

Comparison of Caveolin-1 and PSA in Prostate Adenocarcinoma

Prostat Adenokarsinomunda Caveolin-1 ve PSA'nın Karşılaştırılması

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ABSTRACT

Objective: The aim of the present study was to evaluate caveolin-1 (CAV-1) levels as a possible alternative for the prostate specific antigen in the diagnosis of patients with prostate adenocarcinoma (PCa).

Methods: The study was conducted with 33 cases (mean age 67.2 (45-90) years) and 16 control patients (mean age 56.68 (48-77) years). Blood sample solution results of both the groups were read twice, and the average optical density of the zero standard was subtracted from the solution results' average.

Results: The average levels of prostate-specific antigen (PSA) were 1.1 (± 0.64) for the control group and 12.3 (± 8.7) for patients with adenocarcinoma. The average levels of CAV-1 were 336 (± 41.1) in the control group and 476 (± 66.9) in patients with adenocarcinoma. PCa was detected in 33 patients, 27 of whom underwent prostatectomy, and the remaining 6 began hormone therapy. Of these 33 patients, 2 had a Gleason score of 4, 16 had a Gleason score of 6, 10 had a Gleason score of 7, 3 had a Gleason score of 8, and 2 had a Gleason score of 9. Patients with PCa had higher PSA and CAV-1 than the control group ($p < 0.05$). CAV-1 (correlation parameter: 0.43) and PSA (correlation parameter: 0.48) were observed to increase with age ($p < 0.05$). A positive linear correlation was observed between PSA and CAV-1 in all of the cases, but this relationship was not significant for cases with PCa ($p > 0.05$).

Conclusion: The level of CAV-1 was found to be higher in patients with PCa. CAV-1 can be used as an alternative for PSA, but it is not superior to PSA with respect to diagnosis, cost, and testing difficulty. In spite of the challenges its examination presents, CAV-1 is a protein, which should be tested in areas, such as early diagnosis, active surveillance, hormone refractory PCa, and radical prostatectomy.

Keywords: Caveolin, prostate carcinoma, PSA, prostate-specific antigen

ÖZ

Amaç: Bu çalışmanın amacı prostat adenokarsinomu (PCa) olan hastaların tanısında prostat spesifik antijen (PSA) için olası bir alternatif olarak Caveolin-1 (CAV-1) seviyelerini değerlendirmektir.

Yöntemler: Çalışma 33 hasta ve 16 kontrol grubu olmak üzere iki gruba ayrılmıştır. Her iki grubun kan örneklerinden ELİSA kiti ile CAV-1 düzeyleri çalışıldı. Sonuçlar tanı öncesi PSA düzeyi ile karşılaştırılarak istatistiksel olarak analiz edildi.

Bulgular: Çalışmada hasta grubunun yaş ortalaması 67,2 (45-90) iken kontrol grubunu ortalama yaş 56,68 (48-77) idi. PSA ortalaması kontrol grubu için 1,1 ($\pm 0,64$), adenokarsinomlu hastalar için 12,3 ($\pm 8,7$) idi. Kontrol grubunda ortalama CAV-1 düzeyi 336 ($\pm 41,1$), adenokarsinomlu hastalarda ise 476 ($\pm 66,9$) idi. Hastaların 27'sine prostatektomi yapıldı, geriye kalan 6'sına ise hormonoterapiye başlandı. Bu 33 hastadan 18'inin Gleason Skoru (GS) 4 ve altında, 10'u GS 7, 3'ünün GS 8 ve 2'si GS 9 idi. Prostat adenokarsinomu olan grupta daha yüksek PSA ve CAV-1 düzeyleri saptandı ($p < 0,05$). CAV-1 (korelasyon parametresi: 0,43) ve PSA (korelasyon parametresi: 0,48) yaşla birlikte arttı ($p < 0,05$). Tüm olgularda PSA ile CAV-1 arasında lineer pozitif korelasyon gözlenirken, bu ilişki PCa'lı olgularda anlamlı değildi ($p > 0,05$).

Sonuç: Prostat adenokarsinomu olan hastalarda CAV-1 değeri daha yüksek bulundu. Prostat kanseri tanısı için yeni bir belirteç olarak kullanılabilir. Ancak tanı, maliyet ve test zorluğu düşünüldüğünde PSA'dan üstün değildir. CAV-1 erken tanı, aktif surveians, hormon refrakter PCa ve radikal prostatektomi gibi alanlarda test edilmesi gereken bir proteindir.

Anahtar kelimeler: Caveolin, PSA, prostat spesifik antijen, prostat kanseri

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INTRODUCTION

Prostate cancer is the most frequently observed neoplasia and the second most common reason for cancer-related deaths in men (1, 2). Approximately, one out of five men is diagnosed with prostate cancer. It is the fourth leading cancer in the world, and the incidence and mortality rates differ in each country (3). Beginning with the first half of the 1990s, new screening tests and developments in treatment caused dramatic changes in the phase of diagnosis and mortality. PSA belongs to the serine proteases multigene family localized on the kallikrein gene family locus on chromosome 19, identified in 1986 (4). PSA is currently used as a standard screening method, but the changes in PSA levels are insufficient for the diagnosis of prostate adenocarcinoma (PCa), resulting in a significant number of unnecessary biopsies. Accordingly, there is a search for potential alternative markers for the diagnosis of PCa, one of which is caveolin-1 (CAV-1), a glycoprotein.

The purpose of the present study was to compare the CAV-1 levels of patients diagnosed with prostate cancer to their PSA results in order to evaluate if CAV-1 promises to be an alternative marker for PSA.

Caveolin-1

CAV-1 is a protein coded with the CAV1 gene in humans. This gene is a candidate repressor and a negative regulator of the Ras-p42/44 MAP cascade. CAV-1 and CAV-2 are located nearby on chromosome 7, and they express the proteins that form a stable hetero-oligomeric complex.

Caveolae, which are a special type of lipid raft, are small (50-100 nm) invaginations of the plasma membrane in many vertebrate cell types, especially in endothelial cells and adipocytes. Formation and maintenance of caveolae is primarily due to the protein caveolin, a 21 kDa protein. There are three homologous genes of caveolin expressed in mammalian cells: CAV-1, CAV-2, and CAV-3. The normal secretion of the caveola is through highly differentiated epithelium cells, endothelium, heart muscle cells, adipocyte, and osteoblasts. Caveola contains highly concentrated signal molecule, G protein, tyrosine kinase receptors, and endothelial nitric oxide synthesis. These molecules interact with the caveolin protein containing 20 amino acids of CAV-1 called CAV-1 frame area (CAV-1 scaffolding domain, CSD). With the aid of the CSD-mediated activities, mobile sections of the caveola organize the signalization between the intracellular organelles and between the inside and the surface of the cell. A study conducted with mouse and human cells has reported that with respect to malignity development, CAV-1 plays a complicated role on the type of the cell, growth factor, and cell adhesion (5). Under certain conditions, CAV-1 can repress tumor formation (6). CAV-1 was also shown to be related to multiple mechanisms and to play a role on the progression of the malignity (7).

Patients with metastatic prostate cancers have higher intracellular CAV-1 expression levels than the normal population (8). Various studies have also shown that it plays an important role in hepatoma, leukemia, nose and pharynx carcinoma, oral cancers, breast cancer, and bladder or prostate cancer. CAV-1 rs3807987/rs7804372 genotype is thought to be responsible for upper urethral tumors (9).

In the reported cell series of fatal prostate cancers, biologically, in vitro active CAV-1 protein is secreted, which is effective with respect

to cellular vitality and clonal growth in prostate cancer (10, 11). Secreted CAV-1 was observed to display an anti-apoptotic quality in cancer formation. This quality could also be found inside the CAV-1 cells (10, 12). In addition, CAV-1-mediated autocrine activities are displayed. A recent study has reported that cancer cells absorb this recombinant CAV-1 protein. Endothelial cells increase the angiogenic efficiency of the recombinant CAV-1 protein both in vivo and in vitro and mediate nitric oxide synthesis signalization in vivo (13).

Patients with cancer relapse following radical prostatectomy were reported to display high levels of serum CAV-1 (14).

New biomarkers, such as CAV-1, can be a strong indicator of the clinical result for various aggressive cancer types in humans (14).

METHODS

The study was conducted with 49 patients (33 in the experimental group and 16 in the control group). Oral informed consent was obtained from all the participants. The local ethics board approved the study. A total of 33 patients whose age ranged from 45 to 90 years, had no other malignancy in a different organ, had recently received a diagnosis of prostate adenocarcinoma, had received no prior treatment, and were planned to undergo either radical prostatectomy, radiotherapy, chemotherapy, or hormone therapy were included in the study as the experimental group. A limited number of patients who met the inclusion criteria but had a PSA level >50 were excluded from the study with statistical concerns. Blood samples were collected from both groups.

Sera

Blood samples were left to clot for 30 min before using a serum separator tube to centrifuge the samples for 15 min at a 1000-gram cycle. The resulting serum was immediately analyzed. We divided an equal amount of samples to heparin, citrate, or EDTA tubes and kept them at -20 °C. We refrained from repeating the congealment-defrosting procedure. Before usage, reactivities and samples were heated at room temperature of °C. Samples, both standard and control solutions, were analyzed twice.

Range of Analysis

Standard curve concentrations for ELISA tests were 2000 pg/mL, 1000 pg/mL, 500 pg/mL, 250 pg/mL, 125 pg/mL, 62.5 pg/mL, and 31.2 pg/mL. This analysis recognized recombinant and natural human CAV-1. No significant cross-reactivity or interaction was observed. For CAV-1, a minimal detectable dose is typically <7.8 pg/mL. The sensitivity or lowest level of determination for this analysis is defined as the lowest protein concentration that can be distinguished from zero.

Each standard, control, and sample solution was read twice, and average measurements were obtained. Thereafter, the zero standard's average optical density was subtracted from this average measurement. Using a computer software capable of forming a four parameter logistic curve, we cleaned out the data to form a standard curve. The most compatible axis was determined by regression analysis.

The present study used a human caveolin-1 ELISA kit (microplate 96 test research kit; Cusabio Biotech Co., Ltd., China).

RESULTS

The present study was conducted in Taksim Training and Research Hospital Urology Clinic with 33 experimental group patients with

a mean age of 67.2 (45-90) years and 16 control group patients with a mean age of 56.68 (48-77) years. PCa was detected in all 33 patients, 27 of whom had prostatectomy, and the remaining 6 began hormonotherapy. Of these 33 patients, 2 had a Gleason score of 4, 16 had a Gleason score of 6, 10 had a Gleason score of 7, 3 had a Gleason score of 8, and 2 had a Gleason score of 9. In 3 patients who received biopsy, adenocarcinoma was detected on all cores. One patient had an area suspicious for metastasis, 2 patients had bladder stone, and 1 patient had cystic lesion in the liver.

PSA and CAV-1 were found to be higher in cases with PCa than in the control group (see Table) ($p < 0.05$).

CAV-1 (correlation coefficient: 0.43) and PSA (correlation coefficient: 0.48) were observed to increase with age (see Figure 1) ($p < 0.05$).

A linear correlation was observed between PSA and CAV-1 on all cases included in the study ($p < 0.05$).

In the linear regression graph that includes patients whose PSA was > 10 , there is no significant linear relationship between CAV-1 and Gleason score. Average scores were compared statistically using t-test. Linear regression analyses and Pearson correlation coefficients were used to examine the relationship between the two groups.

DISCUSSION

Prostate cancer is one of the major health problems for the contemporary male society. In Europe, approximately 2.6 million

people are diagnosed with cancer annually, and prostate cancer makes up 11% of all male cancers (15, 16).

During diagnosis, patients are tested for PSA and digital rectal examination (RT). However, PSA tests do not provide definitive information for cancer diagnosis. Consequently, there is a need for a new diagnostic parameter. A study has documented that men with benign prostate hyperplasia have higher serum CAV-1 levels than men with prostate cancer (17). In our study, blood samples of patients with prostate cancer had statistically high levels, but in blood from patients having cancer, CAV-1 had the lowest level at 357 pg/mL, and the highest level was detected in the control group patients at 410 pg/mL, respectively. Whether these patients with low PSA levels have cancer is open for debate. However, we know that PSA level is not a definitive diagnostic parameter. Even though we found a linear correlation between patients' PSA result and their CAV-1 levels, separate analyses of the control group and the cancer group did not provide similar result.

Raventós and colleagues have studied 280 patients and reported that based on the results of the prostate biopsies conducted according to the D'Amico criteria, cancer in one core or minimum tumor value of 0.45 cm³ provides guidance for deciding between radical surgery and active surveillance (18). In our study, the biopsy percentage of patients with prostate cancer did not have a statistically significant relationship with CAV-1 levels. Neither did the linear regression graph of the PSA result of these patients provided significant results. Such changes in the CAV-1 and PSA levels serve as a guideline in our decisions about low-grade patients who would benefit from active surveillance.

Guang Yang and colleagues conducted a study in which they analyzed 189 radical prostatectomy specimens using the Cox regression model and reported that CAV-1 is an independent prognostic factor for indicating progression. CAV-1 levels were related to not only Gleason score, lymph node positivity, metastasis, and positive surgical margins but also the progression of prostate cancer (19).

In our study, on the other hand, there was no significant relationship between the Gleason score and CAV-1 levels.

Tahir et al. (20) studied 419 patients diagnosed with PCa and indicated that a combination of serum PSA > 10 ng/mL, serum CAV-1, and biopsy Gleason score can predict recurrence. In our study, regression graph of patients with PSA scores > 10 failed to provide a significant result. This suggests that our results do not support the findings of Tahir and colleagues.

CAV-1 loss in the prostate cancer stroma was shown to be related to recurrence, survival, and tumor progression (21).

In light of this information, even though CAV-1 levels were high in patients with prostate cancer, our results indicate that it is not related to the Gleason score, tumor volume, or PSA levels. Therefore, this information is not sufficient for deciding which patient should be considered under active surveillance. Thousands of patients worldwide undergo unnecessary biopsy due to high PSA, indicating high costs and loss of workforce. In our study, the control group patients had higher CAV-1 levels than patients with prostate cancer, and the question regarding which patients can be spared of prostate biopsy remained unanswered.

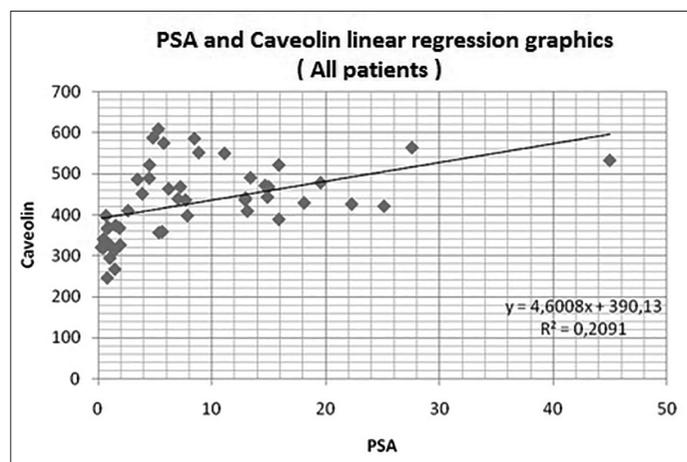


Figure 1. Correlation between PSA and caveolin

Table. Comparison of two groups (prostate cancer and control groups)

	PCa(+)	PCa(-)	p
Average value of caveolin	476±66.9 (357-608)	336±44.1 (247-410)	<0.05
Average age	67.3±9.1 (45-96)	56.7±7.6 (48-77)	<0.05
Average PSA	12.3±8.7 (3.47-45)	1.1±0.64 (0.34-2.64)	<0.05

Since the CAV-1 ELISA kit is not routinely used, automatic equipments for evaluating the level of this marker are not developed. Measuring CAV-1 levels require human power. Since it is still on the research phase, it is used for company-supported research rather than that for diagnostic purposes. As a result, its testing cost per unit is 3–4 times higher than routinely used PSA.

CONCLUSION

The widespread use of blood testing for PSA resulted in an increase in the number of prostate biopsies for early diagnosis of prostate cancer. Out of four men who undergo prostate biopsy due to high PSA, only one has prostate cancer. Furthermore, considering some men have normal levels of serum PSA, tumor diagnosis can be late in patients with prostate cancer. There are currently genetic and molecular studies, such as the PCA3 gene tested on a urine sample that are expected to aid the diagnosis of prostate cancer (22). In conclusion, in spite of the testing difficulties and high costs related to this marker, CAV-1 research is promising. Therefore, CAV-1 tests should be further researched for the diagnosis and surveillance of prostate cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethic Committee of Taksim Training and Research Hospital (TAEH EK /2010).

Informed Consent: Verbal informed consent was obtained from the patients who participated in this study.

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