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The Diagnostic Importance of High Mobility Group Box-1 in Urine as a Tumor Marker in Prostate Cancer: Descriptive Research

Prostat Kanserinde İdrarda Tümör Belirteci Olarak High Mobility Group Box-1'in Tanısal Önemi: Tanımlayıcı Araştırma

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ABSTRACT Objective: The aim of the study was to demonstrate the diagnostic value of urinary high mobility group box 1 (HMGB1) level as a non-invasive tool that can be potentially used for diagnosis and during follow-up in patients with prostate cancer. **Material and Methods:** Forty-two patients with histopathologically confirmed prostate cancer from 40 to 75 years of age, 30 patients with an acute urinary tract infection (UTI) and 33 agematched healthy controls were enrolled in the study. Age, gender, body mass index (BMI) and urinary HMGB1 levels of the study groups were evaluated. The association of clinical features [prostate specific antigen (PSA), perineural invasion, Gleason score] with urinary HMGB1 levels was investigated in patients with prostate cancer. **Results:** While age and BMI were not different among the 3 groups (p=0.265 and p=0.254 respectively), PSA levels were significantly different (p<0.001). A significant difference was detected in urinary HMGB1 levels among the 3 groups (p<0.001). Additionally, a significant correlation was observed between Gleason scoring and urinary HMGB1 levels when compared among patients with low-, intermediate- and high-grade prostate cancer (p=0.003). Also, there was a significant difference in urinary HMGB1 levels between perineural invasion-positive and negative patients (p=0.04). **Conclusion:** Compared to control group, patients with a UTI and prostate cancer patients had higher HMGB1 levels. Urinary HMGB1 levels were much higher in prostate cancer patients than in controls. Urinary HMGB1 levels may be used as a non-invasive tool for diagnostic and screening purposes in prostate cancer patients in future controlled studies involving larger patient samples.

Keywords: Non-invasive screening test; prostate cancer; prostate cancer screening; urinary high mobility group box 1; tumor marker

ÖZET Amaç: Çalışmanın amacı, prostat kanserli hastalarda tanı ve takip sırasında potansiyel olarak kullanılabilecek, invaziv olmayan bir araç olarak idrar yüksek hareketli grup proteini 1 [high mobility group box 1 (HMGB1)] düzeyinin tanısal değerini göstermektir. **Gereç ve Yöntemler:** Çalışmaya yaşları 40 ile 75 arasında değişen histopatolojik olarak doğrulanmış prostat kanseri olan 42 hasta, akut idrar yolu enfeksiyonu (İYE) olan 30 hasta ve yaşları eşleştirilmiş 33 sağlıklı kontrol dâhil edildi. Çalışma gruplarının yaş, cinsiyet, beden kitle indeksi (BKİ) ve idrar HMGB1 düzeyleri değerlendirildi. Prostat kanserli hastalarda klinik özelliklerin [prostat spesifik antijen (PSA), perinöral invazyon, Gleason skoru] idrar HMGB1 düzeyleri ile ilişkisi araştırıldı. **Bulgular:** Üç grup arasında yaş ve BKİ farklı değilken (sırasıyla p=0,265 ve p=0,254), PSA düzeyleri anlamlı derecede farklıydı (p<0,001). Üç grup arasında idrar HMGB1 düzeylerinde anlamlı fark tespit edildi (p<0,001). Ayrıca düşük, orta ve yüksek dereceli prostat kanserli hastalarla karşılaştırıldığında Gleason skorlaması ile idrar HMGB1 düzeyleri arasında anlamlı bir korelasyon gözlendi (p=0,003). Ayrıca perinöral invazyon pozitif ve negatif hastalar arasında idrar HMGB1 düzeyleri açısından anlamlı fark vardı (p=0,04). **Sonuç:** Kontrol grubuyla karşılaştırıldığında, İYE hastalarında ve prostat kanseri hastalarında HMGB1 düzeyleri daha yüksekti. İdrar HMGB1 seviyeleri prostat kanseri hastalarında kontrollere göre çok daha yüksekti. İdrar HMGB1 düzeyleri, daha büyük hasta örneklerini içeren gelecekteki kontrollü çalışmalarda prostat kanseri hastalarında tanı ve tarama amacıyla invaziv olmayan bir araç olarak kullanılabilir.

Anahtar Kelimeler: Noninvaziv tarama testi; prostat kanseri; prostat kanseri tarama; idrar yüksek hareketli grup proteini 1; tümör belirteci

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The most common cancer in men is prostate cancer. It is 6th in cancer related deaths.[1] Prostate cancers generally tend to grow slowly and are low grade.[2] Early stage prostate cancer (i.e. Stages T1 and T2) is confined to the prostate gland. In Stage T3 (locally advanced prostate cancer), the cancer has extended through the capsule of the prostate gland. Stage T4 prostate cancer is cancer that has spread to other parts of the body.[3]

Prostate specific antigen (PSA) test and transrectal ultrasound-guided prostate tissue biopsies are the priority in the diagnosis of prostate cancer. However, PSA testing for screening is still controversial.[4] It has been recognized that PSA is a marker with a high organ specificity but low cancer specificity. Different pathological conditions in the prostate (such as benign prostatic hyperplasia or infection of prostate) can raise the serum PSA levels.[5] Serum PSA screening was shown to reduce disease-specific mortality. However, the mortality benefit of PSA led to a large number of prostate biopsies up to 70-80%.[3] This resulted in overdiagnosis and subsequent overtreatment due to detection of clinically insignificant disease, increasing the risk of unnecessary morbidity. Although serum PSA measurement does not exactly fit the description of a perfect marker, it is still most commonly used screening method for the diagnosis prostate cancer. Nevertheless, various biomarkers which are more effective than PSA have been introduced with the attempt to overcome problems associated with low cancer specificity of PSA. Thus, research efforts have focused on developing an ideal biomarker in recent years.[6]

High mobility group box 1 (HMGB)-1 and 2 proteins are nuclear nonhistone proteins found in mammals and eukaryotic cells.[7] HMGB1 is a 215 amino acid protein weighing 30 kDa. It contains two positively charged and one negatively charged fields. This provides HMGB1 with an important feature for recognizing and specifically binding DNA structures.[8]

HMGB-1 is involved in cell differentiation, DNA repair, transcription, somatic recombination and extracellular signaling.[9] Apart from its nuclear functions, it acts as an extracellular signaling molecule.[10] Studies have shown overexpression of HMGB1 gene in cancerous cells originating from the epithelial tissue of the prostate and ovarian cancer.[11,12]

Purpose of this study is to test the availability of HMGB1 in urine as a simple, fast and reliable test for diagnostic and follow-up in patients with prostate cancer.

MATERIAL AND METHODS

STUDY DESIGN

The study included 42 prostate cancer patients between the ages of 40-75, 30 urinary tract infections (UTI) patients, and 33 healthy volunteers. Age, body mass index (BMI), gender and urinary HMGB1 levels (U-HMGB1) were recorded. The relationship of U-HMGB1 with clinical features (PSA, perineural invasion, Gleason score) was investigated in patients with prostate cancer.

TEST METHODS

Ten cc urine samples were collected from study patients and healthy controls. The samples were centrifuged after the supernatants were transferred into microtubes and stored at -80 ºC until the time of ELISA testing. Prostate cancer patients were subdivided into three groups as low grade (Gleason score ≤6), intermediate grade (Gleason score of 7 (3+4 or 4+3) or high grade (Gleason ≥8).[13]

U-HMGB1 were quantitatively measured using Cloud-Clone ELISA kits (Catalog Number SEA399 Hu, USA). The double-antibody sandwich enzyme immunoassay technique was used for the assay. The test has a detection range of 60.5 to 4,000 pg/mL and a sensitivity of 28.3 pg/mL. The coefficients of variation within and between assays were 8.3% and 9.1% respectively.

That the study had been reviewed and approved by a certified Clinical Research Ethical Committee of SANKO University, the number 3 and date of September 19, 2019. Signed consent was obtained from all participants before the study started. The study was conducted in accordance with the principles set forth in the Declaration of Helsinki.

TABLE 1: Demographic and clinical data of the study groups.

	Prostate cancer (n=42)	Urinary tract infection (n=30)	Controls (n=33)	p value
Age (years)	65.7±10.7	61.8±10.7	64.2±7.2	0.265*
BMI (kg/m^2)	29.7±3.6	31.03±4.4	29.15±5.6	0.254*
PSA (ng/mL)	22 (5.9-240)	1.5 (0.6-8.5)	1.2 (0.7-2.5)	p<0.001**
HMGB1 (pg/mL)	142.3 (9.1-3170.1)	40.3 (10.3-201.1)	29.3 (9.1-145.8)	p<0.001**

*One-Way analysis of variance; **Kruskal-Wallis test; BMI: Body mass index; PSA: Prostate specific antigen; HMGB1: High mobility group box 1.

ANALYSES

The Graph Pad Instat (v.3.05, Graph Pad Software Inc., San Diego, CA) statistical software was used to analyze the data from all samples. The Student's unpaired t-test, Kruskal-Wallis test, one-way analysis of variance, chi-square test, Mann-Whitney U test and correlation analysis were used to compare patient group data with control group data. A p-value less than 0.05 was considered statistically significant. Cut-off values were determined using the Youden index 1 levels.

RESULTS

A total of 105 people participated in the study, including 42 prostate cancer patients, 30 UTI patients and 33 healthy controls. BMI, age, PSA and U-HMGB1 of the three groups are shown in Table 1. All three groups showed a normal distribution of age and BMI with no statistically significant inter-group difference (p=0.265 and p=0.254 respectively). PSA levels and U-HMGB1 differed significantly among 3 groups (both p<0.001). Bilateral comparisons were made between the groups. Accordingly; p=0.001 for prostate cancer group versus UTI group; p=0.017 for UTI group versus controls and p<0.001 for prostate cancer group versus controls. Thus, the latter difference was highly significant. Correlations of U-HMGB1 with the demographics, and tumor and PSA characteristics of prostate cancer patients are presented in Table 2.

While U-HMGB1 were not correlated with BMI and age, a positive correlation was observed between U-HMGB1 and serum PSA concentrations in 42 prostate cancer patients (r=0.84, p<0.001). In addition, U-HMGB1 were compared among patients with low, intermediate or high-grade prostate cancer, revealing a significant association between Gleason scores and U-HMGB1 (p=0.003). Bilateral comparisons were made to see which group caused the difference and showed no difference between low grade and intermediate grade (p=0.376). However, differences were observed between low and high grade (p=0.002) and between intermediate and high grade (p=0.004). Additionally, a significant difference was observed between perineural invasion-positive and -negative patients (p=0.04). Cut-off values were calculated by performing receiver operating characteristic analysis. The cut-off value between prostate cancer and UTI was 100.45 pg/mL, 32.97 pg/mL for the control group and UTI, and 113.75 pg/mL between the control group and the prostate cancer (Figure 1, Figure 2, Figure 3).

TABLE 2: Correlation between HMGB1 values and clinical data in prostate cancer patients.

	HMGB1	
Prostate cancer (n=42)	r value	p value
Age	-0.03	0.847
BMI	-0.21	0.181
PSA	0.84	p<0.001
Gleason score		
Low grade (n=14)	49.05 (9.1-2132.1)	0.003*
Intermediate grade (n=14)	131.3 (22.8-501.1)	
High grade (n=14)	187.6 (45.1-3170.1)	
Perineural invasion		
No (n=21)	110.5 (9.1-2132.1)	0.004**
Yes (n=21)	156.7 (25.6-3170.1)	

r: Coefficient of correlation; *Kruskal-Wallis test; **Mann-Whitney U test; Low grade: Gleason score ≤6, intermediate grade: Gleason score 3+4 or 4+3, High grade: ≥8; HMGB1: High mobility group box 1; BMI: Body mass index; PSA: Prostate specific antigen.

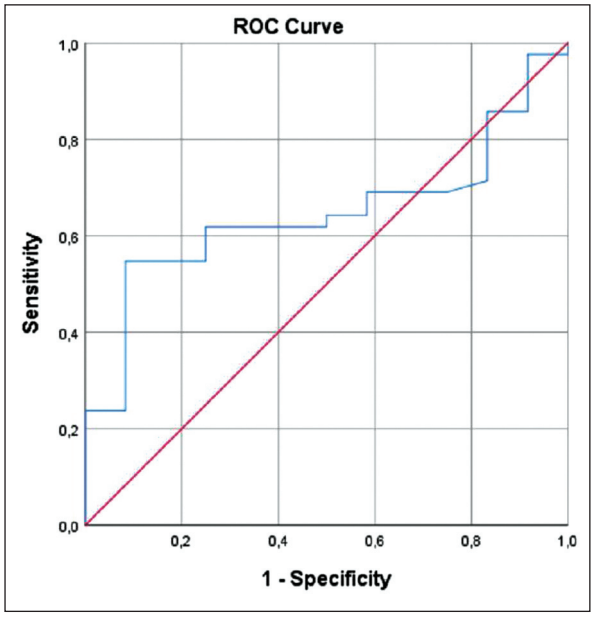

FIGURE 1: ROC curve analysis between renal cell carcinoma and urinary tract infection. The area under the curve was 0.818 (95% CI 0.710-0.926) for HMGB1 (p<0.001).
ROC: Receiver operating characteristic; CI: Confidence interval; HMGB1: High mobility group box 1.

DISCUSSION

In the current study, U-HMGB1 were found higher in prostate cancer patients in comparison to patients with an UTI and controls, in direct proportion to the tumor grade. This suggests increased expression of HMGB1 in tumor cells.

Prostate cancer follows a rather unusual course when compared with other types of cancer since it progresses slowly. Low-grade prostate cancer is mostly latent and approximately 25% of the cases show aggressive progression.[12]

HMGB1 is a nuclear non-histone protein which is involved not only in inflammation but also cancer; extracellularly, it binds to the receptor for advanced glycation end products receptor and plays an important role in cancer progression and metastasis by activating key signaling pathways including nuclear factor kappa B, p38 and p44/42 mitogen-activated protein kinase.[14] In a 2019 study, Lv et al. found that upregulation of HMGB1 plays a central role in the development and metastasis of prostate cancer.[15]

Studies in human and mouse models have shown overexpression of extracellular HMGB1 in metastatic prostate cancer, and it has been found to have a positive correlation with tumor aggressiveness.[16] Addi-

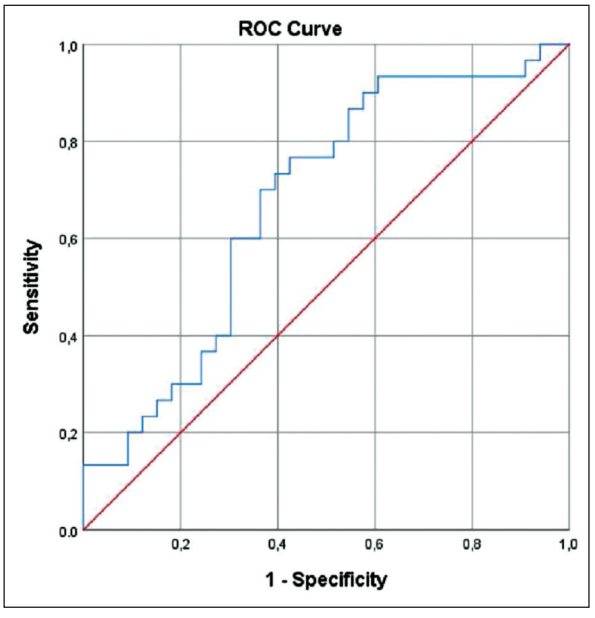

FIGURE 2: ROC curve analysis between urinary tract infection and controls. The area under the curve was 0.704 (95% CI 0.571-0.837) for HMGB1 (p=0.005).
ROC: Receiver operating characteristic; CI: Confidence interval; HMGB1: High mobility group box 1.

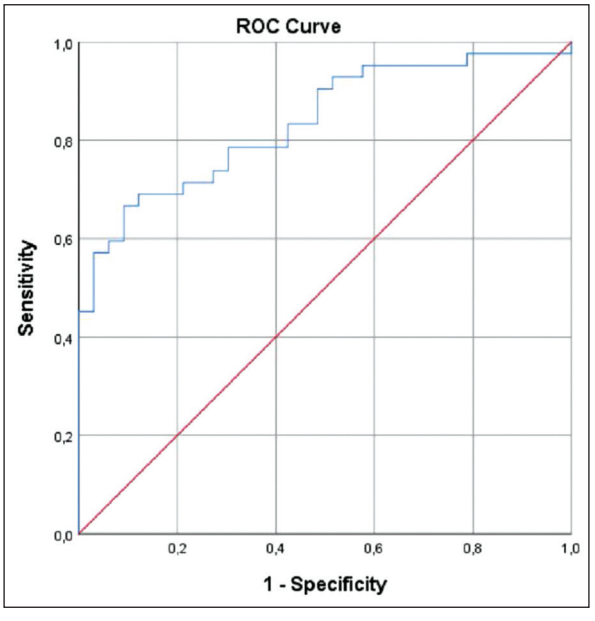

FIGURE 3: ROC curve analysis between renal cell carcinoma and controls. The area under the curve was 0.897 (95% CI 0.819-0.974) for HMGB1 (p<0.001).
ROC: Receiver operating characteristic; CI: Confidence interval; HMGB1: High mobility group box 1.

tionally, the HMGB1 mRNA level has been shown to be much higher in Mat Lylu tumors, an aggressive rat prostate tumor, than in Dunning R-3327-H tumor, a benign rat prostate cancer.[16,17] It has been suggested that specific mechanisms are responsible for the pathogenic effects of HMGB1 on prostate cancer and metastasis. A recent study reported that increased expression of HMGB1 was associated with the presence of aggressive prostate cancer and poor prognosis and can be used as a biomarker to discriminate high risk patients from low risk patients.[18] HMGB1 has been shown to activate androgen receptor and sex steroid hormone receptors.[19] Additionally, HMGB1 has been shown to directly interact with the Ets transcription factor, increasing the activity of Ets target gene transcription. The Ets transcription factors were found to contribute to angiogenesis and metastasis of prostate cancer.[20] It was also reported that chronic inflammation is one of the key risk factors in prostate tumor and HMGB1 promotes malignant progression by activating proinflammatory cytokines.[21]

The use of urinary markers in the screening, diagnosis and follow-up of treatment response in prostate cancer draws attention because theoretically sampling is easy. However, the prostate cancer antigen 3 (PCA3) gene test has been predominantly assessed in several studies.[22] Urinary markers are classified in three groups including protein-based, DNA-based and RNA-based markers.[23] Conflicting results have been reported for urinary protein-based biomarkers (Annexin A3, matrix metalloproteinases and the urinary/serum PSA ratio). As a matter of fact, more than 1,500 types of proteins were identified through detailed examination of human urine and accordingly, the use of these proteins as biomarkers would be very difficult.[24] Urinary DNA-based markers have primarily focused on methylation and hypermethylation of GSTP1.[25] The most widely studied group includes urinary RNA-based markers. Mainly, the PCA3 test, ERG fusion gene, SPINK1, TMPRSS2-transcript expression levels of GOLPH2 and their combinations have been investigated in prior studies.[23] PCA3 gene, initially referred to as DD3, is a gene that expresses a non-coding RNA on chromosome 9. The expression of non-coding mRNAs by the PCA-3 gene is 60- to 100-fold greater in malignant tissues.[26] Although not approved by the U.S. Food and Drug Administration yet, the PCA3 test [Progensa™ PCA3 (Gen-Probe, San Diego, CA)] has become commercially available. Non-coding mRNAs of the PCA3 gene as identified by the Reverse transcription polymerase chain reaction method in the first voided urine following a digital rectal examination can be demonstrated in up to 90% of prostate cancer patients.[21] Extensive studies have shown that PCA-3 test has a sensitivity of 66% and a specificity of 89% in patients undergoing prostate biopsy.[27] PCA-3 test results are not affected by prostate volume or the presence of prostatitis. Currently, PCA3 test is primarily used for follow-up of patients with elevated PSA, decision making for repeat biopsy and monitoring of prostate cancer patients under active surveillance. However, although the PCA-3 test may yield positive results even in small tumor volumes, it does not inform about aggressiveness of the tumor.

A total of 105 subjects participated in the study including 42 prostate cancer patients, 30 patients with a UTI and 33 healthy controls. The study subjects did not differ significantly with respect to age or BMI ($p=0.265$). A significant difference was observed between the three group in serum PSA levels ($p<0.001$). The median serum PSA concentration was 22 ng/mL in prostate cancer patients, 1.5 ng/mL in patients with a UTI and 1.2 ng/mL in healthy controls. As expected, serum PSA concentrations were considerably higher in prostate cancer patients and relatively lower in patients with a UTI. As predicted, serum PSA concentrations were well below the reference values for prostate cancer diagnosis in healthy controls. Despite the abundance of data in literature regarding the critical PSA level for the diagnosis of prostate cancer, the current guidelines suggest a PSA level between 2.5 and 4.0 ng/mL.[28]

In the present study, U-HMGB1 were significantly different among 3 groups ($p<0.001$). Moreover, prostate cancer patients showed much higher U-HMGB1 in comparison to controls [$p<0.001$ (Bonferroni correction $p<0.017$)]. We found that the cut-off values for U-HMGB1 level were 100.45 pg/mL to differentiate prostate cancer patients from patients with UTI, 32.97 pg/mL to differentiate UTI patients from controls and 113.75 pg/mL to differentiate

prostate cancer patients from controls. We also observed a significant difference in terms of U-HMGB1 among low-, intermediate- and high-grade prostate cancer patients and found that the significance resulted from the difference between U-HMGB1 of low-grade and high-grade patients (p=0.002; Bonferroni correction p<0.017). Additionally, U-HMGB1 were much higher in perineural invasion-positive prostate cancer patients than in perineural invasion-negative prostate cancer patients (p=0.04). Our findings are consistent with those reported by previous studies and the originality of our study was to perform non-invasive assessment of HMGB1 protein in the urine.

There are some limitations in our study. First of all, the number of patients participating in the study was small. Secondly, in our study, U-HMGB1 was not examined in any other cancer group other than prostate cancer.

CONCLUSION

In conclusion, elevated serum levels of HMGB1 were shown in former studies in patients with cancer and inflammation. The originality of our study lies in the fact that we used a non-invasive method to quantitate HMGB1 protein in the urine. In our study, U-HMGB1 concentrations were found higher in patients with a UTI and prostate cancer patients than control group. Specifically, patients with prostate cancer showed significantly higher HMGB1 levels versus controls. This result, in accordance with the literature; shows that HMGB1 is more expressed in tumor cells.[14]

The use of U-HMGB1 for diagnostic and screening purposes in prostate cancer patients may be further investigated in future controlled studies involving larger patient samples.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mustafa Solakhan, Necla Benlier;* ***Design:*** *Mustafa Yıldırım, Hülya Çiçek;* ***Control/Supervision:*** *Mustafa Yıldırım, Hülya Çiçek;* ***Data Collection and/or Processing:*** *Ömer Aydın Yıldırım, Necla Benlier, Mustafa Solakhan;* ***Analysis and/or Interpretation:*** *Necla Benlier, Mustafa Yıldırım, Hülya Çiçek;* ***Literature Review:*** *Mustafa Solakhan, Osman Barut;* ***Writing the Article:*** *Mustafa Solakhan, Necla Benlier;* ***Critical Review:*** *Mustafa Yıldırım, Hülya Çiçek;* ***References and Fundings:*** *Mustafa Solakhan, Osman Barut;* ***Materials:*** *Mustafa Solakhan.*

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