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ORIGINAL ARTICLE

THE SERUM LEVELS OF TRACE METALS IN NIGERIAN MALES WITH DIFFERENT PSA VALUES

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Prostate cancer (PCa), the primary disease of men over 50 years of age is on the increase worldwide. Most PCa grows slowly from overt clinical disease to the stage that lead to death. The gradual course of PCA development provides opportunity for intervention. Supplement of diet taken by PCa patients may be an effective intervention because certain micronutrients had been implicated in cancer prevention. The present study is designed to determine the levels of trace metals in 80 Nigeria males having different concentrations of serum prostate surface antigen (PSA) using atomic absorption spectrophotometer. The serum levels of PSA were measured with Beckman Coulter Access Immunoassay automated machine. Subjects with PSA values 5-10ng/ml had significantly high serum levels of Zn, Fe, Cd and Mn but significantly low level of Se compared with the controls (PSA 0-4ng/ml). Subjects with PSA >10ng/ml had significantly low levels of Mn, Mg and Se compared with the controls. Subjects with PSA values 5-10ng/ml had significantly reduced level of Se compared with subjects with PSA >10ng/ml. Only Se was low in all subjects with PSA >4ng/ml, therefore there is a possibility that Se intake may reduce the risk and progression of PCA.

Key words *: Trace elements, cancer, PSA, supplementation*

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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 (1). The incidence of prostate cancer varies from country to country, with the highest incidence is in the Western world and the lowest is in Asia. Data for the year 2000 showed that the incidence in the USA was 140 per 100,000 population, whereas in Japan it was 22 per 100,000 population and for China it was 1.54 per 100,000 population.(2). Hospital and cancer registry data show increasing prostate cancer incidence in Nigeria, which was previously regarded as a low incidence region (3)

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 (1,2,3). Lifestyle, environmental exposure and diets have direct effects on circulating levels of trace elements (2). More so, susceptibility to cancers was previously related to diets, environmental factors and lifestyle (4). But the role of trace elements in cancers has been a subject of conjecture and reports of different authors are often conflicting and contradictory. Some (5,6) but not all (7) studies suggested an inverse relationship between Se and PCa mortality. Modest to moderate inverse associations were observed in two case-control studies for dietary Zn and Zn supplement use in PCa patients (8). Other case-control studies in PCA patients had not observed a protective association for dietary (9) or combined dietary and supplemental (10) Zn intake. There was a study that found a positive association between blood Cd and total serum PSA (11). Others found that cadmium exposureis not consistently associated with prostate cancer incidence (12).

Despite intense efforts on cancer research, little is known about the etiology of prostate cancer. Moreover, treatment of advanced forms of the

Table 1 : Mean (±SD) of trace metals in tests compared with healthy controls

	n	Mg	Zn	Cu	Pb	Cd	Fe	Mn	Se
		µg/dl	µg/dl	µg/dl	µg/dl	µg/dl	µg/dl	µg/dl	µg/dl
Controls	20	27±3	122±23	46±10	21±3	30±3	54±10	21±2	48±12
PSA (5-10ng/ml)	20	28±3	145±26	54±10	22±4	35±3	62±11	31±3	29±3
PSA (>10ng/ml)	20	24±3	113±27	43±11	20±2	35±2	49±11	29±4	45±11
t-,p-values**		1.04,>0.2	2.3,<0.05	2,<0.05	0.5,>0.2	4.6,<0.01	2.1,<0.05	10,<0.01	6.6,<0.01
t-,p-values**		3.8,<0.01	1.4,>0.2	1.1,>0.2	1.4,>0.2	4.7,<0.01	1.8,>0.2	11,<0.01	3.2,<0.01
t-,p-values***		4.4,<0.01	3.5,<0.01	3.1,<0.01	1.7,>0.2	0.0,>0.2	3.5,<0.05	2.1,<0.05	4.2,<0.01

**** Controls compared with PSA 5-10ng/ml***
***** Controls compared with PSA >10ng/ml***
****** PSA 5-10ng/ml compared with PSA >10ng/ml***

disease has had limited success. Nonetheless, epidemiologic studies indicate that Se and Zn (12) may serve as chemopreventive agents that suppress the growth and dissemination of neoplastic prostate cells. It is the opinion of the present authors that further studies on other trace metals may shed new light on the etiology and progression of prostate cancer.

Materials and Methods

Participants:

A total of 80 participants within the age range of fifty-one to sixty-five years were recruited from the Surgery Clinics of the University College Hospital, Ibadan, Nigeria. The subjects were divided into 3 groups depending on the levels of plasma PSA values, viz controls (PSA 0-4ng/ml, n=20), PSA 5-10ng/ml (n=20) and PSA >10ng/ml (n=40). This study excluded patients or controls with inflammations, diabetes mellitus, hypertension, hepatitis, tuberculosis and subjects on hormonal therapy. These were based on responses to questionnaires and clinical investigations.

Collection of blood and measurement of trace metals:

Ten (10) ml of venous blood was obtained from antecubital fossa into plain bottle. The blood sample was allowed to clot, retracted and centrifuged in Centaur MSE centrifuge machine (Fisons, England) at 3,500rpm for 5 minutes after which the serum was separated and stored at -20^{0}C until ready for assay. Serum levels of Cu, Mg, Fe, Zn, Mn, Cd and Se were determined using atomic absorption spectrophotometer (13). The serum levels of PSA were measured with Beckman Coulter Access Immunoassay automated machine.

The data was subjected to statistical analysis using the mean, standard deviation and student's unpaired t-test. p- value <0.05 was accepted as significant.

Results

The result as presented in Table 1 shows that Zn, Cu, Cd, Fe and Mn were significantly raised while Se was significantly reduced in subjects having PSA 5-10ng/ml compared with the controls (PSA 0-4ng/ml). The mean levels of Cd and Mn were significantly raised while Mg and Se were significantly reduced in subjects having PSA >10ng/ml compared with controls. The level of Se was significantly raised while the levels of Mg, Zn, Cu, Fe and Mn were significantly reduced in subjects with PSA >10ng/ml compared with subjects having PSA 5-10ng/ml.

Discussion

It is well accepted that genetic variation alone does not explain the observed differences in incidence of PCa (15). A 120-fold differences in rates of PCA among different countries indicates that there

is substantial variation in occurrence of this disease, and suggests that micronutrients and environmental factors are of importance (15). As indicated in the literatures, studies on PCa patients were only concentrated on Zn estimation and supplementation (14, 16). So far, studies on PCa in Nigeria emphasize on epidemiology of PCa (3). Fifty percent (50%) of subjects with PSA >10ng/ml had PCa. PCa was not present in subjects with PSA 5-10ng/ml or PSA 0-4ng/ml.

Zn is a component of numerous metalloenzymes, anti-oxidant and is important for cell growth and replication, osteogenesis, and immunity (17). Some studies have found an association of lower Zn intake in patients with certain cancers, whilst others have observed no association (12). 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 (18). Studies have found evidence that Zn inhibits human prostate cancer cell growth, possibly due to induction of cell cycle arrest and apoptosis (19). *In vitro,* Zn helps to maintain intra-prostatic balance of testosterone and DHT (18). 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 >10ng/ml.

In *in vitro* an *in vivo* studies, organic and inorganic Se has been demonstrated to inhibit proliferation of normal and malignant cells and inhibit tumor growth (20) through an accumulation of cells in metaphase and increased apoptosis (21). Apoptosis may result from the competition of Se for S-adenosylmethionine with ornithine decarboxylase (21). The anticancer activity of Se has also been attributed to its being a component of glutathione peroxidase (GPX), which protects DNA and cell membrane (20) from peroxide damage by catalyzing conversion of peroxides (ROOR) to hydroxyl acids (ROH) (17). Selenium is also vital for immune system function and may help prevent prostate cancer. Low levels of Se in subjects with PSA values >4ng/ml may explain their susceptibility and progression of PCa.

Copper is an essential trace element needed to absorb and utilise iron. It is needed to make ATP and is also to synthesise some hormones, blood cells and collagen (12). Low level of Cu in subjects with PSA >10ng/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 (22). 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.

Mn forms part of the antioxidant superoxide dismutase (SOD), which helps prevent free radical damage. Free radical generation and oxidative stress are features of PCa patients (4, 12) therefore high levels of Mn in subjects with PSA >4ng/ml is needed for the formation and proper functioning of SOD to neutralize the free radical being generated. Best sources are nuts, seeds, whole grains, leafy green vegetables, tea and pineapple.

Blood Cd reflects both recent and cumulative exposures (13), therefore, older people tend to have higher blood Cd level (11), but their intake of Se and Zn decreases due to age-related changes in diet (12). As PCA risk increases with age, these changes in trace elements exposure may further increase PCA risk. This is supported by the present study where Cd was increased, Se and Zn were reduced in subjects with PSA >10nm/ml. The involvement of high Cd in the pathogenesis of PCA could be linked with fact that Cd affects the amount of testosterone and dihydrotestosterone in the prostate and these hormones are essential for the progression of both benign prostate hyperplasia and prostate cancer (2). Thus, raised levels of Cd in our subjects with PSA >4ng/ml is thus attributed to the progression and development of PCa.

Several trace elements, such as Se, Cu, Mn, 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 (21). The above observation may be part of the reasons why these metals are reduced in our subjects with PSA values >10ng/ml.

Conclusion

The present study has established that the levels of trace elements are not consistent with PSA values. But low levels of essential trace elements may predispose to PCA since most of the essential trace elements (Mg, Zn, Cu, Fe and Se) were reduced at high level of PSA(>10ng/ml).

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