Incidental detection of asymptomatic chronic prostatitis and benign prostate hyperplasia in patients with high serum PSA levels: a preliminary retrospective study

Yüksek serum PSA değerli hastalarda rastlantısal tespit edilen asemptomatik kronik prostatit ve benign prostat hiperplazi: Retrospektif bir ön çalışma

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Abstract

Objective: We aimed to determine the presence of concomitant chronic prostatitis in patients with benign prostatic hyperplasia (BPH) who underwent prostate biopsies because of elevated levels of serum prostate specific antigen (PSA).

Materials and methods: Between August 2008 and January 2010, 229 patients underwent 12-core prostate biopsy because of elevated PSA levels. The correlation between the patients' characteristics and histopathology examination of biopsy specimens was evaluated.

Results: After histopathological evaluation, prostate adenocarcinoma was detected in 77 patients (35.9%). Of the patients with benign biopsy results, 92 patients (42.9%) were diagnosed with BPH, while chronic prostatitis and BPH were detected in 60 patients (28.0%). BPH patients were classified according to PSA levels: between 4.0-10 ng/mL (Group 1, 102 patients) and ≥10 ng/mL (Group 2, 50 patients). The incidence of coexisting chronic prostatitis was higher in Group 2 (29.4% vs. 60.0%). In Group 1, patients with concomitant chronic prostatitis were significantly older than patients without prostatitis (p=0.036). Moreover, patients' characteristics, such as age, total PSA, free PSA, free PSA percentage, and prostate volume were compared between BPH patients with and without chronic prostatitis, and only the total PSA level was significantly different (p=0.002).

Conclusions: High PSA levels do not invariably indicate malignant prostatic disease. The risk of coexisting chronic prostatitis is higher in BPH patients with levels of PSA ≥10 ng/mL.

Key words: Benign prostatic hyperplasia; biopsy; prostate specific antigen; prostatitis.

Özet

Amaç: Yüksek serum prostat spesifik antijen (PSA) düzeyleri nedeniyle prostat biyopsisi yapılan benign prostat hiperplazi (BPH) hastalarında kronik prostatit birlikteliğini değerlendirmeyi amaçladık.

Gereç ve yöntem: Ağustos 2008 ile Ocak 2010 tarihleri arasında PSA yüksekliği sebebiyle 229 hastaya 12-kor prostat biyopsisi yapıldı. Hasta özellikleri ile biyopsi materyallerinin histopatolojik sonuçları arasındaki ilişki değerlendirildi.

Bulgular: Histopatolojik inceleme sonunda 77 hastada (%35.9) prostat adenokarsinomu, 92 hastada (%42.9) BPH, 60 hastada (%28.0) ise BPH ve kronik prostatit birlikte tespit edildi. BPH hastaları PSA düzeyleri 4.0-9.9 ng/mL arası olanlar Grup 1 (102 hasta), ≥10 ng/mL olanlar Grup 2 (50 hasta) olmak üzere iki gruba ayrıldı. Kronik prostatitle birliktelik Grup 2'de daha fazlaydı (%29.4 ile %60.0). Grup 1'de BPH ve kronik prostatit birlikteliği saptanan hastalar, bu birlikteliğin olmadığı hastalarla kıyaslandığında daha yaşlı hastalardı (p=0.036). Bununla birlikte, kronik prostatit beraberliğinde ya da tek başına BPH saptanan hastalar arasında yaş, total PSA düzeyi, serbest PSA düzeyi, serbest/total PSA oranı ve prostat hacmi karşılaştırıldığında sadece total PSA düzeyi istatiksel olarak anlamlı farka sahipti (p=0.002).

Sonuç: Yüksek PSA düzeyi her zaman malign prostat hastalıklarının göstergesi değildir. PSA düzeyi ≥10 ng/mL olan BPH hastalarında kronik prostatit ile birliktelik riski daha yüksektir.

Anahtar sözcükler: Benign prostat hiperplazisi; biyopsi; prostat spesifik antijen; prostatit.

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Prostate specific antigen (PSA) was first reported in prostate tissue in 1970[1] and was measured in human sera in 1980.[2] PSA is a serine protease that is a member of the human kallikrein family, and it is secreted by the prostatic epithelial cells.[3] Although the level of serum PSA is a valuable marker for the detection of prostate cancer, it can also be elevated in benign conditions, such as aging, prostate enlargement, benign prostatic hyperplasia (BPH) and prostatitis.[4] In this study, the characteristics of BPH patients who underwent prostate biopsies in response to elevated serum PSA levels were evaluated with respect to the presence of concomitant chronic prostatitis.

Materials and methods

A total of 214 patients with elevated PSA levels of >4 ng/mL underwent 12-core prostate biopsies between August 2008 and January 2010. Patients' characteristics, such as age and levels of free and total PSA, were recorded. Transrectal 12-core systematic biopsies were performed under ultrasonographic guidance, as described by Hodge et al.,[5] and prostate volume was measured. Additional cores were sampled when hypoechoic lesions were encountered during transrectal ultrasonography. No abnormal digital rectal examination findings or symptoms suggestive of prostatitis were detected among the patients included in the study, and a single dose of quinolone was administered before the biopsy procedure.

Data were analyzed with the Statistical Packages for the Social Sciences 11.5 for Windows (SPSS 11.5) software. Associations between the groups were tested by Student's t-test, and a p value of less than 0.05 was defined as the level of statistical significance.

Results

Of the patients in this study, the mean values of age, total PSA, free PSA, free/total PSA percentage and prostatic volume were 63.99±7.12 years, 15.82±22.34 ng/mL, 2.36±3.30 ng/ml, 16.04±7.33%, and 55.63±2.10 cc, respectively. We performed 12-core prostatic biopsies because of elevated PSA levels (≥4.0 ng/mL). Histopathological evaluations indicated prostate cancer in 62 patients (28.97%), while BPH was reported in 92 patients (42.99%), and BPH with chronic prostatitis was detected in 60 patients (28.03%). PSA values were significantly higher in BPH patients with chronic prostatitis compared with the other patients (p=0.002), while no other significant difference was detected among the patients' characteristics (Table 1).

When BPH patients were classified according to their PSA levels, chronic prostatitis was observed in older subjects with PSA levels of 4-9.9 ng/mL (p=0.036) (Table 2). However, among patients with PSA levels ≥10 ng/mL, no statistically significant differences were observed in terms of age, free/total PSA percentage or prostatic volume (p=0.104, p=0.137 and p=0.896, respectively) (Table 3).

Discussion

In patients without cancer, previous research indicates that age, prostate size, BPH and prostatitis may cause elevated levels of serum PSA.[6] Prostatic inflammation, however, does not seem to cause a clinically significant change in the ratio of free to total PSA.[7,8] For patients with mildly increased PSA levels (4-10 ng/mL), the most likely cause is BPH, rather than prostate cancer. Other benign conditions that can elevate serum PSA levels are acute urinary

Table 1. Age, prostate specific antigen (PSA) levels, and prostate volume in benign prostate hyperplasia (BPH) patients with and without chronic prostatitis (mean±SD)

	BPH (n=92)	BPH+chronic prostatitis (n=60)	Total (n=214)	p value[a]
Age (year)	62.01±6.60	63.37±6.51	63.99±7.12	0.216
tPSA (ng/mL)	8.56±5.80	13.0±11.87	15.82±22.34	0.002
fPSA (ng/mL)	1.61±1.50	2.0±2.35	2.36±3.30	0.213
fPSA/tPSA (%)	17.35±7.63	15.18±6.33	16.04±7.33	0.105
Volume of prostate (cc)	56.66±34.45	63.08±33.95	55.63±2.10	0.265

[a]Student's t-test.

Table 2. Age, free/total prostate specific antigen (fPSA/tPSA), and prostate volume in benign prostate hyperplasia (BPH) patients diagnosed with and without chronic prostatitis. Patients exhibited PSA levels between 4 and 9.9 ng/mL (mean±SD)

	BPH (n=72)	BPH+chronic prostatitis (n=30)	p value[a]
Age (year)	60.83±6.18	63.70±6.23	0.036
fPSA/tPSA (%)	17.34±6.25	16.43±7.18	0.587
Volume of prostate (cc)	50.84±26.36	49.46±20.98	0.849

[a]Student's t-test.

Table 3. Age, free/total prostate specific antigen (fPSA/tPSA), and prostate volume in benign prostate hyperplasia (BPH) patients diagnosed with and without chronic prostatitis. Patients exhibited PSA levels ≥10.0 ng/mL (mean±SD)

	BPH (n=20)	BPH+chronic prostatitis (n=30)	p value[a]
Age (year)	66.25±6.51	63.03±6.87	0.104
fPSA/tPSA (%)	13.90±11.59	13.93±5.18	0.137
Volume of prostate (cc)	77.60±50.80	75.93±39.00	0.896

[a]Student's t-test.

retention, acute prostatitis and prostatic ischemia,[9] although discriminating prostate cancer from benign prostatic conditions in patients who have undergone interventions in the prostate is difficult. One report on this subject suggested that 3% of patients who have undergone surgeries for BPH will develop prostate cancer during their follow-up period.[10]

BPH is a common disease in older men, as 40% to 70% of men over the age of 60 are suspected to have BPH, and the incidence of BPH is increasing along with increasing life expectancy and westernized diets.[11,12] Prostatitis was classified into four distinct categories by an expert consensus conference of the National Institutes of Health (NIH) in 1995. Category IV, known as asymptomatic chronic prostatitis, is defined by the presence of inflammatory cells either in expressed prostate secretions or during histopathological examination of prostatic biopsies from asymptomatic men.[13,14] Prostatic histopathology in the context of the chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has been analyzed in a prospective study by True et al.[15] In their study, 368 patients underwent prostatic biopsies. Chronic prostatitis was detected in 97 patients; however, no inflammatory cells were noted in 67% of the specimens. In fact, only 5% of patients' biopsies exhibited moderate or severe inflammation. In our study, histopathological analyses of patients who underwent prostatic biopsy because of elevated PSA levels demonstrated BPH in 42.9% of patients and BPH with chronic prostatitis (the asymptomatic patient group) in 28% of patients.

Carver et al.[16] determined the prevalence of category IV prostatitis on the basis of indications of inflammation present in expressed prostatic secretions in 300 randomly selected men participating in a prostate cancer awareness screening program. Of the 300 patients, 227 provided specimens for examination. The prevalence of inflammation was 32.2%, suggesting that category IV prostatitis is common. In addition, the investigators determined that men with category IV prostatitis exhibited a significantly higher level of serum PSA than did men with no evidence of prostatitis. Similarly, the incidence of chronic (category IV) prostatitis was 28.03% in our study group, which consisted of patients who reported no symptoms of prostatitis, had not been previously treated because of prostatitis and were subjected to prostatic biopsies only because of high PSA levels.

In another study, Okada et al.[17] evaluated 558 negative needle biopsy specimens obtained from 93 men without a diagnosis of prostate cancer or clinical prostatitis. Inflammation in the specimens was graded and correlated with levels of serum PSA. Serum PSA levels were observed to be significantly correlated with inflammation, particularly with acute inflammation. Similarly, Stancik et al.[18] studied needle biopsies from 404 patients and analyzed the correlation between their results and levels of total and free PSA in the serum. Although the authors could not detect significant differences in total PSA levels between patients with prostate cancer or with prostatitis, free/total PSA ratios were significantly reduced in prostate cancer patients. In our study, patients without cancer (n=152, 71.02% of all patients) were determined histopathologically to exhibit BPH in 92 cases (42.99% of all patients) and BPH with chronic prostatitis (category IV prostatitis) in 60 cases (28.03% of all patients). Of these benign group patients, 102 exhibited PSA levels of between 4.0 and 9.9 ng/mL (47.66% of all patients), while 50 exhibited PSA levels ≥10.0 ng/mL (23.36% of all patients). Total PSA levels were

significantly higher in BPH patients with chronic prostatitis, while no other significant difference was detected among the variables of our study (p=0.002).

In a similar study, Rowe et al.[19] examined the relationship between serum PSA levels and incidental prostatic inflammation. The authors evaluated prostate biopsy results from 175 men and observed that men with acute inflammation exhibited significantly higher ratios of free/total levels of serum PSA than did those with chronic inflammation or BPH. Furthermore, their study reported that the serum free/total PSA ratios were similar in patients with acute inflammation and prostate cancer. Another report indicated that biopsies taken from patients with levels of serum PSA higher than 4.0 ng/mL exhibited 72.5% category IV prostatitis.[20] In a similar study, Potts[21] suggested a screening for category IV prostatitis in men with elevated PSA because of the high prevalence of the disorder (42% in her series of 122 men). In addition, Potts[21] suggested treating the men with prostatitis with appropriate antibiotics and subsequently measuring serum PSA a second time. Four weeks of antibiotic therapy resulted in a 42% reduction in men requiring biopsies. From these results, Potts[21] recommended that antibiotics should only be used if bacterial prostatitis is suspected and that antibiotics should not be used to modulate the levels of serum PSA. This approach is suggested in patients with chronic nonbacterial prostatitis and in asymptomatic men. Particularly in asymptomatic screened men, the use of antibiotics to lower serum PSA is controversial and is probably not advisable.[22] The probability that antibiotics may lower the level of serum PSA in this case is ultimately no higher than the probability that the measurement of serum PSA may have been reduced because of natural fluctuations in serum PSA values.[22] All of the patients in our study exhibited chronic asymptomatic prostatitis. None of the patients were given premedication, except a single prophylactic dose of quinolone, because of the controversy surrounding treatment with antibiotics for high PSA levels in men with asymptomatic prostatitis**.**

On the other hand, histological prostatitis is a common finding among men without clinical prostatitis. Although acute inflammation has been reported to be necessary to induce elevated levels of PSA, a growing body of evidence indicates that subclinical inflammation may also be related to increased PSA levels.[23] Furthermore, several investigators have demonstrated that the treatment of chronic prostatitis, once identified, can decrease PSA levels, suggesting that the utilization of anti-microbial and/or anti-inflammatory drugs may reduce the necessity of prostate biopsies.[24] However, another report noted that 26.9% to 31% of patients presented with a decrease in PSA after the administration of antibiotics or a placebo harbor cancer, as demonstrated through prostate biopsies. Decreases in PSA levels do not indicate the absence of prostate cancer.[25]

Currently, no standardized policy outlines the management of patients with elevated PSA levels. However, the treatment of such patients has provided some guidelines. The first guideline is the immediate referral for prostate biopsy, which discounts any potential role of inflammation in the etiology of increased PSA levels, as well as random PSA fluctuations. The second guideline is the immediate repetition of the PSA test. Importantly, chronic prostatitis may interfere with clinicians' interpretations of PSA levels when screening for prostate cancer. No general guidelines can be uniformly applied to all men with increased PSA levels before recommending prostate biopsy. However, an assessment of the patient's individual condition may result in an algorithmic change to improve the specificity of PSA concentration as a diagnostic tool for prostate cancer and may provide a more acceptable initial treatment than proceeding directly to prostate biopsies. With the support of multicenter, large-scale studies, our preliminary study may provide an algorithmic approach to treating symptomatic prostatitis.

This study indicates that elevated PSA levels may be associated with benign conditions, such as BPH and/or chronic asymptomatic prostatitis. When the PSA level is between 4.0 and 9.9 ng/mL, BPH patients with chronic prostatitis tend to be older, while prostatic volume and free/total PSA percentages were not significantly different in BPH patients with or without chronic prostatitis.

Conflict of interest

No conflict of interest was declared by the authors.

References

1. lbin RJ, Soanes WA, Bronson P, Witebsky E. Precipitating antigens of the normal human prostate. J Reprod Fertil 1970;22:573-4.

2. Kuriyama M, Wang MC, Papsidero LD, Killian CS, Shimano T, Valenzuela L, et al. Quantification of prostate specific antigen in serum by a sensitive enzyme immunoassay. Cancer Res 1980;40:4658-62.
3. Lilja H. A kallikrein like serum protease in prostatic fluid cleaves the predominant seminal vesicle protein. J Clin Invest 1985;76:1899-903.
4. Morote J, Lopez M, Encabo G, de Torres IM. Effect of inflammation and benign prostatic enlargement on total and free serum prostate specific antigen. Eur Urol 2000;37:537-40.
5. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 1989;142:71-5.
6. Ornstein DK, Smith DS, Humphrey PA, Catalona WJ. The effect of prostate volume, age, total prostate specific antigen level and acute inflammation on the percent free serum prostate specific antigen levels in men without clinically detectable prostate cancer. J Urol 1998;159:1234-7.
7. Lilja H, Oldbring J, Rannevik G, Laurell CB. Seminal secreted proteins and their reactions during gelation and liquefaction of human semen. J Clin Invest 1987;80:281-5.
8. Lilja H. Significance of different molecular forms of serum PSA: the free, noncomplexed form of PSA versus that complexed to alpha-1 antichymotrypsin. Urol Clin North Am 1993;20:681-6.
9. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenez M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? J Urol 2004;172:1297-301.
10. Bostwick DG, Cooner WH, Denis L, Jones GW, Scardino PT, Murphy GP. The association of benign prostatic hyperplasia and cancer of the prostate. Cancer 1992;70:291-301.
11. Lu Yao GL, Barry MJ, Chang CH, Wasson JH, Wennberg JE. Transurethral resection of the prostate among medicare beneficiaries in the United States: time trends and outcomes. Prostate Patient Outcomes Research Team (PORT). Urology 1994;44:692-9.
12. Gu F. Epidemiological survey of benign prostatic hyperplasia and prostatic cancer in China. Chin Med J 2000;113:299-302.
13. National Institute of Health/National Institute of Diabetes and Digestive and Kidney Diseases Workshop on Chronic Prostatitis: National Institutes of Health Summary Statement. Executive Summary. Bethesda, MD; 1995.
14. Nickel JC, Nyberg LM, Hennenfent M. Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. Urology 1999; 54:229-33.
15. True LD, Berger RE, Rothman I, Ross SO, Krieger JN. Prostate histopathology and chronic prostatitis/chronic pelvic pain syndrome: a prospective biopsy study. J Urol 1999;162:2014-8.
16. Carver BS, Bozeman CB, William BJ, Venable DD. The prevalence of men with National Institutes of Health category IV prostatitis and association with serum prostate specific antigen. J Urol 2003;169:589-91.
17. Okada K, Kojima M, Naya Y, Kamoi K, Yokoyama K, Takamatsu T, et al. Correlation of histological inflammation in needle biopsy specimens with serum prostate specific antigen levels in men with negative biopsy for prostate cancer. Urology 2000;55:892-8.
18. Stancik I, Luftenegger W, Klimpfinger M, Muller MM, Hoeltl W. Effect of NIH-IV prostatitis on free and free to total PSA. Eur Urol 2004;46:760-4.
19. Rowe EW, Laniado ME, Walker MM, Anup P. Incidental acute prostatic inflammation is associated with a lower percentage of free prostate specific antigen than other benign conditions of the prostate: a prospective screening study. BJU Int 2006;97:1039-42.
20. Bozeman CB, Carver BS, Eastham JA, Venable DD. Treatment of chronic prostatitis lowers serum prostate specific antigen. J Urol 2002;167:1723-6.
21. Potts JM. Prospective identification of National Institutes of Health category IV prostatitis in men with elevated prostate specific antigen. J Urol 2000;164:1550-3.
22. Scardino PT. The responsible use of antibiotics for an elevated PSA level. Nat Clin Pract Urol 2007;4:1.
23. Kwak C, Ku JH, Kim T, Park DW, Choi KY, Lee E, et al. Effect of subclinical prostatic inflammation on serum PSA levels in men with clinically undetectable prostate cancer. Urology 2003;62:854-9.
24. Schaeffer AJ, Wu SC, Tennenberg AM, Kahn JB. Treatment of chronic bacterial prostatitis with levofloxacin and ciprofloxacin lowers serum prostate specific antigen. J Urol 2005;174:161-4.
25. Stopiglia RM, Ferreira U, Silva MM Jr, Matheus WE, Denardi F, Reis LO. Prostate specific antigen decrease and prostate cancer diagnosis: antibiotic versus placebo prospective randomized clinical trial. J Urol 2010;183:940-4.

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