

A STUDY TO EXPLORE THE CORRELATION OF DIHYDROTESTOSTERONE WITH PROSTATE SPECIFIC ANTIGEN IN PATIENTS OF BENIGN HYPERPLASIA OF PROSTATE AND PROSTATIC CARCINOMA IN PATIENTS ATTENDING A TERTIARY CARE HOSPITAL IN EASTERN INDIA

Atrayee roy Chowdhury¹, Sharmistha Chatterjee^{2*}, Mousumi Mukhopadhyay³ and Biswajit Majumder⁴

¹Consultant Biochemist, AMRI Kolkata

²Department of Biochemistry, College of Medicine and Sagore Dutta Hospital, Kamarhati, Kolkata

³Department of Biochemistry, IPGME&R Kolkata

⁴ICVS, R.G.Kar Medical College, Kolkata

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ABSTRACT

Background: Prostate specific antigen (PSA) is the most common tumor marker used for screening of prostatic carcinoma. It is also increased in benign prostatic hyperplasia (BHP).

Aims: The aim of the study is to investigate the relation among PSA and dihydrotestosterone (extracted separately from the transition zone and peripheral zone) in patients of BHP and Ca Prostate.

Materials and Method: Clinically diagnosed and histologically proven cases of BHP and early cases of prostatic Carcinoma, in the age group of 55 to 85 years free of other co-morbidities, were included as cases in the study. Serum testosterone, PSA, FBS, PPBS, urea, creatinine, total protein, albumin, globulin, liver enzymes, complete blood count along with DHT (extracted separately from the transition zone and peripheral zone) were estimated and the data was statistically analysed.

Results: The tissue level of DHT shows significant correlation with serum PSA level in case of BHP when data from transition zone is taken into account ($p=0.0004$) and in case of prostate carcinoma when data from peripheral zone of prostate is used ($P < 0.0001$).

Conclusion: Thus, prostatic tissue level of 5 α -DHT in a zone wise manner may be further explored as a potential marker in order to predict future development of prostate carcinoma in the diagnostic "gray-zone".

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INTRODUCTION

Prostate specific antigen (PSA) is perhaps the most common tumor marker used for screening one of the commonest tumors of the male population, namely prostatic carcinoma. Its diagnostic specificity is controversial as it also increases in benign prostatic hyperplasia (BHP) and other inflammatory conditions.(1) While PSA is a glycoprotein secreted by the prostatic epithelium, dihydrotestosterone (DHT), the 5- α reduced derivative of Testosterone is responsible for growth and development of the normal prostate. This DHT undergoes a remarkable increase in benign prostatic hyperplasia, another extremely common condition of the geriatric male population.(2) Interestingly, PSA is variously expressed in both these conditions. It may be as low as 0.3ng/ml/gm of tissue in BHP or as high as 3ng/ml in the blood per gram of cancer in Prostatic carcinoma. (3) The normal level values in healthy males are usually <4ng/ml.

There is another significant difference in BPH and prostatic cancer. BHP is basically a localised proliferation of the fibronodular and glandular elements in the periurethral region (transition zone) of the prostate occurring in the 5th decade of life. Carcinoma Prostate on the other hand, arises predominantly in the loose fibromuscular stroma containing widely spaced smooth muscle bundles of the peripheral zone of the prostate surrounding the transition and central zones.(4,5) Androgens have been hypothesised to play a role in the pathogenesis of prostatic carcinoma also (6, 7, 8, 9, 10). In this study, we attempted to evaluate the correlation among the serum levels of PSA with the tissue levels of DHT (extracted separately from the transition zone and peripheral zone) in patients of BHP and Ca Prostate.

MATERIALS AND METHODS

The patients were selected from the outdoor and indoor of the Department of Urology, I.P.G.M.E. & R., S.S.K.M. Hospital, Kolkata and the biochemical analyses are done in the

*Corresponding author: Sharmistha Chatterjee

Department of Biochemistry, College of Medicine and Sagore Dutta Hospital, Kamarhati, Kolkata

Department of Biochemistry of the same institution. Clinically diagnosed and histologically proven cases of BHP and early cases of prostatic Carcinoma (i.e. before anti-cancer therapy has been initiated), in the age group of 55 to 85 years free of other co-morbidities, were included as cases in the study. Cases of BHP and Ca Prostate not proven histologically, patients already operated for BHP or Ca Prostate or already receiving anti-cancer therapy were excluded from the study. The cases were divided into two groups. The first group consisted of 32 patients of BHP while the second group comprising of another 33 patients of early prostatic carcinoma. Detailed clinical examination of these patients were performed prior to the collection of the duly filled up and signed Informed Consent Form. The radiological reports (Chest X-ray and ultrasonography reports) were collected for all the patients. Sample of venous blood (for estimation of serum Testosterone, PSA, FBS, PPBS, urea, creatinine, total protein, albumin, globulin, liver enzymes, complete blood count) were collected with proper aseptic precautions and analysed in the department of Biochemistry. The serum levels of testosterone and PSA were estimated from venous blood collected in clot vials by ELIZA kits supplied by Accubind, USA.

Surgical prostate specimens, obtained either by transurethral resection (TURP) or ultrasound guided true cut biopsy of prostate were collected in sterile containers. First, the tissues were cleaned of excess blood, the charred remnants of connective and adipose tissue, weighed and stored in parafilm (or paraffin) at -20°C until extraction. 10 mg of this tissue (obtained by mincing the tissue) was mixed with 500 μl of 50 mMol phosphate buffer (pH 7.4) and homogenised with mortar and pestle. The mincing and homogenisation was done on ice. The tissue homogenate thus obtained was mixed with an equal volume of NaOH and kept at 60°C for 1 hour to dissolve. The solution thus formed was centrifuged at 2000g for 10mins and the supernatant collected which was again centrifuged again at 5000g for 15 minutes. This supernatant was then collected and stored at -20°C till estimation of DHT. The tissue was thawed in an incubator to 23°C prior to estimation of DHT by ELISA.

The tissue level of DHT was assayed by Solid phase enzyme-linked immunosorbent assay (ELISA) based on the competitive principle using a kit supplied by Demeditec Diagnostics GmbH, Lise-Meitner-Straße2, D-24145, Kiel (Germany). The DHT concentration is expressed as pg/mg of wet prostate tissue (prostate tissue is calculated to be present in a concentration of 10 mg/mL or 1 mg/0.1mL in the tissue preparation).

Statistical analysis was done by using statistical package of social science SPSS version 20. Numerical variables were summarized as Mean, Standard Error of Mean and Standard Deviation and the Median and Interquartile Range were calculated. Correlation analysis was employed to explore the association between tissue levels of DHT and serum PSA levels. Pearson's Correlation Coefficient was calculated as both variables were normally distributed.

RESULTS

Correlation analysis was carried out between the tissue level of DHT and the serum PSA level in BHP and Ca prostate patients. Here data from both the zones (viz; peripheral zone and transition zone) have been included.

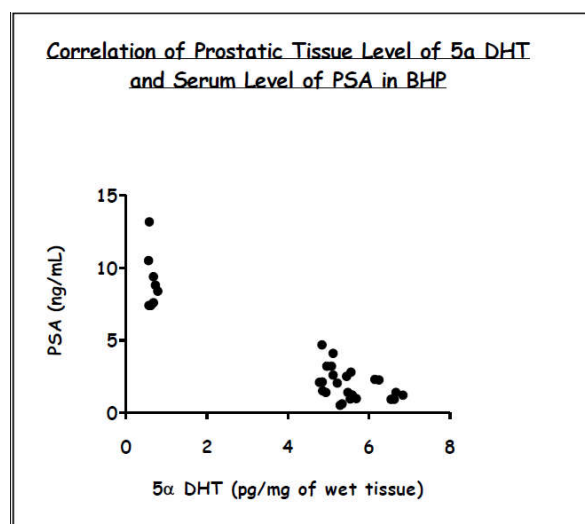


Fig 1 Correlation analysis between tissue DHT level and serum PSA level in BHP patients.

As can be seen from the above plot, there is a clustering of data sets (one for the peripheral zone of prostate and another for the transition zone of prostate). So correlation coefficient could not be calculated for this pooled data. Therefore, correlation analysis has been carried out between the tissue level of 5 α DHT and serum level of PSA in case of BHP separately for data from peripheral and transition zones of prostate.

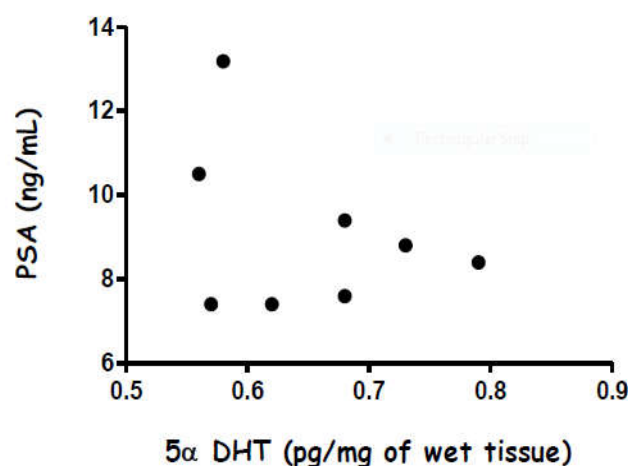


Figure 2 Correlation analysis between tissue DHT level (using data from peripheral zone of prostate) and serum PSA level in BHP patients represented graphically.

Correlation analysis of the above parameters reveals:

- Pearson $r = -0.334$
- 95% Confidence interval = -0.841 to 0.485
- R square = 0.111
- P value (two-tailed) = 0.419 – not significant
- Correlation – not significant

Therefore, as seen from this data, correlation does not exist between tissue DHT level and serum PSA level in case of BHP patients, when data from peripheral zone of prostate is used.

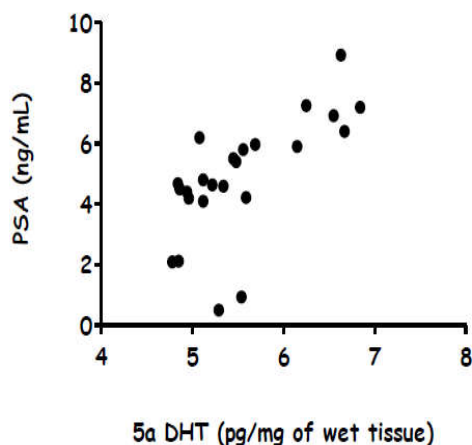


Figure 3 Correlation analysis between tissue DHT level (using data from transition zone of prostate) and serum PSA level in BHP patients graphically.

Correlation analysis of the above parameters reveals:

- Pearson $r = 0.665$
- 95% Confidence interval = 0.357 to 0.842
- R square = 0.442
- P value (two-tailed) = 0.0004 – significant
- Correlation – Significant

Therefore, as seen from the above data, a significant correlation exists between tissue DHT level and serum PSA level in case of BHP patients, when data from transition zone of prostate is considered.

Similarly, correlation analysis was carried out between tissue level of DHT and serum PSA level in Ca prostate patients. Here data from both zones (peripheral zone and transition zone) were included. Subsequent correlation analysis between tissue DHT level (both transitional zone and peripheral zone included) and serum PSA level in Ca prostate patients when represented graphically yielded clustering of data sets (one for peripheral zone of prostate and another for transition zone of prostate). So, correlation analysis between tissue level of 5 α DHT and serum level of PSA in case of Ca prostate has been carried out separately for data from peripheral and transition zones of prostate.

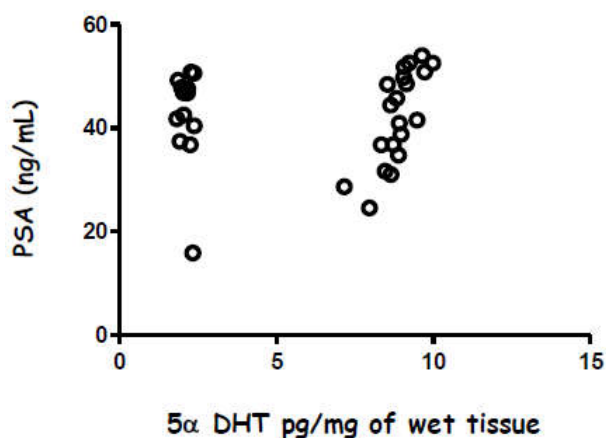


Figure 4 Correlation analysis between tissue levels of DHT (transitional zone and peripheral zone) and serum PSA in Ca prostate patients.

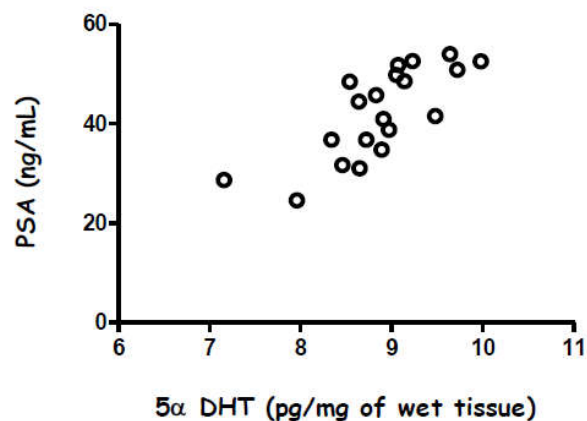


Figure 5 Correlation analysis between tissue DHT level (using data from peripheral zone of prostate) and serum PSA level in Ca prostate patients

Correlation analysis of the above parameters reveals:

- Pearson $r = 0.763$
- 95% Confidence interval = 0.484 to 0.901
- R square = 0.582
- P < 0.0001 – significant (P value is two tailed)
- Correlation – Significant

Therefore, as seen from this data, a significant correlation exists between tissue DHT level and serum PSA level in case of Ca prostate patients, when data from peripheral zone of prostate is used.

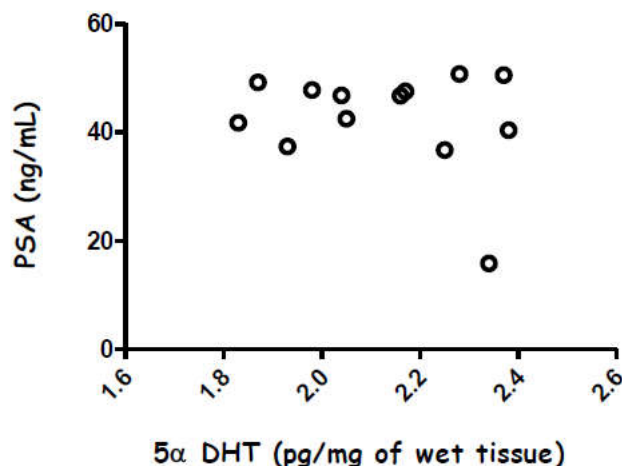


Figure 6 Correlation analysis between tissue DHT level (using data from transition zone of prostate) and serum PSA level in Ca prostate patients

Correlation analysis of the above parameters reveals:

- Pearson $r = -0.233$
- 95% Confidence interval = -0.6947 to 0.3652
- R square = 0.054
- P value (two-tailed) = 0.444 – not significant
- Correlation – not significant

As seen from this data, correlation does not exist between tissue DHT level and serum PSA level in case of Ca prostate patients, when data from transition zone of prostate.

DISCUSSION

In this study correlation analysis has been carried out between prostatic tissue level of dihydrotestosterone and serum PSA level. Here tissue DHT level from both zones (transition zone and peripheral zone) of prostate has been analyzed separately. Correlation analysis between prostatic tissue level of DHT and serum PSA level reveals that, tissue level of DHT does not

correlate with serum PSA level in case of BHP, when data from peripheral zone is taken into account, and in case of prostate carcinoma, when data from transition zone of prostate is used. But tissue level of DHT shows significant correlation with serum PSA level in case of BHP when data from transition zone is taken into account ($p=0.0004$) and in case of prostate carcinoma when data from peripheral zone of prostate is used ($P < 0.0001$).

In case of BHP, absence of correlation between serum PSA level and tissue DHT level from peripheral zone of prostate can be explained by the fact that, BHP primarily involves the transition zone of prostate (not the peripheral zone) (78, 79) and the tissue level of DHT is much lower in the peripheral zone compared to the transition zone in case of BHP. Similarly, in case of prostate carcinoma, absence of correlation between serum PSA level and tissue DHT level from transition zone of prostate can be explained as Ca prostate commonly arises from the peripheral zone of prostate (not the transition zone) (80) and the tissue level of DHT is much lower in the transition zone compared to the peripheral zone in case of prostate carcinoma.

The prostate is a hormone responsive gland that is dependent on DHT to develop. Testosterone, the main circulating androgen is converted to DHT by 5 α reductase. The concentration of PSA depends upon the age, sex and volume of the gland and also to some extent on the androgens. But, the correlation among PSA and testosterone remains controversial with regard to benign and malignant changes in the prostate.(11,12) Numerous studies have been carried out to investigate the correlation among serum testosterone and PSA in carcinoma prostate, but with contradictory results. The ratio of the sTT (serum total testosterone) and PSA is often used as a predictor of Prostatic cancer in inconclusive biopsies considered within the so-called "gray-zone" (PSA of 2.5–10 ng/ml). It was first suggested by Karamanolakis *et al.* (13) and subsequently several studies have been published in literature. There is a paucity of studies to correlate PSA and DHT in benign and malignant conditions of the prostate. In this study, we have tried to explore the correlation among PSA and DHT, (the more active metabolite of testosterone) extracted from the relevant zonal prostatic tissue in both BHP and Carcinoma Prostate. Since inhibitors of 5 alpha reductase have been successfully used in treatment of BHP, the authors feel there is a potential of DHT being used as a marker of prostatic cancer in inconclusive biopsies, and may thus reduce the number of unnecessary surgical interventions.(14). Furthermore, the required amount of prostatic tissue is very little and is easy to achieve following TURP and true cut biopsy of prostate. Our knowledge of the effects of sTT and DHT on the stage and grade of prostate cancer is far from adequate. For this purpose, it is essential to carry out large, well designed studies to specifically investigate the correlation of DHT to PSA, similar to our study in both BHP and Carcinoma Prostate to help in clinical decision making in the diagnostic "gray-zone".

CONCLUSION

Since androgens have been implicated in the pathogenesis of both BHP and Ca prostate, Dihydrotestosterone (the 5- α reduced derivative of Testosterone) the major metabolite of testosterone in prostate is thought to play an important role in the development and progression of both BHP and Carcinoma Prostate. The present study was conducted in the I.P.G.M.E. &

R., S.S.K.M. Hospital, Kolkata among the patients of Benign Hyperplasia of the Prostate and Prostatic Carcinoma attending the outdoor and indoor of The Department of Urology and the blood samples were analyzed for PSA and the tissue level of DHT was estimated in transition zone and peripheral zone of prostate Department of Biochemistry in the same institute. Correlation analysis has also been done between prostatic tissue level of DHT and serum PSA level a zone-wise manner both in patients of BHP and Carcinoma Prostate. The tissue level of DHT shows significant correlation with serum PSA level in case of BHP when data from transition zone is taken into consideration and ($p=0.0004$) and in case of prostate carcinoma patients when data from peripheral zone of prostate is used ($P < 0.0001$). Prostatic tissue level of 5 α -DHT in a zone wise manner may be further explored as a potential marker in order to predict future development of prostate carcinoma in the diagnostic "gray-zone".

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