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Comparison Between Clinical Significance of Serum Proinflammatory Protein Interleukin-6 and Classic Tumor Markers Total PSA, Free PSA and Free/Total PSA Prior to Prostate Biopsy

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A B S T R A C T

The aim of the study was to clarify whether serum levels of proinflammatory cytokine interleukin-6 (IL-6) could be a useful marker in prostate diseases. Serum IL-6 was determined prior to prostate biopsy procedure in 82 patients with prostate adenocarcinoma (PCa), 25 patients with benign prostatic hyperplasia (BPH), 24 patients with high-grade prostatic intraepithelial neoplasia (PIN) and 17 patients with chronic prostatitis. Serum IL-6 levels were compared with total PSA (tPSA), free PSA (fPSA) and the free/total ratio (f/tPSA) serum levels. Statistically significant difference was not found in serum IL-6 levels among the four groups (p=0.088). However, the patients with poorly differentiated PCa with Gleason score (GS) 4+3=7 and >7 had significantly higher serum IL-6 levels than the patients with moderately differentiated PCa with GS 3+4=7 and <7 (p=0.007). The findings suggest that serum IL-6 level might be a potentially useful marker for poorly differentiated PCa.

***Key words**: interleukin-6, serum levels, prostate biopsy, prostate-specific antigen, Gleason score*

Introduction

Prostate cancer is the most common non-skin cancer among adult men worldwide[1]. Screening has been advocated as a means of detecting PCa in the early stages to decrease overall and disease specific mortality[2]. An elevated tPSA level can reflect the presence of cancer but can also be caused by BPH, high-grade PIN, infection, and/or chronic inflammation. All prostate epithelial cells, whether normal, hyperplastic or cancerous, synthesize prostate specific antigen. Neoplastic cells produce somewhat lower tissue levels of tPSA compared to BPH cells although both conditions cause tPSA elevation in the blood. Therefore, it has been suggested that tPSA should be considered as a marker of BPH-related prostate volume, growth, and outcome rather than a reliable marker of PCa[3]. PSA is not the ideal biomarker for PCa detection and management. Elevated levels of IL-6 in men with local PCa and advanced disease made IL-6 candidate biomarker for PCa development and progression[4]. IL-6 is a pleiotropic cytokine involved in prostate regulation and in PCa development and progression. IL-6 acts as a paracrine and autocrine growth stimulator in benign and tumor prostate cancer cells. Recent evidence suggests that the presence of inflammatory factors and cytokines at the tumor site results in tumor cell survival, proliferation, invasion and metastasis[5]. Clinical observations have demonstrated increased IL-6 levels in plasma and serum from patients with castration-resistant prostate cancer (CRPC)[6,7], metastatic PCa[8], biochemical recurrence[9] and poorer overall survival[10]. In the present study, the aim was to compare clinical significance of serum IL-6 levels with classic

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tumor markers (tPSA, fPSA and f/tPSA) in the diagnosis of patients prior to prostate biopsy. In addition, it was attempted to clarify whether serum IL-6 levels could be a useful marker in the diagnosis of various prostate diseases.

Materials and Methods

The research has been carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of our hospital. The written consent was obtained from all patients after full explanation of the procedure. No patients had evidence of active infection or inflammatory disease, other malignant visceral tumor and none were under any treatment for PCa at the time of examination. Patients who underwent digital rectal examination (DRE) or other prostatic manipulation a week prior to prostate biopsy were excluded from the study. Trans-rectal ultrasound (TRUS) guided prostate biopsy was performed on total of 148 patients (aged 33–82) who had tPSA level >4 ng/mL in the serum, and/or positive DRE and/or positive TRUS. Prostate disease was confirmed by needle biopsy of the prostate (twelve-core prostate biopsy samples). A total of 82 patients had PCa, 25 patients had BPH, 24 patients had high-grade PIN and 17 had chronic prostatitis. Out of 82 patients with biopsy confirmed PCa, 61 patients had pathohistologically confirmed moderately differentiated PCa (GS 3+4=7 and <7) and 21 patients had poorly differentiated PCa (GS 4+3=7 and >7). Blood for the measurement of serum IL-6 was collected into nonheparinized tubus prior to prostate biopsy and serum was separated within 1 hour of blood collection. The serum was stored at –70 °C and then thawed just prior to testing. Serum IL-6 levels were analyzed according to the manufacturer's instructions with a highly sensitive enzyme linked immunoadsorbent assay (ELISA) using a sandwich technique (Quantikine human IL-6 immunoassay, R&D Systems). The lowest detectable serum IL-6 level was 1.5 pg/mL. Data were shown as median and total range. Prostate specific markers tPSA, fPSA and f/tPSA were determined in blood samples immediately upon blood collection.

Statistics

Statistical Package for the Social Sciences (SPSS) version 17 was used for the statistical analysis. All of the data were expressed as median and total range. Since the Kolmogorov-Smirnov test (the K-S test) showed that the distribution of dependent variables differed from normality, the nonparametric tests for independent samples (the Kruskal-Wallis test and the Mann-Whitney U-test) were used for data analysis. The significance level of $p < 0.05$ was considered to be statistically significant. The relationship between the variables IL-6 and tPSA was calculated with the Spearman correlation coefficient test. The lowest possible detectible serum IL-6 level was 1.5 pg/mL.

Results

Table 1 shows the data for the four groups of patients with PCa, BPH, high-grade PIN and chronic prostatitis. Median and range of patients' age, serum IL-6 levels, serum tPSA levels, serum fPSA and serum f/tPSA levels are shown for each group.

Table 1 shows that the study included 148 patients, out of which 82 patients had PCa, 25 patients had BPH, 24 patients had high-grade PIN and 17 patients had prostatitis. Median for all patients was C=67 years (range 33–82). The Kruskal-Wallis test did not show a statistically significant difference in the age of the patients with different diagnoses (p=0.121). Also, there was no statistically significant difference in serum IL-6 levels in patients with PCa, BPH, high-grade PIN and prostatitis (p=0.088). Moreover, the tPSA variable showed a statistically significant difference among all four groups of patients (p=0.000). The Mann-Whitney U-test was used as a post-hoc test. It determined a statistically significant difference between PCa and high-grade PIN (p=0.001), as well as a statistically significant difference between PCa and BPH (p=0.001). In short, the patients with PCa had higher tPSA levels than the patients with high-grade PIN and BPH. Furthermore, there was no statistically significant difference in tPSA levels between PCa and prostatitis patients (p=0.052). Also, the Kruskal-Wallis test determined that there was a statistically significant difference among the patients with all four diagnosis in the f/tPSA levels (p=0.000). The post-hoc analysis determined a statistically significant difference between the patients with PCa and high-grade PIN (p=0.000), as well as the difference between the patients with PCa and

TABLE 1
PREBIOPTIC SERUM LEVELS OF IL-6, tPSA, fPSA AND f/tPSA

		age (year)		IL-6 (pg/mL)		tPSA (ng/mL)		fPSA (ng/mL)		f/tPSA (%)	
	N	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
PCa	82	67	33–82	2.09	1.49–16.75	9.20*	2.1–686.3	1.35	0.13–60.90	16*	5–33
PIN	24	67.50	54–80	2.16	1.49–5.93	4.80	1.4–20.0	1.20	0.47–4.17	22	17–37
BPH	25	62	43–76	1.63	1.49–3.84	5.70	1.7–15.3	1.22	0.28–2.72	20	9–40
Prostatitis	17	69	53–73	1.55	1.49–4.61	6.10	1.9–17.8	1.19	0.52–8.12	20	14–46

PCa – prostate adenocarcinoma, PIN – high–grade prostatic intraepithelial neoplasia, BPH – benign prostate hyperplasia, IL-6 – interleukin-6, tPSA – total prostate specific antigen, fPSA – free prostate specific antigen, f/tPSA – free/total prostate specific antigen ratio; *p<0.05 considered statistically significant

TABLE 2
PREBIOPTIC SERUM LEVELS OF IL-6, tPSA, fPSA AND f/tPSA IN THE GROUP OF PATIENTS WITH PCa WITH MODERATELY AND POORLY DIFFERENTIATED PCa

		age (year)		IL-6 (pg/mL)		tPSA (ng/mL)		fPSA(ng/mL)		f/tPSA (%)	
GS	N	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
ἐ7 3+4=7	61	66	33–81	1.76	1.49–16.75	6.90	2.1–42.6	1.18	0.31–6.73	16	7–33
≥7 4+3=7	21	70	49–82	3.30*	1.49–10.67	54.30*	3.3–686.3	7.74*	0.13–60.90	10	5–30

GS – Gleason score, IL-6 – interleukin-6, tPSA – total prostate specific antigen, fPSA – free prostate specific antigen, f/tPSA – free/total prostate specific antigen ratio; *p<0.05 considered statistically significant

BPH (p=0.003) and the patients with PCa and prostatitis (p=0.004). To sum up, the patients with PCa had the lowest t/fPSA levels among the four groups of patients. Finally, a statistically significant difference was not found in fPSA levels among the four groups of patients (p=0.631). Table 2 shows the difference between the groups of patients with moderately (GS 3+4=7 and <7) and poorly differentiated (GS 4+3=7 and >7) PCa.

The group of patients with poorly differentiated (GS 4+3=7 and >7) PCa had higher serum IL-6 levels than the patients with moderately differentiated (GS 3+4=7 and <7) PCa (p=0.007). Furthermore, the nonparametric Mann-Whitney U-test for independent samples determined a statistically significant difference in the tPSA levels between the two groups of PCa patients in which the patients with poorly differentiated PCa (GS 4+3=7 and >7) had higher tPSA than those with moderately differentiated (GS 3+4=7 and <7) PCa (p=0.000). Also, a statistically significant difference was found when compared fPSA within the two groups of PCa patients showing that the patients with poorly differentiated (GS 4+3=7 and >7) PCa had higher fPSA levels (p=0.000). However, there was no statistically significant difference in patients with moderately (GS 3+4=7 and <7) and poorly differentiated (GS 4+3=7 and >7) PCa in the f/tPSA levels (p=0.086). Furthermore, patients with moderately (GS 3+4=7 and <7) and poorly differentiated (GS 4+3=7 and >7) PCa did not show statistically significant difference in their age (p=0.098). The Spearman correlation coefficient test showed the positive correlation between serum IL-6 and PSA levels in patients with PCa (p=0.001).

Discussion

Currently, PSA is the putative biomarker for PCa screening. Although PSA testing has high sensibility, its specificity is rather low, causing clinicians to have doubts with regard to biopsying, since increased false-positive rates, overdiagnosis and overtreatment have been reported to be associated with PSA testing[11]. Therefore, novel biomarkers are needed to improve identification of men at risk of having PCa and predict the natural behavior of the prostate tumor. The use of more sensitive and specific biomarkers will be an appropriate strategy for disease diagnosis, disease staging, disease prognosis, predicting and monitoring clinical response to the therapy.

Clinical and biological data confirm the role of the proinflammatory cytokine IL-6 in PCa and support the inclusion of IL-6 as a marker in patients with PCa. De Marzo et al.[13] described the development of chronic inflammation related to infectious and non-infectious agents, called proliferative inflammatory atrophy (PIA), as precursor lesions of PCa. Nakashima et al.[14] reported that IL-6 is independently associated with survival in a series of 74 patients with PCa. IL-6 predicts biochemical recurrence in patients treated with radical prostatectomy (RP)[15].

The Gleason grading system remains one of the most powerful prognostic factors for PCa, and plays a crucial role in the prediction of metastatic progression after RP[16,17]. Serum IL-6 was significantly elevated in patients with Gleason score >6 (GS>6)[18]. Similarly, the data of serum IL-6 levels obtained in the present study showed elevated levels in poorly differentiated PCa patients (GS 4+3=7 and >7). Additionally, Oguić et al. concluded that higher tumor grade and positive surgical margins are indicators of a worse prognosis in patients[19].

The National Comprehensive Cancer Network (NCCN) guidelines suggested that PCa diagnosed with a pathological GS>7 requires aggressive local radiation and no RP[20]. Clinicians are in need of simple diagnostic modalities, available at initial diagnosis, which may be employed to estimate the clinical significance of cancer and guide their treatment decisions. TRUS guided true cut biopsy is a gold standard in PCa diagnostics[21]. The diagnosis of PCa is based on a combination of DRE, testing of PSA and the TRUS-biopsy. Testing of PSA and DRE are both limited with regard to their low sensitivity and specificity. A serum PSA measurement of 4 ng/ml is often still regarded as the threshold above which prostate biopsy is performed[22]. Several studies have shown an increase in sensitivities and specificities, primarily in the tPSA range of lower 10 ng/mL, for the f/tPSA ratio. They confirm that f/tPSA can better distinguish between patients with PCa from patients with BPH[23,24]. Similarly, the present study confirmed the same evidence for the f/tPSA ratio, which was the lowest for patients with PCa among the four groups of patients. Moreover, our study found that tPSA is higher in poorly differentiated PCa than in moderately differentiated PCa.

To improve the early detection of PCa, various PSA forms seem to be an established way for the early detection of PCa. Early detection measures, such as PSA test-

ing and TRUS guided prostate biopsy combined with the raised public awareness of the disease, most probably resulted in an increase of incidence[25]. It is of great interest to the urologists to avoid unnecessary biopsies and anticipate the distress of treated patients[26,27]. Because of the aforementioned limitations of the different biomarkers, further studies are necessary to find improved markers for the detection of PCa to reduce the number of patients who undergo a prostate biopsy without having PCa.

In conclusion, there was no significant difference in serum IL-6 collected prior to prostate biopsy procedure in patients with PCa, BPH, high-grade PIN and prostatitis. Total PSA is a marker with a low specificity in PCa detection but f/tPSA can better distinguish between patients with PCa from the patients with BPH, high-grade PIN and prostatitis. IL-6 can be an additional marker in detection of poorly differentiated PCa patients (GS 4+3=7 and >7), and thus can provide some helpful guidelines for its adequate management and treatment. Larger prospective studies and the standardization of the assays for the measurement of IL-6 are required to confirm the role of these cytokines as tumor markers in PCa.

REFERENCES

1. PARKIN DM, BRAY FI, DEVESA SS, Eur J Cancer, 37 (2001) 4. — 2. LIN K, LIPSITZ R, MILLER T, JANAKIRAMAN S, Ann Intern Med, 149 (2008) 192. — 3. ROEHRBORN CG, MCCONNELL J, BONILLA J, ROSENBLATT S, HUDSON PB, MALEK GH, SCHELLHAMMER PF, BRUSKEWITZ R, MATSUMOTO AM, HARRISON LH, FUSELIER HA, WALSH P, ROY J, ANDRIOLE G, RESNICK M, WALDSTREICHER J, J Urol, 163 (2000) 13. — 4. LEE SO, LOU W, HOU M, DE MIGUEL F, GERBER L, GAO AC, Clin Cancer Res, 9 (2003) 370. — 5. GERMANO G, ALLAVENA P, MANTOVANI A, Cytokine, 43 (2008) 374. DOI: 10.1016/j.cyto.2008.07.014 — 6. DRACHENBERG DE, ELGAMAL AA, ROWBOTHAM R, PETERSON M, MURPHY GP, Prostate, 41 (1999) 127. — 7. WISE GJ, MARELLA VK, TALLURI G, SHIRAZIAN D, J Urol, 164 (2000) 722. — 8. SHARIAT SF, ANDREWS B, KATTAN MW, KIM J, WHEELER TM, SLAWIN KM, Urology, 58 (2001) 1008. — 9. TWILLIE DA, EISENBERGER MA, CARDUCCI MA, HSEIH WS, KIM WY, SIMONS JW, Urology, 45 (1995) 542. — 10. GEORGE DJ, HALABI S, SHEPARD TF, SANFORD B, VOGELZANG NJ, SMALL EJ, KANTOFF PW, Clin Cancer Res, 11 (2005) 1815. — 11. DRAISMA G, ETZIONI R, TSODIKOV A, MARIOTTO A, WEVER E, GULATI R, FEUER E, DE KONING H, J Natl Cancer Inst, 101 (2009) 374. DOI: 10.1093/jnci/djp001 — 12. MIKOLAJCZYK SD, SONG Y, WONG JR, MATSON RS, RITTENHOUSE HG, Clin Biochem, 37 (2004) 519. — 13. DE MARZO AM, PLATZ EA, SUTCLIFFE S, XU J, GRÖNBERG H, DRAKE CG, NAKAI Y, ISAACS WB, NELSON WG, Nat Rev Cancer, 7 (2007) 256. — 14. NAKASHIMA J, TACHIBANA M, HORIGUCHI Y, OYA M, OHIGASHI T, ASAKURA H, MURAI M, Clin Cancer Res, 6 (2000) 2702. — 15. ALCOVER J, FILELLA X, LUQUÉ P, MOLINA R, IZQUIERDO L, AUGÉ JM, ALCARAZ A, Anticancer Res, 30 (2010) 4369. — 16. EBSTEIN JI, J Urol, 183 (2010) 433. DOI: 10.1016/j.juro.2009.10.046 — 17. PORTER CR, SUARDI N, KODAMA K, CAPITANIO U, GIBBONS RP, CORREA R, JELDRES C, PERROTTE P, MONTORSI F, KARAKIEWICZ PI, Int J Urol, 15 (2008) 889. DOI: 10.1111/j.1442-2042.2008.02105.x — 18. MICHALAKI V, SYRIGOS K, CHARLES P, WAXMAN J, Br J Cancer, 90 (2004) 2312. — 19. OGUIĆ R, CINI E, ĐORĐEVIĆ G, MATUŠAN-ILIJAŠ K, MARKIĆ D, PETKOVIĆ M, Coll Antropol, 34 (2010) 283. — 20. MOHLER JL, J Natl Compr Canc Netw 8 (2010) 145. — 21. MARIČIĆ A, VALENCIĆ M, SOTOSEK S, OGUIĆ R, IVANCIĆ A, AHEL J, Coll Antropol, 34 (2010) 239. — 22. CATALONA WJ, SMITH DS, ORNSTEIN DK, JAMA, 277 (1997) 1452. DOI: 10.1001/jama. 1997.03540420048028 — 23. PERSONS JK, BRAWER MK, CHELI CD, PARTIN AW, DJAVAN R, BJU Int, 94 (2004) 47. DOI: 10.1111/j.1464-410X.2004.04899.x — 24. TANGUAY S, BÉGIN LR, ELHILALI MM, BEHLOULI H, KARAKIEWICZ PI, APRIKIAN AG, Urology, 59 (2002) 261. DOI: 10.1016/S0090-4295(01)01497-2 — 25. ŠPANJOL J, MARIČIĆ A, CICVARIĆ T, VALENČIĆ M, OGUIĆ R, TADIN T, FUČKAR D, BOBINAC M, Coll Antropol, 31 (2007) 235. — 26. STENMAN UH, LEINONEN J, ALFTHAN H, RANNIKKO S, TUHKANEN K, ALFTHAN O, Cancer Res. 51 (1991) 222. — 27. WODRUM DL, BRAWER MK, PARTIN AW, CATALONA WJ, SOUTHWICK PC, J Urol. 159 (1998) 5. DOI: 10.1016/S0022-5347(01)63996-X

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USPOREDBA KLINIČKE ZNAČAJNOSTI PROINFLAMATORNOG PROTEINA INTERLEUKINA-6 U SERUMU I KLASIČNIH TUMORSKIH MARKERA UKUPNOG PSA, SLOBODNOG PSA I SLOBODNI/UKUPNI PSA PRIJE BIOPSIJE PROSTATE

SAŽETAK

Cilj ove studije je bio razjasniti može li razina proinflamatornog citokina, interleukina-6 (IL-6) u serumu biti korisni marker kod bolesti prostate. Serumski IL-6 je bio određen prije biopsije prostate u 82 pacijenta s adenokarcinomom prostate (PCa), 25 pacijenata s benignom hiperplazijom prostate (BPH), 24 pacijenta s intraepitelnom neoplazijom visokog stupnja (PIN) i 17 pacijenata s kroničnim prostatitisom. Razina serumskog IL-6 je uspoređena s ukupnim PSA (tPSA), slobodnim PSA (fPSA) i omjerom slobodni/totalni PSA (f/tPSA) u serumu. Statistički značajna razlika nije nađena u razini serumskog IL-6 između četiri grupe (p=0.088). Međutim, pacijenti s loše diferenciranim PCa s Gleason »scoreom« (GS) 4+3=7 i >7 imali su značajno više razine serumskog IL-6 nego pacijenti sa srednje diferenciranim PCa s GS 3+4=7 i <7 (p=0.007). Rezultati sugeriraju da bi razina serumskog IL-6 mogla biti potencijalni korisni marker kod slabo diferenciranog PCa.