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IJPBS |Volume 2| Issue 2 |APRIL-JUNE |2012|117-122

COMPARATIVE STUDY OF BIOCHEMICAL MARKERS IN PROSTATITIS, BENIGN PROSTATE HYPERTROPHY AND CARCINOMA OF PROSTATE WITH AND WITHOUT METASTASIS

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BIOLOGICAL SCIENCES RESEARCH ARTICLE
RECEIVED ON 09-05-2012 ACCEPTED ON 22-05-2012

ABSTRACT

BACKGROUND: Prostate cancer is a very slow progressing disease of the male reproductive system. High levels of Prostate specific antigen in the serum are might be an indication of either prostate cancer or some conditions like Benign prostate hypertrophy.The Diagnosis is confirmed by histological examinations of biopsy, trans urethral prostate resection or by aspiration cytology.METHODS: A total of 125 male subjects were devided in five groups (I: 25 healthy men selected as control II : 25 individuals with prostatitis. III: 25 men with benign prostate hypertrophy. IV: 25 men with carcinoma prostate without metastasis.V: 25 men with Carcinoma prostate with metastasis.) and different Biochemical parameters like Prostate specific antigen , Total acid phosphatase , Prostate fraction of acid phosphatase, Blood Urea , Serum Creatinine and Serum Uriacid were estimated on the blood samples. Statistical analysis done by Calculating the sensitivity, specificity and diagnostic efficacy by using the best cut off values and ROC curves for different analytes. RESULTS: The present study shows significantly high Prostate specific antigen values in patients of carcinoma prostate with and without metastasis compared to controls and prostatitis. The sensitivity and specificity of Prostate specific antigen was higher than those of Total acid phosphatase and Prostate fraction of acidphosphatase.CONCLUSION: Among the Biochemical markers , the diagnostic accuracy is better with Prostate specific antigen followed by the prostatic fraction of acid Phosphatase for the diagnosis of Hypertrophy and carcinoma of Prostate gland.

KEYWORDS: *Acid phosphatase, Benign prostate hypertrophy,Carcinoma prostate, Prostate specific antigen.*

INTRODUCTION

Prostate cancer tends to develop in men over the age of fifty and although it is one of the most prevalent types of cancer in men, many never have symptoms, undergo no therapy, and eventually die of other causes such as heart/circulatory disease, other unconnected cancers, or old age. On the other hand, the more aggressive prostate cancers account for more cancer-related mortality than any other cancer except lung cancer. Several studies have indicated that perhaps about 80% of all men in their eighties had prostate cancer when they died, but nobody knew, not even the doctor.[1]

Benign prostate hypertrophy, the most commonly found in men over 60yrs and may be associated with diminished androgen secretion. Clinical features are those of progressive obstruction to urinary flow. Prostatitis may be acute or chronic and most commonly occurs in sexually active men, symptoms include fever, malaise, perineal and rectal discomfort, urinary frequency, urgency, dysuria and sometimes urinary retention.[2]

Prostate cancer, the third most common cancer in men and number two cancer killer above the age of 70yrs.The presence of prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. The PSA test increases cancer detection but does not decrease mortality.[3] unlike other tumor markers PSA is organ specific. PSA is synthesized by the epithelial cells lining the acini and ducts of the prostate gland is secreted via

ductal system of prostate and stored in high concentrations in seminal fluid. PSA helps keep the semen in its liquid state.[4] Acid phosphatases are found in small amount in a number of tissues, such as bone, kidney, spleen, liver, pancreas. The estimation is carried out in connection with malignant disease of the prostate. Small increases of acid phosphatase are sometimes seen in diseases of bone: this increase is a non prostate acid phosphatase. Determination of serum acid phosphatase may then be of value in establishing a diagnosis of metastasizing prostate carcinoma.[5] Prostate fraction of acid phosphatase was the first useful serum tumour marker and emerged in the 1940s and 1950s.It was used to monitor and assess progression of prostate cancer until the introduction of prostate specific antigen, which has now largely displaced it. Recent work, suggesting it has a role in prognosticating intermediate and high-risk prostate cancer, has led to renewed interest in this marker.[6] Measurement of serum urea[7] concentration and serum creatinine[8] concentration is widely interpreted to measure the flow of urine and renal function to exclude false positive PSA in clinical practice.

The presents study was designed to evaluate the utility of Prostate specific antigen, Total acid phosphatase, Prostate fraction of acid phosphatase , Blood Urea , Serum Creatinine and Serum Uriacid in differentiating prostatitis, Benign prostate hypertrophy and carcinoma prostate with and without metastasis.

MATERIALS AND METHODS

Selection of subjects:

This study was carried out in the Department of Biochemistry and Urology department at Osmania Medical College and Hospital, Hyderabad.One hundred and twentyfive male subjects age between 48 - 80 years devided in five groups were included in this study.

Group I: Consists of 25 healthy men between 48-65yrs of age, selected as control group without any urinary symptoms and other ill health.

Group II: 25 individuals with prostatitis.

Group III: 25 men with benign prostate hypertrophy with urinary symptoms

Group IV: 25 men with carcinoma prostate without metastasis.

Group V: 25 men with Carcinoma prostate with metastasis.

Inclusion Criteria: Patients were identified on the basis of Signs and Symptoms fallowed by Digital rectal examination and Trans rectal ultrasonography and the diagnosis was confirmed by biopsy.

Exclusion Criteria: Patients with Lower urinary tract infection, received any anti cancerous medication, manipulation of the prostate gland through massage, biopsy or rectal examination before sample collection were excluded from the study

Sample Collection: After obtaining approval from the institutional ethical committee informed consent was taken from all the subjects. 10ml of venous samples was collected in sterile, clean and dry bottles for Blood centrifuged, serum separated the assays performed.

The Fallowing Parameters were estimated on blood samples:

1. Total prostate specific antigen (PSA) by Solid Phase ELISA method.
2. Total acid phosphatase(TAP) by King's method (without addition of Tartrate)
3. Prostate fraction of acidphosphatase(PAP) by King's method(after addition of Tartrate)

Note: Tartrate inhibits the prostatic fraction of the enzyme, the difference in acid phosphate activity without and with tartrate represents the activity of the prostatic fraction

4. Blood urea by Diacetyl monoxime method
5. Serum Creatinine by Jaffey's method
6. serum uric acid by Uricase method

Statistical analysis:

1. Determining Best cut off values for individual markers by using ROC curves with the help of Medcalc 8.2.1.0 version.
2. Calculating the sensitivity, specificity and diagnostic efficacy by using the best cut off values.
3. Determining the areas under the ROC curves for different analytes.

4. Comparing the discriminating capacities of various analysis by comparing the areas under ROC curves of various parameters and by calculating the correlation coefficient by using SPPS – 14 program by using Pearson – Correlation 2 tailed tests

RESULTS

The parameters shown PSA, TAP, PAP, Urea and Creatinine were analyzed in 125 subjects, 100 of patients are with different prostatic disorders and 25 are controls.

The results of the above parameters in different study groups are presented in fallowing table.

Table 1: PSA, in all five groups with 'p' value

Group	Category	PSA Mean ± SD (ng/ml)	TAP Mean± SD (KAunits)	PAP Mean± SD (KAunits)	Urea Mean ± SD (mg/dl)	Creatinine Mean ± SD (mg/dl)	Uricacid Mean ± SD (mg/dl)
I	Controls	1.32 ± 0.44	2.99 ± 0.45	0.93 ± 0.34	29.04 ± 5.35	1.13 ± 0.23	3.02 ± 0.30
II	Prostatitis	1.24 ± 0.35	2.96 ± 0.58	0.72 ± 0.42	24.3 ± 0.02	1.01 ± 0.17	2.52 ± 0.82
III	Benign prostate hypertrophy	8.11 ± 1.47	2.89 ± 0.51	0.61 ± 0.10	40.48 ± 8.85	1.20 ± 0.52	3.49 ± 0.73
IV	Carcinoma prostate	18.14 ± 7.14	7.68 ± 2.19	4.48 ± 2.01	28.04 ± 4.29	2.00 ± 0.56	7.30 ± 0.53
V	Carcinoma prostate with metastasis	66.89 ± 9.42	8.016 ± 3.21	5.15 ± 2.43	39.36 ± 7.27	1.73 ± 0.58	7.17 ± 0.32

The mean values of PSA in all the three groups i.e., BPH, Carcinoma with and without metastases higher than those of controls and this difference is statistically significant (P<0.0001). Whereas the mean values of prostatitis are lower, which are not significant (P= 0.4877).The mean of TAP in BPH and prostatitis are lower than in controls, however these differences are not statistically significant. The mean of TAP in carcinoma prostate with metastasis and without metastasis are higher compared to controls. The difference is statistically significant (P < 0.0001) In group V and IV, the mean values of PAP are higher than controls and this difference is statistically significant (P < 0.001). The mean values of PAP in second group is lower than controls and is not statistically significant (P = 0.0528).When compared to the controls, In group III and V the mean urea value is higher which is statistically significant (p < 0.0001). The mean value of urea in carcinoma without metastasis is not statistically significant (P = 0.4021). The mean values of creatinine are higher in carcinoma than controls and next followed by mean values of carcinoma with metastasis which are statistically significant (P < 0.0001) but in group II and III are statistically not significant (P=0.5611) and (P = 0.0456).

In order to assess the discriminatory capacity of different parameters analysed in patients compared to those of controls, the sensitivity and specificity of these parameters are calculated.

Table 2: ROC Table for I, II, III group Vs IV and V groups

Parameter	Best cutoff values	Sensitivity	Specificity
PSA	> 11	100	100
TAP	> 4	98	98.7
PAP	> 1.6	100	98.7
Urea	> 3.2	52.0	66.7
Creatinine	> 1.2	86.0	85.3
Uric acid	> 5.2	100	100

The specificity of PSA is 100% when I, II and III (Non carcinoma) groups were compared with IV and V (carcinoma) groups. At the best cutoff value, the sensitivity and specificity of PSA is 100% in identifying carcinoma prostate cases from Controls, BPH and prostatitis.The sensitivity and specificity of uric acid is also 100% compared to TAP and PAP with PSA. The sensitivity of PAP is 100% and specificity is less than PSA and TAP sensitivity and specificity are lower than PSA. The PSA sensitivity specificity values are highly diagnostic which are 100%.

Table 3: ROC Table Curve for IV group Vs Group V

Parameter	Best cutoff values	Sensitivity	Specificity
PSA	> 2.8	92	96
TAP	> 6.3	44	84
PAP	> 3.6	72	60
Urea	> 3.2	92	88
Creatinine	> 1.5	40	84
Uric acid	> 7.6	96	28

When ROC curves are taken in between IV and V groups the PSA has got 96% specificity and 92% sensitivity, which are highly diagnostic compared to PAP and TAP the values of which are lower than PSA they are less diagnostic than PSA.The urea sensitivity and specificity are lower than PSA. The uric acid has lower sensitivity and specificity than PSA.

The Diagnostic accuracy was represented by Area under Curve (AUC) table; ROC curves of different parameters are compared to evaluate the differentiating capacities of different analysis. Among the parameters analysed, prostate specific antigen is a better diagnostic marker with area under curve value of ROC followed by Acid phosphatase for distinguishing the control and case group.

Table 4: The AUC for group I, II, III Vs IV & V

Parameter	AUC	SE	95% confidence interval
PSA	1.000	0.000	0.971 – 1.000
TAP	0.998	0.004	0.967 – 1.000
PAP	0.999	0.003	0.969 – 1.000
Urea	0.602	0.052	0.510 – 0.688
Creatinine	0.855	0.037	0.781 – 0.912
Uric acid	1.000	0.000	0.971 – 1.000

The diagnostic accuracy of PSA was 1.000 in identifying carcinoma prostate cases from other groups.

Table 5: The AUC table for group IV Vs group V

Parameter	AUC	SE	95% confidence interval
PSA	0.952	0.032	0.851 – 0.991
TAP	0.498	0.082	0.354 – 0.643
PAP	0.587	0.081	0.439 – 0.724
Urea	0.954	0.031	0.854 – 0.992
Creatinine	0.628	0.079	0.480 – 0.760
Uric acid	0.582	0.081	0.434 – 0.719

Area under curve table of the ROC curves of different parameters is compared to evaluate the differentiating capacities of different analysis. PSA has shown high sensitivity and specificity. AUC value of 1.000 and TAP and PAP AUC value is 1.000.The AUC of PSA is 1.000 in identifying carcinoma prostate cases from controls, BPH and prostatitis cases. Whereas the AUC of PSA is 0.952 in identifying V group cases from IV group cases.

To assess the existence of correlation between different parameters in different groups, the correlation coefficient was calculated.The control groups of PSA has positive correlation with uric acid at 0.05 level, urea has positive correlation with PAP and uric acid at 0.01 level where as with PSA at 0.05 level.In carcinoma with metastasis TAP has positive correlation with PAP and urea at 0.01 level. In carcinoma without metastasis PSA has positive correlation with TAP and uric acid at 0.05 level and TAP has positive correlation with PSA at 0.05 level.In BPH group, PAP has positive correlation with urea at 0.01 level in prostatic group TAP has positive correlation with urea at 0.01 level and PAP has positive correlation with urea and uric acid at 0.01 level. Remaining are not having significant correlation.

DISCUSSION

Stamey et al demonstrated that mean serum PSA concentration were proportionate to the clinical stage. They concluded that higher preoperative serum PSA levels of > 40ng/ml were useful to predict advanced disease, while lower serum levels of < 15 ng/ml were useful to predict organ confined cases. Ercol et al in various stages of prostate cancer suggested that preoperative Serum PSA levels may be useful in stating Carcinoma of prostate. The results clearly indicated that Serum PSA levels greater than 10ng/ml were more common among patients with extra capsular disease. Partin et al and Oesterling et al have shown that, Serum PSA concentrations increase with increasing burden of malignancy in all untreated patients.[9]

It has been reported that though PSA is tissue specific, is not cancer specific. The present study shows highly significantly increases in PSA values in carcinoma patients compared to controls. It is also observed that the PSA values are significantly higher in carcinoma prostate with metastasis than in Carcinoma Prostate without metastasis. Hence this study confirms that the serum PSA values increases in Carcinoma and the increases are related to the tumor burden.

In this study the PAP and TAP mean values are significantly higher in Carcinoma than those of controls. Killian et al compared PSA, PAP and TAP as prostate cancer marker. The order of prognostic reliability was determined to the PSA > PAP > TAP.[10]

PAP was used to monitor and assess progression of prostate cancer until the introduction of prostate specific antigen (PSA), which has now largely displaced it. Recent work, suggesting it has a role in prognosticating intermediate and high-risk prostate cancer, has led to renewed interest in this marker.[11]

In this study also the PSA values of Carcinoma are significantly higher than those of PAP and TAP. Kuriyama et al reported that the PSA sensitivity was 79% but specificity of 59%. Barak et al reported a sensitivity of PSA is of 93.3% and specificity of 97.4% with 4 ng/ml cut off value of PSA. By raising cut off value from 4 to 10ng/ml, their specificity increase to 100% .[9]

In the present study sensitivity and specificity of PSA was 100% when carcinoma is compared with healthy individuals and among 2 groups of malignancy, the sensitivity was 92% and specificity was 96% which is higher than those of PAP and TAP. This shows that the PSA is the better diagnostic marker than those of Acid Phosphatase and its prostate fraction. But the prostate fraction estimation can be used as a supporting measurement along with PSA as another tumour marker. But the Acid Phosphatase alone may not give the diagnosis of prostate Carcinoma.

In the present study as the Carcinoma prostate advances, the sensitivity and specificity of urea increased. This may be due to the increased protein Catabolism in malignancy. The creatinine sensitivity was also more in Carcinoma Prostate than that of controls. The reason for this may be due to the lymphnode enlargement and around prostate area and ureters cause obstruction, even partial obstruction and back flow causes increased creatinine levels in serum.Carcinoma prostate itself leads to partial obstruction to urinary flow.Due to increased back pressure of urinary flow may result into mild increase in Serum creatinine levels.[6]

In this study the mean uric acid levels, its sensitivity and specificity are raised in carcinoma

groups. Increased production of uric acid may be due to enhanced turnover rate of nucleic acids may be due to (i) rapidly growing malignant tissue (ii) increased tissue breakdown after treatment of malignant tumors (iii) increased tissue damage due to trauma and raised rate of catabolism.[12]

SUMMARY AND CONCLUSION

The present study it has been observed that all The patients of prostatits, BPH and carcinoma prostate are over 45yrs.. Urea and creatinine levels are normal, but in BPH cases only urea levels are raised. Uric acid levels are raised in carcinoma prostate where as it is normal in other disorders. TAP and PAP are elevated in Carcinoma group compared to BPH and control groups. PSA is eleavated in carcinoma Prostate with metastasis than in those without metastasis.

In conclusion PSA is clearly the better tumor marker available for prostate cancer detection compared to total acid phosphatase and prostate fraction of acid phosphatase and the increased PSA values were related to tumor burden.

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