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REVIEW ARTICLE

Peyronie's disease development and management in diabetic men

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Abstract

Background: Peyronie's disease (PD) is a fibrosing disorder of the penis resulting in plaque formation and penile deformity that negatively affect sexual and psychosocial function of patients. A multifactorial etiology of PD is assumed with diabetes mellitus (DM) being a potential risk factor.

Objectives: The aim of this narrative review was to investigate diabetes role in PD pathophysiology, diagnosis, and treatment.

Materials and methods: A non-systematic narrative review of original articles, meta-analyses, and randomized trials was conducted, including articles in the pre-clinical setting to support relevant findings.

Results: Diabetes is one of the most common comorbidity observed in PD patients, with a prevalence of about 11% and a strong association with erectile dysfunction (ED). DM is associated with both a higher risk of developing PD and has also an impact on the outcomes of PD's treatments.

Discussion: Evidence from literature underlines that metabolic alterations typical of DM are pivotal factors in the development of PD and resistance to its medical treatment.

Conclusion: The role of DM in development of PD is still debated, while its role in PD development is not completely clear, there is a clear impact of DM on PD treatment outcomes.

KEYWORDS
diabetes mellitus, epidemiology, etiology, peyronie's disease

1 | INTRODUCTION

The first description of Peyronie's disease (PD) is credited to Francois Gigot de la Peyronie, surgeon to King Louis XV more than 250 years ago.[1] It is a common disorder in men characterized by a superficial fibrosis of the penis appearing as a fibrotic plaque which leads to penile deformity with or without concomitant pain.[2] The most common area affected by plaques is the base of the penis, followed by the mid-shaft area and the distal penis.[3] The hallmark acquired penile deformity, consisting of curvature during erection, buckling or penile instability on minimal axial loading, despite maximal erection.[4,5] Schwarzer et al. in a large survey of 8,000 men reported a prevalence of PD of 389:100,000[6]; likewise, DiBenedetti et al. in a population-based study in the USA estimated up to 9% of patients suffering from PD, with a range of variability of 0.5%–13.1%.[7] However, these numbers could be under-estimated for an undoubtful under-diagnosed disease.[8] Indeed, a study conducted by Smith et al. analyzing penis during autopsies supposed a true prevalence of 22%.[9,10]

Besides physical symptoms, PD impacts on sexual function and it is associated with psycho-social distress,[7] for the patients and even for their partners.[11–13] Penile deformity could lead to pain and discomfort during penetrative intercourses.[11] Moreover, shame feeling, and embarrassment coexist with physical symptoms, and they get worsening with the progression of the disease.[11] The pathophysiology of PD is still under debate, although several factors have been associated with the risk of developing the disease.[14–20] The link between PD and advancing age, diabetes mellitus (DM), hypertension, obesity, dyslipidemia, and smoking has been well documented.[21]These links show that metabolic abnormalities may be a cause or contributor to the production of PD plaques. Among these risk factors, diabetes has been more commonly associated with PD. Epidemiological studies have shown PD in type 2 DM patients ranging from 4% to 20%.[21–25] The role of DM in PD's development is still debated. It has been hypothesized that genetic background, vascular and metabolic alterations, and neuropathy may be the mechanisms driving this association.[2] Also, the DM's effect on the PD treatment has been poorly investigated. The aim of this narrative review was to investigate diabetes's role in PD pathophysiology, diagnosis, and treatment.

2 | METHODS

We performed a non-systematic narrative and interpretative literature review.

An extensive research using Medline has been conducted retrieving English articles until February 28, 2022. The search terms included: "Peyronie's disease" OR ("Peyronie" OR "Induratio Penis Plastica") AND ("diabetes" OR "DM" OR "insulin resistance" OR "IR"). Reference lists of retrieved articles were scanned for additional suitable articles.

We included original randomized clinical trials and single-arm studies that investigated the correlation of PD and diabetes in human adults. Meta-analyses and systematic reviews were included when they discussed and made conclusions regarding PD and DM. Relevant studies in preclinical models (i.e., murine or rat models) were inserted to support relevant observed findings in human studies.

2.1 | Etiology of Peyronie's disease

A complete understanding of the etiology and natural history of PD remains elusive.

Modifiable risk factors related to lifestyle and comorbidities, and non-modifiable factors such as surgery, genetic predisposition, and traumas, appear to contribute together to its etiology in a multifactorial fashion.[14,26,27] Overall, risk factors associated with PD include non-gonococcal urethritis; genital and or/perineal trauma, iatrogenic trauma such as urethral catheterization, cystoscopy, trans-urethral surgery, major urological surgery such as radical prostatectomy and radical cystectomy, lower urinary tract lesions, intracavernous drugs injections, smoking, alcohol abuse, hypertension, and diabetes.[15,16,18] Among others, coital trauma resulted an independent predictor of PD in a case–control study, along with ED.[18] Moreover, a history of trauma was more frequent in men younger than 40-years-old compared to those older, in a study of 296 men with PD.[28]

The main theories on the pathophysiology of PD encompass mechanisms such as an inflammatory response secondary to trauma, leading to fibrosis with reduction of elasticity, alteration in wound healing capacity and aberrant deposition of collagen.[3,17] Indeed, hematomas generating between the penile layers after major or micro-traumas to the penile shaft, stimulate the subsequent release of inflammatory cytokines such as TGF-β1, thus triggering an overproduction of collagen, accumulation of fibroblasts and myofibroblasts with loss of elastin fibers.[18,19] Western blot findings from tissue of 36 men undergoing penile prosthetic surgery underlined a significant overexpression of TGF-β1 in men affected by PD compared to those unaffected.[29] Such mechanisms favor the formation of a plaque that progressively builds up with a reduction of elasticity in the affected areas, resulting in morphological changes of the shape of the penis such as depression, curvatures, hourglass deformity, and shortening.[20] In the context of multifactorial etiology, genome-wide association studies suggest a genetic predisposition to PD. It is in fact established that both chromosomal abnormalities, along with single-nucleotide polymorphisms (SNPs) are associated to fibrotic diatheses typical of PD.[26] Such findings are supported by further evidence on chromosomal loci, involved in the WNT signaling pathway, specifically associated with Dupuytren disease that share susceptibility to PD as well.[30,31]

2.2 | The relationship between diabetes mellitus and Peyronie's disease

DM is a condition commonly associated with PD. Epidemiological studies have shown PD in type 2 DM patients ranging from 4% to 20%, and a prevalence of DM in men with PD between 13% and 50%.[21–25]

TABLE 1 Prevalence of Peyronie's disease in epidemiological studies and relationship between diabetes mellitus and Peyronie's disease

Author	Participants	Study period	Country	Prevalence, *n* (%)	Type of population
Prevalence of PD					
Tefekli et al.[23]	5942	ND	Turkey	307 (5.2)	Men with sexual problem seen in an outpatient clinic
Kadioglu et al.[56]	1208	ND	Turkey	63 (5.3)	Field survey in 12 Turkish regions
Habous et al. [36]	1622	2010-2011	Saudi Arabia	319 (19.7)	Retrospective chart review of urology/andrology private patients
El-Sakka et al.[21]	1133	ND	Saudi Arabia	92 (8.1)	Patients with T2DM screened for erectile dysfunction
Pavoneet al.[8]	279	2012-2013	Italy	97 (34)	Assessment of PD prevalence and association with its risk factors in men presenting to an andrology outpatient clinic
Prevalence of DM in men with PD, sample size is referred to as men with PD					
Usta et al.[33]	469	1992-2002	USA	T1DM: 10 (2.1) T2DM: 71 (15.1)	Retrospective evaluation of comorbidities in men with PD
Kadioglu et al.[32]	448	1992-2002	Turkey	Group 1*: 29/71 (40.8) Group 2: 84/377 (22.3)	Evaluation of incidental detection of PD compared to classical presentation
Culha et al.[57]	143	ND	Turkey	35 (24.5)	Assessment of vascular disfunction and impotence in patients with PD
Tefekli et al.[23]	307	ND	Turkey	102 (33.2)	Men with sexual problem seen in an outpatient clinic
Cavallini et al.[42]	437	2006–2012	Italy	56 (12.8)	Evaluation of improvement of PD symptoms after therapy for DM
Kadioglu et al.[58]	1001	ND	Turkey	261 (26)	Assessment of comorbidities in patients with PD
Kadioglu et al.[56]	63	ND	Turkey	11 (17.5)	Field survey in 12 Turkish regions
Prevalence of PD in men with DM, sample size is referred to as men with DM					
Tefekli et al.[23]	951	ND	Turkey	102 (10.7)	Men with sexual problem seen in an outpatient clinic
Arafa et al.[34]	206	2005-2006	Egypt	42 (20.3)	Evaluation of PD prevalence in men with DM and ED
Pavone et al.[8]	59	2012-2013	Italy	24 (41)	Assessment of PD prevalence and association with its risk factors in men presenting to an andrology outpatient clinic
Askary et al.[22]	317	2017-2018	Iran	12 (3.8)	Estimating PD prevalence in men with DM in an Iranian province

Note: *Group 1 refers to men unaware of PD, while group 2 refers to men with a classical presentation of PD.

Table 1 summarizes relevant findings of studies evaluating the relationship between clinical characteristics, such as DM, and prevalence of PD, or vice versa, the prevalence of DM in men with PD. It is of note that PD prevalence varies according to the clinical setting, in that it is higher in studies conducted in men seeking andrological attention for sexual-health-related complains, compared to studies in non-selected populations. In particular, PD prevalence is as high as 34% in selected population (i.e., men with ED of other sexual problems), while it ranges between 5% and 8% when broader inclusion criteria (i.e., epidemiological studies including not only men seeking attention for sexual-health-related complains) were applied.[8,21] A similar effect was observed when comparing estimates of PD or DM prevalence in men with DM or PD, respectively. In a large study of 5942 men seeking andrological attention for sexual problems, at an eight-year follow-up, 5.2% had PD, and of these, 33.2% had DM, with a prevalence of PD in diabetic men with ED of 10.7%.[23] Among key differences in PD presentation in diabetic and non-diabetic men, those with DM were older, had usually a longer duration of PD, and were more likely to have severe PD (defined as a penile curvature > 60°). Among other findings, men with PD and DM were less likely to feel pain with erection and were incidentally diagnosed more frequently.[23] Similarly, Kadioglu et al. observed a higher proportion of men with DM in those incidentally diagnosed with PD in a study of 448 men; they showed that men presenting with ED only, and unaware of penile deformity, were more likely to have DM compared to those presenting with classical signs and symptoms of PD (i.e., penile deformity and pain during sexual intercourse).[32] Moreover, a higher proportion of patients with DM was observed in younger men with PD in a cohort of 296 patients, where 50% of men with PD younger than 40-years-old were also affected from DM.[28] In two other studies evaluating comorbidities in men presenting with PD, a lower proportion of these had type 1 DM compared to type 2 DM.[33] Two other differences are worth noting, when selecting a population with DM and ED, a higher proportion of these also had PD, compared to a larger study of men presenting for generic sexual problems (20.3% vs. 10.7%).[23,34] Overall, these findings show the significant prevalence of DM among patients with PD, although data are heterogeneous due to differences between the selected population.

2.3 | The role of diabetes mellitus in Peronye's disease development

The incidence of PD in men affected by DM suggests a potential role of metabolic alterations typical of a poor glycemic control in the development and evolution of penile structural and functional alterations seen in PD.[21,23,29,35–40] Key factors that explain the relationship between DM and PD involve a complex spectrum of metabolic alteration encompassing an altered wound healing process up to a more generalized inflammatory status.[18,19,21,29,34,41] From a pathophysiological standpoint, it has been observed that arterial insufficiency, along with mixed penile vascular disease, was more frequent in patients with DM and PD, compared to those without DM.[11] Moreover, an impaired wound healing process observed in patients with DM may be a cofactor concurring in plaque development after major and minor penile traumas.[35] It has been also reported that the poor metabolic control observed in patients with DM is associated with elasticity alterations of penile layers.[21] To this regard, patients affected by DM for more than 10 years are six times more likely to have PD compared to those diagnosed with DM since less than 5 years.[21] An impaired nociception typical of diabetic neuropathy is also a key finding in men with PD, leading to less penile pain also because of the lack of fully rigid erections.[21] In another study evaluating comorbidities associated with PD, Habous et al. interestingly found that poorly controlled DM, but not metabolic syndrome, was strongly associated with PD, rising the need for further research in mechanisms specific of glycemic control in the etiology of PD.[36] Another potential mechanism of penile plaques development is hypogonadism, a condition typically associated with DM.[36] In a series of 121 men with PD, Moreno et al. observed a significant association between lower free testosterone levels and the severity of penile curvature; however conflicting results have been reported on this topic.[37,38] Indeed, Kirby et al. showed a comparable prevalence of low testosterone in men either with PD or ED and suggested a potential role of hypogonadism in erectile dysfunction (ED) rather than specifically to plaque formation.[38] Beside the development of PD, DM is in fact also an established risk factor for ED due to vascular and nerve damage.[39,40] The presence of ED in diabetics men makes these patients more prone to suffer from PD due to a participation of multiple factors such as autonomic neuropathy, cavernosal arteriosclerosis, and smooth muscle collagenization.[34] Likewise, ED can be a consequence of PD in diabetics due to endothelial dysfunction secondary to an increased release of TGF-β1 and Endothelin-1, two cytokines involved in tissue remodeling, vasoconstriction, and fibrosis.[29] The result is a decreased release of nitric oxide and prostaglandins unbalancing smooth muscle cell paracrine regulation up to a fibrosis reaction with extracellular matrix deposition, cell atrophy, and hypoplasia.[41] These alterations contribute to a reduction of contractility and decreased tissue compliance leading to ED.[18,19] For example, in a cohort of 1,133 male diabetic Saudi patients screened for ED, it was observed that PD had a prevalence of 8.1%, and men with PD and type 2 DM were 1.14 times more likely to have a severe penile deformity.[21] In these patients, longer duration and poorer metabolic control of diabetes strongly correlated with PD.[21]

2.4 | Outcomes of Peyronie's disease treatment in patients with diabetes mellitus

The treatment of PD is based on both conservative and surgical approaches.

Conservative approaches to PD include observation, oral drugs, topical and intralesional drugs, mechanical therapies, and surgery. Counseling and observation may be appropriate for patients with minimal curvature still allowing sexual intercourse. Of interest, glycemic compensation has been observed to improve PD symptoms. In particular, plaque area and pain diminished in patients undergoing diabetes compensation and antidiabetic therapy administration.[42] In a study performed by Cavallini and Paulis, 36 nonsmoking patients with uncompensated diabetes and PD were compared before and after testing hemoglobin A1c (HbA1c) and serum glucose concentrations at a timeframe of 37 weeks. In these patients, plaque area (6 vs. 4.5 cm^2, p-value = 0.001), penile curvature (24° vs. 20°, p-value = 0.041), and pain (3 vs. 1 pain scale score, p-value = 0.041) were strongly affected by glycemic control.[42]

According to the European Association of Urology (EAU) guidelines on sexual and reproductive health,[43] several drugs have been proposed to treat PD, such as Procarbazine, Vitamin E, alone or in combination with other treatments, Tamoxifen, Coenzyme Q10, Omega-3 fatty acids, Pentoxifylline, L-Arginine, Colchicine and Potassium paraminobenzoate (POTABA). However, only intralesional injections of Clostridium Collagenase (XIAPEX) have been officially approved by food and drug administration (FDA) and it is the only drug currently suggested by EAU Guidelines.[43] On the contrary, American Urology Association (AUA) guidelines suggest also the use of interferon α-2b (moderate recommendation) and intralesional verapamil (conditional recommendation).[44]

Treatment schemes in PD concomitant to DM do not differ from usual therapy proposed by the guidelines.[43] Unfortunately, more severe form of PD and ED, resistant to pharmacological treatments, are often seen in diabetic men.[19,45] As shown by Kendirci et al., comorbidities negatively impact the outcomes of pharmacotherapy, due to concomitant vasculogenic and neurogenic dysfunction.[24] This failure determines how, in those types of patients, with less possibility of regression with topic or local drugs, surgery should be the preferred approach. Surgical treatment is indicated in men with penile deformity that limits sexual intercourse and has been stable in the last 6 months.[46] Surgical options include tunical plication, plaque incision/excision with grafting, and penile prosthesis implantation.[5,47] Tunical plication represents the first line in surgical treatment for patients with good EF, appropriate penile length, curvature < 60° and without deformities.[43] Success rates range from 92%–99% in improving penile curvature with rare adverse events.[48] Plaque incision and grafting show a partial success with 4.6%–67.4% of patients requiring drugs to obtain erections and 0%–11.8% patients completely unable to achieve erections. Successful straightening occurred in 80.0%–96.4%, while penile length was unchanged in 44.2%–95.0%.[49] Unfortunately, grafting of PD has significant long-term risks such as recurrence of penile curvature, penile shortening, ED, altered penile sensation, and

glans hypoesthesia. Penile length loss and new onset of ED are more frequent among diabetic patients and represents the main drawbacks of grafting surgery.[50] Patients should have good baseline EF to tolerate the disruption of tunical integrity and the possible impairment of the veno-occlusive mechanism. For this reason, diabetic men may have a higher risk of post-operative ED.[5] In men with PD and concomitant ED, unresponsive to medical therapy, penile prosthesis implantation with penile modeling or plaque incision is the preferred approach.[51]

Regarding DM effects on curvature recurrence, Salabasas et al. collected a 20-year observational study among men submitted to corrective surgery for PD, analyzing outcome and recurrences in the population. In their series, DM shows a higher prevalence in patients who did not report a recurrence after surgery.[52] Paradoxically, among patients undergoing surgery with a shortening procedure, ì13 (35.1%) in the nonrecurring group had DM compared to a lower rate in the recurring group ($p = 0.042$). Similarly, in the lengthening surgery group, the rate of diabetic patients was significantly higher in the nonrecurring group (5.2% vs. 25.2%).[52] This is probably due to a protective role of DM on curvature recurrence associated with the lack of post-operative nightly erection and the lower cavernosal blood pressure, usually observed in non-diabetic young patients.[52] This hypothesis is strengthened by an animal study, where the tunica albuginea of 13 diabetic New Zealand white rabbits was investigated. In this study, overall thickness and elastic fibers of TA increased by 88% ($p = 0.001$) and 34% ($p = 0.001$), while collagen of corpus cavernosum decreased by 45%, compared to non-diabetic controls ($n = 13$). As a result, the thickened walls of tunica albuginea with lesser inner blood compression from corpus cavernosum might fare better in terms of penile straightness.[53] On the other hand, DM is a significant risk factor for device infection in patients undergoing penile prosthesis implantation to treat PD and concomitant ED.[41] Habous et al., in a 902 men cohort, stratified the risk of device infection after surgery related to the HbA1c level, showing that a threshold level of 8.5% ensures a sensitivity of 80% and a specificity of 65% in predicting the risk of implant infection. The lowest risk of infection (1.3%) occurs in patients with well glycemic control with HbA1c below 6.5%.[45] Similarly, Li et al. in a study published in 2018 analyzing 5085 implantations reported that DM, HIV, and Charles comorbidity index were factors associated with prosthesis removal.[54] These observations were confirmed by a recent meta-analysis in which DM was found to be related to a higher risk of penile prosthesis infection with an odds ratio of 1.53.[55] These findings regarding DM and PD's treatment may not have a major role in the current care algorithm. However, potential effects on treatments result (decrease in the incidence of curvature recurrence and increased risk of implant infection) should be fully discussed with the patient in order to modulate his expectations and to be aware of the possible therapeutic outcomes.

3 | CONCLUSIONS

PD is a common condition with a significant impact on patients' and couples' sexual life. Although the etiology of PD is not fully understood, there is a clear role played by penile trauma followed by abnormal wound healing, genetic background, and comorbidities such as DM. Diabetes is one of the most common comorbidities observed in patients affected by PD and is associated with a higher incidence of ED in these patients. Moreover, men with PD and DM have different presentations of the disease. They tend to be older, have worst curvature, and lower odds of feeling pain with erection. DM's exact role in PD development is still debated in the literature. Among the different proposed mechanisms, a pivotal role is occupied by arterial insufficiency and mixed penile vascular disease as a consequence of DM. Moreover, among the different endocrinological imbalances brought by DM, hypogonadism is believed to be a potential mechanism of the penile plaques development. While its role in the PD development is not completely clear, there is a clear impact of DM on PD treatment outcomes. Patients affected by diabetes seem to have a lower risk of curvature recurrence after surgery for PD and glycemic control has been proved to ameliorate PD's symptoms. However, in men with DM the risk of post-operative ED significantly increases. On the other hand, in men treated with penile prosthesis implantation, uncontrolled glycemic levels are associated with a significantly higher risk of device infection after surgery and diabetic men have an increased incidence of prosthesis removal. In conclusion, due to autonomic neuropathy, cavernosal arteriosclerosis, smooth muscle collagenization, and endothelial dysfunction, diabetes can be considered one of the pivotal factors in the development of PD and resistance to the medical treatment.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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AUTHORs' CONTRIBUTION

P. Capogrosso conceived the study. S. Gianazza, F. Belladelli, R. Leni and F. Masci collected data and drafted the manuscript. P. Rossi, G. Gianesini. P. Maggio, E. Zaffuto, A. Salonia, G. Carcano, F. Dehò and P. Capogrosso revised the manuscript critically for important intellectual content. All Authors approved the final version of the manuscript.

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