The Role of Complex PSA in the Prediction of Prostatic Cancer
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Abstract

Aim of Work: Is to improve diagnostic accuracy of cancer prostate by studying CPSA and other routine diagnostic parameters to obtain a predictive index useful in the post-screening clinical practice.

Subject and Methods: The study included 41 individuals, 26 patients and 15 normal controls matching age and sex. They were divided based on TPSA concentration in serum into: 15 control with TPSA <4.00ng/ml with mean ± S.E. 2.28 ± 0.28, 26 patients with TPSA >4.00ng/ml who were divided into two groups: Group 1: 11 patients with TPSA range 4.0-10.0ng/ml with mean±S.E. 6.37±0.66 and Group 2: 15 patients with TPSA >10.0ng/ml with mean±S.E. 19.38±1.58. Laboratory investigations included the determination of TPSA, FPSA, CPSA, serum Glucose, liver and kidney function tests, serum urea and lipids profile.

Results: Age, weight and BMI were higher in patients than controls. The fasting blood glucose, urea, creatinine, cholesterol, LDL-C and T.G level were significantly higher compared to control group. The levels of TPSA, FPSA and CPSA in group 1 and 2 were significantly higher compared to control group (p<0.05). While the % FPSA level in group 1 and 2 was significantly lower compared to control group (p<0.05). There was a powerful statistically significant correlation between TPSA, FPSA and CPSA. While there was a negative correlation between TPSA and % FPSA Ratio.

Conclusion: The CPSA should be used as a surrogate marker to increase the detection rate of cancer prostate and to reduce unnecessary biopsies as it is an economic test with less chance of errors in diagnosis. Further studies on wide scales are needed to detect if the specificity and sensitivity of CPSA are better than % FPSA in the diagnosis of PCa.

Key Words: Complex PSA – Prostatic cancer – Total PSA – Free PSA.

Introduction

PROSTATE cancer (PCa) is the most prevalent malignancy in men. One in 6 men has a lifetime risk of a PCa diagnosis and a 3.4% chance of death due to PCa [1]. Prostate-specific antigen (PSA) has evolved as a useful marker for assessing the risk of future PCa. Prostate-specific antigen (PSA) has been shown to be the single most significant predictive factor for identifying men at increased risk of developing PCa [2,3]. The TPSA test has been recommended by the American Cancer Society for the early detection of prostate cancer in combination with digital rectal examination (DRE) annually, starting at age 50 years, for men who have a life expectancy of at least ten years. When TPSA levels and/or DRE results are abnormal, prostate biopsy may be performed and used to diagnose cancer [4]. Selective use of PSA screening for men in good health appears to reduce the risk of prostate cancer-specific mortality (PCSM) [5,6].

It has been established that measurement of PSA enables earlier diagnosis, and indeed this might be one of the factors associated with the decrease in prostate cancer mortality. The greatest problem with total PSA assay is the lack of specificity. This lack of specificity compels large numbers of men with elevated PSA levels to undergo biopsy (with its significant economic and psychological cost) [7]. There was a statistically significant advantage for CPSA compared to total PSA in the discrimination between BPH and PCa [8]. α 1 ACT-complexed PSA is more accurate than FPSA to discriminate BPH from PCa in the total PSA range 2.0-10.0ng/ml; also α 1 ACT-complexed PSA is a better option than the FPSA percent. It has been suggested that measurement of CPSA (to ACT) in sera as a single blood test has similar validity for identifying men with PCa as measurement of PSA and FPSA [9]. The amount of CPSA is estimated by measuring the F/TPSA ratio. The F/TPSA ratio provides essentially the same information as that gleaned by measurement of CPSA, but the latter requires only a single analyst determination [10].

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Numerous efforts have been made to improve the effectiveness of diagnosis of early prostate cancer. The use of F/TPSA ratio has become common in an effort to improve the specificity of this test. The use of complex-PSA is a more specific marker for prostate cancer detection. It was found that the single test for CPSA provides statistically significant improvement in specificity by 7.4% as compared with the F/TPSA ratio [11].

The use of CPSA or F/TPSA when the TPSA ranged from 2.0 to 10.0ng/ml might reduce the number of unnecessary biopsies while maintaining a high detection rate [12]. Hence complex-PSA is a very valuable protein marker in human blood for the diagnosis of PCa and differentiating it from BPH. Further efforts to improve the diagnostic performance of TPSA reported that CPSA as a single test improves the specificity and may be preferable over TPSA and FPSA [13].

PSA-ACT was more specific than the % of FPSA and achieved a cancer detection rate of 23.3% on 6-10 core biopsies [14]. Patients with CPSA between 2.0-4.0ng/ml, nearly two-thirds had prostate cancer with Gleason score ≤ 6. The CPSA was highly predictive of the presence of poorly-differentiated prostate cancer [18]. The aim of the study was to improve diagnostic accuracy of cancer prostate by studying CPSA and other routine diagnostic parameters to obtain a predictive index useful in the post-screening clinical practice.

Subjects and Methods

This study was carried out on 41 individuals, 26 patients and 15 normal controls matching age and sex. They were recruited from the Department of Urology in El-Sahel Teaching Hospital during the period from 2012–2014. Meticulous clinical examination was done for all individuals and accordingly they were divided based on TPSA concentration in serum into:

1- 15 individuals as control with TPSA <4.00ng/ml with mean±S.E. 2.28±0.28 their age ranged from 47.00-85.00 years with mean±S.E. 67.67±2.69.

2- 26 patients with TPSA >4.00ng/ml and they were divided into two groups:

   Group 1: 11 patients with TPSA range 4.0-10.0ng/ml with mean±S.E. 6.37±0.66 their age ranged from 60.0-75.0 years with mean±S.E. 69.00±1.70.

   Group 2: 15 patients with TPSA >10.0ng/ml with mean±S.E. 19.38±1.58 their age ranged from 56.0-85.0 years with mean±S.E. 71.40±2.37.

All individuals were subjected to the following:

a- Complete urologic history with a special detailed history of obstructive urinary tract symptoms including: Hesitancy, weak or interrupted stream, post micturation dribbling, sense of incomplete evacuation or urinary retention, hematurea, perineal pain, irritative lower urinary tract symptoms including (frequency, urgency).

b- Laboratory investigations included:

Determination of TPSA:

The total PSA assay is based on microparticle enzyme immunoassay (MEIA) technology according to the method described by Kuriyama et al., [16].

Determination of FPSA:

The free PSA assay is based on microparticle enzyme immunoassay (MEIA) technology according to the method described by Kuriyama et al., [16].

Determination of CPSA:

CPSA assay is based on Chemiluminometric technology.

Determination of serum glucose:

Serum Glucose activity was determined by an enzymatic colorimetric-test (GOD-PAP) by Trinder.

Liver function tests:

   - Determination of serum alanine–Aminotransferase ALT/GPTactivity by a kinetic method according to Babb [18].

Kidney function tests:

   - Determination of serum creatinine activity by a colorimetric method according to Stevens and Levey [19].
   - Determination of serum Urea activity was determined by an enzymatic colorimetric method according to Kaplan et al., [20].

Lipids profile:

1- Cholesterol activity was determined by Allain et al., [21].

2- HDL Cholesterol (HDL-C)activity was determined by Grove [22].

3- Triglyceride activity was determined photometrically by Klotsch SG and McNamara JR [23].

4- Determination of LDL cholesterol (LDL-C).
Results

Table (1): Showed the mean age was significantly higher in group 1 & 2 compared to control group (p<0.05). The mean weight was significantly higher compared to control group (p<0.05). The mean height was significantly lower compared to control group (p<0.05). The mean BMI was significantly higher compared to control group (p<0.05).

Table (2): Showed the mean fasting blood glucose was significantly higher compared to control group (p<0.05). The mean SGPT was significantly lower compared to group 1 (p<0.05) while in SGOT there was no significant difference between the studied groups. The mean level of urea, creatinine, cholesterol, LDL-C and T.G level were significantly higher compared to control group (p<0.05). The mean BMI was significantly higher in group 1 & 2 compared to control group (p<0.05). The mean SGPT was significantly lower compared to group 1 (p<0.05) while in SGOT p<0.05).

Table (3): The mean levels of TPSA, FPSA and CPSA in group 1 and 2 were significantly higher compared to control group (p<0.05). While the % FPSA level in group 1 and 2 was significantly lower compared to control group (p<0.05).

Table (3): Diagnostic markers of prostate cancer among studied groups.

Means was not significant (p>0.05).
* : Show significant difference compared to control (p<0.05).
** : Show significant difference compared to group 1 (p<0.05).

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPSA (ng/ml)</td>
<td>2.28±0.28</td>
<td>6.37±0.66*</td>
<td>19.38±1.58*,**</td>
</tr>
<tr>
<td>FPSA (ng/ml)</td>
<td>0.42±0.06</td>
<td>1.25±0.19*</td>
<td>3.07±0.27*,**</td>
</tr>
<tr>
<td>% FPSA</td>
<td>19.15±1.79</td>
<td>20.06±2.46</td>
<td>15.79±0.69*,**</td>
</tr>
<tr>
<td>CPSA (ng/ml)</td>
<td>1.68±0.20</td>
<td>4.82±0.55*</td>
<td>15.65±1.25*,**</td>
</tr>
</tbody>
</table>

Means was not significant (p>0.05).
* : Significant difference compared to group 1 (p<0.05).
** : Significant difference compared to group 1 (p<0.05).

* : Significant difference compared to controls (p<0.05).
** : Significant difference compared to controls (p<0.05).
**Discussion**

Prostate cancer (PC) is the sixth most common cause of cancer death worldwide and represents the most common solid tumor affecting men, its early detection remains the best approach to improve survival rates. The prognosis for patients with prostate cancer varies greatly and is highly dependent on a number of factors, including age [24]. Age is one of the major risk factors, the results of the present study showed that age was not significant in group 1 compared to control group ($p>0.05$) but it was significantly higher in group 2 compared to control group ($p<0.05$). There was a correlation between age and TPSA ($p>0.05$) Table (5). This coincides with the findings of Liu et al., [25] who concluded that serum PSA levels increased with age. Danni et al., [4] described the rationale of age-specific reference ranges for PSA as the prostate increases in size with age and younger men have lower normal PSA levels than older men. Also this agrees with Schroder who emphasized that the incidence of cancer prostate increases around 15 times in men 65 years or older and it is advised that men undergo TPSA testing starting at 50 years of age and prostate biopsy is recommended if TPSA is higher than 2-4ng/ml of TPSA [26].
The present study showed that the weight was significantly higher both in group 1 and in group 2 compared to control group \((p<0.05)\). Regarding height the results showed that there are no significant differences in group 1 compared to control group \((p>0.05)\) while in group 2 the height was significantly lower compared to control group \((p<0.05)\). The present study showed that BMI was not significant in group 1 compared to control group \((p>0.05)\) but it was significantly higher in group 2 compared to control group \((p<0.05)\). And there was a correlation between TPSA and BMI \((p>0.05)\).

DeNunzio et al., \[27\] elucidated that obesity as measured by BMI, is related to higher mortality among PCa patients and that there may be a positive relationship between BMI and disease stage. On the contrary, Liu et al., \[25\] identified a negative correlation between PSA and BMI mainly due to plasma hemodilution.

The results showed that fasting blood glucose was significantly higher both in group 1 and group 2 compared to control group \((p<0.05)\). There was a also a non significance correlation between fasting blood glucose and TPSA \((p>0.05)\) Table (6). Similarly, Jeon et al., \[28\] observed that the PCa group presented higher levels of blood glucose than the control group. On the contrary, Eun et al., \[29\] reported that fasting plasma glucose was inversely correlated with serum PSA. Moreover Fukui et al., \[30\] and Kevin et al., \[31\] demonstrated that diabetics have a lower risk of prostate cancer than do non diabetics.

In our study SGPT and SGOT were significantly higher in group 1 compared to control group \((p<0.05)\) while was not significant in group 2 compared to control group and group 1 \((p>0.05)\) Table (3). Furthermore, there was a very weak negative correlation between TPSA, SGOT and SGPT \((p>0.05)\) Table (6).

This result is in accordance with Liu et al., \[25\] who stated that BMI, SGPT, HDL and fasting blood sugar were negatively correlated with serum PSA level. This may be due to the significant role of the liver in eliminating serum PSA.

The results showed that creatinine was significantly higher in group 1 and group 2 compared to control \((<0.05)\). Urea was not significant higher in group 1 compared to control group \((p>0.05)\) while in group 2 the mean of urea is significant compared to control group \((p<0.05)\) Table (3).

The present study showed significant correlation between TPSA and creatinine and urea \((p<0.05)\) Table (6). This may be due to the elimination of the FPSA by glomerular filtration through the kidneys \[32\].

The results showed that cholesterol was significant higher in group 1 and in group 2 compared to control group \((p<0.05)\). There was a non significance correlation between cholesterol and TPSA \((p>0.05)\). This result is in accordance with Platz et al., who concluded that men with low cholesterol <200mg/dl had a lower risk of Gleason 8 to 10 prostate cancer than men with high cholesterol \[33\]. On the contrary Liuet al., \[28\] and Prabhat et al., \[34\] delineated that there was no relation between high Gleason score and cholesterol and LDL-C levels.

The results showed that LDL-C was significantly higher in group 1 and in group 2 compared to control group \((p<0.05)\) Table (3). Also, there was a non significance correlation between LDL-C and TPSA \((p>0.05)\) Table (6). This agrees with the findings of Cyrus-David et al., \[35\] who reported that PSA declined by an average of 42% over 5 years among 15 healthy men starting statins. The PSA decline after starting statins was statistically significantly associated with the decline in Low-density lipoprotein (LDL)-cholesterol concentrations. In contrast, Prabhat et al., \[34\] documented no relation was found with high Gleason score and cholesterol and LDL-C levels.

In our study the HDL-C was significantly lower in group 1 and group 2 compared to control group and in group 2 compared to group 1 \((p<0.05)\) Table (3). There was a significant negative correlation between HDL-C and TPSA \((p<0.05)\) Table (6). Similarly, Prabhat et al., \[34\] described that there was a negative correlation between PSA and HDL-C. On the contrary Liu et al., \[25\] determined no relationship could be found between PSA and serum cholesterol or high-density lipoprotein.

The results showed that T.G was significant higher in group 1 and group 2 compared to control group and in group 2 compared to group 1 \((p<0.05)\) Table (3). There was a significant correlation between T.G and TPSA \((p<0.05)\) Table (6). Prabhat et al., \[34\] and Alokiel et al., \[36\] reports that serum T.G was significantly associated with circulating TPSA levels. On the contrary Liu et al., \[25\] suggested that negative correlations existed between PSA and T.G level.

TPSA is the most widely used serum biomarker for early detection and monitoring of PCa \[37\].
TPSA in our study was significantly higher in group 1 compared to control group while TPSA was highly significant in group 2 compared to control group and to group 1 \( (p<0.05) \) Table (4). These results are consistent with Strope and Andriole \[38\] who found that PSA is useful in the early detection, clinical staging and post-treatment monitoring of prostate cancer.

Sturgeon et al., \[39\] reported that when the TPSA is greater than 10.0ng/ml, 40-50% of patients have cancer and biopsy is typically performed. When the TPSA level is in the 4.0-10.0ng/ml range, however, only 25-35% of patients have cancer based on biopsy. Thompson et al., suggested that TPSA levels in serum have been classified into three categories: 0.0-4.0ng/ml, 4.0-10.0ng/ml, and >10.0ng/ml \[40\]. The risk of prostate cancer and the necessity of a biopsy are assessed based on these categories. When the TPSA level is less than 4.0ng/ml, the risk of cancer is considered to be low, and these results are in agreement with our results. On the contrary Stephan et al., \[32\] found that men with PSA 1.01-2.0ng/ml had a 2.5-fold increased risk of PCa compared to men with PSA= 0.5ng/ml, corresponding to a long-term risk close to the population mean. PSA levels between 2.1-3.0ng/ml were associated with a 19-fold increased risk of cancer.

Moreover Stephan et al., \[32\] emphasized that within the range 4.0-10.0ng/ml PSA (gray zone), PSA alone cannot distinguish between PCa and BPH, because only 25-30% of men with this PSA concentration who undergo biopsy do have cancer. In addition, PSA values <4.0ng/ml do not indicate the absence of PCa, because 20-30% of patients with PCa show PSA concentrations in this low range. Similarly Thompson et al., \[40\] documented that there was no PSA level below which prostate cancer can be ruled out, and no level above which prostate cancer is certain and the cancer incidence in patients with PSA levels above 2.0ng/ml differed only slightly from those with PSA between 4.0 and 10.0ng/ml.

The results showed that FPSA was significantly in group 1 compared to control group and highly significant in group 2 compared to control group. Moreover, % FPSA was not significant in group 1 compared to control group \( p>0.05 \) while significant in group 2 compared to control group. Danni et al., published that % FPSA is recommended for the risk assessment of prostate cancer when TPSA concentrations are between 4-10ng/ml. A % FPSA of >25% indicates a low risk of cancer (e.g. probability=8%) where as a % FPSA of <10% suggests a high risk (e.g. probability=56%) \[4\].

This result is in accordance with Laila et al., \[41\] who detected that % FPSA is lower in men with prostate cancer than in men with benign disorders. Therefore, % FPSA enhances discrimination of prostate cancer, and it is frequently used to enhance the diagnostic efficacy of PSA for early detection of prostate cancer in men with moderately elevated TPSA.

Further more Alapont et al., \[42\] observed that FPSA is better to discriminate BPH and PCa than TPSA and FPSA percent should only be used in men with PSA<10.0ng/ml; the improvement in specificity obtained using total PSA >10.0ng/ml as cutoff point for biopsy. Ishidoya et al., \[43\] reported that several investigators in the USA and Europe examined the ability of the % FPSA as a screening tool against the normal population with TPSA between 4.0-10.0ng/ml or <4.0ng/ml. Southwick et al., \[44\] and Raaijmakers et al., \[45\] explained that a low % FPSA has been shown to favor the detection of aggressive cancers, and these results are in agreement with our results. On the contrary Pinsky et al., \[46\] demonstrated that among all men aged 44 to 50 years, the combination of TPSA, FPSA, % FPSA, did not improve the predictive power of PSA alone, albeit enhancements were found for men with TPSA ≥1.2ng/ml, and more notably in men with TPSA ≥2.0ng/ml.

In our study, CPSA was significantly in group 1 compared to control group while CPSA was highly significant in group 2 compared to control group and to group 1 at \( p<0.05 \). Also there was a powerful statistically significant correlation between TPSA and CPSA at \( p>0.05 \). Lucas et al., \[47\] stated that the proportion of PSA that is complexed to ACT (CPSA) is higher and the percentage of FPSA is correspondingly lower in patients with prostate cancer.

This result is in accordance with Roddam et al., \[12\] who said that % FPSA <15 and rising levels of CPSA were associated with an increasing rate of poorly-differentiated cancers and in patients with CPSA between 2.0 and 4.0ng/ml, nearly two-thirds had prostate cancer with Gleason score <6. Saika et al., \[48\] found that significant differences: Setting sensitivity in 90%, specificity was 10.8% for total PSA and 31.7% for PSA: \( \alpha \_1 \) ACT. The use of CPSA when the TPSA ranged from 2.0 to 10.0ng/ml seems to be a reliable tool to improve specificity at high sensitivity levels in men with suspected prostate cancer as it might reduce the number of unnecessary biopsies while maintaining a high detection rate.
Conclusion:

The CPSA should be used as a surrogate marker to increase the detection rate of cancer prostate and to reduce unnecessary biopsies as it is an economic test with less chance of errors in diagnosis. Further studies on wide scales are needed to detect if the specificity and sensitivity of CPSA are better than % FPSA in the diagnosis of PCA.

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