

SERUM COPPER LEVEL AS A PREDICTIVE MARKER IN PATIENTS OF MALIGNANT CANCEROUS PROSTATE AND BENIGN PROSTATIC HYPERPLASIA (BPH) ALONG WITH ITS CORRELATION TO SERUM ACID PHOSPHATASE

Naheed Qadir¹, Jalil Qadir² and Jamil Ahmed Siddiqui³

¹Department of Biochemistry, Peoples University of Medical & Health Sciences, Nawabshah-67450, Pakistan
e-mail: naheed_qadir@yahoo.com

²Department of Forensic medicine & Toxicology, Liaquat college of Medicine & Dentistry, Karachi-75290
E-mail: drjalilqadir@hotmail.com

³Department of Biochemistry, Al Tibri Medical College, Karachi, Pakistan
E-mail: jamilahmedsiddiqui@gmail.com

ABSTRACT

The objective of present study was to estimate and compare the serum copper level in patients with benign prostatic hypertrophy and prostate carcinoma and their correlation with serum acid phosphatase. Prostatic acid phosphatase for Group A was 2.28 ± 0.99 , for Group B 16.03 ± 5.89 and for Group C 46.43 ± 6.22 U/L, respectively. Highly significant P- value of 0.0001 was noted among all the 3 groups; A, B and C. Serum copper levels in Group A 106.88 ± 19.28 , Group B 104.29 ± 17.40 and Group C 92.88 ± 11.28 $\mu\text{g/L}$, respectively. P value between groups A vs B, A vs C and B vs C were noted as 0.052, 0.001 and 0.022, respectively. Serum copper was reduced in group B compared to A, but P value showed no significant difference ($p=0.052$). However, A vs C and B vs C showed statistically significant differences. The present study reports the raised prostatic acid phosphatase, and decreased serum copper levels in carcinoma of prostate gland indicating their diagnostic and prognostic significance.

Key words: Benign Prostatic Hyperplasia, Prostate carcinoma, Prostate acid phosphatase, serum Copper.

INTRODUCTION

Prostate gland which is a part of male reproductive system is considered as an accessory gland of the human body. The main function of the gland is to add secretion to the semen. The disorders of prostate gland are one of the prevalent and leading causes of renal abnormalities of senescence. The prostate gland can be affected by vast type of anomalies like infections, benign hyperplasia and malignancies (Singh *et al.*, 2016). Benign prostatic hyperplasia is one of the frequently encountered problem of urinary tract in late age. Although prostate cancer is a grave health issue of old age, it is the 6th most prevalent type of cancer globally. Prostate gland cancer has diverse and vast etiology, genetic factors, environmental hazards and dietary factors are all included in its etiology and pathogenesis (Sapota *et al.*, 2009). Alcohol consumption, smoking, pollutants, hormonal disturbance and STDs (sexually transmitted diseases) are compiled into the category of environmental factors. Among dietary factors consumption of large amount of fats, deficiency of specific vitamins and trace elements along with other micro nutrients are suggestive to cause prostate cancer (Järup, 2003). Above mentioned factors are involved in causing, by acting directly or indirectly with genes to cause abnormal cellular growth. Some carcinogenic agents of unknown origin can also be present in diet i.e. heavy metals and endogenous hormones either can induce or augment carcinogenesis. It must be noted that certain heavy metals are essential and required for normal cellular function but others can be toxic and carcinogenic (Vinceti *et al.*, 2007). Recent different studies carried on trace elements have put forward a possible role of heavy metals in the induction of cancerous growth. It is theorized that heavy metals impede at the measure and degree of cellular chemicals and metabolically enzyme extent of cell. Increased concentration of heavy metal supplement's or increased dietary intake maybe a possible cause for carcinogenesis (Arnold, 2005). However, the exact role of heavy metal in the induction and augmentation of carcinoma is yet a mystery. It is crucial to recognize the likelihood of heavy metals and their link with causing prostate cancer. Thus, an alteration in the homeostasis of trace elements in relation to prostate gland anomalies is worth to explore. PH (Prostate Hyperplasia) and prostatic carcinoma both have non-identical histo-pathological characteristic, biological behavior, and clinical findings with various metabolic variations are required to be assessed. Altered concentration of specific heavy metals or trace elements in serum has been outlined in earlier research which requires more comprehension. Earlier studies had reported that low levels of zinc in cancer of prostate play pivotal role in the induction of cancer. Likewise, copper has also been suggested in causing cancer, though various works has shown conflicted outcome (Platz and Helzlsouer, 2001). Thus, the role and levels i.e. excessive or deficient quantity of heavy metals or trace

elements causing the pathogenesis of benign prostatic hyperplasia (BPH) and carcinoma of prostate remains elusive. Hence, an exploration space remains that needs to be looked upon for the conceivable relationship and etiological part of heavy metals or trace elements; selenium, copper and zinc need further shedding of light and research. The current work is put forward to assess the blood levels of selenium, copper and zinc in BPH and carcinoma of prostate and their correspondence with acid phosphatase in patients at tertiary care hospital of PUMHS.

MATERIALS AND METHODS

Samples for serum copper and acid phosphatase were taken from 120 patients belonging to PMCH (Peoples Medical College Hospital). The sampling was done through purposive technique preferring Urological and surgical wards, approximate time frame was set for 8 months. Specimens were then analyzed in PUMHS Diagnostic and research laboratory. Specimens of 120 subjects were designated according to the inclusion and exclusion criteria. Subjects were divided into three groups, namely Group A = Control (n=60), Group B = BPH (n= 30) and Group C = Prostate cancer (n= 30). The patients and controls were educated regarding the reason of blood sampling and consent was taken. Five mL of blood was taken by the vein puncture in zinc and copper free containers. Samples were taken with extreme caution to avoid hemolysis of RBCs as they comprise high zinc element. Within one hour taken blood specimen were centrifuged and serum was then refrigerated in polypropylene screw capped test tubes, and stored at -20°C . Two mL of serum was diluted with de-ionized water and then 5 ml of analytical quality high purity concentrated nitric acid was added. Samples were mixed well afterwards and then permitted to stay at room temperature for next 3 hours. Later they were centrifuged for 10 minutes at 2500 rpm. The supernatant obtained was transferred to plastic bottles using chemically cleaned pipette, double distilled water was also added afterwards and then it was conserved at room temperature. The specimen obtained was exposed to atomic absorption spectrophotometer analysis technique for copper levels in serum by using GBC Aventa 2.01 Scientific equipment. Data was then analyzed on SPSS version 22.0 by using student 't' test and chi-square test at 95% confidence level.

RESULTS

The Age group, subjects of Controls, BPH and CA prostate was found to be 59.39 ± 5.88 , 62.44 ± 5.27 and 66.58 ± 3.74 years, respectively. There was no significant age difference among groups A and B (p value 0.009) although Group C patients were older and age had significant difference.

For Serum Acid Phosphatase mean results for Controls (Group A), BPH (Group B) and CA Prostate (Group C) were taken as 5.28 ± 0.99 , 20.03 ± 5.89 and 49.43 ± 6.22 U/L respectively with P value of 0.0001 was found among Group A, B and C. the results indicating increase of serum acid phosphatase in patients of prostate Cancer as compared to patients of Benign Prostatic Hyperplasia and Controls. Serum copper levels were noted as 113.88 ± 19.28 , 109.20 ± 17.40 and 96.88 ± 11.28 $\mu\text{g/L}$, respectively. Serum copper was reduced in group B when compared to A but P value showed no significant difference (p=0.052). Although A vs. C and B vs. C showed Significant P-value of 0.0001 (Table 1).

Table 1. Distribution of Age among the groups (n=120).					
	Mean	SD	SEM	F value	P value
Group A. Controls	59.39	5.88	0.83	13.37	0.038
Group B. BPH	62.44	5.27	1.05		
Group C. Prostate cancer	66.58	3.747	0.74		

Table 2. Serum acid phosphatase levels (U/L) in controls and cases (n=120).					
	Mean	SD	SEM	F value	P value
Group A. Controls	5.28	0.99	0.14	869.6	0.0001
Group B. BPH	20.03	5.89	1.17		
Group C. Prostate cancer	49.43	6.22	1.24		

Table 3. Serum copper levels ($\mu\text{g/dL}$) in controls and cases (n=100).					
	Mean	SD	SEM	F value	P value
Group A. Controls	113.88	19.28	2.72	5.76	0.0001
Group B. BPH	109.20	17.40	3.48		
Group C. Prostate cancer	96.88	11.28	2.25		

DISCUSSION

This study was conducted for the sole purpose of evaluating the copper and PAP levels in normal control designated as Group A, and cases of BPH and Cancer of Prostate designated as Group B and Group C, respectively. Findings of age 64.58 ± 3.74 years of cancer of prostate is less paralleled to Famurewa and Akinosun (2014) which showed mean age of the carcinoma prostate of 71.35 ± 8.45 years which when compared to this study is slightly higher. However, it must be noted that Famurewa and Akinosun did not report significant difference for the age between the controls and prostate cancer subjects ($p < 0.05$) (Karimi *et al.*, 2012). There may be versatile reasons for this age difference. The mean age of Pakistan is on decline and thus this can be one of the reasons. Although another reason can be the geographical difference, along with the age inclusion criteria of the said study. Age which is an independent variable has long been considered to a risk factor for the cancer of prostate among men. It is suggested that prostate gland becomes enlarged at the 5th decade of age, because of the aging process, although it may be because of neoplastic growth as well. One of the tumor markers of carcinoma prostate is PAP, though its sensitivity is low. In present study PAP was noted as 5.28 ± 0.99 , 20.03 ± 5.89 and 49.43 ± 6.22 U/L in controls, and subjects of benign prostatic hyperplasia and prostate cancer, respectively (P- value 0.0001). In the present study the findings are in confirmation to the study by Gabra *et al.* (2014) which has reported raised PAP 45.43 ± 3.2 U/L in their recent study from the University of Fedail, Sudan (Kaba *et al.*, 2014). In current investigation the most important and pivotal research variable has been to dig into the trace mineral i.e. serum copper in patients of carcinoma of prostate and benign prostatic hyperplasia. It was noted that serum copper was 113.88 ± 19.28 , 109.20 ± 17.40 and $96.88 \pm 11.28 \mu\text{g/L}$ respectively. P value among groups A vs. B, A vs. C and B vs. C were noted as, 0.001 and 0.022 respectively. In BPH serum copper was found to be in lower quantity when compared to control group but statistically the variance was non-significant ($p = 0.052$). Although the copper was low in carcinoma of prostate which statistically displayed noteworthy differences. Reduced serum copper level findings are opposite to the past study of Karimi *et al.* (2012) which reported high copper from nails and the hair of the carcinoma of prostate patients (Hurst *et al.*, 2012). This contradistinction can be most probably because of different samples that is serum in current study vs. nails and hair of Karimi *et al.* Another recent study by Singh *et al.* (2015) reported low levels of serum copper in CA prostate patients in India. Singh *et al.* has consistent finding to our current study (Famurewa and Akinosun, 2014). Denoyer (2016) reported recently that high copper content was found in prostate cancer tissue but there was no variation in the serum copper levels in carcinoma prostate patients when compared to controls. Thus, the findings of Denoyer is contradiction to present and past study (Park *et al.*, 2016). The current and present study observed serum copper level to be low in BPH and CA prostate patients. However, additional studies will help to elucidate whether along with clinical diagnosis, serum copper is useful in the different diagnosis of BPH and carcinoma prostate. It is considered by the biochemical evidence presented here ensures the conclusion that altered copper metabolism maybe playing a casual yet pivotal role in BPH and CA prostate.

Conclusion

Serum copper was found to be reduced in both BPH and carcinoma of prostate in the present study. Acid phosphatase was significantly high in carcinoma prostate proving the diagnostic significance of both markers.

REFERENCES

- Arnold, W.N. (2005). Selenium and the prostate. *J Appl Biomed.*, 3: 59–66.
- Denoyer, D. H.B. Pearson, S.A. Clatworthy, Z.M. Smith, P.S. Francis, R.M. Llanos, I. Volitakis, W.A. Phillips, P.M. Meggyesy, S. Masaldan and M.A. Cater (2016). Copper as a target for prostate cancer therapeutics: copper-ionophore pharmacology and altering systemic copper distribution. *Oncotarget.*, 7(24): 37064–37080.

- Famurewa, A. and O. Akinosun (2014). Plasma levels of α -tocopherol, γ -tocopherol and selenium in patients with prostate cancer in Nigeria. *Int J Med Biomed Res.*, 3(3): 161–7.
- Gabra, H.M., A.A. Elmugadam, B.H. Elabid, G.A. Elfadil, M.H. Arbab and E.H. Elssaig (2014). Serum Total Prostatic Specific Antigen and Prostatic Acid Phosphatase Measurement Discriminating Prostate Carcinoma from Benign Prostatic Hyperplasia in Sudanese Patients. *IJPSI.*, 3(1): 36-40.
- Hurst, R. L. Hooper, T. Norat, R. Lau, D. Aune, D.C. Greenwood, R.Vieira, R.Collings, L.J.Harvey, J. A. Sterne, R. Beynon, J. Savović and S.J. Fairweather-Tait (2012). Selenium and prostate cancer: systematic review and meta-analysis. *Am J ClinNutr.*, 96(1): 111–22.
- Järup, L. (2003). Hazards of heavy metal contamination. *Br. Med Bull.*, 68: 167–82.
- Karimi, G., S. Shahar, N. Homayouni, R. Rajikan, N., F. Abu Bakar and M.S. Othman(2012). Association between trace element and heavy metal levels in hair and nail with prostate cancer. *Asian Pac J Cancer Prev.*, 13(9): 4249–53.
- Kaba, M. N. Pirincci, M.B.Yuksel, I.Gecit, M. Gunes, H. Ozveren, H. Eren and H. Demir (2014). Serum levels of trace elements in patients with prostate cancer. *Asian Pac J Cancer Prev.*, 15(6): 2625–9.
- Platz, E.A. and K.J. Helzlsouer (2001). Selenium, zinc, and prostate cancer. *Epidemiol Rev.*, 23(1): 93–101.
- Park, J., S.Y. Cho, S. Jeong, S.B. Lee, H. Son and H. Jeong (2016). Low testosterone level is an independent risk factor for high-grade prostate cancer detection at biopsy. *BJU Int.*, 118: 230-235.
- Sapota, A., A. Darago J. Taczalski and A. Kilanowicz (2009). Disturbed homeostasis of zinc and other essential elements in the prostate gland dependent on the character of pathological lesions. *Biometals Int J Role Met Ions Biol Biochem Med.*, 22(6):1041–9.
- Singh, B. P., S. Dwivedi, U. Dhakad, R.C. Murthy, V. K. Choubey, A. Goel and S.N. Sankhwar (2016). Status and Interrelationship of Zinc, Copper, Iron, Calcium and Selenium in Prostate Cancer. *Indian J ClinBiochem.*, 31(1): 50–6.
- Vinceti, M. M. Venturelli, C. Sighinolfi, P. Trerotoli, F. Bonvicini, A.Ferrari, G. Bianchi, G. Serio, M. Bergomi and G. Vivoli (2007). Case-control study of toenail cadmium and prostate cancer risk in Italy. *Sci Total Environ.*, 373(1): 77-81.

(Accepted for publication December 2018)