Role of Serum Levels of Thymidine Kinase 1 in Diagnosis and Differentiating of Prostatic Tumor

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Abstract

Background: Both benign prostatic (BPH) and prostate (Pca) hyperplasia include prostate enlargement. The distinction between benign prostatic hyperplasia and prostate cancer is a major challenge, since the prostatic specific antigen (PSA) cannot be considered a reliable predictor of prostate cancer. **Aims:** Efficiency of serum thymidine kinase 1 and PSA-related biomarkers in prostate tumor, BPH and PCa diagnosis and differentiation, especially when serum PSA is in the gray (4-10 ng/ml) region and in the pronostic of these patients after surgical therapy**. Subjects and Methods:** A case control and cross-sectional review. There were 110 elderly patients (45-81 years) and 45 controle. Serum experiments involved the use of ELISA technologies to measure tPSA, fPSA, and TK1. **Result:** In comparison to both of the BPH and controls, the mean (±S D) of serum tPSA and fPSA in Pca were significantly improved (all p =0,001) while the mean value of f PCa in comparison with BPH and control was dramatically decreased (p = 0,001) for fPSA/tPSA. There was no difference between BPH and controls in these parameters. In both of the Pca and Controls (P<0.001) the mean TC1 was slightly higher (P<0.001). This serum TK1 has the most receptive and specific diagnostic and differentiating potency in the gray zone of tPSA (4-10 ng/ml), which has tPSA in the gray zone with AUC=1 in the 924 pg/ml cut-off zone.

Conclusion: Serum level of TK1 was superior of tPSA in diagnosis of prostate tumor and differentiating between BPH and PCa.

Keywords*: Serum, Thymidine Kinase 1, prostatic tumor*

Introduction

Prostatic Cancer (PCa) is a complex and heterogeneous disease and the most common malignancy in males worldwide, and the second-leading cause of cancer-associated mortality. While the prevalence of PCa in Arab countries is lower than that in Western countries [(1)]. The majority of PCa cases are indolent and localized at diagnosis, localized tumors can develop into aggressive tumors in the long term [(2)]. A major clinical challenge in prostate cancer clinical management is posed by the inability of current diagnostic tests, such as serum PSA testing, digital rectal examination, and histopathologic grading of tissues, to discern between indolent and aggressive disease [(3)]. Prostate enlargement, is a condition that affects the prostate gland in men. The incidence of occurrence of BPH has recently been estimated at 42% in males aged 51–60, 70% in those aged 61–70 and 90% in males between 81–90 years [(4)]. A homo dimer with an underunit size of 25 kDa is the essential intracellular shape of TK1. In the event of DNA disruption in advance of a new synthesis, intracellular TK1 dimers may be easily transformed into active tetrame [(5)]. TK1 is released from cell death through proliferation; an indicator of cell disruption is the concentration of TK1 in extracellular fluid. Regular cells rarely disintegrate during proliferation and normally, like malignancies, only occur during rapid or non-regulated proliferation. Following its release, TK1 forms

complexes of various molecular weights and enzymes, which is an important element in developing tests [6]. TK1 moves the phosphate from ATP and transforms deoxythymidine (dT) to deoxythymidine (dTMP). Monophosfate is exposed to additional phosphorylation of DNA-incorporated deoxidation thymidin triphosphate (dTTP). dTTP self-regulates TK1's negative feedback DNA precursor synthesis [7]. TK1 activity is regulated by the cell cycle and has a distinct pattern of activity compared with tumor cells in normal proliferating cells [2,8].

Material and Method

This case-control study took place at the University of Baghdad, the Department of Biochemistry, the University and the Ghazi Al-Hariri Hospital for Specialized Surgery/Medical City in September 2019 to March 2020. During this period the study was conducted. The range of patients (45-81 years) included 110 patients; BPH (n=55) and prostatic cancer (n=55) and controls were 45. The consultant Urologist and Oncology Group was able to obtain diagnosis of BPH and PCa. Each individual obtained formal consent. The Scientific Committee of the department of Biochemistry, University of Baghdad (Iraq), accepted our ethics in this regard. Exclusion criteria is any other conditions such as prostatic intraepithelial neoplasia and other non-malignant diseases of the prostate are excluded in this study and Chronic disease cases like renal failure. The peripheral vein venipuncture of each patient and healthy control woman was extracted by five milliliters of blood, transferred to the simple tube and allowed to coagulate over 15-30 minutes and the serum had been isolated by centrifugation over 10 minutes at 2500–3000 rpm, and stored at 20oC, until the day of the assessment of the TPSA, PSA, and Thymidine (TK1).TK1 kits were provided from My BioSource, Inc., USA.

Result

The mean (±SD) values of serum TK1, TPSA, FPSA and fPSA/tPSA ratios of the groups studied are shown in Table 1. Compared to BPH and controls (for all; P<0.001), and Pca serum TK1 levels was significantly higher. The mean value of BPH serum TK1 was significantly higher than that of the controls (P<0.001). Compared to BPH and controls (both P=0.001), the mean (±SD) value of Pca serum tPSA levels was significantly higher. After all, there was no significant difference in tPSA between BPH and controls. In Pca the mean (±SD) value of serum fPSA was slightly higher than in BPH (P=0.001) and controls (P=0.001), respectively. Variance between BPH and controls is also not significant. The mean (±SD) of the fPSA/tPSA ratio of BPH (P= 0.001) is also seen in the same table and the controls (P=0.003) is slightly higher than the Pca ratio with no other significant difference.

Table (1): Mean (±SD) values of the measured serum Biomarkers (TPSA, FPSA, FPSA/TPSA ratio, TK1) of studied groups.

Parameters	BPH (n=55)	Control (n=45)	Pca (n=55)
tPSA (ng/ml)	3.06± 0.77^{NS}	6.78±1.95	31.41±17.96•
fPSA(ng/ml)	0.89±0.44^{NS}	2.25±0.99	6.07±3.32•
fPSA/tPSA ratio	31.28±17.77^{NS}	36.01±18.8	20.96±7.12••
TK1 (pg/ml)	570.09± 150.40••••	1221.29± 122.67••••	205.96± 80.80●●●●

*ANOVA & t-test revealed ● Significant increase in Pca concentrations (tPSA, fPSA) relative to each BPH and control (for both, p=0.001),●● Significant increase in BPH and control (fPSA/tPSA ratio) levels compared with Pca, (p=0.001),●●●● Significant differences between Pca and each of the BHP and Controls (P<0.001) in TK1 levels. NS: non-significant differences in levels between BPH and controls (tPSA, fPSA, fPSA/tPSA ratio)

Table (2) In the difference between Pca and normal subjects, the cutoff value of the serum tPSA level was 4.30 ng/ml with a ROC of 1.00. The serum TK1 level was 1.00 with a cutoff value of 924 pg/ml and ROC and 100 percent sensitivity and 100 percent accuracy for such distinction. The fPSA cutoff value was 2.10 ng/ml with a ROC value of 0.94 and the fPSA/PSA ratio was 28.72 with a ROC value of 0.67. Differentiation by serum tPSA level at a cutoff value of 4.2 ng/ml and ROC of 1.00 between BPH and normal individuals. The ROC values for TK1 was a cutoff value of 924 pg/ml with a ROC of 1.00 for the differentiation between BPH and PCa. Although the fPSA ratio was 1.30 ng/ml and the ROC was 0.92 and the fPSA/tPSA ratio was 83.3 with ROC 0.43. The serum tPSA level at the cutoff value of 10.1 ng/ml has a ROC of 0.83 in the distinction between Pca and BPH. The cutoff value of the fPSA standard was 5.10 ng/ml and the ROC was 0.79.

Table 2: The receiver operator curve (ROC) for (TPSA, FPSA, FPSA/TPSA ratio, TK1) in studied groups

Marker	Diagnostic criteria	Pca vs Control	Pca vs BPH	BPH vs Control
TPSA (ng/ml)	SE	98%	71%	100%
	SP	98%	100%	96%
	PPV	98%	100%	98%
	NPV	98%	77%	100%
	Cut Point	4.30	10.1	4.20
	AUC	1.00	0.85	1.00
FPSA (ng/ml)				
	SE	78%	65%	87%
	SP	100%	100%	80%
	PPV	100%	100%	84%
	NPV	79%	74%	84%
	Cut point	2.10	5.10	1.30
	AUC	0.94	0.79	0.92
FPSA/TPSA ratio	SE	89%	89%	100%
	SP	49%	62%	2%
	PPV	68%	70%	56%
	NPV	79%	85%	100%
	Cut point	28.72	28.72	83.3
	AUC	0.67	0.75	0.43
	SE	100%	100%	100%
	SP	100%	98%	100%
	PPV	100%	98%	100%
	NPV	100%	100%	100%
	Cut point	924	924	412
	AUC	1.00	1.00	1.00

In the gray zone, tPSA was 69 patients (4-10 ng/ml). Fifty-three (73 percent) of them were with PBH and 16 (22 percent) were with PCa, indicating that those with BHT are the largest patients with tPSA gray zone. In PBH and PCa patients in Gray Zone, Table (3) indicates the mean value (±SD) of tPSA, fPSA,fPSA/tPSA, and TK1. The mean value of serum tPSA between Pca and BPH was not substantially different. In Pca, the mean value of serum fPSA in comparison with BPH was significantly lower (P=0.01). The mean FPSA/TPSA ratio value was also considerably lower at Pca than at the BPH stage (P=0.01). In Pca patients, the mean value of serum TK1 was slightly higher than in BPH patients (P<0.0001).

Table (3) Mean (±SD) values of the Age and the measured Serum Biomarker (TPSA, FPSA, FPSA/PSA ratio, TK1)

Parameter	PCa (n=16)	PBH (n=53)	P-value
tPSA (ng/ml)	6.76+1.82	6.66+1.85	0.86
fPSA (ng/ml)	1.58+0.73	2.27+1.00	0.01●
fPSA/tPSA ratio	23.11+8.45	36.73+18.59	0.01●
TK1 (pg/ml)	1078+91.85 ●●	571.30+151.66 ●●	<0.0001 ●●
Test revealed ●significant decrease of (fpsa,fpsa/tpsa ratio) levels in Pca compared to BPH (for p=0.01), ●● significant increase of (TK1) levels in Pca compared with BPH, (p=<0.0001).			

The cutoff value for fPSA/tPSA ratio was found to be 28.72 in gray zone differentiation between BPH-Paca patients and 0.73 for tPSA. The low ROC values of 0.51 and 0.71 were achieved by both tPSA and fPSA at cutoff values 7.6 NG/ml and fPSA at cutoff value 0.90 NG/ml; respectively The ROC was 1.00, and was the excellent biochemical marker for measured differentiations between patients with Pca and BPH with tPSA in the gray zone, Table of Disposition for Patients with TK1 in gray zone at cutoff value 924pg/ml , Table (4)

Table (4):The receiver operator curve (ROC) for (TPSA, FPSA, FPSA/TPSA ratio and TK1) between Pca and BPH groups.

Marker	AUE	Cut-point	SE%	SP%	PPV%	NPV%
TPSA (ng/ml)	0.51	7.6	44%	67%	26%	79%
FPSA (ng/ml)	0.70	0.90	38%	92%	60%	83%
FPSA/TPSA ratio	0.73	28.72	88%	64%	42%	94%
TK1 (Pg/ml)	1.00	924	100%	100%	94%	100%

Discussion

The findings of this study showed that tPSA and Pca volues in Pca were substantially higher in average values than patients with BPH and stable controls (Table 1) [1; 9;10]. Furthermore, the present research finding that the mean fPSA/tPSA ratio in Pca patients has been considerably reduced to those of BPH that is consistent in the fPSA/tPSA ratio [11,12] finds that fPSA/tPSA is significantly lower in Pca than in BPH.

The current study has shown that the best cutoff of tPSA was 10.1 ng/ml for the differentiation of Pca from BPH patients, with 100%, 71% for sensitivity, and AUC 0,85, with 98% for specificity 4,30 ng/ml for Pca and for healthy individuals. In patients with BPH and healthy persons, the optimal cut for tPSA was 4.20 ng/mL with AUC=1.00, respectively (table 2), indicating that tPSA level of 4.25 ng/ml is useful in discriminating prostate diseases from healthy individuals. Razzaghi et al. observed in the evaluation of Cancer of the Prostate Strategic Urologic Research (CAPSURE) cohort in the United States that median of tPSA at diagnosis in the higher screened Swedish counties was 10.80 ng/ml [13]. Erdogan et al. found that PCa was diagnosed in 35.1% of their patients and clinically significant variations in f/t PSA were found in patients with and without PCa [14].

The current study bought a significant increase in the mean value of TK1 serum levels in the Pca group relative to the BPH group and healthy controls and in the BPH patients compared to experiments that had previous studies agreed to (15;6). The results showed that the serum TK1 evaluation was an excellent biochemical marker for differentiating Pca patients from BPH patients and healthy individuals with a cut-off of 924 pg/ml (AUC= 1.00). Serum TK1 is also outstanding for differentiating BPH from healthy controls at 412 pg/ml (AUC =1) (table 2).

TK 1 levels are high in all prostate cancer patients and even higher in patients with severe prostate cancer [16]. It is indicated that serum TK1 can be used in the screening of BPH or PC patients and that tPSA is a less reliable prostate screening method compared to STK1 [15].

The gray zone The Bewildering outcome is characterized by serum tPSA level between 4-10 ng/ml; whether BPH or PCa is the condition, resulting in unnecessary prostate biopsies. Out of a total of 235 patients with tPSA level, Psa2 Liu et al. found that the results of the gray zone biopsy were negative for 179 (76.2%) patients (non-PCa group) and positive for 56 (23.8%) patients (PCa group) [14]. The result found that the serum TK1 level at a cutoff value of 924 pg/ml (AUC=1, Table 4) was the most sensitive and specific biochemical marker for differentiating between PCa and BPH patients with gray-zone tPSA. However, the tPSA, fPSA, fPSA/tPSA ratio serum measurements were poor biochemical markers for differentiating prostatic origin in the gray zone (table 3). It was concluded that serum TK1 concentrations in patients with BPH and PCa were considerably higher relative to healthy people, suggesting that the serum TK1 concentration could be used to monitor for prostate complications. The individual serum TK1 values between BPH patients and PCa patients, it can be impractical to differentiate between these two categories by measuring STK1 concentration alone. BPH patients with elevated STK1 concentrations are expected to have an increased chance of progression of malignancy [15]. Hanousková et al. observed that TK-1 serum levels were dramatically elevated in prostate cancer patients relative to healthy individuals and concluded that the determination of TK-1 serum concentration may be a valuable measure also for prostate cancer risk screening in individuals [16]. TPSA levels above 4 ng/mL and below 10 ng/mL have a ~25 percent risk of PCa occurrence, according to the American Cancer Society, and tPSA levels above 10 ng/mL increase the probability of PCa occurrence by more than 50 percent [17].

Conclusion

In the diagnosis of prostate tumor and differentiating between BPH and PCa, the serum level of TK1 was superior to tPSA, particularly when tPSA was present in the gray zone, which could prevent the need for invasive

prostatic biopsy in such a distinction.

Conflict of Interest: None

Funding: Self

Ethical Clearance: Not required

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