Original Article

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The Relationship Between Peyronie's Disease and Serum Parathormone and Ionized Calcium Levels

Muhammed Masum Canat*, Mehmet Sahin**

*University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital, Clinic of Endocrinology and Metabolism, Istanbul, Turkey

**University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Urology, Istanbul, Turkey

Abstract

Aim: Peyronie's disease's (PD) etiology is still unclear. Many factors that may cause the disease are being investigated. The objective of our study was to clarify the effect of serum parathormone and ionized calcium levels on the pathophysiology of PD.

Methods: The study was designed as a cross-sectional study. Demographic data, physical examinations, laboratory tests, and medical and sexual histories of patients between January 2017 and June 2020 were analyzed. Patients were divided into PD and control groups.

Results: By measuring serum calcium and parathormone levels of patients, we analyzed 38 PD and 40 control group patients and revealed that i) parathormone (p=0.321) and ionized calcium (p=0.286) levels are not related to PD, and ii) cardiovascular disease (p=0.037), diabetes mellitus (p=0.0001), and hypertension (p=0.001) are significantly associated with PD, whereas smoking, alcohol consumption, and dyslipidemia status are not.

Conclusion: The study shows that there is no relationship between serum parathormone and ionized calcium levels and the etiology of PD.

Keywords: Parathormone, Ionized calcium, Peyronie's disease

Introduction

Peyronie's disease (PD) springs from progressive fibrosis of the tunica albuginea that causes curvature or other deformities of the penis. It usually presents with a painful palpable plaque, more often on the dorsal surface of the penis and penile curvature (1). Prevalence rates range from 0.4% to 20.3% and usually increase with age (2). Although the precise etiology of PD remains obscure, the commonly accepted theory is recurrent microvascular injury or trauma to the tunica albuginea. Furthermore, diabetes mellitus (DM), hypertension, obesity, smoking, alcohol use, and dyslipidemia have been associated with PD in some studies (3). Histological findings resembling PD were observed when blood came into contact with the tunica albuginea of rats. In the tissue in contact with blood, the expression of transforming growth factor-β was increased. This finding suggests that changes in extracellular matrix remodeling are related to the pathophysiology of PD (4).

Parathyroid hormone (PTH) is a protein hormone released by the parathyroid glands and is one of several hormones that regulate ionized calcium levels by stimulating osteoclast activity in the bone matrix when blood ionized calcium levels decrease. The PTH level increases calcification in different organs by various mechanisms (5-7). Although the relationship between PTH and transforming growth factors is not fully known, its relationship with the TGF-β receptor has been shown (8). In a study examining fibrosis in the proximal tubules of patients with chronic kidney diseases, it was found that connective tissue growth factor expression in the kidney was increased in those administered PTH, and they proved that it has a noteworthy role in the pathophysiology of fibrosis (9). In addition, when mineralized Peyronie's plaques were examined with energy dispersive X-ray and micro-X-ray fluorescent spectroscopic maps, calcium densities were found to be similar to those of bone (10). By considering all this evidence, we hypothesize that

Address for Correspondence: Mehmet Sahin, University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinic of Urology, Istanbul, Turkey
Phone: +90 532 290 35 87 E-mail: mehmetsahinmd@gmail.com ORCID: orcid.org/0000-0001-6712-7207
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there might be a relationship between serum PTH levels and PD.

In our study, we aimed to investigate whether PTH is effective in the etiology of PD because of its effect on serum calcium levels and possible inflammatory processes.

Methods

Compliance with Ethical Standards

University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinical Research Ethics Committee permission dated 18.03.2023 and numbered 2023.03.107 was obtained for this study.

Study Design

In this cross-sectional study, we performed retrospective analyses of patients who applied to our urology outpatient clinic due to PD between January 2017 and June 2020. Thirty-eight of 363 PD patients whose serum PTH and ionized calcium levels were measured for any reason were included in our study. As the control group, 40 patients who complained of a reason other than PD and whose serum PTH and ionized calcium levels were measured were randomly included in our study.

Patient Evaluation

Demographic data and the medical and sexual histories of the patients were obtained. This information includes several components such as smoking behavior, alcohol consumption, painful erection, degree and direction of penile curvature, ability to vaginal penetration, penile plaques, medications, and comorbidities. The International Index of Erectile Function Questionnaire (IIEF-5) was used to define the erection status of patients (11).

Disease-specific symptoms and the presence of penile fibrotic plaques (observed during the physical examination) help define the diagnosis of PD. By autophotography during erection or physical examination after intracavernosal alprostadil injection, the degree and direction of the concomitant penile curvature were diagnosed. The localization and size of the penile plaques were measured by penile ultrasound performed without intracavernosal injection.

Our sample excludes patients taking hypercalcemia medication. The PTH and serum calcium levels of 363 patients were enrolled retrospectively in the hospital information system. Three hundred and twenty-five of those patients had no serum PTH or ionized calcium level measurements, which made them inconvenient for our analyses, and they were excluded from our sample. The data of the control group was also retrospectively obtained from the hospital information system. Demographic data, comorbidities, smoking, and alcohol consumption were retrospectively obtained from patient files.

A blood test was obtained after 10-12 hours of fasting. The normal ranges for PTH and serum calcium were 10-55 pg/mL and 8.8-10.2 mg/dL, respectively. PTH levels were measured using a Cobas e601 autoanalyzer and a Roche intact PTH measurement kit (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

We performed analyses using the SPSS (Statistical Package Programme for Social Sciences 22.0) program. The distribution of continuous variables [age, body mass index (BMI), IIEF-5 scores, PTH, plasma calcium level] were assessed by performing the Kolmogorov-Smirnov test. To compare the groups, the t-test was used for BMI and plasma calcium level. The Mann-Whitney U test was performed for PTH, IIEF-5 scores, and age. To compare variables including smoking, alcohol consumption, and the presence of comorbidities such as DM, HT, dyslipidemia, and cardiovascular disease (CVD), a chi-square test was used. A p-value lower than 0.05 indicates statistical significance.

Results

We analyzed the data of 78 patients, 38 of whom belonged to the PD group, and the remaining 40 belonged to the control group. Table 1 shows the general characteristics of the two groups.

On the one hand, the difference between the PD group and the control group was not statistically significant for the variables age (p=0.217), body mass index (BMI) (p=0.438), smoking (p=0.286), and alcohol consumption (p=0.546). On the other hand, the differences between the PD and control groups revealed that DM (p=0.0001), hypertension (HT) (p=0.001), and CVD (p=0.037) rates were significantly higher in the PD group.

Table 2 and Figure 1 demonstrate the results of laboratory assessments. First, the mean PTH values of the PD and control groups were 31.92±10.6 pg/mL and 34.78±12.3 pg/mL, respectively, while the difference between these values was not statistically significant (p=0.321). Second, the mean serum calcium values of the PD and control groups were 9.56±0.56 mg/dL and 9.13±0.48 while the difference between these values was not statistically significant (p=0.286). Third, the mean IIEF-5 scores of the PD group and the control group were respectively 20.8±4.4 and 22.1±5.6, while the difference between these values was not statistically significant (p=0.536). Finally, the dyslipidemia difference between these groups was not statistically significant (p=0.376).

Discussion

Because of increased fibrosis in the tunica albuginea and ossification of plaques in PD, we believe that PTH may have a role in the pathophysiology of both mechanisms

Table 1. Characteristics of patients			
	Patients with Peyronie's disease n=38	**Controls n=40**	**p-value**
Age, years, mean ± SD	50.96±10.6 (28-73)	47.37±9.0 (25-76)	0.217*
BMI (kg/m^2), mean ± SD	28.65±4.7	27.92±4.3	0.438**
Smoking, no. (%)	13 (34.2%)	17 (42.5%)	0.286***
Alcohol, no. (%)	6 (15.7%)	5 (12.5%)	0.546***
IIEF-5 score	20.8 ± 4.4	22.1 ± 5.6	0.536*
Comorbidities			
Diabetes mellitus, no. (%)	10 (26.3%)	3 (7.5%)	0.0001***
Hypertension, no. (%)	12 (31.5%)	5 (12.5%)	0.001***
Dyslipidemia, no. (%)	4 (10.5%)	6 (15.0%)	0.376***
Cardiovascular disease, no. (%)	4 (10.5%)	1 (2.5%)	0.037***
Penile curvature, degrees, mean ± SD	35.9±18.6		
Plaque area, cm^2, mean ± SD	4.3±1.9		
SD: Standard deviation; BMI: Body mass index; *Mann-Whitney U; **T-test; ***Chi-square			

Table 2. Results of laboratory assessments			
Parameters (Reference range)	**Patients with Peyronie's disease n=38**	**Controls n=40**	**p-value**
PTH, pg/mL (10-55)	31.92±10.6 (18.75-42.21)	34.78±12.3 (12.23-51.12)	0.321*
Plasma calcium, mg/dL (8.8-10.2)	9.56±0.56 (8.58-10.0)	9.13±0.48 (8.62-9.87)	0.286**
PTH: Parathyroid hormone; *Mann-Whitney U; **T-test			

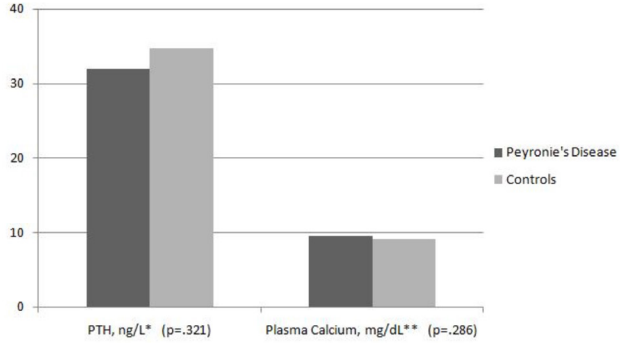

Figure 1. Results of laboratory assessments
PTH: Parathyroid hormone

by upregulating serum calcium levels and effects on connective tissue fibrosis.

TGF-β_1 and TGF-β_2 regulate tissue repair and inflammation through various pathways. After repetitive microtrauma of the tunica albuginea, inflammation occurs in the tissues. It is thought that increasing the amount of acetylated protein in inflamed tissues causes fibrosis by increasing TGF-β_2 expression (12). The relationship between PTH and TGF-β_2 can be demonstrated by the PTH type 1 receptor-transforming growth factor β type 2 receptor complex (8). Therefore, we based our initial hypothesis on the impact of parathormone on tissue inflammation and fibrosis.

Metabolic syndrome is diagnosed by meeting three of the following criteria: abdominal obesity, high blood pressure, high triglyceride, low high-density lipoprotein (HDL), and high blood sugar (13). A positive correlation was found between PTH levels and metabolic syndrome in morbidly obese and elderly patients (14). The link between increased PTH and metabolic syndrome may be explained by correlations with components one by one, such as HT (15), hyperglycemia (16), and low HDL levels (17). An association between PTH and metabolic syndrome has long been predicted. However, the depiction of interactions between metabolic syndrome and primary hyperparathyroidism is hampered by many factors (18). Given the possible association between PD, DM, and CVD, these comorbidities should be screened for in all at-risk PD patients (19). Based on this information, metabolic syndrome has a relationship with PD and PTH. Therefore, we built our second hypothesis on the possible role of PTH in PD. Although we found a significant association between HT, DM, CVD, and PD, we report no significant association between PTH and PD.

DM can cause systemic involvement, such as neuropathy, nephropathy, vasculopathy, and retinopathy. In

addition, DM has negative effects on wound healing (20). Myofibroblasts play a significant role not only in wound healing but also in collagen production. When wound healing is terminated, myofibroblasts undergo apoptosis. Abnormal wound healing may occur if this mechanism does not work. When myofibroblasts are activated due to paracrime interactions, they may contribute to the formation of Peyronie's plaques (21). Studies have shown that high blood glucose levels increase collagen synthesis (22). Moreover, a correlation was shown between the severity of PD and DM (23). In parallel with the literature, we found DM at a higher rate in the PD group.

Hypertension is a dimension of metabolic syndrome. However, mixed outcomes have been reported in recent studies regarding the relationship between HT and PD. While some studies did not show any relationship between HT and PD (24,25), some studies reported a significant relationship (26). We contributed to these mixed outcomes by finding a higher HT in the PD group than in the control group (p=0.001).

CVD is thought to cause weakness in vessel walls and facilitate vessel damage during sexual intercourse. Furthermore, according to previous studies, CVD is associated with PD (27,28). Analogously, we found higher CVD rates in the PD group.

Men with PD have higher rates of HT, DM, and smoking than men without PD (29). The alcohol consumption rate in Dupuytren's disease, which is frequently associated with PD, is higher than that in the normal population (30). Contrary to popular belief, we found no significant difference between smoking and alcohol consumption between patients with and without PD.

Despite many studies, the pathophysiology of PD is still not clearly known. In a study on the status of serum trace elements in PD, serum Mn, Cu, Zn, and Fe levels were reported to be significantly lower in the PD component (31). Calcium is an essential mineral with important physiological functions that cannot be synthesized in the body. PTH plays a critical role in the regulation of serum calcium levels through its effect on bone turnover. Calcium is the main factor in the fibrocalcification of plaques during plaque formation (32). However, we could not detect a significant relationship between serum calcium levels and PD.

Study Limitations

There are several limitations to our study. First, as we performed a retrospective study using data belonging to some patients obtained at a single center, our outcomes may not fully reflect the patient population in other centers. Second, in our study, serum vitamin D levels, which may affect ionized calcium levels and cavernosal TGF-β levels, were not evaluated. Despite these limitations, although it is a small-scale study, it can be considered a pioneering study analyzing the relationship between PTH and PD.

Conclusion

Many factors that may be risk factors for PD are still being investigated. The present study shows that there is no relationship between serum parathormone and ionized calcium levels and the etiology of PD.

Ethics

Ethics Committee Approval: Ethical permission for the study was obtained from the University of Health Sciences Turkey, Basaksehir Cam and Sakura City Hospital, Clinical Research Ethics Committee (dated: 18.03.2023, and numbered: 2023.03.107).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.M.C., M.S., Design: M.M.C., M.S., Data Collection or Processing: M.M.C., M.S., Analysis or Interpretation: M.M.C., M.S., Literature Search: M.M.C., M.S., Writing: M.M.C., M.S.

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