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D-dimer in the Diagnosis of Prostate Cancer

Prostat Kanserinin Tanısında D-dimer

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Abstract

Objective: To investigate the value of D-dimer, a marker of fibrinolysis, in metastatic and non-metastatic prostate cancer.
Materials and Methods: A retrospective analysis was performed on 138 male patients including 52 patients with prostate cancer and 86 with benign prostatic hyperplasia. Participants who had factors that altered D-dimer levels were excluded. The mean ages of the groups were similar (70 ± 8 vs 68 ± 8, p= NS). In addition, data regarding biochemical findings, prostate-specific antigen and hemostatic markers, including D-dimer, were retrieved from the database of our hospital. The cut-off point of D-dimer was 0.5 mg/L. Data from scintigraphy and magnetic resonance imaging (MRI) scans related to metastasis were also considered. Patients who showed findings of metastasis according to scintigraphy and lumbosacral MRI were accepted as having metastases. Positive findings in only scintigraphy in any area were considered suspicious for metastasis.
Results: Patients with prostate cancer had higher D-dimer levels than benign prostate hyperplasia patients (p= 0.024). Sixteen patients with metastatic prostate cancer and suspicious for metastasis had markedly high D-dimer levels compared to benign prostate hyperplasia and non-metastatic prostate cancer patients.
Conclusion: prostate cancer, especially when metastatic, may increase D-dimer levels.

Keywords: D-dimer, prostate cancer, metastasis.

Öz

Amaç: Fibrinolizin bir belirteci olan D-dimerin metastatik ve metastatik olmayan prostat kanserinde değerini araştırmak.
Gereçler ve Yöntemler: 52'si patolojik prostat kanseri ve 86'sı benign prostat hiperplazisi olan 138 erkek hasta retrospektif olarak analiz edildi. D-dimer düzeylerini değiştiren faktörlere sahip katılımcılar dışlandı. Grupların ortalama yaşları benzerdi (70 ± 8'e karşı 68 ± 8, p= NS). Hastanemizin veri tabanından rutin biyokimyasal bulgulara ek olarak prostat spesifik antijen (PSA) ve D-dimer içeren hemostaz belirteçleri toplandı. D-dimerin cut-off noktası 0.5 mg/L idi. Metastaz için sintigrafi ve manyetik rezonans görüntüleme araştırmalarından elde edilen veriler de dikkate alındı. Sintigrafi ve lumbosakral manyetik rezonans görüntülemesine göre metastaz bulguları gösteren hastalar metastazlı olarak kabul edildi. Herhangi bir bölgede sadece sintigrafide pozitif bulgular metastaz için şüpheli kabul edildi.
Bulgular: Prostat kanserli hastaların D-dimer düzeyleri benign prostat hiperplazili hastalara göre daha yüksekti (p= 0.024). Metastatik prostat kanseri olan ve metastaz şüphesi olan 16 hasta, iyi huylu prostat hiperplazisi ve metastatik olmayan prostat kanseri hastalarına kıyasla belirgin şekilde yüksek D-dimer seviyelerine sahipti.
Sonuç: prostat kanseri, özellikle metastatik olduğunda D-dimer düzeylerini artırabilir.

Anahtar kelimeler: D-dimer, prostat kanseri, metastaz.

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Introduction

Prostate cancer (PCa) has been shown to be the second-most common malignancy and the fourth leading cause of death in men worldwide. Epidemiological studies have revealed that its incidence is rising in the era of the prostate-specific antigen (PSA) [1].

Although PCa can be managed in the early stages by surgical intervention or radiation, over time, approximately 7.0% of cases of PCa metastasize and progress to castration-resistant cancer, even with aggressive hormone deprivation therapy [2–4]. The prognosis is poor in men with distant metastases of PCa, in which bone is the most common site of involvement [4].

Today, the routine diagnostic screening tests for PCa include measurement of PSA in the blood, digital rectal examination and, ultimately, a systematic transrectal ultrasound-guided biopsy [5,6]. However, despite the rapidly growing number of candidate biological markers of prognosis and/or response to specific treatments in PCa, to date, none have shown the ability to give a complete understanding of prognosis for PCa in evidence-based urology. Many tools have been used to determine advanced stages of PCa in addition to PSA, comprising C-reactive protein, ceruloplasmin, beta-2-microglobulin, fibronectin and calcitonin etc. [7–9]. In this context, D-dimer, which is another biomarker, has been associated with advanced and metastatic cancers.

D-dimer is produced as a result of cleavage of cross-linked fibrin by the fibrinolytic enzyme plasmin. Therefore high levels of D- dimer indicate activation of coagulation and fibrinolysis [10]. Although not extensively studied, it has also been suggested that PCa increases serum D-dimer levels. However, conflicting data exist regarding the association of D-dimer levels with the stage of the disease [11]. In this study, we aimed to exhibit a presumptive relation of D-dimer levels with PCa.

Materials And Methods

The data were retrieved retrospectively from the database of Sakarya University Medical Faculty Training and Research Hospital which provides tertiary health care. Information regarding male inpatients aged ≥ 50 years who were hospitalised with lower urinary tract symptoms (LUTS) for surgery, cases with increased PSA levels scheduled for transrectal prostate biopsy, and patients with the diagnosis of PCa interned for treatment between May 2011 and October 2020, were used. The patients who had pretreatment or preoperative biochemical tests including D-dimer, and pathologic diagnoses after operation or biopsy, were enrolled in the study. The patients with pathologic diagnosis of BPH who were of a similar mean age were used as a control group. The criteria for exclusion were as follows: presence of active infection including urinary system infection, any malignancy other than PCa, any chronic inflammatory disease such as chronic obstructive pulmonary disease or rheumatoid arthritis, indwelling urethral catheter, any recent operation or trauma, and any record or diagnosis of thromboembolism. Additionally, patients who had taken antithrombotic/antiaggregant agents for other indications were also excluded.

Besides, information were retrieved from the database regarding age, international prostate symptom score (IPSS), the international normalised ratio of prothrombin time (INR), activated partial thromboplastin time (aPTT), scintigraphic and radiologic imaging results. The cut-off point of D-dimer was 0.5 mg/L. The results of the scintigraphic and radiological (magnetic resonance imaging [MRI]) examinations of the patients who had been diagnosed with PCa were used to exhibit metastasis. Patients who showed findings of metastasis according to both lumbosacral skeletal scintigraphy and lumbosacral MRI results were accepted as having metastasis. Radioactive substance uptake in scintigraphy only in areas beyond the lumbosacral region or in the lumbosacral area but not confirmed by MRI was considered "suspicious" for metastasis. The patients could not be detailed regarding stage of PCa retrospectively but dichotomised as metastasis- positive or metastasis- negative cases based on the presence of metastasis.

Statistical Analysis

Because the data regarding D-dimer did not have a Gaussian distribution, Spearman's rho correlation test was used to measure strength and direction of association between nonparametric variables. The Mann-Whitney U test was applied to compare independent groups that did not have sufficient participants for parametric tests. A paired t-test was used for dependent groups who had sufficient number of participants and normal distribution. In this study, statistics were performed using the software package SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were used to reject the null hypothesis.

Results

A total of 138 consecutive male patients were recruited. Eighty-six patients were pathologically diagnosed with benign prostatic hyperplasia (BPH), and 52 with PCa. The basic characteristics of the two groups are presented in **Table 1**. Median D-dimer levels of the BPH and PCa patients were 0.32 mg/L (0.10-6.40) and 0.49 mg/L (0.02-7.29), respectively with a a significant intergroup difference ($p = 0.011$) **(Table 1)**.

Twenty-two (42%) out of 52 PCa patients had D-dimer values above the cut-off value. Ten of these 22 patients were found to have metastatic disease according to scintigraphy and MRI findings. In all metastatic patients (median D-dimer 1.66 mg/L, range 0.60-7.29) D-dimer values were above the cut-off point. The remaining 12 patients also had D-dimer values over the cut-off point including 6 cases suspicious for metastasis, and the remaining 6 patients had not any findings suggesting the presence of metastasis. Thus, 31% of the PCa patients with higher D-dimer levels had significant or suspicious evidence of metastasis. None of the patients had MRI -positive and scintigraphy- negative findings suggestive of metastasis **(Table 2)**.

On the other hand, 17 (20%) patients with BPH had D-dimer levels above the cut-off point, versus 22 (42%) patients with PCa. The ratio of individuals having D-dimer levels above the cut-off value was significantly greater in the PCa patients than in the BPH patients ($p = 0.021$). Among BPH patients, a subgroup with higher D-dimer levels was similar to the other subgroup with normal D-dimer levels regarding age ($p > 0.05$).

Table 1: Basic characteristics of the patients with BPH and PCa

Variables	BPH(n=86)	PCa(n=52)	*p*
D-dimer (mg/L) Median (min-max)	0.32(0.10-6.40)	0.49(0.02-7.29)	0.011
Age years (mean±SD)	67±8	70±8	NS
IPSS Median (min-max)	19(4-33)	15(3-30)	0.009
INR (%) Median (min-max)	1.06(0.81-3.12)	1.19(0.82±9.96)	NS
aPTT (sec) (mean±SD)	26.04±3.50	27.20±3.76	NS

SD: standard deviation; NS: nonsignificant; Pca: prostate cancer; BPH: benign prostatic hyperplasia

Additionally, D-dimer levels were shown to be associated with PSA (rs= 0.287; p= 0.001) and age (rs= 0.362; p= 0.024). Taken Gleason score into consideration for grading PCa, no significant association has been detected between PCa and D-dimer levels (rs= 0.214, p> 0.05) **(Table-2)**.

Discussion

This study showed that D-dimer levels were higher in patients with PCa than in patients with BPH, which is in line with data encountered in the literature [12–14]. Although some BPH patients revealed D-dimer values above the cut-off value, the median value of D-dimer levels was below the cut-off point in patients with BPH. Approximately 31% of PCa patients who were metastatic or suspicious for metastasis had higher D-dimer values than non-metastatic PCa and BPH patients. Similarly, in their study of 49 BPH and 55 PCa patients, Geenen et al. found that levels of D-dimer, as a marker of fibrinolysis, were elevated in the metastatic group compared to the non-metastatic PCa and BPH groups. They also noted that fibrinolysis might not play a prominent role in PCa, since there was no significant intergroup difference regarding another marker of fibrinolysis, plasmin-a2-antiplasmin [13].

D-dimer is a degradation product of cross-linked fibrin. Its presence in plasma is an indirect marker of activation of coagulation followed by reactive thrombolysis. High D-dimer levels combined with other factors were proposed as independent predictors for venous thromboembolism (VTE) in patients with cancer, allowing an overall risk assessment [10,15]. Blom et al. concluded that in the presence of distant metastasis, cancer patients had a highly increased risk of VTE after diagnosis [16]. In our study, all D-dimer levels in 10 patients with distant metastasis and six patients suspicious for metastasis, were above the cut-off point. These results were in accordance with the results reported by Adamson et al., who concluded that high D-dimer levels might have some predictive value in determining bone scan status in untreated PCa patients [12]. In our study, in each of the 22 patients (42%) of the PCa group, D-dimer levels were above the cut-off point, suggesting activation of the hemostatic system This finding is in line with Adamson's conclusion that up to 40% of patients with untreated PCa showed evidence of activation of hemostatic system [12].

On the other hand, Adcock observed evidence of distant metastasis in up to 40% of cases with cancer and concomitant VTE [17]. In our study, 10 out of 22 (46%) patients with PCa and higher D-dimer levels showed strong evidence of metastasis. In contrast, Hong studied antithrombin-III (ATIII), plasminogen, fibrinogen and D-dimer, and concluded that subjects with organ-confined disease and those with an extraprostatic extension of a tumour had not demonstrated any significant differences in the preoperative levels of the four coagulation factors analysed [11].

The methods we used (scintigraphy and MRI) have some limitations, despite their relatively high sensitivity and different specificity in determining PCa metastasis [18–21]. Since a precise diagnostic confirmation method for detecting metastasis is lacking, we could not be sure if the cases with higher D-dimer levels, which were assumed as suspicious or non-metastatic, harbour distant metastasis. Other routine laboratory studies also did not rule out such conditions in these cases.

The hemostatic system seems to play a role in the metastatic capacity of solid tumours [16]. However, the actual mechanism of this coagulopathy in cancer patients is not precise [14]. Tissue factor (TF) is a cell procoagulant found in normal cells, including endothelial cells, macrophages, and -monocytes. Although normal endothelial cells express TF only in response to an inflammatory stimulus, malignant cells constitutively express TF [17]. Tumour cells interact with all parts of the hemostatic system and activate the coagulation cascade with procoagulant factors, such as TF and cancer procoagulant factor. The coagulation cascade eventually results in thrombosis comprising blood cells, such as platelets, monocytes or macrophages [22]. In addition, previously reported studies

Table 2: Distribution of D-dimer values in patients with PCa

D-dimer (mg/L)	Met. (+), (n)	Met. Susp.,(n)	Met. (-), (n)	Total (n)
D-dimer>0.5 (n)	10	6	6	22
D-dimer<0.5 (n)	0	0	30	31
Total (n)	10	6	36	52

Met. (+): metastasis- positive; Met. Susp.: suspicious for metastasis; Met. (-): metastasis- negative.

have shown that D-dimer, a fibrinogen degradation product, is involved in tumor progression due to the ability of tumor cells to transform fibrinogen to fibrin. The rising plasma D-dimer levels may display fibrinogen metabolism within the tumor stroma that is actively remodeling [23]. Also fibrin creates a protective layer on tumor cells, providing resistance to endogenous defense mechanisms, which can facilitate angiogenesis, invasion and metastasis [24].

In this study, D-dimer levels were also shown to be weakly but significantly associated with PSA, which may be due to a relation between D-dimer and PCa. D-dimer was found to be more strongly associated with age when compared to PSA. Although D-dimer levels gradually increase with age, its specificity for venous thromboembolism decreases accordingly [25,26]. This condition increases the frequency of false positive test results in the elderly [27]. Thus D-dimer cut-off points were suggested separately for each decade after 50 years of age [28,29]. Accordingly, although the mean D-dimer levels of BPH patients were below the cut-off point, 17 of 86 BPH patients (20%) had D-dimer values above the cut-off point. However, the mean ages of the 17 patients and the remaining patients were similar (p> 0,05).

The data in this study seem somewhat confusing. One may encounter difficulties when attempting to use D-dimer values for the estimation of metastasis. D-dimer level above the cut-off value may not point to any significant evidence regarding metastasis. But its negative predictive value may be valuable, as shown in **Table 2**.

This study has many limitations. First of all, this is a retrospective study. Secondly, we studied a small number of PCa patients. Another possible limitation is the issue of clinically asymptomatic VTE. These asymptomatic cases could appear in both groups and could not be excluded from the study. No further investigation regarding the elevated D-dimer levels was possible. If any asymptomatic VTE exists, we have assumed it to be distributed among all the patients randomly. The lack of an exact method for confirmation of metastasis presents a challenge regarding metastatic cases.

Conclusion

D-dimer levels are higher in PCa patients than in BPH patients. Patients with skeletal metastasis may have markedly elevated D-dimer levels; furthermore, in conditions of elevated D-dimer levels, the patients may have a higher probability of metastasis compared to a non-metastatic group. In addition, in PCa cases, a D-dimer value below the cut-off point may refer to a non-metastatic condition. We believe that the results of this study justify the need for further investigation of coagulation factors, including D-dimer levels in PCa.

Ethics Committee Approval: We did not obtain ethical approval as the study was retrospective. Informed consent forms were obtained from all patients before the procedure.
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: There is not any contributions who may not be listed as authors. Concept – H.S.S., H.I.C.; Design – H.S.S., H.I.C.; Supervision – H.S.S., H.I.C.; Resources – H.S.S., H.I.C.; Materials – H.S.S., H.I.C.; Data Collection and/or Processing – H.S.S., H.I.C.; Analysis and/or Interpretation – H.S.S., H.I.C.; Literature Search – H.S.S., H.I.C.; Writing Manuscript – H.S.S., H.I.C.; Critical Review – H.S.S., H.I.C.
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