate analysis but low T did not (Table 5).

In this population, a larger number of comorbidities were observed in patients older than 50 years, but this difference did not reach a significant difference. No significant associations were found for penile curvature or plaque size with regard to sex hormone binding globulin, luteinizing

Table 3 Distribution of Peyronie's disease population according to testosterone levels

Risk factors	Low testosterone levels (N = 90)	Normal testosterone levels (N = 31)	*P* value*
Age groups (years)	54.8 (±10.3)	51.1 (±11.35)	0.095
Duration symptoms (months)	18.47 (±21.4)	13.05 (±12.0)	0.270
Erectile dysfunction			0.102
Yes	53 (58.89%)	13 (41.94%)	
No	37 (41.11%)	18 (58.06%)	
Comorbidities			
Hypertension			0.288
Yes	26 (28.89%)	6 (19.35%)	
No	64 (71.11%)	25 (80.65%)	
Diabetes mellitus			0.591
Yes	6 (6.67%)	3 (9.68%)	
No	84 (93.33%)	28 (90.32%)	
Curvature type			0.155
Dorsal	60 (66.67%)	21 (67.74%)	
Ventral	9 (10%)	5 (16.12%)	
Lateral	10 (11.11%)	1 (3.23%)	
No curvature	11 (12.22%)	4 (12.91%)	
Curvature angle (degrees)	54.3 (±24.9)	37.1 (±12.2)	0.006
Plaque size (cm)	2.05 (±0.71)	1.88 (±0.58)	0.446

Values expressed as means ± standard deviation.
*χ^2 and analysis of variance; significance level at $P < 0.05$. Percentages are calculated for a total of 90 patients with low levels of testosterone and 31 patients with normal levels of testosterone.

Table 4 Results of univariate analysis for the ability to intromit and related factors

Characteristics	Odds ratio (95% confidence interval)	*P* value*
Age	0.93 (0.88–0.97)	0.001
Durations symptoms	1.0 (0.96–1.03)	0.865
Diminished penile rigidity	0.1 (0.04–0.28)	0.0001
Plaque curvature	0.98 (0.96–1.01)	0.158
Plaque size	2.21 (0.46–10.6)	0.321
Low testosterone	0.33 (0.12–0.95)	0.039

*Significance level at $P < 0.05$.

hormone, follicle-stimulating hormone, prolactin, and estradiol.

Discussion

This study identified a strong association between PD and low serum T concentrations. Not only did 74.4% of men with PD demonstrate low levels of TT or FT, but low FT was also found to correlate with degree of curvature.

These pilot results suggest a possible causal relationship between T and PD. A MEDLINE search indicates this potential relationship has received only minor investigation to date, with only one publication reporting hormone levels in any detail among men with PD. In this study by El-Sakka [28], only TT was measured, and low T was not defined. The prevalence of low T among men with PD was 11.3%, which compares with 29% in our study when low T was defined by only TT less than 300 ng/dL. As FT more accurately reflects bioavailable T than does TT [24], the 74.4% prevalence rate of low T in our study may serve as a more relevant indication that low T plays a possible role in the development of PD.

Usta et al. [29] retrospectively evaluated 469 patients with PD over a 10-year study period. A wide range of comorbidities were investigated in association with PD. No significant relationship was found for DM, hyperlipidemia, hypercholesterolemia, hypertension, and smoking. Further, there were no significant differences between different comorbidities and patients with normal or low T. Other studies have also searched for relationships between risk factors (serum lipid abnormalities, DM, hypertension, procedures on the penis, hyperuricemia, lipoma and urethritis, cigarette smoking) and PD [30–32]. None of these studies examined serum T concentrations as a risk factor for PD.

The positive association between low T and PD in this study does not seem to be related to socio-demographic factors, as the mean age of the population was relatively young (53.9 years) and the age distribution was similar to other series [2,7,13,14,19,20,28]. Moreover, the strong relationship between low T and severity of penile curvature ($P = 0.006$) argues for a nontrivial relationship.

Why might low T be related to PD? We propose two main possibilities: (i) diminished erectile rigidity and (ii) impaired tissue response to injury. The currently accepted model for the etiology of PD is based on the concept that penile trauma, as a known or occult event (microtrauma), leads to an injury of the tunica albuginea, with PD resulting as a consequence of deranged tissue healing. Microtrauma from penile bending during intercourse may be a key factor, as only 10.6% of men in this study reported known penile trauma, consistent with other studies in which a minority reported known trauma.

Reduced rigidity may lead to greater bending of the penis [33] and thus predispose to penile microtrauma and PD. Low T may contribute to reduced rigidity by the important associations of T with erection [34]. Traish et al. [35] demonstrated in an animal model that castration produces reduced intracavernosal pressure in response to direct nerve stimulation. Additional studies have also revealed structural changes in the corpus cavernosum associated with castration, such as replacement of smooth muscle with adipocytes in the subtunical region [36,37].

There is additional evidence that T has direct central and peripheral actions impacting male sexual function and response in men [35,38]. Kwan et al. reported fewer spontaneous erections in hypogonadal men compared with eugonadal men [39]. T therapy has been shown to improve ED in hypogonadal men [34]. Reyes-Vallejo et al. in a retrospective study of hypogonadal men noted that 61% of patients reported improvement in erections with T replacement therapy [40]. T therapy has also been observed to increase the frequency of nighttime and daytime erections, and duration and magnitude of nocturnal erections [41].

Table 5 Results of multivariate analysis for the ability to intromit and significant factors

Characteristics	Odds ratio (95% confidence interval)	*P* value*
Age	0.95 (0.9–1.0)	0.049
Diminished penile rigidity	0.14 (0.05–0.4)	0.0001
Low testosterone	0.44 (0.14–1.37)	0.156

*Significance level at $P < 0.05$.

The importance of T on tissue response to injury may represent a second mechanism by which low T may predispose to PD. In PD, the evidence suggests an imbalance between profibrotic and antifibrotic factors. For example, transforming growth factor beta-1 (TGF-β1) is overexpressed in PD. TGF-β1 stimulates collagen synthesis by fibroblasts and myofibroblasts, and also induces the production of other profibrotic factors [5]. On the other hand, nitric oxide (NO) has been identified as an important antifibrotic factor based on studies demonstrating that the preservation of nitric oxide synthase (NOS) activity is fundamental in preventing excessive collagen deposition in wound healing [5,42,43]. Several animal and human studies have shown a positive effect of T on the expression of NO [43–48]. Androgens increase the amount of nNOS mRNA by enhancing nNOS gene expression or by decreasing mRNA degradation, resulting in a greater amount of enzyme available for the production of NO in the rat penis [44–48].

Nearly one-third of the patients in this study reported the inability to intromit during intercourse. Although in clinical practice patients frequently report that their curvature interferes with their ability to intromit, we found no correlation in this study with degree of curvature and inability to intromit. Positive correlations included age, self-report of diminished rigidity, and decreased T concentration. T concentration lost significance in multivariate analysis, possibly confounded by its own association with age.

The results of this study must be regarded as exploratory because of the presence of several methodological limitations. These include the retrospective nature of the study, the absence of a control group, and the nonrigorous assessment of erectile function and severity of penile curvature in a clinic population. Nonetheless, the high rate of low T in this population of men with PD and the associations with several aspects of PD suggest that further prospective trials are indicated to evaluate further the possible relationship between low T and PD.

Another item of note that may merit further investigation was the correlation of curvature severity with the E/T ratio. It is unknown how or why estradiol may contribute to PD. Finally, although the correlation between FT and curvature severity was statistically significant, the relatively low absolute value of the *R* coefficient indicates that other factors must also be present. Identifying these additional factors will be an important step in furthering our understanding of PD.

Conclusions

This pilot study suggests a possibly important relationship between low levels of T and PD.

The biggest contribution to low serum T concentration seen in this group of patients with PD was given by low levels of FT, which was also correlated with the severity of penile curvature.

Further prospective trials are needed to confirm this relationship.

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Statement of Authorship

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