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EVALUATION OF ASSOCIATION BETWEEN PEYRONIE DISEASE AND THE PRESENCE OF RISK FACTORS FOR ATHEROSCLEROSIS

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ABSTRACT

Introduction: Peyronie's disease (PD) is a tissue disorder acquired in the tunica albuginea (TA) of the penis and its pathophysiology is not completely understood. The disease is characterized by the development of a fibrous plaque which affects the inner layer of the corpus cavernosumTA. The estimated prevalence of PD is 3 to 9% and its incidence has increased in the last years.
Objective: To determine if atherosclerosis is associated with PD.
Methods: Case-control study. The sample consisted of a total of 56 patients who were treated at the Andrology Clinic of ISCMPA. The variables studied were collected from a questionnaire structured for this study. Laboratory tests and an ultrasound of the carotid were performed in the subjects.
Results: There were no significant associations of life habits with the disease. Very similar glycemic patterns, atherosclerosis and cardiovascular risk were found among cases and controls, with no evidence of a significant association.
Conclusion: The etiology of the disease remains unknown. Our study demonstrated that patients with PD do not have a higher risk of atherosclerosis and its associated risk factors. Future studies should be conducted in order to understand the disease and find ways of prevention and management.

INTRODUCTION

Peyronie's disease (PD) is a tissue disorder acquired in the tunica albuginea (TA) of the penis and its pathophysiology is not completely understood (Gholami *et al*., 2003; Vardi *et al*., 2009). The disease is characterized by the development of a fibrous plaque which affects the inner layer of the corpus cavernosum TA (Paez *et al*., 2007), restricting the elasticity and causing a curvature when erect (Devine *et al*., 1992; Cairoli *et al*., 1995). It is believed that the plaque appears from abnormal wound healing after trauma during coitus and can result in deformation of the erect penis, localized pain and erectile dysfunction (Gonzalez-Cadavid *et al*., 2004 and Devine *et al*., 1988), however, etiology and pathophysiology are not clear. Various etiological agents have been linked to the diseaseonset, such as venereal diseases, corpus cavernosum abscesses, atherosclerosis, diabetes mellitus, medications (eg, beta-blockers) and even autoimmune reactions (Cairoli *et al*., 1999). Clinically, the disease is characterized by a palpable induration, which subsequently leads to penile curvature when erect. Findings such as the difficulty of penetration due to excessive bending or penile flaccidity distal to the fibrotic plaque are common (Devine *et al*., 1997). In most patients the first symptom of PD is a painful erection (Langston *et al*., 2011), however, in some patients, the disease may be asymptomatic. The estimated prevalence of PD is 3 to 9% and its incidence has increased in recent years (Tanagho *et al*., 2010). The disease affects white middle-aged and elderly men (Rosenfeld *et al*., 2011), and 75% of patients have ages between 45 and 65 years (Langston *et al*., 2011).

Atherosclerosis and DP

Atherosclerosis is a disease with slow progression in which the lesions (plaques) develop in large and medium-sized arteries mainly affecting the intima of medium and large-caliber arteries (Sozeri *et al*., 2012; Gonzalez-Gay *et al*., 2012 and

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Lusis, 2000). Although the plaques may be large enough to jeopardize the blood flow, most complications are related to arterial occlusion due to the plaque erosion or rupture. The development of plaques predisposes to dynamic alterations of blood flow, such as branches and bends (Touyz *et al*., 2005). Atherosclerosis is also related to vascular fibrosis which involves accumulation of extracellular matrix (ECM) proteins (collagen and fibronectin) and contributes to structural remodeling and scar formation (Jacob *et al*., 2003). The biomechanical properties of vessels are widely dependent of the relative and absolute amount of collagen and elastin (Arribas *et al*., 2006); the imbalance between them (reduction of excess of collagen or elastin) on the vessel walls leads to vascular fibrosis and increased stiffness (19). The development of atherosclerosis initiatesby activation, dysfunction and structural changes of the endothelium leading to subendothelial retention of plasma lipid components, such as low density lipoprotein (LDL).

Thus, the lipids are susceptible to modification by oxygen radicals and enzymes (such as lipoxygenases and myeloperoxidase) triggering an inflammatory process (Taylor *et al*., 2003). The analysis of the arteries using ultrasound to identify and quantify vascular disease is a good choice for assessing the risk in these patients (http://www.who.int/whosis/database/). According to the World Health Organization (WHO), cardiovascular diseases account for approximately 30% of deaths worldwide, and in developed countries account for 80% of deaths (Kadioglu, 2002). Two-thirds of PD patients are susceptible to risk factors for heart disease, and as a consequence, long-term worsening of erectile function (Derby, 2000), which led us to investigate whether patients with atherosclerotic disease have a greater propensity to develop DP. Clinical and experimental studies have shown that risk factors for systemic vascular disease such as diabetes, lipid abnormalities in serum and hypertension have significant effects on erectile function (Alberti, 2006). The aims of this study were to investigate the association of cardiovascular risk as a risk factor for PD and evaluate if atherosclerosis is associated with PD.

MATERIALS AND METHODS

Study design and population

This is a case-control study with a convenience sample. We evaluated all patients treated between December 2013 and November 2014 at the Andrology clinic of Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), which agreed to participate, totalizing 28 cases and 28 controls. The cases were diagnosed with PD by physical examination (palpation), and controls were patients treated at the same clinic, matched for age. The Research Project was approved by the Ethics Committee of ISCMPA and Universidade Federal de Ciências da Saúde Porto Alegre (UFCSPA).

Clinical Evaluation

PD patients and control patients underwent a physical examination (palpation). The palpation was carried out in one or more plaques in the penile tunica albuginea, characterized by a hardened zone after the traction of the penis. A questionnaire (Appendix 1) containing age, marital status, disease history and lifestyle habits was also completed.

Inflammatory Pattern

Inflammatory pattern was based on the investigationof patient'sinflammatory disease and the C-reactive protein dosing.

Anthropometric variables

Body weight, height and waist circumference were measured during subject evaluation. For abdominal obesity classification we used the cutoff point of ≥ 90 cm for men (World Health Organization, 1998). Based on weight and height values we calculated the body mass index (BMI), obtainedby dividing the weight in kilograms by height in meters squared and classified according to criteria for adults and elderly of theWHOin underweight (<18.5 kg/m^2), normal weight (18.5 to 24.99 kg/m^2), overweight (25- 29.99 kg/m^2) and obesity (≥ 30 kg/m^2) (Sociedade Brasileira de Cardiologia, 2010).

Blood pressure

Blood pressure (BP) of the patients was measured at the study site with a standardized technique. After completion of the study questionnaire, the assessment was done in patients sated down, with legs uncrossed, feet flat on the floor, back reclined on the chair and relaxed. The arm was positioned at heart level, supported with the palm facing upward and the elbow slightly flexed (Wilson, 1998).

Laboratory tests

After collecting data from patients, blood sampleswere taken for laboratory tests. Patients were instructed to fast for 12 hours before exams. The following biochemical tests were performed: total cholesterol and fractions, triglycerides, fasting glucose, glycated hemoglobin and C-reactive protein. The values considered normal were: glucose 70 to 99 m/dL; cholesterol up to 200 mg/dL; triglyceridesup to 150 mg/dL; HDL above 40mg/dL for men and above 50 mg/dL for women; LDL up to 130 mg/dL; C-reactive protein less than 5.0 mg/L and glycated hemoglobin from 4 to 6%.

Calculation of Cardiovascular Risk by the Framingham Score

Considering the variables: age, total cholesterol, HDL cholesterol, blood pressure level, be or not diabetic and/or tobacco user, and calculationg the scores by the Framingham table, we calculate the percentage risk of mortality from cardiovascular disease in ten years (Nogueira, 2004).

Carotid ultrasound

All patients underwent an ultrasound of bilateral carotid for the investigation of presence or absence of plaque. The examinations were performed in the Center of Imaging Diagnostic of ISCMPA by radiologists. To perform the test, patients were positioned supine with the head turned slightly to the opposite examined side. The transverse cut of the common carotid artery was evaluated from the supraclavicular fossa, lateral to the sternocleidomastoid muscle (Nelson *et al*., 2008).

Statistical analysis

The normality of continuous variables was verified by the Shapiro-Wilk test. Univariate analysis of these variables with

groups was performed using the t test for independent samples and data is shown as mean and standard deviation (SD). Nominal variables were displayed by frequency and percentage and the univariate associations analyzed by Pearson's chi-squared test or Fisher's exact test when necessary. The power found was 73.69%. The significance adopted was 5% and the software used for analysis was SPSS version 22.

RESULTS

The average age of individuals affected by DP was 60.68 ± 7.08 years. In individuals without the disease the mean age was 61.46 ± 7.61 years. In both groups, the majority of men were married (70.4% in the cases and 75.0% in controls). The average time of knowledge of the disease was 3.5 ± 2.37 years. In six patients (32.2%) were found two to three plaques, and nine individuals (32.1%) reported feeling pain on the plaque.

As for location, in 13 subjects (48.1%) the plaque was located on the dorsal position and in seven (25.9%) in the left lateral position. The lateral curvature was observed in 13 men (46.5%), followed by upward bending, observed in 9 subjects (32.1%) and the combination lateral and upward bending in 6 subjects (21.4%). The average plaque size was 1.90 ± 1.32 cm, the largest with 4 cm. We do not found significant associations between lifestyle and PD, as shown in Table 1. Most men affected by the PD do not consume alcohol (67.9%) and the majority of both, cases and controls, are not a smoker. According to Table 2, regarding the use of statins, there are no significant associations, since most of cases and controls do not use statins. Very similar glycemic patternswere found, aside of similar patterns of atherosclerosis and cardiovascular risk among cases and controls, with no evidence of significant association, as shown in Table 3. Individuals with PD showed higher rates of total cholesterol, HDL and LDL and lower triglycerides rates. However, these differences for the controls were not statistically significant, as shown in Table 4.

Table 1. Association with life habits

	Cases		Controls		p-values
	n	%	n	%	
Alcoholism					0,177
Alcohol consumption on weekends	9	32,1	15	53,6	
No alcohol consumption	19	67,9	13	46,4	
Tobacco Use					0,422
Yes	5	17,9	2	7,1	
No	23	82,1	26	92,9	

Table 2. Statins use

	Cases		Controls		p-value
	n	%	n	%	
Statins use					0,581
Yes	9	32,1	12	42,9	
No	19	67,9	16	57,1	

Table 3. Glicemic pattern analysis, cardiovascular risk and inflammatory pattern

	Cases		Controls		p-valor
	n	%	n	%	
Glycemic pattern					
Glucose					1,000
Normal	18	78,3	10	76,9	
Abnormal	5	21,7	3	23,1	
Glycated hemoglobin					0,394
Normal	19	86,4	10	71,4	
Abnormal	3	13,6	4	28,6	
Cardiovascular risk					
Presence of plaque in the carotid					0,338
No	17	73,9	8	53,3	
Yes	6	26,1	7	46,7	
Framingham Risk					0,246
Low risk	6	26,1	1	7,1	
Moderate risk	16	69,6	11	78,6	
High risk	1	4,3	2	14,3	
BMI					1,000
Normal	8	28,6	8	28,6	
Overweight	20	71,4	20	71,4	
Diabetes mellitus					0,572
Yes	8	28,6	11	39,3	
No	20	71,4	17	60,7	
Hypertension					1,000
Yes	12	42,9	12	42,9	
No	16	57,1	16	57,1	
Inflammatory pattern					
Inflammatory disease					0,669
Yes	4	14,3	2	7,1	
No	24	85,7	26	92,9	
C reactive Protein					0,687
Normal	17	77,3	8	66,7	
Abnormal	5	22,7	4	33,7	

Table 4. Lipidic pattern

	Cases		Controls		p-value
	Mean	SD	Mean	SD	
Triglycerides	129,74	59,55	154,00	102,70	0,360
Cholesterol	181,13	42,13	180,14	27,89	0,750
HDL	45,70	11,98	44,71	6,54	0,465
LDL	109,78	39,67	100,85	23,56	0,431

DISCUSSION

During the natural history of the disease, a year after diagnosis 40% of men report unchanged penile curvature, around 45% reported increased curvature and less than 15% reported spontaneous resolution of curvature (Nelson, 2008). Among the findings, we noticed the prevalence of lateral curvature then the dorsal curvature, corroborating previous data from the literature (Paez, 2007). The PD has no defined etiology and very little is understood about its pathophysiology. PD is usually treated at its chronic phase when the fibrosis is already installed. The installation phase of the disease and its acute phase are due to an inflammatory reaction, which is still little explored. The albugineal trauma and delamination of the longitudinal and transverse sections of the TA is the most accepted hypothesis as pathophysiology of PD. However, it lacks adequate scientific research. Our research hypothesis is that mechanisms similar to the genesis of the formation of a theroma may contribute to the onset of PD. Maybe, the PD start is related to a change in the sinusoidal endothelium near albuginea, initiating the acute inflammation process, progress to chronic inflammation and the consequent formation of fibrotic and stiff plaque. Patients with atherosclerosis would possess apropitious phenotype for developing inflammation in blood vessels. The endothelial alteration caused by penile trauma or sheer stress in arteries predisposed to atherosclerosis could be a common denominator for the development of both diseases. The penile trauma during intercourse would be a risk factor for triggering the plaque in a patient predisposed to inflammation on the subalbugineous sinusoidal space. We found no differences between the groups in terms of cardiovascular risk. These findings may be related to the study's limitations, such as small groups and the lack of criteria for evaluating the severity of atherosclerosis in the carotid ultrasound.

Conclusion

The disease etiology remains unknown. Even after 250 years since the first description of the disease we are not able to say for sure what are its causes and origin, being trauma the most accepted hypothesis. This study demonstrated that PD patients apparently do not have higher risk of atherosclerosis and its associated risk factors. Future studies with larger samples on the etiology of PD should be performed so we can understand it and therefore find ways of prevention and management.

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