ORIGINAL ARTICLE

Diagnostic value of lipids, total antioxidants, and trace metals in benign prostate hyperplasia and prostate cancer

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Abstract

Background: Considerable overlap exists in the value of total prostate specific antigen (tPSA) in both prostate cancer (Pca) and benign prostate hyperplasia (BPH). Developing an effective biochemical screening test that will complement PSA assay could reduce the associated cost of care and give timely attention to prostate cancer patients even when they are still asymptomatic is therefore desirable. This work was therefore an attempt to evaluate the possible roles of lipids, antioxidants, and trace metals in breaking the diagnostic tie between Pca and BPH.

Materials and Methods: Anthropometric characteristics, total prostate specific antigen (tPSA), serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), Vit. E, total antioxidant status (TAS), and trace metals (Se, Cu, Fe, Zn, and Mn) were determined in 40 patients with histopathological diagnosis of BPH and Pca. Forty age matched control subjects were also recruited from the same community. Informed consent was obtained from all the participants in the study. A *P*-value < 0.05 was considered significant.

Results: There were significant variations in the weight, hip circumference, and body mass index (BMI) across the group but the *post hoc* test did not show any difference between patients with prostate cancer and BPH. Among the biochemical parameters studied, only the total cholesterol and triglyceride differed significantly between patients with BPH and prostate cancer patients. Cut-offs from ROC for BPH and prostate cancer at 88.9 sensitivity and 66.7% specificity (95% CI) were 88.5 mg and 161 mg/dl for triglycerides and cholesterol respectively. Furthermore there were no significant variations in the mean levels of copper and tPSA, Vit E, and LDL cholesterol among the study subjects and the controls.

Conclusion: Prior to prostate biopsy, serum lipid (especially, fasting triglycerides, total cholesterol) could help in early discrimination of patients with BPH from prostate cancer in adjunct to total PSA and other management protocol for diagnosis of prostate cancer. The use of trace metal or antioxidants may have limited advantages. Further studies in this regard will be very desirable to see if this pattern of triglyceride and total cholesterol values in BPH and Pca are sustainable.

Key words: Benign prostate hyperplasia, diagnostic value, lipids, prostate cancer, trace metals

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Introduction

Prostate cancer (Pca) and benign prostate hyperplasia (BPH) are diseases of the male above the age of 50 years worldwide.[1] While BPH is a benign enlargement of the prostate gland requiring medical or surgical intervention to relieve obstruction to urinary flow, prostate cancer is a life-threatening malignancy with grave morbidity and mortality because of its tumor burden and metastatic potentials. The management of benign prostate hyperplasia differs from that of prostate cancer given the different outcomes of their natural history. It is therefore important to have tools that are sensitive and specific enough to make an appropriate

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early diagnosis so as to institute appropriate treatment. This would in turn improve the quality of life of affected persons. There is however a limitation in diagnosis of these diseases due to the considerable overlap in the value of total PSA in both conditions especially in the African population.[2]

Several investigators outside Nigeria have used various diagnostic profiles to discriminate between BPH and Pca. Some workers have compared the ratio of free to total PSA or free to complexed PSA.[3,4] Others have used plasma lipid levels,[5,6] vitamin E (α and γ tocopherol),[7] trace metal-Selenium,[8] and serum to urinary PSA ratio.[9,10] These previous studies have produced varying outcomes with merits and shortcomings. Most clinicians and urologists in Nigeria however use total PSA largely in the initial biochemical investigation of the patients presenting with symptoms referable to the prostate gland. This work was therefore an attempt to evaluate the possible roles of lipids, antioxidants, and trace metals in breaking the diagnostic tie between Pca and BPH.

The human body is constantly exposed to the attack of free radicals. Reactive oxygen species (ROS) collectively described as free radicals such as superoxide (O_2-), hydroxyl (OH-), and other nonradical oxygen derivatives such as hydrogen peroxide (H_2O_2) play a significant role in the pathogenesis of many diseases such as atherosclerosis, diabetes mellitus, cancer, cardiovascular disease, liver disease, lung disease, neurodegenerative disease, inflammatory, and infectious diseases.[11] Free radicals are highly reactive molecules generated by the biochemical redox reactions that occur as part of normal cellular metabolism. Lipid peroxidation caused by free radicals could be prevented by antioxidants defense mechanisms both intracellularly and extracellularly. These include the antioxidant enzymes glutathione, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione S-transferase (GST), and glutathione reductase (GR).[12] Srivastava and Mittal[13] demonstrated increased level of serum lipid peroxide in patients with both benign prostate hyperplasia and cancer. Among the micronutrients the protective role of the various antioxidant vitamins (C, alpha and beta carotene) in fruits and vegetables is of great importance in diet. Fruit consumption has been shown in numerous studies to offer strong protection against certain cancers, especially oral, and pharyngeal, lung, prostate, and pancreatic cancer.[14] Epidemiological studies indicate that selenium and zinc may also serve as chemopreventive agents that suppress the growth and dissemination of prostate cancer.[15] Kamat and Lamm[16] however deduced from their work that reduced fat intake, vit E, selenium, and soy protein are associated with prevention of prostate cancer. In Nigeria, an earlier study[17] suggested the use of selenium supplement among others in the management of prostate cancer.

This study was therefore designed to evaluate the diagnostic role of lipids, trace metals, and antioxidants in patients with BPH and Pca.

Materials and Methods

Total PSA, plasma lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), Vit. E, total antioxidant status (TAS), and trace metals (Se, Cu, Fe, Zn, and Mn) were determined in two groups of 40 patients with histopathological diagnosis of BPH and Pca respectively and 40 age-matched control subjects selected within the same community who gave their consent. The patients were recruited from the urology clinic of the University College Hospital for symptoms referable to prostate disease. Informed consent was obtained from all the patients that participated in the study. Fasting blood sample was collected for lipid analysis. Plasma separated from these samples was refrigerated at -20°C until batch analysis within 2 weeks.

Plasma total antioxidant status was determined by the method of Koracevic *et al.*[18] A standard solution of Fe-EDTA complex reacts with hydrogen peroxide by a Fenton- type reaction, leading to the formation of hydroxyl radicals. These reactive oxygen species degrade benzoate, resulting in the release of thiobarbituric acid reactive substance. The rate of inhibition of color is proportional to the concentration of antioxidative activity.

Trace metal concentration was determined by an atomic absorption spectrophotometer (AAS) using a direct method previously described by Kaneko.[19] The method is based on the principle that atoms of the element aspirated into AAS absorb light of the same wavelength as that emitted by the element when in the excited state.

Vitamin E was determined by the method of Baker[20] which is based on the principle that vitamin E extracted in xylene react with alpha dipyridyl with the production of a red color with ferric chloride read by spectrophotometer at 520 nm.

Lipid fractions were analyzed by methods previously described.[21]

Statistical analysis was done using the SPSS Software version 15.0. The data were expressed as mean ± standard deviation for patients and control separately. Anova (F-value) was used to compare the difference between the means of the three groups studied, while the *post hoc* Student's t test was used to compare the difference between the means of the study subjects; a P value < 0.05 was considered significant.

Results

Table 1 shows the anthropometric characteristics between the study subjects patients and controls. There were significant variations in the weight, hip circumference, and BMI across the group but the *post hoc* test did not

show any difference between patients with prostate cancer and BPH. Among the biochemical parameters studied, only the total cholesterol and triglyceride levels differed significantly between patients with BPH and prostate cancer patients (155.1 ± 49.8 vs. 188.7 ± 31.7 mg/dl $P<01$, 87.9 ± 27.7 vs. 136.7 ± 59.1 mg/dl; $P = 0.0004$ respectively). Receiver operative characteristics with sensitivity and specificity fixed at 88.9 and 66.7% respectively gave cut-off values of 88.5 and 161 mg/dl respectively for triglyceride and total cholesterol as discriminatory between patients with BPH and prostate cancer [Table 2].

Furthermore there were no significant variations in the mean levels of copper and tPSA, Vit E, and LDL cholesterol among the study subjects and the controls [Table 3]. The level of tPSA however did not show any significant correlation with Vit E, LDL cholesterol, and triglyceride respectively among the groups.

Table 1: Anthropometric measurement in study subjects and controls (mean ± SD)

Parameters	Controls $n = 40$	Pca $n = 40$	BPH $n = 40$	*P*-values
Age (years)	65.2 (6.72)	68.5 (9.6)	64.5 (10.3)	0.110
Height (m)	1.7 (0.08)	1.70 (0.1)	1.70 (0.1)	1.002
Weight (kg)	69.6 (14.0)	60.5 (14.9)	69.2 (11.5)	0.004*
Hip circumference (cm)	99.4 (1.9)	91.9 (7.8)	97.7 (6.3)	0.001*
Waist circumference (cm)	87.4 (11.3)	86.2 (6.6)	90.1 (8.7)	0.148
BMI (kg/m^2)	23.9 (4.6)	21.03 (3.9)	24.0 (4.6)	0.004*
Systolic BP (mmHg)	137.7 (29.0)	132.5 (21.5)	138.6 (22.4)	0.488
Diastolic BP (mmHg)	91.1 (129)	86.0 (9.9)	92.3 (14.7)	0.065

Table 2: Receiver operative characteristic for Tg and T/cholesterol in study subjects

Parameter	Cut-off	Sensitivity %	Specificity %
Tg	88.5 mg/dl	88.9	66.7
T/cholesterol	161 mg/dl	88.9	66.7

Table 3: Biochemical parameters in study subjects and controls (mean ± SD)

Parameters	Controls $n = 40$	Pca $n = 40$	BPH $n = 40$	*P*-values
Total PSA (µg/L)	3.2 (2.47)	92.7 (60.5)	55.1 (59.7)	0.002*
Se (µg/dl)	59.7 (12.3)	58.6 (12.8)	57.6 (11.2)	0.741
Cu (µg/dl)	45.9 (6.2)	43.6 (9.5)	41.2 (9.4)	0.051*
Fe µg/dl	61.7 (12.3)	60.6 (12.8)	59.8 (11.3)	0.782
Zn (µg/ml)	114.4 (25.2)	119.8 (25.2)	126.0 (22.4)	0.107
Mn (µg/ml)	36.8 (5.8)	37.1 (7.9)	34.5 (6.4)	0.175
Vit E (mg/dl)	15.2 (1.6)	10.9 (1.0)	10.9 (2.6)	0.001*
TAS (mmol/l)	1.2 (0.43)	1.0 (0.5)	1.0 (0.4)	0.072
T/Cholesterol (mg/dl)	157.1 (27.5)	188.7 (31.7)	155.1 (49.8)	0.001 *†
LDL/cholesterol (mg/dl)	84.9 (4.6)	116.9 (26.9)	108.0 (37.4)	0.003*
HDL/cholesterol (mg/dl)	48.6 (19.3)	44.3 (10.5)	49.9 (14.7)	0.233
Triglycerides (mg/dl)	114 (63.1)	136.7 (59.1)	87.9 (27.7)	0.001*,†

*Anova. †*Post hoc* significant difference between Pca and BPH.

Discussion

The need to increase the diagnostic sensitivity of biochemical tests to enhance discrimination between prostate cancer and BPH has been a topical issue for quite some time. In a resource scarce environment as obtained in many developing countries in Africa, developing an effective biochemical screening tests that will complement PSA assay will therefore reduce the associated cost of care and give timely attention to prostate cancer patients even when they are still asymptomatic.

While the different panels associated with PSA either total, free or complexed PSA or the free to complexed ratio are still nonspecific, the use of total PSA velocity has been found useful. Understanding the pathogenesis of prostate cancer development may therefore throw some light on what early derangement may point to presence of cancer. To this end several workers have looked at various micronutrients, antioxidant vitamins, and trace metals.

The mean circulating triglyceride was found to be significantly different in this study between the study patients and controls. It was also significantly higher (1.6 times) in patients with prostate cancer compared to BPH patients. This observation agrees with the finding of Wuermli *et al.*[6] who observed a positive correlation between serum triglyceride (Tg) and prostate cancer. Furthermore, it was observed that hypertriglyceridaemia may increase the risk of prostate cancer and can thus be used for prognostication. A similar significant difference was observed for total cholesterol in this study between patients with BPH and Pca. It was reported by Freeman and Solomon[22] in a review that a number of studies had demonstrated that cholesterol accumulates in solid tumors and that cholesterol homeostasis breaks down in the prostate with aging and with transition to the malignant state. This could probably account for the level of circulating total cholesterol in this study being lower than 200 mg/dl. Thus among the lipid panel, total cholesterol and triglyceride are a promising tie-breaker between these two disease entities. Receiver operative characteristics (ROC) transformation on the present data supports serum triglycerides greater than 88.5 mg/dl and total cholesterol of 161 mg/dl as increased risk for development of prostate cancer.

Dietary fat is a well-established risk factor in cardiovascular disease. Hypertriglyceridemia and elevated waist circumference have been identified by Kahn and Valdez[23] as a phenotype for higher risk for cardiovascular disease. Others have found increased plasma triglyceride to be associated with the metabolic syndrome.[24] However, obesity as evidenced by the normal BMI in the patients with prostate cancer is not a feature of the patients studied. These findings suggest the interplay of several other factors apart from lipid

in the pathogenesis of prostate cancer. In another study by Van Hemelrijck *et al*.[25] there was a positive association between hypertriglyceridaemia and prostate cancer risk when there was a high glucose level. This has introduced another variable not considered in our study.

The level of trace metals and total antioxidant status were not found to be diagnostic in this study. It could be opined that the level of intake of antioxidants in the study and subject population was significant enough to provide the protection from oxidative stresses especially lipid peroxidation. Unlike the findings in this study Ayidin *et al*.[26] established that an altered prooxidant-antioxidant status may lead to an increase in oxidative damage and play a possible role in prostate carcinogenesis. Consumption of animal fats has been associated with increased prostate cancer risk.[27] A study by Key *et al*.[28] on plasma carotenoids, retinol, and tocopherols on the risk of prostate cancer in Caucasians found none of the micronutrients to be significantly associated with prostate cancer risk. However, a more recent prospective study by Mondul *et al*. observed that men with higher serum retinol level at base line were more likely to develop prostate cancer.[29] While dietary factor was not directly studied in this work, yet an indirect relationship could be inferred from the submission of Chan *et al*.,[30] who together with his colleagues identified the role of Insulin-like growth factor-1(IGF-1) in prostate carcinogenesis. This hormone normally efficiently manages the rate of cell growth and remodeling. In unhealthy conditions IGF-1 becomes more active increasing the formation of new cells and simultaneously inhibiting the removal of old cells - which favors the development of cancer.[30] Consumption of animal-based foods and dairy increases the blood level of this growth hormone. The study further noted that in prostate cancer people with higher than normal IGF-1 have five fold increased risk of advanced stage prostate cancer. This report has also been corroborated in a multicenter prospective meta-analysis[31] that the greater the serum IGF-1 concentration the greater the subsequent risk for prostate cancer.

Conclusion

Before prostate biopsy is carried out, serum lipid (fasting triglycerides >88.5 mg/dl, total cholesterol >161 mg/dl) could help in further discrimination of patients with BPH from prostate cancer patients in adjunct to total PSA for diagnosis of prostate cancer. The use of trace metal or antioxidants has limited advantages. Further studies in this regard will be very desirable to see if this pattern of triglyceride and total cholesterol values in benign prostatic hyperplasia and prostate cancer are sustainable.

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