

·Original Article·

Peyronie's disease: a silent consequence of diabetes mellitus

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Abstract

Aim: To investigate the clinical characteristics of patients with Peyronie's disease (PD) and diabetes mellitus (DM). **Methods:** During an 8-year period, a total of 307 men seen at our outpatient clinic were diagnosed with PD. Clinical characteristics, penile deformities and the erectile status of patients with PD and DM together ($n = 102$) were retrospectively analyzed and compared to patients with PD alone with no risk factors for systemic vascular diseases ($n = 97$). **Results:** The prevalence of PD among men with DM and sexual dysfunction was 10.7 %. The mean age of diabetic patients with PD was (55.9 ± 8.9) years; in the no risk factor group it was (48.5 ± 9.0) years ($P < 0.05$). The median duration of DM was 5 years. The majority of diabetic patients with PD (56.0 %) presented in the chronic phase ($P < 0.05$), and they were more likely to have a severe penile deformity ($> 60^\circ$) than the no risk factor group ($P < 0.05$). In the diabetic group, the most common presenting symptom was penile curvature (81.4 %), followed by a palpable nodule on the shaft of the penis (22.5 %) and penile pain with erection (14.7 %). A total of 19.6 % of patients were not aware of their penile deformities in the diabetic group. Erectile function, provided by history and in response to intracavernosal injection and a stimulation test, was significantly diminished in patients with PD and DM ($P < 0.05$). **Conclusion:** DM probably exaggerates the fibrotic process in PD. Diabetic patients with PD have a higher risk of severe deformity and erectile dysfunction (ED). PD seems to be a silent consequence of DM and should be actively sought in diabetic men. (*Asian J Androl 2006 Jan; 8: 75–79*)

Keywords: Peyronie's disease; diabetes mellitus; erectile dysfunction; penile deformity; fibrosis

1 Introduction

Peyronie's disease (PD) is a localized connective tissue disorder that primarily affects the tunica albuginea of the penis and is characterized by an initial inflamma-

tory reaction followed by fibrous inelastic scar formation [1]. The result is a fibrous plaque on the shaft of the penis that contains an excessive amount of collagen and fibroblastic proliferation [1]. Penile pain with erection and a palpable nodule on the shaft of the penis are other clinical hallmarks during the acute phase of the disease, which lasts for approximately 12–18 months [2]. The chronic phase commences when the penile deformity stabilizes and pain diminishes. Erectile dysfunction (ED), due either to difficulty in penetration as a result of a disabling penile deformity or diminished erectile capacity resulting in an inability to maintain or sustain a satisfac-

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tory penile erection, may be a presenting symptom and is reported in 20.0 %–54.4 % of men with PD in different series [3].

The disease is considered to have a multifactorial etiology in nature. The most widely accepted theory is that it is caused by an abnormal fibrotic reaction of the tunica albuginea to repetitive microtrauma to the erect or flaccid penis, with inherited predisposition to exaggerated fibrotic response [1]. Recent studies have also documented the role of several cytokines, such as transforming growth factor- β (TGF- β), basic fibroblast growth factor and platelet derived growth factor in the pathogenesis and fibrotic reactions of extracellular matrix changes in PD [1, 4–7]. Diabetes mellitus (DM) is also associated with abnormalities in extracellular matrix composition, such as collagen accumulation and fibrosis [8]. The stimulatory influence of hyperglycemia on factors related to extracellular matrix remodeling has been documented in experimental studies [9]. Penile corporeal tissues from diabetic men also demonstrate increased fibrosis [10]. Furthermore, DM is a leading risk factor for sexual dysfunction and 18.3 %–33.0 % of men with PD have been reported to have DM [2, 11].

However, the clinical relationship between DM and PD is still obscure. Thus, the aim of this study is to investigate the demographic findings of patients with both PD and DM and look at how DM affects the clinical characteristics, presenting symptoms and erectile status of patients with PD.

2 Materials and methods

During an 8-year period, a total of 5 942 men with sexual problems were seen at our outpatient andrology clinic. They were evaluated with a detailed sexual and medical history and multiple serum analyses, to investigate the presence of DM, hypertension, hypercholesterolemia, hypertriglyceridemia and ischemic heart disease. Physical examination was focused on abnormalities of external genitalia and the extent of palpable induration on the penis.

According to the National Institute of Health (NIH) Consensus [12], patients with a consistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual intercourse were diagnosed as having ED. All patients in our study were given an intracavernous injection of 60 mg papaverine hydrochloride combined with manual genital self-stimulation (Combined

Injection and Stimulation [CIS] test), performed in private to induce maximal erection and to overcome sympathetic overactivity due to anxiety, in order to assess the degree of tumescence, as well as the location and degree of curvature of the penis [13]. The criteria for a positive erectile response to the CIS test were determined by the occurrence of an erection (buckling pressure > 500 gr) within 10 min and maintaining this state for at least 10 min. In cases where the penile deformity exceeded 30°, the bucklometer was not used to assess the axial rigidity of the penile erection. A vacuum erection device (VED) was used to achieve full erection in patients with a negative response to the CIS test. If present, the degree of curvature of the penis was measured with a protractor during maximum erection in response to the CIS test and/or VED, when patients described the erection they had achieved as similar as or better than they had been at home. Penile deformities were documented by photographs or drawing. A modified Kelami's classification was used to categorize penile deformities as follows: mild deformity, a curvature of 30° or less; moderate, a curvature of 31–60°; severe, a curvature greater than 60° [2, 11].

Of the patients with ED, 16.0 % ($n = 951$) were found to have DM (92 type I DM, 859 type II DM). They were all further evaluated in detail by an experienced diabetologist. The erectile status of patients with uncontrolled DM was assessed after their serum glucose and HgbA1C levels normalized. During the same period, 307 out of a total of 5 942 patients were found to have PD. The clinical characteristics of these patients were also analyzed and 102 of them (33.2 %) (12 type I DM, 90 type II DM) were found to have DM. No risk factor could be identified in 97 men (31.6 %). The remaining men with a risk factor other than DM, such as hypertension, hypercholesterolemia, hypertriglyceridemia or ischemic heart disease, were excluded from the study. The patients with PD and DM characteristics (Group 1) were compared to patients without risk factors (Group 2).

The clinical parameters and erectile status of patients in each group were analyzed and statistical analyses were performed using unpaired *t*-test and the χ^2 test. $P < 0.05$ was considered to be statistically significant. Data were expressed as Mean \pm SD.

3 Results

Of the 5 942 men presenting with sexual problems during the 8-year period, 951 (16.0 %) had DM, 5.1 %

($n = 307$) of the 5 942 men with sexual dysfunction were diagnosed to have PD. The prevalence of DM among men with PD was 33.2 % ($n = 102$), and the prevalence of PD in the diabetic population with ED was calculated to be 10.7 % (102/951).

Of the patients admitted to our clinic with sexual problems, 897 of 951 (94.3 %) with DM and 167 of 307 (54.4 %) with PD complained of ED. The remaining patients complained of sexual problems such as premature ejaculation and penile deformity without PD.

The mean age, degree of deformity, presenting symptoms and duration of PD of both groups are summarized in Table 1. Overall, the mean age of patients with PD was (52.8 ± 9.3) years. The mean age of patients with PD and DM (Group 1) and those with no risk factors (Group 2) was (55.9 ± 8.9) years and (48.5 ± 9.0) years, respectively ($P < 0.05$). The median duration of DM in men enrolled to the study was 5 years (range 3 months–15 years).

In the diabetic group, the most common presenting symptoms were penile curvature (81.4 %), a palpable nodule on the shaft of the penis (22.5 %) and penile pain with erection (14.7 %), usually combined with other symptoms (Table 1). Although the mean degree of deformity was similar in both groups, a higher percentage of diabetic patients with PD exhibited severe penile deformity greater than 60° (Table 1), which was statistically significant ($P < 0.05$). Dorsal curvature was the most common type of deformity in both groups. A total of 20 (19.6 %) men with DM (mean age 63.7 ± 7.3 years), and 9 (9.2 %) men with no risk factors were not aware of their penile deformity, and were identified during standard investigation for ED. This difference was also statistically significant ($P < 0.05$, Table 1). The presenting symptoms in Group 2 were penile curvature (91.0 %), penile pain with erection (29.0 %) and palpable nodule (24.3 %). Penile pain with erection as a presenting symptom was encountered significantly less often in men with DM, when compared with those with no risk factors (Table 1).

In the diabetic group, the median period between the initial diagnosis of DM and the occurrence of PD-related symptoms was 3 years (range 1 month–15 years). Overall, 62.9 % of patients with PD with no risk factors and 44.6 % of patients with PD with DM presented in the acute phase ($P < 0.05$, Table 1).

Evaluations of erectile capacity by history and CIS test are summarized in Table 2. In Group 1, 83.0 % complained of ED by history and 69.0 % had a poor response

Table 1. Characteristics of patients with Peyronie's disease (PD) and diabetes mellitus (DM) (Group 1) and those with PD without risk factors (Group 2). ^b $P < 0.05$, t -test; ^c $P < 0.05$, χ^2 test.

	Group 1	Group 2
<i>n</i>	102	97
Mean age (years)	55.9 ± 8.9	48.5 ± 9.0^b
PD duration (months)	23.7 ± 19.3	12.4 ± 9.5^b
Acute phase	44.0 %	62.9 % ^c
Chronic phase	56.0 %	31.7 % ^c
Mean deformity (degrees)	37.5 ± 3.5	39.6 ± 18.5
= 30°	44.5 %	49.0 %
31° – 60°	31.0 %	40.0 %
> 60°	24.5 %	11.0 % ^c
Symptoms		
Penile curvature	81.4 %	90.8 %
Penile pain with erection ¹	4.7 %	29.0 % ^c
Palpable nodule	22.5 %	24.3 %
Incidentally diagnosed PD	19.6 % ($n = 20$)	9.2 % ($n = 9$) ^c

Table 2. Erectile capacity assessed by history and Combined Injection and Stimulation (CIS) test in patients with Peyronie's disease (PD) and diabetes mellitus (Group 1) and those with PD without risk factors (Group 2). ^b $P < 0.05$, χ^2 test. ED, erectile dysfunction.

	Group 1	Group 2
Potency by history		
Potent	17.0 %	58.1 % ^b
ED (+)	83.0 %	41.9 % ^b
Response to CIS test		
CIS test (+)	31.0 %	69.2 % ^b
CIS test (-)	69.0 %	30.8 % ^b

to the CIS test. In Group 2, 41.9 % complained of ED by history and 30.8 % had a poor response to the CIS test ($P < 0.05$).

4 Discussion

ED is an increasingly common clinical problem around the world and is known to be a frequent complication of DM. The overall incidence of ED in the general population between the ages of 40 years and 70 years is reported to be 52 %. Men with DM develop ED at an earlier age with a significantly high prevalence, ranging from 20 % to 85 % [14]. In a recent study, the prevalence of undiagnosed DM was found to be higher in men with ED than that in the general population [15]. Both neurogenic and vascular factors are important determinants in the pathogenesis of ED. DM also affects both

systems and frequently results in ED as a long-term complication. Numerous studies have shown histopathological changes responsible for ED in diabetic patients [10]. Several authors described ED as another "silent complication" of DM [15].

In addition to the functional problems of the penis, structural abnormalities also attract attention, and PD is the most important acquired deformity of the penis. Although it has been considered a rare condition, large-scale epidemiological studies have demonstrated high prevalence rates of PD, up to 3.2 % [16].

Recently, molecular studies have documented the role of several cytokines, such as TGF- β , as detrimental factors for collagen accumulation and extracellular matrix composition alterations [6]. Studies on patients with DM have also shown extracellular matrix alterations and collagen accumulation to be responsible for several complications such as diabetic nephropathy [6, 8, 9]. Bollineli *et al.* [17] clearly indicated a regulatory role of TGF- β in renal glomerular collagen synthesis, and suggested a possible causal role for enhanced collagen synthesis in the diabetic rat. A systemic change of extracellular matrix metabolism is observed in DM, and it is found in the penis of men with PD, where TGF- β also plays a major role in the pathogenesis [5]. Thus, DM seems to be a major risk factor of PD. The further difficulty in wound healing observed in DM may also be a part of this pathology, and all these mechanisms together suggest that DM exacerbates the pathogenesis of PD. However, a recent study demonstrated that there was no statistical relationship between penile curvature severity and risk factors, including DM [11]. On the contrary, DM had a statistically significant negative impact on the severity of penile deformity and erectile capacity, assessed by history and CIS test in our study (Table 2). This discordance with the paper by Usta *et al.* [11] can be explained by the different demographic characteristics of the study groups, the type and frequency of sexual intercourse, as well as ethnic differences between populations. This should be investigated in further large-scale, multicenter studies by multivariate analysis.

A number of studies and clinical reviews have investigated erectile function in men with DM [14]. Men with DM face problems related to sexual dysfunction at an early age. However, our results indicate that diabetic patients with PD are diagnosed in their mid-50s and their mean age is higher than those with no risk factors (Table 1). Patients with PD and DM also present in the later stages of

the disease. This may be related to the fact that diabetic patients with ED recognize and seek help for their penile deformities later than those without ED or risk factors. These men may also have more crucial problems related to DM which they have to deal with urgently before addressing their sexual dysfunction. This may be another contributing factor in their presenting in the later stages of PD.

Penile pain with erection is a significant presenting symptom in PD [2]. However, our results have shown that this symptom is not prevalent among diabetic patients with PD (Table 1). This may be another factor leading to late presentation and may be explained by the fact that they may not have sufficient rigid erections and that neurological problems may lessen their pain perception. In addition to significantly different presenting symptoms, a total of 19.6 % patients with PD and DM together and 9.2 % patients with PD and no risk factors were not aware of their penile deformity, and were identified during standard investigation for ED. This difference was also statistically significant. The incidence of incidentally diagnosed PD in men presenting with ED was reported to be 16.0 % in a cohort of 448 cases [18], and this ratio correlated well with our results.

Our results show that diabetic patients with PD are more likely to have a severe penile deformity exceeding 60° (Table 1). It can be speculated that systemic changes in extracellular matrix metabolism and increased TGF- β production in response to hyperglycemia [8, 9] and relevant advanced glycation end products [19] in patients with DM and PD exacerbate fibrotic changes in the penis. Another explanation may be the fact that insufficient erections during intercourse in diabetic patients may lead to increased trauma to the penis, resulting in increased fibrotic reaction [1]. All of these factors underline the importance of early diagnosis of problems related to erection in diabetic men, in order to initiate appropriate treatment in the acute phase. Medical treatment has been documented to improve deformities in 30 % of all patients with PD [2]. However, further studies are needed to establish the efficacy of medical treatment in diabetic patients with PD.

Recent experimental studies have documented encouraging results in the prevention of fibrosis and ED. Decorin, an anti-TGF- β agent previously used in the prevention of experimental diabetic nephropathy, has been used in the treatment of an experimental PD-like condition in rats, and its antifibrotic activity has been reported [4].

In another study, the protective effect of amino guanidine on erectile function in diabetic rats has been demonstrated [20]. With our increasing knowledge of the pathogenesis of PD in diabetic patients, significant improvements in the prevention of fibrotic changes of the penis and other organs related to DM will be achieved.

There are several controversies regarding erectile function in men with PD. The prevalence of sexual dysfunction as a presenting symptom is reported in different series to range from 20.0 % to 54.4 % [2, 3]. Although the excessive angulations due to curvature, painful erection, tender plaque and performance anxiety may all contribute to ED, it has been shown that penile vascular abnormalities are responsible for ED in 61 %–70 % of patients with PD [3, 13]. The role of veno-occlusive dysfunction and arterial disease has also been shown in PD with ED, although it is not easy to determine the exact etiologic factor in every case [3, 13]. Furthermore, patients with PD, presenting most commonly in their 50s, may only reflect the conditions of potency of age-matched patients without PD [2, 3]. Although our results suggest a high prevalence of penile vascular abnormalities, further objective studies, preferably with penile Doppler ultrasonography, are needed to clarify vascular abnormalities in diabetic patients with PD. However, the same management algorithm for ED is valid in this group of patients.

In conclusion, PD may be considered another silent consequence of DM, with a prevalence of 10.7 % in diabetic patients with ED. Diabetic patients with PD have strikingly different characteristics. They usually present with severe penile deformity in their mid-50s, most often with ED. Penile pain with erection is less commonly observed, and 19.1 % are not aware of their penile deformity. All of these factors underline the importance of evaluation of erectile function as well as penile deformity in diabetic men.

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