

**EVALUATION OF SOME ANTIOXIDANTS AMONG PROSTATE CANCER SUBJECTS  
ATTENDING FEDERAL TEACHING HOSPITAL OWERRI**

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**ABSTRACT**

The study population comprised 50 men diagnosed with prostate cancer by biopsy within the age bracket of 40 -80 years and 50 matched apparently healthy men without prostate cancer served as control. The prostate cancer subjects were sub divided into 25 subjects on androgen deprivation therapy and 25 treatment naïve subjects. Blood samples were collected aseptically by a phlebotomist and dispensed into plain tubes. The sera obtained were analyzed by standard methods following the manufacturer's standard operating procedure and data obtained was analyzed using Statistical Package for Social Science (SPSS) version 23. The test of significance was determined by student t-test. Values were expressed as Mean  $\pm$  standard deviation. Pearson correlation was also determined and values with  $P < 0.05$  were considered statistically significant. The result showed significantly lower mean levels of glutathione peroxidase, superoxide dismutase, uric acid, ( $p = 0.000$  for all) in prostate cancer subjects ( $261.35 \pm 47.90$  U/L,  $141.34 \pm 21.28$  U/mL,  $4.78 \pm 0.44$  mg/dl, respectively) compared to control subjects ( $422.30 \pm 14.44$  U/L,  $194.83 \pm 9.21$  U/mL,  $7.04 \pm 0.82$  mg/dL respectively). There was a significant higher level of vitamin E ( $p = 0.000$ ) in prostate cancer subjects ( $11.95 \pm 2.41$   $\mu$ g/mL respectively) compared to control subjects ( $6.70 \pm 0.74$   $\mu$ g/mL respectively).

**KEYWORDS:****INTRODUCTION**

Prostate cancer is the uncontrolled growth of cells in the prostate, a gland in the male reproductive system below the bladder. It is an important public health problem, particularly in western countries with trends towards increase in aging population.<sup>[1]</sup> The etiology and the risk factors of prostate malignancy is not well understood, however, certain risk factors are frequently associated to its development. Non-modifiable risk factors include age, race/ethnicity, genetic factors, and family history<sup>[2]</sup> whereas environmental factors, diet, and lifestyle are some modifiable risk factors for prostate cancer.<sup>[3]</sup> The interplay among genetics, environmental influences, and social influences causes race-specific prostate cancer survival rate estimates to decrease, and thus, results in differences observed in the epidemiology of prostate cancer in different countries.<sup>[4]</sup> Hereditary prostate cancer and a genetic component predisposition to prostate cancer have been studied for years. One of the most predisposing genetic risk factors for prostate cancer is family inheritance. Despite the use of prostate-specific antigen (PSA) and some recent clinical trials testing early biomarkers of prostate cancer onset, the incidence

rates of prostate cancer have dramatically increased.<sup>[5]</sup> To date, endocrine therapy (anti-androgens combined with castration) and classical androgen deprivation (orchiectomy or luteinizing hormone-releasing hormone agonists) represent the most effective treatments for advanced and metastatic prostate cancer. Unfortunately, although most patients favorably respond for a long time, progression to castration-resistant disease is nearly universal, and most patients eventually die from recurrent androgen-independent prostate cancer.<sup>[6]</sup>

The cellular antioxidant system (enzymatic and non-enzymatic) that controls ROS production includes enzymes such as glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT), which reduce hydroperoxides while oxidizing cellular glutathione.<sup>[7]</sup> The oxidized glutathione (GSSG) is recycled to GSH by glutathione reductase (GSH-R) utilizing NADPH to reduce GSSG. NADPH is regenerated by glucose-6-phosphate dehydrogenase (G6PDH) in the hexose monophosphate shunt. In addition, glutathione S-transferase (GST), a set of isozymes, catalyzes intracellular detoxification reactions

by conjugating glutathione with ROS, resulting in the generation of less toxic products.<sup>[8]</sup> The antioxidant scavenging system also includes several non-enzymatic antioxidants which are easy to obtain and modify the administration dose, including mitochondria-targeted antioxidant (MitoQ) like coenzyme Q10 and carnosine, which are targeted to the mitochondria, the main source of free radicals; some endogenous antioxidants precursors like inosine, which is metabolized into uric acid (UA) and N-acetylcysteine (NAC) and vitamins C and E.<sup>[9]</sup>

## MATERIALS AND METHODS

### Study Area

The study was carried out at the Federal Teaching Hospital Owerri, Imo State, Nigeria.

### Advocacy, Mobilization and Pre-Survey Contacts

A letter of introduction from the Head of Department of Medical Laboratory Science, Imo State University, Owerri (appendix i) was collected and submitted to the gate keeper Federal Teaching Hospital Owerri, the Chief Medical Director. On request, a research proposal (appendix ii) was submitted to the ethics Committee. The ethical approval letter (appendix iii) was obtained. After several meetings with the nurses at the urology department, clinic days were chosen for the collection of samples. A structured consent form (appendix iv) was issued to the subjects for the purpose of obtaining information regarding their medical and demographic characteristics. Those who qualified to participate in the research gave their consent.

### Study Population/ Sample Size

#### Study Population

The study population was subjects confirmed with prostate cancer through biopsy. A total of one hundred subjects were recruited for this study, fifty confirmed prostate cancer subjects that were evaluated by digital rectal examination (DRE) and prostate-specific antigen level. Patients who were suspicious for prostate carcinoma underwent trans rectal ultrasonography (TRUS) and biopsy. This was further subdivided into twenty five treatment naïve subjects and twenty five subjects on androgen deprivation therapy. Fifty were apparently healthy participants whose prostate specific antigen levels and DRE falls within the normal range that served as the control subjects.

### Selection Criteria

#### Inclusion

Those included are as follows.

- (i) Subjects between the age range of 40 and 80 years.
- (ii) Subjects with confirmed prostate cancer on androgen deprivation therapy that attended the clinic for not less than three months.
- (iii) Subjects who gave consent to participate in the study.
- (iv) Apparently healthy Individuals that served as control subjects.

- (v) Subjects with confirmed prostate cancer without any treatment

### Exclusion

- (i) Subjects below the age of 40 years and above the age of 80 years.
- (ii) Subjects without prostate cancer except the control group
- (iii) Subjects who did not give consent to participate in the study.
- (iv) Subjects who were severely ill.
- (v) Subjects who were diagnosed with benign prostatic hyperplasia.

### Study Design

A cross-sectional study was carried out among prostate cancer subjects.

### Sample collection

Blood samples were collected aseptically, using a 5ml sterile disposable syringe and needle from all the subjects and then were dispensed into labelled gel specimen container. The samples were left to clot after which they were centrifuged at 3,000rpm for 5 minutes to separate, and the sera were obtained. The sera will be extracted using pasteur pipette into the appropriate containers and stored at -20°C prior to use.

### Laboratory Procedures

All reagents were commercially purchased and the manufacturer's standard operating procedure (SOP) was strictly followed.

### Determination of serum superoxide dismutase by Colorimetric method<sup>[10]</sup> as modified by DetectX reagent (2022) catalogue number K028-H1

#### Test Procedure

Standards or diluted samples was placed into the provided transparent microtiter plate. Substrate Preparation mixture and Xanthine Oxidase Preparation mixture was added to each well, ensuring thorough mixing. The mixture was incubated at room temperature for 20 minutes. This allows for the color-generating reaction between Xanthine Oxidase, oxygen, and the colorless substrate. After incubation, a plate reader was used to detect the generated signal at 450nm and SOD activity was calculated using the standard curve.

### Determination of serum vitamin E by colorimetric method<sup>[11]</sup> as modified by Elabscience reagent (2022) catalogue number E-BC-K033-S

#### Test procedure

The following steps were followed.

Step 1 Centrifuge tubes labeled as T and B (i.e. sample/test and blank) were taken. Ethanol (aldehyde free) (750 µ L) and serum (750 µ L) were added in these sample tubes. Serum should be added slowly with mild shaking to obtain a finely divided protein precipitate. The blank was prepared by adding 750 µ L of distilled water and 750 µ L of ethanol (aldehyde free). All the tubes

were covered tightly by wrap paper and shaken vigorously for at least 30 s. Xylene (750  $\mu$  L) was then added in all these tubes. Furthermore, all the tubes were covered tightly by wrap paper and shaken vigorously for at least another 30 s and then centrifuged for 10 min at 3000 rpm.

Step 2 Xylene layer (supernatant) (500  $\mu$  L) was transferred into properly labeled, clean, and small-size test tubes (5 mL volume). To each tube, 500  $\mu$  L of 2,2'-bipyridyl solution was added followed by 100  $\mu$  L of ferric chloride solution and waited for 2 min.

Step 3 The solutions (200  $\mu$  L) from each of these tubes were transferred to a plain ELISA microplate (non-antibody coated). The primary wavelength was set at 492 nm and the absorbance of all the samples (including blank) were measured. The ELISA reader was set in 'rapid measure' mode. The serum  $\alpha$ -tocopherol concentration of each of the sample was obtained by using the standard curve prepared.

#### Preparation of standard curve

Working standard of  $\alpha$ -tocopherol (27  $\mu$  g/mL): 1 mL of stock standard solution was taken and made the volume up to 100 mL with ethanol (aldehyde free) to obtain a concentration of 27  $\mu$  g/mL. This solution is stable at room temperature. Six centrifuge tubes were taken and labeled as B (blank) and S 1, S 2, S 3, S 4, and S 5 for standard solution. In these tubes, 0 (zero), 150, 300, 450, 600, and 750  $\mu$  L of working standard solution (27  $\mu$  g/mL) were added, respectively, and made the volume up to 750  $\mu$  L by adding ethanol (aldehyde free). These solutions (S 1 – S 5) are equivalent to 4, 8, 12, 14, 16, and 20  $\mu$  g/mL of  $\alpha$ -tocopherol concentration, respectively. The entire protocol is shown in Table 1. The absorbance was measured by using 200  $\mu$  L of each of the above-mentioned solutions (including blank) put on a plain ELISA microplate (non-antibody coated) and read in an ELISA reader (ERBA-Lisa Scan II) at 492 nm. A standard curve was plotted with absorbance vs.  $\alpha$ -tocopherol ( $\mu$  g/mL) concentration.

**Determination of serum glutathione peroxidase by colorimetric method<sup>[12]</sup> as modified by Elabscience reagent (2022) Catalogue number E-BC-K096-S**

#### Test procedure

##### Enzymatic reaction

To the non-enzyme tube, 0.2 mL of 1 mmol/L GSH standard solution was added into the tube. To the enzyme tube, 0.1 mL of 1 mmol/L GSH standard solution and 0.1 mL of sample were mixed fully. The tubes and the stock application solution was pre-heated at 37°C water bath for 5 min at the same time. To the tubes, 0.1 mL of stock application solution was added and mixed fully, it was reacted at 37 °C for 5 min accurately. To the non-enzyme tube, 2 mL of acid reagent and 0.1 mL of sample were added. To the enzyme tube, 2 mL of acid reagent was added. It was properly mixed and centrifuged at

3100×g for 10 min, and 1 mL of the supernatant was taken for chromogenic reaction.

#### Chromogenic reaction

To the non-enzyme tube, 1 mL of supernatant was taken from non-enzyme tube and added. To the enzyme tube, 1 mL of supernatant was taken from enzyme tubes and added. To the blank tube, 1 mL of GSH standard application solution was added. To the standard tube, 1 mL of 20  $\mu$ mol/L GSH standard solution was added. In all the tubes, 1 mL of phosphate application solution, 0.25 mL of DTNB solution, 0.05 mL of salt application solution were added. They were mixed properly and allowed to stand for 15 min at room temperature. It was measured spectrophotometrically at 412 nm wavelength.

#### Statistical Analysis

All data generated in this study was subjected to statistical analysis using Statistical Package for Social Science (SPSS) version 23. Student t-test was used to analyze the mean difference between two groups, Pearson correlation was determined, and the level of significance was taken at  $p < 0.05$ . Values were expressed as mean  $\pm$  standard deviation and results were presented in tables.

## RESULTS

**Table 1: Mean  $\pm$  SD Values of Gpx, SOD, Vitamin E and Uric Acid in Prostate Cancer Patients of the Study Population.**

Parameter	Prostate Cancer (n=50)	Control (n=50)	t-value	p-value (0.05)
Gpx (U/L)	261.35 $\pm$ 47.90	422.30 $\pm$ 14.44	- 22.74	0.000
SOD (U/mL)	141.34 $\pm$ 21.28	194.83 $\pm$ 9.21	- 16.31	0.000
Vit. E ( $\mu$ g/mL)	11.95 $\pm$ 2.41	6.70 $\pm$ 0.74	14.73	0.000
Uric Acid (mg/dL)	4.78 $\pm$ 0.44	7.04 $\pm$ 0.82	- 17.19	0.000

#### KEY:

n: population size

\*: Statistically significant ( $P < 0.05$ )

Gpx: Glutathione Peroxidase

SOD: Superoxide Dismutase

#### Vit. E: Vitamin E

Table 1 indicates the antioxidant in prostate cancer patients of the study population. There was a significantly lower level of Gpx, SOD and uric acid ( $p = 0.000$ ) in prostate cancer patients (261.35  $\pm$  47.90 U/L, 141.34  $\pm$  21.28 U/mL and 4.78  $\pm$  0.44 mg/dL respectively) compared to the control (422.30  $\pm$  14.44 U/L, 194.83  $\pm$  9.21 U/mL, and 7.04  $\pm$  0.82 mg/dL, respectively). There was a significantly higher level of vitamin E ( $p = 0.000$ ) in prostate cancer patients (11.95  $\pm$  2.41  $\mu$ g/mL) compared to the control (6.70  $\pm$  0.74  $\mu$ g/mL).

## DISCUSSION

Prostate cancer is solid tumors of glandular origin. Androgens are vital for the normal functioning, growth, and development of the prostate and have been linked to prostate carcinogenesis. Prostate cancer cells that thrive without androgens normally possess a phenotype that is aggressive.<sup>[13-16]</sup> The study revealed significantly lower mean level of glutathione peroxidase in prostate cancer subjects ( $261.35 \pm 47.90$  U/L) compared to controls. ( $422.30 \pm 14.44$  U/L). Glutathione peroxidase is a primary antioxidant defense system that plays a key and fundamental role in the overall defense mechanisms and strategies in biological systems. Decreased level of glutathione in prostate cancer could be related with elevated levels of thiobarbituric acid reacting substances, thus indicating its involvement in lipid peroxidation. Depletion of cellular antioxidants can result from free radical formation due to normal endogenous reactions and the ingestion of exogenous substances and environmental factors. It could also lead to endothelial cell dysfunction and activation supporting atherogenesis.<sup>[17-20]</sup> The decrease may also be as a result of compensatory mechanisms in response to oxidative stress, inactivation of glutathione peroxidase gene, which can be caused by deletion or methylation. This is in accordance with the work of Nattanan *et al.*<sup>[21]</sup> that showed a trend towards glutathione peroxidase scores in prostate cancer patients when compared to healthy men. However, Battisti *et al.*<sup>[22]</sup> stated that glutathione peroxidase maybe increased, reduced or unchanged in prostate cancer which was not consistent with this study. This could be influenced by prostate specific antigen values.. Furthermore, glutathione and glutathione-dependent enzymes have been known to be of central importance in the detoxification of peroxides, hydro peroxides, xenobiotics, and drugs.<sup>[23]</sup> Hence, modification of glutathione-dependent enzyme activities can be explained by the interdependence and dynamics of the glutathione enzyme family pathway.

Table 1 showed significantly lower mean levels of superoxide dismutase in prostate cancer subjects ( $141.34 \pm 21.28$  U/mL) compared to control, ( $194.83 \pm 9.21$  U/mL). A decrease in superoxide dismutase activity may be associated with either a primary defect in people with prostate cancer or with impaired enzyme function as a result of disease processes. It may also be caused by disturbances in the antioxidant defense system in patients with prostate cancer as a result of weakened defense system against reactive oxygen species that could cause the accumulation of free radicals, which may exacerbate the neoplastic process. This is consistent with the work of Joanna *et al.*<sup>[24]</sup> that was carried out on Polish patients, it demonstrated lower superoxide dismutase activity in prostate cancer. Kotrikadze *et al.*, (2008) also reported lower superoxide dismutase activity in patients with prostate cancer. Arsova *et al.*<sup>[25]</sup> showed that the decrease in superoxide dismutase activity was correlated with an increased lipid peroxidation. This fact was explained by the exhaustion of the antioxidant defense system due to

the high intensity of oxidative stress. There was also a significantly lower mean levels of uric acid in prostate cancer subjects ( $4.78 \pm 0.44$  mg/dl) compared to control ( $7.04 \pm 0.82$  mg/dL) which maybe as a result of the neutralization of increasing oxidant compounds in the inflammatory environment. This is in accordance with the study by Benli *et al.*<sup>[26]</sup> which reported that serum uric acid levels in patients with newly diagnosed prostate cancer were lower than those in patients without prostate cancer. However, a study by Sangkop *et al.*<sup>[27]</sup> showed that increased incidence of prostate cancer is related to hyperuricemia, indicating that blood uric acid levels are an independent predictor of prostate cancer. Blood uric acid can promote the growth of prostate cancer cells, and blood uric acid levels are associated with the risk of prostate cancer, recurrence, and death. Therefore, there are currently inconsistent conclusions on the serum uric acid levels in patients with prostate cancer.

## CONCLUSION

This study has shown that antioxidants decreased in subjects with prostate cancer, irrespective of the treatment options. However, levels of total protein were not affected irrespective of the disease condition. Because elevated oxidative stress markers are independently associated with poorer outcomes, this should be addressed in the management of patients with prostate cancer.

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