

Zinc and Prostate cancer:A short Review

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Abstract

Zinc is an important trace element essential for normal growth and development of different tissues of our body and deficiency state leads to impairment of wound healing, multiple ulcerations, diarrhoea, infertility, impaired immunity, night vision and malformation in infants. Recently multiple research work throughout the world have showed Zinc association with different cancers particularly prostatic cancers. The present review article focusses on role of Zinc in the pathogenesis of prostate cancer.

Key Words: Zinc, Association, Prostatic cancer

Introduction

Zinc is one of the important micronutrients or trace elements which is a part of components of oxidative enzymes performing many vital functions. Zinc functions as an antioxidant and is involved in many critical biochemical reactions^{1,2,3}. It also protects DNA from damage and assists in its repair, Zinc is specially important in prostate and may protect it from early damage that could lead to cancer. ZIP1 a transporter of Zinc and a tumor suppressor gene is responsible for active transport of Zinc into prostate cell. One important role of zinc is to change the metabolism of cell in order to produce citrate, an important component of semen. Prostate cell sacrifice enormous amount of energy (ATP) to accomplish this. But when prostate cells become tumorigenic they utilized the Zinc as source of energy(ATP) and proliferate. Prostate cancer cells are generally devoid of Zinc. This allows prostate cancer cells to save energy not making citrate and utilize this energy to grow and spread^{4,5,6,7,8,9,10}.

Source of Zinc

Zinc main source is meat, shell fish, fish, sea fish, whole grain cereals, legumes, poultry, nuts, eggs and seed.

Daily requirement

Daily requirement is 100 mg/day. Overdose 1-2gm/day and can cause nausea, diarrhea, dizziness, drowsiness, hallucination. Deficiency can lead to Growth retardation, acrodermatitis enteropathica, anorexia and diarrhea, altered immune function, impaired night vision, increased incidence of malformations in infants, Infertility particularly male infertility, cancer specially in prostate, breast and Pancreatic cancer^{42,43}.

Zinc and Prostate Cancer association

Prostatic cancer is the most common cancer in men and second leading cause of death from cancer. It usually affects men over 50 years of age. Many risk factors are implicated in its etiopathogenesis like increased consumption of fats, decreased taking of antioxidants and lycopene consumption, genetic predisposition particularly BRCA1 & BRCA 2, Zinc level, androgen and tumor suppressor gene inactivation^{11,12,13,14,15}.

The high concentration of Zinc in the prostate suggests that Zinc may play a role in prostate health. Association between supplemental Zinc intake and prostate cancer risk among 46,964 US men from 1996-200 showed 2,901 new cases of prostate cancer, among which 434 cases were advance cancer. Supplemental Zinc intake at dose up to 100mg/day was not associated with prostate cancer risk. However compared to nonusers men who consumed more than 100mg/day of supplemental Zinc had a relative risk of advance prostate cancer of 2.29(95% CI, p=0.003) and men who took supplemental Zinc for 10 or more years had a relative risk of 2.37(95%CI, p<0.001). It was concluded from this study that Zinc over supply may play a role in prostate carcinogenesis^{16,17,18,19,20}.

Zinc and Transporter Protein

Zinc after absorption is transported by at least 24 Zinc transporter protein synthesized in our body to all cells through out the body. Among these 24 Zinc transporters some move Zinc into the cell, some carry it around inside the cell and some push Zinc out of the cell^{21,22}.

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Prostate cancer progression is facilitated by growth factors that activate signaling cascade and there by promote prostate cancer cell growth, survival, migration. Among this insulin like growth factor(IGF) contribute a major role in which Zinc has an important role. Zinc decreases the survival of androgen independent prostate cancer cells by modulating the expression of IGF system components and its signaling molecules. Thus Zinc may be qualified as a potential agent for treatment of prostate cancer^{23,24,25,26,27}.

The prostate contains highest concentration of Zinc of all soft tissues, but concentrations decreases significantly during prostate cancer. High Zinc levels are essential for prostate health and may limit prostate cancer development. The possible mechanisms include effects on Zinc on inhibition of terminal oxidation, induction of mitochondrial apoptogenesis and suppression NF-Kappa beta activity. Zinc also play an important role in DNA integrity in normal prostate epithelial cells by modulating DNA repair and damage response to proteins especially p53. Recent findings also support the role of Zinc transporters as tumor suppression gene ^{28,29,30}.

In a study in South Carolina, USA it was found that high ground water use and low Zinc concentrations had higher frequency of prostate cancer rate in AfroAmerican Community. Although the data are limited but it can be said that low environmental Zinc exposures and down regulation of prostatic Zinc transporters protein among the ethnic Afro American population in South Carolina USA. Early detection of prostatic cancer is the key to effective treatment of prostate cancer and exploration of citrate, Zinc, other electrolyte as prostatic fluid biomarkers are needed to address this critical prostate cancer issue.

The concentration between Zinc concentration in the prostates peripheral zone to the onset or presence of malignant process were studied in a study. This showed the prostatic carcinoma diagnostic potential is dependent on local Zinc concentration and there is indication that the amount of Zinc depletion could be used as a measure of Gleasons score of the tumor. It was evident from this study that prostate tumor progression is dependent on attenuated MT1/2 whereas Zinc induction of MT1/2 expression results in cellular Zinc restoration. So MT1/2 is a potential biomarker for prostate cancer and the utilization of Zinc in prostate cancer prevention and treatment^{31,32,33,34,35}.

Cadmium exposure has been suggested as a risk factor for prostate cancer. Experimental literature suggest that the carcinoma effect of cadmium is modified by the presence of Zinc. This study revealed a protective effect of Zinc intake on cadmium induced prostate injury and ultimate prostatic cancer progression.

Normal prostatic glandular epithelium has the unique function of accumulating high levels of Zinc. In prostate cancer this capability is lost as an early event in the development of the malignant cells. It was previously reported that ZIP1 is an important zinc uptake transporter in prostate cells and is down regulated in the malignant cells insitu along with depletion of Zinc levels. Two other ZIP family

ZIP2/ZIP3 also important along with ZIP1 involved in unique ability of prostate cells to accumulate high cellular Zinc levels. ZIP1 is important for extraction of Zinc from circulation, ZIP2/ZIP3 are important for retention of Zinc inside the cell. The down regulation of all three transporters in the malignant cells is consistent with the loss of Zinc accumulation in the cells. Since Zinc imposes tumor suppressor effects the silencing of these transporters are required for the manifestations of the malignant cells and supports the concept of ZIP1/ZIP2/Zip3 as tumor suppressor genes and Zinc as a tumor suppressor agent^{36,37,38,39}.

Zinc and metallothioneins

The metallothioneins(MT) are a family of small molecular weight trace metal and free radical scavenging proteins well established to play a role in the resistance to chemo and radiotherapy in human cancers. MT gene expression is upregulated in response to presence of metal ions as Zinc. Because prostatic tissue has the greatest concentration of Zinc in human body this study showed that treatment of prostatic carcinoma with Zinc causes an increase in MT expression, which is significantly associated with resistance to chemo and radiotherapy.

Promyelocytic leukaemia Zinc finger (PLZF) protein, a transcriptional repressor and negative regulator of the cell cycle, has been characterized as a prostatic - androgen responsive gene. Androgen independent cell line DU145 cells lack PLZF gene expression resulting in upregulation of Pbx1 and HoxC8 expression. The Pbx1 and HoxC8 heterocomplex may lead to androgen independent growth in prostatic cancer.

Mutations in mitochondrial DNA are frequent in cancer and the accompanying mitochondrial dysfunction might contribute to or signal tumor pathogenesis. The glandular epithelial cells of peripheral zone of human prostate accumulate high concentrations of Zinc which inhibits the activity of m-aconitase, an enzyme involved in citrate metabolism through Krebs cycle. This causes krebs cycle truncation and accumulation of high concentrations of citrate to be secreted in prostatic fluid. The accumulation of Zinc also inhibits terminal oxidation therefore these cells exhibit inefficient energy production. In contrast malignant cells of prostate is associated with an early metabolic switch leading to decreased accumulation of Zinc and increased citrate oxidation. The efficient energy production of these transformed cells implies increased electron transport chain activity, increased oxygen consumption, and perhaps excessive reactive oxygen species (ROS) production compared to normal prostatic epithelial cells. Because ROS have deleterious effects on DNA, proteins, lipids, the altered intermediary metabolism may be linked with ROS production and accelerated mitochondrial DNA mutations in prostate cancer. Early stages of prostate tumorigenesis based on analysis of models based on the homeodomain protein Nkx3 and Zinc finger protein Egr1 suggests that these transcription factors play distinct role in the initiation and progression of precursor prostatic intraepithelial neoplasia (PIN) lesion. Nkx3 is a candidate prostate tumor suppressor gene that demonstrates haploinsufficiency. The Zinc fingerprint protein Egr1 is over expressed in human and mouse prostate tumors and PIN lesions and regulates the expression of several genes implicated in prostate tumor progression including platelet derived growth factor and insulin like growth factor. The distribution of Zinc homeostasis featured with a significant decrease of cellular Zinc level was well documented to associate with the development and progression of human prostatic malignancy. Zinc treatment induces prostate malignant cell apoptosis through mitochondrial pathway. Metallothionein (MT) is a major receptor/donor of Zinc in the cells.

There are two distinct phases of prostate cancer development. In its early stages, prostate cancer is hormone dependent, requiring the male hormone androgen to grow. As the cancer progresses, it becomes androgen independent, no longer requiring androgens to grow. Due to the two distinct phases of prostate cancer, one study used both early- and late-stage human prostate cancer cell lines. In

addition, it examined benign prostate hyperplasia cells. Although these cells are not necessarily pre-cancerous cells, they represent a stage of increased growth. They compared the cancer and hyperplasia cells to normal prostate cells. These four cell types helped to determine at what stage of carcinogenesis zinc would be most beneficial and how zinc levels affect prostate cancer development. They treated late-stage androgen-independent prostate cancer cells, early-stage androgen-dependent prostate cancer cells, and benign prostate hyperplasia cells with doses of zinc ranging over five-fold concentrations. They then examined the growth and viability of these cells. Surprisingly, zinc had little effect on the viability of the prostate cancer cells, but even low zinc treatments resulted in a marked decrease in cell viability of the benign prostate hyperplasia cells. A similar response pattern was seen when cell growth was examined after zinc treatment.

Zinc and other cancer association

Postmenopausal and obese women are at high risk of developing breast carcinoma, but studies had shown that breast cancer cells have high levels of Zinc in comparison to non cancerous breast cells implicating a role of Zinc in the genesis of breast cancer. Zinc is also implicated in the genesis of Pancreatic cancer. Too much ZIP4, a molecule that enables the transport of Zinc into cells, promote growth and spread of Pancreatic cancer cells.

Although the increase in risk of developing breast, ovarian, and prostate cancer in BRCA1 and BRCA 2 mutation carriers have been studied its impact on mortality is not well qualified. It is evident that there is significant association between BRCA1/2 mutation and increased non cancer mortality. It is assumed that there may be unknown effects of BRCA1/2 mutation on non neoplastic disease that cause death at older age. BRCA2 deficient human cells are deficient in the repair of double strand breaks and DNA cross links through homologous recombination^{44,45}. Elevated expression of Ki67 is associated with aggressive prostate cancers and with high Gleasons score. But this does not differentiate prostate cancer occurring against a BRCA1/2 mutation or sporadic cases without BRCA1/2 mutations⁴⁶.

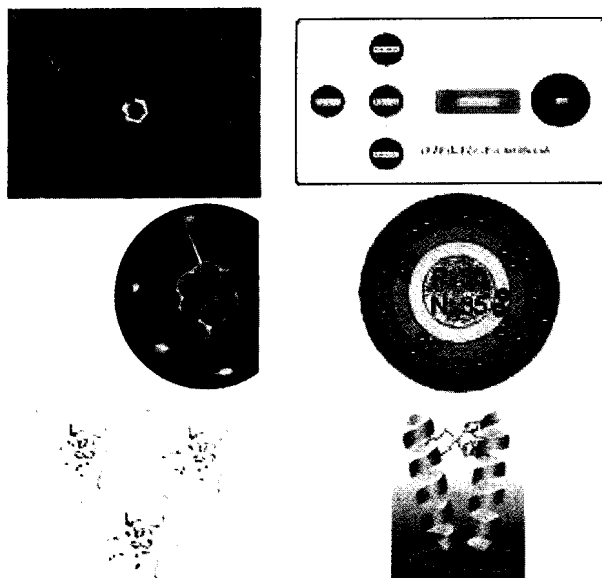
Conclusions

It is evident from the above literatures reviewed that Zinc as a trace element has important role to play in maintaining normal prostatic epithelial cell population

for its production of citrate as a component of normal semen. It also utilizes lot of energy and production of ATP. Normal prostate epithelial cells are high in Zinc content. But when a prostate cell becomes transformed to tumor cells it is low of Zinc and utilised all energy in tumor proliferation and progression. Zinc is transported through 24 zinc transporter protein. Some of which also acts as tumor suppression gene like Zip1, Zip2, Zip3 and these are also down regulated when there is tumor progression. Some mutation in mitochondrial DNA, immediate early gene Egr1 over expression, suppression of Metallothionein (MT) a major receptor/donor of Zinc in the cells are responsible for tumorigenesis in prostate cancer. Zinc supplement has improved and halted progression to tumorigenesis in some studies but not in other studies. So more elaborate scientific research should be carried out to conclude the exact role of Zinc in tumor specially Prostate cancer.



Figur 4: Zinc molecular structure. Zinc binding is mediated by two histadine and two aspartic acid residues mimic size and shape of a DNA molecule.



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