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ESTIMATION OF SERUM PROSTATE SPECIFIC ANTIGEN (PSA) LEVEL IN BENIGN PROSTATE HYPERPLASIA PATIENTS AND ITS CORRELATION WITH AGE AND PROSTATE VOLUME

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ABSTRACT

This study was aimed to estimate serum prostate specific antigen (PSA) levels in patients suffering from benign prostate hyperplasia, and its association with age and prostate volume of patients in an accurate manner, to be useful for therapeutic, especially medical management of disease. Blood samples were taken from eighty patients i.e. thirty healthy men and forty patients follow up medical treatment for eight months. PSA levels were determined by MiniVidus apparatus, by using two steps sandwich fluorescence technique, and the results showed that there is a significant increase ($P<0.01$) in serum levels of newly diagnosed patients compared with healthy controls, also significant difference of decrease in mean levels of PSA in the 8 months follow-up treated patients, which reflects the effectiveness of the medical treatment in lowering PSA levels to the normal values. Frequencies of elevated PSA concentration in serum of healthy Iraqi men and BPH patients showed PSA concentration of 4 mg/ml was selected as the cutoff and the gray zone range between 4-10 ng/ml. Significant positive correlations were found between age, prostate specific antigen and prostate volume all BPH patients in the study. Highest positive correlation (r=0. 54) was recorded between PSA and PV while a lower correlation (r=0. 19) was reported between PSA and age.

KEYWORDS: Prostate Specific Antigen, Benign Prostate Hyperplasia, Prostate Volume, Age

INTRODUCTION

The main secretary proteins of the prostate gland are prostate-specific antigen (PSA), human glandular kallikrein (hK2), prostatic acid phosphatase (PAP) and prostate specific protein (PSP) (Jung *et al*., 2000).

Prostate-specific antigen, also known as kallikrein 3, is an androgen-regulated serine protease, secreted by the ductal and acinar epithelial cells of normal prostate, predominantly into the prostatic lumen (Berman *et al.,* 2012). Its synthesis largely depends on the 5α-dihydrotestosterone concentration in the prostatic tissue, and it is activated enzymatically through cleavage by human kallikrein 2 (hK2). Active PSA proteolytically cleaves seminogelins, which immobilize spermatozoa in the semen coagulum following ejaculation, releasing peptides with antimicrobial activity that protect the sperm from bacterial attack, within the female genital tract *(*De-Lamirande and Lamothe, 2010).

Loeb *et al*., (2012) stated that the normal, healthy prostate gland secretes 0.01–0.02 mg prostate specific antigen per day, while hyperplasia prostate secretes ten times more. Vicki *et al.,* (2013) showed that men, who have prostate cancer may have a higher amount of PSA in their blood; however, a high PSA level does not necessarily indicate prostate cancer.

During conditions such as prostate cancer, the basal epithelial cell sheet and the basement covering are disrupted and PSA may leak into the surrounding stroma and vasculature, so, as a result of that PSA is elevated in the blood and is used as an analytical indicator for prostate diseases as well as a marker for benign prostate hyperplasia in the absence of cancer (legate *al.,* 2008). A number of factors other than prostate cancer, which often raise the PSA levels, were suggested by Tomislav*et al*., (2015) which include: enlargement prostate, older age, prostatitis and certain medications.

EXPERIMENTAL

A total of 80 patients with age ranging between 47- 84 years, who required Urology Consultation at Clinic in Al-Yarmook Teaching Hospital and Al-Jaibachi Private Hospital in Baghdad Governorate, suffering from BPH symptoms were taken for the experimental study. After early diagnosis in each one by the consultant urologist, blood samples were collected from each, before taking any medication. Also, the same samples were taken from apparently healthy (30 males) with age ranged between 45-80 years during the period, extending from March to November, 2015. The age specific range was developed to increase the number of undiagnosed patients younger than sixty years, and to decrease the number of over-diagnosed patients, detected over the age of sixty. The assay principle of this kit combines a two-step enzyme immunoassay sandwich method, with a final florescent detection (ELFA). The Solid Phase Receptacle (SPR) serves the solid phase, as well as the pipetting device, and all of the assay steps were performed automatically by the (Mini VIDAS) device.

For this test, the calibrator, control and the sample test portion were 200 µl.

- The sample was cycled in and out of the SPR several times, to enable fixing the antibody on to the interior wall of the SPR, in order to capture the prostate specific antigen present in the sample.
- The unbound components were eliminated during the washing steps.
- The alkaline phosphatase–labeled antibody was then incubated in the SPR, where it was was bounded with the prostate specific antigen.
- The unbound conjugate was then eliminated during the washing steps.
- The conjugate enzyme catalyzed the hydrolysis of 4-methyl-umbelliferyl phosphate substrate into a fluorescent product (4-methyl- umbel lifer one).
- During the final detection step, the intensity of the fluorescence was proportional to the concentration of prostate specific antigen present in the sample, which it measured at 450 NM.
- At the end, the results were automatically calculated and printed by the device in relation to the calibration curve stored in memory.
- The assay will be completed within approximately 60 minutes, and the concentrations were expressed in ng/ml.

Serum concentration of PSA was statistically analyzed, their data were given as mean ± standard deviation (S.D.), and differences between means were assessed by the Analysis of Variance (ANOVA), followed by Least Significant Difference (LSD). The correlation coefficient was used between some patient's parameters in this study.

RESULTS AND DISCUSSIONS

Results in table (1) show that PSA levels for BPH patients were in the range of 0.9-13.3 ng/ml with a mean value of 3.81 and a stander deviation ±1. 98, while the total PSA levels in healthy men were in the range of 0.54 to 4.3 ng/ml, with a mean value of 1.42 and a standard deviation of ± 0.84. The statistical analysis of results ensures high significant difference (P<0.01) in the mean serum concentration of PSA between BPH patients and healthy men.

Table 1: Prostate Specific Antigen (PSA) of Healthy, Newly Diagnosis and Treated Patients (follow up after 8 Months)

Group	No.	Range Min. – Max.	Mean ± SD	P-Value
Healthy controls	30	0.54 ± 4.36	1.42 ± 0.84 [b]	0.00372 **
Newly diagnosis patients	80	0.97 ± 13.3	3.81 ± 1.98 [a]	
Treated patients	40	0.75 ± 2.29	1.52 ± 0.77 [b]	
** (P<0.01).				

Results showed that significant difference was occurred in mean levels of PSA in the 8 months follow-up treated patients, which reflects the effectiveness of the medical treatment in lowering PSA levels to the normal values. The mean values of PSA in patients and healthy men are different throughout the world. In the study, results indicated a mean PSA of 3.81 ng/ml for BPH patients, while those reported in different countries were: 3.1, 3.6, 6.82 and 8.09 ng/ml by (Okihara *et al*., 2002; Molati*et al*., 2006; Sridevi, 2013 and Busato *et al.*, 2015), respectively.

A low serum PSA level (1.42 ng/ml) was recorded in apparently healthy Iraqi men, which was less than that recorded by Malati and Kumari (2004) for the Asia Pacific Countries (4 ng/ml).

Several factors such as prostate cancer, benign prostatic hyperplasia, prostatitis, ejaculation and prostatic manipulation, including catheterization lead to increase in the serum PSA (Payne and Cornford, 2011). The reason for elevating PSA in BPH patients may be returned to the fact that, PSA is a tissue-specific biomarker of the prostate, so any disruption of the normal anatomic prostatic tissue may lead to increasing PSA level.

The results of the recent study show that, there was a significant decrease (P<0. 05) in the mean of PSA level (3.81 ng/ml with a mean of 1.52 ng/ml at 8 months follow up, after medical treatment). Several studies also have been suggested the possessions and benefits of BPH treatment on decreasing PSA levels in patients (Faydaci *et al*., 2012). In this regard, Toktas*et al*., (2013) demonstrated that there were significant differences in PSA level of BPH patients, before and after medical treatment, while Scardino, (2007) noticed that the changes in PSA level with medical treatment were paralleled to the accidental variations found in healthy men. Heldwein*et al*., (2011) showed that PSA levels tend to fall when repeated after 45 days, regardless of antibiotic therapy.

Frequencies of elevated PSA concentration in the healthy Iraqi men and BPH patients are tabulated in Table (2). For patients under this study, PSA concentration of 4 mg/ml was selected as the cutoff, and the gray zone range as 4-10 ng/ml. In the BPH group, 70% of patients had PSA concentrations less than 4 ng/ml, 27.5% had PSA in the range of 4-10 ng/ml and only two (2.5%) patients had PSA more than 10ng/ml. In the healthy male group, 96.6% had PSA less than 4 ng/ml and 3.3% had concentration ranges of 4-10 ng/ml. On the other hand, none of the healthy males had shown a serum PSA concentration of more than 10 ng/ml.

Table 2: Distribution of Sample Study According to PSA in Newly Diagnosis Patients and Healthy Males

Group		PSA Group			Chi-Square and P-Value
		< 4	4-10	> 10	
Newly diagnosis (80)	No.	56	22	2	12.933 **
	%	70.00	27.50	2.25	0.0001
Healthy control (30)	No.	29	1	0	14.802 **
	%	96.67	3.33	0.00	0.0001
Chi-square and P-value		8.813 ** 0.00473	8.259 ** 0.00566	0.158 NS 0.642	---

**** (P<0.01).**

Very closed result was found by Wondum*et al.*, (1998) who reported that only 2-3% of the BPH patients had a PSA level greater than 10 ng/ml. While Malati *et al*., (2006) reported that a PSA value beyond the upper limit of gray zone (10ng/ml) was 8.2 ng/ml. It is a matter of debate, whether such high concentrations in some BPH patients are due to advanced course of prostate hypertrophy, or due to a very early malignant of prostate at multiple occasions, also may be due to that these patients had large prostate volume, which led to increase PSA levels.

Relation between age, prostate specific antigen and prostate volume (PV) among all BPH patients in the study are presented. Table 3 shows that there was a statistically significant difference in PV (P<0.01) between age groups, and the general increase in PSA level was proportional to the age. The PSA values of the age groups 40–49, 50–59, 60–69 and ≥ 70 were, 2.80, 2.89, 3.04, and 3.37 ng/ml, respectively. The PSA levels were increased with age; the increase was slight in the first three age groups, but it was significant between the age group (60-69) and age group ≥ 70. These results were almost conceded to those previously reported by Helen and Nihad, (2011)**.** However, the PSA levels in Iraqis BPH men patients in all other age groups were generally lower than those of Chinese, Japanese and Korean men (Osterling *et al*., 1993; Shibata *et al*., 1997 and Lee *et al*., 2000), respectively. This could be due to the geographical or racial variation. In this regard, Shah *et al*., (2011) declared that ethnicity may exert a difference in BPH characteristics of men.

Table 3: Relationship between age Group, Prostate Specific Antigen and Prostate Volume

Age Group (Years)	No.	Mean ± SD	
		PSA	Prostate Volume
40-49	2	2.80 ± 1.67 [a]	34.50 ± 3.54 [c]
50-59	11	2.89 ± 1.95 [a]	40.50 ± 5.41 [bc]
60-69	26	3.04 ± 0.28 [a]	44.73 ± 7.37 [b]
> 70	41	3.37 ± 0.32 [a]	51.00 ± 9.30 [a]
LSD value	---	1.907 NS	6.027 **
P-value	---	0.781	0.0026
** (P<0.01).			

Results in table (3) also show a trend of increasing PV with advancing age. The highest PV was recorded among BPH patients of age group >70 years, while the lowest in the 40-49 years group. Consistent with the hypothesis that aging is an etiologic factor of BPH (Lee and Lee, 2014), a tendency of increasing prostate volume (PV) with increasing age return to significant tissue remodeling process that takes place within the prostate, especially in the transition zone (Untergasser *et al.*, 2005). It was postulated that, prostate growth is a result of disturbed balance between apoptotic and proliferative activities with a net reduction in apoptosis. Briganti *et al.*, (2009) showed through histological analysis of glandular and basal epithelial cells of the prostate, a decrease in the apoptotic activity.

Several studies have established age related increases in prostate volume (PV); Zhang *et al.*, (2013) mentioned that larger prostate volumes and transition zone volume were positively associated with increased age, and the mean transition zone volume per age group increased at a faster rate than that of the total prostate volume. Also, Bosch *et al.* (2007), Loeb *et al.*, (2009) and Raza *et al.*, (2017) reported that the mean of prostate volume was increased with age. Another reason for prostate growth was age related change in hormonal and other growth-regulatory factors that affect prostate growth and volume (Kristal *et al.*, 2008). As men become old, testosterone levels fall, and the proportion of estrogen increase, which possibly triggering prostate growth by stromal overgrowth; this return to that the estrogen increases important growth factor (St Sauver *et al.*, 2011).

Table (4) contains the correlation between age, PSA and prostate volume of BPH patients, Overall correlation were: I). PSA and PV ($r = 0.54$, $P < 0.0001$). ii). PV and age ($r = 0.46$, $P < 0.0001$); iii). PSA and age ($r = 0.19$, $P = 0.047$). Highest positive correlation (r=0. 54) was recorded between PSA and PV. Other researchers reported similar positive correlations between PSA level and PV (Lee *et al.*, 2008 and Park et *al.*, 2013). Also, increasing PV and age with correlation rate 0.46 was consistent with studies performed on Swedish, Taiwanese, Indian, Indonesian and Karachi populations (Vesely *et al.*, 2003; Liu *et al.*, 2007; Baruah *et al.*, 2012; Putra *et al.*, 2016 and Raza et al., 2017).

In the present study, a lower correlation (0.19) was reported between PSA and age (r= 0.19) in comparison to other correlations (PSA with PV and PV with age). Such low correlation is weaker than those found in other similar studies. Fayhaa *et al.*, (2013) recorded a correlation of 0.3 was reported between PSA and age. While Collins *et al.*, (1993) found a modest correlation of PSA with age for men with BPH. On the other hand, Romic *et al.*, (1997) found no correlation between the age of patients and volume of the prostate, whereas a correlation was present between PSA prostate volumes only.

Table 4: Correlation Coefficient between Prostate Specific Antigens, Prostate Volume and Age in Patients Group

Variable	Correlation Coefficient-r	P-Value
PSA & Prostate Volume	0.54 **	0.0001
PSA & Age	0.19 *	0.047
Prostate Volume & Age	0.46 **	0.0001
* (P<0.05), ** (P<0.01).		

This diversity in the degree of correlation between age with PSA and age with PV could be attributed to the ethnicity and geographical variations between this study and others. Platz *et al.*, (2000) declared that there was a fundamental difference in the biology of prostate (including PV and PSA) in various ethnicities. While Chalabi *et al.*, (2003) found it was not a community-based, but the samples were obtained from the urology clinic patients suffering of diverse symptoms.

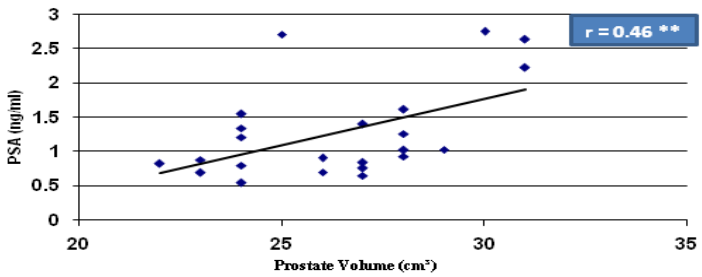

Figure 1: Relationship between Prostate Volume and Prostate Specific Antigen for BPH Patients

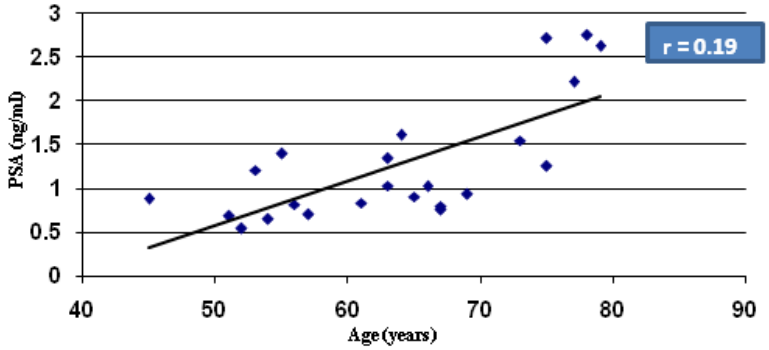

Figure 2: Relationship between Age and Prostate Specific Antigen for Benign Prostate Hyperplasia Patients

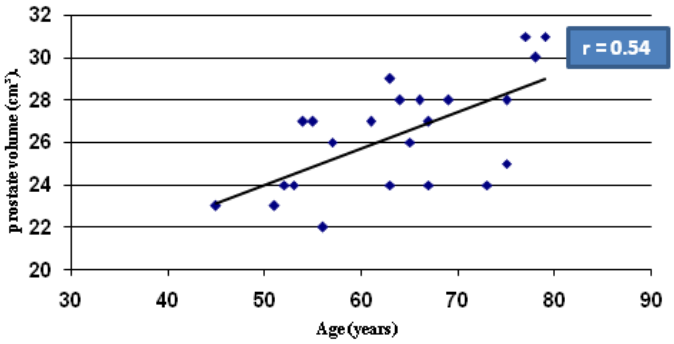

Figure 3: Relationship between Age and Prostate Volume for Benign Prostate Hyperplasia Patients

CONCLUSIONS

The prostate specific antigen (PSA) is a tissue-specific biomarker of the prostate, hence, any disruption of the normal anatomic prostatic tissue may lead to increasing PSA level. Prostate specific antigen levels varied among BPH patients and healthy men, it has positive correlation with prostate volume and age, and results have shown that, the highest positive correlation (r=0. 54) was recorded between PSA and PV.

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