Zinc and Benign Prostatic Hyperplasia (BPH) & Prostate Cancer (PCa) association.

Authors:

Md. Tahminur Rahman[1]*

ATM Mowladad Choudhury[2]

[1] Department of Pathology, AKMMC, Dhanmondi, Dhaka-1205.Bangladesh

[2] Department of Urology, BIRDEM, Shahbag, Dhaka-1000. Bangladesh

*** Corresponding author**

E-mail: mtahminur@yahoo.com

Abstract:

Prostatic lesion like benign prostatic hyperplasia (BPH) and prostatic carcinoma (Pca) are major health problem among increasing aged males. Many risk factors like androgen testosterone and its active metabolites, 5DHT, genetic polymorphism, high fatty diet, inflammatory cytokine, medication etc. are implied in the genesis of BPH and Pca. Several studies in the recent past have shown association of trace element zinc in the genesis of BPH and Pca. We have reviewed different online searches on serum zinc and prostatic lesion with conflicting results. Some are showing its association with the genesis of prostatic lesion, others are opposing it. The present review article highlights some of the important features of the trace element zinc, its transporter and role in prostatic lesion specially BPH and prostatic carcinoma, This will hopefully lead to better understanding of the role of zinc in the etiopathogeneis of BPH and Pca and open research avenues to define better preventative strategies for the management of BPH and Pca.

Key words: Zinc, Zinc transporters, benign prostatic hyperplasia (BPH) prostatic cancer (Pca), Association.

1. Introduction

BPH is an extremely common disorder in men over 50 years of age characterized by hyperplasia of stromal and epithelial cells leading to formation of nodules that when large cause partial or complete obstruction of urethra. Pca is also the second most common cancer in male by incidence and mortality. Many risk factors are attributed in the genesis of BPH and Pca as mentioned before including the trace element zinc. Trace element zinc is very important and it has been shown that its deficiency can lead to diarrhea, growth retardation, different prostatic lesions like BPH, Pca. Zinc ions contribute to a number of biological processes like DNA synthesis, gene expression, enzyme catalysis, neurotransmission and apoptosis. (Ho E, 2004) Zinc dysregulation, deficiency and over supply are connected with various diseases like BPH, prostatic carcinoma. Some of the important molecular mechanisms, alteration in zinc associated with BPH & Pca are discussed below.

2. Zinc and normal prostate

The prostate is a zinc accumulating citrate producing organ and contains a higher level of zinc than most other tissues. (Geovanni Espinosa, 2013; Kolenco V,2013). The protein ZIP1 is responsible for active transport of zinc into prostate cells. Zinc plays an important role to change the metabolism of the cell in order to produce citrate which is an important component of semen and apoptosis. The process of zinc accumulation, alteration of metabolism and citrate production is energy inefficient and prostate cells sacrifice enormous energy (ATP) in order to complete this task. (Franklin RB, 2007).

Zinc (Zn) is an essential micronutrient required for over 300 different cellular processes, (Kelleher SL, 2011) including DNA and protein synthesis, enzyme activity, and intracellular signaling. Prostatic epithelial cells have characteristically high aerobic glycolysis, low respiration rates and high citrate secretions (Harkonen 1981).

Zinc imposes apoptogenic effects and suppressor tumour progression. (Clegg MS 2005) Zinc(II) ions contribute

to a number of biological processes e.g. DNA synthesis, gene expression, enzymatic catalysis, neurotransmission, and apoptosis. (Gumulec J, 2011).

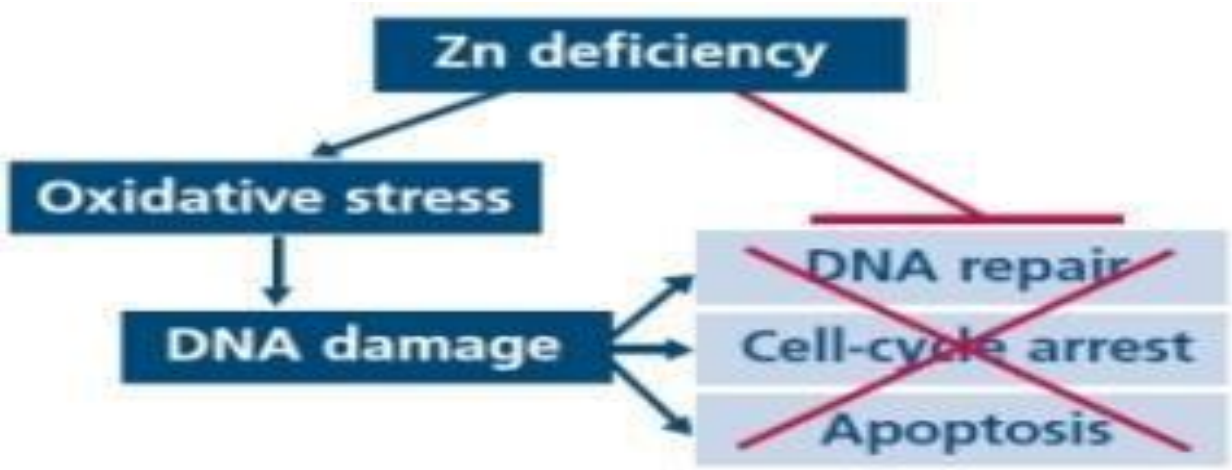

Figure 1: Showing effect of Zinc deficiency in prostatic cells

It is unique that human prostate glandular epithelial cells have the unique capability of accumulating high levels of zinc. This is a property essential to inhibit m-aconitase activity so that citrate can accumulate for secretion into prostatic fluid, which is a major function of the prostate gland. This results in truncated Krebs cycle with the consequence of the lost ATP production that would result from citrate oxidation. The cellular accumulation of zinc also inhibits mitochondrial terminal oxidation and respiration. Additional metabolic effects of zinc accumulation lead to anti-proliferative effects via its induction of mitochondrial apoptogenesis. Zinc accumulation also inhibits the invasive/migration activities in malignant prostate cells. The anti-proliferative effects and the effects on invasion and migration occur through zinc activation of specific intracellular signaling pathways. Consequently, these effects impose anti-tumor actions by zinc. A growing body of experimental evidence support that high zinc levels are essential for prostate health. The possible mechanisms include the effects of zinc on the inhibition of terminal oxidation, induction of mitochondrial apoptogenesis, and suppression of NFκB activity (Yangsong and Emily Ho,2009;Sztalmachova M etal 2012).

The most recent findings are the effects of zinc in the maintenance of DNA integrity in normal prostate epithelial cells (PrEC) by modulating the expression and activity of DNA repair and damage response proteins, especially p53. Zinc depletion in PrEC increased p53 expression but compromised p53 DNA binding activity resulting in an impaired DNA repair function. Moreover, recent findings support the role of zinc transporters as tumor suppressors in the prostate. (Yang Song and Emily Ho, 2009).

3. Zinc and BPH

As stated before, although the healthy human prostate accumulates the highest level of zinc of any soft tissue in the Body (Kolenko V, 2013), this unique property is retained in BPH, but is lost in prostatic malignancy, which implicates changes in zinc and its transporters in carcinogenesis (Costello LC ,2011. HO E, 2009). ZIP4 is an important zinc transporter. ZIP4 expression was detected in 14 prostate carcinoma and 20 BPH tissues by real-time RT-PCR and western blot in a study. (Chen QG, 2012). The expression of ZIP4 mRNA and protein is significantly down-regulated in prostate carcinoma tissues compared with that in BPH tissues. There was no correlation between the ZIP4 expression and the pathologic grade of prostate carcinoma.

Differences between chemical element contents in hyperplastic and nonhyperplastic prostate glands was investigated in a study by neutron activation analysis. (Zaichick V,Zaichick S,Davydova,2015). This study clarified the differences between Ag, Br, Ca, Co, Cr, Fe, Hg, K, Mg, Mn, Na, Rb, Sb, Sc, Se, and Zn contents in hyperplastic (patients with benign prostate hyperplasia (BPH), n = 32) and nonhyperplastic (control group of healthy male inhabitants, n = 32) prostates, by an instrumental neutron activation analysis. Mean values (M ± SEM) for mass fraction (mg/kg, dry mass basis) of chemical elements in glands of patients with BPH were the following: Ag, 0.0346 ± 0.0060; Br, 30.4 ± 3.6; Ca, 2030 ± 165; Co, 0.0716 ± 0.0097; Cr, 1.073 ± 0.119; Fe, 130.0 ± 7.9; Hg, 0.232 ± 0.030; K, 14,470 ± 740; Mg, 1200 ± 80; Mn, 1.19 ± 0.09; Na, 11,610 ± 870; Rb, 14.7 ± 0.8; Sb, 0.163 ±

0.025; Sc, 0.0257 ± 0.0040; Se, 1.243 ± 0.079; and Zn, 1235 ± 92. It was observed that in BPH tissue, the mass fraction of Co ($p < 0.015$), Cr ($p < 0.0002$), Hg ($p < 0.000007$), K ($p < 0.001$), Rb ($p < 0.048$), Sb ($p < 0.0001$), and Se ($p < 0.000001$) were significantly higher than in controls. In the sixth to eighth decades, the mass fractions of almost all chemical elements in hyperplastic prostates did not depend from age.

Correlation between pairs of prostatic chemical element mass fractions indicates that there is a great disturbance of prostatic chemical element relationships with a benign hyperplastic transformation. The results apparently confirm the disturbed homeostasis of Zn and Se and some other chemical elements in the etiology of BPH. Zinc finger E-box-binding protein 2 (ZEB2) is known to help mediate the epithelial-to-mesenchymal transition, and thereby it facilitates cancer metastasis. This study was aimed to explore whether ZEB2 expression differs in prostate cancer (PCa, n=7) and benign prostatic hyperplasia (BPH, n=7) tissues. In PCa tissues, the levels of both immunoreactive ZEB2 and androgen receptor (AR) were found to be significantly higher ($P<0.05$) when compared with BPH tissues. Co-regulation of AR and ZEB2 prompted us to investigate the role of androgenic stimuli in ZEB2 expression. ZEB2 expression was found to be significantly ($P<0.05$) upregulated after androgen stimulation and down regulated following AR silencing in LNCaP cells, an androgen-dependent PCa cell line. This finding suggested AR as a positive regulator of ZEB2 expression in androgen-dependent cells. [Jacob S, 2014].

Molecular targets in benign prostate hyperplasia (BPH) were searched in a PCR Array based screening of 84 genes was performed in a study of those, expression of ZFP91 (ZFP91 zinc finger protein) was notably up regulated. Limited data concerning the function of ZFP91 product show that it is a potential transcription factor up regulated in human acute myelogenous leukemia and most recently found to be the non-canonical NF-κB pathway regulator. As for prostate cell lines examined, all expressed ZFP91 mRNA. Western blotting analysis showed markedly higher protein levels of ZFP91

in all cancer cell lines in comparison with normal (PrEC) cells. In conclusion, the up regulated ZFP91 mRNA in BPH, not accompanied by parallel changes in ZFP91 protein levels, together with ZFP91 protein abundance in prostate cancer cell lines suggest ZFP91 involvement in these prostate diseases. (Paschke L, 2014)

The effects of zinc (Zn(2+)) concentrations on cultured benign prostatic hyperplasia (BPH) smooth muscle cell (SMC) proliferation, the effects of Zn(2+) were studied in primary cultures of human BPH SMC, stimulated with either 10-μM lysophosphatidic acid (LPA) or LPA in combination with 100-nM testosterone were studied in a shidy. Deoxyribonucleic acid replication and protein synthesis using [(3)H]-thymidine and [(35)S]-methionine incorporation were measured. The bell-shaped concentration response of Zn(2+) on cultured BPH SMC proliferation suggests that changes in prostate Zn(2+) concentrations, during aging, diet, or inflammatory conditions, may be of importance in the pathogenesis of BPH. (Adolfsson PI, 2015).

Zinc α2 glycoprotein has also been recently identified by proteomics in prostatic tissue showing different values in patients with prostate cancer and benign prostatic hyperplasia. (Katafigiotis I, 2012)

4. Zinc and Pca development

Prostate cancer (PCa) is one of the most commonly diagnosed malignancies in men and the second leading cause of male cancer mortality. Prostate cancer cells are generally devoid of zinc.

This allows the prostate cancer cells to save energy and utilize this energy to grow and spread. The absence of zinc is thought to occur via a silencing of a gene that produces the transporter protein ZIP1. Zinc level in malignant prostate tissue are 62-75% lower than in normal tissue. In addition, prostate cancer patients have lower zinc levels in blood compared to healthy controls. Zinc (Zn) levels in formalinfixed paraffin embedded tumor and tumor-adjacent non-neoplastic tissue of never- and ever-smokers with prostate cancer was studied in one research. (Dudas CL, Kandegedera A, Kryvenko ON, Gupta N, Rybicki BA, Dou Q P,

Mitra B. 2014) Smokers (*N* =25) had significantly higher Cd (median ppb, *p* =0.03) and lower Zn (*p* =0.002) in non-neoplastic tissue than never-smokers (*N*=21). Metal levels were not significantly different in tumor tissue of smokers and non-smokers. Tissue Zn levels were also higher in smokers with distant recurrence (tumor, *p* =0.039 and adjacent non-neoplastic, *p*=0.028). They also observed high levels of Zn in ever-smoker smoking cases with recurrent disease.

Prostate cancer is considered unusual in that risk of the disease is generally associated with low Zn levels (Costello LC 2011). At least two previous studies, however, found increased risk of advanced or fatal prostate cancer in men using high levels of Zn supplements (Leitzmann MF 2003) or multivitamin supplements containing Zn (Lawson KA 2007), although Zn is generally considered to have protective effects for prostate cancer, overall. Work by Prasad et al. [Prasad AS,Mukhtar H, Beck FW,Adhami VM,Siddiqui IA,Hafeez BB,Kucuk O 2009] using the transgenic adenocarcinoma of the mouse prostate (TRAMP) model suggests that both high and low Zn levels may be associated with greater tumor weight compared with tumors in mice with normal Zn levels. Zn imbalance, therefore, may play a role in prostate recurrence among smokers.

Several typical characteristics of prostate tissue have been identified including the ability to accumulate zinc(II). However, this feature of prostate cells is lost during carcinogenesis and, thus, prostate cells are unable to accumulate zinc(II) ions in high levels. Therefore, it is expected that zinc(II) ions can significantly contribute to the progression of tumor disease and to the ability of prostate cell lines to metastasize. Zinc(II) ions caused elevated expression of Ki-67, a marker of proliferation, extremely low expression of p53, high expression of Bcl-2 and no changes in the expression of p53. Experimental data show different effect of zinc(II) ions on expression of the above-mentioned regulatory genes, which may give us more information on their impact on cancer development and progression with possible using for cancer therapy. (Sztamachova M, 2012) Zinc finger X-

chromosomal protein (ZFX) is a member of the zinc finger family of proteins. (Jiang H, 2012) ZFX is in important in several cancer types, including prostate cancer.

A marked decrease in the level of zinc is a consistent characteristic of prostate cancer; which results from down-regulation of ZIP1 zinc transporter. RREB-1 transcription is involved in the down-regulation of ZIP1 gene expression; and over expression of RREB-1 resulted in a decrease in the abundance of hZIP1 in the plasma membrane of PC-3 cells; whereas siRNA knock down significantly increased hZIP1 expression. Prostate TMAs and tissue sections showed an inverse relationship between RREB-1 and hZIP1 staining. RREB-1 overexpression results in down-regulation of hZIP1 and contributes to the loss of hZIP1 expression and zinc in prostate cancer. This is an early event in prostate carcinogenesis. (Jiang R, 2012. Zou J, 2011).

The prostate cancer-up-regulated Myc-associated zinc-finger protein (MAZ) modulates proliferation and metastasis through reciprocal regulation of androgen receptor. MAZ and AR are interrelated and that MAZ plays an important role in PCa pathogenesis, which could be a potential therapeutic target. Zinc α2-glycoprotein has also been recently identified by proteomics in prostate tissue showing different values in patients with prostate cancer and benign prostate hyperplasia. Zinc finger protein X-linked (ZFX) is a highly conservative mammalian gene with related functions in cell survival and proliferation. However, there are limited reports on regulation of ZFX as a therapeutic target in cancer treatment. The expression of ZFX in prostate cancer with matched normal adjacent tissues (n=45) and benign prostatic hyperplasia (BPH) tissues (n=16) were observed by immune histochemical analysis. The effect of lentiviral siRNA (small interference RNA)-mediated dysfunction of ZFX on the proliferation of prostate cancer cells was studied, caspase-1, -3 and -9 by western blotting and colorimetric assay. Prostate cancer specimens appeared significantly higher (42.2% of cases being positive) than that observed in normal adjacent tissues (11.8% of cases being positive) and BPH

tissues (12.5% of cases being positive). (Jiaol et al, 2013).

5. Zinc as preventive factor for Pca

Experimental studies have provided evidence that zinc has a protective effect against development and progression of prostate cancer; however, epidemiological studies have reported inconsistent findings. One study has evaluated the association between pre-diagnostic serum zinc and prostate cancer risk in a cohort of multiethnic population. (Leitzmann MF2003). This case-control study is nested within the multiethnic Cohort of African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in Hawaii and California. The analysis included 392 prostate cancer cases and 783 controls matched on age, race/ethnicity, date/time of blood draw and fasting status. Conditional logistic regression was used to estimate odds rations (OR) and 95% confidence intervals (CI). The mean serum zinc concentrations did not significantly differ between cases (94.9 μg/dl) and controls (93.9 μg/dl). No association was found between serum zinc levels and prostate cancer either overall or by tumor stage/grade. In ethnic specific analyses, positive associations were found in Japanese Americans (OR for the highest vs. the lowest tertile= 2.59, 95% CI: 1.09-6.17) and lotions (OR=2.74, 95% CI:1.05-7.10), whereas no association was observed in African Americans and whites.

They found no evidence to support an inverse relationship between serum zinc and prostate cancer risk, and, to the contrary, found a suggestion in the ethnic specific results of a possible increase in risk; however, blood concentrations of zinc may not adequately reflect the levels in prostate tissue. They advocated a further study with a larger sample size, and if possible, with assessment of zinc tissue levels, which is warranted to confirm these findings. Many dietary compounds have been considered to contribute to cancer prevention including zinc, which has a pivotal role in modulating apoptosis. However, the mechanism for zinc-mediated prostate cancer chemoprevention remains enigmatic. Exposure to zinc induced apoptosis and resulted in Tran's activation

of p21 (WAF1/Cip1) (Yang N, 2013) in a Smad-dependent and p53-independent manner in prostate cancer cells. These results suggest a new avenue for regulation of zinc-induced apoptosis.

6. Zinc transporters and Pca

Zinc transporters were shown to play roles in the development of prostate, bladder, and renal cancer, genome-wide association study (GWAS) datasets was conducted for variants in 24 zinc transporter genes. At least ten ZnT and fourteen Zip family members have been identified in mammals and their tissue expression, cellular localization and regulation are very different. (Lichten LA, Cousins RJ, 2009) Since it has been recognized that high zinc levels are essential for prostate health, a loss of function or dysregulation of certain zinc transporters could result in the impairment of zinc homeostasis and predispose prostate cells to the development of cancer low intracellular zinc content in human prostate cancer tissues or prostate epithelial cancer cell lines. hZIP1, hZIP2, and hZIP3 gene and/or protein expressions were down regulated in human prostate adenocarcinomatous glands and malignant cell lines. (Franklin RB 2005).

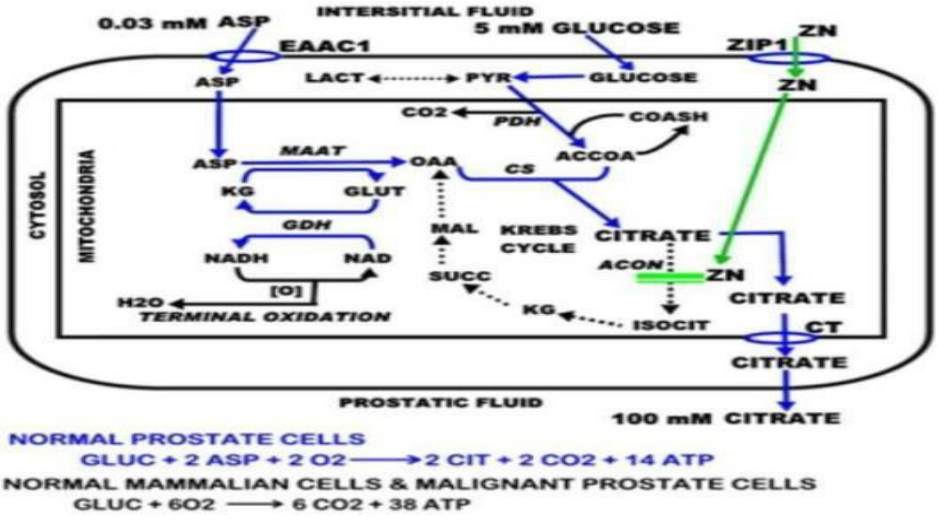

Figure 2: Alteration in ZIP protein in normal prostate cell, normal mammalian cells and malignant prostate cells.

A ZIP11 variant, rs8081059, was significantly associated with increased risk of renal cell carcinoma. No zinc transporter variants were associated with prostate cancer risk. The ability of prostate cells to accumulate zinc is thought to be due to the expression and activity of the zinc uptake transporter, ZIP1. (Wu L, 2015) To avoid the anti-tumor effects of zinc, in prostate cancer the malignant prostate cells exhibit a silencing of ZIP1 gene expression accompanied by a depletion of cellular zinc. So it is regarded that ZIP1 is a tumor suppressor gene in prostate cancer. In addition to prostate cells, similar tumor suppressor effects of zinc have been identified in several other types of tumors.

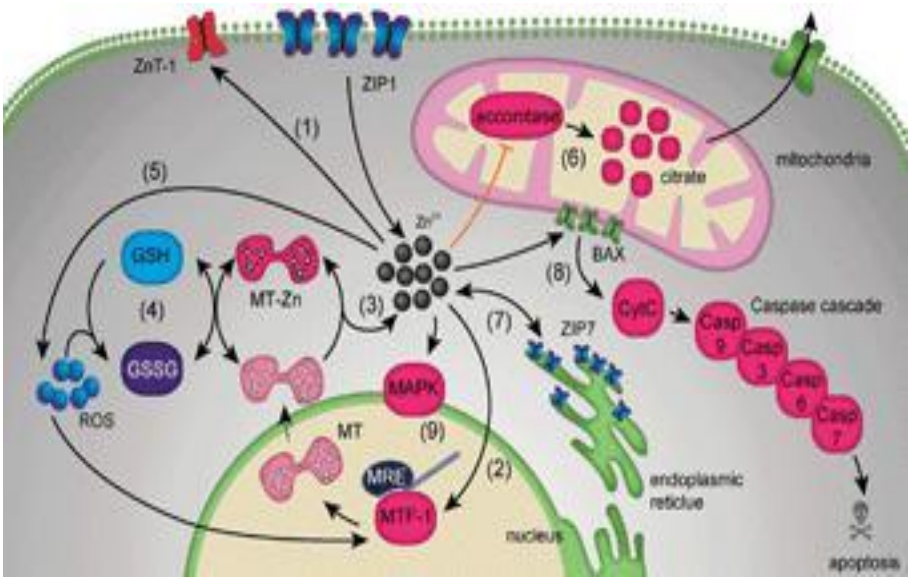

Figure 3: Showing Monitoring of the prostate tumour cells redox state and real-time proliferation by novel biophysical techniques and fluorescent staining

7. Serum Zinc and prostatic lesions

Zinc is a very important trace element and different studies have shown their association with diarrhea, growth retardation and different prostatic lesion including BPH. Serum zinc level was studied in different parts of the world with conflicting results. One study in Bangladesh showed gradual progressive increase level of serum zinc in benign, premalignant and malignant lesion of prostate. In BPH the serum zinc level was (mean±SD) 101±26.15, in HGPN 147±20.95 and prostate cancer 139±11.09.

This gradual increase in zinc level was statically significant ($p<0.017$) (Rahman MT, 2012). In another study in India, researchers found strong correlation between plasma zinc level and various prostatic diseases out of 80 cases studied (20 normal, 50 BPH, 10 cancers). Serum zinc was analyzed by atomic absorption photometry; the mean zinc level in normal was 94.5±10.38, BPH, 145.4±9.67 and 59.6±3.08 which were highly statistically significant. Another study measured zinc, vitamin A, albumin, copper and retinoid binding protein content in 27 patients with BPH and 19 patients with prostate cancer. A significantly lower zinc level was found in cancer groups ($p<0.05$) (Banudavi S, 2010).

Previously, two other studies showed different type of results. In one study in India, the researchers found strong correlation between plasma zinc levels and various prostatic diseases.

Out of 80 cases studied (20 normal, 50 benign, 10 carcinomatous) serum zinc level analyzed by atomic absorption spectrophotometer the mean±SD plasma zinc level in the normal case was 94.5±10.38, for benign prostatic lesion it was 145.4±9.67, 162.4±2.22, 172±5.27 (78% rise compared to normal patient) in those with fibromusclualr prostate, chronic prostatitis and benign prostatic hyperplasia respectively. Patients with malignancy had a plasma zinc level of 59.6±3.08, (37% fall compared to normal patients). There was high statistically significant prostatic disease. Another study measured zinc, vitamin A, albumin, copper and retinoid binding protein content in 27 patient with benign prostatic hyperplasia and 19 patients with prostate carcinoma. A significantly lower ($p<0.05$) level of serum zinc was found in cancer groups as well as a significant zinc/vitamin A correlation ($p<0.05$). (Banudavi S, 2010).

8. Conclusion

Zinc is an essential trace element required for normal prostatic function. Dysregulated zinc concentration, i.e. either excess or less can lead to different prostatic lesions like BHP, PIN, Pca but the research results are conflicting. Prostatic zinc concentration are lowered in Pca but serum zinc levels are shown to rise in BPH, PIN and fall in Pca. Zinc exerts its effect by various transporter

proteins and variability in transporter protein can lead to BPH or Pca. Zinc can act both as preventive component in preventing prostatic lesion or also can augment neoplastic proliferation of prostate. So more research based on more elaborate studies, including a larger number of patients, global study across the world can lead to a useful conclusion which can guide future diagnosis, treatment, management of prostatic lesions more definitely and scientifically.

Acknowledgement:

The authors wish to thank different websites, portals, pubmed and other publication sites from which the reference articles and figures are downloaded, reviewed and printed.

References

Ho E. (2004). Zinc deficiency, DNA damage and cancer risk. The journal of nutritional biochemistry. Oct;15(10):572-8.

Geovanni Espinosa.(2013) Nutrition and benign prostatic hyperplasia. Curr Opin Urol, 23:38-41.

Kolenko V, Teper E, Kutikov A, Uzzo R. (2013). Zinc and zinc transporters in prostate carcinogenesis. Nat Rev Urol. Apr;10(4):219-26.

Franklin RB, Costello LC. (2007). Zinc as an anti-tumor agent in prostate cancer and in other cancers. Arch Biochem Biophys. 2007 Jul 15;463(2):211-7.

Costello LC, Franklin RB. (2011). Zinc is decreased in prostate cancer: an established relationship of prostate cancer! J Biol Inorg Chem. Jan; 16(1): 3-8

Colegg MS, Hanna LA, Niles BJ, Momma TY, Keen CL. (2005). Zinc deficiency-induced cell death, IUBMB Life. Oct; 57(10):661-9.

Gumulec J , Masarik M, Krikzkova S, Adam V, Hubalek J, Hrabeta J, Eckschlager T, Stiborova M, Kizek R.(2011) Insight to physiology and pathology of zinc (II) ions and their actions in breast and prostate carcinoma. Curr Med Chem.;18(33):5041-51.

Yang Song and Emily Ho (2009). Zinc and prostate cancer. Curr Opin Clin Nutr Metab Care. November; 12(6): 640-645.

Sztamachova M, Hlavna M, Gumulec J, Holubova M, Babula P, Balvan J, Sochor J, Tanhauserova V, Raudenska M, Krizkova S, Adam V, Eckschlager T, Kizek R, Masarik M. Oncol Rep. (2012) Sep; 28 (3) : 806-14.

HO E, Song Y. (2009). Zinc and prostatic cancer. Curr opin clin nutr metab care. Nov; 12(6):640-5.

Chen QG, Zhang Z, Yang Q, Shan GY, Yu XY, Kong CZ. (2009) The role of zinc transpoerter ZIP4 in prostate carcinoma. Urol Oncol. 2012 Nov-Dec;30(6):906-11.

Zaichick V, Zaichick S, Davydov G. (2015) Differences between chemical element contents in hyperplastic and nonhyperplastic prostate glands investigated by neutron activation analysis. Biol Trace Elem Res. Mar;164(1):25-35.

Jacob S, Nayak S, Fernandes G, Barai RS, Menon S, Chaudhari UK, Kholkute SD, Sachdeva G. (2014) Androgen Receptor as a regulator ZEB2 expresison and its implications in epithelial-to-mesenchymal transition in prostate cancer. Endocr Relat Cancer. May 8;21(3):473-86.

Paschke L, Rucinski M, Ziolkowska A, Zemleduch T, Malenowicz W, Kwias Z, Malendowicz LK. (2014) ZFP91-a newly described gene potentially involved in prostate pathology. Pathol oncol res. Apr;20(2): 453-9.

Adolfsson PI, Bloth B, Hägg S, Svensson SP. (2015). Zinc induces a bell-shaped proliferative dose-response effect in cultured smooth muscle cells from benign prostatic hyperplasia. Urology. Mar;85(3):704.e15-9.

Katafigiotis I, Tyritizis SI, stravodimos KG, Alamanis C, Pavlakis K, Vlahou A, Makridakis M, Katafigioti A, Garbis SD, Constatntinides CA. (2012). Zinc α2-glycoprotein as a potential novel urine biomakre for the early diagnosis of prostate cancer. BJU Int. Dec; 110(11 Pt B): E688-93.

Dudas CN, Kandegedara A, Kryvenko O N, Gupta N, Rogers C, Rybicki BA, Dou QP, Mitra B (2014). Prostate tissue metal levels and prostate cancer recurrence in smokers. Biol trace elem. February: 157(2): 107-112.

Prasad AS, Mukhtar H, Beck FW, Adhami VM, Siddiqui IA, Din M, Hafeez BB, Kucuk O. (2010) Dietary zinc and prostate cancer in the TRAMP mouse model. J Med Food. 13(1):7076.

Jiang H, Zhang L, Liu J, Chen Z, Na R, Ding G, Zhang H, Ding Q.(2012). Cancer Gene their. Knockdown of zinc finger protein X-linked inhibits prostate cancer cell proliferation and induces apoptosis by activating caspase -3 and caspase-9. Oct; 19(10): 684-9.

Jiang R, Wang JC, Sun M, Zhang XY, Wu H. (2012) .Zinc finer X-chromosomal protein (ZFX) promotes solid agar colony growth of osteosarcoma cells. Oncol Res.;20(12): 565-70.

Zou J. Milon BC, Desouki MM, Costello LC, Franklin RB. (2011) HZIP1 zinc transporter down regulation in prostate cancer involves the overexpression of ras responsive element binding protein-1 (RREB-1). Prostate. Oct 1:71(14): 1518-24.

Jiao L, Li Y, Shen D, Xu C, Wang L, Huang Gk, Chen L, Yang Y, Yang C, Yu Y, Sun Y. The prostate cancer up regulated myc associated zinc finger protein (MAZ) modulates proliferation and metastatis through reciprocal regulation of androgen receptor. Med Oncol. 2013; 30(2):570.

Leitzmann MF, Stamper MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. (2003) Zinc supplement use and risk of prostate cancer. J Natl Cancer Inst. 95(13):1004-1007.

Lichten LA, Cousins RJ. (2009). Mammalian Zinc Transporters: Nutitional and physiologie regulation. Annual review of nutrition. Apr 27. It is the most recent and compete review about the research in zinc transporters.

Franklin RB, Feng P, Milon B, Desouki MM, Singh KK, Kajdacsy-Balla A, et al. (2005) hZIP1 zinc uptake transporter down regulation and zinc depletion in prostate cancer. Mol Cancer Sep 9.4:32

Wu L, Chaffee KG, Parker AS, Sicottee H, Petersen GM. (2015) Zinc transporter genes and urological cancers: integrated analysis suggests a role for zip11 in bladder cancer. Tumor Biol. Sep:36(10): 7431-7.

Rahman MT, Mumu MA, Kabir Y, Chodhury MM, Saiedullah M. (2012) Serum zinc level and prostatic lesion. Mymensingh Med J. Oct; 21(4): 679-83.

Banudavi S, Senthikumar K, Sharmila G, Arunkumar R, Vijayababu MR; Arunakaran J. (2010) Effect of Zinc onj regulation of insulin like growth factor signaling in human androgen independent prostate cancer cells. Clin Chim Acta. Feb; 411(3-4): 172-8.

Banudavi S. (2010) et al Chemopreventive effects of zinc on prostate carcinogentesies induced by N-methy-N-Nitrosourea and Testeterone in adult male Sprague-Dawley rats. J Cancer Res Clin Concol. June 16. (Epub ahead of print).

