Abstract

Background: Whereas that systemic inflammation (SI) affects 40–60% of patients on hemodialysis (HD) is characterized by serum C-reactive protein (CRP) level elevation or proinflammatory interleukin production or both. We evaluated the association between SI and total (tPSA) and free PSA (fPSA) in patients on HD with tPSA <4ng/ml.

Methods: Sixty patients with chronic kidney disease (CKD) undergoing HD and 20 controls were included. Inclusion criteria were patients aged 18-60 years; tPSA < 4 ng/mL without clinically detectable prostate cancer; and patients undergoing HD for >6 months. Patients were excluded if they had local infections or SI. Hs-CRP was measured using turbidimetry, and tPSA and fPSA levels using immunoluminescence. Overall, 27 patients had inflammation (hs-CRP >5 mg/L) and 33 had no inflammation (hs-CRP was ≤5 mg/L). In the control group, hs-CRP was ≤ 1 mg/L.

Results: There was no significant difference in mean levels among groups 3 and 4 for age (p= 0.058), tPSA (p=0.74) and fPSA (p=0.30). The SI did not promote differences between groups 1, 2 and 4 for the levels of tPSA (0.71 ± 0.18 vs 0.67 ± 0.15 vs 0.67 ± 0.11; p=0.69) and fPSA (0.34 ± 0.01 vs 0.34 ± 0.01 vs 0.35 ± 0.01, p= 0.59). As well as maintained no correlation with tPSA and fPSA (p> 0.05).

Conclusion: The results of this study suggest that systemic inflammation is no associated with changes fractions of tPSA and fPSA in chronic hemodialytic patients without clinically detectable cancer (PSA<4ng/ml).
Introduction
The discovery of prostate-specific antigens (PSA) and its availability as a routine laboratory test have revolutionized the diagnosis, screening, risk stratification, staging, monitoring of treatment outcomes, and recurrence detection of patients with prostate cancer (PC) [1]. PSA levels are considerably altered by several tumor-independent states, metabolism, liver or renal function or both, and inflammation, and sometimes, yield false positive results [2]. Systemic inflammation (SI) has been shown to be highly prevalent in patients with Chronic Kidney Disease (CKD) and hemodialysis (HD), inducing elevated serum levels of proinflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), interleukin-1Beta (IL-1Beta) and C-reactive protein (CRP) [3]. Cumulative evidence has indicated a tight, cause–effect link between oxidative stress, inflamm-aging (chronic inflammatory process) and immunosenescence [4]. Immunosenescence is characterized by a decreased ability of the immune system to respond to foreign antigens and maintain tolerance to self-antigens, resulting in an increased susceptibility to infection and cancer [4]. Previous studies have shown that the risk for cancer increases in patients with CKD, whether or not they are on dialysis, compared with the general population [5,6]. PSA levels < 4.0 ng/mL are considered the cutoff point prevalence in the screening of patients with PC in clinical studies. Patients may not be considered at high risk for PC if they are at the cut-off point, based on their age, race, and prostate volume [7]. This cut-off point is not as safe to exclude false negatives in patients with PC not despicable in people with CKD. Liu et al [8] examined 343 biopsy results of Chinese patients aged 30-91 years with PSA levels ≤ 4.0 ng/mL, and found that the detection rate was 16.28%, 17.17%, 21.82%, and 25.00% in patients with PSA levels 0-1.0 ng/mL, 1.1-2.0 ng/mL, 2.1-3.0 ng/mL, and 3.1 to 4.0 ng/mL, respectively. Choi et al [9] reviewed 3414 prostate biopsies in men with average ages of 55-69 years, and found a prevalence of 23.7% (202/852) for high-grade or insignificant PC no patients with PSA between 3-4 ng/mL.

Objective
Considering non-depressive prevalence of CP and chronic inflammatory process in chronic kidney disease/hemodialysis, we performed a cross-sectional study to evaluate the association between serum tPSA and fPSA levels and SI in men without clinical presentation of prostate disease with PSA levels < 4 ng/mL.

Methods
This prospective prevalence study was conducted at the Center of Hemodialysis of the University Hospital of Brasilia between June 2009 and July 2010. We assessed inflammation via serum high-sensitivity CRP (hs-CRP) measurements in the group case and control. Case group was subdivided in group 1 (with inflammation - CRP > 5 mg/L, n=27), group 2 (without inflammation - CRP ≤5 mg/L, n=33) based on the recommendation of National Kidney Foundation [10] and group 3 ( group 1 + group 2). In the control group 4 (n=20), subjects from the health promotion general outpatient clinic of the same hospital had normal glomerular filtration rate (GFR) and 90 ml/min/1.73m²; low cardiovascular risk was defined as normal CRP values (≤1 mg/L) [11]. The study was approved by the Research Ethics Committee of the Faculty of Medicine of the University of Brasilia under protocol 024/2009.

Patients were included in the study if they were aged 18-60 years, had a tPSA < 4 ng/mL, without clinically detectable PC, and if they underwent HD for >6 months. Patients received high-flux hemodialysis using fistula as vascular access in three 4-h dialysis weekly sessions. Exclusion criteria were local infection or SI. Patients with acute or chronic liver disease, rectal examination in the previous week, prostate biopsy in the previous 4 months, cystoscopy, history of urinary tract infection, clinical signs
of acute or chronic infection/inflammation, positive serology for hepatitis B, C, or HIV, vascular access infection, leukocytosis, fever, or hypoproteinemia were not included in the study.

Blood samples were collected for analysis at the same time, between 8:00 a.m. and 10:00 a.m. in the clinical laboratory of the same hospital. The samples were taken from the arteriovenous fistula immediately before the first weekly HD session in the case group and on a previously scheduled day in the control group. Five milliliters of blood were collected via arm venoclysis without anticoagulant administration. The blood was centrifuged at 3500 x g for 20 min, and the supernatant was collected in a centrifuge tube and maintained at -20°C until tPSA, free prostate-specific antigen (fPSA), and CRP measurements were collected. Serum CRP levels were measured using turbidimetry in the automatic analyzer BN II (Dade Berhing, kit Dade Berhing, USA). tPSA and fPSA levels were measured via enzyme immunochemoluminescence by using the automatic analyzer Immulite 2000/Siemens. Specific kits in addition to calibrators and controls recommended by the manufacturer were used to quantify measurements. All statistical analyses were performed using SPSS® for Windows, version 24.0. After analyzing the sample distribution by using the Shapiro–Wilk normality test, differences between three independent quantitative variables were evaluated using one-way ANOVA test when was normal distribution curve. Those between two independent quantitative variables with normal distribution curve were evaluated using t-test. Statistical significance was set at p < 0.05 to reject the null hypothesis.

Results
There was no significant difference (Table 1) in mean levels among groups 3 and 4 for age (46.00 ± 8.02 vs 42.45 ± 5.18, p= 0.058), tPSA (0.69 ± 0.17 vs 0.67 ± 0.11, p=0.69) and fPSA (0.34 ± 0.01 vs 0.34 ± 0.01 vs 0.35 ± 0.01, p= 0.59). As well as maintained no correlation (Table 2) with tPSA and fPSA (p> 0.05).

Table 1. Comparative evaluation of Age (years) and PSA (ng/mL) serum level between Case/control.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ranges</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>SD1</th>
<th>p-value</th>
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<td></td>
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<td>33-60</td>
<td>60</td>
<td>46.00</td>
<td>46.00</td>
<td>8.02</td>
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<tr>
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<td>42.45</td>
<td>43.00</td>
<td>5.18</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>Group 3</td>
<td>0.50-1.10</td>
<td>60</td>
<td>0.69</td>
<td>0.64</td>
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<td>0.67</td>
<td>0.68</td>
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<tr>
<td>fPSA 3</td>
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<td></td>
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<td>0.32-0.38</td>
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<td>0.34</td>
<td>0.35</td>
<td>0.01</td>
<td>0.30</td>
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<tr>
<td>Group 4</td>
<td>0.33-0.38</td>
<td>20</td>
<td>0.35</td>
<td>0.35</td>
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</table>

Table 2. Correlacional evaluation of CRP (mg/L) and PSA (ng/mL) serum level in groups case.

<table>
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<tr>
<th>Variables</th>
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<th>p</th>
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<tr>
<td>tPSA x CRP &gt; 5mg/L</td>
<td>27</td>
<td>0.169</td>
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</tr>
<tr>
<td>fPSA x CRP &gt; 5mg/L</td>
<td>27</td>
<td>0.074</td>
<td>0.71</td>
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<tr>
<td>tPSA x CRP ≤ 5mg/L</td>
<td>33</td>
<td>0.244</td>
<td>0.17</td>
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<tr>
<td>fPSA x CRP ≤ 5mg/L</td>
<td>33</td>
<td>0.118</td>
<td>0.51</td>
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<td>Group 3</td>
<td></td>
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<tr>
<td>tPSA x CRP</td>
<td>60</td>
<td>0.190</td>
<td>0.14</td>
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<tr>
<td>fPSA x CRP</td>
<td>60</td>
<td>0.046</td>
<td>0.72</td>
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Discussion

Our work has its merit of being the first study to evaluate the possible association between serum tPSA and fPSA levels and SI in CKD/HD. The dilemma of performing prostate biopsies leading to biopsies with increased risks for bleeding, sepsis, and increased costs in patients with serum PSA levels < 4 ng/mL and without clinical suspicion of PC is significant. Especially because 20% of detectable PCs occur in patients with this PSA levels [12] and frequent association of SI with HD [13] The behavior dual of the serum levels of PSA in studies with patients in HD, elevated time; time without change, made us think about the possibility of systemic inflammation being a factor to be considered in the analysis and interpretation of PSA levels in these patients.

Studies in the non-uremic population demonstrated the possible association of inflammation with elevation of PSA levels. Lippi G et al [14] performed PC screening in a sample population (n = 302) over 35 years old found that CRP levels > 5 mg/dL were associated with PSA levels > 2.5 mg/dL, compared with PSA < 2.5 ng/mL. McDonald et al [15] evaluated several inflammatory markers in a sample of 3164 healthy men aged > 40 years without prostatic diseases and found a positive association in those with PSA ≥ 4 ng/mL, compared with PSA <4 ng/mL; this association was not maintained after adjusting for age and other variables.

Our results showed that SI did not interfere with PSA levels because there were no differences (Table 1) or correlations (Table 2) between group of cases (groups 1 and 2) and group 4 of healthy patients. We results are differ to Sánchez [16] compared PSA serum levels between 190 patients on low-flow membrane HD (mean age, 55 years) and 237 non-uremic patients (mean age, 56 years) and found higher PSA levels in patients on HD; significant differences were seen among patients <50 years, fPSA (p ≤ 0.007) and tPSA (p ≤ 0.000). And Rodríguez et al. [17] compared a sample of 32 patients on low-level HD and 64 controls with preserved renal function and similar mean ages, they found higher significant fPSA levels (p = 0.0001) and similar of tPSA levels (p = 0.87) when compared case and control.

On the other hand our results are similar from the authors with Maoujoud et al [18] evaluated the influence of ESRD on concentrations of five tumor markers, including PSA, in 76 patients maintained on low-flow HD. They found that PSA levels were higher in the HD group (n = 76), compared with the control group of healthy volunteers (n = 50); no statistically significant difference was observed between the groups (p = 0.271). Zhang et [19] assessed the impact of uremia and hemodialysis on tumor markers, including PSA, in 143 patients maintained on low-flow HD versus 143 non-hemodialytic uremic patients and 429 healthy control patients. They found non-expressive percentages of tPSA and fPSA elevations, 9.75% and 11.3% (group with HD) and 8.76% and 10.8% (group without HD) with no statistical difference was observed between groups. Mehmet et al [20] compared tPSA and fPSA levels in a sample of 35 patients on HD and 35 control patients with normal renal function. They did not reported the dialysis modality used unfortunately and did not find a difference in PSA levels between cases and controls.

This divergent results can be partially explained by incomplete information regarding the type of membrane used (high-flux membranes are permeable to the fPSA molecule; low-flux membrane is impermeable to PSA fractions), conclusions based on measurements performed after HD sessions without proper correction of hemoconcentration. Change in the methodology of measuring PSA differences in calibration, cross-reactivity to PSA homologous antigens, Kit manufacturer has an important contribution [21].

In our study the stability of levels of tPSA should be explained by their impermeability to high-flux membrane. fPSA serum levels; not significantly los-
ses through the high flux membrane should be com-
pensated by permanent stimulus to the production
of fractions of fPSA promoted by the chronic syste-
mic inflammation and normality of binding proteins
in the patients in HD or the both corroborated for to
compensate the loss low transmembrane and avoid
large changes in the levels [22]. The limitations of
the present study were use of PCR as a non-specific
marker of inflammation and possible PSA bias rela-
ted to prostate volume/ethnicity.

Conclusion
The results of this study suggest that systemic in-
flammation is no associated with changes fractions
of tPSA and fPSA in chronic hemodialytic patients
without clinically detectable cancer (PSA<4ng/ml)).
Further investigations are needed to confirm the
results.

Abbreviations
hs-CRP, high-sensitivity C-reactive protein; CRP, C-
reactive protein; IL-6, Interleucin-6; SI, systemic in-
flammation; PC, prostate cancer; ESRD, end-stage
renal disease; Chronic Kidney Disease (CKD), HD,
hemodialysis; PSA, prostate-specific antigen; fPSA,
free prostate-specific antigen; tPSA, total prostate-
specific antigen; tumor necrosis factor-alpha (TNF-
alpha), interleukin- 1Beta (IL-1Beta)

Compliance with Ethical Standards

Competing interests
The authors declare that they have no competing
interests.

Ethical approval
Approved by the Research Ethics Committee of the
Faculty of Medicine of the University of Brasilia un-
der protocol 024/2009.

Informed consent
Informed consent was obtained from all individual
participants included in the Study.

Authors’ contribution
GPS drafted the manuscript. and VPXG critically re-
viewed it and makes addition.

The authors declared the final version of manus-
script.

References
1. Printz C. Early-stage prostate cancer, PSA screening rates
2. Trapé J, Filella X, Alsina-Donadeu M, Juan-Pereira L, Bosch-
Ferrer A, Rigo-Bonnin R, et al. Increased plasma concentrations
of tumour markers in the absence of neoplasia. Clin Chem Lab
3. Akchurin OM, Kaskel F. Update on inflammation in chronic
Oxidative stress, inflamm-aging and immunosenescence. J
5. Cheung CY, Chan GCW, Chan SK, Ng F, Lam MF, Wong
SSH, et al. Cancer Incidence and Mortality in Chronic Dialysis
Association of dialysis with the risks of cancers. PLoS One. 2015
Apr 13; 10 (4):e0122856.
7. Stephan C, Miller K, Jung K. Is there an optimal prostate-specific
antigen threshold for prostate biopsy? Expert Rev Anticancer
8. Liu X, Tang J, Fei X, Li QY. Prostate-specific Antigen (PSA)
Density and Free to Total PSA Ratio in Diagnosing Prostate
Cancer with Prostate-Specific Antigen Levels of 4.0 ng/ml or
Prevalence of high-grade or insignificant prostate cancer in
Korean men with prostate-specific antigen levels of 3.0-4.0 ng/
10. KDOQI. KDOQI Clinical Practice Guideline and Clinical Practice
Recommendations for anemia in chronic kidney disease: 2007
update of hemoglobin target. Am J Kidney Dis. 2007 Sep; 50
(3):471-530.
11. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk


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