Research Article

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Serum proPSA as a marker for reducing repeated prostate biopsy numbers

Tekrarlanan prostat biyopsi sayısı azaltılma belirteci olarak serum proPSA

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Abstract

Introduction: Prostate specific antigen (PSA) has a lower sensitivity and specifity range of 4–10 ng/mL. We aimed to investigate the effectiveness of pPSA in reducing number of prostate biopsies.
Methods: This study enrolled 80 patients aged 50 years or older whom had serum total PSA levels between 4 ng/dL and 10 ng/dL. Age, prostate volume, tPSA, fPSA, pPSA, PSA%, pPSA%, t/pPSA, f/pPSA, p/fPSA, p/tPSA, f/p/tPSA, p/f/tPSA, PSAD, fPSA/PSAD, pPSA/PSAD, (Prostate Health Index) PHI, (t/f/pPSA)/tPSA, and PHI2 (New Prostate Health Index) biopsy results were compared between subjects BPH and PCa.
Results: Out of 80 subjects, 23 (29%) had PCa and 57 (71%) had BPH. Prostate volume was 51.65 mL in PCa and 64.85 mL in non-PCa group ($p > 0.05$). The rate of PCa increased as prostate volume was reduced and age increased. fPSA, PSA%, p/f/tPSA, fPSA/PSAD values were significant in favor of respectively; BPH, BPH, PCa and BPH ($p < 0.05$).
Discussion: Using prostate health index (PHI) was beneficial for predicting PCa. In addition, using pPSA in formulas such as (PHI2) pPSA/(fPSA*√tPSA), p/f/tPSA, (t/f/pPSA)/tPSA may also be useful. This study suggests that the use of pPSA may have a role in reducing the number of prostate biopsies in differentiating PCa and BPH.

Keywords: Prostate cancer; Prostate biopsy; PSA; proPSA, Prostate health index.

Özet

Amaç: Prostat spesifik antijen (PSA) 4–10 ng/mL aralığında düşük sensitivite ve spesifiteye sahiptir. Biz prostat biyopsilerinin sayısını azaltmak için proPSA (pPSA) ve türevlerinin etkinliğini göstermeyi amaçladık.
Yöntem: Elli yaş ve üzeri, PSA serum değeri 4–10 ng/mL arasında olan 80 hasta çalışmaya dahil edildi. Yaş, prostat hacmi, tPSA, sPSA, pPSA, PSA%, pPSA%, t/pPSA, s/pPSA, p/sPSA, p/tPSA, s/p/tPSA, p/s/tPSA, PSA Dansitesi (PSAD), sPSA/PSAD, pPSA/PSAD, Prostat Sağlık İndeksi (PHI), (t/s/pPSA)/tPSA, ve Yeni Prostat Sağlık İndeksi (PHI2) değerleri benign prostat hiperplazisi (BPH) ve prostat kanseri (PCa) arasında t-test, MANOVA ile karşılaştırıldı.
Bulgular: Seksen hastanın 23'ü (29%) PCa ve 57'si (71%) BPH idi. Prostat hacmi PCa'da 51.65 mL, PCa olmayan grupta 64.85 mL olarak bulundu ($p > 0.05$). PCa oranları prostat hacmi azaldıkça ve yaş arttıkça artmaktaydı. fPSA, PSA%, p/f/tPSA, fPSA/PSAD değerleri sırasıyla BPH, BPH, PCa ve BPH olarak anlamlılık göstermekteydi ($p < 0.05$).
Sonuç: PHI kullanılması PCa'nın öngörülmesinde faydalıydı. Buna ilaveten, PHI2, pPSA/(sPSA*√tPSA), p/s/tPSA, (t/s/pPSA)/tPSA benzeri farklı formüller içinde pPSA kullanıldığında PCa ve BPH'nın ayırtedilmesinde prostat biyopsi sayısının azaltılmasında bir rol oynayabilir.

Anahtar Kelimeler: Prostat Kanseri; Prostat Biyopsisi; PSA; proPSA; Prostat Sağlık İndeksi.

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Introduction

Prostate-specific antigen (PSA) is the most widely used marker in the early diagnosis, treatment and monitoring of prostate cancer (PCa). However, despite being an organ-specific marker, PSA is not perfect because of the uncertainties it creates. It has low sensitivity and specificity for the diagnosis of PCa, particularly in conditions when total PSA (tPSA) in serum is in the range of 4–10 ng/mL [1]. Despite the development of various formulations in which PSA kinetics and PSA derivatives such as tPSA, free PSA (fPSA) and proPSA (pPSA) are used in order to increase the sensitivity and specificity of PSA, no significant progress has yet been achieved. No markers or formulae are currently available to permit diagnosis of PCa solely on the basis of serum markers without biopsy.

The probability of PCa being detected in the first biopsies of patients with serum tPSA values of 4–10 ng/dL is 20%–25%. Biopsy is therefore repeated after a specific interval. The probability of identifying PCa from repeat biopsy results is low. The search for serum and urine markers for the purpose of preventing repeated prostate biopsies is therefore continuing. Persisting PSA elevations in patients undergoing biopsy therefore necessitate a second biopsy or saturation biopsy, and in the event of small acinar proliferation (ASAP), prostatic intraepithelial neoplasia (PIN) benign prostate hyperplasia (BPH) or prostatitis at repeat biopsies a third biopsy or even saturation biopsy may be required [2]. Biopsy is an invasive procedure. Although it has few complications, symptoms such as sepsis, bleeding or bloody ejaculation can be troubling to patients [3]. It is therefore desirable to reduce the need for biopsy, and biopsy should be performed on cases with a high probability of diagnosis of cancer. However, it is also important that diagnosis of patients with PCa should not be delayed.

While research concerning PSA is continuing, the higher specificity of pPSA in particular in the sera of patients with PCa and increased pPSA in histopathological terms at pathological examination of tissues with PCa in some recent studies have directed to the attention of researchers toward this marker. pPSA and its derivatives and the prostate health index (PHI) have been increasingly reported in the literature [4]. ProPSA is a precursor of PSA consisting of 244 amino acids. It is largely secreted from cancerous tissue in the peripheral zone. It is frequently described as [-7]pPSA, although another important form is [-2]pPSA, which consists of 239 amino acids. Although subsequent research has also identified [-1], [-5], [-6] and [-4]pPSAs, the most stable form has been defined as [-2] pPSA (p2PSA) [5].

This study used sera from 80 consecutive patients presenting to the urology clinic, with normal prostate at rectal finger examination and serum tPSA levels of 4–10 ng/dL. The purpose of this study was to compare pPSA and its derivatives with prostate biopsy results and to investigate, in a Turkish population, whether the PHI, which has recently become popular and approved for routine use in various countries, can play an effective role in reducing biopsy numbers. This study also describes comparative studies of various formulations added by ourselves.

Materials and methods

Patients and characteristics

Permission for the study was granted by the Ordu University Non-Interventional Research Ethical Committee (No. 58293865-50 dated 20/02/2013). Eighty consecutive patients aged 50 or more presenting to our hospital's urology clinic in 2013–2014, with tPSA values of 4–10 ng/dL and electing to undergo biopsy were included in the study. Patients were informed about the pre- and post-biopsy procedures and potential complications, and informed consent forms were obtained. Patients with a doubtful condition at rectal finger examination (such as nodule or areas of hardness) and with urinary tract infection were excluded.

Age, prostate volume, tPSA, fPSA, pPSA, PSA%, pPSA%, t/pPSA, f/pPSA, p/fPSA, p/tPSA, f/p/tPSA, p/f/tPSA, PSA density (PSAD), fPSA/PSAD, pPSA/PSAD, [(pPSA/fPSA)*√tPSA] (PHI) and (t/f/pPSA)/tPSA [pPSA/(fPSA*√tPSA)] (PHI2) defined by ourselves were compared among patients with PCa and BPH diagnosed at biopsy.

Specimen collection and preparation

Sera separated from blood collected for the investigation of tPSA and fPSA were stored at – 80°C until pPSA assay. Total PSA and fPSA tests were performed using Abbott brand kits on an Abbott Architect i2000 immunoanalyzer. ProPSA assay (proPSA kit Cusabio Human proprostate specific antigen Catalog No: CSB-ET027786HU) (CUSABIO, China) was performed on an Quantitative Sandwich Enzyme Immuno Assay (ELISA) method (BioTek Instruments, Inc., Winooski, VT05404 USA) using the quantitative sandwich enzyme immunoassay technique.

Table 1: PCa and non-PCa patients: comparison to PSA, pPSA, PHI, PHI2 and the other formulations.

	Non-PCa (n) (%71)	Mean ± SE	PCa (n) (%29)	Mean ± SE	p-Value
Years	57	65.16 ± 1.18	23	69.17 ± 1.80	0.826[a]
Prostate volume (mL)	48	64.85 ± 4.54	17	51.65 ± 6.57	0.129[b]
tPSA (ng/mL)	57	6.41 ± 0.19	23	6.30 ± 0.48	0.718[b]
fPSA (ng/mL)	57	1.31 ± 0.07	23	0.98 ± 0.12	0.005[b]
pPSA (ng/mL)	57	0.14 ± 0.01	23	0.18 ± 0.03	0.161[b]
PSA%	57	20.54 ± 0.92	23	15.41 ± 1.35	0.002[b]
pPSA%	57	2.19 ± 0.26	23	3.03 ± 0.47	0.103[b]
t/pPSA	57	81.27 ± 8.66	23	77.52 ± 18.13	0.384[b]
f/pPSA	57	16.17 ± 1.73	23	11.14 ± 2.39	0.060[b]
p/fPSA	57	0.14 ± 0.03	23	0.67 ± 0.47	0.060[b]
p/tPSA	57	0.02 ± 0.003	23	0.03 ± 0.004	0.103[b]
f/p/tPSA	57	2.77 ± 0.34	23	1.77 ± 0.39	0.094[b]
p/f/tPSA	57	0.02 ± 0.006	23	0.11 ± 0.06	0.039[b]
PSAD	48	0.13 ± 0.01	17	0.15 ± 0.025	0.219[b]
fPSA/PSAD	48	14.49 ± 1.49	17	7.88 ± 1.02	0.013[b]
pPSA/PSAD	48	1.50 ± 0.24	17	1.76 ± 0.50	0.601[b]
PHI	57	0.34 ± 0.07	23	1.74 ± 1.27	0.052[b]
(t/f/pPSA)/tPSA	57	0.77 ± 0.01	23	0.81 ± 0.01	0.009[b]
PHI2	48	0.06 ± 0.01	23	0.27 ± 0.17	0.051[b]

[a]Student t-test. [b]Multivarite analysis (MANOVA).

Statistical analysis

Statistical analyses were performed on SPSS® 16 software using Multivariete analysis (MANOVA) and the t-test. Significance was set at $p < 0.05$.

Results

PCa was present in 23 (29%) of the 80 patients and BPH was present in 57 (71%) of the 80 patients (Table 1). Mean age of the patients with PCa was 69.17, and 65.16 in the non-PCa patients ($p > 0.05$). Prostate volumes could not be determined in six cases among the patients with PCa presenting to the urology clinic and in nine cases among the non-PCa patients. Prostate volume was 51.65 mL in patients with PCa ($n = 17$) and 64.85 mL in non-PCa subjects ($p > 0.05$). In terms of general picture, fPSA, PSA%, fPSA/PSAD was statistically significant in favor of BPH ($p < 0.05$), while p/f/tPSA, and (t/f/tPSA)/tPSA were significantly in favor of PCa ($p < 0.05$) according to the MANOVA analysis.

Using MANOVA, examination of the results for proPSA itself and the formulae in which it was used revealed insignificance in terms of its presence in pPSA%, t/pPSA, f/pPSA, p/fPSA, p/tPSA, f/p/tPSA, pPSA/PSAD ($p > 0.05$). When PHI and PHI2 results were analyzed p values were found too close to the 0.05 significancy values (respectively; $p = 0.052$, $p = 0.051$) (Table 1).

Discussion

PSA is routinely used in the diagnosis of PCa and is one of the most widely used tumor markers. However, although this marker is a sensitive test for the prostate, it is not a specific test for prostate cancer. Definite diagnosis is made with prostate biopsy. The range between 4 and 10 ng/mL is regarded as the gray zone. Cancer is observed at a mean level of 20%–25% in the first biopsy in this gray zone. Second, third and even saturation biopsies are therefore performed in this patient group [6].

Although ProPSA is not significant by itself in studies in the literature, it has been shown to be of considerable significance within the PHI [7]. In other words, when pPSA is used in various formulations it has been shown to elicit more significant results than PSA and pPSA by itself in the diagnosis of PCa. It therefore seems appropriate for pPSA to be used in varying formulations as a marker to reduce biopsy numbers in current practice. However, studies of proPSA have addressed very diverse groups. It has been used at all ranges of tPSA in the literature [5]. We considered only patients in the gray zone, those with tPSA levels of 4–10 ng/mL, and their results, and compared these with information from the literature.

In a multicenter European study of patients with tPSA levels of 2–20 ng/mL, Lazzeri et al. reported a mean pPSA value of 14.7 pg/mL in 382 patients with PCa and a mean value of 15.0 pg/mL in 264 patients without cancer. The

difference was not statistically significant. However, when the PHI was evaluated, the index was higher in patients without cancer, and high significance was reported [PCa = 38.0; non-PCa = 48.2] [4]. In a multicenter study of 892 patients with normal rectal examination findings and tPSA levels of 2–10 ng/mL, Catalona et al. [7] reported PHI scores of 49 in patients with PCa and 34 in those without. However, the US Food and Drug Administration has only approved the PHI test in subjects with tPSA of 4–10 ng/mL [8]. A multicenter study from Japan evaluated pPSA% values and PHI values between classified and non-classified groups; median pPSA% was 2.44 and PHI 60.3 in the classified group, compared to pPSA% of 1.88 and PHI of 47.8 in the non-classified group, the differences between the groups being statistically significant [9]. In our study, pPSA values were 0.18 ng/mL in cases with PCa and 0.14 ng/mL in non-PCa cases. The difference was not statistically significant. PHI values were 0.34 in non-PCa cases and 1.74 in patients with PCa. In agreement with the literature, we didn't identify a statistically significant difference by using MANOVA. But, in multivariete analysis PHI results were similar with 0.05 significancy values. Although pPSA% was 3.03 in PCa cases and 2.19 in non-PCa cases, the difference was not significant.

Khan et al. [10] reported 90% sensitivity and 44% specificity for pPSA investigated in order to avoid unnecessary biopsy in subjects with tPSA values between 4 and 10 ng/mL, while Miyakubo et al. reported 33% sensitivity for f/tPSA and 75% sensitivity for t/pPSA'nın. In our study, t/pPSA values were 77.52 in cases with PCa and 81.72 in BPH cases. Despite the decrease in PCa cases, the difference was not statistically significant. Patient numbers need to be increased in order to assess sensitivity and specificity.

Miyakubo et al. [11] reported significant elevation in p/fPSA and p/f/tPSA values in subjects with cancer among patients with PSA levels between 4.1 and 10 ng/mL. In our study, p/fPSA was quite high in PCa patients, at 0.67. Our p/f/tPSA values in patients with cancer were 0.11, significantly higher compared to the non-PCa group. Catalona et al. [12] revealed in pathological studies that these values were useful for PCa, that the best marker in this context was p2PSA, and that aggressive cancers could be identified by this means. pPSA has been reported to be potentially highly useful in young patients, with a long life expectancy, before the development of complications [11, 12]. p/fPSA and p/f/tPSA ratios may be important in risk determination together with the Gleason score component before proceeding to definitive treatment, particularly in young males with a long life expectancy [11]. In our study, however, although p/fPSA was higher in PCa patients than in BPH patients, (0.67 and 0.14, respectively), the difference was not statistically significant.

Mikolajczyk et al. [13] reported that pPSA% had greater specificity and a higher positive predictive value for PCa than PSA% in patients with tPSA values between 4 and 10 ng/mL, while de Vires et al. [14] reported that pPSA% was not correlated with prognosis of PCa at tPSA values < 15 ng/mL, but that in the gray zone, at tPSA values of 4–10 ng/mL, a high pPSA level was associated with poor prognosis. In our study, PSA% in PCa cases was 15.41, significantly lower in comparison to non-PCa cases, while pPSA% values, at 3.03, were slightly higher compared to the non-PCa cases, although this elevation was not statistically significant.

PHI is described as significant when other formulations of ProPSA are evaluated in the literature. PHI was also evaluated in our study and found significantly different between two groups by univariate anaysis while the p value was near 0.05 (0.052) by MANOVA. The similar conclusion can be made for PHI2 since there is a significant difference between PCa and non-PCa groups with univariate analysis despite a borderline p-value (0.051) with multivariate analysis. The PHI index represents a mathematical equation [(pPSA/fPSA)*√tPSA]. High PHI values are reported to be associated with a high probability of cancer [5, 15]. One meta-analysis of 12 separate studies reported that PHI is 81% specific when tPSA values of 4–10 ng/mL are considered [15]. These findings show that both pPSA and PHI increase specificity in reducing the number of unnecessary biopsies for determination of PCa, although there is no analysis of cut-off values for these tests. No cut-off value was specifically revealed in our study. However, PHI elevation was observed in cases with PCa compared to those without PCa (PCa = 1.74; non-PCa = 0.34). Catalona et al. reported that PHI values do not change with age, for which reason it can easily be applied to both young and old patients in determination of prostate cancer [5, 7].

In one wide-ranging study, Miyakubo et al. investigated f/tPSA, p/tPSA, p/fPSA, p/f/tPSA and PSAD in patients with tPSA values of 4–10 ng/mL. They concluded that only f/tPSA ratios differed significantly at values between 4.1 and 10 ng/mL in cases with cancer compared to non-cancer cases, that the others also increase, and rose still further as Gleason scores increased [11]. In our study, the p/tPSA ratio was 0.03 in cases with PCa and 0.02 in non-PCa cases, but the difference was statistically insignificant, despite rising in PCa.

In agreement with the literature, our analysis results showed that pPSA is not significant in the differential diagnosis of PCa and BPH. This finding may have been affected by the limited patient number. Additionally, the results

for pPSA, t/pPSA, f/pPSA, p/fPSA, p/tPSA, f/p/tPSA and pPSA/PSAD, other parameters associated with pPSA, also exhibited no significant differences between the two diseases. In contrast, the parameters p/f/tPSA and (t/f/pPSA)/tPSA in which pPSA was used were significantly in favor of PCa. When multivariete analysis was used only p-values in the PHI vs PHI2 were in significancy borderline statistically. One recently published study of p2PSA% and PHI showed that both parameters were highly significant with pathological findings in radical prostatectomy and expressed tumor aggressivity [16]. Yu et al. evaluated PHI results in 261 patients with normal rectal examination by finger and transrectal ultrasonography. They reported that PHI, particularly at tPSA values of 10.1–20 ng/mL, was the best marker of biopsy results [17]. A recent systematic review of 6912 patients assessing clinical use of [-2]proPSA and evidence reported pPSA sensitivity of 90% and sensitivity of 13% [18].

Conclusion

In conclusion, pPSA values differ among the studies in the literature. Examination of multicenter studies with larger patient numbers shows that pPSA is by itself of no value in determining PCa, but that it is significant within formulations, and particularly in the PHI. In our study, proPSA was not significant by itself in PCa. However, and in agreement with the literature, PHI may be a useful test in predicting PCa. In addition, it may be useful to study pPSA in some cases within formulations [(PHI2) pPSA/(fPSA*√tPSA), p/f/tPSA, (t/f/pPSA)/tPSA]. On the basis of these findings, routine use of pPSA has a place in reducing biopsy numbers in the differentiation of PCa and BPH. However, case numbers need to be increased for these analyses, and subgroup studies are now also required.

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