The Role of Pentraxin-3, Fetuin-A and Sirtuin-7 in the Diagnosis of Prostate Cancer

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Purpose: Prostate cancer is the most commonly diagnosed type of cancer and one of the leading causes of cancer-related death in men. Numerous efforts have been made to improve existing diagnostic methods and develop a new biomarker to identify patients with prostate cancer. In line with current literature, we preferred new serum-based biochemical markers as Pentraxin-3, Fetuin-A and Sirtuin-7 in the present study.

Materials and Methods: A total of 174 patients aged 42-76 years were included in the study. Patients with prostate cancer (n = 38) were enrolled as Group 1 and patients with benign prostatic hyperplasia (n = 136) as Group 2. The serum levels of Pentraxin-3, Fetuin-A and Sirtuin-7 levels were compared between the groups.

Results: The mean age of the patients was 61.9 ± 7.6 years (p = .001). The mean serum Prostate Specific Antigen levels 32.0 ± 59.6 (2.6-336) ng/mL and 10.0 ± 11.3 (2.5-77.4) ng/mL in Group 1 and 2, respectively (p = .029). The mean serum levels of Pentraxin-3 and Fetuin-Ain Group 1 were statistically significantlydifferent from Group 2(3.3 ± 4.4 ng/mL vs 1.8 ± 2.4 ng/mL, p = .002 and 466.8 ± 11.0 µg/mL vs 513.3 ± 11.0 µg/mL, p = .041,respectively). There was no significant difference between Group 1 and 2 according to serum levels of Sirtuin-7 (12.7 ± 8.2 ng/mL vs 12.7 ± 12.4 ng/mL respectively, p = .145).

Conclusion: Pentraxin-3, Fetuin-A and Sirtuin-7 may be effective in the diagnosis of prostate cancer in light of the current literature. In this study, it was found that Pentraxin-3 and Fetuin-A were significantly different in the diagnosis of prostate cancer. Larger-scale prospective studies are needed to determine the importance of Pentraxin-3 and Fetuin-A in the diagnosis of prostate cancer.

Keywords: pentraxin-3; fetuin-A; sirtuin-7; prostate cancer; biochemical marker

INTRODUCTION

Prostate cancer (PCa) is among the most commonly seen cancers in men and comprises 15% of newly-diagnosed cases.[1] In spite of developments in diagnosis and treatment, many people die due to this disease. Intense research continues around the world to prevent this disease. While some risk factors like age and family history have been defined, the definite cause is still unknown.[2] However, people with certain behavior or living in certain regions are known to have increased PCa incidence. Additionally, when people living in regions with low risk of PCa move to riskier regions, the PCa development risk of these people displays similarities to people living in this region.[3,4] When all this information is assessed together, it brings to mind that there are some preventable risk factors contributing to development of PCa.

The most notable among these risk factors is sexual behavior. Sexual behavior without control, especially, is an important public health problem around the world. It is considered to be a risk factor for development of PCa. Studies associated PCa with many sexual behaviors like age of first sexual relations, number of partners and ejaculation frequency. However, the underlying cause has not been fully revealed. Among the causes given most focus is the accumulation of a variety of toxic matter in prostate tissue or the inflammatory process caused by microbial agents.[5,6] However, it is difficult to reach a definite conclusion from studies on this topic because there is no standardization of topics like patient selection, information gathering method and time. Most were performed retrospectively. To our knowledge, to date there is no study comparing the sexual behavior and inflammatory parameters of prostate cancer patients with healthy people. This study was prospectively planned to resolve this deficiency about the topic.

The aim of the study was to compare sexual behavior and inflammatory markers measured in serum among people with prostate cancer diagnosis with healthy peers. Additionally, to identify whether there are precautions which can be recommended to protect healthy people from cancer.

MATERIALS AND METHODS

Study Population

From April 2013 to April 2020, information from male

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Received December 2020 & Accepted September 2021

Table 1. Prostate volume and serum biochemistry analysis of both groups

Parameters	Group 1 (n=38) (median±SD)(range)	Group 2 (n=136) (median±SD) (range)	*p*
Age (year)	65.5 ± 8.3 (43-76)	62.0 ± 8.4 (42-75)	0.101
Prostat Volume (cm3)	51.5 ± 28.7 (23-140)	55.0 ± 35.8 (16-241)	0.288
Total PSA (ng/mL)	9.2 ± 59.6 (2.6-336)	6.5 ± 11.3 (2.5-77.4)	0.029*
PSA Density (ng/mL2)	0.24 ± 0.96 (0.02-4.80)	0.12 ± 0.24 (0.03-1.77)	0.006*
Serum Albumin (g/dL)	4.5 ± 0.3 (3.6-4.8)	4.3 ± 0.3 (3.4-4.8)	0.077
Serum CRP (mg/L)	1.1 ± 0.7 (0.1-2.4)	1.2 ± 0.7 (0.1-2.5)	0.645

*:statistically significant difference

patients aged over 40 years attending hospital was recorded prospectively by a single expert. All patient data, diagnosis, and follow-up duration were prospectively recorded by a doctor specialized in the topic. Patients were persuaded to provide accurate information during their first interview. They were told that this was important for treatment. If they did not remember the answer to questions or did not want to answer, it was not recorded in the study. Patients had sexual behavior like age of first sexual relations, number of sexual partners and monthly ejaculation numbers and laboratory values recorded in detail. Patients gave permission for information to be used in research. Blood samples were taken in the morning after overnight fasting. Blood samples of patients were taken after underlying pathologies like UTI were excluded during the first visit. Patients were assessed for prostate cancer with PSA and digital rectal examination (DRE). Causes such as constipation, urinary tract infection (UTI) and urethral interventions which may cause benign PSA elevation were excluded. High values were checked 2 weeks later. PSA value > 4 ng/mL or suspect DRE findings were accepted as biopsy criteria and the study included patients positive for PCa as a result of prostate biopsy. Patients attending check-ups with no complaints with PSA value ≤ 3 ng/mL and without suspect DRE were included in the control group.

The control group was randomly selected from among people with similar basic features to the control group. The study was performed in a single tertiary hospital serving a region with population of nearly 800,000, very homogeneous structure and receiving very little immigration. The two groups were similar in terms of risk factors like nutrition, genetic and environmental factors.

Procedures

Patients were divided into 2 groups of the control group and prostate cancer (PCa) group. The study recorded a total of 654 patients abiding by the criteria including 263 PCa patients and 392 control patients. Parameters like age, comorbid diseases, sexual behavior (like age of marriage, number of partners, mean ejaculation frequency), PSA value, sedimentation, C-reactive protein (CRP), neutrophil lymphocyte ratio (NLR, neutrophil count/lymphocyte count), and systemic inflammatory index (SII, neutrophil count x platelet count/lymphocyte count) were compared between the groups.

Inclusion and exclusion criteria

The study included circumcised male patients over the age of 40 years, who granted consent, could remember sexual behavior and did not avoid talking about these topics. Patients who could not remember or did not want to talk about sexual behavior, who spoke inconsistently during examinations, with cognitive disorders, using psychiatric medication or with psychiatric disease, with previous PCa diagnosis, UTI or history of pelvic radiotherapy and, for the control group patients with elevated PSA values, were excluded from the study. The study received permission from the local ethics committee (Number: 025/2020).

Statistical analysis

Data obtained in the research was analyzed with the Statistical Package for the Social Sciences (SPSS) version 21 program. Descriptive statistics are number and percentage for categoric variables and mean, standard deviation, median, minimum and maximum values with interquartile range (IQR) for numerical variables. Normal distribution of numerical variables was assessed with the Kolmogorov-Smirnov test. For comparison of numerical variables, the student t test was used for variables abiding by parametric conditions, while the Mann Whitney U test was used for variables not abiding by parametric conditions. Analysis of categoric variables used the chi-square test. In situations with type 1 error level below 5%, $P < .05$ was accepted as statistically significant.

RESULTS

The study used data collected from a total of 654 patients, with 262 (40.1%) in the PCa and 392 (59.9%) in the control group. Mean age was identified as 61.81 ± 8.49 (41-85) years in the control group and 67.65 ± 9.08 (43-97) years in the PCa group ($P < .001$). The comorbid diseases and habits of groups are given in Table 1. Laboratory parameters (median ± IQR) were compared

Table 2. Serum PTX3, FETUA, SIRT7 levels compared between groups with Mann Whitney U Test

Parameters	Group 1 (n=38) (median ± SD) (range)	Group 2 (n=136) (median ± SD) (range)	*p**
Serum Pentraxin-3 levels (ng/mL)	1.6 ± 4.5 (0.2–17.6)	1.1 ± 2.4 (0.1–15.2)	0.002**
Serum Fetuin-A levels (µg/mL)	469.9 ± 110.5 (250.0–657.1)	523.9 ± 119.3 (290.6–913.6)	0.041**
Serum Sirtuin-7 levels (ng/mL)	10.7 ± 12.4 (2.9– 91.4)	9.3 ± 8.2 (4.1– 48.7)	0.145

* Mann-Whitney *U* Test
**:statistically significant difference

Table 3. PTX3, FETUA, SIRT7 levels in Group 1 patients according to ISUP grade

Parameters*	ISUP Grade group1 (n=18)	ISUP Grade group 2 (n=4)	ISUP Grade group3 (n=4)	ISUP Grade group4 (n=6)	ISUP Grade group5(n=6)	*p***
SerumPentraxin-3 Levels (ng/mL)	1.4 ± 5.3 (0.2–17.5)	1.6 ± 0.9 (0.9–3.1)	2.9 ± 2.2 (1.6–6.6)	1.1 ± 4.7 (0.9–12.9)	1.6 ± 1.9 (1.0–11.4)	0.281
Serum Fetuin-A Levels (µg/mL)	448.9 ± 107.4 (250.0–621.9)	491.6 ± 147.0 (345.0– 620.4)	539.4 ± 108.2 (373.7–613.2)	531.1 ± 98.6 (331.3–570.7)	371.2 ± 135.5 (322.2–657.1)	0.787
Serum Sirtuin-7 Levels (ng/mL)	11.0 ± 5.2(4.1–25.5)	11.8 ± 4.9(9.5–19.9)	10.1 ± 4.8(4.4–14.5)	8.0 ± 4.9(5.3–16.8)	15.9 ± 16.2(7.9–48.7)	0.614

* Values are expressed as median ± SD (range)
**Kruskal-Wallis Test

in the control and PCa patients. Median PSA values were 1.03 ± 1.15 (0.10 - 3) ng/mL in the control group and 8.29 ± 13.28 (4.10 - 1381) ng/mL in the PCa group (*P* = .001). Testosterone levels were 5.87 ± 2.97 (1.32-13.90) ng/dL and 5.34 ± 2.7 (2.31-16.14) ng/dL, respectively (*P* = .024). When groups were compared in terms of CRP, fibrinogen, NLR and SII score, inflammatory markers were identified to increase in the cancer group. This increase was statistically significant (**Table 2**).

The groups were compared in terms of marital age, lifelong number of sexual partners and monthly ejaculation frequency. As data were non-parametric, results are given as median (mean rank) ± IQR. When groups were compared in terms of sexual behavior, median age of marriage was 18 (261.63) ± 6 years in the control group and 20 (323.23) ± 5 years in the PCa group (*P* = .001). The lifelong median number of partners was 1 (299.87) ± 1 in the control group and 1 (367.75) ± 9 in the PCa group (*P* = .001) and this difference was significant. Additionally, the lifelong median ejaculation frequency (monthly) was determined as 12 (382.53) ± 5 for controls and 10 (230.02) ± 4 for the PCa group (*P* = .001) (**Table 3**).

DISCUSSION

Though some risk factors have been defined like aging, family history and genetic features, the definite cause is still unknown. Like many cancers, it is considered that multifactorial risk factors are effective. The aim of this study was to investigate whether there was a correlation between sexual behavior, inflammatory parameters in serum and PCa. In this study, the most important finding is that there was a correlation between PCa with sexual behavior and inflammatory parameters compared to the control group. It is known that the incidence of PCa increases in people living in certain regions or with certain forms of behavior. A study in our neighboring country of Iran reported the 3-year cancer frequency per 100,000 people was 11.2%.[7]

Studies on this topic have reported that Asian males have 10-15 times increased PCa risk compared to males living in western countries, while African-American males have 1.6 times increased PCa risk compared to Caucasians.[8] The difference in this disease between geographies is implied to be possibly due to some risky personal behaviors related to this disease.

There is increasing evidence showing sexual behavior, a significant health problem around the world, is an important risk factor for PCa development. This topic + attracted attention to sexual behavior like partner numbers, especially, but also age of first sexual relations and ejaculation frequency.[9]

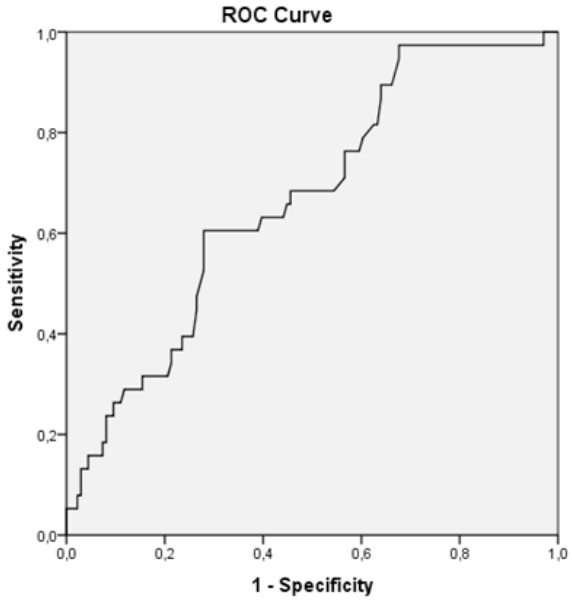

Figure 1. ROC analysis compared serum PTX3 levels between Group 1 and Group 2 (*p* = 0.002).
(AUCserumpentraxin-3=0.667, 95%CI: 0.574-0.760)

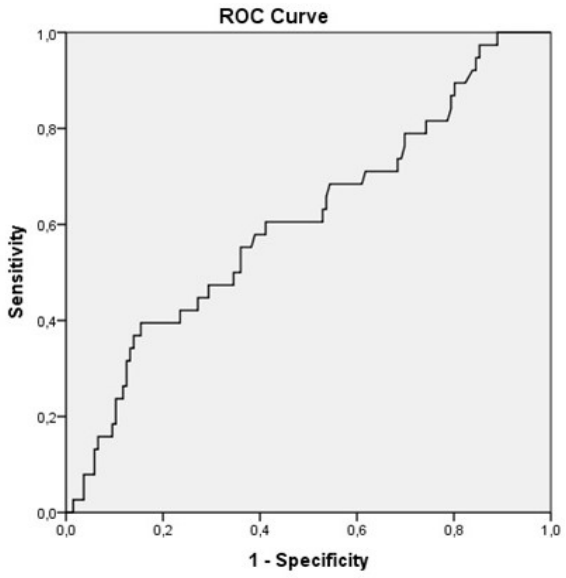

Figure 2. ROC analysis compared serum FETUA levels between Group 1 and Group 2(*p* = 0.041).
(AUCserumfetuin-A=0.608, 95%CI: 0.504-0.713, OR:2.190)

Some studies have investigated the correlation between ejaculation frequency and PCa. Rider et al. reported that in the absence of risky sexual behavior, increased ejaculation frequency has protective effects against PCa.[10] Another study by Jian et al. reported that there was a significant correlation between sexual behavior like reduced sexual partner numbers, advanced age for first sexual relations and moderate levels of ejaculation frequency with reduced PCa risk.[11] Some authors reported the protective ejaculation frequency is 1-4 times per week.[12] In our study, the cancer group was identified to have reduced ejaculation frequency compared to the control group. The protective number is not known in our study. In spite of broad investigation of the literature about ejaculation, the protective effect is not fully understood. According to the most accepted view, increased ejaculation frequency is effective by preventing accumulation of some carcinogenic material within prostate fluid.[13,14]

We think ejaculation may be effective through a different route. Like the mechanical cleaning effect of urine, frequent ejaculation may prevent access to or colonization of prostatic tissue by a variety of microorganisms. Additionally, sexual activity means a certain level of physical activity, mental calmness and better communication with partners. In conclusion, continuing active sexual life may have beneficial contributions by making the person feel good about themselves, and have positive effect on the vascular system by better perfusion and oxygenation of tissues leading to benefits for immune system cells. This is very important for the battle with cancer cells. We think there is a need for more comprehensive studies to say anything definite about this topic.

Increased partner numbers is an important public health problem increasing the risk of many sexually-transmitted diseases. Many studies have proposed that sexual activities without control and with many people is an important risk factor for PCa development.[15] A meta-analysis by Jian et al. investigated the correlation between partner numbers and PCa. The authors reported that each increase in partner numbers by 10 increased cancer risk by 1.1 times.[11] These results were supported by other researchers. In our study, the partner number was significantly increased in the PCa group compared to the control group.

The reason for the correlation between partner numbers and PCa has not been fully explained. One of the views proposed about this topic associates increased sexual activity with high androgen levels and proposed that high hormone levels may trigger cancer development.[16] However, many studies have shown no relation between PCa and androgens. In our study, contrarily, the cancer group had reduced androgen levels compared to the control group. This is not surprising to us; we know the androgen levels reduce in elderly patients. Another view which is a focus in the correlation between partner numbers and cancer is the inflammatory process caused by sexually transmitted infections (STI).[17-19] Independent of vector, there are studies in the literature reporting STI experienced in any period of life increases cancer risk by 50%.[20,21]

We know the correlation between cancer and the inflammatory process from many cancers in the gastrointestinal system, thyroid, pancreas, bladder and pleura.[22,23]

Chronic inflammation results in collection of many immune system cells and increases in a variety of mediators and cytokines. Increasing reactive oxygen species (ROS) in this process affect the physiological conditions required by normal cells. If this toxic material is not removed from tissues, lipid peroxidation and DNA injury may develop.[24,25] In prostate tissue, chronic infection beginning for a variety of reasons may begin the cancer development process with the same mechanism.[26,27] A study by Taghavi et al. supports this view. The authors investigated the correlation between Polyomavirus hominis 1 (BK virus, BKV), known to cause latent infection, with prostate specimens. The results of the study reported the BKV infection was more prevalent compared to BPH in PCa specimens.

In our study, inflammatory parameters were investigated differently to many studies. Inflammatory parameters examined in serum from PCa patients were identified to be increased compared to the control group. According to our knowledge, this study is the first to compare prostate cancer patients in terms of partner numbers and inflammatory parameters to date. In spite of not knowing STD history, we think agents transmitted through the sexual route with increased partner numbers may have caused a chronic inflammatory process triggering cancer development in patients included in the study. We do not fully know why these patients married at younger ages and how partner numbers and ejaculation frequency changes in which periods of life. Sexual relations with many partners at younger ages may cause marriage at later ages and less sexual relations after marriage.

The results of our study identified that the number of partners was increased and the ejaculation frequency was reduced in the PCa group compared to the control group. Additionally, compared to the control group, the PCa group had increased inflammatory parameters like CRP, sedimentation, fibrinogen, NLR in serum and SII. People included in the study were statistically similar in terms of geography, genetics and nutritional characteristics, which is very important in terms of homogenization. This allows the opportunity to compare people with similar features (control and PCa group) in terms of sexual behavior and inflammatory parameters. These results show that in addition to unchangeable risk factors like aging, genetics and family history, there are risk factors which are preventable with simple precautions. When the literature and our study results are interpreted together, sexual behavior appears to be a changeable risk factor for prevention of cancer.

There are some limitations to our study. The first is that information related to sexual life was based on patient statements. It is not possible to know if there were situations involving forgetting or purposely providing misleading information. However, information was not obtained from patients with any survey or by telephone. All diagnosis and treatment processes were completed by the same person. This situation is important in terms of receiving accurate information from patients and for standardization of the study. It is not known if the group used as control in the study included undiagnosed cancer cases (due to silent progression of many cancer cases, lack of reliable PSA value). Additionally, in the cancer group, there was no evidence for diseases related to STIs available, like serologic tests. However, this situation is valid for the control group.

CONCLUSIONS

In conclusion, this prospective study obtained important results. It was identified that the partner number was increased and ejaculation frequency reduced in the PCa group compared to the control group and that these patients married at later ages. Additionally, an increase in systemic inflammatory markers was observed in the cancer group. These results show the presence of increased inflammatory processes in the PCa group with increased partner numbers. These results, when assessed with the literature, lead to consideration that increased partner numbers and reduced ejaculation frequency may begin or ease the inflammatory background for cancer development. These results indicate there are some precautions that may be taken for this disease. Providing necessary sexual information from a young age, taking protective precautions against sexually transmitted diseases and increasing the frequency of ejaculation were identified as changeable behaviors for PCa.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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