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ASSESSMENT OF FREE PROSTATIC SPECIFIC ANTIGEN/TOTAL PROSTATIC SPECIFIC ANTIGEN RATIO, LIPOPROTEINS, ESTRADIOL AND C – REACTIVE PROTEIN IN PROSTATIC TUMORS

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ABSTRACT

Background: Prostate tumors, especially prostate cancer have severe complications such as spreading to neighboring organs. **Objectives:** This study was performed to compare between levels of free prostatic specific antigen (fPSA)/ total prostatic specific antigen (tPSA) ratio, lipoproteins, estradiol and C-reactive protein with prostatic cancer and benign prostatic hyperplasia patients. **Materials & Methods:** This study was designed as prospective case control and it was done in Soba University hospital and Khartoum Teaching hospital in Khartoum state. It was performed on 200 men (50–65 years old); 100 healthy individuals as controls and 100 patients; 50 patients with prostate cancer and 50 with benign prostate hyperplasia who were diagnosed by biopsy and histopathology. **Results:** There was significant increase in the mean value of total PSA in PCa patients and BPH more than controls with (P-value 0.003). Free PSA also showed significant increase in PCa patients and BPH more than controls with (P-value 0.040). The ratio of free to total PSA was decreased in PCa patients (7 %), but increased in BPH (34 %) and in control (67 %) with P-value (0.000).

The mean value of serum cholesterol, triglyceride, n LDL and HDL were significantly low in PCa than BPH and control with (P-value 0.035, 0.000, 0.015 and 0.002) respectively. The mean of serum Estradiol level and CRP was increase in PCa than BPH and control with (P-value 0.025 and 0.000) respectively. **Conclusion:** Serum fPSA/tPSA ratio was less than 25% in patients with PCa. Total cholesterol, HDL and LDL were low in concentration in PCa patients than in those with BPH patients and control. Serum Estradiol levels increases in PCa patients more than in BPH patients and control. Serum CRP concentration was higher in PCa patients than in those with BPH and control.

KEYWORDS: Prostate cancer, Inflammation, Hormone, Sudanese.

INTRODUCTION

The human prostate gland is a small accessory reproductive organ weighing about 25 g in adult men. It is located inferior to the urinary bladder neck and above the urogential diaphragm.[1] The prostate gland produces a protease-rich fluid that constitutes about 30 % of the ejaculate. This secretion is transported to the urethra via prostatic ducts. It is slightly acidic (pH 6.5), serous fluid in which several major secretory products can be identified. It contains high concentration of prostatic acid phophatase (PAP) and prostate specific antigen (PSA).[2] Prostate cancer is a disease in which cancer develops in the prostate. It occurs when the cells of prostate mutate and begin to multiply out of control. These cells may spread (metastasize) from the prostate to other parts of the body, especially the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, erectile dysfunction and other symptoms.[3] Prostate cancer develops most frequently in men over fifty. This cancer can occur only in men, as the prostate is exclusively of the male reproductive tract. It is the most common type of cancer in men in the United States, where it is responsible for more male deaths than any other cancer, except lung cancer.[4] However, many men who develop prostate cancer never have symptoms, undergo no therapy, and eventually die of other causes. Many factors, including genetics and diet have been implicated in the development of prostate cancer.[5] Prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. Prostate-specific antigen testing increases cancer detection but does not decrease mortality.[6] The United States Preventive Services Task Force in 2012 recommended screening for prostate cancer by using the PSA testing, due to the risk of over-diagnosis and over-treatment with most prostate cancer remaining asymptomatic.[7] Early prostate cancer usually causes no symptoms. Sometimes, however,

prostate cancer does cause symptoms, often similar to those of diseases such as benign prostatic hyperplasia. These include frequent urination, nocturia, difficulty starting and maintaining a steady stream of urine, hematuria, and dysuria.[8] About a third of patients diagnosed with prostate cancer have one or more such symptoms, while two thirds have no symptoms.[9] The primary risk factors are obesity, age and family history. Prostate cancer is very uncommon in men younger than 45, but becomes more common with advancing age. The average age at the time of diagnosis is 70.[2] In the United States in 2005, there were an estimated 230,000 new cases of prostate cancer and 30,000 deaths due to prostate cancer.[10] Men who have first-degree family members with prostate cancer appear to have doubled the risk of getting the disease compared to men without prostate cancer in the family.[11] This risk appears to be greater for men with an affected brother than for men with an affected father. Genetic background may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variants. Men who have a first-degree relative (father or brother) with prostate cancer have twice the risk of developing prostate cancer, and those with two first-degree relatives affected have a fivefold greater risk compared with men with no family history.[12] In the United States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men.[13] In contrast, the incidence and mortality rates for Hispanic men are one third lower than for non-Hispanic whites. PSA is a protein produced by the cells of the prostate gland. PSA is present in small quantities in the serum of normal men, and is often elevated in the presence of prostate cancer and in other prostate disorders.[14] A blood test to measure PSA is the most effective test currently available for the early detection of prostate cancer. Rising levels of PSA over time are associated with both localized and metastatic prostate cancer.[15] Plasma lipids, have been reported to participate in many types of cancer and, in particular, in prostate cancer development and metastasis.[16] The effect of Estradiol (and estrogens) upon male reproduction is complex. Estradiol is produced in the Sertoli cells of the testes. There is evidence that Estradiol functions to prevent apoptosis of male sperm cells.[17] Measuring of CRP values can prove useful in determining disease progress or the effectiveness of treatments.[18] The objective of this study was performed to compare between levels of serum fPSA/tPSA ratio, Lipoproteins, Estradiol and C- reactive protein with prostatic cancer and benign prostatic hyperplasia patients.

MATERIAL AND METHODS

Case Control hospital based Study. This study was conducted in Soba University Hospital and Khartoum Teaching Hospital in Khartoum state. From January 2012 to January 2014. This study was performed on 200 men (50–65 years old); 100 healthy individuals as controls and 100 patients; 50 patients with prostatic cancer and 50 with benign prostatic hyperplasia. Fasting venous blood samples were collected into plain container after using 70% alcohol swab as antiseptic; then blood was stand for 30minutes at room temperature, then serum was separated using ordinary centrifuge (3000RPM) and then was stored at -85°C.

Total and free PSA and estradiol determined by manual Enzyme Linkage Immuno Sorbant Assay (ELISA). Total cholesterol, triglycerides, HDL and LDL were measured by fully automated chemistry analyzer (Mindray BS-200). C-reactive protein was measured using i-Chrome fluorescence immunoassay (EU Biotech Development LTD, London, UK) with a coefficient of variation (CV) intra- and inter assay of 4.2 and 7.2%, respectively, (lower (L) and upper (U) limits of detection 0.1–300 mg/L).

Statistical analysis was performed using SPSS 11.5 software (SPSS, Chicago, IL); the Results were analyzed into two ways: by using analysis of variants (One way ANOVA) between three variables as mean ± standard deviation (SD). Differences were considered significant at a *p*-value $\leq$0.05., according to the data distribution.

The original protocol was approved by the Ethics committee of Ministry of Health). All subjects were having verbal informed consents.

RESULTS

The results were expressed as (mean $\pm$ standard deviation). The (mean $\pm$ standard deviation) of total PSA level in patients with BPH (22ng/ml $\pm$ 2.1), PCa patients (809ng/ml $\pm$ 18.2) and in control (0.9ng/ml $\pm$ 0.2) and P-value was 0.003, free PSA level in BPH (7ng/ml $\pm$ 1.3), in PCa (47ng/ml $\pm$ 5.8) and in control (0.6ng/ml $\pm$ 0.1) and P-value was 0.040 and PSA ratio in BPH (34% $\pm$ 3.1), in prostate PCa (7%$\pm$ 0.7) and in control (67 %$\pm$ 5.6) and the P-value was 0.000 (Table 1).

Table 2 shows the (mean $\pm$ standard deviation) of serum cholesterol level in patients with BPH (148 mg/dl $\pm$ 4.1), PCa patients (113 mg/dl $\pm$ 2.3) and in control (120 mg/dl $\pm$ 3.6) and P-value was 0.035, Triglycerides level in BPH (121 mg/dl $\pm$ 5.3), in PCa (83 mg/dl $\pm$ 3.8)

and in controls (120 mg/dl ± 4.1) and P-value was 0.000, HDL level in BPH (61 mg/dl ± 3.5), in PCa (43 mg/dl ± 1.3) and in control (65 mg/dl ± 5.3) and P-value was 0.002 and serum LDL level in BPH (90 mg/dl ± 4.7), in PCa (58 mg/dl ± 2.8) and in control (81 mg/dl ± 0.6) and P-value was 0.015.

Table (3) shows the (mean ± standard deviation) of serum Estradiol level in BPH (135pg/ml ± 4.7), in PCa (214pg/ml ± 6.5) and in control (38pg/ml ± 1.3) and P value was 0.025 and CRP level in BPH (59 mg/ml ± 2.3), in PCa (101 mg/ml ± 5.3) and in control (1.4 mg/ml ± 0.2) and P value was 0.000.

Table 1: Comparison between means of serum total PSA, free PSA and PSA ratio in patients with PCa, BPH and control.

	Total PSA		Free PSA		PSA ratio	
	Mean (ng/ml)	SD	Mean (ng/ml)	SD	Mean %	SD
PCa	809	18.2	47	5.8	7	0.7
BPH	22	2.1	7	1.3	34	3.1
Control	0.9	0.2	0.6	0.1	67	5.6
P value	0.003		0.040		0.000	

Table 2: Comparison between means of serum cholesterol, TG, HDL and LDL in patients with PCa, BPH and control.

	Cholesterol		TG		HDL		LDL	
	Mean (mg/dl)	SD	Mean (mg/dl)	SD	Mean (mg/dl)	SD	Mean (mg/dl)	SD
PCa	113	2.3	83	3.8	43	1.3	58	2.8
BPH	148	4.1	121	5.3	61	3.5	90	4.7
Control	120	3.6	120	4.1	65	5.3	81	0.6
P value	0.035		0.000		0.002		0.015	

Table 3: Comparison between means of serum Estradiol and CRP in patients with PCa, BPH and control.

	Estradiol		CRP	
	Mean (pg/dl)	SD	Mean (mg/ml)	SD
PCa	214	6.5	101	5.3
BPH	135	4.7	59	2.3
Control	38	1.3	1.4	0.2
P value	0.025		0.000	

DISCUSSION

Data linking serum lipid/lipoproteins levels and PCa are limited. It has been noted that total cholesterol and HDL were decreased in patients with PCa compared to BPH and controls, this agrees with *Kazuhiko et al* who summarized findings from epidemiologic investigations of the relationship between HDL-C and prostate disease, low HDL-C level was observed to be a risk and prognostic factor of prostate tumor in a few epidemiologic examinations, despite the fact that the general linkage amongst HDL and prostate malignancy has not been absolutely settled.[19] In recent studies in patients with PCa and in men who died from PCa , a decrease in HDL level was found, although low in total cholesterol levels was not observed.[20] It is well known that prostate cancer metastasis to subcutaneous fat deposit is rare. But prostate cancer cells have been shown to migrate to adipocytes within bone marrow where metastases are very common.[21] Chemical analysis of the prostate cancer has shown that the prostate cancer cell takes up lipid directly as an energy source in early metastatic development.[21] A recent report by Platz *et al*. suggesting that lipids signaling effect in prostate cancer may relate strongly to cellular migration and aggressive metastatic behavior, rather than simply to local proliferation.[22] The present study observed high level of serum CRP in PCa patients compared to BPH and Controls. Conflicting results have been published about circulating levels of CRP and PCa; some authors found that CRP is more strongly associated with cancer death risk.[23] While others found a strong association between CRP and PSA.[24] This result suggests that inflammation participates in tumor progress. Rising serum CRP suggests a poor prognosis. High CRP is shown in prostate cancer patients who develop bone metastasis.[25] And also this result agrees with study of Youngjun *et al* who found that C - reactive protein level of prostate cancer group was higher than that of BPH group. Inflammation may be correlated with prostate cancer according to the serum CRP level.[26] In this study higher level of fPSA in prostate cancer patients more than PBH and control. Also found a lower ratio between fPSA and total PSA (was lower than 25%) and this result consistent with study done by Catalona *et al*. who found that men with prostate cancer have ratio of free (unbound) PSA to total PSA is decreased and risk of cancer increases if the free to total ratio is less than 25%.[15] Despite earlier findings recent research suggests that rise in PSA ratio may have value in prostate cancer prognosis. Men with prostate cancer whose PSA level increases by more than 2.0 ng/ml during the year before the diagnosis of prostate cancer have a higher risk of death.[27] Results of sex hormones in this study found that patients with PCa have higher levels of serum Estradiol more than BPH and controls and these findings concurs with study done by Travis *et al*.[28] Also results of this study are in

consistent with results of Gabriela *et al* and Roddam *et al* who found that patients with PCa and BPH presented higher values of Testosterone and Estradiol levels when comparing to PBH patients and Controls.[29] Findings of this study for prostate cancer are agree with studies of Eaton *et al* and Ross *et al* who reported that there was difference in concentration of Testosterone, Estradiol in PCa patients and BPH patients.[30] The patients in study done by Morgentaler *et al* who reported that age is risk factor for PCa.[31] Testosterone and Estradiol levels were correlated, because aromatization of androgens in peripheral tissues is a major source of Estradiol in men.[32] Because Estradiol (hypothesized to have a positive association with prostate cancer risk) were significantly correlated with testosterone levels (hypothesized to have a positive association with risk of PCa.[33] Findings of this study also agrees with study done by Huggins *et al* who found that higher levels of serum Estradiol levels in patient with PCa more than BPH patients.[34] In this study; all patients who showed prostate cancer by biopsy have fPSA/tPSA ratio less than 25%, high Estradiol and CRP concentration than its reference values. From this study recommends that fPSA/tPSA ratio should be measured regularly in men above 50 years, Total and free PSA level must be used to identify the development of Prostatic cancer, Serum lipids should be measured in men of BPH continuously to avoid high concentration of serum LDL that can lead to myocardial infarction, High level of Estradiol and CRP may be used to replace prostatic biopsy, Needs further studies to see if can replace prostatic biopsy for the diagnosis of PCa.

CONCLUSION

In conclusion, this study provides confirmatory data about PCa &BPH and its strong associations with lipids, Estradiol and CRP. All patients with PCa have PSA ratio (fPSA/ tPSA) less than 25%., Serum Total PSA and fPSA were higher in patients with PCa than BPH and controls. Serum Total PSA and fPSA were higher in patients with PCa than BPH and controls, Total cholesterol, TG, HDL and LDL were lower in concentration in PCa patients than in BPH and controls Serum CRP level of the prostate cancer group was higher than that of the BPH group. Inflammation may be part of the process of prostate cancer development on the basis of the serum CRP level. Serum Estradiol levels increases in patients with PCa than in BPH and control There was a correlation between Cholesterol, TG, HDL and LDL with Estradiol level in PCa and BPH.

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