Comparative Significance of Prostate Specific Antigen (PSA) and Prostatic Acid Phosphatase (PAP) in Prostatic Carcinoma

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This randomised control study was conducted at a teaching hospital to study the comparative rise of serum prostate specific antigen (PSA) and serum prostatic acid phosphatase (PAP) levels in prostatic cancer patients and to observe any relationship between these levels with stage, grade and volume of the tumor. One hundred and thirty seven patients above the age of fifty years were studied in three batches of carcinoma prostate, benign prostatic hyperplasia and normal control. Serum PSA and serum PAP levels were estimated alongwith digital rectal examination, transrectal ultrasonography and biopsies in group A & B. Results showed correlation in serum PSA level rise and stage of carcinoma prostate as well as tumor volume. Serum PAP level rise was only in higher grades and bigger tumor volume. No correlation of both with tumor grade. So it is concluded that the role of serum PAP level as tumor marker for prostate cancer cannot be supported. In spite of limitations, serum PSA level is a far better although not ideal tumor marker for carcinoma of the prostate.

Key words: PAP (Prostatic Acid Phosphatase), PSA (Prostate Specific Antigen, BPH(Benign Prostatic Hyperplasia) DRE (Digital Rectal Examination), TRUS (Transrectal ualtrasonography)

The incidence of carcinoma prostate is next to lung cancer and it is the third leading cause of death in Western countries[1]. It is a disease of aging, rare below forty year. As the age advances, the incidence and the mortality rate increases logrythmically[2].a The peak is reached in eight decade of life[3]. The clinical course of the disease is unpredictable. It is usually asymptomatic in early stages and is diagnosed when advanced. According to a survey by American college of surgeons, in 40% cases of cancer prostate, it has already spread beyond the prostate at the time of diagnosis[4]. In Pakistan, situation is not very different.

To reduce the mortality rate of prostate cancer, it is necessary to detect it when is organ confined and initiate definitive treatment. This urged the investigators all over the world to find an ideal tumor marker for prostatic carcinoma. Prostatic acid phosphatase (PAP) and prostate specific antigen (PSA) are the two widely used tumor markers for monitoring the clinical course of the patients with prostatic carcinoma[5].

Human acid phosphatases are heterogeneous group of glycosylated enzymes. They are grouped into six iso-enzyme families found in numerous body tissues in different proportions. Among these iso-enzyme 2 contributes 95% to 99.9% of the total acid phosphatases secreted by the prostate. So it is this iso-enzyme referred to as "prostatic acid phosphatase"[6]. Its activity increases at the site of bony metastasis from the prostatic cancer The serum PAP estimation is a cheaper procedure and has been used for over half century for monitoring the metastatic disease. Its value as a tumor marker is limited because of presence in other tissues, high levels even in BPH and localized carcinoma prostate.

Wang in 1979 isolated an antigen from prostatic tissue present in BPH and carcinoma prostate but not in any other human tissue, so named as prostate specific antigen. PSA is a glycoprotein single chain polypeptide with a molecular weight of 33000-34000 daltons consisting of 93% amino acids and 7% carbohydrates. It is localized in prostatic epithelial lining cells of the acini and ducts and is involved in the liquefaction of the seminal coagulum that is formed at ejeculation[5]. Its serum level rise in all stages of prostatic carcinoma more high in more advanced disease[7]. It may be elevated in BPH, prostatis and prostatis infraction[8]. Different diagnostic and therapeutic procedures effect its serum levels and two to three weeks may be necessary for serum PSA levels to achieve a baseline level due to its long half life[9].

Though PSA estimation is time consuming and expensive as compared to PAP, it enables a significant reduction in other costly investigations currently used in management of carcinoma prostate Thus we have planned to compare the significance of serum PSA with serum PAP levels in monitoring the patients with prostatic carcinoma.

Materials and Methods

This randomized control study was conducted at the Department of Urology, Mayo Hospital, Lahore. One hundred and thirty seven patients above the age of fifty years were studied in three batches. A number of fifty biopsy proved, patients with adenocarcinoma of the prostate were placed in Group A. Fifty patients of BPH, biopsy proved, were placed in Group B and thirty seven normal subjects as a control were placed in Group C. The patients were referred to us through Urology Outpatients Department with obstructive or irritative bladder symptoms. Normal persons were persuaded through posters and banners to get themselves evaluated for this

purpose and were declared normal when no abnormality was detected by evaluation protocol.

Serum PSA and PAP estimation was done in all the above one hundred and thirty seven subjects. Venous blood samples (3cc) were obtained randomly before digital rectal examination. Comparative significance of serum PSA and PAP levels were studied in relation to stage, grade and tumor volume in the Group A patients. Patients previously treated for BPH and prostatic carcinoma were not included in the study.

Patients were evaluated with history, general physical examination, digital rectal examination, ultrasonographay (abdominal and transrectal) and biopsy. In all the three groups, DRE was done by a single doctor in knee elbow position after emptying the bladder. Consistency firm or hard, if hard localized or any extension, surface smooth or nodular, if nodular size, site and number and size of prostate in grams approximately was assessed. Transrectal ultrasonography was performed in all the subjects with a Bruel and Kjar model 1846 scanner using a 7MHZ transducer. All measurements were performed by a single sonographer. Subjects were asked to come with empty distal gut and full bladder. DRE was performed prior to TRUS to exclude any other abnormality. Tip of the probe was covered by a condom and 15 ml of water inflated it. After proper lubrication, the probe was gently inserted into the anus and pushed 8-9cm in the rectum in lithotomy position. then condom was ballooned with 60ml of water. Air in the balloon was removed for clear picture. Scanning was started from the base of the bladder, seminal vesicles, towards the apex of the prostate in 0.5cm increments. The prostate volume was estimated in cubic centimeters. Prostate was scanned in all the three dimensions, all the lobes and capsule. Echogenicity of the focal defects were labeled as hypoechoic or hyperechoic in comparison to the normal peripheral zone of the gland.

Biopsy was done in Group A & B patients after TRUS, by means of which site was also decided. Tissue for histopathology was taken trasnperineally under guidance of TRUS after taking all aseptic measures and injecting local anaesthesia with 18 gauge tru-cut biopsy needle. Multiple biopsies were taken. No antibiotic was used prophylactically or afterwards. All the patients in Group A,B, and C were evaluated for laboratory investigations, urine complete examination, blood chemistry in terms of Hb %, ESR., TLC,DLC, blood urea and serum creatinine. Serum PSA estimation was done by immunoenzymatic kit Eurogenetics PSA quantitative. Normal serum PSA value was upto 5 ng/ml. Serum PAP estimation was done with immunoenzymatic kit (Merkitest kit) by spectrophotometer. Normal serum PAP value was upto 3.7µ/L.

Group A patients were further evaluated with bone scan, liver scan, x-ray pelvis and x-ray chest PA view. All biopsies were examined and reported in the Department of Pathology, K.E. Medical College, Lahore. Grading of the tumor was done into Grade I well differentiated, Grade II moderately differentiated and Grade III poorly differentiated carcinoma. Staging was done clinically with the help of history, general physical examination, DRE, ultrasonography (abdominal and trans-rectal, bone and liver scan, x-ray pelvis and chest following modified Jewet and Whitmore staging system.

Stage A	Not palpable on DRE but detected on histopathology report done for BPH.
A-1	1-3 foci or less than 5% of specimen. Well differentiated.
A-2	More than 3 foci or more than 5% of specimen. Well or moderately or poorly differentiated.
Stage B	Tumor palpable on DRE but confined within the capsule
B-1	Nodule confined to the prostate and involving less than 50% of one lobe
B-2	More than 50%
B-3	Bilobar involvement
Stage C	Local extension beyond the prostate
C-1	Capsular erosion
C-2	Seminal vesicle extension
C-3	Both
Stage D	Metastases
D-1	Positive obturator, hypogastric & external or common iliac lymph nodes or ureteric obstruction causing hydronephrosis but normal bone scan.
D-2	Bone or soft tissue metastasis and involvement of lymph nodes outside the pelvis.

Patients in Group A were further subdivided into three subgroups on the basis of volume of the tumor.

i. less than 5cc
ii. 5-10cc
iii. more than 10cc

Results

Fifty patients of carcinoma prostate comprised Group A. Fifty patients BPH in Group B and thirty seven normal subjects in Group C comprised control group. Age distribution in thirty seven normal subjects of Group C was mean age 59.7±08.4 (50-80) years. The mean serum PSA level was 1.4±0.9 (0.6-4.2)ng/ml. The mean serum PAP level was 0.7±0.3(0.2-1.8) µ/L. The mean prostate volume was 25.3±4.7 (17.1-34.2)cc. In fifty patients of BPH Group B the mean age was 61.5±7.0(51.81) years. The mean prostate volume was 45.6±17.0(18.3-84.3)cc. The mean PSA value was 4.5±2.7(1.1-13)ng/ml. The mean serum PAP value was 1.4±0.7(0.5-3.2)µ/L. Twelve (24%) patients in Group B had serum PSA levels more than 5ng/ml but less than 10ng/ml. Two (4%) patients had level raised above 10ng/ml showing PSA levels false positive for prostate cancer.

In fifty patients of carcinoma Group A mean age was 70.8±8.6 (55.91) years. The mean prostate volume was 43.1±16.5(18.1-84.3)cc. In this group in DRE 21(42%)a patients had smooth prostatic surface and 29(58%) and nodular prostatic surface. Forty one (82%) patients had

hard prostate while 9(18%) had firm. On abdominal ultrasound, lymph nodes were detectable only in 6(12%) patients. Ureteric involvement was seen in 18(36%) of patients. On transrectal ultrasonography, focal defects were detected in 47(94%) patients. All of these focal defects were hypoechoic. Prostatic capsule was eroded in 27(54%). Seminal vesicles were involved in 9(18%) unilaterally and 1(2%) had bilateral involvement. Bone scan was positive for metastasis in 20(40%) and liver scan in 1(2%). Three (6%), 9(18%), 16 (32%) and 22 (44%) patients fell in Stage A,B,C, & D respectively. Two (4%) patients had serum PSA level below 5ng/ml, 6(12%) had serum PSA level less than 10ng/ml and 42(84%) had more than 10ng/ml

Table 1 The mean serum PSA value in carcinoma (Stage A,B,C,D) BPH and normal groups

Group	n=(%)	Mean PSA (ng.ml)	S.D±	Range (ng/ml)
Carcinoma				
Stage A	3(6%)	9.5	7.0	4.8-17.5
Stage B	9(18%)	19.2	10.7	3.8-34.6
Stage C	16(32.%)	64.8	38.2	8.0-130
Stage D	22(44%)	196.4	91.6	34.6-381-7
BPH	50(36.50%)	4.6	2.7	1.1-13
Normal	37(27.01%)	1.4	0.9	0.6-4.2

Serum PAP level was within normal range in 22(44%) patients and it was above the normal range in 28(56%) patients (Table 2).

Table 2 The mean serum PAP value in carcinoma (Stage A,B,C,D) BPH and normal groups

Carcinoma Group	n=(%)	Mean PAP (μ/L)	S.D±	Range (μ/L)
Stage A	3(6%)	1.6	0.1	1.5-1.8
Stage B	9(18%)	2.3	0.8	1.4-3.6
Stage C	16(32.%)	3.9	1.1	2.4-6.1
Stage D	22(44%)	18.5	11.5	3.7-38.9
BPH	50(36.50%)	1.4	0.7	0.5-3.2
Normal	37(27.01%)	0.7	0.3	0.2-1.8

All of them proved to be adenocarcinoma of the prostate on histopathology. Nine (18%), 17 (34%) and 24(48%) patients were in Grade I, II and III respectively (Table 3, 4).

In three patients of Stage A, one (33.3%) had Grade I and 2(66.6%) had Grade II. None (0%) had Grade III. In nine patients of stage B, 3(33.3%) had Grade I, 2(22.2%) had Grade II and 4(44.4%) had Grade III carcinoma. In 16 patients of stage C, 3(18.7%), 5(31.2%) and 8(50%)a had Grade I, II and III respectively. In 22 patients of stage D, 2(9.2%), 8(36.3%) and 12(54.5%) had Grade I, Grade II and III carcinoma of the prostate respectively. Statistically serum PSA was significantly raised (P<0.05) when stage D was compared with stage A, B,C and control (BPH & Normal) groups. Also significantly raised when C was compared with control but no difference in serum PSA value (P>0.05) in comparison of Stage A,B and C with one another (Table1). Serum PAP was significantly raised (P<0.05) only when Stage D was compared with A,B,C BPH and normal subjects. It was not significantly raised (P<0.05) when all the other groups (A,B,C BPH and normal) were compared with one another.

On the basis of tumor volume, out of fifty patient of Group A, 38 (76%) patients fell in subgroup I, tumor volume less than 5cc, ten (20%) patients fell in subgroup II, tumor volume between 5-10cc and 2(4%) patients fell in subgroup III, tumor volume more than 10cc (Table5 & 6)

Table 3 Coordination of mean PSA levels with different grades of carcinoma Group A.

Grade	Number of patients PSA <5ng/ml	PSA <10ng/ml	PSA >10ng/ml	Total (%)
I	2(22.2%)	1(11.1%)	6(66.7%)	9(100%)
II	0(0%)	3(17.6%)	14(82.4%)	17(100%)
III	0(0%)	2(8.4%)	22(91.6%)	24(100%)

Table 4 Correlation of mean PAP levels with different grades of carcinoma Group A

Grade	Number of patients PAP <3.7μ/L	PAP >3.7μ/L	Total (%)
I	6(66.6%)	3(33.3%)	9(100%)
II	7(7(41.2%)	10(58.8%)	17(100%)
III	9(37.5%)	15(62.5%)	24(100%)

Table 5 Correlation of mean PSA levels with three tumor volume subgroups of carcinoma Group A

Group	PSA <5ng/ml	PSA <10ng/ml	PSA >10ng/ml	Total (%)
I	2(5.2%)	6(15.9%)	39(78.9%)	38(100%
ii	0(0%)	0(0%)	30(100%)	10(100%)
iii	0(0%)	0(0%)	2(100%)	2(100%)

Table 6 Correlation of mean PAP levels with three tumor volume subgroups of carcinoma Group A

Group	PAP <3.7μ/L	PAP >3.7μ/L	n= (%)
I	21(65.2%0	17(44.8%)	38(100%)
ii	1(10%)	9(90%)	10(100%)
iii	0(0%)	2(100%)	2(100%

Among 38 patients in subgroup I, 3(7.9%) were in stage A, 9(23.6%) were in Stage B, 13 (34.2%) were in stage C and 13(34.2%) were in stage D. In subgroup ii, no patient was in stage A & B, three (30%) were in stage C and 7(70%) in Stage D. In subgroup iii, all the two patients were in stage D. Statistically serum PSA value was significantly different (P<0.05) in all the three subgroups. Serum PAP level was also significantly different (P<0.05) in all the three subgroups, when compared with one another.

Discussion

Carcinoma of the prostate continues to be a leading cause of cancer death in American men[10]. Incidence of carcinoma of the prostate has been increasing due to an increased aging population, as well as improved methods of diagnosis. Early detection of prostate cancer is difficult due to lack of symptoms associated with localized tumor[9]. It is dependent largely on laboratory studies such as serum PAP and PSA levels, DRE, TRUS and scanning techniques like bone scan. To avoid a series of damaging, painful and costly investigations, people all over the world are searching for a simple, safe and cheap tumor marker. This with a single reading will make them able to diagnose the prostate cancer with its degree of invasiveness and course of disease with prognosis. Serum PSA has been used in the early detection, management and follow up in the patients if carcinoma prostate. For over half a century, serum PAP has been a gold standard for the purpose but serum PSA is shown to be much more sensitive tumor marker than serum PAP for carcinoma prostate with a correlation of the stage of the disease[11].

In this study we have compared prostate specific antigen(PSA) and prostatic acid phosphatase (PAP) in different stages, grades and tumor volume in cancer prostate. Inspite of inaccuracies, digital rectal examination remained the basis for clinical staging in carcinoma prostate. It had high yield in clinically localized tumors. About 50% of these lesions were outside the prostate when staged otherwise[12]. Most of the patients with stage B tumor on DRE were grouped in stage C or D when other available means of staging were used. We faced the same problem and in our study, it had a limited sensitivity in detecting the small tumors, which really had great potential for cure.

Transrectal ultrasonography has emerged as the best imaging modality for the prostate[13]. Different workers found echogenicity of the prostate tumor to be hypoechoic in 60 to 94% of cases and isoechoic in low percentage while hyperechoic very rare. Sometimes there is considerable overlap. In our study all tumors were found to be hypoechoic. TRUS is a valuable compliment to DRE for diagnosing cancer of prostate. It has the capacity to characterise the tumor by location, volume and extent, abdominal ultrasound detects lymph nodes and ureteric involvement. Radio isotope bone scan is a very sensitive method in detecting the metastasis Our study confirmed it. Clinical staging is most accurate when results of ultrasonography are combined with DRE, biochemical markers and scanning studies[9].

Biopsy and histological diagnosis is superior to all the serum markers. Still the search for better serum marker for prostatic carcinoma has not ended. Ideal serum tumor marker is one that is expressed only by the cancer cells when tumor achieves biological importance. However, this perfect tumor marker has not yet been achieved[14]. For long time prostatic acid phosphatase (PAP) has been used extensively in the diagnosis and staging of prostatic cancer as well as to monitor the response to therapy[6]. Recently another prostate enzyme has been identified, characterized and found to be produced exclusively by prostatic tissue called prostate specific antigen. PSA is considered to be the most meaningful and useful tumor marker in prostate cancer biology[9]. It had a direct correlation with prostate size as is evident from our control group i.e. 24% of the BPH patients had PSA level upto 10ng/ml and 5.2% even normal subjects had raised upto 10ng/ml. All of these patients had prostate more than 50 grams.

Oesterling and associates (1988)[15] studied one hundred and seventy eight men with prostatic cancer and found that pre-operative serum PSA levels showed a statistically significant correlation with pathological stage. Hudson et al (1989)[16] also found in 73% of 386 patients with prostate cancer that serum concentration of PSA was increased proportionately with advancing clinical stage (A through D). Only 43% of 238 patients had increases serum PAP levels above the normal. The increased sensitivity of PSA was most pronounced in early stage disease as compared to PAP. Perin et al 1990[17] showed in 347 amen that mean serum PSA levels for patients with prostatic cancer increased progressively as pathological stage progressed.

In our study 84% patients of prostate cancer had an elevated serum PSA levels while 44% had elevated serum PAP levels. The percentage of patients with an elevated PSA increased progressively through stage A,B,C and D. The serum concentration was more than normal limit in 33.3% patients of stage A, 56% with stage B, 81% with stage C and 100% with stage D. Serum concentration of PAP did not rise above the normal in stage A and B of the carcinoma prostate. In stage C, 43.7% patients had raised level. In stage D, 95.5% had raised level. Despite the fact that considerable overlap existed among all the stages, still we agree that serum PSA concentration is directly proportional to the clinical stage. The increase in serum concentration of PSA with increasing stage is due to the increasing tumor volume. This is not the case with serum PAP levels. The sensitivity of PSA was pronounced in early stages as compared to PAP.

Perin and associates (1990)[17] found in 331 patients a positive correlation between serum PSA level and the degree of cellular differentiation for individual pathological stage. The failure of serum PSA to predict pathological stage more accurately may be related to decreased PSA production by higher grade tumors. Our study showed a direct but poor correlation between the PSA and histological grade with overlapping values of PSA in different grades of prostate cancer. Serum PAP levels were also directly correlated with the grade but only true in advance stage disease. High grade tumors were seen even in tumors of less than 2cc volume.

Stamey et al (1987)[9] proved a strong direct correlation between the tumor volume and serum PSA level but not between the tumor volume and serum PAP level. McNeal in 1990 showed that low grade tumors were rarely more than 1cc whereas high grade tumors were

almost always larger than 1cc. Our study showed the same in majority of cases but not as a rule. Our study also showed the similar results as far as PSA was concerned but PAP did not reflect any rise in small capsule confined tumors. In extracapsular tumors, it did rise with increasing tumor volume.

Conclusion

It is difficult to estimate the progressional tumor behaviour before and after the treatment. In search of ideal tumor marker, PAP is not unique to the prostate and has been detected in many body tissues. Its sensitivity for stage A and B was 0% and for stage C and D, it was 43 and 68%. It did not show any correlation with the grade of tumor. PAP in case of small tumors less than 5cc did not rise while in larger tumors more than 5cc did rise. It is evident here that role of PAP as tumor marker for prostate cancer cannot be supported. PSA is prostate specific but not tumor specific. Its rise above normal in all stages of carcinoma prostate is correlative but false negative, false positive and overlapping results in different stages are present. It does not reflect degree of anaplasia. It correlates with tumor volume. In spite of limitations, it is a far better but not ideal tumor marker for prostatic carcinoma.

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