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Original Research Article

Comparative Levels of Urinary Prostate-specific Antigen and Microseminoprotein-beta in Men with and without Prostate Cancer

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Abstract:

Introduction: The role of urinary proteomics in the diagnosis of prostate cancer (PCa) is undefined. Levels of urinary biomarkers such as prostate-specific antigen (PSA) and microseminoprotein-beta (MSMB) may differ between men with and without PCa.

Objective: We tested this hypothesis using urine samples before and after digital rectal examination (DRE) in men with an indication for prostate biopsy.

Materials and Methods: This prospective cohort study was done in Department of Urology, GRMC, Gwalior and approved by the institutional ethics committee and all individuals provided informed consent for inclusion. Men scheduled to undergo transrectal ultrasound (TRUS)-guided biopsy of the prostate for suspicion of PCa due to either elevated PSA (>4 ng/mL) or a nodule on DRE were recruited. A sterile urine culture was confirmed before inclusion.

Results: Seventy-seven patients were recruited of whom 32 had PCa (Group A) and 45 had no cancer (Group B) on biopsy. The median (interquartile range) serum PSA was 49.6 (0.2–254) ng/ml. The median urine PSA (29.5 vs. 26.4 mg/dl) and MSMB (1.7 vs. 2.4 mg/dl) were similar in both groups at baseline. However, post-DRE, both these metabolites rose in Group B but not in Group A, resulting in significantly higher post-to-pre values in Group B versus Group A. The post-DRE urine PSA/MSMB ratio was also significantly different between the groups.

Conclusions: Urinary PSA and MSMB rose significantly after DRE only in men without PCa. Post-DRE urine PSA, MSMB, and PSA/MSMB ratio can differentiate PCa from benign pathology in men with an indication for prostate biopsy.

Keywords: Prostate specific antigen, microseminoprotein-beta, prostate cancer, TRUS, DRE.

Introduction

Among men's cancers, prostate cancer (PCa) is one of the most prevalent.[1] Because of high serum levels of prostate-specific antigen (PSA), PCa is suspected abnormalities in the digital rectal examination (DRE) and prostate biopsy results resulted in a conclusive diagnosis. These operations are invasive and linked to complications.[2] Biopsy and serum PSA have specific limitations. Low predictive value is found for PCa, particularly when PSA is 4 to 10 ng/ml a substantial percentage of prostate biopsy

results were negative close to 66%.[3,4]. Additionally, every cancer found through biopsy is not aggressive and does not require therapy. Thus, there is a chance of discovering something during a biopsy. Possibly non-treatable clinically indolent tumors small percentage of clinically important malignancies was missed since a biopsy is not always a positive result.

It may be possible to reduce the number of people who undergo biopsies and raise the yield of malignancies that need to be treated by improving PSA's specificity. An essential tool is magnetic resonance imaging (MRI) in this evaluation. MRI is a pricey modality, though is not always available and liable to misunderstandings.[5] Additional noninvasive techniques comprise the evaluation of biological fluids such as serum, sperm, and plasma include biomarkers or urine to choose which men will have prostate biopsies.

The collection of a urine sample is painless, simple, and convenient. Urine biomarkers may be protein, DNA, or RNA-based.[6] A source of urinary exosomes has been found PCa's new biomarker acquisition target. One such protein biomarker is PSA in the urine. In post-DRE urine, there has been a trend toward a reduced level of PSA and prostatic acid phosphatase expression in people with PCa the proportion of serum to urine PSA has reportedly been greatly reduced in patients with PCa and can tell it apart from benign prostatic hyperplasia BPH in patients with blood PSA levels varying ranging from 2.5 to 10 ng/ml. [7] Microseminoprotein-beta (MSMB), also called prostate secretory protein of 94 amino acids, is one of the most highly secreted proteins by the prostate gland. As its expression is lost in tumorigenesis, it has been identified as a potential biomarker of PCa risk, detection, and prognosis. A common variant, rs10993994, in the 5' region of the gene which encodes MSMB, has been proposed as a risk factor for PCa.[8]

Material and Method

This prospective cohort study was done in Department of Urology, GRMC, Gwalior and approved by the institutional ethics committee and all individuals provided informed consent for inclusion. Men scheduled to undergo transrectal ultrasound (TRUS)-guided biopsy of the prostate for suspicion of PCa due to either elevated PSA (>4 ng/mL) or a nodule on DRE were recruited. A sterile urine culture was confirmed before inclusion.

Methodology

All individuals provided a morning urine specimen followed by a DRE, including prostatic massage. Prostatic massage was performed using firm pressure, sufficient to depress prostate by about 1 cm, with three strokes for each lobe. Each stroke applied from the lateral to midline and from the base to the apex for each lobe.[9] Immediately after the DRE, urine was collected as the post-DRE sample. The pre-DRE urine collected was also used for a routine urine examination. The outcome measures included the estimation of pre-DRE and post-DRE urine samples for PSA, MSMB, and their ratio for the assessment of their discriminative ability for PCa. A predetermined sample size was not calculated and it was a based on convenient sampling. Both the pre-DRE and post-DRE samples were used for the estimation of urinary total PSA and MSMB protein level by ELISA. Patients with PCa on biopsy were labeled as Group A and were staged for disease on the basis of the Gleason score of their prostate biopsy, and clinical staging was done according to the 7th American Joint Committee on Cancer version.[16] The laboratory investigators were blinded to the disease and clinical grouping of the patients. All data were entered into a prospective database.

Statistical Analysis

Data so obtained were subjected to statistical analysis. Data analysis was done by SPSS software ® version 22.0. Descriptive statistical analysis, which included

frequency and percentages, was used to characterize the data. Inferential statistics included chi-square test and independent samples t test for different dependent variables of the study and p <0.05 was considered statistically significant.

Results

Table 1: Urinary prostate-specific antigen and β-microseminoprotein before and after digital rectal examination

Parameter	Group A	Group B	*P*-value
Number of patients, *n*	32	45	-
Age (years), mean±SD	66.5±6.5	63.7±7.2	0.07
Serum PSA, median (IQR), ng/ml	41.2 (1.2-769.2)	7.64(0.01-37)	0.01
Abnormal digital rectal examination, *n* (%)	22 (75)	18 (40)	0.02
Prostate volume (cc), mean±SD	52.4±31.5	49.2±21.9	0.57
Patients undergoing multiparametric MRI, *n* (%)	20 (62.5)	21 (46.7)	-
Patients undergoing MRI-TRUS fusion biopsy, *n* (%)	01 (3.2)	12 (26.7)	-
Urine PSA, median (IQR), mg/dl			
Pre-DRE	29.5 (0.3-229.6)	26.4 (0.2-299.8)	0.53
Post-DRE	20.05 (0.2-181.1)	107.4 (2.4-617.5)	0.01
P (within groups)	0.21	0.001	-
Urine MSMB, median (IQR), mg/dl			
Pre-DRE	1.7 (0.2-8.5)	1.5 (0.1-21.1)	0.46
Post-DRE	2.3 (0.1-9.8)	4.96(0.4-27.5)	0.04
P (within groups)	0.06	0.01	-
Urine PSA/urine MSMB ratio, median (IQR)			
Pre-DRE	17.5 (0.2-1163.8)	25.7 (0.2-509.06)	0.51
Post-DRE	8.9 (0.1-69.7)	22.3 (2.2-63.9)	0.02
Urine PSA/serum PSA ratio, median (IQR)			
Pre-DRE	0.4 (0.1-14.8)	6.4 (0.1-88.6)	0.01
Post-DRE	0.3 (0.1-19.1)	13.5 (0.4-44273.4)	0.01

As per table 1 Seventy seven patients were included in the study. Of 77 patients, 32 had cancer and were included in Group A while 45 with a negative biopsy were included in Group B. The mean age (± SD) was 64.9 (±7.6) years and median (IQR) serum PSA was 49.2 (0.2–254) ng/ml. The median (IQR) serum PSA was 41.2 (1.15–769.2) ng/ml in Group A and 7.6 (0.01–37.06) ng/ml in Group B. The mean prostate volume (±SD) was 52.4 (±31.5) cc in Group A while 49.2 (±21.9) cc in Group B. Both the age and the prostate volume were comparable between the two groups they were not significant. Twenty-four patients (75%) in Group A had abnormal DRE, while 27 patients (60%) of Group B had abnormal DRE findings. Baseline urinary PSA and MSMB were similar in both groups. Both urinary PSA and MSMB values rose significantly after DRE in Group B (median PSA from 26.4 to 107.9 mg/dl, median MSMB from 1.5 to 4.9 mg/dl but not in Group A (median PSA from 29.5 to 20.03 mg/dl [P = 0.21]; median MSMB from 1.7 to 2.4 mg/dl.

Table 2: Urinary prostate-specific antigen and β-microseminoprotein before and after digital rectal examination in patients with serum prostate-specific antigen <10 ng/ml

Parameter	Group A	Group B	*P*-value
Number of patients, *n*	8	34	-
Urine PSA, median (IQR), mg/dl			
Pre-DRE	31.2 (16.2-72.3)	26.2 (10.0-89.2)	0.91
Post-DRE	45.4 (5.3-58.6)	85 (18.7-250.4)	0.05
Urine MSMB, median (IQR), mg/dl			
Pre-DRE	2.2 (1-2.8)	1.6 (1.1-5.6)	0.92
Post-DRE	4.2 (2.2-7.5)	4.1 (1.7-10.9)	0.73
Urine PSA/urine MSMB ratio, median (IQR)			
Pre-DRE	24.2 (12.6-32)	22.2 (5.4-43.7)	0.81
Post-DRE	8.1 (1.9-13.3)	21.6 (9.2-32.3)	0.02

As per table 2 Eight patients in Group A and 34 patients in Group B had serum PSA <10 ng/ml. Similar to the trend seen in the overall cohort, post DRE urinary PSA rose significantly in Group B such that while pre-DRE values were similar in the two groups, post-DRE values were significantly higher in Group B (median [IQR] 45.7 [5.3–58.6] mg/dl vs. 89 [18.7–250.4] mg/dl, P = 0.05). However, unlike the overall cohort, urine MSMB values were similar in both groups before and after DRE. Urine PSA to urine MSMB ratio replicated the trend of the overall cohort and was similar in the two groups before DRE (P = 0.89) but was significantly higher in Group B after DRE (P = 0.02).

Discussion

Our findings of higher urine PSA and MSMB levels post-DRE compared to pre-DRE samples in PCa-free participants are consistent [10]. They the components of postprostatic massage urine were described sample with proteomic research, and they reported the usefulness of these ingredients as possible therapeutics and diagnostics PCa target areas. They also reported low urine PSA values in post-DRE samples from PCa patients. In men without PCa, cellular architecture within the prostate gland is maintained with intact cell membranes, ductal anatomy, and normal drainage of prostatic secretions into the urethra. Prostatic manipulation may stimulate secretion of proteins and other molecules/exosomes into the urethra through the intact ducts, causing a rise. However, in PCa, there is cellular disarray with compression/stenosis and disruption of prostatic ducts with neovascularity and loss of cellular polarity with the release of secreted molecules into the blood circulation across the basement membrane leading to rising in serum levels of PSA. It is known that DRE results in increased serum PSA,[11,12] and thus, prostatic manipulation may not liberate any additional urinary PSA, explaining the rise in post-DRE PSA specifically in men without PCa.

Low urinary PSA among men with PSA below 10 ng/mL and having PCa have also been previously reported and study found urinary PSA to be significantly lower in patients with PCa as compared to BPH for men with serum PSA between 2.5 and 10 ng/ml. They also reported urinary PSA/serum PSA ratio to be significantly higher for BPH patients than for PCa patients, both overall and in the subgroup with serum PSA between 2.5 and 10 ng/ml, suggesting that urinary PSA could identify men with PCa. Similar results have been reported with urinary MSMB.[13] In benign prostate, MSMB regulates cell growth by promoting apoptosis while in malignancy, there is loss or decreased MSMB expression, leading to uncontrolled growth of cells. This difference becomes more prominent in post-DRE urine samples, and the rationale appears to be similar to that for urinary PSA. Prostatic massage liberates MSMB in men with normal glands (without PCa), causing a rise while there is no additional release in men with PCa, thus heightening the difference between the two groups.

The role of urine PSA and MSMB ratio has been scarcely reported in literature. As this ratio includes two parameters, urine PSA and urine MSMB, both of which differ significantly between cancer and controls independently, it is likely that the ratio may accentuate the discriminatory ability, and our findings of significance on all three parameters confirm these assumptions. A study reported higher AUC for urine/serum PSA ratio than for total PSA or free to total PSA ratio for the diagnosis of PCa in the subgroup of patients with serum PSA between 4 and 10 ng/ml.[14] On the contrary in a study, including 110 patients, did not find urinary-to-serum PSA ratio to improve the diagnostic and prognostic ability for PCa over serum PSA alone.[15]

Conclusion

Those without PCa but not those with PCa experienced a significant increase in urinary PSA and MSMB after DRE. The two groups' post-DRE levels were significantly

different from one another. The Urinary PSA to MSMB ratio also revealed similar patterns there may be a use for these non-invasive urine biomarkers in identifying patients with PCa who are more likely to be men with a prostate biopsy recommendation.

References

1. Roethke MC, Kuru TH, Schultze S, Tichy D, Kopp-Schneider A, Fenchel M, et al. Evaluation of the ESUR PI-RADS scoring system for multiparametric MRI of the prostate with targeted MR/TRUS fusion-guided biopsy at 3.0 Tesla. Eur Radiol 2014;24:344-52.
2. You J, Cozzi P, Walsh B, Willcox M, Kearsley J, Russell P, et al. Innovative biomarkers for prostate cancer early diagnosis and progression. Crit Rev Oncol Hematol 2010;73:10-22.
3. Ploussard G, de la Taille A. Urine biomarkers in prostate cancer. Nat Rev Urol 2010;7:101-9.
4. Duijvesz D, Luider T, Bangma CH, Jenster G. Exosomes as biomarker treasure chests for prostate cancer. Eur Urol 2011;59:823-31.
5. Shui IM, Lindström S, Kibel AS, Berndt SI, Campa D, Gerke T, et al. Prostate cancer (PCa) risk variants and risk of fatal PCa in the national cancer institute breast and prostate cancer cohort consortium. Eur Urol 2014;65:1069-75.
6. Mhatre DR, Mahale SD, Khatkhatay MI, Achrekar SK, Desai SS, jagtap DD, et al. The rs10993994 in the proximal MSMB promoter region is a functional polymorphism in Asian Indian subjects. Springerplus 2015;4:380.
7. Peng T, Zhang L, Zhu L, Mi YY. MSMB gene rs10993994 polymorphism increases the risk of prostate cancer. Oncotarget 2017;8:28494-501.
8. Graves HC, Sensabaugh GF, Blake ET. Postcoital detection of a male-specific semen protein. Application to the investigation of rape. N Engl J Med 1985;312:338-43.
9. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, et al. American Joint Committee on Cancer Staging Manual. 7th ed. New York: Springer; 2010.
10. Drake RR, White KY, Fuller TW, Igwe E, Clements MA, Nyalwidhe JO, et al. Clinical collection and protein properties of expressed prostatic secretions as a source for biomarkers of prostatic disease. J Proteomics 2009;72:907-17.
11. Chybowski FM, Bergstralh EJ, Oesterling JE. The effect of digital rectal examination on the serum prostate specific antigen concentration: Results of a randomized study. J Urol 1992;148:83-6.
12. Coleen MA, Thomas JD, David SM, Anthony PP, Lana T, Jill W, et al. Effect of digital rectal examination on serum prostate-specific antigen in a primary care setting. The internal medicine clinic research consortium. Arch Intern Med 1995;155:389.
13. Bolduc S, Lacombe L, Naud A, Grégoire M, Fradet Y, Tremblay RR. Urinary PSA: A potential useful marker when serum PSA is between 2.5 ng/mL and 10 ng/mL. Can Urol Assoc J 2007;1:377-81.
14. Iwakiri J, Granbois K, Wehner N, Graves HC, Stamey T. An analysis of urinary prostate specific antigen before and after radical prostatectomy: Evidence for secretion of prostate specific antigen by the periurethral glands. J Urol 1993;149:783-6.
15. Walter s KM, Stram DO, Le Ma rchand L , Klein RJ , Valtonen-Andre C, Peltola MT, et al. A common prostate cancer risk variant 5' of microseminoprotein-beta (MSMB) is a strong predictor of circulating beta-microseminoprotein (MSP) levels in multiple populations. Cancer Epidemiol Biomarkers Prev 2010;19:2639-46