Diagnostic Value of Plasma Pentraxin3- Level For Diagnosis of Erectile Dysfunction

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Purpose: Erectile dysfunction (ED) is a sexual dysfunction described as the inability to develop or maintain an erection of the penis adequate for sexual intercourse, and its prevalence increases with age. Seen as a common sexual disorder worldwide, organic causes are the underlying reason for 80 percent of ED cases, with the most characteristic pathology responsible for organic ED being atherosclerosis. This study investigates the diagnostic value of plasma PTX-3 levels in arterial ED.

Materials and Methods: This study included a total of 45 patients who were admitted to the urology and cardiology outpatient clinics of the Medical Faculty of Canakkale Onsekiz Mart University (COMU) and consented to participate in this study. Patients were categorized into three equal groups in number: (1) patients with ED diagnosed with coronary artery disease (CAD) (15 patients in total); (2) patients with ED not having coronary artery disease or any other equivalent diseases (diabetes mellitus, hypertension and hyperlipidemia) (15 patients in total); and (3) ordinary patients with no ED (15 patients in total). An interview was conducted at the andrology polyclinic with each patient in order to ascertain detailed information on their medical and sexual history and on demographic characteristics. All patients were also administered the International Index of Erectile Function (IIEF) questionnaire.

Result: The findings from this study investigating the diagnostic value of plasma PTX-3 levels in ED were statistically significant for two comparisons: the differences between the peripheral blood and cavernous blood values of the patient groups (group 1 and 2) and the control group (group 3), and the differences between the peripheral blood and cavernous blood values of group 2 (patients with ED who do not have CAD) and the control group (group 3).

Conclusion: As PTX-3 is more specific than the formerly recognized biochemical markers in endothelial dysfunction, it can be used in the diagnosis of vascular originated ED.

Keywords: atherosclerosis; coronary artery disease; erectile dysfunction; pentraxin-3 (PTX-3); sexual function.

INTRODUCTION

Erectile dysfunction (ED) is a sexual disorder involving the inability to have an erection for the purpose of engaging in sexual intercourse and/or the inability to maintain an erection for the same purpose[1,2]. ED increases with age and is a widespread health problem throughout the world[3]. The etiology of ED includes organic (vascular, neurogenic, hormonal, cavernosal) and psychological reasons[1,4,5].

Organic causes are responsible for approximately 80% of ED cases, and among these causes, atherosclerotic disease of the penile arteries ranks first[6]. In studies conducted over the last twenty years, disorders of endothelial functions have been shown to be the main cause behind the development of complications related to atherosclerotic plaques[7,8]. Smoking, hypertension (HT), diabetes mellitus (DM), hypercholesterolemia, age, obesity and sedentary lifestyle are the biggest risk factors for ED and also serve as common risk factors associated with atherosclerosis[9,10]. For this reason, ED and vascular diseases are believed to be related with each other at the endothelium level[11]. As a result of endothelial dysfunction, endothelial nitric oxide (NO) decreases, and decreased NO activity plays an important role in the pathogenesis of ED[12]. ED and atherosclerosis thereby originate as a result of endothelial dysfunction[13].

The studies conducted in recent years have sought to secure early detection of the endothelial dysfunction, which results in atherosclerosis. One of the best known markers used for this purpose are acute phase proteins. Accumulation of C-reactive protein (CRP) has been detected within atherosclerotic lesions and has been shown to be correlated with an increase in cardiovascular diseases, in both healthy and high risk individuals. CRP belongs to the pentraxin family of proteins, whose members have a characteristic pentameric structure[14,15,16]. CRP is synthesized in the liver as a response to the inflammatory process, and it functions as a non-specific marker of inflammation[17,18]. Consequently, pentraxin-3 (PTX-3) has been commonly studied recently as a new marker. PTX-3, the foremost representative member of the long pentraxin group of the pentraxin family, is synthesized in endothelial cells, fibroblasts and smooth muscle cells. These cells, which are sources of pentraxin, are structures that have a direct role in atherosclerosis and are therefore thought to be a more specific marker for the development of atherosclerosis[17,18].

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Table 1. The median age, BMI values and IIEF Scores of the study groups

	GROUP 1	GROUP 2	GROUP 3
AGE (yr)	63,8 (55-76)	62,0 (50-71)	52,8 (55-70)
BMI (kg/m^2)	28,8 (24,4-34,6)	28,7 (22,4-36,0)	25,2 (22,6-29,1)
IIEF Score	5,6 (5-7)	5,7 (5-7)	24,1 (22-25)

Abbreviations: BMI, Body Mass Index; IIEF, International Index of Erectile Function.

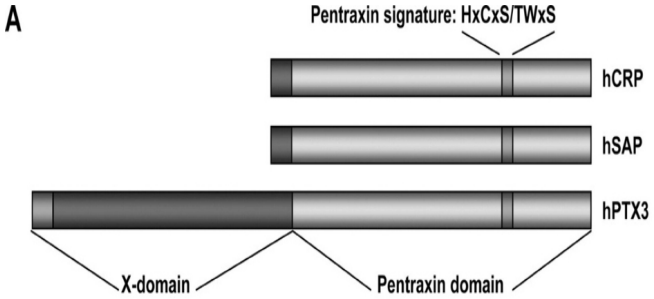

Figure 1. Pentraxin family

In this study, the importance and role of PTX-3 level in the diagnosis of arterial ED has been investigated. In the literature review, there were no studies found that used the level of PTX-3 to aid in the diagnosis of ED. This study, therefore, is the first of its kind on this subject.

MATERIALS AND METHODS

Study Population

A total of 45 patients, who had presented to urology and cardiology outpatient clinics of COMU Faculty of Medicine between 2013 and 2014, were included in this study.

Inclusion and Exclusion Criteria

Patients were divided into three groups, with group 1 composed of patients with ED who had been diagnosed with coronary artery disease, group 2 composed of patients with ED who had neither coronary artery disease nor equivalent diseases (DM, HT, hyperlipidemia), and group 3 composed of normal patients, who had no ED. The patients were selected from among those who had presented to urology and cardiology outpatient clinics during the dates indicated above. To give a clearer picture of the participants, group 1 included patients diagnosed with CAD and ED who were receiving routine follow-up care at the cardiology outpatient clinic; group 2 included patients with ED, but for whom tests administered for diagnosis of CAD were shown to be negative; and group 3 included patients with no ED who were presenting to the urology outpatient clinic.

Procedures

A coronary angiography was performed on patients with anginal chest pain complaints and high risk of apparent ischemia and cardiovascular event, as indicated by the stress test results. Exclusion criteria for this study included diagnosis of a rheumatologic disease, diagnosis of a malignant disease, previous treatment for ED, acute infectious disease, and chronic renal insufficiency.

A detailed examination of the medical and sexual history of the patients who agreed to participate in the research was conducted. Additionally, information on the demographic characteristics of the patients was obtained, and all patients were administered the IIEF questionnaire. Peripheral blood samples were obtained from brachial vein with standard vaccinator, while cavernosal blood samples were taken with insulin injector in order to measure their levels of pentraxin-3. The blood samples were centrifuged in 3000 cycles for 10 minutes and then kept at a temperature of -20°C until the day of evaluation.

Radiologic Evaluation; A penile color Doppler ultrasonography was performed on the patients in the radiology clinic after they were administered an intracavernosal injection of 1 cc (60 mg) papaverin at intervals of 5, 10, 15 and 20 minutes by taking Doppler samples from bilateral cavernosal artery lumina. The cut-off value for maximum peak systolic speed was 35 cm/s. Measurements under this value were evaluated as having arterial insufficiency. The patients who were diagnosed with arterial insufficiency were included in the study.

PTX-3 Measurement; Pentraxin-3 levels were measured by using a Biocer ELISA kit. The testing principle was based on the method of quantitative sandwich enzyme assay. A streptavidin- covered plate was incubated with biotinized monoclonal antibodies specific to pentraxin-3. After washing the plate, (the standards were washed at an earlier time), the plasma samples were placed into the holes and PTX-3 was attached to biotinized antibodies. Following the washing of the unattached proteins, specific enzyme-linked conjugate was added for PTX-3. Next, a rewashing was performed and the substrate was then added. The color changed according to the concentration of PTX-3, and this process was stopped by adding acidic solution. The density of the color was measured in 450 nm. Absorbances were in direct proportion to the concentration of PTX-3. A standard curve was drawn with the values

Table 2. Comparison of PTX-3 values between the patient groups

	Group 1 Median ± standart deviation	Group 2 Median ± standart deviation	*P*
Cavernous	1,8 ± 2,9	1,4 ± 2,3	0,575
Peripheric	2,2 ± 3,4	1,5 ± 2,4	0,300

p: Mann Whitney *U* Test

Table 3. Comparison of PTX-3 values between the patient groups and the control group

	All patients Median ± standart deviation	Control Median ± standart deviation	*P*
Cavernous	1,6 ± 2,6	0,3 ± 0,0	< 0,001
Peripheric	1,8 ± 0,0	0,3 ± 0,0	0,009

p: Mann Whitney *U* Test

Table 4. Comparison of PTX-3 values between the patients having ED but no CAD and the control group

	Group 2 Median ± standart deviation	Control Median ± standart deviation	*P*
Cavernous	1,4 ± 2,3	0,3 ± 0,0	< 0,001
Peripheric	1,5 ± 2,4	0,3 ± 0,0	0,001

p: Mann Whitney *U* Test

Table 5. Comparison of PTX-3 values in cavernous and peripheric blood samples of group 1

	Cavernous Median ± standart deviation	Peripheric Median ± standart deviation	*P*
Group 1	1,8 ± 2,9	2,2 ± 3,4	1,000

of absorbance corresponding to the concentrations of PTX-3, whose samples were calculated in nanogram/ml by using the standard curve.

Statistical Analysis

The analyses of collected data were performed with the SPSS19-version software package. The suitability of the variables to the normal distribution was examined using the Shapiro-Wilk test. For the presentation of the defining data, the median, standard deviation, minimum values and maximum values were used. The Mann-Whitney *U* test was used for non-parametric data in the comparison of variables between groups, while for comparison of the variables of measurement within the groups, the Wilcoxon test was used. Kruskall-Wallis variance analysis was applied for the comparison of the median values of the three groups. *P*-values below 0.005 were accepted as statistically significant.

RESULTS

The median age of all patients participating in the study was 52.3 years. Further breaking it down, the median age of the patients in group 1 was 63.8 ± 7.0 (min-max: 55-76), 62.0 ± 7.1 (min-max: 50-71) in group 2, and 52.8 ± 2.4 (min-max: 55-70) years in group 3 (control group). In all patients (group 1 and group 2), arterial ED was confirmed with penile Doppler ultrasonography and a PSW < 35cm/s. The IIEF-5 test was between 5-7 for all the patients, meaning that they had severe ED, while for the control group, IIEF-5 was between 22-25, indicating that there was no ED (**Table 1**).

The BMI of the patients in group 1 was 28.8 ± 2.6 (min-max: 24.4-34.6), 28.7 ± 3.3 (min-max: 22.4-36) in group 2, and 27.2 ± 1.3 (min-max:23.6-29.1) in the control group (**Table 2**).

When the patients were evaluated in terms of PTX-3, there was statistically significant difference between the PTX-3 values in the cavernous and peripheral blood samples of the patients in group 1 and in group 2 ($P < .05$) (**Table 3**). In comparing the PTX-3 values in the cavernous and peripheral blood samples of the patient groups to those in the patients of the control group, the values in the former were significantly higher statistically ($P < .05$) (**Table 4**). In Group 1, the PTX-3 value in cavernous and peripheral blood samples was higher than that of the patients in the control group and a statistically significant difference was detected ($P = .05$). In Group 2, the PTX-3 value in cavernous and peripheral blood samples was significantly higher statistically than that of the patients in the control group ($P < .05$) (**Table 5**). In comparing the patients in group 1 to those in group 2 in terms of the values of PTX-3 in cavernous and peripheral blood samples, there was no significant difference ($P = 1.000$) (**Table 6,7**). Lastly, when the values of PTX-3 were compared according to BMI, there was no significant difference in the cavernous and peripheral blood samples between normal weight patients and obese patients ($P > .05$) (**Table 8**).

DISCUSSION

Vasculogenic, neurogenic, anatomic, hormonal, psychologic and drug-related factors play a role in the pathophysiology of ED[19]. Although a dysfunction in any one of these factors suffices for the occurrence of ED, the event is generally multifactorial. Changes in the blood flow of the penis in vasculogenic ED cause cavernosal artery insufficiency, while changes in backflow cause corporal veno-occlusive problems. In both situations, the endothelium and the endothelium-derived mediators, which function actively in penile vascularisation, play the basic role. As a result, despite the patient's libido being normal, they are either unable to have an erection or to maintain one.

Atherosclerosis and atherosclerotic plaques are the main factors responsible for the development of complications in disorders of endothelium functions. ED and vascular diseases are therefore related with each other at the endothelium level. Considering that the endothelial structure is located throughout the entirety of the body, studies focusing on this subject have aimed to provide early detection of this process. For this purpose, Pentraxin-3 (PTX-3), which is a member of a new pentraxin family of proteins, has been examined. PTX-3 is the prototypical member of the long pentraxins of the pentraxin family, which also includes CRP (**Figure1**)[20,21]. In the vascular endothelium cells,

Table 6. Comparison of PTX-3 values in cavernous and peripheric blood samples of group 2

Group 2	Cavernous Median ± standart deviation	Peripheric Median ± standart deviation	*P*
	1,4 ± 2,3	1,5 ± 2,4	0,061

Table 7. Comparison of PTX-3 values in cavernous and peripheric blood samples between groups of normal and obese patients

	Normal Median ± standart deviation	Obese Median ± standart deviation	*P*
Cavernous	2,1 ± 3,1	0,5 ± 0,2	0,416
Peripheric	2,5 ± 0,1	0,4 ± 0,1	0,226

Table 8. PTX-3 values in cavernous and peripheric blood samples

	Cavernous Median ± standart deviation	Peripheric Median ± standart deviation
Group 1	1,8 ± 2,9	2,2 ± 3,4
Group 2	1,4 ± 2,3	1,5 ± 2,4
Group 3	0,3 ± 0,0	0,3 ± 0,0
All patients	1,6 ± 2,6	1,8 ± 0,0
Normal BMI	2,1 ± 3,1	2,5 ± 0,1
Obese	0,5 ± 0,2	0,4 ± 0,1

fibroblasts and smooth muscle cells, PTX-3 is locally synthesized. These cells are structures that have a direct role in atherosclerosis. Because PTX-3 is locally synthesized and not effected by a first pass through the liver, it is thought to be more specific than CRP.(17,18) Suliman et al. asserted that PTX-3 was an independent marker for endothelial dysfunction and peripheral injury[21,22]. Similarly, Inoue et al. suggested that the level of plasma PTX-3 was independent of the risk factors of cardiovascular disease, such as high cholesterol, smoking, HbA1c, gender and obesity[23]. In the present study, however, there was no association between obesity and the levels of PTX-3.

PTX-3 has been investigated more recently in the diagnosis of CAD and has begun to be
recognized as a more specific marker. For example, Ustundag et al. reported that PTX-3 plasma levels had risen in a more specific manner than cardiac troponin values six hours after chest pain[24]. Additionally, Fibrizia et al. suggested that PTX-3 was an important acute phase protein for atherosclerosis in cardiovascular diseases, acute coronary syndrome and peripheral vascular diseases[25].

In 2014, Gerald et al. reported that ED and coronary artery CAD were different clinical
appearances of the same disease[26]. Three groups were formed in the present study: group 1 included patients with CAD and ED, group 2 included patients with ED but no CAD; and group 3, the control group, included patients who had neither ED nor CAD. No difference was found between the cavernosal blood values of PTX-3 and the peripheral blood values of PTX-3 within group 1 and group 2. Although no statistical difference was detected in these values for group 1, the *P* value result of 0.061, being so close to the significant value established in this study, could gain greater significance in new studies conducted with a wider range of groups than that used in the present study, which was conducted with relatively small groups.

When the PTX-3 values of the peripheral and cavernosal blood samples taken from group 1 and group 2 were compared with those taken from group 3, the PTX-3 values of both the peripheral and cavernosal blood samples of the group 1 and 2 were statistically found to be significantly high. . This finding was similar to the results obtained in the comparison between the control group (group 3) and the patients who had been diagnosed with CAD. The PTX-3 value of both the peripheral and cavernosal blood samples of group 2 patients, those who had only ED but neither CAD nor an equivalent of CAD, was statistically significantly higher than that of the patients in the control group (group 3), the results of which show that findings derived from CAD that had been determined to be significant were relevant for patients with ED. PTX-3 values also rise in peripheral endothelial dysfunction. When group 1 and group 2 were evaluated individually, no significant difference was found between the levels of PTX-3 in cavernosal blood samples and those in peripheral blood samples.

CONCLUSIONS

Since PTX-3 is more specific than the formerly employed biochemical markers, PTX-3 can be used for the diagnosis of arterial ED patients. Given that the results can be further proven with a wider series, PTX-3 may be utilized in routine medical practice prior to applying the penile color Doppler Ultrasonography, which is a more invasive and relatively more expensive tool. Future studies should be improved by involving more groups with different medical conditions, particularly focusing on patients with IIEF scores lower than those indicating arterial ED.

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CONFLICT ON INTEREST

None declared

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