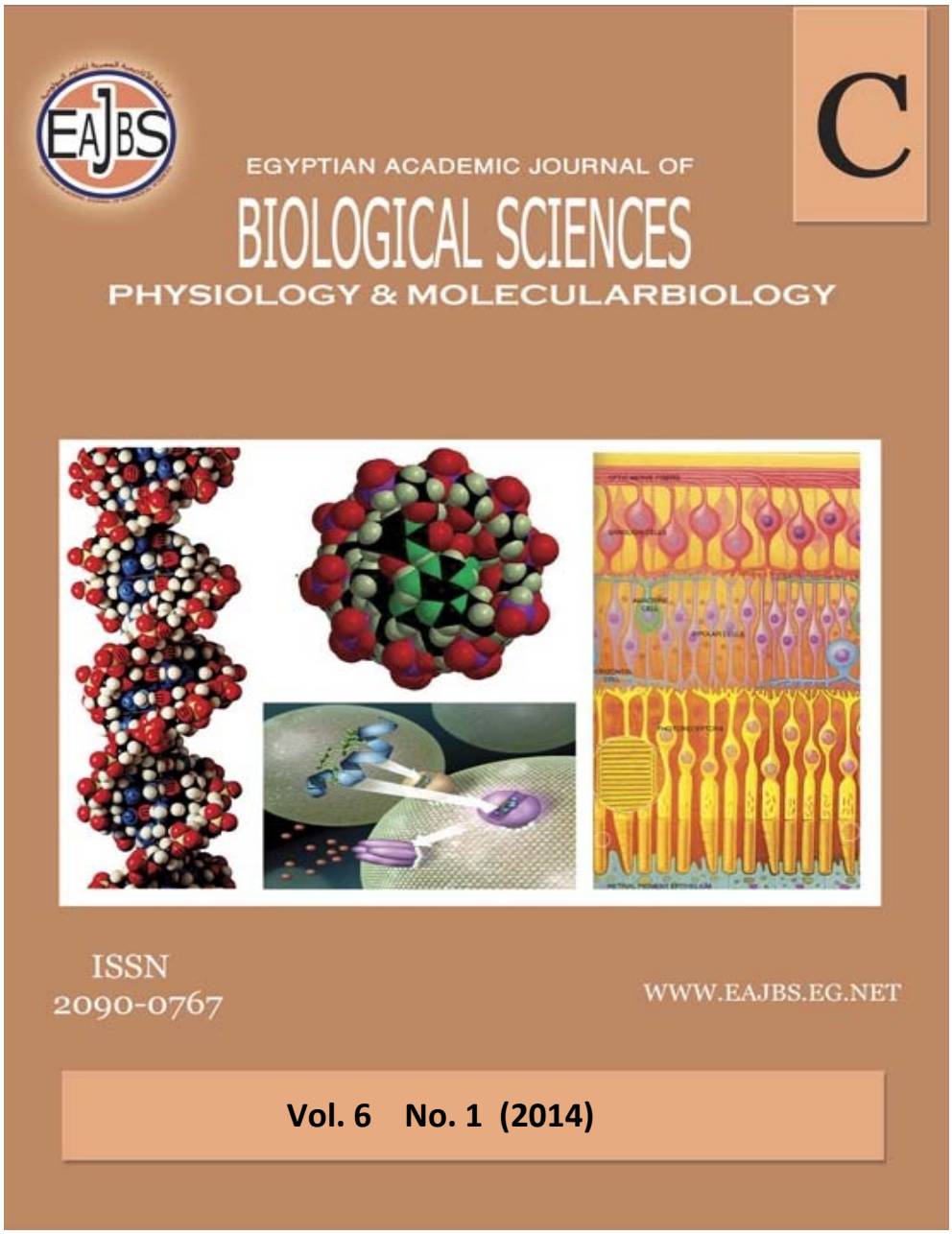

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Use of Free to Total Prostate-Specific Antigen Ratio to Improve Differentiation of Prostate Cancer from Benign Prostate Hyperplasia

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ABSTRACT

Objectives: The aim of this study is to evaluate the use of F/TPSA ratio to improve differentiation of Prostate Cancer from Benign Prostatic Hyperplasia in Sudanese patients in Khartoum state.

Methods: A prospective, analytical, hospital based, Case control study. This study was carried out in Fedail Medical Hospital during the period of 2010 to 2012. This study was performed on 200 patients as study group and 100 healthy volunteer as control group. Serum levels of TPSA and FPSA were measured by Roche immunoassay e411.

Results:

Detection rate of PCa for serum TPSA level 4- 10 ng/ml and serum TPSA level of 10 to 20 ng/ml was (32%) and (54%), respectively. Mean F/TPSA ratio value was significantly lower in PCa patients (16 ± 9ng/ml) than in BPH group (30±7g/ml). Among patients with serum PSA level of 4 to 10 ng/ml (n = 93), mean F/TPSA ratio in BPH group (n =63) was (32 ± 5) and in PCa group (n = 30) was (14 ±5) (P <0.001). For serum PSA level of 10-20 ng/ml (n = 43), mean F/TPSA ratio in BPH group (n = 18) was (25 ±7) and in PCa group (n = 25) was (16 ± 9) (P <0 .001).

Conclusion: Determination of F/TPSA ratio improves differentiation of PCa from BPH. This study recommends a cut-off value of 18% to be applied to Sudanese patients.

INTRODUCTION

Prostate cancer is the second leading cause of cancer-related deaths for men in the United States (Jemal *et al*. 2007), and the first genitourinary tract cancer (Al-Samawi and Aulaqi 2013). It has been suggested that screening for prostate cancer may have reduced its mortality rates, but this remains controversial (Hoffman 2006). Current American Cancer Society guidelines for prostate cancer screening recommend a digital rectal examination and prostate-specific antigen (PSA) measurement annually for all men 50 or older if they have a minimum life expectancy of 10 years (Smith *et al*. 2004).

Prostate Specific Antigen (PSA) is a protein manufactured solely in the prostate. The prostate glands manufacture this protein in large quantities. The PSA level in the blood can vary by about 20% from day to day (Sölétormos *et al*. 2005). The Food and Drug Administration (FDA) in 1994, approved serum PSA to be used as an early detection of prostate cancer. Like so many serum tumor markers, it is produced by both normal and cancerous glands. In men with prostate cancer, the serum levels can be elevated in both localized and advanced or disseminated disease. PSA levels are generally proportional to the size of the tumor. However, there is a significant overlap between PSA levels found in cancer and benign prostatic hyperplasia (BPH) cases (Carter *et al*. 1997). PSA exists in multiple isoforms. Although there are many complexes forms that circulate in low concentrations in blood, the 2 principal forms that are measured by current methods are PSA complexed with α1-antichymotrypsin (complexed PSA) and uncomplexed, or free, PSA (FPSA). The introduction of free PSA (FPSA) testing has introduced a greater level of specificity in identifying early prostate cancer (Catalona *et al*. 2000, American Urological Association). In 1998, the FDA approved FPSA testing as a diagnostic aid for men with total PSA (TPSA) values between 4-10 ng/ml. In men without prostatic cancer, the ratio of FPSA / TPSA is more than 25%. A ratio of less than 25% is found in men with prostatic adenocarcinoma (Lilja and Stenman 1996).

Many patients with PSA concentrations greater than10 ng/ml have advanced disease. Although the medical decision points for percentage of FPSA are also equally controversial, it is generally accepted that measuring FPSA and calculating the percentage FPSA aids in distinguishing cancer from other benign prostate conditions such as benign prostate hyperplasia, particularly for the population in the diagnostic gray zone (Smith *et al*. 2004, Tanguay and Begin 2002, Gann *et al*. 2002). The lower the FPSA/TPSA ratio, the greater the likelihood of cancer (Tanguay and Begin 2002).

METHODS

The laboratory results of 200 patients (100 of them diagnosed with PCa and another hundred diagnosed with BPH) in the period of December 2010 to March 2012, were included in the study. A Biopsy was used to detect the presence of cancer cells in the prostate. PCa patients were stratified according to their Gleason scores to:

a) Well differentiated group included scores (2/10, 3/10, 4/10).
b) Moderate differentiated group included scores (5/10, 6/10, 7/10).
c) Poor differentiated group included scores (8/10, 9/10, 10/10).

TPSA was measured for all these patients using the Roche immunoassay e411. Ninety-three patients' TPSA was in the range of 4-10 ng/ml. with the mean age of 66±9 years. Thereafter, serum FPSA and TPSA were measured; the Free to total PSA ratio was calculated from dividing FPSA by TPSA and multiply by100. Receiver Operating Characteristics (ROC) curves were generated for TPSA, and F/TPSA. P value < 0.050 was considered statistically significant.

RESULTS

Serum TPSA (6±2ng/ml) in the PCa group was higher than that (6±1ng/ml) in BPH group but no significance was achieved ($p>0.050$). F/TPSA ratio in the PCa group was significantly lower than that of BPH group (14±5 vs 32±6; P <0 .001) when the TPSA range 4-10ng/ml (Table 1) while in the TPSA range 10-20 ng/ml serum TPSA (14±3ng/ml) was higher than that (13±3ng/ml) in BPH group but no significance was achieved ($p>0.050$). F/TPSA ratio in the PCa group was significantly lower than that of BPH group (16±9 vs 25±7; P <0 .001) (Table 2).

Table 1: Comparison between the mean of TPSA, FPSA and F/TPSA in the study groups within the range 4-10ng/ml.

Parameter	PCa (30) mean±SD	BPH (63) mean±SD	P value
TPSA (ng/ml)	6±2	6 ±1	0.650
FPSA (ng/ml)	1± 0	2±1	0.000
F/TPSA (%)	14±5	32±6	0.000

Table 2: Comparison between the mean of TPSA, FPSA and F/TPSA in the study groups within the range10-20 ng/ml.

Parameter	PCa (25) mean±SD	BPH (18) mean±SD	P value
TPSA (ng/ml)	14±3	13±3	0.290
FPSA (ng/ml)	2±1	3±1	0.009
F/TPSA (%)	16±9	25±7	0.000

The detection rate of prostate cancer was 32% for TPSA value within range of 4-10ng/ml, and cancer detection rate of 58% for TPSA in the range of 10-20 ng/ml. In this study, the sensitivity and specificity for TPSA was (95% and 96%) respectively; the positive predictive value was (0.960) and the negative predictive value was (0.950).

In Figure1 the ROC curves according to the range of TPSA 4-10ng/ml are analyzed. In men with TPSA between 4-10ng/ml, the AUC for F/T PSA was significantly higher than that for TPSA (0.204 vs 0.330, P <0 .001). In men whose values of TPSA were in the range of 10-20ng/ml (Fig 2), the AUC for F/T PSA was significantly higher than that for TPSA (0.337 vs 0.381, p<0.050). Overall F/TPSA cut-off of (18%) produced sensitivity of 98% and specificity of 99% within the TPSA range of 4-10 ng/ml.

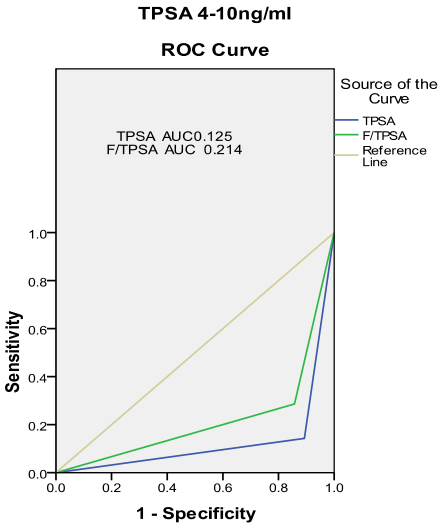

Fig. 1: The ROC curves that analyze the efficacy of TPSA and F/T PSA ratio when the range of TPSA 4-10 ng/ml

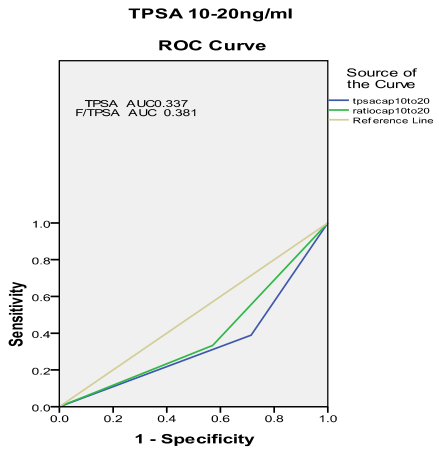

Fig. 2: The ROC curves that analyze the efficacy of TPSA and F/TPSA ratio when the range of TPSA 10-20 ng/ml.

DISCUSSION

PSA was the preferred serum marker for PCa (Osterling 1991). It is also found in abnormal concentrations in normal and benign changes of the prostate such as BPH and other non-neoplastic prostatic lesions (Chan *et al*. 2006). The clinically applicable reference values of TPSA are from 0-4.0ng/ml, but even within the "normal" range of PSA there is also the risk of cancer

albeit at a smaller rate of 2%. Intermediate values, i.e., value from 4.0-10.0ng/ml could be seen in patients with BPH, prostatitis, PIN and PCa (Osterling 1991, Zivkovic 1998). In our study there were no significant variations in means of the TPSA among PCa and BPH in the two ranges, i.e, 4-10 and 10–20 ng/ml.

It is widely accepted that in patients with elevated serum TPSA concentration, patients with PCa tend to have lower F/TPSA ratio values than patient with benign prostate disease. This study supports this theory, showing that F/TPSA was significantly lower in prostatic carcinoma group than benign prostatic hyperplasia group. Even, when patients were subdivided into groups with serum PSA levels of 4-10 and 10-20 ng/ml, the mean of F/TPSA ratio showed statistically significant differences ($p<0.010$). Current study results showed that regardless of TPSA, the mean of F/TPSA ratio is a useful diagnostic modality for detecting PCa in the gray zone. F/TPSA ratio, as first shown by Stenman and colleagues (Stenman *et al*. 1991), and Christensson and associates (Christensson *et al*. 1993), can more efficiently distinguish subjects with BPH from those with cancer than serum TPSA levels alone(Catalona *et al*. 1993).

Some researchers suggested that the measurement of F/TPSA ratio can increase the specificity of PSA testing and may be useful in the differentiation of PCa from benign diseases, especially when TPSA is <10 ng/ml(Martinez *et al*. 2000, Partin *et al*. 1996). However, in the present study, it was found that PCa detection rates were only 32.2% and 54.3% when TPSA was in the ranges of 4.0-10.0 ng/ml and 10.0-20.0 ng/ml, respectively. Therefore, it is necessary to explore the diagnosis efficacy of PCa using of F/TPSA ratio with TPSA levels in the range of 4.0-20.0 ng/ml. This is consistent with the results reported by Morote, *et al* (Morote *et al*. 2002).

In this study as Figure1&2 shows, the ROC curves according to the ranges of TPSA were analyzed. In patients with serum levels of TPSA between 4-10 ng/ml, the AUC for F/TPSA ratio was higher than that for serum TPSA (0.214 vs 0.125). In patients whose values of TPSA was in the range of 10-20 ng/ml, the AUC for F/TPSA ratio was nearly same as that for serum TPSA (0.381 vs 0.377). These results confirm that the use of F/TPSA ratio is essential in gray zone, while TPSA level >10 ng/ml, then further testing of F/TPSA ratio is not necessary (BARUT|UOĞLU *et al*. 2009). A cutoff of 25% or less free PSA is recommended for patients with PSA values between 4 and 10ng/mL and a palpably benign gland, regardless of patient age or prostate size (Catalona *et al* 1998). In some western countries a cut-off value between 20% and 25% for F/TPSA ratio has been recommended(Ito *et al*. 2003). However in this study, a cutoff of ≤18 F/TPSA ratio for serum TPSA 4-10 ng/ml is detected to collimate Sudanese patients to TRUS guided biopsies. Use of percent free PSA increased PSA specificity: 29% of negative biopsies would be spared while retaining 95% sensitivity (Alan *et al* 1996). %fPSA and age-specific PSA cutoffs enhanced PSA specificity for cancer detection, but %fPSA maintained significantly higher sensitivities (*et al*. 2000). At a sensitivity of 95%, the specificity was 18% in the 4–10 ng/ml tPSA range (Andrew *et al*. 005).

CONCLUSION

The use of F/TPSA ratio can improve prostate cancer detection and reduce unnecessary biopsies when TPSA is within the range of 4-10 ng/ml. However, results in this study suggest that in contrast to step wise testing, the clinicians request TPSA and F/TPSA ratio measurements simultaneously. Since these types of requests are not cost-effective, they may increase the burden of the disease.

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ARABIC SUMMARY

استخدام نسبة F/TPSA لتحسين التمايز بين سرطان البروستاتا من فرط تنسج البروستات الحميد

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الأهداف :الهدف من هذه الدراسة هو تقييم استخدام نسبة F / TPSA لتحسين التفريق بين سرطان البروستاتا من تضخم البروستاتا الحميد في المرضى السودانيين في ولاية الخرطوم.

الطرائق : أجريت هذه الدراسة في مستشفى فضيل الطبي خلال الفترة من عام 2010 الى 2012. وقد اشتملت الدراسة على 200 مريض كمجموعة دراسة و 100 من المتطوعين الأصحاء كمجموعة تحكم. تم قياس مستويات المصل TPSA و FPSA باستخدام التقنية المناعية من شركة روش E411 .

النتائج : معدل الكشف عن سرطان البروستات لمستوى TPSA في المصل 4 - 10 نانوغرام /مل و مستوى TPSA من 10إلى 20 نانوغرام /مل كان 32٪ و54٪، على التوالي . قيمة F / TPSA أقل بكثير في المرضى الذين لديهم PCA (16 ± 9ng/ml) مما كانت عليه في المجموعة BPH (30 ± 7g/ml). بين المرضى الذين لديهم مستوى PSAفى المصل من 4 إلى 10 نانوغرام /مل كانت نسبة F / TPSA في مجموعة BPH (32 ± 5) ومجموعة PCA (14 ± 5) (P <0.001). أما لمستوى PSA فى المصل من 10 - 20 نانوغرام /مل فان نسبة F / TPSA في مجموعة BPH كان (25 ± 7) وفي مجموعة PCA كان (16 ± 9) (P <0 .001)

الاستنتاج : تحديد نسبة F / TPSA يحسن التفريق بين PCA من .BPH وتوصي هذه الدراسة بقيمة قطع من 18٪ ليتم تطبيقها على المرضى السودانيين

الكلمات المفتاحية: تضخم البروستاتا الحميد نسبة F / TPSA، سرطان البروستاتا.