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EVALUATION OF SUPEROXIDE DISMUTASE, GLUTATHIONE, VITAMINS C, E AND TRACE ELEMENT STATUS IN PROSTATE CANCER PATIENTS IN ORLU TEACHING HOSPITAL, IMO STATE.

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Abstract

The evaluation of superoxide dismutase, glutathione, vitamin C, E and trace elements status in prostate cancer patients in Orlu Imo State was carried out. The study group included one hundred and fifty prostate cancer patients with prostate specific antigen (PSA) values greater than 5ng/ml between the ages of 45-75 as (test subject) while male public and civil servants with PSA value less than 4ng/ml of the same age bracket served as the control subjects. Copper, and selenium were measured using atomic absorption spectroscopy, while, zinc, superoxide dismutase, glutathione, vitamin C and E were measured with different test kits. From the study the serum level of Copper, , superoxide dismutase, glutathione, selenium and Vitamin C of prostate cancer patients of the various groups were significantly decreased (Se 68.1±16.3 66.6±14.9 65.7±12.4, SOD 65.8± 22.2 59.8±16.3 55±14.6, GP 2.36 ±0.5 2.2±0.53 1.8±0.6 , Cu .51±3.6 .46±3.3 .39±2.8, Vitamin C 2.2±15.8 2.1±14.5 2.0±4.3) when compared with their respective controls (Se 89.4 ±20.4, SOD 95.1± 31.8 , GP 4.15 ± 0.28, Cu .81 ±5.7, Vitamin C 2.7 ±19.4), while zinc and Vitamin E showed a significant decrease in group 2 and 3 ($p<0.05$) (Zn .34 ±2.4 .18 ± 1.3, Vitamin E .57±4.0 .73± 5.1) and no significant difference in group 1, ($p>0.05$) (Zn .49 ± 3.4 Vitamin E 8.9± 6.3) when compared with their respective control groups (Zn .52 ± 3.7 , Vitamin E 0.82± 5.8). low levels of essential trace elements and antioxidants may predispose to Prostate cancer since most of the essential trace elements and antioxidants (Zn, Cu, Se, SOD, GP, vitamin C and E) were reduced at high level of PSA (>5ng/ml).

Keywords: Superoxide Dismutase, Glutathione, Vitamins C, E, Trace elements, Prostate.

Introduction

Prostate cancer is the sixth most important cancer in the world, and its incidence in blacks has been on the increase in men of 50 years and above (Yawe *et al.,* 2006). The incidence of prostate cancer varies from country to country, with the highest incidence in the Western world and the lowest in Asia. Data for the year 2000 showed that the incidence in the USA was 140 per 100,000 populations, whereas in Japan it was 22 per 100,000 populations and for China it was 1.54 per 100,000 populations (Tomohiro and Kumiko, 2007).

Prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa) are the most frequent pathologies of the prostate gland (Bracarda *et al.,* 2005). Prostate cancer is the most common cancer among men in Europe and United States. There is lack of epidemiological data on the exact prevalence of this disease in India. Because the screening for prostate cancer is not routine, the incidence of prostate cancer in India is always under recorded (Platz *et al.,* 1997) BPH is a worldwide health problem that causes morbidity in older men (Mc Connell *et al.,* 1994). Although the exact cause of BPH is not known, the presence of androgens,

especially dihydrotestosterone, and ageing are considered to be the major factors (Kobayashi, 1990). Hospital and cancer registry data show increasing prostate cancer incidence in Nigeria, which was previously regarded as a low incidence region (Ukoli *et al.,* 2003). The reasons for this high degree of variability between countries are multi-factorial and include the availability of improved detection methods, increasing westernisation of lifestyle, environmental exposure and genetics (Tomohiro and Kumiko, 2007). Lifestyle, environmental exposure and diets have direct effectson circulating levels of trace elements (Tomohiro and Kumiko, 2007). Moreso, susceptibility to cancers was previously related to diets, environmental factors and lifestyle (Fernandes *et al.,* 1979).

Prostate cancer is the uncontrolled growth of abnormal cells originating from the prostate, a small gland in the male reproductive system. Hallmarks of this disease include the following: genomic instability; the capacity of abnormal cells to resist cell death, evade growth suppression, and induce proliferative signals; chronic inflammation resulting in tumor promotion; and angiogenesis, invasion, and metastasis to distant organs (Hanahan and Weinberg, 2011). These hallmarks are often driven, at the most fundamental level, by dysregulation of gene expression. The classic view of cancer etiology is that genetic alterations, arising from exposure to exogenous genotoxic agents and endogenous oxidants, damage DNA and induce mutations, resulting in nonfunctional proteins that underlie disease progression. Historically, genetic abnormalities and mutations were cited as primary causative factors; however, epigenetic mechanisms are now recognized as playing an equal or perhaps greater role in cancer development (Boumber and Issa, 2011). Furthermore, prostate cancer is the second leading cause of cancer death among men in the United States (US) and is the most commonly diagnosed non-cutaneous cancer, with 1 in 6 men expected to be diagnosed with this disease in their lifetimes (Tomohiro and Kumiko, 2007). In 2012, an estimated 241,740 new cases were diagnosed in the US and approximately 28,170 men died of prostate cancer (American Cancer Society, 2012). While 81% of prostate cancers are diagnosed in the early stage and treated effectively with surgery or radiation, these treatments often result in poorer quality of life due to side effects like incontinence, impotence, or declining bowel function (Gallagher and Fleshner, 1998). Current treatments for advanced prostate cancer are largely palliative. Many known risk factors for prostate cancer are non-modifiable, including age, race, and genetic factors; whereas modifiable risk factors associated with prostate cancer include obesity, physical activity, and possibly dietary factors (Baade *et al.,* 2009). Prostate cancer screening is controversial due to over diagnosis and overtreatment of non-fatal disease, and the United States Preventive Services Task Force strongly recommends against prostate-specific antigen (PSA) screening for prostate cancer (Djulbegovic *et al.,* 2010). Because prostate cancer has a long natural history, mainly non-modifiable risk factors, and an incidence rate that far exceeds the mortality rate, a focus on prevention over screening or early detection offers an appealing area of investigation. Goals for prevention strategies should focus on reducing cancer incidence and delaying cancer diagnosis until the individual succumbs to other causes (Meyer *et al.,* 2005).

Prostate cancer (PCa) is one of the most common cancers in aged men. Literature data suggest that combination of several anthropometric, biochemical, clinical, and genetic factors could contribute to its development (Frydenberg *et al.*, 1997). Screening for PCa usually includes determination of prostate-specific antigen (PSA) levels combined with digital rectal and/or abdominal or rectal ultrasonography of the prostate (Van der *et al.*, 2005).

Prostate cancer (PCa) is one of the most common cancers in aged men and the most commonly diagnosed cancer in men and the second leading cause of cancer deaths (American Cancer Society, 2012). It is estimated that 220,000 cases of PCa may be diagnosed yearly and this is expected to increase with the expanding geriatric population (Jarrard, 2005). The combination of molecular/biochemical relationships is required to identify critical events in Prostate cancer process. The role of trace elements and antioxidant such as glutathione, superoxide dismutase, vitamin C and E in cancers have been a subject of arguments and reports of different authors are often conflicting and contradictory. Moreover, treatment of advanced forms of the disease has had limited success. Nonetheless, epidemiologic studies indicate that Se and Zn (Verougstraete *et al.,* 2003) may serve as chemopreventive agents that suppress the growth and dissemination of neoplastic prostate cells. Due to inconsistent reports regarding to the antioxidant capacity and trace elements status during the pathogenesis of prostate cancer among men in Nigeria and Imo State in particular. In the present study, the superoxide dismutase, glutathione, vitamin C, E and trace element status of prostate cancer patients will be evaluated among men attending clinic at the Urology/histopathology unit of Imo State University Teaching Hospital Orlu. The aim of this study is to evaluate vitamin C, E, copper, selenium, zinc, superoxide dismutase and glutathione status of prostate cancer patients.

Materials and Methods

Study Area

The study was conducted in Orlu metropolis, which is in Imo State, South – East Nigeria. The geographical coordinates are 5° 47’ 0" North, 7° 2’ 0" East**.** Orlu has numerous eatery centers and hotels, with a population

comprising workers in the private sector, civil servants, students, traders, self-employed, motor mechanics, farmers etc.

Study population and Enrollment

A random sampling of subjects of one hundred and fifty (150) prostate cancer patients with prostate specific antigen (PSA) level greater than 5.0ng/ml and histopathological report confirming its presence. The subjects were between the ages of 45-75 as (test subject) while public and civil servants with PSA level less than 4.0ng/ml and histopathological report confirming its absence of the same age bracket serve as the control subjects. The test subjects were selected amongst those attending the Out Patient Urology/Histopathology Department of Imo State University Teaching Hospital, Orlu. The test subjects were grouped into three different groups, (Group 1: prostate cancer patients within the age bracket 45-55, Group 2: prostate cancer patients within the age bracket of 56-65 and Group 3: prostate cancer patients within the age bracket of 66-75. All the test subjects were in normal diet (three meals per day), and not taking any drug except the chemotherapeutic drugs which is a part of their routine care, with no religion restrictions concerning any type of meat.

The study was approved by the ethical board of Imo State University Teaching Hospital Orlu.

Selection Criteria:

Inclution Criteria

Prostate cancer patients attending Imo State University Teaching Hospital.

Exclusion Criteria

Patients suffering from active liver disease.
Patients suffering from other associated diseases.
HIV-positive TB patients.
Patients who did not indicate interest in the study.

Sample Size Determination

Samples were collected from prostate cancer patients derived from IMSUTH Orlu, which serves as a referral centre for more than five hundred (500) patients.

Sample size is calculated using the formula below (Araoye, 2003)

$$n = \frac{(z^2\ pq)}{d^2}$$

Where:

n = the desired sample when the population is greater than 10,000

z = the desired normal deviation given as 2 which corresponds to the 95% confidence level.

P = the current prevalence rate as 0.05

q = 1 – p

d = degree of accuracy desired, usually set at 0.05.

The required sample size is calculated as follows:-

$$n = \frac{(2)^2(0.05)(0.05)}{(0.05)^2} = \frac{400}{}$$

Therefore a minimum sample size for the study will be 400

Sample Collection

Using 10ml sterile plastic syringe, 7.0ml of whole blood was drawn from each subject. Serum was separated using electric centrifuge at 3000 RPM for five minutes. The separated serum was carefully transferred to sterile container, stored at 2^0C - 4^0C prior to use.

Laboratory Procedures:

All the reagents used were commercially purchased and manufacturers' Standard Operating Procedures were strictly followed.

A. Estimation of Ascorbic acid Colorimeteric Method by Baker and Frank (1949)

The estimation of plasma L-ascorbic acid was done by colorimetric method.

Principle

Ascorbic acid reduces phosphotungstic acid in acidic medium to blue phosphotungstate chromogen, which has absorption maximum at 700 nm.

Determination of Alpha –tococpherol Vitamin-E

The estimation of serum Alpha-Tococpherol was done by colorimeter method of Baker and Frank (1949)

Principle:

The serum Alpha –tocopherol is determined by Emmerie-Emmerie Engel reaction which is based on the reduction by tocopherol of ferric to ferrous ions which is then form a red complex with α,α'-Dipyridyl.Tocopherols and carotene are first extracted into xylene and the extinction read at 460 nm to measure carotenes. A correction is made for these after adding ferric chloride and reading at 520 nm.

C Copper Estimation by Atomic Absorption Spectroscopy

Estimation of serum copper, was done by Atomic Absorption Spectrophotometer (AAS), Parkin Elmer model-3030.

Principle

Vapourised atoms in the ground state absorb light at very narrowly defined wavelengths. If these atoms in the vapour state are excited they can return in the ground state by emitting light of the same discrete wavelengths as the line spectrum. In AAS the ionic form of the element is dissociated from its chemical bond and by attesting free electrons produced by the consumption process is placed in the atomic ground state. In this form, it is capable of absorbing light at the specific wavelength of its line spectrum.

$A_e \rightarrow$ +−++Ionized metal + Electron Ground state metal atom hvA+0. A Ground state metal ion + light excited atom. AhvA+0.

Excited atom Atom with ground state energy level + photon.

In AAS a beam of radiant energy containing the line spectrums of the element to be measured is passed through a flame containing vaporized metal to be determined. The source of radiant energy is a hollow cathode lamp. The wavelength of absorbed radiant energy is the same as that which would be emitted if the element were excited. With the aid of monochrometer a measurement is made of the attenuation of one of the wavelengths of the incident light. This attenuation is caused by photons interacting with ground state atoms in the flame .The absorbance of light and concentration of atoms in the flame are related by Beer lambert's law, only a small percentage of the atoms are in a form capable of absorbing radiant energy emitted by hollow cathode lamp.

D Determination of Serum Zinc

This was based on the colorimetric method described by Makino *et al.*, (1982), using reagent kit (Randox Laboratories, United Kingdom) for the assay.

Principle:

Zinc present in sample is chelated by 5 – Br-PAPS 2-(5-bromo-2-phyridyllazo)–5–(N-Propyl-N–sulfo propylamino) - phenol in the reagent. The formation of this complex is measured at a wavelength of 560nm.

E Superoxide Dismutase Estimation:

Method of Superoxide Dismutase Estimation by Marklund and Marklund (1977)

Principle

The role of superoxide dismutase (SOD) is to accelerate the dismutation of the toxic superoxide radical (O_2^-) produced during oxidative energy process, to hydrogen peroxide and molecular oxygen and the rate of reduction with superoxide anion is linearly related to xanthine oxidase activity and is inhibited by SOD.

This method employs xanthine and xanthine oxidase (XOD) to generate superoxide radicals which react with 2-(4-iodophenyl) 3-(4-nitrophenol)-5 phenylthtraxolium chloride (I.N.T) to form a red formazon dye. The superoxide dismutase activity is then measured by the degree of inhibition of this reaction.

$$\text{Xanthine} \xrightarrow[O_2^-]{\text{SOD}} \text{uric acid} + O_2^-$$

F Glutathione Estimation by Glutathione Fluorometric Assay Kit

(Catalog #K264-100;)

Principle

O-phthalaldehyde (OPA), reacts with GSH, generating fluorescence, so GSH can bespecifically quantified. Adding a reducing agent converts GSSG to GSH. Reducing agent is then added to destroy excess quencher and convert GSSG to GSH.

G Selenium Estimation by Niedzielski *et al., (*2002)

Principle

Selenium reacts with 2,3-diaminenaphthalene in the presence of bromide ions acting as a catalyst, forming a complex which can be extracted by cyclohexane in an acid environment. The maximum absorption of the complex is at 378.5nm.

Statistical Analysis

Data obtained from the study was presented in the form of tables, while the results were analyzed using SPSS statistical computer software (Version 16). Each parameter of serum trace elements, and antioxidants was expressed as mean $\pm$ S.D. A parametric test, the analysis of variance (ANOVA) was used for comparisons of three or more mean values of the parameters

Results

In table 1, the mean serum value of selenium, superoxide dismutase, glutathione, Copper, and Vitamin C in prostate cancer patients showed a significant decreased ($p<0.05$) , while zinc and vitamin E show no significant difference in ($p>0.05$) when compared with the controls .

Table 1: The mean value of Copper, Zinc, selenium, superoxide dismutase, glutathione, Vitamin C and E in group 1 (45-55years) prostate cancer patients.

Parameters	Test	Control	P-Value
Vitamin C (µmol/l)	2.2 ± 15.8	2.7 ± 19.4	p<0.05
Vitamin E (µmol/l)	.89 ± 6.3	.82 ± 5.8	p>0.05
Copper (µmol/l)	.51± 3.6	.81 ± 5.7	p<0.05
Zinc (µmol/l)	.49 ± 3.4	.52 ± 3.7	p>0.05
Selenium (µg/l)	68.1 ± 16.3	89.4 ± 20.2	p<0.05
Supersoxide dismutase (µg/l)	65.8 ± 22.2	95.1± 31.8	p<0.05
Glutathione (µmol/l)	2.4 ± 0.5	4.15 ±0.28	p<0.05

Table 2: The mean value of Copper, Zinc, selenium, superoxide dismutase, glutathione, Vitamin C and E in group 2 (56-65years) of prostate cancer patients

Parameters	Test	Control	P-Value
Vitamin C (µmol/l)	2.1 ± 14.5	2.7 ± 19.4	p>0.05
Vitamin E (µmol/l)	.57 ± 4.0	.82 ± 5.8	p<0.05
Copper (µmol/l)	.46 ± 3.3	.81 ± 5.7	p<0.05
Zinc (µmol/l)	.34 ± 2.4	.52 ± 3.7	p<0.05
Selenium (µg/l)	68.1 ± 14.9	89.4 ± 20.2	p<0.05
Supersoxide dismutase (µg/l)	59.9 ± 16.3	95.1± 31.8	p<0.05
Glutathione (µmol/l)	2.2 ± 0.53	4.15 ±0.28	p<0.05

From the above table, there was a significant decrease (p<0.05) in the mean serum value of copper, zinc selenium, superoxide dismutase, glutathione and Vitamin E of prostate cancer patients when compared with their respective controls. Vitamin C showed no significant difference (p>0.05).

Table 3: The mean value of Copper, Zinc, selenium, superoxide dismutase, glutathione, Vitamin C and E In group 3 (66-75years) prostate cancer patients.

Parameters	Test	Control	P-Value
Vitamin C (µmol/l)	2.0 ± 4.3	2.7 ± 19.4	p>0.05
Vitamin E (µmol/l)	.73 ± 5.1	0.82 ± 5.8	p<0.05
Copper (µmol/l)	.39 ± 2.8	.81 ± 5.7	p<0.05
Zinc (µmol/l)	.18 ± 1.3	.52 ± 3.7	p<0.05
Selenium (µg/l)	65.7 ± 12.4	89.4 ± 20.2	p<0.05
Supersoxide dismutase (µg/l)	55.0 ± 16.3	95.1± 31.8	p<0.05
Glutathione (µmol/l)	1.8 ± 0.6	4.15 ±0.28	p<0.05

Table 3 shows that the mean value of selenium, superoxide dismutase, glutathione, of serum level of Copper, Zinc, Vitamin C and E showed a significant decreased in prostate cancer patients (p<0.05) when compared with the control subjects.

Table 4: The mean value of Copper, Zinc, selenium, superoxide dismutase, glutathione, Vitamin C and E In group among different age groups of prostate cancer patients

Parameters (µmol/l)	Control	40-55yrs	56-65yrs	66-75yrs
Vitamin C	2.7 ±19.4	*2.2±15.8	2.1±14.5	2.0± 4.3
Vitamin E	0.82± 5.8	.**89± 6.3	.57±4.0	.73± 5.1
Copper	.81 ±5.7	*.51±3.6	.46±3.3	.39± 2.8
Zinc	.52 ± 3.7	*.49 ± 3.4	.34 ±2.4	.18 ± 1.3
Selenium (µg/l)	89.4 ±20.4	*68.1±16.3	66.6±14.9	65.7±12.4
Supersoxide dismutase(µg/l)	95.1±31.8	*65.8±22.2	59.8±16.3	55±14.6
Glutathione (µmol/l)	4.15± 0.28	*2.36±0.5	2.2±0.53	1.8±0.6

Key

(*) = Significantly higher than group 1 and 2

(**)= Non significantly higher than group 1 and 2

The above table , the serum value of Copper, Zinc, selenium, superoxide dismutase, glutathione and Vitamin C shows a significant decrease (p<0.05) with the increase in age and years of prostate cancer patients.

Discussion

In the present study, there was a significant decrease in the serum zinc level among the various groups, the value declines as the year increases. Zn is a component of numerous metalloenzymes, anti-oxidant and is important for cell growth and replication, osteogenesis, and immunity (Groff and Gropper, 2000). Some studies have found an association of lower Zn intake in patients with certain cancers, whilst others have observed no association (Verougstraete *et al.,* 1977). Zn is regarded as a "cellular protector" for the prostate, therefore normal human prostate accumulates the highest levels of Zn of any soft tissue in the body (Silvera and Rohan, 2001). Studies have found evidence that Zn inhibits human prostate cancer cell growth, possibly due to induction of cell cycle arrest and apoptosis (Platz and Helzlsoner, 2001).

Invitro*,* Zn helps to maintain intra-prostatic balance of testosterone and DHT (Silvera and Rohan, 2001). Based on these cellular activities of Zn, it might have been consumed during PCa pathogenesis therefore giving the reason for low plasma Zn level in subjects with PSA >5ng/ml. In vitro and in vivo studies, organic and inorganic Se has been demonstrated to inhibit proliferation of normal and malignant cells and inhibit tumor growth (Griffin 1982) through an accumulation of cells in metaphase and increased apoptosis (Redman *et al.*, 1997).

Copper level decreased significantly in the groups and the decrease is age dependent among prostate cancer patients. Copper is an essential trace element needed to absorb and utilize iron. It is needed to make ATP and is also to synthesis some hormones, blood cells and collagen (Verougstraete *et al.,* 2003). Low level of Cu in subjects with PSA >5g/ml may explain significantly low level of Fe in this group. Moreover, the continuous need of Cu in collagen synthesis of prostate gland might have caused the reduction of circulatory Cu. The main function of iron is in haemoglobin, which is the oxygen-carrying component of blood (Thum and Anker, 2007). Iron is also part of myoglobin which helps muscle cells store oxygen and it is also essential for the formation of ATP. The fatigue experienced by PCa patients might be as a result of oxygen starvation caused by low level of Fe as shown by the present study.

Furthermore selenium value showed a significant decrease among all the test groups, this is because anti-proliferative effects of different of selenium. Webber *et al.* (1985) showed that inorganic selenium (sodium selenite) inhibits the growth of DU145 (androgen-unresponsive) PCa cells at a concentration of 1 µmol/L.

Several trace elements, such as Cu and Zn are bound to proteins (metallo- and metalloid- proteins) in the prostate gland. Currently, it is known that some of these elements play a role in the apoptosis of different cells and redox processes (Redman *et al.,* 1997). The above observation may be part of the reasons why these metals are reduced in our subjects with PSA values >5ng/ml.

Furthermore, in the present study, there was a significant decrease in the vitamin E level in group 2 and 3 within the 56 years and above age bracket of prostate cancer patients. The α Tocopherol β Carotene (ATBC) study, conducted by the U.S. National Cancer Institute and the National Institute for Health and Welfare of Finland from 1985 to 1993, determined whether certain vitamin supplements would prevent lung cancer and other cancers in a group of 29,133 male smokers in Finland (Heinonen *et al.,* 1998). The 50- to 69-year-old participants took α-tocopherol (50 mg) or β-carotene (a precursor of vitamin A), or their combination, or a placebo pill. In this study, α-tocopherol was found to reduce PCa incidence by 32% and mortality by 41% during an 8-year study period (Heinonen *et al.,* 1998). Further analysis showed an inverse relationship between serum α-tocopherol concentration and incidence of PCa, with a stronger effect on advanced disease (Weinstein, 2007). Studies have evaluated the anti-proliferative effects of vitamin E formulations in several experimental settings. For example, Yin *et al.,* (2007) demonstrated that VES imparts therapeutic and preventive effects against PCa

Vitamin C shows a significant decrease among all the test groups when compared with the control subjects, which may be as a result of decrease in serum zinc level which is a component of numerous metalloenzymes, anti-oxidant and is important for cell growth and replication, osteogenesis, and immunity. Also vitamin C it represents the primary antioxidant defense in blood, (Levine *et al*., 1996) is able to react with virtually all oxygen species, and can terminate free radical chain reactions (Bowen *et al*, 1998). Vitamin C also has crucial interactions with a number of other antioxidants. Glutathione is important in recycling oxidized vitamin C, and vitamin C itself is crucial to the regeneration of lipid-bound vitamin E (Mertz, 1980). Based on these cellular activities of vitamin C, it might have been consumed during PCa pathogenesis therefore giving the reason for low plasma vitamin C level in subjects with PSA >5ng/ml. The mean serum value superoxide dismutase and glutathione showed significant decrease among the test groups, the decrease may be occur as a result of compensatory mechanisms in response to oxidative stress.

Conclusion

The present study has established that the levels of vitamin C and E are not consistent with prostate

cancer patients. However low levels of essential trace elements and enzymatic antioxidants may predispose to PCa since most of the essential trace elements and antioxidants (Zn, Cu, selenium, superoxide dismutase, glutathione, vitamin C and E) were reduced at high level of PSA (>5ng/ml).

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