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Original Article

How is the association between urinary prostate cancer antigen 3 (PCA3) levels and Gleason scores in patients suspicious of prostate cancer?

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Abstract: Introduction: Prostate cancer is one of the most common cancers in men which is mostly slow growing and responses well to treatments if early diagnosed. Urinary prostate cancer antigen 3 (PCA3) assay is a new method with effective results in diagnosing prostate cancer. The aim of this present study was evaluate the correlation between urinary PCA3 and Gleason scores in patients who are suspicious of prostate cancer and undergo tissue biopsies. Methods: This is a cross-sectional study which was performed in 2017-2018. The patients included this study complain of prostate problems and were selected from Nour hospital, Ali-Asghar hospital and Ordibehesht clinic in Tehran, Iran. Urinary PCA3 levels were checked in all patients and then they went under prostate biopsies. Amounts of PCA3 and Gleason scores were collected and analyzed using SPSS software. Findings: We evaluated a total number of 80 patients. 40 patients had prostate cancer and 40 had no cancer. We indicated that no significant relation was reported between Gleason scores and urinary PCA3 levels. Levels of urinary PCA3 were higher in patients with prostate cancer than in patients with no cancer (P=0.007). Discussion: Generally, urinary PCA3 test is indicated as a non-invasive method to improve the specificity of prostate cancer diagnosis and its potential predictive value was studied in numerous clinical researches, but here we found higher PCA3 levels in patients with prostate cancer than in patients with and other prostate problems. We conclude that PCA3 functions as a diagnostic test and its changes in prostate cancer need to be further studied in different populations and races.

Keywords: Prostate, Gleason, PCA3

Introduction

Prostate cancer is one of the most common cancers among men. Studies in 84 countries indicated that especially in developed countries, prostate cancer is the most common cancer among male patients [1]. The trends are also growing in developing countries [2]. In some patients it develops so rapidly and invades other tissues and might also spread by the means of metastasis thorough vessels and lymphatic [3, 4]. Clinical presentations of prostate cancer vary among cases from no obvious clinical presentation to urinary problems and pelvic or back pain [5, 6]. Higher ages, positive familial history for prostate cancer and carcinogens are the most important factors which could increase the risk of developing prostate cancer in men [7]. Surveys on the 5 years survival rates for prostate cancer have indicated excellent results in the United States which is notable [8, 9]. Early diagnosis and treatments play pivotal roles in this outstanding survival rate [10].

There are different kinds of methods to diagnose prostate cancer including physical examinations, laboratory data, prostate volume, family history, ethnicity and also tissue biopsy from prostate gland. Prostate-Specific Antigen (PSA) is one of the most common specific markers for diagnosing prostate cancer and is commonly used in early diagnosis and also evaluation of treatment responses [10, 11]. Higher amounts of serum PSA could be associated with prostate cancer but it should also be noted that in some conditions, this increased rates would be false. Such conditions are: benign prostate hyperpla-

Table 1. The prevalence of Gleason scores among patients with prostate cancer

Gleason Scores	Prevalence (%)
2+2	1 (2.5%)
3+3	5 (12.5%)
4+3	13 (32.5%)
3+4	9 (22.5%)
5+4	5 (12.5%)
4+5	7 (17.5%)

sia (BPH) [12]. Some studies also declared that biases can have a significant impact on the results of PSA test and its use as a screening method for prostate cancer [13]. Another marker which could be utilized to evaluate prostate cancer is Prostate cancer antigen 3 (PCA3) which could be measured in urine. PCA3 is in fact a prostate-specific messenger RNA (mRNA) which is highly expressed by prostate cancer cells and its urinary levels could be measured [14, 15]. Based on genetic origin of PCA3, its levels could be different in different populations and races [16, 17]. Accumulative lines of evidence have indicated that measuring the urinary amounts of PCA3 is a better technique compared to assessing serum PSA levels [18]. Some other studies declare that PCA3 combined with other markers such as TMPRSS2: ERG will improve the accuracy of prostate cancer detection [19]. Based on histological and pathological features of cells and the degree of changes, a Gleason score might be given by expert pathologists from 1 to 5 [20]. Different studies have assessed PCA3 levels in different populations but so far, no previous study was performed on Iranian population to assess urinary PCA3 levels and its relations to Gleason scores. In this study, with concern of the prevalence and importance of prostate cancer, we aimed to evaluate amount of urinary PCA3 in suspected patients and compare these results with their Gleason scores.

Methods and material

This is a cross-sectional study which was performed in 2017-2018 on patients with complaints of prostate problems. Our study populations were selected from Nouri hospital and Farshadi clinic in Tehran, Iran. This study was approved by ethical committee of Tehran University of Medical Sciences. All patients who were more than 50 years of age and who were candidate for prostate biopsy due to any complains of prostate problems including pain, frequent or urgent need to urinate, nocturia, recurrent voiding symptoms and intermittency were included to our study. Patients with abnormal physical examinations and abnormal digital rectal examinations (DRE) and also high PSA levels were also included. Patients with any history of surgical procedures on their prostate, patients with any signs of prostatitis and those patients with histories of cancer or chronic diseases were excluded from our study. Based on inclusion and exclusion criteria, 89 patients were randomly chosen and included. The aim and method of the study were explained to each patient and a written consent was signed by each one of them. Demographic data were collected from patients. Urinary PCA3 was measured for each patient and afterward, patients underwent prostate biopsy. Gleason scores and amounts of urinary PCA3 were collected and analyzed by SPSS software version 24.

Results

In this study, 80 patients were included. 40 patients had prostate cancer and Gleason scores were reported for them. 40 other patients had no prostate cancer and as a result no Gleason scores were reported. The lowest PCA3 level among patients with cancer was 0.6 and the highest reported PCA3 was 20.7. Mean urinary PCA3 level among patients with prostate cancer was 4.43±3.44 and the mean PCA3 levels among those with no cancer were 2.92±1.53. The most prevalent Gleason score was 3+4 (32.5%). Prevalence of Gleason scores are summarized in **Table 1**. One Way ANOVA analysis and the evaluation between Gleason score and urinary PCA3 levels indicated no significant relation between PCA3 and Gleason score (P=0.889) (**Table 2**). Distribution of urinary PCA3 in both groups is provided in **Figure 1**. Further analysis also showed that urinary PCA3 levels were significantly lower among controls than in patients with prostate cancer (P=0.007). We also provide sensitivity and specify analysis for PCA3 based on our results in **Table 3**. Based on ROC curve, the area under curve was 0.668 and with considering of 3.55 cutoff, the sensitivity and specificity were obtained 47.5% and 15%, respectively (**Figure 2**).

Discussion

As mentioned above, overdiagnoses and over treatments of prostate cancer were reported by

Table 2. Relation between Gleason scores and urinary PCA3

GS	Mean PCA3 levels	Std. Deviation	95% Confidence Interval for Mean		*P*-value
			Lower Bound	Upper Bound	
2+2	4.6000	.	.	.	
3+3	3.9200	3.57309	-.5166	8.3566	
3+4	5.1000	5.17896	1.9704	8.2296	
4+3	4.7667	1.68819	3.4690	6.0643	
4+5	2.8000	.77782	1.8342	3.7658	
5+4	4.2714	2.68124	1.7917	6.7512	
Total	4.4325	3.44528	3.3306	5.5344	0.889

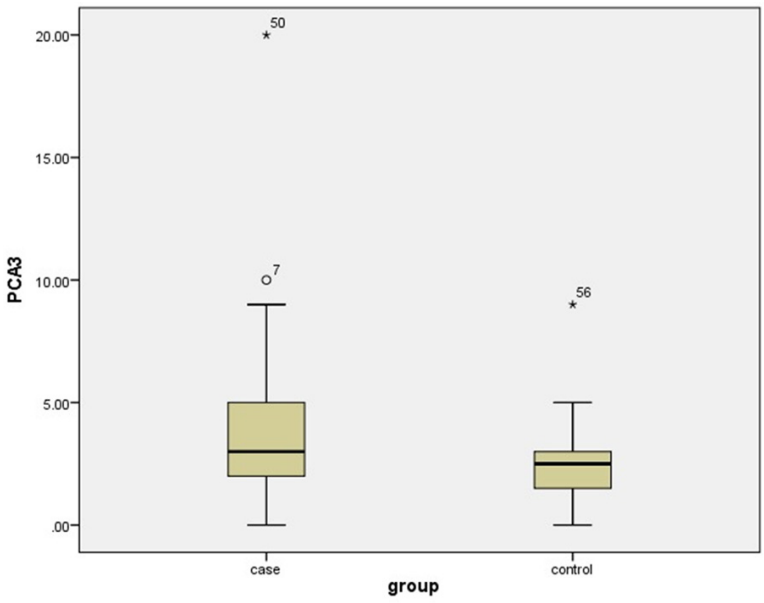

Figure 1. Distribution of urinary PCA3 in both groups.

Table 3. Investigating sensitivity and specify of urinary PCA3 based on our results

Area	Cutoff	Sensitivity	Specificity	95% Confidence Interval	
				Lower	Upper
0.668	3.55	47.5%	15%	0.55	0.78

using PSA in different studies and nowadays, more efforts are devoted to find out a better diagnostic and screening test. Urinary PCA3 has been used as a helpful method in different studies. In this study we found no statistically significant relation between Gleason score and PCA3 levels. But we indicated a lower PCA3 levels in patients with no prostate cancer. Investigating on PCA3 levels, it has been indicated that the sensitivity of this test ranges from 46.9% to 95%, and specificity ranges from 21.6% to 100% in different studies for diagnosing prostate cancer [21]. These variations in ranges could also be due to population differences. There have been also studies, discussing PCA3 cutoff levels which suggested a cutoff level of 35 for serum PCA3 [22] but here based on our analysis, we showed a cutoff level of 3.55 for urinary PCA3. We also indicated that sensitivity of this test for diagnosing cancer is 47.5% and its Specificity is 15% which is also lower than previous reports. These differences could be also due to our limited study population and also possible effects of race on this test. As Stephan and colleagues reported, PCA3 is a reliable antigen for diagnosing prostate cancer which could be more valuable when combined with other markers such as TMPRSS2:ERG [19]. Lazzeri and colleagues reviewed the different biomarkers in diagnosis of prostate cancer and compared the usage of PSA and PCA3. They concluded that PCA3 is a new prostate cancer screening method and could prevent over diagnosis and over treatments as consequences of PSA misleading results [23]. These results could be accounted as valuable data about different biomarkers for diagnosis of prostate cancer and show that PCA3 is a functional and novel method of PCA screening tests. In a study by Wei and colleagues which was performed in 2015, they worked on urinary amount of PCA3 in 207 Chinese patients suspected to

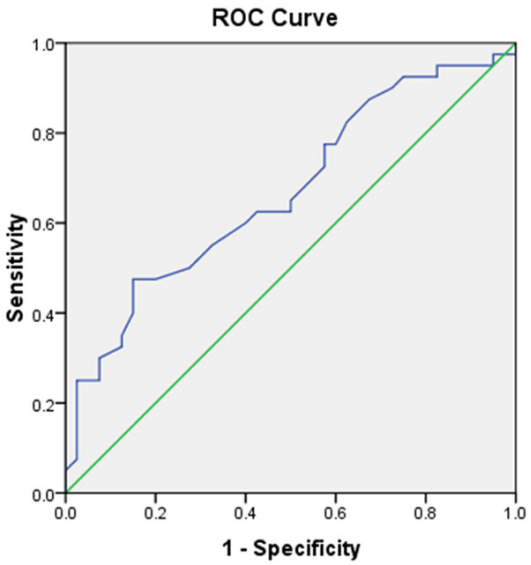

Figure 2. Sensitivity and specificity analysis for urinary PCA3 based on ROC curve.

prostate cancer and concluded that amounts of urinary PCA3 levels are directly correlated with Gleason scores. They reported that patients with higher amounts of PCA3 had higher Gleason scores and such differences were significant [24]. These results indicate a direct relation between PCA3 levels and Gleason scores in Chinese population. In our data analysis method no significant correlation was found between these two factors in Iranian patients. This could be due to racial differences in PCA3 amounts because as mentioned above, PCA3 has an untranslated prostate-specific mRNA origin which is dependent to genetics and races. Furthermore we indicated that in patients with no cancer and no Gleason scores, PCA3 amounts were lower. Among different studies on the relation of PCA3 and prostate cancer, some paradoxical results could be observed. In a recent study by Alshalalfa et al. they reported that higher prevalence of prostate cancer with higher grades is observed among European population who have lower urinary amounts of PCA3 [25]. These results also could put an emphasis on genetic and race dependency of urinary PCA3 and its relations with Gleason score.

Different lines of evidence had surveys on effectiveness of PCA3 in diagnosing prostate cancer in different populations. For instance, Ochiai and colleagues included 647 Japanese patients with elevated PSA and reported higher amounts of PCA3 in patients with positive biopsies for prostate cancer and finally concluded that PCA3 is superior marker than PSA [26]. On the other hand Shen et al. reported a higher PCA3 levels in Chinese patients with prostate cancer but they also reported no significant correlation between urine PCA3 levels and Gleason score [17]. Ramos and colleagues also surveyed 64 Latin American patients and reported that PCA3 is a specific marker for prostate cancer diagnosing in Chilean population [16]. Furthermore, Tosoian and colleagues had a survey on 260 American men and reported no significant relation between PCA3 levels and Gleason score [27]. All these results indicate that urinary PCA3 measurements could be a specific diagnosing method for prostate cancer in different populations. In this study, we included 89 Iranian patients and indicated that PCA3 levels are higher in those with prostate cancer but no significant correlation was observed between PCA3 levels and Gleason score. It should also be noted that we performed the current study on 89 patients and we consider this sample size too small for investigating population differences of urinary PCA3 levels. Taken together, we showed that urinary PCA3 level is elevate in patients with prostate cancer, but did not correlate with cancer grades. Some population based differences are observed in different studies which could be due to genetic origin of PCA3. We suggest that more studies on different populations and different races are required.

Conclusion

This study put emphasis on the fact that although PCA3 is a new and effective method in diagnosing prostate cancer, but amounts of PCA3 vary in races. It should also be noted that we found higher PCA3 levels in patients with prostate cancer than in patients with other diagnosis and other prostate problems. We conclude that PCA3 functions as a diagnostic test and its changes in prostate cancer need to be further studied in different populations and races.

Disclosure of conflict of interest

None.

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