Risk factors for Peyronie's disease: a case-control study

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OBJECTIVE

To test some hypotheses about risk factors for Peyronie's disease (PD).

PATIENTS AND METHODS

In a case-control study, 82 patients with PD, consecutively diagnosed at the first author's institution, were compared with 246 men visiting the same institution for dermatological diseases. Univariate and multivariate logistic regression analyses were used to assess the data.

RESULTS

From the multivariate logistic regression analysis the risk factors for PD were: a history of genital and/or perineal injuries, transurethral prostatectomy, cystoscopy, diabetes mellitus, hypertension, lipoma, propranolol in therapy, Dupuytren's contracture in the medical history, ever having smoked, alcohol consumption, fibromatous lesions of the genital tract of the partner, and surgical intervention on the genital tract of the partner.

CONCLUSION

The results of the present study are in line with the hypothesis that, in addition to genetic predisposition, trauma of the penis and systemic vascular diseases are risk factors for PD. Smoking and alcohol consumption also seem to have some role in the development of the disease.

KEYWORDS

Peyronie's disease, risk factors, epidemiology

INTRODUCTION

Plastic induration of the penis is a fibrous infiltration of the intercavernosal septum of the penis. In the early phase of the disease, the patient presents with a nodule or plaque, usually noticed accidentally, but occasionally complaining of a deviation on erection. Later symptoms are a harder plaque, stable penile deformity during erection and erectile dysfunction. This disease was first described in 1743 by the French surgeon Francois de la Peyronie [1]. To date, the cause remains unknown. The most widely accepted theory is that Peyronie's disease (PD) is initiated by microtrauma to the penis [2–4].

The incidence of PD has continuously increased during the last 30 years. In Germany, a survey of 8000 men showed that the prevalence of the disease was 3.2% [5]. A multicentre population-based study in Italy reported a prevalence of 7.1% [6]. In the present study, we tested some hypotheses about risk factors for PD.

PATIENTS AND METHODS

A case-control study was conducted in Belgrade (Serbia and Montenegro) from January 2000 to June 2004. The case group comprised 82 patients with PD (diagnosed by history and examination, i.e. the presence of a well-defined palpable plaque in the penis) consecutively diagnosed at the Department for Skin and Venereal Diseases in Belgrade. The vast majority of patients presented because of the presence of palpable nodes in the penis and the fear that it could be malignant. For each case, three controls (246 men altogether) were selected among those visiting the same institution for dermatological diseases (they had neither a history nor signs of PD). Cases and controls were matched by year of birth (± 1 year) and place of residence (all were from Belgrade).

One dermatologist interviewed all participants. The following data were obtained using a questionnaire (Appendix): basic demographic and anthropometric characteristics, alcohol consumption, cigarette smoking, age at first intercourse and number of lifetime sexual partners, history of sexually transmitted disease, genital injuries and invasive procedures on the penis, and selected diseases in the personal and family history, with data about venereal diseases, fibromatous lesions and surgical interventions in the genital tract of the participants' sexual partners. For statistical analysis univariate and multivariate logistic regressions were used [7].

RESULTS

Table 1 presents the results of univariate logistic regression analysis. Cases and controls did not differ in their age, education, occupation and marital status. Alcohol consumption was more frequent among cases ($P < 0.01$), and cases were more frequently 'ever smokers' ($P < 0.01$). Cases and controls did not differ either in the duration of alcohol consumption and the type of beverages consumed, or in the duration of smoking and average number of cigarettes smoked. There were no differences between cases and their controls in the body mass index, age at first sexual intercourse, and the number of lifetime sexual partners.

Cases more frequently reported urethritis nongonorrhoica ($P < 0.05$), genital and/or perineal injuries ($P < 0.01$) and invasive procedures on the penis like catheterization ($P < 0.01$), cystoscopy ($P < 0.01$) and TURP ($P < 0.01$; Table 1). Invasive procedures on the penis were reported in 24 PD cases (29.2%) and 20 controls (8.1%). Of those with PD, six had three invasive procedures on the penis, another six had two and 12 had only one. In all but one of those who had had TURP the intervention was preceded by catheterization and cystoscopy, and in 11 of 16 patients who had cystoscopy, it was preceded by

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TABLE 1 The distribution of patients with PD and their controls according to selected characteristics, including diseases and injuries of genitourinary tract, interventions on the genitourinary tract and in their sexual partners

Variable	Cases (82)	Controls (246)	P*
N (%):			
Age, years			
<50	7 (8.5)	23 (9.3)	
50–59	16 (19.5)	50 (20.3)	
60–69	35 (42.6)	98 (39.8)	
≥ 70	24 (29.2)	75 (30.4)	0.77
Formal education:			
Elementary	10 (12.2)	24 (9.8)	
Secondary	42 (51.2)	105 (42.7)	
High	30 (36.6)	117 (47.6)	0.11
Occupation:			
Agricultural worker	–	1 (0.4)	
Industrial worker	32 (39.0)	66 (26.8)	
Trade and service sector worker	18 (22.0)	57 (23.2)	
Administration worker	3 (3.7)	12 (4.9)	
Professional	26 (31.7)	107 (43.5)	
Other	3 (3.6)	3 (1.2)	0.11
Marital status:			
Single	5 (6.1)	19 (7.7)	
Married	68 (82.9)	188 (76.4)	
Divorced	4 (4.9)	18 (7.3)	
Widowed	5 (6.1)	21 (8.5)	0.50
Ever smoked	30 (36.6)	41 (16.7)	<0.01
Alcohol consumption	40 (56.1)	71 (28.9)	<0.01
Type of alcoholic beverages most frequently consumed:			
Beer	3 (6.5)	9 (12.7)	
Wine	4 (8.7)	9 (12.7)	
Strong spirits (liquor)	33 (83.0)	53 (74.6)	0.19
Mean (SD):			
Body mass index, kg/m^2	26.1 (3.1)	26.6 (3.9)	0.26
Age at first sexual intercourse, years	18.4 (2.8)	18.8 (3.9)	0.37
Number of lifetime sexual partners	22.3 (24.4)	23.2 (27.7)	0.79
Duration of smoking, years	36.8 (13.5)	33.2 (13.5)	0.27
Cigarettes smoked per day	23.9 (11.8)	24.0 (12.3)	0.96
Duration of alcohol consumption, years	32.3 (12.8)	31.3 (12.4)	0.67
Diseases and injuries			
Mean (SD):			
Personal history of:			
Gonorrhoea	17 (20.7)	50 (20.3)	0.94
Urethritis nongonorrhoica	9 (10.9)	7 (2.8)	<0.05
Syphilis	1 (1.2)	–	0.27
Genital and/or perineal injuries	19 (23.2)	5 (2.0)	<0.01
Urethral catheterization	17 (20.7)	13 (5.3)	<0.01
Cystoscopy	16 (19.5)	11 (4.5)	<0.01
TURP	9 (11.0)	–	<0.01
Sexual partner history of:			
Sexually transmitted diseases	10 (12.2)	3 (1.2)	<0.01
Fibromatous lesions of the genital tract	37 (45.1)	9 (3.7)	<0.01
Surgical intervention on the genital tract	14 (17.1)	19 (7.7)	<0.05

**Univariate logistic regression analysis.*

catheterization. Among the controls, four had had two invasive procedures and 16 only one. As shown in Table 1, cases more frequently reported certain conditions in their sexual partners, e.g. sexually transmitted diseases ($P < 0.01$), fibromatous lesions ($P < 0.01$) and surgical interventions in the genital tract ($P < 0.05$).

In comparison with controls, cases more frequently reported a history of diabetes mellitus ($P < 0.01$), hypertension ($P < 0.001$), hyperlipidaemia ($P < 0.01$) and lipoma ($P < 0.01$; Table 2). A high serum level of uric acid was reported by 3.7% of cases and 1.2% of controls, but the difference was not statistically significant. Cases and controls did not differ significantly in the duration of these diseases and the type of therapy for diabetes and hypertension. The only exception was therapy with propranolol, which was more frequently used by cases than by controls ($P < 0.01$). A higher proportion of cases than controls were affected by Dupuytren's contracture ($P < 0.01$); 9.8% reported a familial history of Dupuytren's contracture, vs none of the controls. A familial history of gout was also more common among cases than among controls ($P < 0.10$). There were no differences between cases and controls in the family history of PD. Of all participants, only one control reported the presence of this disease in the family.

A multivariate logistic regression analysis was used to identify independent relationships among the factors with PD (Table 3); all the variables that according to univariate analysis were related to PD at $P \leq 0.10$ were included. The risk factors for PD are listed in Table 3; when TURP and Dupuytren's contracture in the family history were excluded from the model, because of their co-linearity with the outcome (they were reported only by cases), cystoscopy was also a risk factor for PD (odds ratio 7.1, 95% CI 1.8–27.6).

DISCUSSION

As noted, the most widely accepted theory is that microtrauma of penis initiates PD; in the present study about a quarter of cases had accidental genitoperineal injury, and 29% reported iatrogenic injury during diagnostic or therapeutic procedures (catheterization, cystoscopy, TURP). A history of trauma to a flaccid or erect penis during sexual intercourse was reported in 21–40% of

patients with PD [2,4]. PD is usually seen in men in their fifties [8]; in older men the tissues become less elastic, and deforming force during coitus can bend the penis and cause minor trauma [9]. In the study of Carrieri *et al.* [10] a history of invasive procedures on the penis was the strongest risk factor (odds ratio 16.1, 95% CI 1.8–142) for PD. Perimenis *et al.* [9] reported that 21.6% patients with PD had a history of penile fracture or auto-injections of vasoactive drugs for treating previous erectile dysfunction. However, in the study of Zargooshi [11] severe, acute trauma of penile fracture and moderate, chronic buckling injury of *taqaandan* (a history of forcefully bending the erect penis) were not associated with the later development of PD.

Trauma to or excessive bending of the erect or flaccid penis may result in bleeding into the subtunical spaces. Fibrin deposition in the tunica albuginea is an initial consequence of microvascular injury and it may be a precursor to plaque formation [4,12]. Some men respond to mechanical tunical stress and vascular trauma with an aberrant or hyperactive wound-healing response that genetically predisposes them to forming a plaque [3,4].

The association of PD with smoking and alcohol consumption in the present study was also reported by others. La Pera *et al.* [6] found smoking to be a risk factor for PD and the relative risk progressively increased with the number of cigarettes smoked. Smoking supports the oxidative and degenerative processes that have been assumed to be pathogenetic for PD [6]. Prolonged heavy drinking can cause disturbances in body chemistry, like hyperlipidaemia, which may contribute to disease of the heart and blood vessels, and thus have an influence on hypertension. In the present study diabetes and hypertension were significantly related to PD. Diabetes, serum lipid abnormalities and hypertension are risk factors for systemic vascular diseases, which have a significant effect on erectile function [13,14]. The impact of these risk factors on the pathogenesis of PD is obscure. Kadioglu *et al.* [15] reported that hypercholesterolaemia and diabetes were identified in 67.5% of their patients with PD. Schwarzer *et al.* [5] found that the incidence of PD was three times greater in diabetics than non-diabetics. Culha *et al.* [16] also found a close relationship between diabetes mellitus and PD. On the contrary, Lindsay *et al.*

TABLE 2 Selected diseases in the personal and family history of patients with PD and the controls

Variable	Cases (82)	Controls (246)	P*
N (%):			
Personal history of:			
Diabetes mellitus	26 (31.7)	26 (10.6)	<0.01
Type of therapy:			
Insulin	0	3 (11.5)	
Oral	12 (46.2)	12 (46.2)	
Diet	14 (53.8)	11 (42.3)	0.19
Hypertension	46 (56.1)	69 (28.0)	<0.01
Therapy of hypertension with:			
β-blockers	9 (22.0)	21 (31.3)	
Angiotensin-converting enzyme inhibitors	18 (43.9)	23 (34.3)	
Ca^{2+}-channel blockers	6 (14.6)	17 (25.4)	
Diuretics	9 (22.0)	8 (11.9)	
Other†	6 (14.6)	6 (9.0)	0.49
Propranolol in therapy	27 (32.9)	14 (5.7)	<0.01
Hyperlipidaemia	24 (29.3)	39 (15.9)	<0.01
Uricacidaemia	3 (3.7)	3 (1.2)	0.18
Lipoma	33 (40.2)	21 (8.5)	<0.01
Dupuytren's contracture	32 (39.0)	3 (1.2)	<0.01
Mean (SD) duration, years, of:			
Diabetes mellitus	4.0 (2.9)	9.6 (5.1)	0.15
Hypertension	9.1 (7.0)	9.2 (8.5)	0.96
Hyperlipidaemia	4.6 (4.0)	5.5 (6.3)	0.55
Uricacidaemia	8.0 (5.3)	13.3 (5.8)	0.34
Lipoma	16.4 (10.3)	13.6 (7.3)	0.28
Therapy with propranolol	3.5 (4.2)	1.6 (1.7)	0.21
N (%):			
Family history of:			
PD	–	1 (0.4)	0.63
Dupuytren's contracture	8 (9.8)	–	<0.001
Gout	3 (3.7)	2 (0.8)	0.09

**Univariate logistic regression analysis. †Medication angina pectoris, arrhythmia and circulatory disorders.*

TABLE 3 Risk factors for PD according to multivariate logistic regression analysis

Variable	Odds ratio (95% CI)
History of:	
Genital and/or perineal injuries	5.6 (1.1–29.2)
TURP	207.7 (10.4–4160.9)*
Diabetes mellitus	6.6 (2.1–20.9)
Hypertension	3.3 (1.1–9.9)
Lipoma	10.3 (3.2–33.0)
Propranolol in therapy	13.8 (3.4–57.0)
Dupuytren's contracture	205.9 (29.0–1461.2)
Ever smoked	5.5 (2.0–15.1)
Alcohol consumption	6.2 (2.2–17.4)
Fibromatous lesions of the genital tract of the partner	13.7 (3.9–46.7)
Surgical intervention on the genital tract of the partner	5.6 (1.5–21.6)

**To calculate the odds ratio it was assumed that one of the controls had had the same intervention.*

[8] reported that the incidence of diabetes mellitus was low among men with PD. Carrieri *et al.* [10] did not find that a history of diabetes and arterial hypertension were associated with PD.

It was postulated that risk factors for systemic vascular diseases could influence the occurrence of PD, by weakening the vasculature and causing its rupture during sexual intercourse [17], and/or by causing a hypoxic microenvironment in the erectile tissue, which aggravates fibrosis through exaggerated activation of TGF-β [18].

From the present results, therapy with propranolol is a risk factor for PD. The association of PD with β-blocker therapy was reported by others [5,19]. It is probable that this relationship is secondary; therapy, especially propranolol, has been used for a variety of cardiovascular diseases and more frequent use of propranolol by men with PD than by the controls might simply indicate that PD is more frequent among those with cardiovascular disorders.

The present finding that nongonorrhoical urethritis was related to PD was also reported by Carrieri *et al.* [10]. The association of PD with venereal diseases or some other infectious diseases has not been reported previously. Hauck *et al.* [20] found no 16S rDNA (a highly sensitive marker for the presence of bacteria in inflammatory processes) in tunica albuginea specimens.

The greater frequency of sexually transmitted diseases, fibromatous lesions of the genital tract and surgical intervention on the genital tract in sexual partners of the present men with PD was reported previously by Carrieri *et al.* [10]. Possibly such changes in the genital mucosa of female sexual partners make penetration more difficult, thus promoting injuries to the penis.

The importance of genetic factors in the development of PD is supported by the fact that PD frequently occurs together with Dupuytren's contracture, which is inherited in an autosomal dominant pattern [2,10]. In the present study, 39% of cases and only 1.2% of controls had Dupuytren's contracture, and this condition was present in family members of eight cases and in none of the controls. Data from other studies are inconsistent. In that by Carrieri *et al.* [10] 20% of cases were affected by Dupuytren's contracture.

Perimenis *et al.* [9] and Kadioglu *et al.* [15] reported that Dupuytren's contracture was related to a small percentage of cases with PD. The present relationship between PD and a family history of gout, and that in the study of Carrieri *et al.* [10], also suggests an influence of genetic factors on the development of PD. The same could be true for the association between PD and lipoma (benign subcutaneous tumours composed of fat cells), found in both the study by Carrieri *et al.* [10] and in the present study. It is known that familial lipoma syndrome, which appears in early adulthood and consists of hundreds of slowly growing lesions, is an autosomal dominant trait. However, none of the present study participants had more than a few lipomas, and unfortunately we had not asked them questions about any family history of lipomas.

In conclusion, the present results are in line with the hypothesis that in addition to genetic predisposition, microtrauma of the penis has the greatest impact on the occurrence of PD. Systemic vascular diseases, smoking and alcohol consumption also seem to have some role in the development of the disease.

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CONFLICT OF INTEREST

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Abbreviations: **PD**, Peyronie's disease.

APPENDIX

The questionnaire

1. Diagnosis

2. Month and year when first symptoms and signs of the present disease appeared

3. Year of birth

4. Body height

5. Body weight

6. Education: 1. Elementary 2. Secondary 3. High

7. Occupation

8. Marital status: 1. Single 2. Married 3. Divorced 4. Widowed

9. At what age did you have your first sexual intercourse?

10. How many sexual partners did you have in your life?

11. Have you ever had any venereal disease? 1. NO 2. YES

12. If YES, which one? How many times?
a. Gonorrhoea
b. Urethritis nongonorrhoica
c. Syphilis
d. Genital wart
e. Other

13. Have you ever had genital and/or perineal injury? 1. NO. 2. YES

14. Have you had any of the following interventions, and when (age/s)?
a. Urethral catheterization 1. NO. 2. YES
b. Cystoscopy 1. NO. 2. YES
c. Transurethral prostatectomy 1. NO. 2.YES

15. Has your sexual partner ever been treated by a doctor for:
a. Sexually transmitted disease 1. NO. 2 YES
b. Fibromatous lesions of the genital tract 1. NO. 2 YES

16. Has your sexual partner ever had surgical intervention on the genital tract? 1. NO. 2 YES

17. Have you ever been told by a doctor that you have diabetes? 1. NO. 2. YES

18. If YES, at what age?

19. Type of therapy for diabetes: 1. Insulin 2. Oral therapy 3. Diet

20. Have you ever been told by a doctor that you have high blood pressure? 1. NO. 2. YES

21. If YES, at what age?

22. What have you been using for therapy of high blood pressure?

23. Do you use propranolol for therapy? 1. NO. 2. YES

24. If YES, how long?

25. Have you ever been told by a doctor that you have uricacidaemia? 1. NO. 2. YES

26. If YES, at what age?

25. Have you ever been told by a doctor that you have hyperlipidaemia? 1. NO. 2. YES

26. If YES, at what age?

27. Have you ever smoked? 1. NO. 2. YES

28. If YES, for how many years have you smoked?

29. What average number of cigarettes per day have you smoked?

30. Have you ever consumed alcohol? 1. NO. 2. YES

31. If YES, for how many years have you drunk?

32. What type of alcoholic beverages have you drunk most frequently? 1. Beer 2. Wine 3. Hard liquor

33. Has any of your family members ever been told by a doctor to have:
a. Gout 1. NO. 2. YES 3. DO NOT KNOW
b. Peyronie's disease 1. NO. 2. YES 3. DO NOT KNOW
c. Dupuytren's contracture 1. NO. 2. YES 3. DO NOT KNOW

34. Presence of Dupuytren's contracture in patient 1. NO. 2. YES

35. Presence of lipoma in patient 1. NO. 2. YES

36. If YES, how long?