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Clinical value of prostatic specific antigen level in serum of the lesions of prostate gland and its importance as a screening test and tumour marker for carcinoma of prostate gland correlated with histopathology

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Abstract
Prostate Cancer is the leading cancer in older men. when detected early (organ confined), it is potentially curable by radical prostatectomy. Therefore, early detection is important and PSA is widely used for this purpose. It is considered one of the most promising tumour markers available PSA is an extremely useful tumour marker and is used to detect and monitor treatment of prostate cancer.
Prior to introduction of testing for prostate specific antigen(PSA), two-thirds of prostate cancers were discovered after they were incurable. By this test, physicians / surgeons can now catch most prostate cancers before they spread beyond the prostate.
PSA is produced by the prostate, a male sex gland about the size of a walnut that makes the fluid that carries sperms. Raised level of PSA normally is not found in a blood. In men with prostate disease, however, PSA levels in the blood may rise; two leading causes are: benign prostatic hyperplasia (BPH) and prostate cancer. PSA levels under 4 ng/ml are considered normal whereas above 10 ng/ml are cause for biopsy. In the " diagnostic gray zone ", its levels between 4 and 10 ng/ml, the free PSA test can help differentiate between cancer and benign conditions such as BPH.
PSA exists in multiple forms in the blood. Most of it remains bound to proteins, but some is free floating. In the early 1990 s, it was discovered that measuring the ratio of " free to total " PSA could further help in distinguishing prostate cancer from benign prostate disease.

Keywords: prostatic enlargement, PSA level, histopathology

Introduction
In the 1970s, several groups independently discovered prostate antigens for use in forensics and as tumor markers. [13].
In 1971, Hara and colleagues identified a protein in seminal plasma that they named ϒ- sweminoprotein. Li and Beling isolated the same protein from deminal plasma and called it protein E1 because it had slow β- mobility in electrophoresis and a molecular weight of 31,000 Da [13].
In 1978, Sensabaugh characterized this glycoprotein with isoelectric points between 6.5 and 8.0 and MW of approximately 30,000 Da. And called it p 30 [13].
In 1979, Wang and Co-works purified a protein from prostatic tissue and called it prostate specific antigen. ϒ-Seminoprotein, p30, and PSA are biochemically very similar. PSA is found in normal, benign, hypertrophic, and malignant prostatic tissues. Originally it was thought that PSA was solely expressed in prostate tissue. However, it was later found that PSA also is expressed in numerous other tissues, most notably hormonally regulated tissue such as breast tissue. Low concentration of PSA is found in the sera from women as well as in the nipple aspirate fluid [13].
PSA testing by itself is limited in the screening or detection of early prostate cancer because PSA is specific for prostatic tissue but not for prostate cancer. BPH is a common disease in men 50 years of age and older. Studies have shown that PSA concentrations in patients with BPH are similar yet statistically different from those associated with early prostatic cancer.
The clinical sensitivity of PSA is 78% at the typically used cut-off of 4.0 ug/L. By lowering the cut-off to 2.8 ug/L. sensitivity increases to 92%, whereas specificity decreases from 33 to 23 %.
Raising the cut offs to 8 ug/L. Improves the specificity to 90%. Cut offs lower than 4 ug/L. have been suggested. such as by the national comprehensive cancer network (NCCN).
The use of serum PSA together with DRE is more accurate and sensitive than digital examination alone. 4 DRE testing has been determined to be optional according to recent ACS guideline. 5 and 6.
PSA is a single chain glycoprotein that is 7% carbohydrate. It has 237 amino acid residues and four carbohydrate side-chains with linkages at amino acid 45 (asparagines), 69 (serine), 70 (threonine), and 71 (serine). The N-terminal amino acid is isoleucine, and the C- terminal residue is proline. Its MW is 28,430 Da. And it has isoelectric points from 6.8 to 7.2 because of its various isoforms [1, 2].
The complete gene encoding PSA has been sequenced and located on chromosome 19. It is similar to the kallikrein-1gene with 82%homology. Functionally, PSA is a serine protease of the kallikrein. It is produced exclusively by epithelial cells of the acini and ducts of the prostate gland.

PSA is secreted into the lumina of the prostate duct. In seminal fluid, PSA cleaves seminal vesicle- specific proteins into several low molecular weight proteins as part of the process of liquefaction of the seminal coagulum. Therefore PSA possesses chymotrypsin –like and trypsin –like activity.

The half-lives at least 2 to 3 weeks are required for the serum PSA to return to baseline concentration after certain procedures, including transrectal biopsy, transurethral resection of the prostate, and radical prostatectomy.

Benign prostatic conditions, such as BPH and prostatitis, can also elevate PSA concentrations.

Three major forms of PSA exist in the serum : free PSA, bound PSA, and complex PSA. PSA immunoassays are widely used to detect early- stage prostate cancer, to evaluate disease progression. And to assess therapeutic response.

In addition to the total serum PSA level, the ratio of free to total PSA has become an important variable for distinguishing between males with benign and malignant prostate. The percentage of free serum PSA is lower in males with prostate carcinoma than in those with benign prostate hyperplasia or with no apparent prostatic disease.

In addition to prostate cancer, a number of benign (not cancerous) conditions can cause aman's PSA level to rise. The most frequent benign prostate conditions that cause an elevation in PSA level are prostatitis and benign prostate hyperplasia (BPH). There is no evidence that prostatitis or BPH leads to prostate cancer, but it is possible for a man to have one or both of these conditions and to develop prostate cancer as well [4, 5].

There is no specific normal level of PSA in blood but generally most doctors considered PSA levels of 4.0 ng/ml and lower as normal. But more recent studies have shown that some men with PSA levels below 4.0 ng/ml have prostate cancer and that many men with higher levels do not have prostate cancer.

In addition, various factors can cause a man's PSA level to fluctuate. For example, a man 's PSA level often rises if he has prostatitis or a urinary tract infection. Prostate biopsies and prostate surgery also increase PSA level. Conversely some drugs- including finasteride and dutasteride, which are used to treat BPH – lower a man's PSA level. PSA level may also vary somewhat across testing laboratories.

In general, however, the higher a man 's PSA level, the more likely it is that he has prostate cancer. Moreover, continuous rise in a man 's PSA level over time may also be a sign of prostate cancer. Approximately 80% of men with PSA concentration more than 4.0 ug/L at diagnosis have organ – confined disease. this deceases to 70% AND 50% for PSA concentration of 4 to 10 ug/L [14].

PSA concentration can not be used to determine the pathological stages. The concentration of PSA can serve as a guide and is more useful;l in evaluating the presence of metastasis. Patients with PSA level less than 20 ug/L rarely have bone metastasis [11, 12].

Material and Methods

In the study of Random collection of 50 cases of prostatic enlargement, were tested for PSA level, Acid phosphatase level before surgical operation and Histopathological examination was done after surgical operation. Elisa method was applied for test of PSA level. In present study of 50 cases of prostatic enlargement, all cases were randomly collected from Varun Arjun medical college and Rohilkhand Hospital, Banthra, Shahjahanpur, Uttar Pradesh, India. All PSAlevel were tested according to ELISA method [5, 6, 7].

Principle of test

The ELISA method is based on a two-site sandwich ELISA method. Sample and diluents are added to the wells coated with monoclonal antibody against PSA. PSA in the serum binds to the antibody coated on the well. Unbound proteins are washed off. HRP labelled anti-PSA antibody is then added to the mixture. Unbound protein and HRP conjugate are washed off. Upon the addition of the substrate, the intensity of color is proportional to the concentration of PSA in the samples. A standard curve is prepared by plotting color intensity and the concentration of the PSA.

Materials required - 5 ml and 10 ml graduated pipettes, beakers, flasks, and cylinders, 10 ul to 1000 ul. adjustable single channel micropipettes, disposable tips, 50 ul to 300 ul adjustable multichannel micropipette, disposable tips and reservoir, Micro well strip reader capable of reading at 450 nm. method and procedure - as in ELISA method.

Result

Table 1: Showing level of Acid phosphatase in prostatic Enlargement

Acid phosphates level	No. of cases	percentage
2.5-5.0	3	6
5.1- 7.5	10	20
7.6- 9.5	33	66
9.6 - above	4	8

In 50 cases of prostatic enlargement, 3 cases show acid phosphatase level upto 5.0 UI/L,

10 cases revealed 5.1 to 7.5 UI/L, 33 cases revealed 7.6 to 9.5 UI/L and 4 cases revealed above 9.6 UI/L. Later on 4 cases further investigated by PSA level which revealed prostatic carcinoma which was finally proofed by histopathology.

Table 2: Showing PSA level in all 50 cases

Prostatic Diseases	Number of cases	Test results (range) of PSA
1-BPH	23	Between 1.0 to 10.0 ng/ml
2-BPH with chronic prostatitis	13	Between 1.0 to 12.0 ng/ml
3-BPH with Acute prostatitis	10	Between 4.0 to 14.0 ng/ml
4- Prostatic Carcinoma	4	Between 40.0 to 60.0 ng/ml

Above table no- 2, shows 23 BPH whose PSA level found between 1.0 to 10.0 ng/ml, 13 cases were BPH with chronic prostatitis whose PSA level found between 1.0 to 12.0 ng/ml, 10 cases were BPH with acute prostatitis whose PSA level found between 4.0 to 14.0 ng/ml and 4 cases revealed prostatic carcinoma whose PSA level found between 40.0 to 60.0 ng/ml of which later on diagnosed finally by histopathology.

Observations

The test data were recorded in excels work — sheet and

analyzed for result. All the 50 cases of prostatic enlargement were conducted for serum PSA level and serum acid phosphatase level. Analysis was done in deferent type of prostatic lesions. Table shows as follows:

Table no- 3 showing level of acid phosphatase in deferent prostatic lesions diagnosis confirmed by Histopathological examination.

Table 3: Showing serum acid phosphatase level in deferent prostatic diseases

Serum Acid phosphatase level U/L			Biopsy
Done by α – Nephthylphosphate kinetic method			Histopathological diagnosis approved
ACP level	Number of case	percentage	
2.5-5.0	3	6	BPH
5.1-7.5	10	20	BPH with chronic prostatitis
7.6-9.5	33	66	BPH with acute prostatitis
9.6- above	4	0	Carcinoma prostate

1- SAP (Serum acid phosphatase)Level were within 2.5-5.0 range - in 3 cases of Benign prostatic hyperplasia 2- SAP Level were recorded within 5.1 – 7.5- in 10 cases of Benign prostatic hyperplasia with chronic prostatitis. 3- SAP level were recorded within 7.6 to 9.5 in 33 cases of BPH with acute prostatitis. 4 - SAP Level was recorded severely increased. in 4 cases of Adenocarcinoma Total of 50 cases of prostatic enlargement admitted in Varun Arjun medical college and Hospital Shahjahanpur and KPC medical college and Hospital Jadavpur, Kolkata-700032, were assessed for eligibility from December 2014 to December 2016. All 50 cases were Investigated routinely in the pathological laboratory for Hb%, TLC, DLC,, Blood Urea, Acid Phosphatase, PSA level, Urine examination for albumin, sugar and microscopic examination. Histopathology was done special for correlation. Serum acid phosphatase and PSA were estimated in all the cases.

Table 4: Showing present prostatic enlargement diagnosed by rectal digital examination in deferent age group

Prostatic enlargements in age incidence in study group (50 CASES)		
Age in years	No. of cases	Percentage
31- 40	1	2%
41- 50	7	14%
51- 60	13	26%
61- 70	16	32%
71-80	10	20%
81-90	3	6%

The highest incidence of prostatic enlargement is seen in 6th decade followed by 5th decade and least in 3 rd decade.

Presenting clinical symptoms and their percentage in prostatic enlargement-- Out of the 50 cases, 92% patients presented with frequency of micturation followed by 90% of acute retention with dysuria and 16% presented with retention with overflow. 6 % presented with Haematuria.

Duration of illness and their percentage--- The maximum duration was 10 months and minimum duration was 10 days. 27 cases out of 50 cases, whose duration was between 1 month and 3 months (54%) and few cases had duration between 10 months and 12 months (2%).

In the rectal digital examination of 50 cases of prostatic obstruction, the massive enlargement was seen in 3 cases (6%), 27 cases (54%) showed moderate enlargement and rest 20 cases (40%) showed mild enlargement, 17 cases out of 27 cases of moderate enlargement were between 5th and 6th decade. Out of 50 cases, 41 cases (82%) had firm in consistency, only one case (2%) showed firm to hard in consistency.

Almost all 47 cases (94%) had lateral lobe enlargement, only 3 cases (6%) had a medium groove obliteration, out of 47 cases, 36 cases were in 5th to 7th decade.

Blood urea levels at the time of admission -- The prostatic obstruction of 50 cases, whose blood urea was measured at the time of admission. The maximum 45 cases (90%). whose blood urea were in normal range, 5 cases (10%), out of 50 cases revealed above 40 mg %.

Out of 50 cases, 40 patients (80%) showed acid phosphatase in normal range (2.5 to 11 UI/L) and 2 patient (4%) showed higher level. The maximum number 33 cases (66%) fall in the range of 7.6 to 9.5 U/L.

Table 5: Showing serum PSA level in all cases and finally diagnosis confirmed by Histopathological Examination.

Prostatic Diseases	Number of cases	Test results (range) of PSA
1-BPH diagnosis confirmed by histopathological examination	23	Between 1.0 to 10.0 ng/ml
2-BPH with chronic prostatitis diagnosis confirmed by histopathological examination	13	Between 1.0 to 12.0 ng/ml
3-BPH with Acute prostatitis diagnosis confirmed by histopathological examination	10	Between 4.0 to 14.0 ng/ml
4- Prostatic Carcinoma diagnosis confirmed by histopathological examination	4	Between 40.0 to 60.0 ng/ml

The above table no- 5 shows PSA level was found 1- 10 ng/ml in BPH, and in the BPH with chronic prostatitis shows mildly raised level upto 12.0 ng/ml. BPH with acute prostatitis shows 4.0 to 14.0 ng/ml. In prostatic carcinoma, specially in advanced cases which also shown bone marrow metastasis, PSA level were 40.0 to 60.0 ng/ml.

Discussion

A study of pre-operative serum acid phosphatase of 50 cases of prostatic obstruction (prostatic enlargement) has been done to evaluate the reliability of the prostatic acid phosphatase regarding its accuracy and dependability and to correlate from serum acid phosphates with post operative histopathology.

Patients admitted to Varun Arjun medical college and Hospital from 2015 to june 2017.

With symptoms of prostatic obstruction between, were duly interrogated and after physical examination, including rectal examination, clinical diagnosis based on rectal examination were done.

Acid phosphatase is specific for specified for diagnosis of prostatic enlargement as Gutman *et al.* (1938) found that carcinomatous prostatic tissue contained large amount of acid phosphatase. The high acid phosphatase content of prostatic carcinoma indicates that the tumour is not exposed functionally embryonic cells but represent a type of malignancy of physiologically mature cells. Serum acid phosphatase is raised in carcinoma of prostate with metastasis but

Seldom above normal or in suspicious range, is the growth confined to the gland.

In about 40% cases of patient with carcinoma of prostate, the acid phosphates are raised above normal. A reading between 9-11 Ul/L is practically suspicious of carcinoma of prostate

And above 11.00 Ul/L is practically diagnostic. Very high level can be found at time in patient showing extensive bone marrow involvement.

ACP was an independent predictor of tumor recurrence in prostatic carcinoma

Nesbit and Baunn (1951**)** have shown raised serum acid phosphatase level in 39.9 % of malignant prostate. But in present study, out of 3 cases of carcinoma prostate, 2 cases were obtained with suspicious limit of acid phosphates for carcinoma and one case obtained was having acid phosphatase more than 11 U/L unit. Two cases which showed high level acid phosphatase, bone marrow were done for confirmation of bone marrow metastasis. They showed bone marrow metastasis.

Conclusion

In our present study of 50 cases of prostatic enlargement, following conclusions were drawn as follows:

Dysuria, frequency, thinness of stream and poor force are the early symptoms of prostatic obstruction. Acute retention was the presenting complaint in majority of cases. The duration of the symptoms was short (10-2 month) in malignant condition in comparison to benign hyperplasia (1-10 months). The size of the prostate assessed by rectal examination was not proportional to the severity and duration of symptoms. Prostate acid phosphatase is a reliable method in diagnosing metastasing carcinoma of prostate gland, infiltrated into bone marrow. Serum acid phosphatase level above the normal is always significant for prostatic lesions. Bone marrow was conducted to all patients who showed high level of acid phosphatise (above 11.0UI/L) for bone marrow metastasis.

PSA level is always correlated with clinical stage of prostate cancer or lesion. Higher PSA concentration and higher percentages of patients with elevated PSA concentration are associated with advanced stages. PSA has also been found to correlate with stages of tumor extension and metastases, cancer volume and cancer grade [8, 9, 10].

High level of PSA noted in 50 cases of prostatic enlargement in prostatic carcinoma, 4 cases of prostatic carcinoma found which were diagnosed by histopathology revealed 40.0 to 60.0 ng/ml. Later on all 4 cases were conducted for bone marrow examination which revealed marrow metastasis.

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