Özgün araştırma / Original research

Comparison of serum c-reactive protein levels between benign prostate hyperplasia and prostate cancer in patients undergoing prostate biopsy

Prostat biyopsisi uygulanan hastalarda serum c-reaktif protein düzeylerinin benign prostat hiperplazisi ve prostat kanseri arasında karşılaştırılması

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Abstract

Objective: It has been argued that prostate cancer may have an association with inflammation. Prostate specific antigen is widely used for diagnosis, treatment, and follow-up of prostate cancer. C-reactive protein is a widely utilized marker of inflammation. We compared serum CRP values between benign prostate hyperplasia (BPH) and prostate cancer (PCa) diagnosed by prostate biopsy performed in patients with a tPSA level greater than 4.0 ng/dl.

Material and Methods: Serum CRP and sedimentation rate were retrospectively assessed in 182 patients who had a tPSA level above 4.0 ng/dl and were scheduled to undergo prostate biopsy. Pathology results of 175 patients could be accessed. CRP levels of patients with BPH and PCa were compared with each other using Wilcoxon-Mann Whitney U and Kruskal Wallis tests. A p value of less than 0.05 was considered statistically significant.

Results: Both the analyses taking a CRP cut-off level of 0.5 mg/dl and quantitative serum CRP levels failed to show any significant difference between the BPH group (0.59+0.11 mg/dl) and the PCa group (0.55+0.18 mg/dl) (p=0.779; p=0.192). Sedimentation rate was also similar in the BPH and PCa groups (18.98 mm/hour vs 18.18 mm/hour; p=0.870).

Conclusion: Our study could not demonstrate any significant difference between serum CRP levels of patients with BPH and PCa.

Key Words: PSA, Prostate biopsy, CRP, BPH, Prostate cancer

Özet

Amaç: Prostat kanserinin inflamasyonla ilişkisi olabileceği düşünülmektedir. Prostat spesifik antijen prostat kanserinin tanı, tedavi ve takiplerde yaygın olarak kullanılmaktadır. C-reaktif protein inflamasyonda yaygın kullanılan bir belirteçtir. Çalışmamızda tPSA'sı >4,0 ng/ml olan ve biyopsi yapılmış hastalarda biyopsi sonucu benign prostat hiperplazisi (BPH) ve prostat kanseri (PCa) gelenler arasındaki serum CRP değerlerini karşılaştırdık.

Gereç ve Yöntemler: tPSA >4,0 ng/dl olan ve biyopsiye karar verilen 182 hastada serum CRP ve sedimentasyon hızlarına bakıldı. Retrospektif değerlendirme yapıldı. 175 hastanın patolojik verilerine ulaşıldı. BPH ve PCa arasındaki CRP'ler Wilcoxon-Mann Whitney U ve Kruskal Wallis testleri yöntemleriyle çalışılarak karşılaştırıldı. İstatisiksel değerlendirmede p<0.05 değeri anlamlılık kriteri olarak kullanıldı.

Bulgular: Hem serum CRP cut-off değeri 0,5 mg/dl olarak alındığında hem de cut-off değeri gözönüne alınmadan serum değerleri dikkate alınarak yapılan değerlendirmelerde BPH grubu (0,59+0,11 mg/dl) ve PCa grubu (0,55+0,18 mg/dl) arasında istatistiksel anlamlı fark bulunamadı (p=0,779; p=0,192). BPH olgularında sedimentasyon hızı değerleri (18,98 mm/saat) ile PCa sedimentasyon hızı değerleri (18,18 mm/saat) birbirine benzerdi, aralarında istatistiksel anlamlılık saptanmadı (p= 0,870).

Sonuç: Çalışmamızda; BPH ve PCa hastalarının arasında serum CRP değerleri arasında anlamlı fark bulunamadı.

Anahtar Kelimeler: PSA, Prostat biyopsisi, CRP, BPH, Prostat Kanseri

Introduction

In men, prostate cancer (PCa) is the most common cancer and the second leading cause of death (1). Today, prostate specific antigen (PSA) is widely used for both diagnostic purposes and monitoring treatment outcomes (2). There is a need for a better prediction tool in addition to PSA both for guiding treatment and monitoring progression. Many parameters apart from PSA, PSA derivatives and kinetics have been used for confirming diagnosis and determining prognosis of PCa; CRP has been reported to be one of the most powerful markers (3). C-reactive protein is widely used for the treatment and monitorization of a variety of disorders (4-6). Systemic inflammation plays an active role for the initiation, persistence, progression, metastasis, and clinical outlook of cancer (7). C-reactive protein is an acute phase reactant widely used in clinical practice; it is produced by hepatocytes (8). It is used to predict the disease development and determine prognosis in urological cancers including PCa (9, 10). However, some authors have reported that it does not play a significant role in the management of patients with PCa (11). Hence, this is still a controversial subject. Herein, we compared serum CRP levels on the basis of biopsy results in patients who had a tPSA of ≥4.0 ng/ml and who underwent prostate biopsy. We aimed to compare serum CRP levels in patients with benign prostate hyperplasia (BPH) and PCa to determine in which of the disorders CRP level was markedly elevated.

Material and Methods

Patients and their demographic properties: One hundred and eighty-two patients who underwent prostate biopsy between 2012 and 2015 were retrospectively studied. The medical data of 175 patients could be accessed and thus only these patients were included in the final analysis. Of these, 113 had BPH and 62 had PCa. Patients with or without lower urinary system symptoms (LUTS) were tested for PSA whenever they visited our outpatient clinic or they requested this test to be done. One hundred and seventy-five patients who had a tPSA level of ≥ 4.0 ng/ml and who had an accessible biopsy result were enrolled in the study after the exclusion of other etiologies causing PSA elevation. Patients with chronic disorders that would potentially affect CRP levels, and those with urethral catheterization, acute prostatitis, or urinary infection were excluded. All patients routinely underwent prostate volume (PV), postvoiding residual urine (PVR), tPSA, CRP and sedimentation rate testing before biopsy procedures. CRP levels and sedimentation rates were compared between patients who were diagnosed to have PCa and BPH.

Serum CRP analysis: Serum CRP cut-off level was accepted 0.5 mg/dl. Levels above this cut-off were considered to represent inflammation. Levels below 0.5 mg/dl were scored "0" point and those above 0.5 mg/dl were scored "1" point. Additionally, statistical analyses were also performed taking into account quantitative CRP levels. Blood samples were studied using the immunoturbidimetric method with Architect C 8000 autoanalyzer (Abbott Diagnostic) device and Archem Diagnostics kits (Lot: 862, Ref: 02R04-3)

Sedimentation Rate Analysis: Sedimentation rate was analyzed with SDM-100 automatic ESR analyzer device using the Westergren method. The measurement unit was determined mm/hour. The device periodically measures sedimentation thickness of erythrocytes in blood samples taken into specifically designed test tubes and sends the calculated results to Laboratory Information System in accordance with the Westergren method described below. *Westergren Method:* A user "reads" level of sediment at regular intervals using "Infrared Barrier" method within a time period specified by the selected study method. The readings are mathematically computed and printed in accordance with the Westergren method (12).

Statistical Analysis: BPH and PCa were compared with respect to age, serum CRP level, and sedimentation rate. Age, CRP, sedimentation rate, tPSA, prostate volume (PV) and postvoiding residual urine (PVR) were compared with the use of Wilcoxon-Mann Whitney U test, Kruskal Wallis test, Student t test. Statistical significance was set at $p<0.05$.

Results

This study included a total of 182 patients who had a total PSA level of ≥4.0 ng/ml and who underwent prostate biopsy. All patients had their CRP levels and sedimentation rates measured before prostate biopsy procedures. Biopsy results could not be accessed in 7 patients. One hundred and thirteen patients with a biopsy result consistent with BPH and 62 with PCa were enrolled. The

BPH and PCa groups had mean ages of 64.26 and 68.77 years, respectively (p=0,001). The mean CRP level was 0.59±0.11 mg/dl in the BPH group and 0.55±0.18 mg/dl in the PCa group. No significant difference was found between BPH and PCa (p=0,779) with respect to pathological CRP levels above a CRP cut-off level of 0.5 mg/dl. Similarly, when cut-off level was discarded and the comparison was performed over numeric values, both groups were still statistically similar to each other (p=0,192). BPH and PCa groups also had statistically similar sedimentation rates (18.98 mm/hour vs 18.18 mm/hour; p= 0.870) (Table 1). tPSA, PV and PVR results are seen table 1.

	BPH	PCa	p
Age (y)	64,26±0,75 (41-82)	68,77±1,26 (43-88)	0,001*
CRP (ng/dl)	0,59±0,11 (0,01-5,09)	0,55±0,18 (0,02-6,83)	0,779* 0,192[1]
Sedimentation Rate (mm/saat)	18,98±2,11 (2,0-62,0)	18,18±3,00 (1,0-61,0)	0,870
tPSA (ng(dl)	8,30±6,23 (2,28-42,0)	32,49±4,14 (3,54-150,0)	0,000**
Prostate Volume (ml)	61,03±3,15 (15-153)	50,29±3,29 (5-132)	0,128**
Post Voiding Residual Urine (ml)	48,0±5,84 (0-300)	55,96±1,02 (0-433)	0,630**

Table 1. Age in BPH and PCa, CRP and average sedimentation rate, minimum-maximum values and standard error, p values p<0.05; Wilcoxon-Mann Whitney U (CRP, *cut-off 0,5 ng/dl; less "0" and bigger "1") and Kruskal Wallis test, Wilcoxon-Mann Whitney U test (CRP[1] quantitative measurement values), ** Student T test; p<0.05

Discussion

Recently, Prostate Spesific Membrane Antigen (PSMA); prostate stem cell antigen, epithelial growth factor receptors, pAKT, nuclear kappa B, Macrophage inhibitor cytokine-1, Matrix metalloproteinase (MMP); MMP-1, and MMP-9, microRNA, and ILs have been used in addition to PSA to predict PCa (13-15). Nevertheless, it is difficult to continuously monitor these parameters' levels during the progression phase of the disease. On the other side, inflammatory markers can easily be determined in serum and plasma and could be widely used in a variety of clinical conditions.

C-reactive protein is a member of acute phase reactants family; it is a cheap, non-invasive means to assess inflammation and thus very widely used in clinical practice (16). Prognosis is worse in patients with elevated CRP levels. CRP possess some biological functions including the activation of the complement system (17). Serum CRP is routinely requested before biopsy in the urology clinic. The purpose is to determine basic CRP values, early prediction of the presence of urogenital infection and to plan the management of potential infections. However, there is no rationale for requesting CRP before biopsy in the literature. This subject should be evaluated with different studies.

Dai et al. evaluated 7490 patients in a meta-analysis and concluded that there is an association between serum CRP level and survival in patients with urological cancers. In that meta-analysis the majority of PCa patients had metastatic prostate cancer receiving docetaxel chemotherapy (18). We compared the results of patients who had a tPSA of greater than 4.0 ng/dl and who underwent prostate biopsy procedure. We currently recommend prostate biopsy to patients with a tPSA level of ≥4.0 ng/ml. This may be a limitation of our study. Perhaps it will be necessary to compare the results of this study with those patients reported from other clinics that perform prostate biopsy for tPSA levels of less than 4.0 ng/ml.

Nakashima et al. showed that CRP was an independent prognostic factor in patients with PCa (19). Lehrer et al. reported that CRP level was higher in patients with PCa metastases compared to those without, and it was correlated to the presence of metastases (20). In contrast, Van Hemelrijck et al. refused an association between CRP level and PCa (21). Genetic variations and gene polymorphisms have also been reported in CRP studies, although the notion that serum CRP level and PCa is correlated has been denied. Some gene polymorphisms such as rs1800947, rs2808630 and rs3093075 have been linked to aggressiveness of PCa (22).

Studies aiming at showing a relationship between PCa and CRP failed to show such a relationship for local and locally advanced disease. Nevertheless, CRP appears to be of clinical significance with regard to metastatic disease and predicts prognosis and survival. All of our study group consisted of local or locally advanced disease. Only a few studies have studied this subject in the literature. We routinely study CRP and sedimentation rate before prostate biopsy. By this practice we aim to find out and

record baseline CRP levels to be used later when complications, such as sepsis, develop after biopsy.

Studies have reported that analgesic and anti-inflammatory drugs are the leading nonprescription medications used by the elderly population, having a rate of 40-60% (23). Considering the increased rate of analgesic use, CRP levels may have been altered in both BPH and PCa patients. Perhaps duration of use and doses of these drugs may be important modifiers. In a domestic study conducted on nursing home residents, 20.8% of the participants were using these medications (24). Another study indicated that the usage rate of nonprescription medications was 72.5% (25). The situation is similar in other countries, especially in USA. Multidrug use and nonprescription drug use are particularly common among the elderly population (23, 26-28). Therefore, drug effect seems almost inevitable. In addition, study results may have been influenced by the effects on body functions and biochemical parameters. Therefore, this interaction should be taken into account in such studies. We do not know how serum CRP levels are affected in populations using uncontrolled medication use, and population-based studies are needed on this subject. There was no recent active analgesic and anti-inflammatory drug use among our patients applying to the department of urology for having prostate biopsy.

Kim et al. retrospectively compared serum CRP levels of 140 patients with BPH and 63 patients with PCa who had a PSA level above 4.0 ng/ml and they reported higher CRP levels among patients with PCa compared to those with BPH (5.14 mg/L vs 3.98 mg/L, respectively) (29). Their study population also included patients with metastatic PCa. Our study population, on the other hand, consisted of patients with local and locally advanced PCa. Our BPH group, however, had similar characteristics with that in the study of Kim et al. The mean serum CRP level was 0.59 mg/dl (0.01 - 5.09) in our BPH group and 0.55 mg/dl (0.02 - 6.83) in our PCa group. Maximum sedimentation rates were similar in both groups, with the BPH group having a sedimentation rate of 62 mm/hour and the PCa group 61 mm/hour. Only one patient with BPH also had chronic prostatitis detected in biopsy examination, and that patient had a CRP level of 0.21 mg/dl. It is unknown why serum CRP level was as high in BPH as in PCa. Perhaps this was due to the gene polymorphism in our society. Further studies are needed on this subject.

Turkish population still widely prefers using anti-inflammatory drugs for all types of pain. Randomized controlled studies can be conducted in patient populations which were not allowed to use anti-inflammatory drugs. However, the likelihood of using anti-inflammatory drugs before study enrollment would still be higher. To our knowledge, anti-inflammatory drugs are effective on the acute stage of inflammation. Although it is known that these medications also act on inflammation in chronic use, the chronic effects long after a few doses of these medications on inflammation and CRP levels are unknown and it is equally challenging to study these effects. Therefore, gene polymorphism and long-term episodic anti-inflammatory drug use may have led to different results in our study than the literature reports. Perhaps, same problems may have applied to other studies in which no elevation of CRP levels were observed. Unfortunately, this subject is not sufficiently clear in former studies. CRP levels were reduced as long as COX-2 inhibitors were used in both experimental and clinical studies (30). It has been proposed that COX-2 inhibitors may be used for chemoprevention of PCa. Kramer et al. similarly reported that chronic inflammation and infection play a role in the etiology of PCa (31). Unlike our study, McLennon et al. reported that chronic inflammation, observable in 14% in the first biopsy samples existed in nearly all repeat biopsy samples taken 5 years later (32). Similarly, PCa risk was reduced by aspirin, acetaminophen, and other non-steroidal anti-inflammatory drugs (33); significant reductions have even been observed in PSA when aspirin was administered to patients with latent PCa (34). These studies suggest that inflammation plays a role in the initiation and progression of PCa. Perhaps inflammation is only one of multiple risk factors for PCa. Immunohistochemical studies have shown the presence of CRP in both cytoplasms and nuclei of PCa tumor cells (11, 35); the authors stated that elevated CRP level may indicate that tumor will spread outside prostate tissue, locally advance, and even metastasize. However, the role of inflammation in the development of PCa has not been clearly explained despite the above mentioned stud-

ies (36). Many studies to date have indicated that CRP is associated with survival and poor prognosis in other advanced stages, metastatic and castration-resistant stage, and patients receiving chemotherapy (3, 4, 18).

Our study has some limitations. These include its retrospective nature, taking a tPSA cut-off level of $\geq$ 4.0 ng/dl, the absence of subgroup analyses, and the inability to enroll all stages of PCa. Prospective, large-scale studies that will exclude subjects using anti-inflammatory drugs, include all PSA levels, and study CRP gene polymorphisms are needed.

Although CRP molecules have been shown within PCa tumor cells by immunohistochemical studies, PCR studies failed to confirm this finding, suggesting that there is an ongoing uncertainty surrounding the relationship between CRP and PCa (4, 11).

Conclusion

The uncertainty surrounding the role of CRP in prostatic diseases continues. We failed to show any significant difference between CRP levels of patients with BPH and PCa. However, we do not know yet whether analgesic and anti-inflammatory drugs widely consumed in our country have influenced CRP levels determined in our study. Subgroup analyses in which separate analyses of local and locally advanced stages are performed and in which the gleason score is included are needed. Therefore, there is a need for multicenter, prospective, randomized, controlled studies with subgroup analyses, which will also study gene polymorphisms.

References

1. Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 2003; 21: 1232-7.
2. Ayyıldız SN, Ayyıldız A. Prostat kanseri tanısında PSA, PSA türevleri, ProPSA ve prostat sağlık indeksi. Turk J Urol 2014; 40: 82-8.
3. Liu Z-Q, Chu L, Fang J-M, et al. Prognostic role of C-reactive protein in prostate cancer: a systematic review and meta-analysis. Asian J Androl 2014; 16: 467-471.
4. Graff JN, Beer TM. Editorial. The role of C-reactive protein in prostate cancer. Cancer 2013; 15: 3262.
5. Aletaha D, Smolen J. The simplified disease activity index (SDAI) and clinical disease activity index CDAI: a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005; 23 : 100-S108.
6. Young B, Gleeson M, Cripps AW. C-reactive protein: a critical review. Pathology 1991; 23:118-124.
7. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008; 454: 36-44.
8. Hurlimann J, Thorbecke GJ, Hochwald GM. The liver as the site of C-reactive protein formation. J Exp Med 1966; 123: 365-78.
9. Guo YZ, Pan L, Du CJ, et al. Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. Asian Pac J Cancer Prev 2013; 14: 243-8.
10. Yu Q, Yu XF, Zhang SD, et al. Prognostic role of C-reactive protein in gastric cancer: a meta-analysis. Asian Pac J Cancer Prev 2013; 14: 5735-40.
11. Elsberger B, Lankston L, McMillan DC, et al. Presence of tumoural C-reactive protein correlates with progressive prostate cancer. Prostate Cancer Prostatic Dis 2011; 14: 122-8.
12. Sox HC Jr, Liang MH. The erythrocyte sedimentation rate: guidelines for rational use. Ann Intern Med 1986; 104: 515-523.
13. Mimeault M, Johansson SL, Batra SK. Pathobiological implications of the expression of EGFR, pAkt, NF-KB and MIC-1 in prostate cancer stem cells and their progenies. PloS ONE 2012; 7: 31919.
14. Ozden F, Saygin C, Uzunaslan D, et al. Expression of MMP-1, MMP-9 and TIMP-2 in prostate carcinoma and their influence on prognosis and survival. J Cancer Res Clin Oncol 2013; 139: 1373-82.
15. Mengus C, Le Magnen C, Trella E, et al. Elevated levels of circulating IL-7 and IL-15 in patients with early stage prostate cancer. J Transl Med 2011; 9: 162-168.
16. Saito K, Kihara K. Role of C-reactive protein in urological cancers: a useful biomarker for predicting outcomes. Int J Urol 2013; 20: 161-71.
17. Allin KH, Nordesgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci 2011; 48: 155-170.
18. Dai J, Tang K, Xiao W, et al. Prognostic significance of C-reactive protein in urological cancers: a systematic review and meta-analysis. Asian Pac J Cancer Prev 2014; 15: 3369-3375.
19. Nakashima J, Kikuchi E, Miyajima A, et al. Simple stratification of survival using bone scan and serum C-reactive protein in prostate cancer patients with metastases. Urol Int 2008; 80: 129-33.
20. Lehrer S, Diamond EJ, Mamkine B, et al. C-reactive protein is significantly associated with prostate-specific antigen and metastatic disease in prostate cancer. BJU Int 2005; 95: 961-2.

21. Van Hemelrijck M, Jungner I, Walldius G, et al. Risk of prostate cancer is not associated with levels of C-reactive protein and other commonly used markers of inflammation. Int J Cancer 2011; 129: 1485-92.
22. Markt SC, Rider JR, Penney KL, et al. Genetic variation across C-reactive protein and risk of prostate cancer. Prostate 2014; 74:1034-42.
23. Kutsal YG. Polypharmacy in elderly. Turkish J Geriatr 2006; 37-44.
24. Arslan S, Atalay A, Kutsal YG. Drug use in older people. J Am Geratr Soc 2002; 50: 1163-1168.
25. Esengen S, Seckin U, Borman P, et al. Drug consumption in a group of elderly residents of a nursing home: relationship to cognitive impairment and disability. J Am Med Dir Assoc 2000; 1: 197-201.
26. Wu JY, Leung WY, Chang S, et al. Effectiveness of telephone counselling by a pharmacist in reducing mortality in patients receiving polypharmacy: randomised controlled trial. BMJ 2006; 333: 522-529.
27. Steinman MA, Seth Landefeld C, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 2006; 54: 1516-23.
28. Cannon KT, Choi MM, Zuniga MA. Potentially inappropriate medication use in elderly patients receiving home health care: a retrospective data analysis. An J Geriatr Pharmacother 2006; 4: 134-43.
29. Kim Y, Jeon Y, Lee H, et al. The prostate cancer patient had higher C-reactive protein than BPH patient. Korean J Urol 2013; 54: 85-88.
30. Gupta S, Adhami VM, Subbarayan M, et al. Suppression of prostate carcinogenesis by dietary supplementation of celecoxib in transgenic adenocarcinoma of the mouse prostate model. Cancer Res 2004; 64: 3334-43.
31. Kramer G, Mitteregger D, Maj-Hes A, et al. Chronic inflammation as promotor and treatment target in benign prostate hyperplasia (BPH) and in prostate cancer. Urologe A 2007; 46: 1095-6.
32. MacLennon GT, Eisenberg R, Fleshman RL, et al. The influence of chronic inflammation in prostatic carcinogenesis: A 5-year follow up study. J Urol 2006; 176: 1012-6.
33. Jacobs EJ, Newton CC, Stevens VL, et al. A large cohort study of long-term acetaminophen use and prostate cancer incidence. Cancer Epidemiol Biomarkers Prev 2011; 20: 1322-1328.
34. Fowke JH, Motley SS, Smith JA, et al. Association of nonsteroidal antiinflammatory drugs, prostate specific antigen and prostate volume. J Urol 2009; 181: 2064-70.
35. McCall P, Catlow J, McArdle PA, et al. Tumoral C-reactive protein and nuclear factor kappa-B expression are associated with clinical outcome in patients with prostate cancer. Cancer Biomark 2011-2012; 10: 91-9.
36. Lucia MS, Torkko KC. Inflammation as a target for prostate cancer chemoprevention: pathological and laboratory rationale. J Urol 2004; 171: 30-4.