Evaluation of Zinc in Patients of Prostatic Carcinoma

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Abstract

Background: Zinc is an essential trace element, with the primary function to manufacture proteins and nucleic acid. It has an important role in the healthy functioning of the prostate gland.

Objective: To assess the correlation of serum zinc level with the progression of prostatic carcinoma.

Methodology: This cross-sectional study was done on 100 subjects with enlarged prostate, who underwent prostatectomy, were selected from Urology OPD, Shaikh Zayed Hospital, Lahore from October 2011 to November 2017. A total of 70 individuals who were positive for prostate malignancy were included in the patient's group, and 30 individuals found to be negative for prostate malignancy, were included in the control group. The patient group was further divided into subgroups based on Gleason's score and stages of prostate cancer. Analysis of serum zinc was performed in the patient and the control group. SPSS version 20 was used for data analysis.

Results: Mean serum zinc value (46.75±2.89 ug/dl) among prostate cancer patients was significantly lower from mean serum zinc value (88.27±7.8 ug/dl) of the control group (p-value 0.001). Serum zinc level in 1A (Stage 1), 47.89±3.96; 1B (Stage 2), 46.08±1.97; 1C (Stage 3), 45.35±3.06; and 1D (Stage 4), 42.51±2.68 had an inverse correlation to Gleason Score, showing serum zinc level decreased in subgroups as their Gleason Score, and stage of prostate carcinoma progressed.

Conclusion: In this study, it may be concluded that serum zinc has a negative correlation to tumor progression and may be used as a biochemical indicator for its progression and prognosis.

Keywords: Serum Zinc, Prostate malignancy, Gleason Score

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Introduction

Zinc has been shown to be essential for 300 enzymatic reactions in the body. It has both a catalytic and structural role in enzymes.[1] Zinc is required in the human body to manufacture proteins and nucleic acids. It is integral to normal growth and developmental rate. Zinc is required for the healthy functioning of the prostate gland. It potentiates the effects of thyroid hormone and testosterone. It is also involved in hair growth, mental well-being, effective immune response, and cell perception.[2] Normal RBCs contain about 10 times more concentration of zinc than in serum. There is a diurnal variation in serum zinc concentration. With increasing age zinc level decreases and in women it is lower than in men.[3] Normal serum value range is 80 – 120 mg/dl.[4]

Prostate carcinoma is one of the most lethal diseases of men and has been actively studied for many years. Every year 3.2 million Europeans are diagnosed with different cancers and prostatic carcinoma is the second most common male malignancy in the European Union.[5] Deaths due to prostate cancer are second to lung carcinoma which occurs in men.[6] Prostate cancer grades refer to the degree of aggressiveness and progression of the tumor. The Gleason grade or score is used to classify prostate cancer. The Gleason grade ranges from 1 to 5, and grade 5 is having the worst prognosis.[7,8] Prostate cancer stage is determined on the basis of DRE (Digital Rectal Examination) and ranges from stage 1 to 4; stage 4 being the most advanced one.

Zinc status in biological fluids of prostate cancer patients has been investigated by many researchers. A study was done on Zinc and retinol levels in serum of the patients with prostatic carcinoma, benign hyperplasia (BPH), and control subject. A significantly low level of mean serum zinc level was found in the cancer group. The results indicated that zinc level was disturbed in malignancy showing the possible significance of this in relation to the pathogenesis of carcinoma of the prostate.[9] The role of zincs was evaluated by adding zinc acetate to cancerous prostate cells in monolayer culture, they detached from the culture dishes, and viability was lost after 4-8 hours. Most by cell death were due to necrosis, and there was an increase in protein (thymosin).[10] In one study, results highlighted the role of zinc was, to inhibit human prostatic carcinoma cell

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growth, which may be due to cell cycle arrest and apoptosis induction.[11] It was proposed that decreased zinc levels in the body lead to the growth and spread of prostate cancer.[12] The exposure of malignant prostate cells to zinc solution, resulted in increased cellular zinc level which resulted, in cytotoxic effects, including inhibition of cell proliferation, induction of apoptosis, and inhibition of cell migration.[13] High levels of zinc are cytotoxic to malignant cells. The development of malignancy requires that serum zinc level is decreased to a level that is not cytotoxic to the malignant cells.[14,15] It was reported that the measurement of zinc level facilitates prostate cancer detection.[16,17]

In the current study serum concentrations of zinc were assessed in patients with prostatic carcinoma and compared with controls. Then the results of serum zinc levels were correlated with various stages of prostate carcinoma which can form the basis of non-invasive biochemical indicator for the prognosis of prostatic cancer.

Methodology

It was a cross-sectional study, conducted in Urology Department, Shaikh Zayed Hospital, Lahore from October 2011 to November 2017. A total of 100 males who were admitted due to an enlarged prostate gland were included in the study.

Exclusion Criteria: Individuals with diabetes, tuberculosis, any malignancy, any systemic disease, and those who had taken replacement therapy of minerals during the last six months were excluded from the study.

All the study subjects underwent surgery, prostatectomy was done and prostate tissue was sent for histopathology. The prostate cancer diagnosis was confirmed on biopsy.

Grouping: On the basis of biopsy reports study subjects were divided into the following two groups: Patients (70 in number), who were diagnosed as cases of prostate carcinoma on biopsy; Controls (30 in number), who were proved benign cases of prostate enlargement on biopsy.

Gleason scores and cancer stages were obtained from the hospital record. The patients were divided into subgroups on the basis of Gleason score and stage of prostate cancer. On the basis of Gleason score and stages, the patients were divided into following four subgroups: Subgroup 1A, patients with Gleason score 1-2 and stage 1; Subgroup 1B, patients with Gleason score 3-4 and stage 2; Subgroup 1C, patients with Gleason score 4-5 and stage 3, and Subgroup 1D, patients with Gleason score more than 5 and stage 4. Gleason score (GS) was awarded by the histopathology department after examining the prostate biopsy specimen. A score between 2 to 10, is associated with the worst phenotype and prognosis. The cancer stages were awarded by urologists who were treating these patients.

Biochemical Analysis: Serum Zinc level in the patient group and in the control group. The above-mentioned trace element (Zinc) were estimated by using atomic absorption spectrophotometer (AAS) 800 Perkin Elmer Company (USA) available at Pakistan Council of Scientific and Industrial Research Laboratories (PCSIR) Lahore. One-way ANOVA was used in the current study because it involved 4 groups of patients. Data were analyzed on SPSS version 20. Tukey's test was applied to know exactly which results (mean) are significantly different from each other. Ethical approval was sought from the Ethical Committee of the Hospital.

Results

The distribution of patients in different subgroups on the basis of Gleason Score and stages of prostate cancer is given in Table-I. The first subgroup comprised of 10 cases (14.23%) the second subgroup of 13 cases (18.57%) third subgroup of 21 (30%) and the fourth subgroup contained 26 (37.14%) cases.

The mean serum zinc level in patients with Ca prostate was 46.75±2.89 ug/dl which was significantly low (p-value 0.001) than the mean serum zinc level in controls which was 88.27±7.8 ug/dl (Table-II). Comparison of serum zinc level among subgroups on the basis of Gleason score showed that there were significant low levels of zinc (p-value 0.001) in subgroups having higher Gleason score (Table III, IV).

The result of zinc levels showed an inverse correlation to Gleason Score. Serum zinc level decreased when Gleason Score increased in subgroups.

Table-I: Distribution of patients in subgroups on the basis of Stages and Gleason Score of Prostate Cancer.

Subgroups	Number of Patients (n=70)	Percentage
1A (Stage 1)	10	14.23%
1B (Stage 2)	13	18.57%
1C (Stage 3)	21	30%
1D (Stage 4)	26	37.14%

Table-II: Comparison of serum Zinc levels between Prostate Cancer and control groups.

Zinc (ug/dl)	Patients (n = 70)		Control (n = 30)		t-Value	p-Value
	Mean ±SD	95% Confidence Interval	Mean ±SD	95% Confidence Interval		
	46.75 ±2.89	46.06-47.44	88.27 ±7.8	79.76-96.78	-9.948	0.001

Table-III: Tukey's test showing comparison of serum Zinc levels among Subgroups on the basis of Gleason Score in patients with Prostate Cancer.

Comparison among Groups	Mean Difference	Std. Error	p-value
1A (GS 1-2) vs 1B (GS 3-4)	1.55	0.71	0.058
1A (GS 1-2) vs 1C (GS 4-5)	2.54	0.66	0.001
1B (GS 3-4) vs 1D (GS 5 and more)	3.98	0.61	0.001

Table-IV: Comparison of serum Zinc level among subgroups on the basis of stages of Patients with Prostate Cancer.

Parameters	1A (Stage 1) (n = 10)	1B (Stage 2) (n = 13)	1C (Stage 3) (n = 21)	1D (Stage 4) (n = 26)
Zn (µg/dl)	47.89±3.96	46.08±1.97	45.35±3.06	42.51±2.68

Discussion

Various studies have been conducted to find out the biochemical markers of prostate cancer which could play important role in diagnosis, assessment of progression, and management.[12,13] From these studies, it has been speculated that the trace elements are involved at different levels in the causation and development of prostate cancer. The current study was conducted on 100 individuals admitted with the enlarged prostate gland and 70 of them were diagnosed as prostate cancer patients, and the other 30 subjects diagnosed with benign prostate enlargement, were taken as controls. In this current study, the status of trace element (zinc) and its correlation with various clinicopathological parameters (Gleason score and stages in patients of prostate cancer) was evaluated.

Serum zinc levels in the prostate cancer group were found significantly low than controls (p=0.001) in this study. The mean serum zinc level was 46.75±2.89 µg/dl in cancer patients as compared to 88.27±7.8 µg/dl in controls. Similar results were reported in a study by Feustel A et al which showed significantly lower levels of serum zinc ($p<0.05$) in the group with prostate malignancy as compared to the benign prostatic hyperplasia group.[18] The results of serum zinc in the current study are in agreement with those reported by Ogunlew et al who measured the serum zinc levels in prostate carcinoma patients and in individuals without prostate carcinoma. The serum zinc levels in prostate carcinoma patients were low ($p>0.05$) as compared to those without prostate cancer.[19] Serum Zinc level among subgroup on basis of Gleason Score and stages were compared and they showed that there were significant low levels of Zinc (p-value > 0.05) in subgroup having higher Gleason Score.

In one study conducted by Masion et al, it was observed that serum Zinc level decreases as stages of prostate carcinoma progress and it is significantly low (p-value > 0.05) as compared to patients with benign hypertrophy of the prostate.[20] Zinc may have an important role in prostate cancer pathogenesis. There is a unique capability of normal prostate tissue that traps zinc from blood circulation. The prostate has 10 times higher zinc levels than in other soft tissue. The concentration in whole prostate tissue appears to increase with increasing distance from the urinary bladder. This is very significant because the peripheral zone is the area where the carcinoma appears most commonly.[21] The loss of capability to keep high levels of zinc is an important factor in the growth and spread of malignant prostate cells. It was revealed that zinc inhibits hyperactive calcium signals in malignant cells, which do not happen in normal cells and cancer cell growth is inhibited by it.[22] Costello reported that increased zinc levels are found in the mitochondria of normal prostate epithelial cells. The increased intramitochondrial accumulation of zinc inhibits aconitase activity and decrease citrate oxidation. This will depress Kreb's

cycle and lower ATP production. These correlations form the basis of a new concept about zinc and citrate-related metabolism in prostate malignancy. The malignant prostate cells are unable to accumulate high zinc levels which result in increased citrate oxidation and more ATP production, essential for rapid progression seen in prostate malignancy.[23] Based on these cellular activities, it is assumed that zinc might have been consumed during prostate cancer pathogenesis, therefore giving the reason for low serum zinc levels in the patients group.

Conclusion

Results of this study revealed that zinc status has a link with the cancer grading of prostate cancer patients. Measuring serum zinc will be a simple and non-invasive method of describing the progression of prostate cancer and predicting the treatment. Serum Zinc level has a negative correlation to tumor progression. Although it is far away to use zinc as an independent marker for progression of concern, these results provide some initial hint to use it as an indicator for the progression of the disease.

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