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Original Article

Is Peyronie's an IgG4-related disease?

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Abstract

Objective: We believe that IgG4 may have a role in the pathogenesis of Peyronie's disease (PD), and this role could be particularly beneficial for developing new strategies; therefore, we aimed to investigate the role of IgG4 in PD.

Methods: This study included 3 groups with a total of 139 subjects: (I) PD group (n=61), (II) control group (n=48), and (III) benign prostatic hyperplasia (BPH) group (n=30). IgG4 measurement was performed using the enzyme-linked immunosorbent assay. Plaque size, penile curvature, and the presence of concomitant impotence were evaluated in the PD group. Impotence was assessed based on the International Index of Erectile Function (IIEF).

Results: A significant difference was observed between the PD and control groups and between the PD and BPH groups with regard to IgG4 levels, while no significant difference was found between the BPH and control groups (p=0.0001, p=0.002, and p=0.07, respectively). The IgG4 levels were significantly higher in the PD than in the other groups. The cutoff value determined between the groups was 87.5, 82, and 31.5, respectively. Mean plaque size was 2.0±1.01 cm, and a significant relationship was found between plaque size and IgG4 concentration (p=0.02). Mean penile curvature was 35.6±25.1°, and a significant relationship was found between penile curvature of >60° and IgG4 concentration (p=0.001). Mean IIEF score was 19 (range, 7-25). Moreover, no significant relationship was found between erectile dysfunction and IgG4 concentration. Penile pain was present in 24 (39.3%) patients with PD.

Conclusion: The IgG4 levels were significantly increased in patients with PD, which implies that IgG4 may have a role in the pathogenesis of PD. This finding could be particularly beneficial for developing new strategies. Future studies with larger patient series are needed to substantiate our findings.

Keywords: Etiology of Peyronie disease, IgG4, IgG4 related disease, Peyronie disease

Introduction

Peyronie's disease (PD) is a chronic disease of the tunica albuginea of the corpus cavernosum, characterized by excessive fibrosis and plaque formation, affecting 3%-13% of men (1). Although the exact etiology of PD remains unknown, the transforming growth factor beta 1 (TGF-ß1) is believed to play a role in the induction of collagen production by fibroblasts/myofibroblasts, thereby leading to dominant expression of type III collagen, which is often seen in inflammatory pathologies in the tunica albuginea, which is characterized by type I collagen expression (2). As a result, morphological problems, such as curvature, shortening, contraction, hourglass deformity, and notch defect, as well as functional problems, such as erectile dysfunction (ED), may occur. After PD begins to occur, it is divided into two phases: acute and chronic or stable phase. The most obvious symptom in the acute phase is pain during erection. An increase in the degree of curvature is observed. If the disease is found to remain unchanged for three months clinically, the patient should be considered to be in the stable phase. In some patients, spontaneous regression can be observed within the first year after diagnosis, while approximately 45% remain stable and 40% show progression (2).

Elevated serum IgG4 concentrations and lymphoplasmacytic infiltrate with IgG4-positive plasma cells are the hallmark features of IgG4-related disease (IgG4-RD). IgG4-RDs manifest dense lymphoplasmacytic infiltrations with a predominance of IgG4-positive plasma cells in the affected tissue, usually accompanied by some degree of fibrosis and often by obliterative phlebitis and an increased number of eosinophils. Although the pathogenesis causing these manifestations remains unclear, IgG4 expression is believed to be induced by various species of pathogens, thereby preventing innate immunity and ultimately leading to persistent inflammation (3). Moreover, when inflammation becomes chronic, it may result in fibrosis (4).

This study aimed to investigate the relationship between PD and IgG4. The role of IgG4 in PD pathogenesis has been investigated. There is very little data in the literature on this subject.

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Methods

The study protocol was approved by the Sanko University local ethics committee (2019/05-03). Written informed consent was obtained from the patients who participated in this study. This study was conducted between April 2015 and December 2019. This study included 3 groups with a total of 139 subjects: (I) PD group (n=61), (II) control group (n=48), and (III) benign prostatic hyperplasia (BPH) group (n=30). This study started with 89 patients with PD. It was found that 9 of them had diabetes mellitus (DM), 6 had hypertension (HT), 4 had coronary artery disease (CAD), 6 had rheumatological diseases and chronic inflammation, and 3 had cancer. These patients were excluded from the study. This study was completed with 61 patients with PD. The BPH group started work with a total of 52 patients. Among these, 6 patients had DM, 5 had HT, 2 had CAD, 6 had different chronic diseases, and 3 had acute infectious diseases. These patients were excluded from the study. This study was completed with 30 patients. Fasting serum samples were obtained from each participant and were stored at -80°C. IgG4 measurement was performed using the enzyme-linked immunosorbent assay. PD was diagnosed based on patient history and physical examination findings. On physical examination, presence of plaques, plaque size, and the degree of penile curvature were recorded. Differential diagnosis was established using the PD questionnaire (5). The control group included voluntary healthy subjects with no known diseases and no active drug use. The BPH group consisted of voluntary patients with BPH and with no systemic diseases who had been recently diagnosed and initiated on drug therapy in our urology outpatient clinic. In the PD group, plaque size, penile curvature, and the presence of concomitant impotence were recorded for each patient. Additionally, plaque localization was assessed (Table 1). The relationship between plaque size and IgG4 was evaluated by comparing patients with serum IgG4 level above and below the upper limit (135 ng/L). Impotence was assessed based on the International Index of Erectile Function (IIEF), and the patients were classified into 3 categories based on the severity of ED on a scale of 1-25: (i) moderate-severe ED (1-11), (ii) mild ED (12-21), and (iii) no ED (22-25).

Table 1. Clinical features of patients with Peyronie's disease.

	Group 1 (n=61)
Plaque size (cm)	2.0±1.01
Plaque localization (n)	
Dorsal/dorsolateral	19 (31.1%)
Lateral (right/left)	10 (16.4%)
Ventral/ventrolateral	21 (34.4%)
Septum	11 (18.1%)
Duration of PD (month)	14.5±7.1
Curvature angle (º)	35.6±25.1
<60º (n)	41 (67.2%)
>60º (n)	20 (32.8%)
Pain	
yes	24 (39.3%)
no	37 (60.7%)
IIEF score	19 (725)

IIEF: International Index of Erectile Function; PD: Peyronie's disease.

Main Points

- Peyronie's disease may be IgG4 related disease.
- Treatment may give better results in patients with IgG4 positive.
- In some patients with PD, IgG4 may be responsible for the etiology.

Statistical analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences software for Windows version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). The variables were investigated using visual and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether they were normally distributed. Descriptive analyses were presented using tables of frequencies for the ordinal variables and using medians and interquartile range for the non-normally distributed and ordinal variables. Because the fasting IgG4 levels were not normally distributed, nonparametric tests were conducted to compare these parameters, as well as to compare the ordinal variables. The Mann-Whitney U test was used to compare the fasting IgG4 levels between the groups. The Kruskal-Wallis rank test or the Fisher exact test, where appropriate, was used to compare the proportions in different groups. P-value of less than 0.05 was considered to show a statistically significant result. Cutoff points were found based on the Youden index (Youden index=sensitivity+specificity-1 point that makes the equation maximum).

Results

The mean duration of PD was 14.5±7.1 months. There was no significant relationship between the duration of PD and IgG4 levels. No significant difference was observed among the 3 groups with regard to patient age (p=0.397, p=0.08, and p=0.12, respectively; Table 2) and body mass index (p=0.865). However, a significant difference was observed between the PD and control groups and between the PD and BPH groups with regard to IgG4 levels, while no significant difference was found between the control and BPH groups (p=0.0001, p=0.002, and p=0.07, respectively; Figure 1). Although the IgG4 levels were higher in the BPH group than in the control group, no significant difference was found. The cutoff value determined between the patient and control groups was found to be 87.50 (Figure 2). The cutoff value determined between the patient and BPH groups was found to be 82 (Figure 3). The cutoff value determined between BPH and control groups was found to be 31.5 (Figure 4). The mean plaque size was 2.0±1.01 cm, and the plaques were mostly localized in the dorsal, dorsolateral, ventral, ventrolateral, lateral, and septal aspects of the penis. A significant relationship was detected between plaque size and IgG4 concentration (p=0.02). Mean penile curvature was 35.6±25.1°, and a significant relationship was found between penile curvature of >60° and IgG4 concentration (p=0.001). In terms of impotence, mean IIEF score was 19 (range, 7-25). Moreover, no significant relationship was found between ED and IgG4 concentration. Penile pain was present in 24 (39.3%) patients with PD, while no pain was reported by 37 (60.7%) patients.

Table 2. Results between the groups.

	Peyronie's disease (n=61)	Healthy control (n=48)	Benign prostatic hypertrophy (n=30)	p
Age (year)	52±13.3	49±13.1	55±8.7	0.397[a]
IgG4 (mg/dL)	101.5 (15-235)	30.5 (4-114)	61 (14-140)	0.0001[b]
BMI (kg/m^2)	24.37±3.5	25.3±2.8	26.6±3.1	0.865[c]

[a]Kruskal-Wallis rank sum test. Between groups I and II, 0.397; between groups I and III, 0.08; and between groups II and III, 0.12.
[b]Mann-Whitney U test. Between groups I and II, 0.0001; between groups I and III, 0.002; and between groups II and III, 0.07.
[c]Mann-Whitney U test. Between groups I and II, 0.865; between groups I and III, 0.526; and between groups II and III, 0.785.
BMI: body mass index.

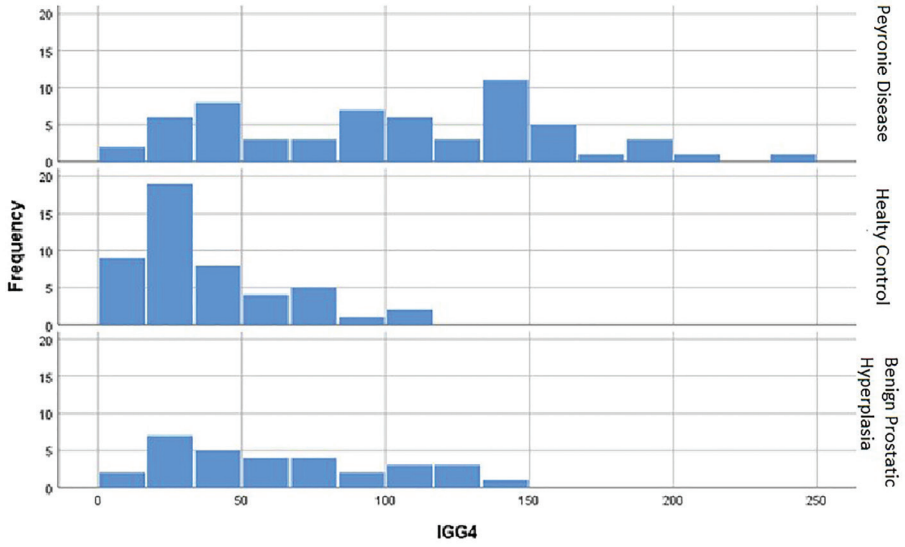

Figure 1. Distribution of IgG4 levels between the groups.

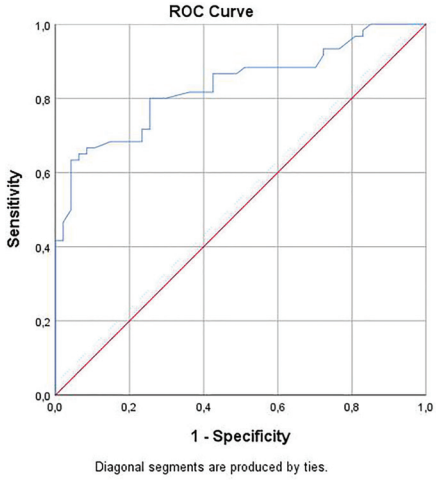

Figure 2. Patient and control group ROC analysis (cut-off value: 87.50). The area under the curve for IgG4 is 0.834 (95% CI; 0.758-0.909).

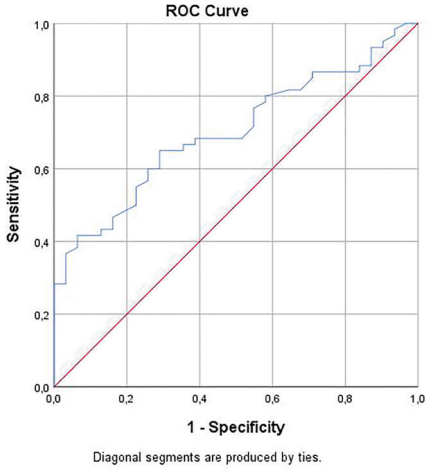

Figure 3. Patient and BPH group ROC analysis (cut-off value: 82). The area under the curve for IgG4 is 0.719 (95% CI; 0.595-0.807).

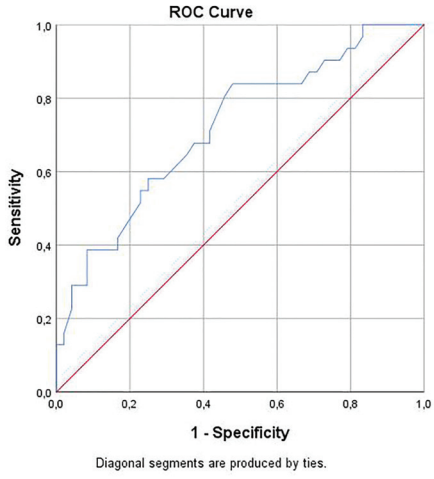

Figure 4. BPH and Control group ROC analysis (cut-off value: 31.5). The area under the curve for IgG4 is 0.701 (95% CI; 0.595-0.807).

Discussion

The results indicated that the IgG4 levels were higher in the PD group than the control group. Additionally, a significant relationship was found between plaque size, penile curvature, and IgG4 concentration.

Although there have been numerous studies investigating the pathophysiological mechanisms in PD, the exact mechanism of PD remains unknown. Lucattelli et al. (6) induced a rat model of spontaneous PD and reported that hypoxia-inducible factor-1 (HIF-1) and HIF-1 target genes may play an important role in the pathogenesis of PD. El-Sakka et al. (8) suggested that microtrauma induces TGF-β1 expression, thereby leading to inflammation and fibrosis, ultimately resulting in typical manifestations of PD, including plaque formation and penile curvature (7). Similarly, Zimmerman et al. (9) found that serum TGF-β1 levels were significantly elevated, and the tumor necrosis factor-α and interleukin-6 (IL-6) levels were significantly decreased in patients with PD when compared with control subjects. Another study reported that nitric oxide synthase was reduced by reactive oxygen species (10). In a previous systematic review, Ventimiglia et al. (11) found a significant relationship between PD and autoimmune diseases and also suggested that there was a significant relationship between PD and human leukocyte antigens, and hence, a relationship between PD and autoimmune diseases. Additionally, recent genetic studies have also indicated that the Wnt Family Member 2 (WNT2) locus may play a role in increased susceptibility to PD (12).

Accumulating evidence suggests that there are numerous immune-mediated mechanisms responsible for fibro-inflammatory processes in IgG4-RD. Moreover, autoimmune and infectious agents may act as potential immunological triggers of the disease. Various ILs, including IL-4, IL-5, IL-10, and IL-13, and transforming growth factor β (TGF-β) are overexpressed in IgG4-RD as a result of the activation of T-helper 2 (Th2) cells and regulatory T (Treg) cells. These cytokines lead to increased eosinophilia and enhanced production of both IgG4 and IgE and also contribute to the progression of fibrosis, which is the hallmark of IgG4-RD. Massive infiltration of inflammatory cells results in organ injury. Additionally, epithelial injury arises from tissue inflammation and immune complex formation (13). Yamamoto et al. (4) suggested that the pathogenesis of IgG4-RD is characterized by Th2-cell-dominant immune responses and abundant infiltration of Treg cells, which produce IL-10, into the organs involved. The authors also noted that IgG4-RD is also predominantly associated with a Th2-cell cytokine profile and that Treg cells and TGF-β produced by IL-10 are associated with elevated serum IgG4 levels and fibrosis (4). Taken together, these findings implicate that there are shared TGF-β-mediated mechanisms between PD and IgG4-RD. To our knowledge, there has been no study investigating the relationship between IgG4-RD and PD, and there are several case reports documenting elevated IgG4 level in cases of Zoon balanitis (14). In this study, IgG4 levels were significantly higher in patients with PD than in the control subjects, with 22 (36%) of the patients with PD having an IgG4 level above the upper limit (235 mg/dL) (range, 135-235). In contrast, a significant relationship was found between elevated IgG4 levels and plaque size and penile curvature, which could provide useful information regarding the severity of fibrosis in patients with elevated IgG4 levels.

In our study, the IgG4 levels were insignificantly higher in the other patient group (BPH group) when compared with the control group. To the best of our knowledge, the IgG4 levels have not been evaluated in patients with BPH. Nonetheless, there are several studies reporting on IgG4-related prostatitis in which the patients were detected with serious lower urinary tract symptoms, normal prostate-specific antigen levels, and elevated IgG4 levels. Moreover, the patients were also detected with lymphoplasmacytic infiltration, storiform fibrosis, and diffuse IgG4-positive plasma cells in immunohistochemical examination (15-17). In this study, the IgG4 levels were significantly higher in the patients with PD when compared with those with BPH.

Since this study had a small patient population, no immunohistochemical analysis of tissues was performed, and no information was provided regarding the long-term follow-up and treatment processes of the patients.

In conclusion, we believe that IgG4 may have a role in the pathogenesis of PD, and this role could be particularly beneficial for developing new strategies. Additionally, we suggest that IgG4 should be considered in idiopathic patients. Future studies with larger patient series are needed to substantiate our findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Sanko University (Approval Date: 2019; Approval Number: 2019/05-03).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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Conflict of Interest: The authors have no conflict of interest to declare.

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