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Original Article

Fibrinogen and D-dimer levels in prostate cancer: Preliminary results

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ABSTRACT

Background: Prostate cancer is one of the most common malignancy in men. The main risk factors for coagulation activation and thrombosis are malignancy and older age. The thrombosis risk may be associated with increased level of coagulation markers such as fibrinogen and D-dimer. The aim of this study is evaluate the relationship between coagulation markers and prostate cancer.

Methods: This prospective study includes the patients who underwent transrectal ultrasound guided prostate biopsy and prostate surgery was performed between January 2015 and January 2016. Plasma prostate specific antigen (PSA), free PSA (fPSA), percentage fPSA, D-dimer and fibrinogen levels were measured before the procedures. The patients were divided into two groups according to the pathology results. The patients with benign prostate hyperplasia were in group 1 and the patients with prostate cancer were in group 2.

Results: There were 76 patients in the current study. There were 53 patients in group 1 and 23 patients in group 2. The mean age of the patients, PSA, fPSA, fibrinogen and D-dimer levels was 65.33 ± 7.47 years, 8.21 ± 4.59, 1.41 ± 0.74 ng/ml, 309.75 ± 80.46 mg/dl, 0.42 ± 0.39 ug/ml in group 1. In group 2; the mean age of the patients, PSA, fPSA, fibrinogen and D-dimer levels was 66.08 ± 6.7 years, 145.69 ± 509.35, 7.32 ± 15 ng/ml, 312.16 ± 69.48 mg/dl, 1.09 ± 2.11 ug/ml. The prostate biopsy and transurethral surgery were performed in 64(%84.21) and 12(%15.79) patients.

Conclusion: The present study demonstrated that plasma D-dimer level was higher in patients with prostate cancer. Further studies that include large number of patients are needed to define the relationship between prostate cancer and coagulation disorder.

1. Introduction

Prostate cancer is the second most common cancer among men in the world[1] and has become a significant health problem in developed and developing countries.[2] The studies have shown that there was an association between cancer and hemostasis.[3] Malignancy and increased age are the main risk factors for coagulation activation and thrombosis.[4] The increased risk of thrombosis in cancer patients may be associated with high levels of coagulation markers (fibrinogen) and thrombogenesis markers (D-dimer) are likely evidence of this process.[5]

Fibrinogen is a 340-kDa glycoprotein that is mainly synthesized by hepatocytes and converted to insoluble fibrin by activated thrombin, and it is one of the important indicators of the coagulation system.[6] Plasma fibrinogen is an acute phase protein and fibrinogen level increases during malignancy and systemic inflammation. D-dimer is a degradation product of fibrin which is produced by plasmin-induced fibrinolytic activity.[7] It is a biomarker that indicates the activation of hemostasis and fibrinolysis. Elevated plasma levels may be associated with cancer, pregnancy, infectious diseases, trauma, surgery, and venous thromboembolism.

The fibrinogen level increases and is determined to be an unfavorable prognostic factor in some malignancies, such as those of the digestive system, gynecologic malignancies, urologic neoplasms, and soft tissue sarcomas.[6] High level of D-dimer is a prognostic factor associated with increased mortality risk in patients with brain tumors, lymphomas, and breast, lung, stomach, colorectal, pancreatic, and prostate cancers.[7] The aim of this study is to examine the levels of D-dimer and fibrinogen in patients with prostate cancer and compare them to those in patients with benign prostate hyperplasia.

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2. Materials and methods

A prospective study that includes patients who underwent transrectal ultrasound guided prostate biopsy and prostate surgery was performed between January 2015 and January 2016. Plasma prostate specific antigen (PSA), free PSA (fPSA), percentage fPSA, D-dimer, and fibrinogen levels were measured before the procedures (prostate biopsy and transurethral resection). Prostate biopsy was performed under local anesthesia with at twelve cores. Percentage fPSA was calculated as fPSA/PSA $^{\times}$ 100. Venous blood samples were collected into citrate tubes by sterile atraumatic venipunctures. Plasma D-dimer and fibrinogen levels were measured by Enzyme-linked immunosorbent assay (ELISA) (Diagnostic Stago, France) and Clauss method (Sysmex, Japan). Plasma fibrinogen levels were considered to be normal between 175mg/dL and 350mg/dL and D-dimer levels were considered to be normal between 0ug/mL and 0.5ug/mL.

Patients with a history of coagulopathy, venous or pulmonary embolism, using anticoagulant therapy, a history of acute or chronic prostatitis, radiotherapy, prostate surgery or biopsy previously and a pathological report of high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation, were excluded from the study. The PSA, fPSA, percentage fPSA, D-dimer, and fibrinogen levels, and patient age and pathology reports were recorded. The patients were divided into two groups; Group 1 had benign prostate hyperplasia and Group 2 consisted of patients with prostate cancer. The statistical analyses were performed using MedCalc Statistical Software demo version 16.2.0 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). The data of groups were compared with the independent sample *t* test and $P < 0.05$ was considered as statistically significant.

3. Results

There were 76 patients in the present study. Of these, 53 patients were in Group 1 and 23 patients were in Group 2. The mean age of the patients was 65.33 ± 7.47 years and 66.08 ± 6.7 years in Group 1 and Group 2, respectively. The 12 prostate biopsy cores were performed in all patients. The patients' characteristics are shown in Table 1. There was a statistically significant difference for fPSA between the groups. In Group 2, D-dimer levels were higher (1.09ug/mL and 0.50ug/mL, $P = 0.03$) than in the patients in Group 1. There were no significant differences in PSA, percentage of fPSA, fibrinogen, and age between the groups. The patients were diagnosed using transrectal ultrasound guided prostate biopsy and transurethral prostate surgery. Transrectal prostate biopsy and transurethral surgery were performed in 64 and 12 patients, respectively.

Table 1
The biochemical results of the patients.

	Group 1	Group 2	*P*
Patients *n* (%)	53 (100)	23 (100)	
Age (yr)	65.33 ± 7.47	66.08 ± 6.7	0.681
PSA (ng/mL)	8.21 ± 4.59	145.69 ± 509.35	0.051
fPSA (ng/ml)	1.41 ± 0.74	7.32 ± 15.00	0.007*
Percentage fPSA (%)	18.33 ± 7.50	18.81 ± 8.85	0.816
Fibrinogen (mg/dL)	309.75 ± 80.46	312.16 ± 69.48	0.902
D-dimer (ug/mL)	0.42 ± 0.39	1.09 ± 2.11	0.030*
Diagnosis			0.816
Transurethral resection *n* (%)	9 (16.98)	3 (13.04)	
Prostate biopsy *n* (%)	44 (83.01)	20 (86.95)	

Percentage fPSA: fPSA/PSA × 100.
* Statistically significant.
fPSA, free PSA; PSA, prostate specific antigen.

With the cancer group, 13 patients and six patients were reported as Gleason 6 and Gleason 7, respectively. Gleason 8 and Gleason 9 were detected in two patients. Of these patients, four were treated with hormonal therapy and eight were treated with radical prostatectomy. Radiotherapy was performed in six patients and the remaining five patients refused the treatment options.

4. Discussion

Prostate cancer is the one of the most common cancer among men.[8] The use of screening methods including digital rectal examination and PSA testing are important to detect prostate cancer. These screening methods may lead to prostate biopsy, which is necessary to confirm the diagnosis of prostate cancer. Transrectal ultrasound guided prostate biopsy can be performed, which is the gold standard method for histopathological diagnosis of prostate cancer.[9] Although transrectal ultrasound guided sextant prostate biopsy was described by Hodge et al, six-core biopsy is an inaccurate means of cancer detection and has a 10–30% false negative rate.[10] European Association of Urology 2015 guidelines suggest 10–12 systematic cores for initial diagnosis.[11] The authors reported the prostate cancer detection rate was 13.3–35% in patients who underwent six and 12 prostate biopsies, respectively.[8] The 12 prostate biopsy protocol was performed in all patients in the current study.

The pathogenesis of cancer-associated thrombosis depends on patient characteristics, tumor histology, stage, and treatment-related factors.[12] Abnormalities of the coagulation system have been investigated in cancer patients and it is reported that plasma levels of factors were altered.[13,14] In cancer patients, systematic activation of coagulation occurs and this activation leads to augmented thrombin generation followed by fibrin formation.[15] It has been suggested that fibrin may contribute to tumor growth and facilitate the tumor invasion and metastasis by promoting angiogenesis and formation of a protective fibrin shield on tumor cells that makes the tumor cells resistant to endogenous defense mechanisms. The interaction of fibrin, platelets, and tumor cells leads to the formation of aggregates that promote endothelial adhesion and metastatic potential.[7] Fibrin degradation products have a strong angiogenic efficacy.

Fibrinogen is one of the important coagulation system factors and systemic inflammatory markers which enhances the progression and invasive potential of tumor cells through several mechanisms.[6] Firstly, fibrinogen is deposited around solid tumors and provides a table framework to the extracellular matrix of the tumor. It also serves as a scaffold to support some growth factors to tumor cells such as vascular endothelial growth factor, and fibroblast growth factor, and promotes tumor proliferation and angiogenesis. Tumor cells have fibrinogen receptors; intercellular adhesion molecule-1 and $\alpha 5\beta 1$ integrin. These receptors play a role as a bridging factor between fibrinogen and tumor cells, thus enhancing the endothelial adhesion of tumor cell emboli in the vasculature of target organs, leading to the occurrence of metastasis. Additionally, fibrinogen promotes β3-integrin-mediated adhesion of tumor cells to platelets, and the platelet-tumor cell aggregates thus formed could shield tumor cells from the immune system and lead to increase of metastatic tumor cells.[6] The fibrinogen levels are increased because of tumor-associated cytokines or endogenous synthesis by tumor cells themselves in cancer patients.[16] The endogenous fibrinogen has a key role in promoting the growth of lung and prostate cancer cells through interaction with fibroblast growth factor.[17]

D-dimer is one of the fibrin degradation products and the level of D-dimer is a result of fibrinolysis activation.[12] Elevated plasma D-dimer levels are seen in patients with various cancer types, because procoagulant factors lead to constitutive activation of the

coagulation cascade with resultant thrombin generation followed by fibrin formation.[18] Fibrin may also conversely form a protective shield on malignant tumor cells, to protect them from endogenous defense mechanisms and promoting angiogenesis, invasion, and metastasis of the tumor. Tumor cells themselves may convert fibrinogen to fibrin and the fibrin is used for support, to appear new vessels, invasion and remodeling tumor stroma.[19]

Elevated D-dimer levels have been reported in patients with breast, prostate, gynecologic, and lung cancers without clinical thrombosis.[12] D-dimer levels were highest in patients with pancreatic cancer and lowest in patients with prostate cancer. The authors from the Vienna Cancer and Thrombosis Study reported that elevated D-dimer level was a prognostic parameter associated with increased mortality risk in patients with lymphomas, brain tumors, pancreatic, prostate, breast, lung, stomach, and colorectal cancers.[7] The authors from Korea found that D-dimer levels were significantly higher in patients with prostate cancer than the patients without prostate cancer at prostate biopsy.[19] In another study, the investigators showed a significant increase of D-dimer level in patients with advanced prostate cancer compared with age-matched controls and patients with localized prostate cancer.[4] By contrast, Caine et al[5] investigated the D-dimer levels after radical prostatectomy and found no significant difference 3 months and 12 months after surgery.[5] The present study demonstrated that the D-dimer level was higher in patients with prostate cancer than the other patients without cancer, with a significant difference ($P < 0.05$).

The authors found strong evidence that an elevated plasma fibrinogen level was an independent predictor of worse overall survival in patients with solid tumors.[20] The patients with increased level of fibrinogen have a significantly poorer disease-free survival and cancer-specific survival. Thurner et al[16] found that there was a significant association between an elevated plasma fibrinogen level and poor cancer specific survival and overall survival in patients with prostate cancer. Caine et al[5] found the significant fall in fibrinogen level after radical prostatectomy 3 months and 12 months after the surgery. By contrast, Hong et al[19] found that there was no difference between fibrinogen levels in patients with prostate cancer compared with others. That study showed higher fibrinogen levels in patients with advanced prostate cancer than patients with organ confined disease, without a significant difference. In the current study, there was no significant difference in plasma fibrinogen levels between the groups ($P = 0.886$).

This study includes a small number of patients and coagulation parameters (fibrinogen, D-dimer) were not checked again after first measuring the levels. Other hemostatic system factors were not analyzed. The stage of the patients with prostate cancer was not homogenous and the conditions that affect coagulation parameters, such as trauma and inflammatory process, could not be eliminated.

In conclusion, patients with prostate cancer had higher plasma D-dimer levels than the other patients. If studies support our findings in the future, plasma D-dimer level may be a diagnostic marker for prostate cancer. Further studies are needed to define the relationship between the coagulation system and prostate cancer.

Conflict of interest

There is no conflict of interest.

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