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ORIGINAL ARTICLE

Changes in prostate specific antigen value in patients with COVID-19

Cambios en el valor del antígeno prostático específico en pacientes con COVID-19

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Abstract

Objectives: *To evaluate changes in prostate-specific antigen (PSA) values in patients with coronavirus disease 2019 (COVID-19).* **Method:** *Male patients who were admitted to our flu outpatient clinic with cough, fever, weakness, and bone and joint pain were evaluated. The acute phase reactants of erythrocyte sedimentation rate, C-reactive protein, ferritin, and fibrinogen were measured both at the time the patients first presented at the clinic and 1 month after recovery from COVID-19 infection. PSA and free PSA were also measured at the same time. The difference in acute phase reactants and PSA values during active COVID-19 infection and after recovery was assessed using the paired samples t-test.* **Results:** *The mean PSA values of the patients were 2.73 ± 3.7 μg/L in the period of active infection, and 2.04 ± 2.32 μg/L 1 month later (p = 0.12). In the 29 patients with PSA values in the gray zone, the PSA values were determined as 6.6 ± 4.4 μg/L during infection and 4.1 ± 2.9 μg/L after treatment (p = 0.001).* **Conclusion:** *The results of this study showed that PSA values in the gray zone during COVID-19 infection decreased after treatment when the patient recovered.*

Keywords: *COVID-19. Infection. Prostate. Prostate-specific antigen.*

Resumen

Objetivo: *Evaluar cambios en los valores de antígeno prostático específico (PSA) en pacientes con COVID-19.* **Método:** *Se evaluaron pacientes de sexo masculino que ingresaron a nuestra consulta externa de gripe con tos, fiebre, debilidad, dolor óseo y articular. Los reactivos de fase aguda de la velocidad de sedimentación de eritrocitos, la proteína C reactiva, la ferritina y el fibrinógeno se midieron tanto en el momento en que los pacientes se presentaron por primera vez en la clínica como un mes después de la recuperación de la COVID 19. El PSA y el PSA libre también se midieron al mismo tiempo. La diferencia en los reactivos de fase aguda y los valores de PSA durante la infección activa por COVID-19 y después de la recuperación se evaluó mediante la prueba t de muestras pareadas.* **Resultados:** *Los valores medios de PSA de los pacientes fueron 2.73 ± 3.7 μg/L en el periodo de infección activa y 2.04 ± 2.32 μg/L un mes después (p = 0.12). En los 29 pacientes con valor de PSA en la zona gris, los valores de PSA se determinaron como 6.6 ± 4.4 μg/L durante la infección y 4.1 ± 2.9 μg/L después del tratamiento (p = 0.001).* **Conclusión:** *Los resultados de este estudio mostraron que los valores de PSA en la zona gris durante la COVID-19 disminuyeron después del tratamiento cuando el paciente se recuperó.*

Palabras clave: *COVID-19. Infección. Próstata. Antígeno prostático específico.*

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Introduction

The use of prostate-specific antigen (PSA) as a serum marker has revolutionized the diagnosis of prostate adenocarcinoma[1]. Although PSA is organ-specific, it is not cancer-specific, so elevated PSA values may be seen in benign prostatic hypertrophy (BPH), prostatitis, and other non-malignant conditions[2]. PSA is a serine protease from the human kallikrein family, also known as kallikrein-3, which is a glycoprotein produced by the prostate gland[3]. Kallikreins are acute phase reactants, have proteolytic properties, and play an important role in many infections[4-6].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) resulted in a global pandemic on a scale unprecedented for the last 100 years. The diagnosis and treatment of many diseases, especially cancers, was delayed due to the COVID-19 pandemic. Articles have been published about the duration of this reasonable delay in urological cancers[7]. This situation has highlighted the importance of cancer screening during a pandemic. Is it logical to see PSA for screening purposes in patients with COVID-19 at the time of active disease? Is it reasonable to take a biopsy from patients with PSA levels in the gray zone after COVID-19 treatment? The aim of this study was to evaluate changes in PSA values in patients with COVID-19.

Method

This study was conducted between April 2020 and September 2021 after obtaining the approval of the Local Ethics Committee (E-21-594). The Clinical Trials number is NCT05009186. Male patients who were admitted to our flu outpatient clinic with cough, fever, weakness, and bone and joint pain were evaluated. Samples were taken from all of these patients for polymerase chain reaction (PCR) tests with both oral and nasopharyngeal swabs. All patients provided written informed consent. Patients with positive PCR test results were included in the study. The age of the patient and urea, leukocyte, hemoglobin, platelet, and creatinine values of the patients were recorded. Urinalysis and urine culture were taken from all patients. The acute phase reactants of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and fibrinogen were measured both at the time the patients first presented at the clinic and 1 month after recovery from COVID-19 infection. PSA and free PSA were also measured at the same time. Patients whose symptoms improved and with a negative PCR test result were considered recovered.

Patients were excluded from the study if they were aged < 45 or > 70 years, if they had lower urinary tract symptoms, urinary tract infection, a history of prostate biopsy and previous high level of PSA, or a history of prostatitis.

Statistical analysis

Data analyses were performed with PASW 18 software (Statistical Packages for the Social Sciences/ IBM, Chicago, IL, USA). The Kolmogorov-Smirnov and P-P plot tests were used to verify the normality of the distribution of continuous variables. The results were reported as mean ± standard deviation values for data showing normal distribution or median (minimum–maximum) values when data distribution was skewed. All statistical tests were two-tailed. The difference in acute phase reactants and PSA values during active COVID-19 infection and after recovery was assessed using the paired samples t-test. There was determined to be a 91% chance of correctly rejecting the null hypothesis of no difference between active disease and control conditions with 30 participants. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 130 patients who met the study criteria were enrolled, and as 39 did not attend follow-up appointments, they were excluded and an analysis was made of 91 patients. The mean age of the patients was 59 ± 6.7 years. The mean PSA values of the patients were 2.73 ± 3.7 μg/L in the period of active infection, and 2.04 ± 2.32 μg/L 1 month later ($p = 0.12$). The values of the patients before and after treatment are shown in table 1.

In the 29 patients with PSA values in the gray zone, the PSA values were determined as 6.6 ± 4.4 μg/L during infection and 4.1 ± 2.9 μg/L after treatment ($p = 0.001$) (Fig. 1). The PSA values decreased in 25 of the 29 patients in the gray zone and an increase was observed after treatment in four.

A statistically significant improvement was determined in the ferritin and fibrinogen values, as the other acute phase reactants ($p = 0.0001$, $p = 0.04$, respectively). The mean ESR and CRP values were determined as 30.6 ± 20.8 mg/L and 71.5 ± 56.9 mg/L during COVID-19 infection and as 11.9 ± 11.5 mg/L

Table 1. Changes in serum parameters of patients during COVID-19 and after 1 month of COVID-19

Parameters	Values during COVID-19	Values post COVID-19	p
ESR	30.6 ± 20.8	11.9 ± 11.5	0.10
Ferritin (ng/mL)	701.2 ± 600.8	153.7 ± 180.2	0.0001*
Fibrinogen (mg/dL)	580.4 ± 168.7	344 ± 92.4	0.04*
CRP(mg/L)	71.5 ± 56.9	5.5 ± 9.4	0.97
WBC (mcL)	7.48 ± 2.9	9 ± 8	0.57
Platelet (mcL)	207.8 ± 73.4	257 ± 54	0.01*
Hemoglobin (g/dL)	14.3 ± 1.3	14.5 ± 1.5	0.0001*
Urea (mg/dL)	38.7 ± 18.2	34.2 ± 13.7	0.0001*
Creatinine (mg/dL)	1.08 ± 0.51	0.97 ± 0.44	0.0001*
PSA (µg/L)	2.7 ± 3.7	2.04 ± 2.3	0.12
fPSA (µg/L)	0.52 ± 0.93	0.5 ± 0.49	0.01*

*Statistically significant (paired samples t-test). ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; COVID-19: coronavirus disease 2019; PSA: prostate-specific antigen; WBC: white blood cell; fPSA: free prostate-specific antigen.

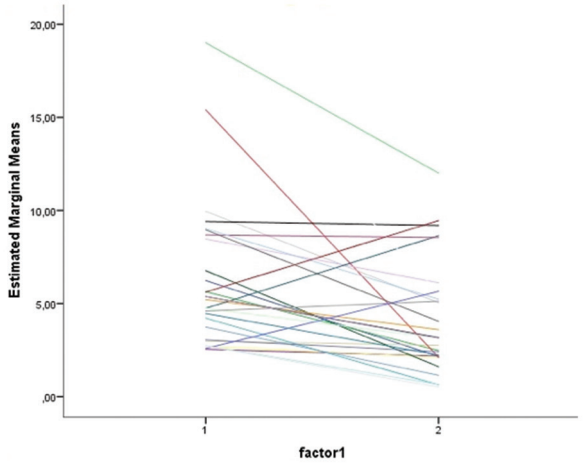

Figure 1. *The change in mean prostate-specific antigen values after treatment is shown in the gray zone with a spaghetti plot.*

and 5.5 ± 9.4 mg/L after recovery (p = 0.10, p = 0.97, respectively) (Table 1). When the relationships between ferritin, ESR, fibrinogen, CRP, and tPSA were evaluated with bivariate correlation analysis, with the exception of ESR, no acute phase reactant was determined to be statistically significantly correlated with PSA. A statistically significant but weak positive correlation was determined between ESR and PSA (p = 0.04, r = 0.21).

Discussion

Acute phase reactants are inflammation markers that vary at a significant rate in serum concentrations during inflammation. They can be separated into two main groups as those showing positive and negative changes according to the serum concentrations during inflammation. The acute phase reactants showing a positive change which are used most in clinical practice are CRP, ferritin, and fibrinogen. The concentrations of these increase during acute and chronic inflammation. The most well-known negative acute phase reactants are albumin, transferrin, and retinol-binding protein. Positive acute phase reactants reach the highest levels during acute trauma and acute inflammation[8,9]. ESR measures the distance that red blood cells in anticoagulated blood fall in a vertical tube after 1 h. Fibrinogen reduces the load on the red blood cell surface and this causes them to collect together rapidly, and as a result ESR increases[10].

Plasma kinins are another acute phase reactant, which is an important part of the inflammatory response as an important mediator of increased vascular permeability[11]. During septicemia, the plasma kallikrein-kinin system is activated, and components of this protease system are seen to function during sepsis[12]. PSA is a serine protease of the human kallikrein group[3], and is expected to be elevated in the plasma as a response to infection. This antigen has an important place in the screening and diagnosis of prostate cancer.

Prostate cancer is the second most commonly seen cancer in males in the USA and Europe[13,14] and is the second most common cancer-related cause of death in males[13]. However, an elevated PSA value is not cancer-specific and may be related to other prostate pathologies such as inflammation and BPH[15]. As the structure of the prostate tissue deteriorates in prostate cancer, prostatitis, and prostate infarction, the amount of PSA released into the blood increases. Therefore, PSA in the blood may be elevated. As PSA synthesis is increased in BPH, this also increases PSA[16]. Despite the disadvantages, PSA measurement remains the gold standard method in current prostate cancer screening as no new biomarker has been determined[17].

Prostate inflammation can cause an increase in PSA level, and this can lead to confusion on the subject of the use of PSA and PSA kinetics in the diagnosis of prostate cancer. The use of empirical antibiotics followed by repeated PSA measurement

is a matter of debate. In a previous study that analyzed patients with Type IV prostatitis and high PSA levels (National Institutes of Health classification), no significant difference was determined in the fall in PSA between the group given antibiotics and the group given placebo (59.2% vs. 53.1%). There was also no significant difference in respect of patients with a decrease in PSA and diagnosis of prostate cancer after treatment with antibiotics or placebo (31% vs. 26.9%)[16]. In the European Association of Urology guidelines, empirical antibiotic treatment is not recommended to lower PSA in the gray zone, but if the patient has an active urinary tract infection, it is recommended that PSA is measured again after antibiotic therapy.

Although there are many studies in literature related to prostatic inflammation, elevated PSA, and empirical antibiotic treatment, to the best of our knowledge there are few studies that have investigated the relationship between systemic infection and serum PSA level. In the patients in the current study, the mean PSA value was 2.73 ± 3.7 μg/L in the period of active COVID-19 infection and 2.04 ± 2.32 μg/L 1 month later. Despite the fall in the mean plasma PSA values, the difference was not statistically significant (p = 0.12). In the 29 patients with PSA values in the gray zone, the mean values were determined as 6.6 ± 4.4 and 4.1 ± 2.9 μg/L during COVID-19 infection and at 1 month later, respectively. The difference was determined to be statistically significant (p = 0.001). Correspondingly, In a newly published study by Cinislioglu et al., which similarly evaluated the relationship between COVID-19 and PSA, the total PSA values obtained during COVID-19 infection were found to be higher than the PSA values obtained before the infection and in the follow-up after the infection[18].

In the early periods of the pandemic, it was thought that the SARS-Cov-2 only involved the lungs, whereas over time it was understood that the virus could target tissues which express angiotensin-converting enzyme 2, which is the SARS-CoV-2 receptor[19]. Moreover, this virus uses transmembrane protease serine 2 receptor to enter the host cells and spread the infection. This receptor is found in the prostate as well as in organs such as the lungs, colon, and liver[20]. This makes the prostate a target organ for the virus[21]. As a result, impairment of the basal membrane structure of the prostate by the virus involving the prostate and causing inflammation could be a reason for elevated PSA. What is more, when it is considered that PSA is an antigen of the kallikrein group and kallikreins have an important role against inflammation during systemic infection, an increase can be expected in plasma PSA level. Therefore, when evaluating the results of this study, it can be said that COVID-19 infection may lead to an increase in PSA values in males aged > 45 years. A significant decrease was observed after recovery from the systemic infection, especially in the gray zone PSA values (2.5-10 μg/L).

In four of the current study patients with gray zone PSA values, the PSA value was determined to have increased after treatment. When these patients were evaluated, it was found that the other acute phase proteins had also increased. The reason for this was thought to be a continuation of the systemic inflammatory effect of COVID-19 infection despite the negative PCR test.

The main limitation of this study was that prostate biopsies were not taken from the patients. If prostate biopsies had been taken, the importance of the fall in the PSA values in respect of cancer would have been able to be determined more objectively. However, it would not have been ethical to take a biopsy from each patient in this type of study.

Conclusion

The results of this study showed that PSA values in the gray zone during COVID-19 infection decreased after treatment when the patient recovered. It can be recommended that for males aged > 45 years with COVID-19 infection, plasma PSA measurements are taken after recovery from the infection. When it is considered that a large proportion of the population has been exposed to COVID-19 and the majority of those have had a mild symptomatic course with the effect of vaccination, it can be recommended that if PSA is measured and a gray zone PSA value is determined, the PSA measurement should be repeated at least 1 month after recovery from the infection.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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