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The Change in tPSA, fPSA and f/tPSA Levels in Men Undergoing Hemodialysis Effect of Hemodialysis on Serum PSA Levels

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ABSTRACT

Purpose: This study aimed to assess the impact of hemodialysis treatment and different dialysis membranes with varying surface areas on serum levels of total prostate-specific antigen (tPSA), free prostate-specific antigen (fPSA), and the fPSA/tPSA ratio in patients undergoing hemodialysis treatment.

Material and Methods: The study was conducted at the Central Laboratory of....Hospital in May, June, and July 2020. tPSA, fPSA, and fPSA/tPSA ratios measured in pre-dialysis and post-dialysis samples were determined. Correlation between pre-dialysis and post-dialysis of fPSA and tPSA levels and patients' ultrafiltrates were evaluated. The fPSA, tPSA, and fPSA/tPSA measured in pre-dialysis and post-dialysis samples grouped according to membrane type were compared.

Results: The fPSA levels and fPSA/tPSA ratios of pre-dialysis samples were significantly lower than post-dialysis samples. tPSA values were not significantly different in pre-dialysis and post-dialysis samples. According to membrane types, it was found that pre-dialysis and post-dialysis tPSA, fPSA, and fPSA/tPSA were not significantly different. There was a positive correlation between difference in fPSA concentrations measured in pre-dialysis and post-dialysis samples and ultrafiltrate (rho=0.380). A positive correlation was found between difference in tPSA concentrations measured in pre-dialysis and post-dialysis samples and ultrafiltrate (rho=0.562).

Conclusion: Post-dialysis fPSA values and fPSA/tPSA ratios were found to be elevated in patients receiving hemodialysis treatment due to hemoconcentration and other potential effects of dialysis. Therefore, interpreting fPSA values and fPSA/tPSA ratios in patients undergoing hemodialysis treatment according to current clinical decision limits may lead to misinterpretation. In this group of patients, the use of tPSA testing is safe as it remains unaffected by dialysis treatment.

Keywords: Prostate Specific Antigen, Biological Tumour Markers, Dialysis

Hemodiyaliz Uygulanan Erkeklerde tPSA, fPSA ve f/tPSA Düzeylerindeki Değişim Hemodiyalizin Serum PSA Düzeylerine Etkisi

ÖZET

Amaç: Çalışmanın amacı hemodiyaliz tedavisinin ve değişen yüzey alanlarına sahip farklı diyaliz membranlarının total prostat spesifik antijen (tPSA), serbest prostat spesifik antijen (fPSA) ve fPSA/tPSA serum seviyelerine olan etkisini değerlendirmektir.

Gereç ve Yöntemler: Çalışma Mayıs, Haziran ve Temmuz 2020 tarihlerinde Kemalpaşa Devlet Hastanesi Merkez Laboratuvarında gerçekleştirildi. Diyaliz öncesi ve diyaliz sonrası örneklerde ölçülen tPSA, fPSA ve fPSA/tPSA oranları belirlendi. Diyaliz öncesi ve diyaliz sonrası fPSA ve tPSA seviyeleri ile hastaların ultrafiltratları arasındaki korelasyon değerlendirildi. Örnekler diyalizde kullanılan membran tipine göre gruplandırılarak diyaliz öncesi ve diyaliz sonrası fPSA, tPSA ve fPSA/tPSA düzeyleri karşılaştırıldı.

Bulgular: Diyaliz öncesi numunelerde fPSA seviyeleri ve fPSA/tPSA oranları, diyaliz sonrası numunelerdeki düzeylere göre anlamlı derecede düşüktü. tPSA değerleri diyaliz öncesi ve diyaliz sonrası örneklerde anlamlı farklılık göstermedi. Membran tiplerine göre gruplandırıldığında diyaliz öncesi ve diyaliz sonrası tPSA, fPSA ve fPSA/tPSA düzeylerinde anlamlı farklılık olmadığı bulundu. Diyaliz öncesi ve diyaliz sonrası örneklerde ölçülen fPSA değişimi ile ultrafiltrat arasında pozitif bir korelasyon vardı (rho=0.380). Diyaliz öncesi ve diyaliz sonrası numunelerde ölçülen tPSA konsantrasyonlarındaki değişim ile ultrafiltrat arasında pozitif bir korelasyon bulundu (rho=0,562).

Sonuç: Hemodiyaliz tedavisi alan hastalarda hemokonsantrasyon ve diyalizin diğer potansiyel etkilerinden dolayı diyaliz sonrası fPSA değerlerinin ve fPSA/tPSA oranlarının diyaliz öncesi düzeylere göre yüksek olduğu bulunmuştur. Hemodiyaliz tedavisi gören hastaların fPSA değerlerinin ve fPSA/tPSA oranlarının hasta grubuna özel olmayan karar limitlerine göre değerlendirilmesi yanlış klinik yorumlara yol açabilir. Çalışmamız verilerine göre hemodiyaliz tedavisi gören hastalarda tPSA testinin kullanımı fPSA testine göre daha güvenilirdir.

Anahtar Kelimeler: Prostat Spesifik Antijen, Biyolojik Tümör Belirteçleri, Diyaliz

Most patients receiving treatment for end-stage renal disease reside in countries with aging populations. As a result, the increase in the geriatric population, particularly in developing nations, is likely to lead to a rise in end-stage renal disease (1, 2).

The incidence of malignancy among hemodialysis patients is higher compared to the general population. This situation is related to prostate cancer (PCa), which involves one-third of older men (3, 4). Based on the 2020 GLOBOCAN estimates of cancer incidence and mortality by the International Agency for Research on Cancer, prostate cancer is the second most prevalent type of cancer in Turkey (5). In this context, PCa is a problem in patients receiving hemodialysis due to end-stage renal failure.

Prostate-specific antigen (PSA) is a glycoprotein produced in the secretory epithelium of the prostate gland which enables liquefaction of semen fluid. It is synthesized in the prostatic duct epithelial cell and released into the seminal lumen by exocytosis. PSA is bound to the protease inhibitor alpha1-antichymotrypsin or alpha2-macroglobulin, making it a complex molecule. Only a small fraction of PSA is present in free form in the serum. In prostate diseases where there is damage to the basal membrane and lumen structure, PSA leaks into the bloodstream at a higher rate, leading to an increase in serum PSA levels (6).

PSA is commonly utilized as a screening test for the early detection and follow-up of PCa. The guidelines on PCa by the European Association of Urology (EAU) recommend that an increase in PSA level and persistently high serum PSA concentration are adequate indicators for deciding on a biopsy (7). Patients receiving hemodialysis treatment often have oliguria or anuria. As a result, patients in this group may experience minimal or no symptoms of prostatism. Therefore, determining the serum PSA levels in these patients becomes more crucial. However, it remains uncertain whether hemodialysis treatment affects total PSA (tPSA) and free PSA (fPSA) levels, which are utilized as markers for PCa, and whether their use is valuable for patients undergoing hemodialysis treatment (8, 9).

The aim of this study was to assess the impact of hemodialysis and dialysis membranes with varying surface areas on the levels of tPSA, fPSA, and the free PSA/total PSA ratio (f/tPSA ratio) in patients undergoing hemodialysis treatment.

Material and Methods

The study was conducted at the Central Laboratory of the İzmir Kemalpaşa State Hospital in May, June, and July of 2020. The fPSA and tPSA tests were performed in the ADVIA Centaur XP Immunoassay System (Siemens Diagnostics, Tarrytown, NY, USA) in our laboratory and the chemiluminometric method was used for both tests. The f/tPSA ratio was calculated by dividing the fPSA value by that of tPSA. The tPSA measurement procedure detects fPSA and PSA - α1 antichymotrypsin complex. Internal quality control of tPSA and fPSA tests is performed daily. The analytical variation (CVa) of tPSA and fPSA tests in May, June and July was calculated with the formula "Standard Deviation × 100 / laboratory mean of internal quality control result".

Blood samples that were accepted to our laboratory for routine biochemistry tests before and after hemodialysis treatment of male patients undergoing hemodialysis treatment for end-stage renal failure were included. Patients with PCa, suspected PCa on rectal examination, transurethral endoscopic intervention in the past month, and urinary tract infection (>5 white blood cells in high magnification area) were excluded. The fPSA, tPSA levels and f /tPSA ratio measured in pre- and post-dialysis serum were compared. Type of membrane used in hemodialysis and the amount of fluid lost by the patients after dialysis (ultrafiltrate) were obtained retrospectively.

The study evaluated the correlation between the differences in pre- and post-dialysis concentrations of fPSA and tPSA tests and patients' ultrafiltrates. The serum samples were categorized based on the type of dialysis membrane used during the dialysis process. The fPSA, tPSA, and f/tPSA ratios measured in pre-dialysis and post-dialysis samples were compared based on the type of membrane used.

Statistically Analysis

SPSS 23.0 (IBM, Chicago, USA) package program was used for statistical evaluation of the data. The normality of variables was determined by the Kolmogorov-Smirnov and Shapiro-Wilk tests.

The difference between the nonparametric variants was determined using Wilcoxon signed-rank test. Values were defined as the median and 25 – 75th percentile. The number of negative, positive differences and ties between pre- and post-dialysis values was analysed. Spearman's test was used for correlation analysis. Correlation coefficient

(rho) value was accepted as weak correlation between 0.000-0.49, moderate correlation between 0.50-0.69 and strong correlation ≥0.70. A p value of <0.05 was considered significant.

Results

To ensure that the data obtained were not significantly impacted, we calculated the analytical variation of the fPSA and tPSA tests for the months during which the tests were conducted. The mean, standard deviation and CVa values calculated for internal quality control levels in May, June and July 2020 and manufacturer's declared CV values are presented in Table 1. We found that the analytical CV values we calculated for the fPSA and tPSA tests were below the values declared by the manufacturer.

The number of serum samples included in the study before and after hemodialysis treatment during this period was 51. Analysis of pre-dialysis and post-dialysis samples revealed that fPSA levels (p = 0.000 for both parameters), tPSA levels (p = 0.000 for both parameters), and f/tPSA ratios (p = 0.001 and p = 0.005, respectively) were not normally distributed.

The median age (25 – 75th percentile) of the patients was 68 (62 - 74). The reason for dialysis treatment was idiopathic in 33 patients and diabetes mellitus in 18 patients. Patients receive dialysis treatment twice a week (n=12) and three times a week (n=39).

The median values (25th and 75th percentile) of tPSA, fPSA and f /tPSA of pre- and post-dialysis were presented in Table 2. tPSA values were not significantly different in pre- and post-dialysis (p= 0.567). The median value of the fPSA levels of the pre-dialysis samples was significantly lower than the fPSA levels of the post-dialysis samples (p = 0.009). The median value of f /tPSA of the pre-dialysis samples was significantly lower than f /tPSA of the post-dialysis samples (p = 0.001) (Figure 1).

The patients were divided into two groups according to the dialysis membrane used. The first group was of serum samples of patients undergoing hemodialysis using a high-flux polyethersulfone membrane with a surface area of 1.9m2 and an ultrafiltration coefficient (KUF) of 76 mL / h / mmHg. In the second patient group, a high flow membrane with a surface area of 1.7m2 and KUF of 74 mL /hr /mmHg was used for hemodialysis. The numbers of patients in the first and second groups were 27 and 24, respectively.

When analyzed according to the membrane types used, it was found that pre- and post-dialysis fPSA, tPSA and f / tPSA levels were not different according to membrane type. The p values for "High-flux membrane with a surface area of 1.7m2" were 0.977, 0.985, 0.845, and the p values for "High-flux membrane with a surface area of 1.7m2" were 0.06, 0.71, and 0.912, respectively. The median and 25th - 75th percentile of fPSA, tPSA and f /tPSA in pre- and post-dialysis samples grouped by membrane type are presented in Table 3.

Table 1. Mean, standard deviation, and coefficient of variation values for the levels of internal quality control during May, June, and July 2020

	tPSA				fPSA			
Internal quality control	Mean (ug/L)	SD (ug/L)	CV (%)	Manufacturer's declared CV (%)	Mean (ug/L)	SD (ug/L)	CV (%)	Manufacturer's declared CV (%)
Level 1	0,35	0,01	2,02	5.97	0,16	0,005	3,33	4.3
Level 2	3,42	0,04	1,22	2.60	1,73	0,05	2,94	3.5

SD: Standard deviation
CV: Coefficient of variation

Table 2. Median and 25th - 75th percentile values of tPSA, fPSA, and f /tPSA in pre-dialysis and post-dialysis serum samples

	Before Dialysis		After Dialysis		P Value
Parameters	Median	25 – 75th percentile	Median	25 – 75th percentile	
tPSA (ug/L)	1,02	0.17 – 1.03	1,08	0.21 – 1.31	0.567
fPSA (ug/L)	0,75	0.13 – 0.91	0,81	0.17 – 1.03	0.009
f /tPSA (%)	0.705	0.44 – 0.75	0.706	0.43 – 0.81	0.001

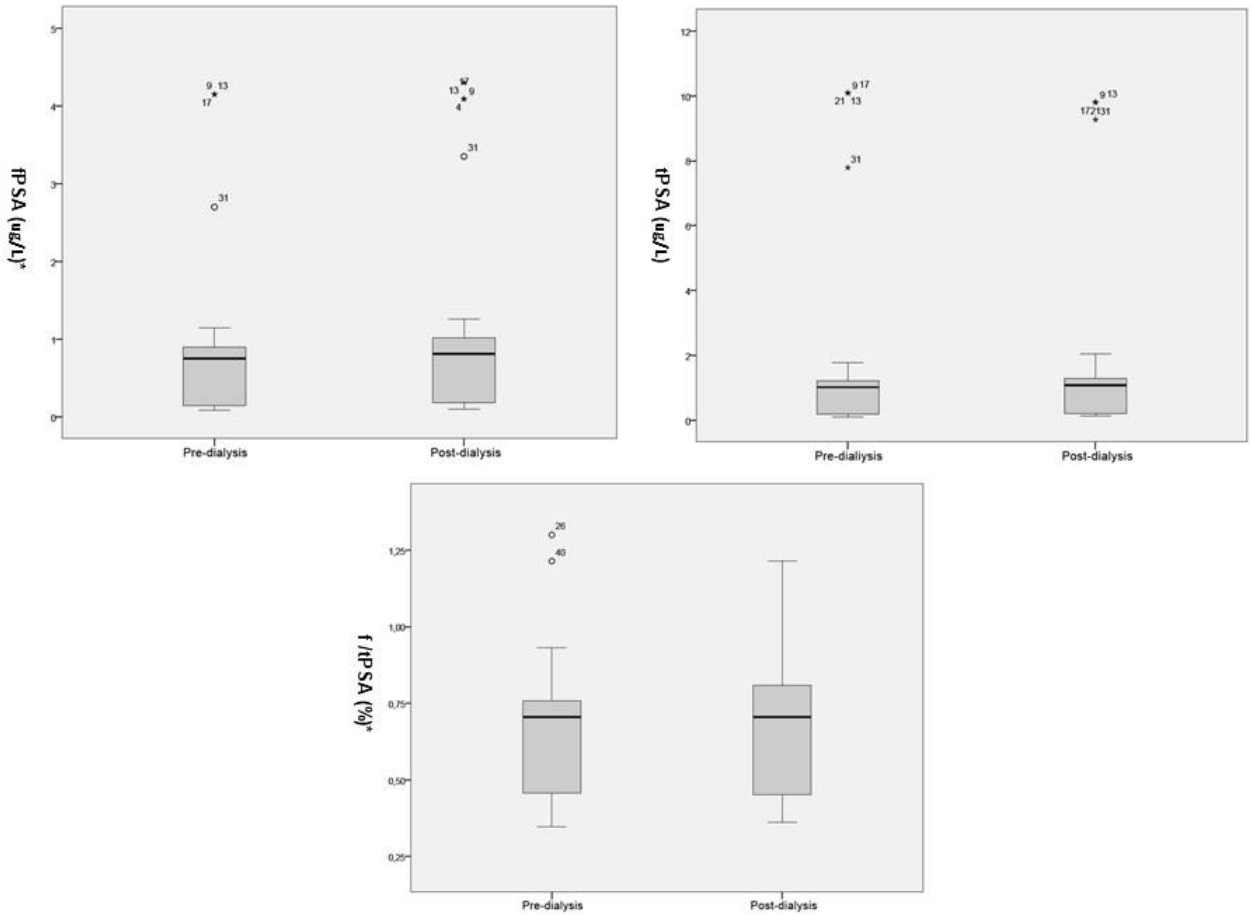

Figure 1. *Box-plots of pre and post-dialysis concentrations of tPSA, fPSA levels, and f /tPSA ratio. Post-dialysis fPSA and f /tPSA levels are significantly higher than pre-dialysis levels. * = Significant difference (p<0.05)*

Table 3. The median and 25th - 75th percentile values of fPSA, tPSA, and f /tPSA in pre-dialysis and post-dialysis samples grouped according to membrane type

Tests	High-flux membrane with a surface area of 1.7m2, KUF of 74 mL/hr/mmHg				P Value	High-flux membrane with a surface area of 1.9m2 KUF of 76 mL/h/mmHg				P Value
	Pre-Dialysis		Post-Dialysis			Pre-Dialysis		Post-Dialysis		
	Median	25 – 75th percentile	Median	25 – 75th percentile		Median	25 – 75th percentile	Median	25 – 75th percentile	
fPSA (ng/mL)	0,63	0,22 - 0,75	0,59	0,26 - 0,89	0.977	0,88	0,13 - 0,91	0,93	0,15 - 1,06	0.06
TPSA (ng/mL)	1,11	0,375 - 1,43	1,06	0,42 - 1,31	0.985	1,12	0,16 - 1,22	1,14	0,17 - 1,27	0.71
f /t PSA (%)	0,59	0.42- 0.74	0,63	0.41 – 0.80	0.845	0.73	0.64 – 0.94	0,71	0.64 – 0.90	0.912

KUF: Ultrafiltration coefficient

There was a positive correlation between the difference in fPSA concentrations measured in the pre- and post-dialysis samples and the ultrafiltrate (rho = 0.380) (p=0.01). A positive correlation was determined between the difference in tPSA concentrations measured in pre- and post-dialysis samples and the ultrafiltrate (rho = 0.562) (p=0.002).

Discussion

There are uncertainties regarding the clinical use of the PSA test in patients undergoing hemodialysis (10). Although serum PSA levels are considered a useful serum marker for the early detection of PCa in patients receiving long-term hemodialysis treatment (3, 11), controversial reports about PSA levels in patients receiving hemodialysis have also been presented. According to the data of patients undergoing hemodialysis treatment and diagnosed with prostate cancer by PSA screening, it has been reported that the PSA test is useful in middle-aged and older hemodialysis patients. However, it has been reported that diagnosis and treatment should be considered according to the patient's clinic after the PSA test was measured high (3). Majoud et al. reported that post-dialysis PSA levels were higher than pre-dialysis significantly (12). There are also studies reporting that there is no significant difference in serum PSA levels analysed before and after hemodialysis (13, 14).

In our study, post-dialysis fPSA results were significantly higher than pre-dialysis fPSA. In the correlation analysis, we found a weak correlation between the amount of ultrafiltrate and the difference in fPSA levels before and after dialysis (rho = 0.380). This shows that the significantly higher post-dialysis fPSA levels in our study than predialysis fPSA levels cannot be attributed only to hemoconcentration. The active fraction of tPSA is in complex with alpha2-macroglobulin or alpha1-antichymotrypsin while a small amount is found in serum as unbound (6). The decrease in plasma alpha1-antichymotrypsin or alpha2-macroglobulin proteins after dialysis treatment may be one of the factors contributing to the increase in plasma fPSA values after dialysis. In the study, the hemoconcentration status of the patients was not evaluated according to the haematocrit values. This is one of the limitations of the study.

When serum samples were grouped according to the type of high-flux membrane used in dialysis, there was no significant difference in fPSA and tPSA values before and after dialysis (Table 2).

Diabetes was found to be the cause of chronic renal failure in the 18 patients we examined. The transportation of proteins across the glomerular barrier is dependent on the physical properties of the molecules, as well as the charge and pore size of the glomerular capillary wall. Molecules with a molecular weight of 40-50 kDa are eliminated through glomerular filtration, reabsorption, and catabolism. The excretion of low molecular weight molecules decreases as the severity of renal failure increases. It has been reported that fPSA levels of patients with chronic kidney disease are higher than the healthy population (15). In diabetic nephropathy, the decrease in heparan sulfate content of the glomerular basement membrane results in reduced permeability to negatively charged macromolecules, such as albumin. While complex PSA (90 kDa) is not excreted by the kidneys, fPSA (a 28 kDa protein) is primarily eliminated through glomerular filtration (16, 17). As a result, the renal clearance of fPSA could potentially vary in patients with diabetic chronic renal failure. However, in our study, the samples were not categorized based on the etiology of chronic renal failure, which represents a limitation of our research.

In conclusion, our study data revealed that fPSA values and f/tPSA ratios were elevated in patients receiving hemodialysis treatment due to hemoconcentration and other potential dialysis effects. Therefore, interpreting fPSA values and f/tPSA ratios in patients undergoing hemodialysis according to current clinical decision limits may lead to misinterpretation. However, the use of tPSA concentrations in patients undergoing hemodialysis treatment is safe as it remains unchanged with dialysis treatment.

Declarations

Funding

The present study was not funded by any corporation.

Conflicts of Interest

The authors declare no conflict of interest.

Ethics Approval

All protocols for this study were approved by the Harran University Clinical Research Ethics Committee (Decree Date and No: 22 June 2022 / HRÜ.22/06/2022)

Availability of Data and Material

All data is available

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