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Smoking, diabetes, blood hypertension: Possible etiologic role for Peyronie's disease?
Analysis in 279 patients with a control group in Sicily

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Summary
Objective: To assess the proportion of patients with Peyronie's Disease (PD) and the possible association with its potential risk factors in the general population of the central and western Sicily in our weekly andrological outpatient clinic.
Materials and methods: We recruited a sample of 279 consecutive patients consulting our andrological outpatient clinic. Two arms were created: the first one composed by PD patients (men with symptoms suggestive for PD), the second one composed by patients with other andrological diseases (control arm). For each patient we evaluated the age, cigarette smoking, diabetes, blood hypertension and erectile function. In the PD arm we administered validated questionnaires to determine the erectile function status by the International Index of Erectile Function 5 (IIEF-5) and the pain status during erection by the Visual Analogue Scale (VAS). A univariate analysis was conducted using R software.
Results: We enrolled 279 consecutive patients. The number of PD patients was 97 (34,7%). The univariate analysis showed a correlation between PD and cigarette smoking (p = 0.0242), blood hypertension (p < 0.001), erectile dysfunction (p < 0.001). No significant association was observed between diabetes and PD (p = 0.358).
The median age of PD arm was 60 years and the median age of the control arm was 63,5 years; therefore the median age of PD arm resulted lower than the median age of the control arm (p = 0,031).
Conclusions: Peyronie's disease is more common than we might think; furthermore it can be diagnosed among young patients. According to our results, cigarette smoking and blood hypertension may be considered statically significant risk factors for developing PD. On the contrary diabetes seems not to be a risk factor for PD. According to our results PD should be sought also in young patients. Further studies are necessary to confirm that removing the indicated risk factors may reduce the incidence of PD.

KEY WORDS: *Peyronie's disease; Age; Diabetes; Cigarette smoking; Blood hypertension; Erectile dysfunction; Pain.*

INTRODUCTION

Peyronie's Disease (PD) is an andrological condition of unknown pathogenesis. The interest for such disease derives not only from its sexual, physical and psychological aspects but also from its undefined etiological, epidemiological,physiopathological aspects since it was described for the first time in 1743 by *Francois Girot de La Peyronie*. These features of the disease have influenced also the treatment, nowadays not curative. The use and the success of oral therapies for Erectile Dysfunction (ED) in the last years have contributed to uncover the hidden sexual pathologies leading the patient to the specialist. However PD is underdiagnosed and the time between diagnosis and therapy is still excessive (1). PD seems to be a pathology of connective tissue, a disorder of the penile tunica albuginea that determines a scar or a palpable plaque, often in the dorsal surface of the penis that could determine a penile curvature and change of length and diameter of the penis during erection. The condition often associated to PD is the ED, but it is hard to understand if the ED is a consequence of penile fibromatosis or a psychological consequence to the altered body image linked to the penile curvature or to the pain during intercourse. The physiopathological theories for the disease are multiple: trauma during intercourse with an aberrant healing (2), genetic predisposition, autoimmune disorder, over-expression of pro-inflammatory cytokines (3) etc. Probably the genesis of this disease is multi-factorial (4). There are no certainties even about therapies: nowadays a medical therapy does not exist with a tested clinical effectiveness. The surgical approach is recommended specially when the disease is stabilized, after 6-12 months from the first appearance of symptoms, when the acute inflammatory process is ended and there are no recent changes in penis deformity. However the surgical approaches are even burdened by limits (e.g. penis size reduction, possible relapse of the curvature, alteration of penile sensitivity and ED). The studies on the prevalence of PD are limited; the epidemiological data from literature are different for types of population studied and according to the different definition of the disease. The prevalence of PD in general population ranges between 0.39% (5) and 7.1% (6), but it goes up to 20.3% in diabetic patients with ED (7). The data on

possible epidemiological and symptomatic links in patients affected with PD and other comorbidities (diabetes and smoking habits) are multiple and there are no univocal conclusions. For these reasons the aim of our study was to evaluate the possible association of PD with other pathologies and life-styles in a cohort of 279 consecutive patients from central-western Sicily who consulted our andrology outpatient clinic.

MATERIALS AND METHODS
From October 2012 to November 2013 we recruited a sample of 279 consecutive male outpatients consulting our andrological outpatient clinic. The main diseases were: benign prostatic enlargement (BPE), erectile dysfunction (ED), varicocele, premature ejaculation (PE), lower urinary tract symptoms (LUTS), infertility, prostatitis and PD. The patients were divided into two arms: the first arm was composed by PD patients, the second arm was composed by patients with other diseases without signs and symptoms suggestive for PD and it was considered as control arm.
Inclusion criteria in the first arm were presence of a scar or a palpable plaque under penis surface; penis curvature; pain in erection or during intercourse with penile curvature, PD naive patients or with a previous diagnosis of PD. Previous surgical treatment of PD was not considered an exclusion criteria.
An accurate clinical history was recorded during the first visit, the presence of comorbidity was evaluated and an accurate physical examination was performed. A database including age, cigarette smoking, diabetes, blood hypertension and erectile function for each patient was created. Validate questionnaires to analyze the ED status (*IIEF-5*) (8) and pain (*VAS*) (9) were administered to the patients of PD arm. According to IIEF-5 five classes of ED were indentified: severe (5-7); mild (8-11); low-mild (12-16); low (17-21); normal (22-25).
According to VAS four classes of pain were identified: severe pain (8-10); mild pain (5-7); low-mild pain (2-4); low/no pain (0-1).
All analysis was conducted using R software. To check on a relation among potential risk factors and PD an univariate analysis was performed using Wilcoxon signed-ranks test for age and Pearson X2 test for the other qualitative variables (diabetes, blood hypertension, smoking and erectile dysfunction).

RESULTS
A total number of 279 consecutive male patients was enrolled. Among them, 59 (21%) patients had diabetes, 158 (57%) had blood hypertension, 178 (64%) were smokers and 128 (46%) had ED (Table 1).
The PD arm included 97 (34.7%) patients, the control arm included the remaining 182 (65.3%) patients. The median age was 60 (range 25-78 years) in the PD arm, and 63.5 (range 21-81 years) in the control arm (p = 0.031) (Table 2).
Among the initial 279 patients, 128 (46%) had ED and 151 (54%) had no history of ED. Among patients with ED, 67 (52%) had also PD, while among patients with-

out ED the diagnosed patients with PD were 30 (20%) (p < 0.001).
According to IIEF-5 the patients in the PD arm presented these scores: 0 patients severe; 7 (7.2%) patients mild; 23 (23.7%) patients low-mild; 37 (38.1%) patients low; 30 (30.9%) patients normal.
The patients affected with PD who referred pain during erection were 65 (67%). According to VAS the patients were divided in: 0 patients severe; 14 (14.4%) patients mild; 36 (37.1%) patients low-mild; 47 (48.4%) low/no pain (Table 3).
In our sample 178 (64%) patients were smokers and 101 (36%) were not smokers. Among the smokers PD was diagnosed in 71 (40%) patients, while it was diagnosed in 26 (26%) patients among the not smoker ones (p = 0.024).
One-hundred fifty-eight (57%) patients had blood hypertension and 121 (43%) referred normal blood pres-

Table 1.
Basal characteristic of population.

Number of patients 279 (100%)		
Diabetes		
	Yes	59 (21%)
	No	220 (79%)
Smoking		
	Yes	178 (64%)
	No	101 (36%)
Blood hypertension		
	Yes	158 (57%)
	No	121 (43%)
Erectile dysfunction		
	Yes	128 (46%)
	No	151 (54%)

Table 2.
Summary of statistics demonstrating age influence on the presence or absence of PD.

Age	Median	Mean	Sd	P-value
PD arm	60	59,1	8,3	· 0,031
Control arm	63,5	60,2	13,9	PD = Peyronie's disease

Table 3.
IIEF-5 and VAS scores in PD population.

IIEF-5	
	Number of patients with percentage
Disease stratification	
Severe (5-7)	0
Mild (8-11)	7 (7,2%)
Low/mild (12-16)	23 (23,7%)
Low (17-21)	37 (38,1%)
Normal (22-25)	30 (30,9%)
VAS	
Disease stratification	
Severe (8-10)	0
Mild (5-7)	14 (14,4%)
Low/mild (2-4)	36 (37,1%)
Low/no pain (0-1)	47 (48,4%)
VAS: Visual Analogue Scale	

IIEF-5 = International Index of Erectile Function 5.

Table 4.
*Percentages of patients with PD disease
in relation to risk factors.*

		PD patients	P-value
Diabetes			
	Yes	24 (41%)	0,358
	No	73 (33%)	
Smoking			
	Yes	71 (40%)	0,0242
	No	26 (26%)	
Hypertension			
	Yes	69 (44%)	< 0,001
	No	28 (23%)	
Erectile dysfunction			
	Yes	67 (52%)	< 0,001
	No	30 (20%)	

sure. Among patients with blood hypertension PD was diagnosed in 69 (44%) patients; among patients with normal blood pressure it was diagnosed in 28 (23%) patients (p < 0.001).

Fifty-nine (21%) patients had diabetes and 220 (79%) were not diabetic. Among diabetic patients PD was diagnosed in 24 (41%), while it was diagnosed in 73 (33%) of not diabetic patients (p = 0.358) (Table 4).

DISCUSSION

In Italy pathologies such as diabetes mellitus and blood hypertension are widely diffused. From a recent study published in 2012 the prevalence of diabetes in a region of Italy is shown to rise from 3.0% in 2000 to 4.2% in 2007 (40% more in only 7 years). The incidence shows a rate of 4 cases per 1000 per year (10). In other Italian regions higher prevalence values are published (11).

The overall prevalence of blood hypertension is about 24.4% in a population of three European macro-areas; among them, a third was under antihypertensive treatment, but a significant rate (56%) was unaware of high levels of blood pressure. The prevalence in the region of Abruzzo was 28.87% (12).

In Italy the current smokers are the 21.7% (22.7% in 2011 and 20.8% in 2012) of general population (13). Despite diabetes the trend of the habit of smoking is in a weak but progressive decrease so that, maintaining constant the ratio between those who start to smoke and those who quit, the prevalence at the end of next three decades is going to stabilize at 12.1% for women and 20.3% for men (14).

A definite analysis of prevalence of PD is impossible because of different definitions of disease, poor knowledge of disease also in health sector and patients' reluctance to show this condition. The epidemiologic data are extremely variable and depend mostly on methods of enrolling patients, on geographic differences and on characteristics of population chosen as sample. The prevalence of the disease seems to be directly proportional to ageing (6). In our study a lower median age is shown in the PD arm compared to control group (p = 0.031) (Table 2).

This data may indicate that in our sample the diagnosis is not related to ageing and therefore the disease should be sought also in young patients. In one of the most quoted studies about this argument, the prevalence of PD in general population of Rochester (*Minnesota, USA*) is 0.39%. Blood hypertension was the most associated disease in patients with PD, nevertheless no difference in the prevalence of diabetes was highlighted in the ill population in comparison to local general population (5). Diabetes, nevertheless, is one of the diseases mostly associated to PD in different studies. In another study (*Sommer et al, 2002*) the prevalence of patients affected with PD in the population of the area of Koln (*Germany*) is 3.2%. In this report the percentage of diabetic patients with PD was 18.3% versus 6% of diabetic patients without PD. The 40.8% of patients with PD had also ED. No further correlation between PD and other disorders or life-style (e.g. smoking) was demonstrated (15).

In the study by *Arafa et al. (2007)* the prevalence of PD among patients with diabetes and ED is 20.3%. A significant correlation was found between PD and age, obesity and smoking. Moreover all the patients with PD presented ED (7). The diabetes might condition the gravity of the disease because it would worsen the micro-circulation of penis and determine a considerable fibrotic process due to disease (16-17). In our survey among the 59 patients with diabetes the PD patients were 24 (41%), while among 220 without diabetes the PD patients were 73 (33%). In spite of a higher percentage of disease in diabetic patients demonstrated in our study, no statically significant difference between PD arm and control arm was shown (p = 0.358). Therefore the diabetes would not be associated to the disease and its absolute prevalence among PD patients might be casual or dependent from confounding external factors. The percentage of PD among the 128 patients with ED is 52%, while the percentage of PD patients among the 151 without ED is lower (20%) (p < 0.001); according to the data of literature in our survey a statistically significant association between PD and ED was evident; the analysis of results obtained administering the IIEF-5 to affected patients demonstrated that most of patients with PD had ED from low to mild gravity; however it was not possible to establish if ED was a consequence of PD and to quantify how the PD affected the erectile function.

The only Italian multicentric study (*La Pera et al, 2001*) reports a prevalence of PD in general population of 7.1%, with a significant correlation between smoking and diagnosis of PD. No significant correlations with other diseases (cardiovascular, diabetes, alcoholic abuse) were found (6). In our survey among the 178 smokers the patients affected with PD were 71 (40%), while among the 101 not smokers the PD patients were 26 (26%). According to data presented in literature these percentages resulted statistically significant and therefore smoking could be considered an important risk factor for PD and consequentially a lifestyle to evaluate during anamnestic work-up of PD patients (p = 0.024).

However the high rate of statistical association between smoke and PD did not explain how smoking habit may influence the pathogenesis of disease and the macroscopic alterations caused. In a study by *El Sakka (2006)* the prevalence of PD in patients with ED is 7.9%, with a

significant association between PD and other typical risk factors of ED such as obesity, age, smoking habit, and conditions like diabetes, hypercholesterolemia and psychological disorders (18).

In a study by *Mulhall et al. (2004)* the prevalence of patients with PD in a population screened for prostate cancer was 8.9% with coexistence of conditions such as blood hypertension and diabetes in the population with PD (19). In our sample among the 158 patients with blood hypertension 69 (44%) had PD, while among the 121 patients without blood hypertension the patients not affected with PD were 28 (23%); therefore the percentage of PD and blood hypertension patients is nearly twofold of the percentage of PD patients without blood hypertension (p < 0.001).

This result, as Mulhall's study reported, could show a very strong association between PD and blood hypertension. Blood hypertension could be considered an important risk factor for PD and consequentially a clinical parameter to evaluate during diagnostic work-up of PD patients. Blood hypertension and smoking are shown to be differently associated to PD, even though the etiological and pathophysiological factors of this association are unknown.

Our study was not an epidemiological prevalence study, although the percentage (34.7%) of PD patients in a series of consecutive outpatients during an year was a relevant data; this condition is still probably underestimated, as an autoptic study showed (20).

The analysis of VAS demonstrated that 67% of patients with PD had pain during erection: this not less important aspect showed how the disease may cause a very frequent painful symptomatology.

CONCLUSIONS

PD is more common than we might think. The social and cultural changes in Italian population, in primis the progressive use of treatment for ED, probably are going to determinate a higher prevalence of the disease in the future. According to our results smoking habit and blood hypertension are shown to be potential risk factors for PD; despite some studies diabetes would not be shown to be related with the onset of disease.

In the literature the prevalence of PD seems to be related to ageing; on the other hand, our results suggest that the age of disease onset could be not so advanced, therefore the presence of the disease should be evaluated also among young patients. Erectile dysfunction is frequently associated to the disease and it is often the reason why patients consult a physician as well as for the pain. Pain during erection, even though not so important in our sample, is widely diffuse among PD patients and influences their sexual and relational lives.

In our opinion this study has two biases, the small number of patients and the lack of information about the diabetic patients (type 1 or type 2, treated or untreated); these biases do not allow to make definitive conclusions about association between PD and its potential risk factors: further studies are necessary to confirm if smoking and blood hypertension have a causal relationship for determining the PD condition. The frequent association

showed between these pathologies and abuse conditions should lead the physician to evaluate also the possible sexual dysfunctions not revealed by the patients.

In a study of 2011, 11420 American over 18 years men were enrolled in an online interview about PD symptoms, previous diagnosis or treatment for PD.

The prevalence of the disease ranges from 0.5% (diagnosis of PD) to 13% (diagnosis, treatment and symptoms of PD), but the most interesting data is that among people who asked for a therapy, 74% did not obtain any treatment from the first physician and 92% did not obtain diagnosis of PD (1). Therefore a better understanding of the symptoms and signs of the disease are desirable, especially among general practitioners, to avoid to underestimate a pathology of high impact on the relational psychological life.

Smoking cessation and blood pressure control could be precautions to reduce the incidence and recurrence of PD in the general population.

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