ISSN: 03875547
Volume 45, Issue 02, April, 2022

# Appraisal of Serum Selenium, Copper, Zinc, Vitamin C and E Levels in Benign Prostatic Hyperplasia Patients

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**Keywords:**
Selenium, Copper, Zinc, Vitamin C, Vitamin E and Benign Prostatic Hyperplasia

**ABSTRACT**

The study was proposed to evaluate serum selenium, copper, zinc, vitamin C and E in benign prostatic hyperplasia patients in AL-Hilla city. The study comprises of a total 91 men which consist of patients and control groups, the patients group comprises 48 men with benign prostatic hyperplasia while the control group comprises 43 apparently healthy men. The study results revealed a significant reduction in serum selenium, zinc, vitamin C and E concentrations in BPH patients in comparison with those of control group and the copper/zinc ratio were significantly increased in BPH patients group in comparison with those of control group, while serum copper concentration were non-significantly increased in BPH patients group in comparison with those of control group. In conclusion, the decreasing of antioxidants in BPH resulting in imbalance between oxidant and antioxidant agents that increase the oxidative stress which may be important factor for development and exacerbation of BPH.



## 1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate gland that characterized by hyperplasia of the stromal and glandular epithelial cells which happens in the periurethral transition zone of the prostate that surrounds the urethra [1- 3]. In BPH, the prostate size is increased, therefore resulting in the urine flow obstruction that accounts for the lower urinary tract symptoms [4], [5].

The obstruction encourage changes in detrusor function, compounded by age related changes leading to urgency, urinary frequency, and nocturia, the most difficult lower urinary tract symptoms [5], [6]. In severe cases, BPH may lead to irreversible bladder damage, renal failure and death [7]. Several causes are now thought to be important in the BPH development and progression, these includes age (8), genetic component [9], lifestyle factors [10], inflammation, and oxidative stress [11], [12].

Oxidative stress is a state caused by an imbalance between the oxidant and antioxidant system of the body. In health, oxidants and antioxidants remain in balance state, but in conditions of oxidative stress, there is a large number of oxidants than the antioxidant. The increase in oxidant production in cells categorized by the release of free radicals that resulting in cellular disintegration [13], [14]. Free radicals atoms are unstable and highly reactive that reversibly or irreversibly damage many biochemical molecules, such as carbohydrate,

protein, lipid and nucleic acid, the damaging of these biomolecules causing a cellular damage and diseases [13], [15], [16].

There are two forms of radicals, the first is reactive oxygen species such as superoxide, hydrogen peroxide and hydroxyl radical while the second are reactive nitrogen species such as nitric oxide [17], [18]. Antioxidants are molecules or compounds that bind and inactivate the free radicals. Thus, antioxidants defend against oxidative stress and preclude the cells damage. There are two types of antioxidants, the first is endogenous antioxidants such as copper/zinc superoxide dismutase, selenium containing glutathione peroxidase and catalase [19], [20], [21] while the second is exogenous antioxidants such as alpha-tocopherol (vitamin E), β-carotene (vitamin A) and ascorbic acid (vitamin C) [22].

Trace elements are inorganic molecules which essential for life. Although these elements required in a small amount by body tissues, but they are very essential for normal body functions [23]. The essential trace elements have many functions such as structural elements, stabilizers, important for hormonal function, enzymes cofactors and activating or inhibiting enzymatic reactions [24], [25]. Trace elements including selenium, copper and zinc are an important elements that play an essential role in maintaining normal oxidants/antioxidants state [26].

Selenium is a nutritionally essential trace element. It is incorporated into a number of enzymes, some of which have antioxidant functions. In humans there are 25 selenoproteins and many of these are enzymes that act to protect the body against oxidative damage. Selenium has a probable protective effects against many diseases [27], [28]. Copper is an essential trace element, it required in the diet because it plays an important role such as enzymes cofactor, redox reaction, iron metabolism, energy production, and melanin synthesis [29], [30].

Zinc is an essential trace element and it represent as main constituent of more than three hundred enzymes in the body which make different functions including, enzyme activity, intracellular signaling and protein and DNA synthesis [31], [32]. Also, zinc found in the prostate, it play an important role in the normal prostate function [30], [33], [34].

Vitamin C is a water-soluble compounds that required for a variety of biological functions. Its biological functions includes, antioxidant by protecting cellular structures from free radicals and it act as a enzymes cofactor, such as hydroxylases that participate in collagen synthesis, and synthesis of certain neurotransmitters [35- 37]. Vitamin E is a fat-soluble compounds that important for normal functions of the body [38], [39]. Vitamin E is participate in many processes against free radicals in turn avert muscular and cellular injury [40], [41]. Because some trace elements and vitamins have an essential role in oxidative state, this study was purposed to evaluate serum selenium, copper, zinc, vitamin C and E in benign prostatic hyperplasia patients.

## 2. Materials and Methods

The study comprises of a total 91 men which consist of patients and control groups. The patients group comprises 48 men with benign prostatic hyperplasia while the control group comprises 43 apparently healthy men. All individuals of groups are obtained from AL-Hilla city and selected by urologist. The range of age of both groups are between 45 year to 70 year. Any subjects with diabetes mellitus, endocrine diseases, renal disease, hepatic disease, malignancies, drug, alcohol and smoking were excluded from this study.

Seven milliliters of blood by vein puncture were drawn from all subjects of both groups and the blood was placed in tube, then the sera were obtained by centrifugation of blood. The sera were stored at -20˚C till the

analysis. Serum selenium concentration was estimated by atomic absorption spectrophotometer while serum copper and zinc concentrations were estimated by spectrophotometric kit. Serum vitamin C (42) and vitamin E (43) by colorimetric methods SPSS were used for statistical analyses.

**3. Results**

The main features of BPH patients and healthy control groups as revealed in table (1-1). The study results revealed a significant decrease in serum selenium, zinc, vitamin C and E concentrations in BPH patients in comparison with those of control group and the copper/zinc ratio were significantly increased in BPH patients group in comparison with those of control group, while serum copper concentration were non-significantly increased in BPH patients group in comparison with those of control group as publicized in table (1-2).

The outcomes in table (1-3) illustrate a significant negative relationship between serum copper and zinc concentrations in BPH patients and control groups, while there are a none-significant relationship among serum selenium and copper or zinc concentrations in BPH patients and control groups.

**Table (1-1)** The Main Features of Study Groups

| Feature | Group | Mean ± SD | P-Value |
|---|---|---|---|
| **Number** | Control | 43 | - |
| | Patient | 48 | |
| **Age (year)** | Control | 55.59 ± 7.12 | > 0.05 |
| | Patient | 56.18 ± 5.91 | |
| **Prostate Specific Antigen (ng/mL)** | Control | 1.42 ± 0.49 | < 0.001 |
| | Patient | 5.62 ± 1.41 | |
| **Duration of disease (year)** | Patient | 5.66 ± 2.36 | - |

**Table (1-2)** Mean Serum Selenium, Copper, Zinc, Vitamin C and Vitamin E Concentrations of Study Groups

| Parameter | Group | Mean ± SD | P-Value |
|---|---|---|---|
| **Selenium (ng/mL)** | Control | 92.72 ± 10.65 | < 0.01 |
| | Patient | 72.31 ± 8.24 | |
| **Copper (µg/dL)** | Control | 96.54 ± 21.32 | > 0.05 |
| | Patient | 103.12 ± 27.30 | |
| **Zinc (µg/dL)** | Control | 89.72 ± 17.21 | < 0.05 |
| | Patient | 71.36 ± 12.25 | |
| **Copper/Zinc ratio** | Control | 1.11 ± 0.19 | < 0.01 |
| | Patient | 1.52 ± 0.23 | |
| **Vitamin C (mg/dL)** | Control | 1.24 ± 0.32 | < 0.001 |
| | Patient | 0.67 ± 0.18 | |
| **Vitamin E (mg/dL)** | Control | 1.36 ± 0.41 | < 0.001 |
| | Patient | 0.72 ± 0.27 | |

**Table (1-3)** Correlations Among Serum Selenium, Copper and Zinc Concentrations of Study Groups

| Parameter | Group | Selenium (ng/mL) (r) | Copper (µg/dL) (r) | Zinc (µg/dL) (r) |
|---|---|---|---|---|
| **Selenium (ng/mL)** | Control | - | -0.03 | 0.04 |
| | Patient | - | -0.07 | 0.08 |
| **Copper (µg/dL)** | Control | -0.03 | - | - 0.53* |
| | Patient | -0.07 | - | -0.42* |
| **Zinc (µg/dL)** | Control | 0.04 | - 0.53* | - |
| | Patient | 0.08 | -0.42* | - |

(*) This refer to significant relationship ($P < 0.05$)

**4. Discussion**

Many diseases increased with age. In men, one of the most important pathological condition that related to age is BPH. Several studies obtain an increase the oxidative stress with aging, for this reason the BPH may be aggravated with oxidative stress [44- 46]. Some trace elements includes selenium, copper and zinc are essential components of metalloenzymrs and some molecules such as vitamin C and vitamin E which act as intra and extra cellular antioxidant, for this reason all these parameters can be used to evaluate the antioxidant stat in BPH [47- 49].

Selenium is a cofactor to antioxidant enzymes such as selenium dependent glutathione peroxidases. Selenium dependent glutathione peroxidases are responsible for the reduction of hydrogen peroxide to harmless products and prevent lipid damage. This role aids to maintain membrane integrity, and decreases the probability of propagation of additional oxidative damage to bio-molecules such as DNA, lipoproteins and lipids with the linked increased risk of several diseases [50], [51]. In addition to its incorporation in glutathione peroxidase, selenium have a role in the induction of apoptosis, that prevents cellular proliferation [52], [53].

In this study, serum selenium concentration significantly lower in BPH patients in comparison with those of control group, this results are in consistence with the with the results of [54- 56] studies. The decreasing of serum selenium concentration lead to decrease the antioxidant, decrease the apoptosis and increase cellular proliferation in BPH patients.

Copper is a cofactor of many enzymes for example superoxide dismutase [57]. Serum copper concentration were non-significantly changed in BPH patients group in comparison with those of control group and this agreement with [56], [58] studies. Conversely this results differed from those described by [54], [59] studies who did find a significant changed in serum copper concentration of BPH patients group in comparison with those of control group.

Zinc is an essential constituent of prostatic fluid and has been assumed to show an important roles in the normal prostate function. In the body, the amount of zinc in the prostate are higher than in other tissues [60-62]. The zinc accumulation in normal prostate results in two essential effects (metabolic and proliferative effect). The metabolic effect zinc includes the inhibition of citrate oxidation by inhibit aconitase activity, consequently the citrate can accumulated that result in reduction of Krebs cycle with a decrease in ATP production, also it inhibits mitochondrial oxidation and respiration. The proliferative effect of zinc includes inhibition of prostatic cell proliferation through the induction of apoptogenesis [63], [64].

Zinc is important for the many transcription factors and proteins that involved in the regulation of gene

transcription, also it is an essential component of a potent antioxidant enzyme (copper/zinc superoxide dismutase). As a result, zinc may play a important role in the avoidance of prostatic disease by averting oxidative stress [65], [66].

Serum zinc concentration significantly lower in BPH patients in comparison with those of control group, this results are in consistence with the [54], [55] studies. Conversely this results differed from those described by [56], [58] studies who did not find a significant changed in serum zinc concentration of BPH patients group in comparison with those of control group. In BPH patients group, the decreasing of serum zinc concentration lead to decrease the antioxidant, metabolic and anti-proliferative effects that may be lead to increase of oxidative stress and DNA damage.

Although copper is an essential element for humans, the higher copper concentration can lead cancer by creating DNA damage by free radicals. Various in vitro and in vivo studies have recognized the fact that increase copper and decrease zinc leads to increased oxidative stress and DNA damage [66], [67].

In this study, a significant increase in the copper/zinc ratio raised in BPH patients group in comparison with those of control group, this results are agreement with the [59] study. Also the outcome of this study show a significant negative relationship between serum copper and zinc concentrations in BPH patients and control groups, this results are agreement with the [58] study. From this results the increasing the copper/zinc ratio and negative relationship between serum copper and zinc concentrations indicate to increase oxidant (copper) and decrease antioxidant (zinc), this lead to increase the free radicals formation, decrease the antioxidant that lead to increase of oxidative stress.

Vitamin C is a powerful antioxidant with the ability to clean up free radicals within, and outside the cell. It act directly on peroxyl radicals or indirectly by boosting the antioxidant properties of vitamin E. This effects help to control lipid peroxidation of cellular membranes and preventing DNA damage by decreasing reactive oxygen species or reactive nitrogen species and protects proteins involved in DNA repair [68- 71].

Vitamin E incorporated into cellular membranes and shields the body structures that protect them from oxidative damage. It protects cell membranes from lipid peroxidation by scavenging the superoxide radical anion and dismisses oxidative chain reactions [72], [73]. Vitamin C and E act with each other to protect lipid structures against peroxidation. Hence, the depletion of vitamin C can be lead to decrease in the regeneration of vitamin E i.e the increasing the consumption of vitamin E and finally decease the action of vitamin E.

In this study, it was observed that the antioxidant vitamins, namely, vitamin C and E, were significantly lower in BPH patients group in comparison with those of control group, this results are in consistence with the [74], [75] studies. The decreasing in serum vitamin C and E in BPH patients may be due to an increase the oxidants, these antioxidants act as defense system to prevent oxidative damage in these patients.

In conclusion, the decreasing of antioxidants in BPH resulting in imbalance between oxidant and antioxidant that increase the oxidative stress which may be important factor for development and exacerbation of BPH. Hence, they may be need of supplementation of selenium, zinc, vitamin C and vitamin E to replace this deficiency.

**5. References**

[1] Robert G., Descazeaud A., Nicolaïew N., et al. Inflammation in benign prostatic hyperplasia: A 282 patients' immunohistochemical analysis. Prostate. 2009; 69:1774-1780.

[2] Miller J., and Tarter T. Combination therapy with dutasteride and tamsulosin for treatment of symptomatic enlarged prostate. Cli Interv Aging. 2009; 4: 251-258.

[3] Strandberg J. Comparative pathology of benign Prostatic hyperplasia. In: Leper Hgedd. Prostatic Disease. Philadelphia, W.B Sanders. 2000; 37 (6): 329-343.

[4] Luo G., Foo K., Kuo T., et al. Diagnosis of prostate adenoma and the relationship of its site to bladder outlet obstruction. Singapore Med J. 2013; 54: 482-486.

[5] Neal D., Ramsden P., Sharples L., et al. Outcome of elective prostatectomy. BMJ. 1989; 299: 762-767.

[6] Babinski M., Manaia J., Cardoso G., et al. Significant decrease of extracellular matrix in prostatic urethra of patients with benign prostatic hyperplasia. Histol Histopathol. 2014; 29: 57-63.

[7] Roehrborn C., and Connell J. Etiology, pathophysiology, epidemiology, and natural history of benign prostate hyperplasia. In: Walsh P., Retik A., Vaughan E. and Wein, A., editors. Campbell's Urology. 8th ed. Philadelphia (PA): WB Saunders. 2002; 1297-1336.

[8] Altok M., Bagci Ö., Umul M., et al. Chromosomal aberrations in benign prostatic hyperplasia patients. Investig Clin Urol. 2016; 57: 45 49.

[9] Parsons J. Benign prostatic hyperplasia and male lower urinary tract symptoms: Epidemiology and risk factors. Curr Bladder Dysfunct Rep. 2010; 5: 212 218.

[10] Parsons J. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. J Urol. 2007; 178: 395-401.

[11] Bostanci Y., Kazzazi A., Momtahen S., et al. Correlation between benign prostatic hyperplasia and inflammation. Curr Opin Urol. 2013; 23: 5 10.

[12] Shen M., and Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. Genes and Development. 2010; 24 (18):1967–2000.

[13] Agarwal A., Gupta S., and Sharma R. Role of oxidative stress in female reproduction. Reproductive Biology and Endocrinology RB and E. 2005; 3: 28.

[14] Lelli J., Becks L., Dabrowska M., et al. ATP converts necrosis to apoptosis in oxidant-injured endothelial cells. Free Radic Biol Med. 1998; 25 (6): 694-702.

[15] Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet. 1994; 344: 721-724.

[16] Szczepanska M., Kozlik J., Skrzypczak J., et al. Oxidative stress may be a piece in the endometriosis puzzle. Fertility and Sterility. 2003; 79: 1288-1293.

[17] Ashok A., Sajal G. and Rakesh K. Role of oxidative stress in female reproduction. Reproductive Biology and Endocrinology. 2005; 3 (28): 1-21.

[18] Pierce J., Cackler A. and Arnett M. Why should you care about free radicals? RN. 2004; 67: 38-42. 61. Osborn B., Haney A., Misukonis M., et al. Inducible nitric oxide synthase expression by peritoneal macrophages in endometriosis-associated infertility. Fertil Steril. 2002; 77: 46-51.

[19] Halliwell B. Role of free radicals in neurodegenerative diseases: therapeutic implications for antioxidant treatment. Drugs Aging. 2001; 18: 685- 716.

[20] Singh R., Khanna R., Kaw J., et al. Comparative effect of Benzanthrone and 3-Bromobenzanthrone on hepatic xenobiotic metabolism and antioxidative defense system in guinea pigs. Arch Toxicol. 2003; 77: 94-99.

[21] Vendemiale G., Grattagliano I., and Altomare E. An update on the role of free radicals and antioxidant defense in human disease. In J Clin Lab Res. 1999; 29: 49-55.

[22] Pietta P. Flavonoids as antioxidants. J Nat Prod. 2000; (63): 1035-1042.

[23] Waugh A., Grant A., and Ross W. Anatomy and Physiology in Health and Illness. 9th ed. Churchill Livingstone, Spain. 2001; 307-311.

[24] Feinendegen L., and Kasperek K. Medical aspects of trace element research. Trace Elem. Anal. Chem. Med. Biol. 1980; 1-17.

[25] Huang Y., Sheu J., and Lin T. Association between oxidative stress and changes of trace elements in patients with breast cancer. Clin Biochem. 1999; 32 (2): 131-136.

[26] Pourjafar M., Khalil B., Saeed S., et al. Correlations between Serum Trace Elements (Selenium, Copper and Zinc) and Antioxidant Vitamins (Vitamin A, E and C) in Clinically Healthy Dromedary Camels. J. Fac. Vet. Med. Istanbul Univ. 2014; 40 (1): 7-13.

[27] Rayman M., Infante H., and Sargent M. Food-chain selenium and human health: spotlight on speciation. British Journal of Nutrition. 2008; 100: 238-253.

[28] Fairweather-Tait S., Yongping B., Martin R., et al. Selenium in Human Health and Disease. Antioxidants & Redox Signaling. 2011; 14 (7): 1337-1383.

[29] Vassiliev V., Harris Z., and Zatta P. Ceruloplasmin in neurodegenerative diseases. Brain Res. Brain Res. Rev. 2005; 49: 633-640.

[30] Carl A., Edward R., and David E. Vitamins and trace elements. Tietz Fundamentals of clinical chemistry. 6th ed. 2008; 476-508.

[31] Ishii K., Otsuka T., Iguchi K., et al. Evidence that the prostate-specific antigen (PSA)/Zn2+ axis may play a role in human prostate cancer cell invasion, Cancer Lett. 2004; 207 (1): 79-87.

[32] Gumulec J., Masarik M., Krikzkova S., et al. Insight to physiology and pathology of zinc (II) ions and their actions in breast and prostate carcinoma. Curr Med Chem. 2011;18 (33): 5041-5051.

[33] Mengel M., and Schwiebert L. Family medicine: ambulatory care & prevention. McGraw-Hill Professional. 2005; 268-269.

[34] Shanker A. Mode of action and toxicity of trace elements. In: Prasad MNV, editor. Trace Elements: Nutritional benefits,environmental contamination, and health implications. John Wiley & Sons, Inc. 2008.

[35] Gann P. Randomized trials of antioxidant supplementation for cancer prevention: first bias, now chance--next, cause. Jama. 2009; 301:102-103.

[36] Gaziano J., Glynn R., Christen W., et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2009; 301:52-62.

[37] Carr AC, Frei B. Does vitamin C act as pro-oxidant under physiological conditions? FASEB Journal 13 (1999): 1007-1024.

[38] Meydani S., Han S., and Wu D. Vitamin E and immune response in the aged: molecular mechanisms and clinical implications. Immunological reviews 205. 2005; 269-284.

[39] Gornick M., Drywien M., Frackiewicz J., et al. Alpha-Tocopherol May Protect Hepatocytes Against Oxidative Damage Induced by Endurance Training in Growing Organisms. Adv Clin Exp Med. 2016; 25: 673-679.

[40] Bennett P., and Brown M. Clinical Pharmacology. Churchill Livingstone. 2003; 735-774.

[41] Baraka T. Clinical evaluation of Vitamin A, ß-Carotene, Vitamin E and cortisol levels in Health and Selected Diseases in Camels (Camelus dromedarius) in Egypt. J. Am. Sci. 2012; 8 (1): 106-111.

[42] Nino H., and Shah W. Vitamins, in Fundamentals of Clinical Chemistry, N.W. Tietz, 2nd edi, 1986; 547-550.

[43] Fabianek J., DeFilippi J., Richards T., et al. Micromethod for tocopherol determination in blood serum,Clinical Chemistry. 1968; 14 (5): 456-462.

[44] Minciullo P., Inferrera A., Navarra M., et al. Oxidative stress in benign prostatic hyperplasia: A systematic review. Urol Int. 2014; [Epub ahead of print].

[45] Rupam D., Bijoyananda D., and Mustafa A. Study of Relationship of Prostate Volume, Prostate Specific Antigen and age in Benign Prostatic Hyperplasia. International Journal of Contemporary Medical Research. 2017; 4 (7): 1582-1586.

[46] Atalay M., and Laaksonen E. Diabetes, oxidative stress and physical exercise. J. Sports Science and Medicine. 2002; 1: 1-14.

[47] Flores C., Puga M., Wrobel K., et al. Trace elements status in diabetes mellitus type 2: Possible role of the interaction between molybdenum and copper in the progress of typical complications. Diabetes Res Clin Pract. 2011; 91: 333-341.

[48] Merendino R., Salvo F., Saija A., et al. Malondialdehyde in benign prostate hypertrophy: A useful marker? Mediat Inflamm. 2003; 12 (2):127-128.

[49] Ray G., Batra S., Shukla N., et al.. Lipid peroxidation, free radical production and antioxidant status in breast cancer. Breast Cancer Res Treat. 2000; 59 (2): 163-170.

[50] Abdulkerim K., Rasim M., Mustafa A., et al. Selenium: Its metabolism and relation to exercise. Pak. J. Pharm. Sci. 2016; 29 (5): 1719-1725.

[51] Yusra S., Salwa H., and Nahi Y. Arsenic, Selenium, Zinc, Copper, Hormonal changes, and oxidative stress in AL-Basra and Missan provinc¬es patients with prostate tumors. Iraqi Journal of Cancer and Medical Genetics. 2018; 11 (1): 42-49.

[52] Griffin A. Role of selenium in the chemoprevention of cancer. Adv Cancer Res. 1979; 29: 419-442.

[53] Waters D., Shen S., Cooley D., et al. Effects of dietary selenium supplementation on DNA damage and apoptosis in canine prostate. J Natl Cancer Inst. 2003; 95 (3): 237-241.

[54] Engin K., Yasar O., Murat Z., et al. Oxidative stress parameters in patients with prostate cancer, benign prostatic hyperplasia and asymptomatic inflammatory prostatitis: A prospective controlled study. Adv Clin Exp Med. 2017; 26 (7): 1095-1099.

[55] Meludu S., Ezenwelu V., Onah C., et al. Prostatic Alteration of Serum Levels of Carcino-Embryonic Antigen, Zinc and Selenium among Patients with Benign Prostatic Hyperplasia and Cancer of the Prostate. European academic research. 2017; 5 (3): 1626-1642.

[56] Ayse E., Burcu U., Engin K., et al. Evaluation of trace element levels in patients with prostate cancer, benign prostatic hyperplasia and chronic prostatitis. Gülhane Tıp Derg. 2016; 58: 27-32.

[57] Gupte A., and Mumper R. Elevated copper and oxidative stress in cancer cells as a target for cancer treatment. Cancer Treat Rev 2009; 35 (1): 32-46.

[58] Ghani M., Khan M., Ahmed M., et al. Serum Zn and Cu Levels in Patients with Benign Prostate Hyperplasia (BPH) and Prostate Carcinoma (PCa) and their Association with the Stage of the Disease in Carcinoma of Prostate Patients. Journal of Applicable Chemistry. 2015; 4 (4): 1248-1263.

[59] Rekha C., and Praveena V. Serum Zinc and Copper Levels in Benign and Malignant Lession of Prostat. Int J Pharm Bio Sci. 2014; 5 (3): 926-930.

[60] Platz, E., and Helzlsouer, K. Selenium, Zinc and Prostate Cancer. Epidemiologic Review. 2001; 23: 93-101.

[61] Gómez Y., Arocha F., Espinoza F., et al. Zinc levels in prostatic fluid of patients with prostate pathologies. Investigacion Clinical. 2007; 48 (3): 287-294.

[62] Zaichick Y., Sviridova T., and Zaichick S. Zinc concentration in human prostatic fluid: normal, chronic prostatitis, adenoma and cancer. International Urology and Nephrology. 1996; 28: 687-694.

[63] Costello L., Franklin R., and Feng P. Mitochondrial function, zinc, and intermediary metabolism relationships in normal prostate and prostate cancer. Mitochondrion. 2005; 5: 143-153.

[64] Tahminur R., and Mowladad C. Zinc and Benign Prostatic Hyperplasia (BPH) & Prostate Cancer (PCa) association. Medical Research Archives. 2016; 4 (7): 1-16.

[65] Wu T., Sempos C, Freudenheim J., et al. Serum iron, copper and zinc concentrations and risk of cancer mortality in US adults. Annals of Epidemiology. 2004; 14: 195-201.

[66] Maret G., and Jan F. Vitamins C and E: Beneficial effects from a mechanistic perspective. Free Radic Biol Med. 2011; 51 (5): 1000-1013.

[67] Mehmet K., Necip P., Mehmet B., et al. Serum Levels of Trace Elements in Patients with Prostate Cancer. Asian Pacific Journal of Cancer Prevention. 2014; 15 (6): 2625-2629.

[68] Olorunnisola O., Ajayi A., Okeleji L. et al. Vitamins as Antioxidants. J Food Sci Nutr Res. 2019; 2 (3): 214-235.

[69] Kagan V., Serbinova E., Forte T., et al. Recycling of vitamin E in human low density lipoproteins. J. Lipid Res. 1992; 33: 385-397.

[70] Suarna C., Hood R., Dean R. et al. Comparative antioxidant activity of tocotrienols and other natural lipid-soluble antioxidants in a homogeneous system, and in rat and human lipoproteins. Biochim. Biophys. Acta. 1993; 1166: 163-170.

[71] Verlangieri A., and Bush M. Effects of d-a-tocopherol supplementation on experimentally induced primate atherosclerosis. J. Am. Coll. Nutr. 199; 11: 131-138.

[72] Prokopowicz A., Sobczak A., Szula M., et al. Effect of occupational lead exposure on α- and γ-tocopherol concentration in plasma. Occupational and Environmental Medicine. 2013; 70: 365.

[73] Serbinova E., Kagan V., Han D. et al. Free radical recycling andintramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. Free Radic. Biol. Med. 1991; 10: 263-275.

[74] Romanda D., Obioma N., and Ignatius M. Oxidative Stress Indicators in Patients with Prostate Disorders in Enugu, South-East Nigeria. BioMed Research International. 2014; 1-6

[75] Aryal M., Pandeya A., Das B. et al. Oxidative Stress in Patients with Benign Prostate Hyperplasia. J Nepal Med Assoc. 2007; 46 (167): 103-106.