Peyronie's Disease and Autoimmunity—A Real-Life Clinical Study and Comprehensive Review

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ABSTRACT

Introduction. Although heavily investigated over the last decades, Peyronie's disease (PD) pathogenesis remains unclear.

Aim. We sought to investigate the association between PD and autoimmune diseases (ADs) in men seeking medical help for sexual dysfunction in the real-life setting.

Methods. Complete sociodemographic and clinical data from a homogenous cohort of 1,140 consecutive Caucasian–European men were analyzed. Health-significant comorbidities were scored with the Charlson Comorbidity Index and ADs were stratified according to International Classification of Diseases, Ninth Revision classification.

Main Outcome Measures. Descriptive statistics and multivariate logistic regression models tested the association between ADs and PD.

Results. PD was diagnosed in 148 (13%) of the 1,140 men; of PD patients, 14 (9.5%) had a comorbid AD; conversely, the rate of ADs in non-PD patients was significantly lower ($\chi^2 = 24.7$; $P < 0.01$). Both patient age and AD comorbidity achieved multivariable independent predictor status for PD (odds ratio [OR]: 1.05; $P < 0.01$ and OR: 4.90; $P < 0.01$, respectively).

Conclusions. Our observational findings showed that ADs are highly comorbid with PD in a large cohort of same-race individuals seeking medical help for sexual dysfunction in the real-life setting. **Ventimiglia E, Capogrosso P, Colicchia M, Boeri L, Serino A, La Croce G, Russo A, Capitanio U, Briganti A, Cantiello F, Mirone V, Damiano R, Montorsi F, and Salonia A. Peyronie's disease and autoimmunity—A real-life clinical study and comprehensive review. J Sex Med **;**:**–**.**

Key Words. Peyronie's Disease; Sexual Dysfunction; Autoimmune Disease; Psoriasis

Introduction

Peyronie's disease (PD) is a localized disorder of the connective tissues characterized by the presence of fibrotic alterations originating in the tunica albuginea and/or septum of corpora cavernosa [1]. Though heavily investigated over the last decades, PD pathogenesis remains unclear [2]. The mainstream theory currently describing PD onset and development implies a trigger, such as a penile trauma [1,3], followed by a status of local impaired wound healing that eventually results in fibrosis and plaque formation [2,4,5].

Besides this hypothesized stream of events, several risk factors and associated conditions were found to be comorbid with PD [6], including cigarette smoking [7], diabetes and hypertension [8,9], and Dupuytren's contracture [10].

Considering the associated conditions allegedly involved in PD pathogenesis, some authors have looked at a possible role played by the immune system. In this context, Willscher et al. [11] first reported a significant relationship between PD and histocompatibility antigens of the B7 cross-reacting group. Moreover, an association between PD and HLA-A1 and DQw2 was recently reported [12], as was an association with HLA-DQ5 [13] and HLA-B27 [14]. A drawback of these studies, however, was that they usually included a limited number of patients, and the results were rarely confirmed, if not denied, by other authors [12,15,16]. Besides HLAs, other components of the immune response have been investigated. Anti-elastin antibodies, for example, have been detected in the serum of patients with PD [17]. Moreover, Schiavino et al. [18] reported 75% of their PD patients to have a positive immunologic test and 38% to carry autoantibodies.

Molecular markers of fibrosis and inflammation have been inquired as well in this context. Zimmerman et al. [19] reported increased serum transforming growth factor (TGF)-β1 levels and decreased serum tumor necrosis factor-α and interleukin-6 levels in PD patients as compared with healthy controls. Conversely, Pavone et al. found no difference in cytokine genes expression at plaque level (even though case and control groups were not homogeneously comparable) [20]. Alterations of apoptosis gene expression observed in PD plaques have been allegedly involved in the fibrosing process following a status of local inflammation [21], as they may eventually result in abnormally prolonged fibroblast activity and survival. Likewise, epigenetic modifications seem to play a role fostering fibrosis [22]. Preclinical data also showed how local antigen-driven immune response at the level of the tunica albuginea, such as the case of a rat tunica albuginea allograft, induces similar alterations to those observed in PD plaques [23]. If, on one hand, inflammation—which is considered the basis of autoimmune diseases (ADs)—is regarded as an established component in PD onset and consolidation [2], these data, on the other hand, are still insufficient for completely supporting an autoimmune hypothesis.

Considering the reported findings in terms of increased frequency of determined HLA haplotypes found in PD patients, usually associated with particular ADs [24,25], and the apparent increased prevalence of immune system laboratory alterations usually observed in AD [18], this study aimed to investigate AD prevalence in a cohort of patients seeking medical help for new-onset sexual dysfunction, focusing on those with PD.

Materials and Methods

Population

The analyses were based on a cohort of 1,149 consecutive Caucasian–European sexually active heterosexual men seeking medical help for new-onset sexual dysfunction between January 2010 and April 2013 at a single academic outpatient clinic. To this aim, erectile dysfunction (ED) was defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance [26]. Premature ejaculation was defined as a sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within about 3 minutes of vaginal penetration and the inability to delay ejaculation on all or nearly all vaginal penetrations, with negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy [27,28]. Low sexual desire/interest was used as a convenient umbrella term to refer to the clinical condition where the individual complains of a modification in his usual level of sexual interest or desire [29]. For the specific purpose of this exploratory study, patients with certain symptoms and signs of either acute inflammatory phase or fibrotic phase PD were considered, according to the descriptive definition of PD suggested by the European Association of Urology guidelines [1].

Patients were comprehensively assessed with a detailed medical and sexual history, including sociodemographic data. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI) [30] both as a continuous or a categorized variable (i.e., 0 vs. 1 vs. ≥2). We used the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification.

Hypertension was defined when antihypertensive medication was taken and/or for high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic). Hypercholesterolemia was defined when lipid-lowering therapy was taken and/or high density lipoproteins cholesterol was <40 mg/dL. Similarly, hypertriglyceridemia was defined when plasma triglycerides were ≥150 mg/dL [31]. ADs were thoroughly assessed and stratified according to the same ICD-9 classification (http://www.icd9data.com/). Measured body mass index (BMI), defined as weight in kilograms by height in square meters, was considered for each patient. For BMI,

we used the cutoffs proposed by the National Institutes of Health [32]: normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and class ≥1 obesity (≥30.0 kg/m^2).

Moreover, patients were requested to complete the International Index of Erectile Function (IIEF) [33].

Literacy problems as well as other reading and writing problems were excluded in all patients.

Data collection followed the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to provide their own anonymous information for this and future studies.

Main Outcome Measures

The primary end point of this study was to assess AD prevalence in a large series of Caucasian–European sexually active men consecutively seeking medical help for new-onset sexual dysfunction focusing on those affected by PD. The secondary end point was to test potential associations between AD and PD.

Statistical Analyses

Data are presented as means (median; range). Clinical and sociodemographic characteristics of the patients are presented as means (median) and ranges. The statistical significance of differences in means and proportions was tested with the two-tailed *t*-test and the χ^2 test, respectively. Exploratory analyses were initially applied to all variables in a preliminary analysis, and variables were maintained when relevant to the results. Univariable and multivariable logistic regression analyses tested the association between predictors and PD. Two models were developed: Model 1 included age, BMI, categorized CCI, hypertension, Dupuytren's disease, AD, and cigarette smoking; model 2 included age, BMI, categorized CCI, hypertension, Dupuytren's disease, AD, and cigarette smoking. Statistical analyses were performed using SPSS statistical software, v 13.0 (IBM Corp., Armonk, NY, USA). All tests were two sided, with a significance level set at 0.05.

Results

Table 1 lists the characteristics and the descriptive statistics of the entire cohort of patients. PD and ADs were found in 148 (13%) and in 34 (3%) patients, respectively.

Table 2 depicts the characteristics and the descriptive statistics of PD as compared with non-PD patients. Patients with PD were significantly older, had a higher BMI, and a higher IIEF-Erectile Function score (all $P < 0.01$). Moreover, higher rates of patients with diabetes, hypertension, Dupuytren's disease, smokers (all $P \leq 0.02$) were found among men with PD compared with non-PD individuals. Similarly, ADs were more frequent among PD patients than non-PD individuals ($P < 0.01$). To this regard, psoriasis, psoriatic arthritis, and rheumatoid arthritis (all $P \leq 0.03$) were more frequently diagnosed in PD patients compared with non-PD patients, whereas autoimmune thyroiditis, systemic lupus erythematosus, vitiligo, granulomatosis with polyangiitis, and systemic sclerosis were not. Moreover, according to CCI scores, no differences were observed in terms of comorbidity burden between these two subcohorts of patients.

Table 3 details logistic regression models testing the associations between clinical predictors and PD. According to univariable logistic regression model, higher age and BMI, hypertension,

Table 1 Patients' characteristics and descriptive statistics

No. of patients	1,140
Age (years)	
Mean (median)	48.75 (48)
Range	18–89
BMI (kg/m^2)	
Mean (median)	25.46 (24.99)
Range	14.69–43.21
BMI (NIH classification), n (%)	
18.5–24.9	570 (50.0)
25–29.9	439 (38.5)
≥30	131 (11.5)
CCI	
Mean (median)	0.49 (0.00)
Range	0–8
CCI, n (%)	
0	978 (77.0)
1	104 (9.1)
2+	158 (13.9)
Primary reason for office evaluation	
ED	665 (58.3)
PE	173 (15.2)
LSD/I	128 (11.2)
PD	148 (13.0)
Other sexual disorders	26 (2.1)
IIEF-EF domain	
Mean (SD)	16.2 (17)
Range	0–30
Hypertension, n (%)	165 (14.5)
Diabetes, n (%)	112 (9.8)
Dupuytren's disease, n (%)	4 (0.4)
Current/previous smokers, n (%)	260 (23.7)
Autoimmune diseases, n (%)	34 (3.0)

BMI = body mass index; CCI = Charlson Comorbidity Index; ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-Erectile Function; LSD/I = low sexual desire/interest; NIH = National Institutes of Health; PD = Peyronie's disease; PE = premature ejaculation; SD = standard deviation

Table 2 Patients' characteristics and descriptive statistics according to PD diagnosis

	PD (n = 148)	Other (n = 992)	*P* value	95% CI
Age				
Mean (median)	57.16 (61)	47.50 (47)	<0.01	−12.3 to −7.0
Range	18–79	18–89		
BMI				
Mean (median)	26.37 (26.12)	25.32 (24.84)	<0.01	−1.7 to −0.4
Range	19.31–39.20	14.69–43.21		
BMI (NIH classification), n (%)				
18.5–24.9	62 (42.0)	508 (51.2)	0.08	χ^2: 5.0
25–29.9	63 (42.7)	376 (37.9)		
≥30	23 (15.3)	108 (10.9)		
CCI	0.52 (0)	0.48 (0)	0.66	−0.2 to 0.1
CCI, n (%)				
0	108 (72.8)	770 (77.6)	0.32	χ^2: 2.3
1	18 (17.6)	86 (8.7)		
2+	22 (15)	136 (13.7)		
IIEF-EF				
Mean (median)	20.4 (24)	15.5 (15)	<0.01	−7.7 to −2.1
Range	1–30	0–30		
Hypertension, n (%)	55 (37.2)	110 (11.1)	<0.01	χ^2: 31.2
Diabetes, n (%)	27 (18.2)	85 (8.6)	<0.01	χ^2: 13.6
Dupuytren's disease, n (%)	3 (2)	1 (0.1)	<0.01	χ^2: 13.7
Current/previous smokers, n (%)	46 (31.1)	224 (22.6)	0.02	χ^2: 5.6
Autoimmune diseases, n (%)	14 (9.5)	20 (2)	<0.01	χ^2: 24.7
Psoriasis	4 (2.7)	6 (0.6)	0.01	χ^2: 6.5
Psoriatic arthritis	3 (2.0)	1 (0.1)	<0.01	χ^2: 13.7
Rheumatoid arthritis	2 (1.4)	2 (0.2)	0.03	χ^2: 4.9
Autoimmune thyroiditis	2 (1.4)	4 (0.4)	0.14	χ^2: 2.21
SLE	0 (0)	1 (0.1)	0.70	χ^2: 0.2
Vitiligo	2 (1.4)	3 (0.3)	0.07	χ^2: 3.2
Granulomatosis with polyangiitis	0 (0)	2 (0.2)	0.58	χ^2: 0.3
Systemic sclerosis	1 (0.6)	1 (0.1)	0.12	χ^2: 2.43

BMI = body mass index; CCI = Charlson Comorbidity Index; CI = confidence interval; IIEF-EF = International Index of Erectile Function-Erectile Function; NIH = National Institutes of Health; PD = Peyronie's disease; SLE = systemic lupus erythematosus

diabetes, Dupuytren's disease, and ADs were all associated with PD (all $P \leq 0.02$). Conversely, CCI was not. According to multivariable logistic regression models, considering the variables of both models, only age, cigarette smoking, and ADs achieved independent predictor status for PD (all $P < 0.01$), whereas all other variables did not.

Discussion

We retrospectively evaluated, in the real-life setting over a 40-month period, the prevalence and predictors of PD in a cohort of consecutive, sexually active, heterosexual, Caucasian–European men seeking medical attention for the first time for

Table 3 Univariable (UVA) and multivariable (MVA) logistic regression models (OR; *P* value [95% CI]) predicting PD in our patients

	UVA	MVA Model 1	MVA Model 2
Age	1.04; <0.01 [1.03–1.05]	1.05; <0.01 [1.03–1.06]	1.04; <0.01 [1.03–1.06]
BMI	1.07; <0.01 [1.03–1.12]	1.05; 0.09 [0.99–1.10]	1.04; 0.12 [0.99–1.10]
CCI 0	—; 0.32	—; 0.23	—
CCI 1	1.50; 0.14 [0.87–2.61]	0.78; 0.43 [0.43–1.43]	—
CCI 2+	1.16; 0.55 [0.71–1.90]	0.62; 0.10 [0.35–1.10]	—
ADs	5.08; <0.01 [2.51–10.29]	4.90; <0.01 [2.06–11.69]	4.76; <0.01 [2.00–11.32]
Hypertension	1.71; 0.01 [1.18–2.52]	0.95; 0.82 [0.61–1.48]	0.90; 0.65 [0.58–1.40]
Diabetes mellitus	2.38; <0.01 [1.48–3.82]	—	1.47; 0.15 [0.87–2.47]
Dupuytren's disease	20.5; 0.01 [2.1–198.4]	2.97; 0.39 [0.25–34.63]	3.31; 0.34 [0.29–37.87]
Cigarette smoking	1.55; 0.02 [1.06–2.26]	2.09; <0.01 [1.38–3.17]	1.97; <0.01 [1.30–2.98]

AD = autoimmune disease; BMI = body mass index; CCI = Charlson Comorbidity Index; CI = confidence interval; OR = odds ratio; PD = Peyronie's disease

sexual dysfunction. To this specific aim, we used the descriptive definition of PD suggested by the European Association of Urology guidelines [1]. We found that 1 out of 10 men presenting for sexual dysfunction in the everyday clinical practice setting had PD. Of these, about 1 in 10 suffered from a comorbid AD. Moreover, our findings confirmed previous data suggesting higher rates of PD in men with diabetes mellitus [9], hypertension [8,34], cigarette smoking [7,34], and Dupuytren's disease [10]. However, the presence of ADs emerged as strong independent predictor for PD, thus outperforming both diabetes mellitus and hypertension. As a whole, these observations paint a worrisome picture from the everyday clinical practice.

A major strength of our analysis lies in the fact that we precisely assessed, with a consistent method, the prevalence and characteristics of PD in men extrapolated from a homogenous cohort of same-race patients who consecutively came to our outpatient clinic seeking their first medical help for sexual dysfunction. In this context, we found that one-tenth of patients suffering from PD in the everyday clinical practice are men with clinically evident comorbid ADs. This supports previous speculations of a potential autoimmune pathogenesis for PD.

Despite an autoimmune hypothesis being alluded to by several authors [12–14,17], currently published evidence is not strong enough to support such a challenging statement. As a matter of fact, our study provides a stand-alone evidence of PD–ADs associations. In this context, inflammation is thought to play a key role during the sequence of events leading to penile plaque formation [35]. As the onset of the latter process is likely initiated by occasionally occurred micro-traumata [5,36], it is reasonable to assume that in predisposed patients, the immune system is involved in promoting and maintaining a local inflammatory status favorable for fibrosis. This early injury provokes delamination of the tunica albuginea resulting in small hematoma. Further inflammation and accumulation of leukocytes may follow, thus fostering reactive oxygen species production and myofibroblast/fibroblast recruitment, activation, and proliferation [35,37]. As a result, this deranged wound healing process leads to chronic lymphocytic and plasmacytic infiltration of the tunica albuginea and the surrounding erectile tissues, as commonly observed in PD plaques [38].

Numerous pathological pathways found in PD pathogenesis are often observed in ADs [18,39], though an "autoimmune systemic frame" including all of these processes is still lacking for PD patients. To this aim, psoriasis and some of its features may be regarded as paradigmatic when addressing the possible aspects shared between the two pathological conditions. Psoriasis emerged as the most frequent comorbid AD (i.e., 50% of the cases) in our cohort of PD patients. Psoriatic patients suffer from a diverted wound healing process; more precisely, healing appears to be accelerated as compared with non-psoriatic controls [40], even in areas not affected by the disease. A similar diverted wound healing process occurs after penile microtraumata in PD. Likewise, the Koebner phenomenon, often occurring both in psoriatic patients and in those with other ADs, is characterized by hyper-reactivity to normal stimuli resulting in tissue injury with fibrotic deposition [41]. Clinical assonances are well balanced by molecular and preclinical ones. In this context, TGF-β1, one of the most relevant mediators of PD [5,42], was found in elevated levels in the epidermis and serum of psoriatic patients [43]; moreover, TGF-β1 serum levels seemed to correlate with disease severity and decreased following successful treatment [43]. Similarly in PD patients, not only are serum and lesional levels of TGF-β1 elevated [42,44] but they seem to play an active role in the pathogenesis of fibrosis [44]. Likewise, up to 30% of patients affected by psoriasis will develop psoriatic arthritis [45], and about half of those affected by psoriatic arthritis carry HLA-B27 [46]. As aforementioned, Ralph et al. confirmed a significant association between PD and HLA-B27 [14].

Psoriasis per se (and psoriatic arthritis) provides an opportunity to foresee the main features PD might share with ADs. Indeed, PD patients were found to have higher levels of C-reactive protein (CRP) compared with controls [18]; though nonspecific, CRP is a reliable marker of systemic inflammation and immune activation often increased in ADs. Whether the systemic inflammation observed in PD is a marker of an underlying autoimmune/inflammatory process somehow involved in creating a local milieu favorable for penile fibrosis or is a mere epiphenomenon of PD pathogenetic process (with ADs contingently occurring) is a question we cannot address with our currently available data. Moreover, the HLA-B27 association described in both PD [14] and ADs (particularly, ankylosing spondylitis, acute anterior uveitis, type II psoriasis, and consequently psoriatic arthritis [46]) might not only subtend an

overlapping genetic predisposition shared by both these conditions, but may prompt speculations of an active role potentially played by HLA-B27 in PD pathogenesis. HLA-B27 is known to actively contribute to ankylosing spondylitis pathogenesis: the "arthritogenic peptide" hypothesis suggests that the disease-associated HLA-B27 might present disease-triggering microbial peptides that exhibit molecular mimicry with specific arthritogenic self-peptides, thus enhancing the HLA-B27 restricted cross-reactive cytotoxic T-cell response directed against self-peptide and resulting in chronic inflammation [25]. These speculations are partially hindered by two main considerations: (i) the association reported by Ralph et al. [14], though significant, is much weaker than those observed between HLA-B27 and other ADs, and thus does not exclude a possible association with an allele in linkage disequilibrium with HLA-B27 rather than HLA-B27 itself; and (ii) in our current series, no patient simultaneously presented with PD and ankylosing spondylitis, nor have other similar cases been previously reported by other authors in the literature. Speculatively speaking, this is curious, as ankylosing spondylitis is one of the rare ADs occurring more commonly in men than women [47].

Small population size is one of the main reasons for contradictory results concerning the PD–HLAs association [14,15]. Clustering PD patients in AD-comorbid and non-comorbid groups might help to shed light on a possible previously missed or underestimated association. As a matter of fact, should such an association exist, it is reasonable to hypothesize that it could be responsible for those very AD-comorbid PD patients.

One factor leading some authors to speculate about PD autoimmune genesis was a small number of reported cases describing PD patients diagnosed with scleroderma [48]. Scleroderma is an autoimmune connective tissue disease characterized by fibrosis and microvascular injury in affected organs [49]. Urological manifestations of this disease are usually limited to renal involvement and ED [50]. To this regard, previous reports of PD diagnosed in patients with scleroderma were quite unusual; these patients were young, with extensive fibrosis of the tunica albuginea, and complained of atypical symptoms [48]. We found only one man with PD-comorbid scleroderma, without displaying any atypical features reported by other authors. Despite resembling PD in a somehow evocative fashion, scleroderma is not one of the most frequent comorbid ADs found in our population; this may be partly explained by the fact that in comparison with other ADs, scleroderma rarely occurs in males [51]. However, scleroderma matches psoriasis in terms of TGF-β1 involvement in its pathogenesis; TGF-β receptor expression levels were found to be elevated in scleroderma cells, which correlated with increased binding of TGF-β and resulted in elevated production of collagen type I by scleroderma fibroblasts [52]. Data from animal models further support the role of TGF-β1 in promoting scleroderma-related fibrosis [53]. As a whole, TGF-β signaling would act as a multifaceted supporter of fibrosis regardless of the baseline pathological condition [54], thus providing a possible connective pathway between PD and a systemic condition capable of inducing fibrosis, such as ADs.

Our study is not devoid of limitations. First, though these data relate to a relatively large cohort of same-race individuals who were assessed with a consistent method, this was an observational hospital-based study, raising the possibility of selection biases. Therefore, several larger studies across different centers and populations will be needed to substantiate our findings. Second, the current analyses were implemented in a cross-sectional real-life setting (only focused on patients seeking medical help for new-onset sexual dysfunction), which lacked a comparison with a same-race, age-matched cohort of "sexually" healthy individuals. Third, the analyses lacked data regarding penile plaque characteristics and autoimmune biomarkers, which might be of importance when comparing alterations in patients presenting comorbid ADs with those who were not.

Conclusions

This observational real-life study resulted in novel evidence showing that almost 1 out of 10 Caucasian–European men seeking their first medical attention for PD in the daily clinical practice of an outpatient clinic has a previously diagnosed AD. In the same cohort of men, comorbidity with ADs emerged as an independent predictor of PD after accounting for well-known risk factors alleged to be involved in PD pathogenesis. Because of the retrospective and observational nature of the study, we cannot derive general conclusions; therefore, additional studies in larger population-based samples are needed to confirm these results and to further characterize the poten-

tial role of autoimmunity as a trigger and main stream of PD pathogenesis.

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