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Does serum prostate specific antigen levels correlate with the prostatic inflammation in elderly patients without clinically proven prostate cancer?

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ABSTRACT

Objectives: To determine the whether histological prostatic inflammation correlates with serum prostate specific antigen (PSA), free PSA (fPSA) and percent of fPSA (%fPSA) levels in elderly patients without clinically proven prostate cancer.

Methods: A total of 115 patients without clinically proven prostate cancer with transrectal prostate biopsy were included in this retrospective study. Patients were divided two main groups as patients with and without histologic prostatic inflammation. A grading of the histological prostatic inflammation was performed and patients with prostatic inflammation were divided into three subgroups. The age, prostate volume, serum PSA, fPSA and %fPSA levels were compared between patients with and without prostatic inflammation. Correlation between the parameters and grade of prostatic inflammation was also investigated.

Results: Serum PSA and %fPSA levels were significantly higher in men with histologically proven prostatic inflammation (15.47 ± 15.28 ng/mL vs. 11.67 ± 8.12 ng/mL; $p = 0.002$ and 19.8 ± 0.7 vs. 15.79 ± 0.9; $p = 0.01$, respectively). The mean serum PSA levels were significantly different among the subgroups ($p = 0.02$) and prostatic inflammation correlated positively with the PSA levels ($r = 0.320$, $p < 0.001$).

Conclusions: Our findings suggested that reporting the grade of prostatic inflammation in elderly patients may help avoiding unnecessary repeat biopsies if elevated serum PSA level is the only indication for initial prostate biopsy.

Keywords: Inflammation, prostate, prostate specific antigen, elderly, men

The serum prostate-specific antigen (PSA) is the most important and widely used marker in the screening, detection, and monitoring of prostate cancer (PCa) [1]. Millions of prostate biopsies are performed annually, most commonly due to an elevated PSA level. In addition to PCa, benign conditions such as benign prostatic hyperplasia (BPH) and prostatic inflammation can also increase the serum PSA levels [1, 2]. Histological findings of the prostatic inflammation in prostate biopsy or prostatectomy specimens are common in asymptomatic patients, as well as those with BPH [2]. Several studies have investigated the relationship between serum PSA level and histological prostatic inflammation in asymptomatic males; how-

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ever, the results have been controversial [3-5]. The previous studies were performed using either the intensity or the extent of neutrophilic infiltration in the prostate for grading the inflammation with a relatively lower number of specimens.

In the present study, we aimed to determine whether the histological prostatic inflammation correlates with serum PSA, free PSA (fPSA) and percent of fPSA (%fPSA) levels in elderly patients without clinically proven prostate cancer.

METHODS

The institutional ethical board approved the study (Approval ID: 2017/565). Data of the patients who underwent transrectal ultrasound guided 12-core prostate biopsy between January 2004 and January 2006 due to elevated serum PSA levels or abnormal digital rectal examination findings were collected retrospectively. A total of 260 patients were identified and patients with a history of documented acute/chronic prostatitis, symptoms related to acute/chronic prostatitis, urinary tract infection and abnormal digital rectal examination findings were excluded. Previous prostate biopsy and/or surgery, radiotherapy, 5-alpha reductase inhibitor treatment, and a history of urethral catheterization and non-steroidal antiinflammatory drug usage 2 weeks before the prostate biopsy were other exclusion criteria. Moreover, patients with diagnosis of PCa or high grade prostatic intraepithelial neoplasia on the current biopsy were also excluded.

All serum PSA and fPSA levels were measured in the same institute and device (Immulite 2000, DPC, Los Angeles, CA, USA). The %fPSA was calculated as the free/total serum PSA ratio . A urine analysis was performed just before the biopsy to rule out the evidence of urinary tract infection. Transrectal ultrasonography (Logic 400 machine, GE, Milwaukee, WI) with a 7.5-MHz endorectal probe was used to determine the prostate volume and to guide the needle biopsy. The total of 12-core prostate sampling was performed during the transrectal ultrasound guided prostate biopsy (TRUS-Bx) for each man in the lateral decubitus position, using an 18-gauge needle and an automatic biopsy gun. All patients received oral ciprofloxacin (500mg twice daily) for 7 days starting from the night before the biopsy and an enema at the morning of the procedure.

The pathological specimens of the patients diagnosed with benign prostatic pathologies were underwent further histological evaluation to determine the degree of inflammation by a single uropathologist (CB). The newly designed grading system based on the intensity and the extent of the prostatic tissue neutrophilic infiltration and tissue destruction to categorize and determine the grade of prostatic inflammation was used (Table 1 and Fig. 1). The degree of prostatic inflammation was evaluated in all 12 biopsy cores and grades of the inflammation were scored from 1 to 3.

Finally, men were classified to patients with and without prostatic inflammation and the parameters were statistically compared between patients with and without prostatic inflammation. Patients with prostatic inflammation were also classified to 3 subgroups according to grade of prostatic inflammation and correlation between the parameters and grade of prostatic inflammation was also investigated.

Statistical Analysis

Data were analyzed using SPSS-16 for Windows (SPSS Inc., Chicago, IL). Test of normality was determined with Shapiro-Wilk test. Kruskal Wallis Test, Mann Whitney U Test and Spearman correlation test were used to analyze the statistical differences. The results are expressed as mean ± SD while $p < 0.05$ was

Table 1. Classification of the prostatic inflammation according to intensity and the extent of the neutrophilic infiltration

Grade of inflammation	Description
Grade 1	Scattered neutrophilic infiltrate in < 6 biopsy cores (Fig. 1A).
Grade 2	Scattered neutrophilic infiltrate in ≥ 6 biopsy cores or scattered neutrophilic infiltrate in <6 biopsy cores with intensifying in some focal areas (Fig. 1B).
Grade 3	Heavy neutrophilic infiltrate intensifying in some focal areas in ≥ 6 biopsy cores and/or destruction of glands in any cores (Fig. 1C).

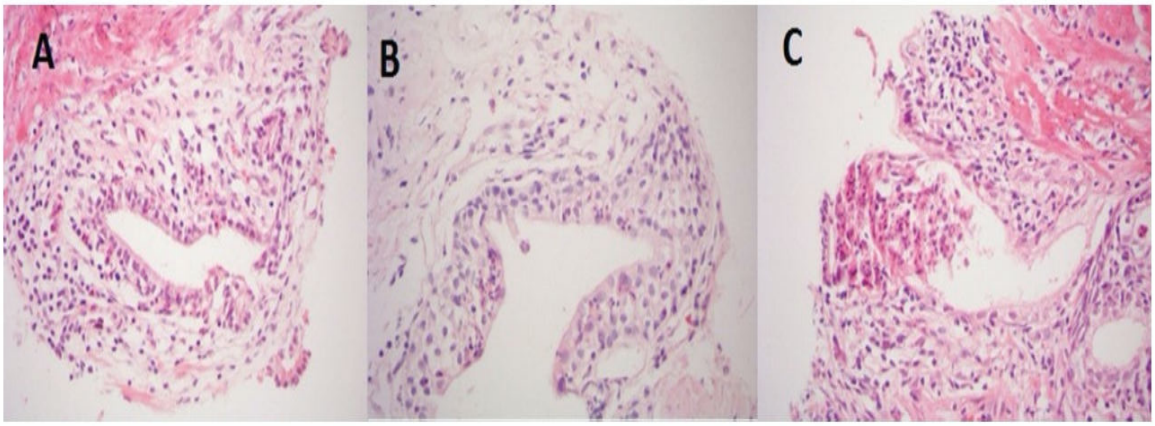

Fig. 1. (a) Scattered neutrophilic infiltrate in stroma, and in gland epithelia. Hematoxylineosin stain, orginal magnification ×400. (b) Conspicuous neutrophilic infiltrate in gland epithelia. Hematoxylin-eosin stain, orginal magnification ×400. (c) Destructed gland with heavy neutrophilic infiltrate. Hematoxylin-eosin stain, orginal magnification ×400.

considered as statististically significant.

RESULTS

Of the 260 men 115 met the inclusion criteria. The mean age, prostate volume, serum PSA and fPSA levels and %fPSA levels were 64.7 ± 7.56 years, 51.4 ± 24.7 cm 3, 12.66 ± 10.73 ng/mL and 17.52 ± 1.2, respectively. Prostatic inflammation was diagnosed in 50 (43.47%) patients. Mean serum PSA and %fPSA levels were significantly higher in men with histologically proven prostatic inflammation (15.47 ± 15.28 ng/mL vs. 11.67 ± 8.12 ng/mL; $p = 0.002$ and 19.8 ± 0.7 vs. 15.79 ± 0.9; $p = 0.01$, respectively). However, the mean age (65.4 ± 7.0 vs. 63.3 ± 9.8 years), serum fPSA level (2.09 ± 1.44 vs. 2.67 ± 4.2 ng/mL) and prostate volume (51.7 ± 24.0 vs. 51.86 ± 27.1 cm3) were similar in patients with and without prostatic inflammation ($p = 0.32$, $p = 0.08$ and $p = 0.42$, respectively).

Table 2 summarizes the demographics and characteristics of the patients among the prostatic inflammation subgroups. Mean age and prostate volume were similar between the subgroups ($p = 0.27$ and p = 0.64, respectively). In the subgroup analysis, the grade of prostatic inflammation was significantly correlated with the serum PSA levels (r = 0.320, $p < 0.001$). The mean PSA level of the patients with grade 3 prostatic inflammation was significantly higher than those of with grade 1 inflammation ($p = 0.001$). Serum fPSA levels, on the other hand, were similar among different groups ($p = 0.07$). However, percent of fPSA was correlated negatively with the grade of prostatic inflam-

Table 2. Patient characteristics and the parameters according to inflammation subgroups

Characteristics	Inflammation severity within the prostate gland			*p* and r value	*p* value
	Grade 1	Grade 2	Grade 3		
Patients (n)	30	11	9		
Age (year)	65.0 ± 8.9	61.3 ± 5.9	60. 2 ± 6.1		0.27*
Prostate volume (cm3)	47.5 ± 23.2	56.3 ± 30.4	61.0 ± 34.0		0.64*
PSA (ng/ml)	13.8 ± 10.3	13.3 ± 10.8	29.0± 29.7	**< 0.001†** r = 0.320	**0.02***
fPSA (ng/ml)	2.09 ±1.8	2.05 ±2.5	5.4 ± 8.3		0.07*
%fPSA	16.2 ± 0.7	15.6 ± 1.2	13 ± 1.9	**0. 01†** r = - 0.286	0.06*

Data presented as mean ± standard deviation. PSA = prostate-specific antigen, fPSA = free prostate-specific antigen. *Kruskal Wallis Test, †Spearman correlation test.

mation (r = -0.286, p = 0.01).

DISCUSSION

With the widespread application of PSA based screening, most of the current prostate biopsies are performed due to elevated PSA levels [1]. However, an important percentage of these patients do not have PCa as other factors such as BPH, prostate volume, and the age of the patients can also result in increased PSA levels [1]. On the other hand, TRUS-Bx may fail to detect cancer in up to 30% of patients [6], making the faith of the patients with negative biopsies more challenging. However, excluding the patients with elevated PSA levels because of benign conditions may decrease the necessity of repeated prostate biopsies. In the present study, we found that serum PSA level were significantly higher in men with prostatic inflammation. Moreover, we determined a significant correlation between serum PSA level and prostatic inflammation, graded on a 3-point scale. Approximately 70 to 90% of PSA is bound to alpha-1-antichymotripsin in serum and called total PSA. The remaining 10 to 30% of the PSA which is not bound to serum proteins represents the fPSA. As such in PSA, there are controversial results about the correlation between prostatic inflammation and serum fPSA and %fPSA levels [3, 4]. Our findings revealed that despite fPSA levels were comparable among the groups, %fPSA was significantly lower in patients with prostatic inflammation. A negative correlation with %fPSA and prostatic inflammation were also determined. We thought that it could be explained by the increased serum total PSA levels with prostatic inflammation, while the fPSA was stable. In our opinion, according to our results, unnecessary repeat biopsies may be avoided in elderly patients with elevated serum PSA levels who have high grade prostatic inflammation and normal digital rectal examination findings. In this group of men, the only determinant of elevated serum PSA levels seems to be prostatic inflammation without histologic PCa and its indicator abnormal digital examination findings. Therefore, detailed intensity and extent of neutrophilic infiltration within the prostate gland should be provided in the pathology reports of the biopsies. However, the possibility of PCa should always be kept in mind, and these patients should be closely followed up with serial digital rectal examination and serum PSA measurements. Or, as such in recent years, the use of various imaging techniques such as contrast-enhanced ultrasound, sonoelastography, and multiparametric prostate magnetic resonance imaging (mpMRI) may be rationale [7-9].

Two possible mechanisms exist explaining why prostatic inflammation increases the serum PSA levels. One of them is, the epithelial cells surrounding the affected area may be stimulated to produce PSA through unknown substances released in association with the inflammatory processes [10]. The other possible mechanism is that the disturbance of the prostate duct integrity by the inflammation causes leakage of PSA from the acini and ductal lumina to the interstitium [11]. It seems that our findings may support both of the mechanisms. However, higher serum PSA levels with higher grade which exhibits significant destruction of the prostate tissue clearly supported the second mechanism. In the literature, whereas some previous reports have not showed an association between the serum PSA level and prostatic inflammation, several studies have successfully demonstrated clear evidences about the association between them [3, 5, 12-14]. Hasui *et al*. [14] investigated a total of 42 patients who underwent transurethral resection of the prostate (TURP) and demonstrated a statistically significant positive correlation between histological acute prostatitis and serum PSA levels with a 0.765 correlation coefficient. However, the authors reported that the correlation between serum PSA and the extent of chronic-inactive prostatitis was not significant [14]. Okada *et al*. [5] also confirmed the findings of Hasui *et al* using TRUS-Bx specimens. The authors investigated the correlation between histological prostatic inflammation and serum PSA level in 93 patients and found that the degree of acute inflammation was the only parameter correlating significantly with serum PSA levels in patients with a prostate volume smaller than 25 mL [5]. In 2012, Man *et al*. [15] reported that the aggressiveness and extent of prostatic inflammation in 120 asymptomatic prostatitis patients were significantly correlated with level of serum PSA. The other study published by Stimac *et al*. [4] in 2014 reported a significant negative correlation of inflammation aggressiveness with fPSA (r = -0.31, p = 0.001) and %fPSA (r = -0.43, p < 0.001), but not with PSA, in 106 patients with lower than 10 ng/mL PSA levels.

In a large sample study investigated 6238 men aged 50 years to 75 years with PSA levels between 2.5 ng/mL and 10 ng/mL, it has been reported that prostatic inflammation upon first biopsy reduces the odds of PCa in repeat biopsies, presumably reflecting an elevated PSA as a result of inflammation (16]. A most recent study published by Kato *et al*. [17] in 2016 which attempted to clarify the association between PCa detection and various risk factors in 24-core repeat saturation biopsies has revealed that patients with asymptomatic inflammation appear to have a lower risk of PCa. The authors concluded that it should be considered that inflammation may cause persistent elevated PSA in patients with a negative initial biopsy, leading to unnecessary repeat biopsy [17]. Almost all previous papers used grading systems relying either on the intensity or extent of inflammation [5, 18]. In the present study, the inflammation was categorized more profoundly, using both the intensity and the extent of inflammation. We evaluated all the 12 specimens, as well, for each patient which may predict the extent of the inflammation more precisely. We took into consideration the age, prostate volume and digital rectal examination findings of the patients, three parameters with proven effects on PSA levels, as well. In our opinion, the most important superiority of the current study was the exclusion of patients with positive digital rectal examination findings even if they had no PCa diagnosis on TRUS-Bx. Therefore, the exclusion of PCa diagnosis was performed optimally in our study cohort and strengthened our results. In 2015, Umbehr *et al*. [19] investigated the association of intraprostatic inflammation and serum PSA in 224 men excluding the patients with abnormal digital rectal examination findings and histologically diagnosed PCa. Nevertheless, they considered only patients with serum PSA levels < 4 ng/mL. The authors found that prostatic inflammation was associated with higher serum PSA. Our findings were comparable with Umbehr *et al*.'s results [19] and we confirmed their report in men with any PSA levels. Finally, a recent systematic literature review published in 2018 and investigated two randomized trials and nine cohort studies with a total 1011 patients have demonstrated that antibiotic treatment exhibit a decrease in serum PSA levels of the patients with asymptomatic prostatitis [20]. Result of that systematic literature review can be accepted as a clear evidence of the elevated serum PSA levels with chronic inflammation. And, our findings were coherent with this hypothesis.

Limitations

The present study had some limitations. First the efficacy and reproducibility of the grading system has not been validated. Secondly, the inflammatory cells were only visually determined based on hematoxylin-eosin staining and morphology. We did not stain for immune cell surface markers and did not use image analysis. Thirdly, we could have performed mpMRI to exclude the diagnosis of PCa more successfully. We think that it can be an interesting topic for future researches. Beyond the limitations, the exclusion of patients with suspicious digital rectal examination findings even if they had no PCa diagnosis on TRUS-Bx provided an optimal exclusion of PCa diagnosis and strengthened our findings.

CONCLUSION

In conclusion, prostatic inflammation was correlated with serum PSA and %fPSA levels. We concluded that histologically proven prostatic inflammation may be used to prevent unnecessary repeat prostate biopsies in elderly patients who underwent TRUS-BX and diagnosed with benign pathologies. However, more investigations are needed and furtherstudies are awaited. Moreover, the possibility of PCa should be kept in mind, and these patients should be followed periodically.

Authors' Contribution

Study Conception: EK, AÇ; Study Design: MZT, ÇB; Supervision: EK; Funding: EK; Materials: ÇB, YB; Data Collection and/or Processing: AÇ, YB; Statistical Analysis and/or Data Interpretation: MZT, ÇB; Literature Review: AÇ, YB; Manuscript Preparation: AÇ, MZT and Critical Review: ÇB, EK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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