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Prostate-specific antigen density in prostate cancer screening in diabetes mellitus patients

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ABSTRACT

Objectives: The purpose of this study was to examine the function of prostate-specific antigen (PSA) and prostate-specific antigen density (PSAd) in the screening of prostate cancer in individuals with Diabetes Mellitus (DM).

Methods: This study was retrospective and cross-sectional. 467 patients who underwent transrectal ultrasound-guided 10-12 core prostate biopsy between 01 January and 31 December 2022 were included. Through the hospital information management system, the demographics, radiological, biochemical, and pathological results of the patients were scanned.

Results: PSAd>0.15 ng/mL/cm³ and total PSA (t-PSA)>8.58 ng/mL were substantially associated with an elevated probability of the existence of cancer when all patients were included. PSAd>0.19 ng/mL/cm³ and t-PSA>11.34 ng/mL were shown to be strongly associated with an elevated risk of cancer in patients with DM (P<0.001). PSAd>0.14 ng/mL/cm³ and t-PSA>8.49 ng/mL were substantially associated with an elevated probability of cancer presence in individuals without a diagnosis of DM. PSAd>0.15 ng/mL/cm³ and t-PSA>8.58 ng/mL were substantially associated with an elevated probability of cancer presence in individuals with fasting blood glucose (FBG) <126 mg/dL (P<0.001). It has been established that PSAd cannot be utilized as a marker to predict cancer in people with FBG≥126 mg/dL (P=0.070). Higher cancer risk was substantially correlated with t-PSA values of >5.73 ng/mL (P=0.001).

Conclusions: The change in prostate volume brought on by high blood glucose levels might be the cause of PSAd's lack of selectivity. Patients with DM are a special group in prostate cancer screening, and this should be considered when establishing cancer screening algorithms.

Keywords: Prostate-specific antigen (PSA), PSA density, prostate cancer, diabetes mellitus, risk estimation

It is known that many cancer types are more common in patients with Diabetes Mellitus (DM) [1-3]. However, no consensus has been reached on this issue in prostate cancer [4-7]. Studies suggesting that DM is protective against prostate cancer are at least as many as those offering the opposite. Furthermore, numerous studies have demonstrated that DM patients had more aggressive prostate cancer [8]. According to a recent study, people with blood glucose levels ≥126 mg/dL cause prostate-specific antigen

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(PSA) to lose its selectivity. As a result, patients may not receive an early cancer diagnosis and present at more advanced stages of the disease [9].

DM is an endocrinological disease characterized by high blood glucose due to decreased insulin secretion or insulin resistance. Its prevalence has been increasing rapidly in recent years [10]. It is a significant cause of mortality and morbidity due to obesity, coronary artery disease, and cancer. Because both diseases are becoming more prevalent as people age, the increased frequency of this condition raises the risk of prostate cancer in DM patients.

PSA is the key test used in prostate cancer screening [11]. For many years, the preferred approach for screening for prostate cancer has been PSA density (PSAd), which is computed by taking the prostate volume into account [12]. Detection of PSAd >0.15 ng/mL/cm³ is essential for many clinicians. When a digital rectal examination reveals a suspicion of cancer and/or the PSA or PSAd is higher than the threshold value, a prostate biopsy is carried out under the supervision of transrectal ultrasonography (USG) [13]. In patients diagnosed with cancer due to biopsy, treatment is planned after determining the risk group according to the D'amico risk classification [14].

According to the guidelines of the Urological Association, using PSA and PSAd values together with a physical examination for prostate cancer screening is recommended. The validity of these screening tests in DM patients is questioned, though. Studying the relationship between PSA, PSAd, and DM could provide a deeper understanding of how diabetes influences prostate health, whether through direct effects on the prostate or indirectly through factors like insulin resistance, inflammation, or other metabolic changes. By exploring this relationship, clinicians could refine diagnostic tools or adjust for the influence of DM when interpreting PSA or PSAd, leading to more accurate prostate cancer screenings and better patient management. In this study, we are interested in understanding how DM might impact PSA and PSAd, which are key metrics for prostate cancer detection, to improve diagnosis and treatment strategies.

METHODS

The study was approved by the, A cross-sectional, retrospective approach was used for the study. Following approval by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2011-KAEK-25 2022/05-13 and date: 18.05.2022), 467 patients who underwent transrectal USG (trUSG)-guided 10-12 core prostate biopsy between January 1 and December 31, 2022, were included. The patients gave their informed written permission. The patient's demographic characteristics and radiological, biochemical, and pathological results were obtained by scanning through the hospital's information management system. Patients with a diagnosis of DM were enrolled based on the statement in the medical history questioned before the biopsy.

Total PSA (t-PSA), total testosterone, fasting blood glucose, and hemoglobin A1c (HbA1c) values were analyzed among the biochemical test results. The American Diabetes Association (ADA) recommended 126 mg/dL as the cut-off threshold for hyperglycemia [9]. By dividing the t-PSA value by the prostate volume, PSAd was computed.

The D'Amico risk classification, which divides patients based on pretreatment PSA, clinical stage, and biopsy Gleason score (GS), was used to establish prostate cancer risk groups [14]. As a result, three risk categories were created for the patients: low risk (PSA <10 ng/ml and cT1-cT2a or GS), intermediate risk (PSA: 10–20 ng/ml or cT2b or GS7), and high risk (PSA >20 ng/ml or ≥cT2c or GS≥8).

Statistical Analysis

A priori power analysis was used to establish the necessary sample size for the study. Satir and Demirci's study [9] was used as a reference for determining the sample size. When the fasting blood glucose level was less than 126, the study's results demonstrated an area under the curve (AUC) of 0.59 for the existence of cancer. Based on this AUC value, n=467 was the minimum sample size needed for the study with a type I error of 5% and a power of 90%. To determine if the variables had a normal distribution, the Shapiro-Wilk test was employed. Numbers and percentages were used to represent categorical data, while the median (minimum-maximum) was used to represent continuous variables. The groups were compared using the Mann-Whitney U and Kruskal Wallis tests based on the findings of the normalcy test. After overall significance, the Bonferroni-Dunn test was ap-

plied for subgroup analysis. The chi-square test was applied for group comparisons including categorical data. To determine the total PSA's sensitivity and specificity in identifying the presence of cancer, receiver operator characteristics (ROC) analysis was used. The SPSS Software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) was used in analyzing the data. P-values <0.05 were regarded as statistically significant.

RESULTS

The overall features of the patient cohort are presented in Table 1. The mean HbA1c was calculated as 5.69. There were 81 patients with a fasting blood glucose (FBG) value ≥126 mg/dL. There were 159 people whose pathology revealed they had cancer.

Table 2 presents biochemical variable comparisons between prostate cancer risk groups and cancer presence. HbA1c readings showed no change between the risk groups (P=0.579). The FBG measurements showed no change between the groups (P=0.614). There was no difference in the proportion of patients with FBG levels <126 mg/dL and ≥126 mg/dL across the groups (P=0.722). In contrast, total PSA measurement differed between risk groups (P<0.001). The low-risk group's median t-PSA level was 5.92 ng/mL, the intermediate-risk groups was 11.17 ng/mL, and the high-risk groups was 30.67 ng/mL. Subgroup analyses revealed that the high-risk group had a higher t-PSA level than the low-risk and intermediate-risk groups (P<0.001 and P<0.001, respectively), and the intermediate-risk group had a higher median t-PSA level than the low-risk group (P<0.001). Testosterone levels did not differ across the groups (P=0.110). The PSAd indicated a difference (P<0.001) between the groups. The low-risk group's median PSAd level was 0.08 ng/mL/cm³, the intermediate-risk group's median PSAd level was 0.18 ng/mL/cm³, and in the high-risk groups was 0.45 ng/mL/cm³. PSAd in the high-risk group was found to be greater than in the low-risk and intermediate-risk groups (P<0.001 and P<0.001, respectively), while PSAd in the intermediate-risk group was found to be greater than in the low-risk group (P<0.001) within the subgroup analyses.

HbA1C and FBG levels did not differ between the groups of benign and malignant patients when analyzed based on cancer status (P=0.766 and P=0.477, respectively). There was no significant difference (P=0.465) in the pattern of distribution of patients with FBG levels <126 and ≥126 mg/dL based on their cancer status. The t-PSA measurement varied (P<0.001) throughout the cancer groups.

For benign patients, the median t-PSA level was 6.56 ng/mL, but for malignant patients, it was 11.17 ng/mL. The groups' testosterone levels did not differ from one another (P=0.168). The median PSAd level was 0.09 ng/mL/cm³ in benign patients and 0.19 ng/mL/cm³ in malignant patients. According to PSAd, there was a statistically significant (P<0.001) difference between the groups.

ROC curve characteristics for total, diabetic, and non-diabetic patients were shown in Table 3. When PSAd is >0.15 ng/mL/cm³ and t-PCA is >8.58 ng/mL, ROC curve analysis was also used to determine the specificity and sensitivity of PSAd and t-PCA for predicting the existence of cancer. The PSAd area under the curve was found to be 0.750 (sensitivity: 60.38%, specificity: 82.14%, P<0.001) and 0.756 (sensitivity:

Table 1. General characteristics of the participants

Age (years) (n=467)	66 (47-88)
Total PSA (ng/mL) (n=467)	7.40 (0.66-576)
HbA1c (Hb%) (n=407)	5.69 (4.19-10.98)
Fasting Blood Glucose (mg/dL) (n=454)	99 (65-448)
<126	373/454 (82.20%)
≥126	81/454 (17.80%)
Diabetes Mellitus (n=467)	100/467 (21.40%)
Hypertension (n=206)	64/206 (24.50%)
Testosterone (ng/dL) (n=264)	462.81 (10.14-1009.40)
Cancer (n=467)	
Benign	308/467 (66%)
Malign	159/467 (34%)
Prostate volume (mL) (n=467)	70 (22-282)
PSA density (ng/mL/cm³) (n=467)	0.11 (0.01-5.65)

Data are shown as median (interquartile range) and n (%).

Table 2. **Comparisons of the biochemical variables between prostate cancer risk groups and cancer presence**

Prostate cancer risk groups							Cancer Status			
	n	Low	n	Intermediate	n	High	n	Benign	n	Malign
HbA1c (Hb%)	41	5.69 (4.89-8.58)	40	5.69 (4.59-8.38)	55	5.70 (4.59-10.48)	271	5.69 (4.59-10.48)	136	5.69 (4.59-10.48)
P value				0.579[a]				0.766[b]		
FBG (mg/dL)	46	101 (70-255)	44	100 (65-325)	66	97 (66-250)	298	98 (65-448)	156	99 (65-325)
P value				0.614[a]				0.477[b]		
FBG (mg/dL)										
<126		37 (80.40%)		38 (86.40%)		56 (84.80%)		242 (81.20%)		131 (84%)
	46		44		66		298		156	
≥126		9 (19.60%)		6 (13.60%)		10 (15.20%)		56 (18.80%)		25 (16%)
P value				0.722[c]				0.465[c]		
Total PSA (ng/mL)	47	5.92 (1.34-9.74)	45	11.17 (5.38-19.90)	67	30.67 (5.28-576)	308	6.56 (0.66-69.33)	159	11.17 (1.34-576)
P value				**<0.001[a]**				**<0.001[b]**		
Testosterone (ng/dL)	25	478.12 (10.30-788.48)	28	506.13 (10.14-956.23)	37	412 (11.20-898.97)	174	462.81 (139.66-1009.40)	90	455.10 (10.14-956.23)
P value				0.110[a]				0.168[b]		
PSA density (ng/mL/cm^3)	47	0.08 (0.01-0.30)	45	0.18 (0.06-0.43)	67	0.45 (0.06-5.65)	308	0.09 (0.02-1.65)	159	0.19 (0.01-5.65)
P value				**<0.001[a]**				**<0.001[b]**		

Data are shown as median (interquartile range) and n (%). HbA1c=glycated haemoglobin, PSA=prostate-specific antigen, FBG=fasting blood glucose

[a]Kruskal Wallis Test, [b]Mann Whitney U Test, [c]Chi-Square Test

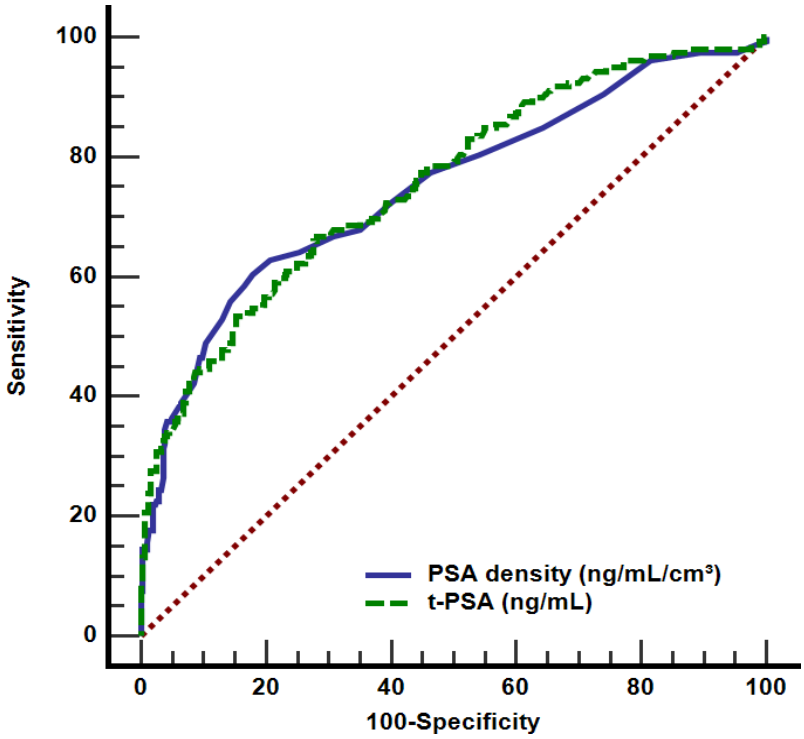

Fig. 1. (for all patients). Receiver-operator characteristic (ROC) curves for determining the presence of cancer when PSAd is > 0.15 ng/mL/cm³ and total PSA (t-PSA) is > 8.58 ng/mL.

66.04%, specificity: 72.40%, P<0.001), respectively (Fig. 1). These values indicate a substantial correlation between an elevated PSAd of >0.15 ng/mL/cm³ and a t-PCA of >8.58 ng/mL with the existence of cancer. Nonetheless, there was no statistically significant distinction in the cancer prediction abilities of PSAd and t-PCA (P=0.690).

In diabetic patients, when PSAd is >0.19 ng/mL/cm³ and t-PCA is >11.34 ng/mL, ROC curve analysis was also carried out to determine both the specificity and sensitivity of PSAd and t-PCA for predicting the existence of cancer. The PSAd area under the curve was found to be 0.760 (sensitivity: 60.53%, specificity: 93.55%, P<0.001) and 0.806 (sensitivity:

Table 3. ROC curve characteristics for total, diabetic, and non-diabetic patients

	Total (n=467)		Diabetic (n=100)		Non-Diabetic (n=367)	
	PSA density	Total PSA	PSA density	Total PSA	PSA density	Total PSA
Sensitivity	60.38%	66.04%	60.53%	57.89%	62.81%	66.94%
Specificity	82.14%	72.40%	93.55%	93.55%	77.64%	70.73%
Cut-off Value	>0.15	>8.58	>0.19	>11.34	>0.14	>8.49
Jouden J Index	0.43	0.38	0.54	0.51	0.40	0.38
Standard Error of AUC	0.03	0.02	0.05	0.05	0.03	0.03
AUC	0.750	0.756	0.760	0.806	0.745	0.742
Comparison of AUCs	P=0.690		P=0.225		P=0.892	

AUC: Area Under Curve

57.89%, specificity: 93.85%, P<0.001), respectively. These values indicate a substantial correlation between an elevated PSAd of >0.19 ng/mL/cm³ and a t-PCA of >11.34 ng/mL with the existence of cancer. The ability of t-PSA and PSA density to predict cancer, however, did not vary from one another (P=0.225) (Table 3).

ROC curve for fasting plasma glucose is shown in Table 4. For those with an FBG <126 when PSAd is >0.15 ng/mL/cm³ and t-PCA is >8.58 ng/mL, ROC curve analysis was also carried out to determine both the specificity and sensitivity of PSAd and t-PCA for predicting the existence of cancer. The area under the curve values for PSAd and t-PSA were 0.774 (sensitivity 64.12%, specificity 82.14%, P<0.001) and 0.762 (sensitivity 68.70%, specificity 72.31%, P<0.001), respectively. Accordingly, PSAd values >0.15 ng/mL/cm³ and t-PCA values >8.58 ng/mL indicate a substantial correlation between an elevated risk of cancer existence.

For those with FBG ≥126 mg/dL both the specificity and sensitivity of PSAd for cancer, prediction was also estimated using ROC curve analysis. After conducting the study, it was concluded that PSAd was not a reliable indicator of cancer risk in patients with FBG ≥ 126 mg/dL. The PSAd area under the curve was 0.634 (sensitivity 52%, specificity 83.93%, P=0.070) when PSAd was more than 0.15 ng/mL/cm³. However, a significant correlation was found between t-PCA levels of more than 5.73 ng/mL and a greater probability of cancer (AUC=0.713, sensitivity 80%, specificity 51.79%, P=0.001).

DISCUSSION

When comparing groups of patients with benign conditions to those with malignant prostate cancer, no significant differences were observed in HbA1c or FBG levels. PSA density and t-PSA show significant differences between prostate cancer presence and risk groups. PSAd>0.15 ng/mL/cm³ and t-PSA>8.58 ng/mL were substantially associated with an elevated probability of cancer presence in individuals with FBG <126 mg/dL. We determined that PSAd cannot be utilized as a marker to predict cancer in people with FBG≥126 mg/dL. Higher cancer risk was substantially correlated with t-PSA values of >5.73 ng/mL.

Several studies have reported an inverse association between DM and the risk of developing prostate cancer [15, 16]. Men with diabetes tend to have a lower incidence of prostate cancer compared to non-diabetic men. This may be due to lower testosterone levels in diabetic men, as testosterone is a known driver of prostate cancer growth. While diabetes may reduce the overall risk of prostate cancer, elevated blood sugar levels (hyperglycemia) have been associated with more aggressive prostate cancer phenotypes [17]. Hyperglycemia may promote tumor progression through mechanisms such as insulin resistance, chronic inflammation, and oxidative stress. Insulin resistance and elevated levels of insulin-like growth factor 1 (IGF-1) are common in individuals with diabetes or metabolic syndrome. These factors may promote prostate cancer progression by stimulating cell prolif-

Table 4. ROC curve characteristics for fasting plasma glucose

	Fasting blood glucose <126 (n=373)		Fasting blood glucose ≥126 (n=81)	
	PSA density	Total PSA	PSA density	Total PSA
Sensitivity	64.12%	68.70%	%52	80%
Specificity	82.64%	72.31%	83.93%	51.79%
Cut-off value	>0.15	>8.58	>0.15	>5.73
Jouden J index	0.47	0.41	0.36	0.32
Standard error of AUC	0.03	0.03	0.07	0.06
AUC	0.774	0.762	0.634	0.713
Comparison of AUCs	0.450			-

PSA=Prostate-Specific Antigen, AUC=Area Under Curve

eration and inhibiting apoptosis [18]. Screening and monitoring of blood sugar levels in men with prostate cancer may be important, especially in those with aggressive disease. Lifestyle interventions, such as weight loss and glycemic control, could potentially reduce the risk of prostate cancer progression.
Multiparametric MRI (mpMRI) has become a cornerstone in the diagnosis and management of prostate cancer. It combines T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging to improve the detection of clinically significant prostate cancer [19]. The advantages of mpMRI are Improved detection of clinically significant prostate cancer, reduced detection of low-grade, indolent tumors, and better localization of tumors for targeted biopsies.

PSAd can find its place in prostate cancer screening models as an easy-to-apply method. Although PSAd has lost popularity in the last 20 years, it is considered an important parameter in study risk prediction. According to Yusim *et al*. [20], individuals with PSAd values between 0.09 and 0.19 and prostate volumes less than 33 milliliters had a higher predictive value for clinically relevant prostate cancer. Omri *et al*. [21] discovered similarly that the International Society of Urological Pathology (ISUP) PCa class group and PSAd level were directly correlated. As a result, they concluded that PSAd is a practical, affordable, and easy-to-use tool for individuals who have small and medium-sized prostates while making treatment decisions. Both studies emphasized that PSAd is more valuable when the prostate volume is low. According to our research, individuals with blood glucose levels of 126 and higher had a loss of PSAd's selectivity for prostate cancer. This study's result is consistent with previous research, given that people who had elevated blood sugar levels had increased prostate volume. PSAd may play a critical role in improving the specificity of prostate cancer detection, especially in patients with high blood sugar or diabetes. Adjusting PSA levels for prostate size, it helps to reduce the confounding effects of benign conditions and gives a clearer indication of whether prostate cancer may be present, making it a more reliable diagnostic tool in such cases.

The American Urological Association and the European Association of Urology both recognize biopsy as a screening technique in situations where the t-PSA test result is more than 3-4 ng/mL [22]. For screening, life expectancy should be at least 10-15 years, general health status should be good, and the person should be informed about prostate cancer screening [23]. Men who belong to an ethnic minority and have a family history of prostate cancer are considered high-risk individuals and should be screened [24]. However, the PSA test does not have a threshold value that all authors accept [25]. PSA levels are influenced by several variables, including age, acute prostatitis, ejaculation, catheterization, and certain comorbidities and drugs [23]. The link between diabetes, prostate cancer, and PSA has been examined in recent research. The PSA threshold that is most frequently employed in current practice to assess whether a biopsy is necessary (3-4 ng/mL) appears to be different from other thresholds in patients with diabetes [23]. However, if the normal PSA threshold (3-4 ng/mL) is used in diabetic patients, the possibility of missing smaller tumors in these patients is considered high [26-28]. The present study observed higher t-PSA threshold values in diabetic patients. A previous study showed that t-PSA had no value in predicting cancer in individuals with 126 mg/dL and above blood glucose levels. In the present study, while t-PSA helped predict cancer in individuals with a blood glucose level of 126 mg/dL and above, it was observed that the threshold values increased. Diabetes mellitus (independent of blood glucose regulation) is also associated with increased t-PSA cut-off values.

CONCLUSION

This study highlights the complex interplay between glycemic markers, PSA parameters, and prostate cancer risk. While HbA1c and FBG levels did not differ significantly between benign and malignant prostate conditions, PSAd and t-PSA emerged as valuable indicators for predicting prostate cancer risk, particularly in individuals with FBG levels below 126 mg/dL. However, PSAd loses its predictive utility in individuals with elevated blood glucose levels (≥126 mg/dL), likely due to increased prostate volume associated with hyperglycemia. Additionally, t-PSA thresholds for cancer prediction were higher in diabetic patients, underscoring the need for adjusted diagnostic criteria in this population. These findings align with existing

literature, which suggests that diabetes may reduce overall prostate cancer risk but is associated with more aggressive disease phenotypes and altered PSA dynamics. The integration of metabolic profiling, PSA parameters, and advanced imaging techniques like mpMRI could enhance prostate cancer screening and risk stratification. Moving forward, personalized approaches that account for glycemic status, prostate volume, and PSA thresholds may improve diagnostic accuracy and guide clinical decision-making, particularly in high-risk populations. Further research is needed to refine these strategies and optimize prostate cancer management in the context of metabolic disorders.

Ethical Statement

The study was approved by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2011-KAEK-25 2022/05-13 and date: 18.05.2022).

Authors' Contribution

Study Conception: AS, HD; Study Design: AS, HD; Supervision: HD; Funding: N/A; Materials: N/A; Data Collection and/or Processing: AS, HD, AE, GAÖ; Statistical Analysis and/or Data Interpretation: GO; Literature Review: AS; Manuscript Preparation: AS, GO, AE, GAÖ and Critical Review: HD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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