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Serum Antioxidant Enzymes, Haematological Values and Uric Acid Concentrations in Prostatic Disease Patients: An Investigative Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ANA and OOC designed the study. Authors RIR and NNE performed the statistical analysis. Authors ANA and INS wrote the protocol and wrote the first draft of the manuscript. Authors OOC, RIR and AKN managed the analyses of the study. Authors ANA, AKN and NNE managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: In this study, the haematology, serum antioxidant enzymes, and uric acid concentrations in prostatic disease patients attending the Nephrology Department of Abia State University Teaching Hospital, Aba were evaluated.

Methodology: A total of one hundred and ten (110) adult males (aged 40-80 years) comprising of sixty (60) prostatic disease patients and 50 normal subjects were recruited. The prostatic disease patients comprised of 30 prostatitis, 20 Benign Prostatic Hyperplasia (BPH), and 10 prostate cancer patients. Haematological parameters, antioxidant enzyme levels, and uric acid concentration were

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determined on blood samples collected from the subjects between January 2017 and December 2019.

Results: Results obtained following analysis indicated a significant fall in red blood cell count, haematocrit levels and haemoglobin concentrations in all the prostatic disease patients when compared with control subjects ($p<0.05$) but no significant difference was observed between the values of these parameters in the three categories of patients studied ($p>0.05$). Leukocyte and lymphocyte counts in the patients also did not significantly differ from those of the control subjects ($p>0.05$) but platelets counts were significantly lower ($p<0.05$). Significant elevations were observed in monocytes and granulocytes counts of prostatitis and prostate cancer patients ($p<0.05$). Serum antioxidant enzymes activities including superoxide dismutase (SOD) and glutathione peroxidase (GPx) were lower in the prostatic disease patients than in the control ($p<0.05$) with SOD and GPx levels being lowest in prostatitis and prostate cancer patients respectively while serum uric acid concentration was only higher than control in the prostatitis patients ($p<0.05$).

Conclusion: We, therefore, conclude that complications and deaths due to prostatic diseases may be due to the systemic effects of anaemia and fall in the body's antioxidant defense line accompanying the conditions.

Keywords: Benign prostate hyperplasia; prostatitis; prostate cancer; prostatic diseases.

1. INTRODUCTION

Medical records and available literature indicate that there is currently an upsurge in the number of men suffering from Prostatic diseases. Despite ongoing efforts, prostatic diseases continue to be a source of morbidity and mortality among men across the globe and Africa in particular [1]. It is also well established that prostatitis, Benign Prostatic Hyperplasia (BPH), and prostate cancer are the most common forms of prostatic diseases [2-7]. Of these diseases BPH accounts for up to 48% of all cases. Clinical signs associated with each of these diseases also appear to have overlapped, making specific diagnosis of each of the diseases even more difficult [8]. Recent reports have shown that prostate cancer is the second most common type of cancer and that prostatic diseases remain the sixth major cause of cancer death among men globally [9]. Deaths due to prostatic diseases have been linked to associated complications such as urinary retention and its accompanying toxicity effects, urinary tract infections, bladder stones, bladder damage, and kidney failure [8].

Although, BPH is not a known risk factor for prostate cancer, its role in increasing the chances of prostate cancer development has been reported [10]. Studies have also shown that chronic inflammation, race, ethnicity, environment, diets, and family history of occurrence are all risk factors in the development of prostatic diseases [11,12]. Although the aetiology and pathogenesis of prostatic diseases remain hazy, oxidative stress from endogenous and exogenous sources has been fingered as a possible pathway for their development [13]. The fact that increasing the antioxidant defense line of the body has been effective in the prevention of prostatic diseases further exposes the relationship between oxidative stress and this group of diseases. Endogenous antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), etc are reportedly the major agents of protection against prostatic diseases. This is due to their scavenging effects on free radicals which are established sources of systemic stress [14,15,16]. Therefore, the serum levels of these antioxidants enzymes may be of value in the diagnosis of prostatic diseases.

Uric acid is an organic compound that is endogenously produced in animals as a purine metabolite by the liver and excreted by the kidneys. Although high serum uric acid concentration is known to precipitate renal problems, recent findings have revealed its antioxidant values. In fact, uric acid is known to constitute about 66.6% of total plasma antioxidant capacity due to its double bond structure and high dissociation constant [17]. Hence the levels of serum uric acid in prostatic disease patients may be a yardstick for assessing the severity of the disorder and may therefore be a parameter to be considered in the diagnosis of prostatic diseases. In this study, haematological values, antioxidant strength, and uric acid concentrations in prostatic disease patients who attended the Nephrology Department of the Abia State University Teaching Hospital were assessed and presented to add to

the body of currently available data needed for prostatic disease diagnosis.

2. MATERIALS AND METHODS

2.1 Area of Study/Recruitment of Subjects

The study was conducted at the Abia State University Teaching Hospital, Aba, Abia State. A total of one hundred and ten (110) adult males (aged 40-80 years) comprising of sixty (60) certified prostatic patients by clinicians at the Nephrology Department of the Health Facility and whose PSA values were above 4 ng/ml and fifty (50) normal subjects with no trace of prostatic disease as control. The collected samples were transported to the Veterinary Biochemistry Laboratory, College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike, where all analyses were done.

2.2 Collection of BloodSample

Ten milliliters of venous blood was collected from each of the recruited subjects and dispensed into heparinized bottles for antioxidant studies and EDTA bottles for haematological analysis. Another portion of blood was dispensed into plain bottles, allowed to clot and then centrifuged to collect serum which was used for serum uric acid analysis.

2.3 Determination of Serum Superoxide Dismutase (SOD) Concentration

The method used is based on the principle that superoxide radicals generated from xanthine and xanthine oxidase will react with 2-(4-iodophenyl)-3- (4-nitrophenol)-5-phenyltetrazolium chloride (INT) to form a red formazan dye. Therefore the superoxide dismutase (SOD) activity measured was the degree of inhibition of this reaction. Briefly, 5ml of heparinized whole blood was centrifuged at 3000 rpm for 10 minutes to remove its plasma content. The collected cells were washed with about 3 ml of 0.9% NaCl solution about four (4) times. Each washing was followed by centrifuging for 10 minutes at 3000 rpm. After washing, 2mls of cold redistilled water was added and mixed and allowed to stand at 4°C for 15 minutes. The resulting lysate was diluted with 0.01mol/L phosphate buffer (pH 7.0). For each sample tested, three test-tubes labeled sample, standard, and sample diluents and containing 0.05 ml of sample, standard and sample diluents respectively. About 1.7 ml of the mixed substrate (xanthine 0.05 mmol/L, I.N.T 0.025mmol/l) was added into each test tube followed by 0.25 ml of xanthine oxidase (80 u/l). Initial absorbance A_1 of the contents of each test tube was read before the final absorbance A_2 in a further 3 minutes. SOD in units/min of the samples were then obtained from a standard SOD calibration curve and expressed in units/g haemoglobin.

2.4 Determination of Serum Glutathione Peroxidase (GPx) Concentration

This method is based on the principle that glutathione peroxidase (GPx) catalyzed the oxidation of (GSH) by cumene hydroperoxide. In the presence of glutathione reductase (GR) and NADPH the oxidized glutathione (GSSG) was converted to the reduced form with the oxidation of NADPH to $NADP^+$. The decrease in absorbance was measured at 340nm wavelength with a spectrophotometer. Briefly, 0.05ml heparinized whole blood was diluted with 1ml diluting agent (Randoxransel diluting agent), incubated for 3minutes at 25°C before the addition of 1ml haemoglobin reagent (Potassium phosphate 10.3mmol/L, Potassium ferricyanide 6.08mmol/L, Potassium cyanide 7.68 mmol/L, and surfactant 0.1%v/v). From the diluted sample, 0.02ml was added to the test-tube labeled sample and 0.02ml of distilled water into the test-tube labeled blank. Reagent R1 was added to each of the test-tubes, mixed and the initial absorbance read at 340nm and after 2 minutes final absorbance was also read.

GPx concentration in U/L of haemolysate = 8412 x change in Absorbance.

2.5 Determination of Haematological Values

Haematological parameters including total red blood cells (RBCs) count, haemoglobin content, packed cell volume, total white blood cells (TWBC) count, total platelets count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and differential WBC counts were determined at once for each blood sample using a haematology analyzer (Model BC-2300, Mindray) following standard procedures.

2.6 Determination of Uric Acid Concentration

Serum uric acid concentration for each blood sample was determined using a uric acid commercial test kit produced by Randox

Laboratories, UK, in accordance with standard protocol.

2.7 Statistical Analysis

All values were expressed as means±SD. Data were analyzed using one-way ANOVA followed by the post –hoc Duncan multiple range test for analysis of biochemical data using SPSS version 11. Test values were considered statistically significant at P<0.05.

3. RESULTS

3.1 Effects of Prostatic Disease on Serum Antioxidant Enzymes Concentrations

Out of a total of 60 prostatic diseases patients (40-80 years) who were diagnosed at the Nephrology Department of Abia State University Teaching Hospital, Aba, 30 had prostatitis (Group 1), 20 had benign prostate hyperplasia (Group 2) while 10 had prostate cancer (Group 3). All categories of prostatic disease patients studied had significantly lower SOD values when compared with SOD activities of the normal (control) subjects (P<0.05). No significant difference in SOD values between these three categories of prostatic disease patients (P>0.05), however, the trend observed in the SOD activities showed that SOD activities of patients with prostatitis was<SOD activities of BPH<SOD activities prostate cancer patients (Table 1). Glutathione peroxidase (GPx) activities were also significantly lowered in the prostatic disease patients when compared with control subjects (P<0.05) with the order of activities being GPx activity in Prostate cancer patients<GPx activities of prostatitis patients<GPx activities BPH patients (Table 1). Serum uric acid concentration was significantly increased in patients with prostatitis when compared with control (p<0.05) while patients with BPH and prostate cancer had uric acid concentrations that did not significantly differ from control (p>0.05). Within the prostatic disease patients, uric acid concentration was higher in those suffering from prostatitis than those with BPH and prostate cancer (Table 1).

3.2 Effects of Prostatic Diseases on Haematological Values

Red blood cell count, PCV, and haemoglobin values in prostatic disease patients were significantly lower than the values obtained in the control subjects (p<0.05) with no significant difference observed in the values of these parameters amongst the different categories of patients studied (p>0.05). The values of WBC counts did not also significantly different between the patients and normal subjects but platelet counts were significantly lower in the patients (p<0.05) with BPH patients having the least values, followed by patients with prostatitis before those with prostate cancer. MCV and MCH values were significantly lower in the prostatic disease patients when compared with control (Table 3). The number of lymphocytes in these prostatic disease patients did not significantly differ from that of the control subjects. However, significant elevations were observed in monocytes and granulocytes counts of the patients with prostatitis and prostate cancer (Table 4).

4. DISCUSSION

The fact that a series of physiological and biochemical changes usually accompanies the onset of prostatic diseases like prostastitis, benign prostate hyperplasia, and prostate cancer is well supported by the results of the current study. Fall in the levels of antioxidant enzymes (SOD and glutathione peroxidase) may not be unconnected with the generation of more free radicals within the body, causing depletion in the body's antioxidant defense architecture. The role of free radicals in the development of oxidative stress diseases is well established [18,19]. The higher levels of superoxide dismutase (SOD) observed in control subjects compared with the prostatic disease patients suggest strongly the link between oxidative stress and prostatic diseases. Similar findings have been reported by Olinski et al [20]. Ayadin et al. [21] corroborated this finding by reporting that higher SOD values were observed in BPH than prostate cancer patients. The former had suggested that altered pro-oxidant-antioxidant balance may lead to an increase in oxidative damage in prostate cancer patients and consequently may play a role in prostate carcinogenesis with severe fall in SOD concentrations. We however attribute our own findings to higher inflammatory activities that take place in BPH patients. The relationship between inflammation in BPH patients and clinical data used in diagnosis has also been reported [22].

The serum concentrations of glutathione peroxidase (GPx) in all categories of patients studied were significantly lower than that of the control subjects, agreeing strongly with the results obtained by Arsova-Sarafunoska et al [23]. This fall in GPx levels may be due to an imbalance in the degree of oxidative stress and antioxidant status of the patients as was reported

by Aydin et al. [21]. It is also suggestive that reduced GPx concentrations in the patients may be a result of the generation of more amounts of reactive oxygen species (ROS) which plays significant roles in the emergence of oxidative stress diseases including cancer.

Serum uric acid concentration was only significantly higher than control in the prostatitis patients and suggests an increased level of inflammation [24]. The formation of abundant urate crystals in patients with chronic prostatitis has been reported [25]. Although no significant difference was found between the uric acid concentrations of the prostatic cancer patients and that of the control subjects, available data indicate a positive correlation between prostate cancer and low uric acid levels [26].

Table 1. Antioxidant concentrations in patients with prostatic diseases

Subjects	SOD Concentration (U/gHb)	GPx Concentration (U/gHb)	Uric acid (mg/dl)
Prostatitis patients	651.21±161.28*[a]	27.21±3.11*[a]	4.98±0.38*[a]
BPH patients	672.40±128.72*[a]	30.56±3.61*[a]	4.49±0.21
Prostate cancer patients	729.63±139.10*[a]	24.83±2.98*[b]	4.33±0.45[b]
Normal (control)	1380.87±121.94	38.61±3.04	4.20±0.19

*Values represent the mean ± SD for N =30 for prostatitis patients, 20 for BPH patients, 10 for prostate cancer patients, and 50 for control. Values in the same column marked * are significantly different from control (P<0.05) while those bearing the same letter of the alphabet are not significantly different from each other (p> 0.05)*

Table 2.Effects of prostatic diseases on haematological values

Subjects	RBC $x10^6/mm^3$	PCV (%)	Hb (g/dl)	WBC $x10^3/mm^3$	Platelets $x10^3/mm^3$
Prostatitis	4.20±0.35*[a]	38.50±3.32*[a]	12.50±1.20*[a]	5.03±0.89[a]	201.43±12.56*[a]
BPH	4.31±0.28*[a]	38.21±3.91*[a]	12.85±1.33*[a]	4.61±0.94[a]	194.14±10.23*[a]
Prostate cancer	4.34±0.24*[a]	40.30±3.65*[a]	13.10±1.26[a]	4.83±0.76[a]	218.55±9.56*[a]
Control	5.53±0.31	43.70±2.12	14.20±2.10	4.46±0.58	236.09±11.78

*Values represent the mean ± SD for N =30 for prostatitis patients, 20 for BPH patients, 10 for prostate cancer patients, and 50 for control. Values in the same column marked * are significantly different from control (P<0.05) while those bearing the same letter of the alphabet are not significantly different from each other (p> 0.05)*

Table 3. Effects of prostatic diseases on haematological values

Subject	MCV (fl)	MCH (pg)	MCHC (g/dl)
Prostatitis	92.10±2.71*[a]	28.52±2.78[a]	32.05±1.97[a]
BPH	92.80±4.90*[a]	29.10±3.14[a]	33.50±1.80[a]
Prostate cancer	93.05±4.38*[a]	24.50±3.51*[a]	30.50±2.05[a]
Normal (control)	98.70±3.34[b]	34.25±2.70[b]	33.50±1.96[a]

*Values represent the mean ± SD for N =30 for prostatitis patients, 20 for BPH patients, 10 for prostate cancer patients, and 50 for control. Values in the same column marked * are significantly different from control (P<0.05) while those bearing the same letter of the alphabet are not significantly different from each other (p> 0.05)*

Table 4. Effects of prostatic diseases on differential WBC values

Subjects	Lymphocytes $x10^3/mm^3$	Monocytes $x10^3/mm^3$	Granulocytes $x10^3/mm^3$
Prostatitis	2.38±0.32	0.78±0.03*[a]	2.00±0.17*[a]
BPH	2.39±0.42	0.74±0.03[b]	1.51±0.13[b]
Prostate cancer	2.51±0.72	0.84±0.02*[c]	2.50±0.15*[c]
Control	2.40±0.30	0.75±0.05	1.53±0.17

*Values represent the mean ± SD for N =30 for prostatitis patients, 20 for BPH patients, 10 for prostate cancer patients, and 50 for control. Values in the same column marked * are significantly different from control (P<0.05) while those bearing the same letter of the alphabet are not significantly different from each other (p> 0.05)*

The fact that haematological parameters including RBC, PCV, and Hb lowered significantly in the prostatic patients when compared with control values suggests that anaemia is among the clinical manifestations of prostatic diseases to control subjects. Similar results were reported in a similar study by Obeagu et al. [27]. Androgen deprivation, decline in quality of nutrition, bone marrow infiltration treatment related toxicity and chronic inflammatory states have all been fingered in the pathogenesis of anaemia in prostatic disease patients [1]. The low level of testosterone in prostatic disease patients reported by these authors may also be among the possible causes of anaemia in the patients. This is because testosterone is reported of great value in the enhancement of erythropoietin formation in the kidney leading to the production of more blood cells. Cancer treatment usually lowers or wipes out most male hormones found in the body testosterone [28]. Another pathway is the induction of a regulatory hormone, hepcidin by inflammatory cytokines and subsequent formation of hypoferraemia usually associated with anaemia and iron-restricted erythropoiesis [29,30]. The fall in platelet counts observed in this study was also reported by Nieden et al. [31].

5. CONCLUSION

We, therefore, conclude that anaemia, thrombocytopenia, and low antioxidant enzymes values may be clinical characteristics of prostatic diseases and that complications in the patients and deaths may be due to these anaemia and fall in the body's antioxidant defense line. These parameters may therefore be of value in the diagnosis of prostatic conditions in men.

CONSENT AND ETHICAL APPROVAL

Informed consent was obtained from all subjects recruited for the study, while ethical approval for the study was obtained from the Ethical Committee of the Abia State University Teaching Hospital, Aba, Abia State with Ref number ABSUTH/MAC/117/VOL.1/10.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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