PEYRONIE'S DISEASE

The Prevalence and Predictors of Penile Pain in Men with Peyronie's Disease

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ABSTRACT

Introduction: Penile pain is one of the most stressful symptoms in men with Peyronie's disease (PD).

Aim: To evaluate the prevalence, clinical presentation and risk factors associated with penile pain in men with PD as well as to assess the psychosocial impact.

Methods: We revised our institution's database of men diagnosed with PD. The information collected included penile pain assessments, and the scores of the PD Questionnaire (PDQ), Self-Esteem and Relationship Questionnaire (SEAR) and Center for Epidemiologic Studies Depression Scale Questionnaire (CES-D). Descriptive and comparative statistics were used. Logistic regression analyses were performed to evaluate predictive factors associated with penile pain.

Main outcome measures: Penile pain descriptive assessment and factors associated with penile pain in men with PD. Comparison of SEAR, CES-D and PDQ domain scores of men with and without penile pain.

Results: 431 men with PD were included for this analysis with a mean age of 55.9 years. Penile pain was reported by 36.7%; 65.2% of those had painful erection, 7% pain with flaccid state only, and 20% in both stages. The median pain severity was 3 with erection and 1 with flaccid stage. After adjusted logistic regression analyses, advanced age was associated with less pain (OR 0.94, $P \leq 0.001$). Men with penile pain had no significant difference in CES-D and SEAR mean scores compared to men without penile pain. The PDQ scores for the physical/psychological symptoms domain and the bother domain were significantly higher in men with penile pain (12 vs 8.7; $P < 0.01$ and 9 vs 7.1; $P < 0.01$ respectively). Men with penile pain had a higher rate of clinically significant bother scores than men without penile pain (52% vs 35%, $P \leq 0.001$).

Conclusion: Penile pain is common in men with PD. It was more common in young men and was associated with physical and psychological bothers in this population. **Flores JM, Salter CA, Nascimento B, et al. The Prevalence and Predictors of Penile Pain in Men with Peyronie's Disease. Sex Med 2021;9:100398.**

Key Words: Penile Pain; Peyronie's Disease; Sexual Dysfunction; Erectile Dysfunction; Depression

INTRODUCTION

Peyronie's disease (PD) is a pathological condition of the tunica albuginea of the penis characterized by an accumulation and disruption of collagen organization.[1] The prevalence of PD is estimated to between 1-11%.[2-4] Patients with PD usually complain of penile deformity, and sometimes, pain and erectile dysfunction (ED).[5] Studies have reported that about one third of PD patients experience ED,[6] about half suffer depressive symptoms and relationship difficulties and the majority some degree of emotional problems.[2,3]

According to 2015 AUA guidelines, a careful medical history and physical exam of the penis are used to document the signs and symptoms that present in men with PD. This includes assessment of penile deformity, penile pain, characterization of plaque, and any effect on sexual function, mental health, or relationships.[7] PD

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has 2 phases, acute and stable. The acute phase may characterize by penile pain, plaque tenderness, and progression of deformity. Almost half of all patients experience worsening of penile morphological changes in the first year after onset.[1] In the stable phase, there is generally no progression of the disease, with abatement of penile pain and plaque tenderness.[8]

Penile pain is one of the most stressful, restrictive and difficult symptoms in men with PD, with a prevalence cited between 20-70%.[5] Paulis et al described a mean score of 4.7/10 in patients' rating of a visual pain scale and Pryor et al reported that pain in men with PD is rarely severe.[5,6] Studies have attempted to elucidate factors associated with penile pain in men with PD, and suggest a higher prevalence in younger patients and a lack of correlation with plaque size, degree of curvature or calcification status.[6,9] Usually penile pain in patients with PD resolves within 12-18 months.[10]

While penile pain can have a broad impact on men's psychosocial well-being, few studies have focused on the overall impact of penile pain. Men with PD report more psychological distress, a higher prevalence of depressive symptoms, more sexual dysfunction and lower self-esteem.[6,11,12] The aim of our study was to address the following questions: "Are there factors associated with more pain among men with PD?" and "Is there any association between penile pain and psychosocial impact in men with PD?". We evaluated the prevalence, clinical presentation, risk factors, and psychosocial impact associated with penile pain in men with PD.

METHODS

Study Population: After institutional review board approval was obtained (IRB 16-405), the computerized database of PD patients treated at our institution was reviewed retrospectively. All patients did consent for health data review for research purpose. For this study, we collected the following data: patient age, PD duration (in months), relationship (yes/no and duration), erection hardness scale (between 1 large but not hard to 4 full erection),[13,14] penile pain, penile curvature (degree, direction and location: base, mid-shaft, distal), history of penile trauma, difficulty penetrating, psychological bother, prior treatments for PD, calcification status evaluated during curvature assessment with doppler ultrasound, penile instability, defined as penile buckling after an axial force application,[15,16] anxiety disorder, and depression both completed as part of the past medical history checklist. This information was collected during the patient's first visit and serially thereafter. We excluded patients who did not complete the surveys. Data for this analysis was collected between January 2014 and December 2019.

Pain Assessment: Men with PD reported whether they had penile pain in the flaccid and/or erect state. The assessment of penile pain included the severity of pain which was rated by patients using a visual analog scale between 0 (no pain) and 10 (worst pain imaginable).

Questionnaires: Patients completed three validated instruments in a serial fashion: the PD Questionnaire (PDQ), Self-Esteem and Relationship Questionnaire (SEAR) and the Center for Epidemiologic Studies Depression Scale Questionnaire (CES-D). The SEAR questionnaire was validated in 2004 to evaluate psychosocial variables in men with erectile dysfunction. It has 14 items, divided into two domains: sexual relationship (8 items) and confidence (6 items); with the confidence domain comprising of self-esteem (4 items) and overall relationship (2 items) subscales. All questions were scored from 1 (almost never/never) to 5 (almost always/always), except questions 8 and 11 which have reverse scores (with 5 as almost never/never to 1 as almost always/always). The total score for this questionnaire is scored between 0 to 100, with a higher score indicating a better outcome.[17]

The CES-D questionnaire, first reported in 1977, was designed to measure depressive symptoms in the general population. The CES-D questionnaire has 20 questions each scored between 0-3 which are associated with the frequency of the days that the patients have experienced depression. The total score for this questionnaire is between 0-60, with a higher score related to more depressive symptoms.[18] We reported and compared the SEAR and CES-D questionnaire scores between men with PD who had penile pain versus men with PD without penile pain.

The PDQ is a self-administered and standardized questionnaire that was created for the intralesional collagenase trials (IMPRESS I and II). It has proven to be highly responsive to symptom changes in men with PD, which makes it a useful and effective tool for clinical practice and clinical research. PDQ evaluates symptoms and psychological effects in patients with PD who have had vaginal intercourse within the last 3 months considering the most recent sexual experience when completing the questionnaire. The PDQ has 3 domains that are independently scored as the sum of all responses: 6 items Likert-type scaled between 0-4 for psychological/physical symptoms (total domain score range between 0 to 24); 3 items rated between 0-10 for penile pain (total domain score range between 0-30); 4 PD symptom bother items scored between 0-4 and two categorical no scored questions as yes/no (total domain score range between 0-16). A higher score means greater negative impact.[19-22] We reported and compared the PDQ scores for each domain between PD men with and without penile pain.

Statistical Analyses: All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). Descriptive statistics were reported as mean ± standard deviation (SD) and/or medians with interquartile range (IQR) for continuous variables and as percentages for categorical variables. To statistically compare the groups, continuous variables were assessed with two-sample t-tests and categorical variables by chi-square-tests. Logistic regression univariable (UVA) and multivariable (MVA) analyses were performed to evaluate factors associated with penile pain. Factors considered included: Age, PD duration, partner, history of PD treatment, erection hardness scale (EHS), instability. Results were reported as odds ratios with a 95% confidence interval. Factors that were significantly associated with

pain in unadjusted models were included in a single adjusted model. Type I error was set to 0.05 for all comparisons.

RESULTS

Patient Population: A total of 431 men with PD and complete data were included in this analysis. At baseline, the mean ± SD patient age was 55.9 ± 11.6 years, with a mean PD duration of 20.6 ± 35.6 months, and 84% were in a relationship, with a mean duration of 245.7 ± 174.3 months. 53% had the penile curvature located in the midshaft, most of the men had a dorsal curvature, and 16% had plaque calcification. The median EHS was 3 (IQR = 3-4), 52% indicated some difficulty penetrating, and 16% had instability. 7% of the men reported a history of penile trauma as well. Table 1 summarizes the PD characteristics.

Penile Pain Characteristics: Penile pain was reported at baseline by 36.77% of the men; 65.2% of these men described pain with erection only, 7% with flaccid state only, 20% in both states, and 7.6% reported penile pain without identifying in which penile stage it presented. The median pain severity reported was 1 (IQR = 1-2) in those experiencing flaccid pain, and 3 (IQR = 1-5) in those experiencing erect pain. Table 2 summarizes The Penile Pain characteristics.

Table 2. The penile pain characteristics in patients with PD

	Patients (n)	Patients (%)	Pain severity, median, (IQR)
Men reporting pain	158	36.7%	
Men with ONLY erect pain	103	65.2%	3 (1-5)
Men with ONLY flaccid pain	11	7.0%	1 (1-2)
Men with erect and flaccid pain ('global pain')	32	20.3%	Erect pain, 4 (2-6) Flaccid pain, 1 (1-3])
Men not reporting pain type	12	7.6%	
Men without any pain	273	63.3%	

Peyronie's disease (PD), Interquartile range (IQR).

Penile Pain Predictors: Unadjusted UVA logistic regression analyses indicated that advanced age (OR 0.94, 0.92-0.95, $P < 0.001$), longer PD duration (OR 0.99, 0.98-1.00, $P = 0.016$), and being in a relationship (OR 0.52, 0.31-0.87, $P = 0.012$) were associated with a decreased odds of pain,

Table 1. Sample characteristics in the total patients with PD and with/without penile pain

Variables	All men with PD N = 431	Men with penile pain N = 158 (36.7%)	Men without penile pain N = 273 (63.3%)	*P* value
Patient age (years, mean ± SD)	55.9 ± 11.6	50.7 ± 12.2	59.1 ± 10.0	<0.001*
PD duration (months, mean ± SD)	20.6 ± 35.6	14.5 ± 22.2	24.1 ± 41.2	0.016*
Partner %	84	78	87	0.012*
Duration in relationship (Months, mean ± SD)	245.7 ± 174.3	210.7 ± 166.9	264.6 ± 175.6	0.004*
EHS (1-4, median [IQR])	3 [3-4]	4 [3-4]	3 [2-4]	0.010*
Men with PD curvature location				0.076
Base/proximal (%)	19	19	19	
Midshaft (%)	53	46	57	
Distal/Retrocoronal (%)	28	35	24	
Men with PD curvature direction				0.987
Dorsal (%)	53	54	53	
Ventral (%)	13	14	13	
Left (%)	25	24	26	
Right (%)	9	9	8	
Difficulty penetrating (%)	52	83	37	0.224
Prior treatment for PD (%)	19	26	16	0.014*
Calcification (%)	16	17	15	0.606
Degree of primary curvature	37.9 ± 20.8	37.7 ± 21	38.1 ± 20.6	0.888
Instability (%)	16	24	12	0.008*
History of penile trauma (%)	7	8	6	0.489
Anxiety (%) (a)	12	13	11	0.602
Depression (%) (a)	15	16	15	0.744

Peyronie's disease (PD), standard deviation (SD), Interquartile range (IQR), Erection Hardness Scale (EHS)
(a) By patient report, past medical history,
*significant *P*-value.

whereas higher EHS (OR 1.32, 1.07-1.63, P = 0.010), prior treatment for PD (OR 1.84, 1.13-2.98, P = 0.014), and penile instability (OR 2.2, 1.24-3.98, P = 0.008) were associated with an increased odds of pain. Table 3 summarizes UVA analysis in men with PD with and without penile pain.

Despite higher frequencies of distal curvature location and difficulty penetrating among men with penile pain, these factors were not significantly associated with higher odds of pain when compared to men without pain. After adjusted MVA logistic regression analysis, only age was associated with pain, with advanced age associated with less pain (OR 0.94, 0.91-0.97, $P \leq 0.001$). Table 4 summarizes MVA analysis in men with PD with and without penile pain. None of the other significant predictors (PD duration, relationship status, prior treatment for PD, instability, and EHS) were significant after adjustment.

Psychosocial Impact: The mean ± SD overall CES-D score of the entire study population was 10.9 ± 9.2; not statistically significant different between men with and without penile pain was observed (11 ± 9 vs 10 ± 9; P = 0.69). Based on CES-D scores, 27% of the subjects had depression (CES-D score ≥16); 30% of men with penile pain vs 25% of the men without penile pain (P = 0.35). The mean SEAR score was 57.8 ± 23; there was no difference in mean SEAR scores between men with and without penile pain (57.7 ± 24 vs 57.8 ± 23; P = 0.99). The PDQ physical/psychological symptoms domain mean of all study subjects was 9.9 ± 6.4; men with penile pain had a significantly higher mean score compared to men without penile pain (12 ± 6 vs 8.7 ± 6; $P < 0.01$). The mean score of the PDQ bother domain was 7.8 ± 4; men with penile pain had a significantly higher mean bother score compared to men without penile pain (9 ± 4 vs 7 ± 4; $P < 0.01$). According to the PDQ bother domain, 41% had clinically significant bother scores (≥9); 52% of men with penile pain had clinically significant bother scores vs 35% of the men without penile pain (P <0.001). Table 5 summarizes the psychosocial data.

Table 4. Adjusted multivariable analysis of penile pain in patients with PD

Factor	OR	95%CI	*P*-value
Age	0.94	(0.91, 0.97)	<0.001*
PD duration	0.99	(0.98, 1.00)	0.083
Partner	0.89	(0.41,1.91)	0.758
History of PD treatment	1.36	0.70, 2.64)	0.362
EHS	1.07	(0.81, 1.40)	0.635
Instability	0.98	(0.56, 1.69)	0.927

Peyronie's Disease (PD), Odds ratio (OR), Confident interval (CI), Erection Hardness Scale (EHS)
*significant *P*-value.

DISCUSSION

Penile pain is one of the most stressful symptoms in men with PD, and unfortunately, not much information has been published on the prevalence, natural history or predictors of penile pain in this population. During the acute phase of PD, the signaling pathway activated via prostaglandin E2 leads to inflammation and edema, which results in irritation of nerve endings and is ultimately responsible for the penile pain with or without

Table 3. Unadjusted univariable analysis of pain predictors in patients with PD

Variables	OR	95%CI	*P* value
Patient age	0.94	(0.92, 0.95)	<0.001*
PD duration	0.99	(0.98, 1.00)	0.016*
Partner	0.52	(0.31, 0.87)	0.012*
EHS	1.32	(1.07, 1.63)	0.010*
Men with PD curvature location			0.076
Curve location: base/ Proximal	1.17	(0.64, 2.13)	
Curve location: midshaft	REF	REF	
Curve location: distal/ retrocoronal	1.80	(1.08, 2.98) *	
Difficulty penetrating	1.67	(0.73, 3.82)	0.224
Prior treatment for PD	1.84	(1.13, 2.98)	0.014*
Calcification	1.18	(0.63, 2.20)	0.606
Degree of primary curvature	1.00	(0.99, 1.01)	0.888
Instability	2.22	(1.24, 3.98)	0.008*
Anxiety (%) (a)	1.17	(0.64, 2.15)	0.602
Depression (%) (a)	1.10	(0.64, 1.89)	0.744

Peyronie's disease (PD), Odds ratio (OR), Confident interval (CI), Erection Hardness Scale (EHS)
(a) By patient report, past medical history
*significant *P*-value.

Table 5. Penile pain, sexual self-esteem and depression assessments

	All patients	Patients with penile pain	Patients without penile pain	*P* value
CES-D sum (Mean ± SD)	10.9 ± 9.2	11.2 ± 9.2	10.8 ± 9.3	0.69
Depression (CES-D score ≥ 16) (%)	27	30	25	0.35
SEAR sum (Mean ± SD)	57.8 ± 23.4	57.7 ± 24	57.8 ± 23.1	0.99
PDQ physical/ psychological symptoms (Mean ± SD)	9.9 ± 6.4	12 ± 6	8.7 ± 6.3	<0.01*
PDQ pain (Mean ± SD)	5 ± 5.9	8.6 ± 6.3	2.9 ± 4.4	<0.01*
PDQ bother (Mean ± SD)	7.8 ± 4	9 ± 3.8	7.1 ± 3.9	<0.01*
Clinically significant bother (PDQ bother of ≥ 9)	41	52	35	<0.01*

Peyronie's Disease Questionnaire (PDQ), Self-Esteem and Relationship Questionnaire (SEAR) and the Center for Epidemiologic Studies Depression Scale Questionnaire (CES-D), Standard deviation (SD),
*significant *P*-value.

erection in PD patients.[23,24] During the stable phase, it is postulated that chronic inflammation leads to the death of these nerve endings, which would explain the decrease of penile pain in this phase of PD.[23,24] Mulhall et al reported that in a cohort of 246 men with PD, patients who described penile pain at baseline, all of them stated penile pain improvement and 89% a complete resolution after 12 months of the disease onset.[1]

Our findings showed that around 37% of men with PD reported experiencing mild to moderate penile pain; most of them had pain with erection, some had pain both during erection and flaccid stage, and the lowest frequency was observed in men experiencing penile pain in the flaccid state only. Similar findings have been reported by other authors, Paulis et al found that 51% of men with PD had penile pain, and Pryor et al reported that penile pain was the first symptom in 39% of men with PD.[5,6]

Another finding in our study was that age was the most significant factor associated with penile pain among men with PD, older patients having less penile pain compared to younger patients. In our cohort, a significant difference in age was observed between men with and without pain (50 vs 60 years, $P < 0.001$). Paulis et al, reported similar findings, stating that in a subgroup of 116 men with PD and ED, men under 40 years had significantly more frequent penile pain than older patients (90% vs 39.5%, $P < 0.0001$).[6] We did not find erectile function as a predictor of pain after adjusted in MVA. It was observed that men with penile pain had higher median EHS values than men without penile pain, and it was a factor associated with penile pain in UVA, however, after adjusting for other factors in MVA, EHS did not show a significant association with penile pain. Paulis et al, in a cohort of 309 patients with PD, stated no difference was observed in the rate of penile pain between men with PD and ED vs men with normal erectile function (48% vs 53%, $P = 0.481$).[6]

We also showed that the degree, direction and the location of penile curvature were not predictors of penile pain in our population. Walsh et al, in a cohort of 114 men with PD and no ED, described that curvature >60° was significant predictor for sexual disability only (OR 3.23, 1.08-9.67).[25] Also, in our study no significant association was found between penile pain and plaque calcification, or, after adjusted assessment, penile instability. Burri et al, in a cohort of 119 men with PD the strongest complaint was concern about the appearance of the penis which was significantly more problematic than the sexual difficulties induced by penile pain. Futrthermore, in Burri et al analysis penile pain assessed by PDQ questionnaire pain subscale score was not significantly associated with ED, the degree of penile curvature, age, plaque size or calcification.[9]

There also is a lack of research studying the overall impact of penile pain in this population, including sexual function, self-esteem and depression. Terrier and Nelson, in a systematic review showed that approximately 50% of men with PD suffered from depressive symptoms and up to 80% reported distress associated with PD.[22,26] CES-D and SEAR are both validated questionnaires to measure depressive symptoms in the general population and to evaluate psychosocial variables in men with ED respectively. PDQ is a validated questionnaire precisely elaborated to evaluate symptoms and psychological effects in patients with PD. In our study, we did not find difference in CES-D and SEAR scores between men with PD with and without penile pain. Salter et al, in a retrospective study to evaluate patient bother and penile girth in a cohort of 131 men with PD, also reported no significant differences in CES-d and SEAR questionnaires scores in men with PD and girth changes ≥ 1 cm compared to men with PD and girth changes ≤ 1 cm.[16]

Since the introduction of the PDQ, there has been an increase in research studying the association between PD and psychological and sexual domains.[9] Our study did not find any significant difference in self-esteem or depressive symptoms in men with or without penile pain. However, our analyses of PDQ data showed that men with penile pain scored significantly higher for the physical/psychological symptoms domain as well as on the bother domain compared to men without pain in patients with PD. Research and clinical experiences indicates that men with PD report more psychological distress, higher prevalence of depressive symptoms, more sexual dysfunction, and lower self-esteem.[11,27,28] Studies have found that around 80% have psychological symptoms, 48-62% depression (which increase with a longer duration of PD), 37.5% ED, and 54% relationship problems.[6,12] A retrospective study of 417 cases reported that men with pain during intercourse had significantly lower scores

on the international index of erectile function (IIEF) and was associated with bother in men with PD.[3] It is worth noting that the assessment of erectile function using the IIEF is fraught with difficulty, given that many PD patients are incapable of having intercourse due to penile deformity and thus accurate completion of the IIEF is impossible.

The study by Paulis et al found that penile pain was not associated with ED, except when considering pain severity on a 0-10 scale: men with PD and ED had significantly a higher mean pain score compared to men with PD without ED (5.2 vs 4.5, $P = 0.003$), however, it is likely that this difference is not clinically significant.[6] Smith et al evaluated factors associated with emotional or relationship difficulties in men with PD in a cross-sectional study with 245 patients. These authors found that, despite a higher frequency of penile pain in men with emotional problems (84% vs 16%), only relationship problems and loss of penile length were significantly associated with emotional problems in unadjusted and adjusted models.[2] Finally, in our cohort, those who had penile pain scored significantly higher for the physical/psychological symptoms domain as well as for the bother domain compared to men without penile pain. Over half of the men with penile pain had also clinically significant PDQ bother domain scores (≥9). According to a previous study, a bother score of 9 on the PDQ represented an optimal cut-off score to indicate clinically significant bother and to refer these patients to a mental health professional.[29]

The clinical implication of our study is that pain is common and has a significant physician and psychosocial impact on PD patients. Thus, greater attention should be paid to the presence of pain, its nature and magnitude to refer to a mental health professional accordingly. Although we believe that our study has several strengths, including large patient number, the use of validated instruments, the most significant is that it is the first report describing and characterizing penile pain and its psychological and sexual impact in men with PD. Nonetheless, there are limitations: the retrospective nature of the study (although all data was collected prospectively on every patient in an identical fashion and only the data analysis was retrospective) may be a concern; the subjects of the study were from a single institution; the validated inventories precluded including gay men; and the subjective nature of pain assessment.

CONCLUSION

Penile pain was reported in over 1/3 of men with PD. It was more common in young men and was associated with physical and psychological bother in this population.

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STATEMENT OF AUTHORSHIP

Conceptualization, JMF, CAS, and JM; Methodology, JMF, CAS, ES, and JM; Investigation, JMF, CAS, BN, JT, HT, HB, EM, and LJ; Writing – Original Draft, JMF and JM; Writing – Review & Editing, JMF, and JM.

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