Research Article

Evaluation of Changes in Zinc Levels in Patients Suffering from Cancer

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Abstract | Cancer is abnormal and uncontrolled cell division. Some cancers may eventually spread into other tissues. There are more than 200 different types of cancer. Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity or excessive drinking of alcohol. Other factors include certain infections, exposure to ionizing radiation and environmental pollutants. In this study zinc level in serum of cancer patients was observed. For this purpose, the blood of 50 cancer patients was taken from MAYO HOSPITAL Lahore. The patients are suffering from different type of cancers such as, breast cancer, lung cancer, uterus cancer, oral cavity cancer, esophageal cancer, urinary bladder cancer, blood cancer and brain tumor. In addition to serum zinc level of cancer patients many other parameters were also studied such as, age limit, weight of cancer patients, effect of smoking on cancer patients, effect of radiation on cancer patients, effect of chemicals on cancer patients, infections in cancer patients and physiological changes in some patients. The experimental work had been done in city lab and research center Lahore to evaluate the serum zinc concentration. The sample zinc level is estimated by using the spectrophotometer in laboratory. The level of zinc in cancer patients was observed lower than the optimum value. Male have much lower concentration as compare to females, therefore male are more susceptible to cancer than female. In the nutshell Zinc is an effective anti-inflammatory and antioxidant agent, including as a natural cancer treatment.

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1. Introduction

Zinc, the 23rd most abundant element in the earth's crust having atomic number 30 and atomic weight 65.37, is vital in the living world. The percentage of Zinc can be analyzed in various body fluids such as saliva, plasma, blood as well as in human excreta. Zinc is important for the function of numerous cellular processes and critical for growth however, it may also play an important role in cancer aetiology and outcome (Grattan *et al.*, 2012). The relationship between zinc and cancer aetiology and progression has been extensively studied with contradictory results. Zinc supplementation has beneficial effects on cancer by decreasing angiogenesis and induction of inflammatory cytokines while increasing apoptosis in cancer cells (Prasad *et al.*, 2007). Zinc is essential to rapidly growing tissues and seems to act protectively on the growth of both normal and cancer cells (Cui *et al.*, 2007). Zinc has been ascribed roles in the metabolic functions and interaction of malignant cells. (Schrauzer, 1979). The zinc content of leukaemic leukocytes has been found to be reduced, and it has also been reported that zinc deficiency enhances the carcinogenic effects of nitrosomethyl benzylamine. Zowezak found an increase in serum copper/zinc

ratios in patients with cancers of the lung, breast, gastrointestinal tract and gyneocological malignancy. Nutritional zinc deficiency in rats increases oesophageal cell proliferation and the incidence of N-nitrosomethylbezylamine (NMBA) induced oesophageal tumors. Replenishing zinc with a zinc sufficient diet reduces these effects in zinc deficient rats. Zinc replenishment rapidly induces apoptosis in oesophageal epithelial cells and thereby substantially reduces the development of esophageal cancer (Fong *et al*., 2001). Zinc serves an important role in breast cancer during the cancer cell fission and replication, and the polymerase needs zinc to serve as a co-factor for activation. Therefore, as breast cancer cells rapidly increase, they consume large amounts of zinc resulting in lower zinc concentrations. It is believed that trace elements play important roles in biological processes relevant to breast cancer, especially those elements that are essential components of antioxidants (Gaur, 2013). As an activator of many enzymes involved in the synthesis of DNA and RNA, zinc has been the subject of investigations regarding its importance in biochemical processes and antioxidant defense. Some studies have shown that zinc can induce apoptosis in cancer cells and inhibit cell proliferation (Bargellini, 2003). High levels of zinc supplementation had a positive effect on reducing oxidative stress and improving immune responses in cancer patients. However, some studies have indicated that zinc serves as a co-factor for cancer cell fission and replication (Wang *et al*., 2006). The concentration of zinc in the prostate is higher than that in any other soft tissue in the body (Zaichick *et al*., 1997). Zinc levels in prostate adenocarcinoma are markedly lower than those in the surrounding normal prostate tissues. Several findings that link zinc with the suppression of prostate cancer cell growth (Feng *et al*., 2000) and inhibition of prostate tumor cell invasion (Ishii *et al*., 2001) suggest that high intraprostatic zinc levels may protect against prostate carcinogenesis. Zinc enhances the activity of telomerase (Nemoto *et al*., 2000), an enzyme thought to be responsible for unlimited proliferation of tumor cells and whose activity is increased in prostate cancer. Zinc has also been found to antagonize the potential inhibitory effect of bisphosphonates on prostate tumor cell invasion (Boissier *et al*., 2000). Gastric cancer (GC) is considered as most fourth common cancer in the world (Parkin, 2004). Several factors can increase risk of GC. Zinc plays an anti-carcinogenic role through structural stabilization of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and ribosome. Zinc is of importance for the functions of many transcription factors and proteins involved in the recognition of specific DNA sequences and regulation of gene transcription. Zinc has a protective effect against free-radical injury (Wu *et al*., 2004). In previous studies, it has been reported that serum Zn concentrations were decreased in patients with ovarian, cervical, bladder and renal cancer (Cunzhi *et al*., 2003). Zinc deficiency can promote a variety of human cancers including esophageal as well as cancers related to the lung, head, and neck. Zinc supplementation has been shown to reduce the number of tumors and carcinogenic severity. Incubation with cigarette components results in increased cell migration in several human cell lines, including colon, prostate, gastric, breast, and ovarian cancer cells (Jeon *et al*., 2016).

2. Materials and Methods

Most of the experimental work was done in the City lab and Research center Lahore to estimate the level of zinc in serum of cancer patients.

2.1 Collection of clinical specimens

A total of 50 blood samples had been collected from Oncology ward of MAYO HOSPITAL Lahore.

2.2 Patients recruitment

The patients whose blood was isolated having different types of cancer such as, breast cancer, uterus cancer, blood cancer, brain tumor, lung cancer, urinary bladder cancer, oral cavity cancer and esophageal cancer.

2.3 Sample

Serum or plasma unhemolized. Use heparin salt as anticoagulant. Zinc is reported to be stable in serum for 7days at 2-8°C.

2.4 Procedure to collect sample

Process of obtaining blood sample:

- A band is wrapped around the arm, 3-4 inches above the collection site.
- The site is cleaned with 70% alcohol.
- The needle cap is removed and with a small and quick thrust, the vein is penetrated using the needle
- The required amount of blood sample is collected. The wrap band is removed, gauze is placed on the collection site, and the needle is removed

- The blood is immediately transferred into the blood container, which has the appropriate preservative/ clot activator/ anti-coagulant
- The syringe and the needle are disposed into the appropriate "sharp container" for safe and hygienic disposal.

2.5 Spectrophotometer

It is the instrument which was used in laboratory to estimate the level of zinc in serum of cancer patients.

2.6 Test principle

Zinc reacts with the chromogen present in the reagent forming a colored compound which color intensity is proportional to the zinc concentration present in the sample.

Zinc + Nitro- PAPS → purple color complex

2.7 Material required

Normal laboratory equipment, spectrophotometer UV/VIS with thermostatation, Automatic micropipette, cuvette in optical glass or monouse in optical polystyrene, distilled water.

2.8 Procedure

- First we centrifuge the blood sample in centrifuge machine for 5 minutes at 290 rpm.
- After the centrifuge process the blood serum was separated from the blood cells which sink down in the tube and serum comes on surface.
- The zinc assay kit comprises of four reagents Reagent 1, Reagent 2, Reagent 3 and standard whose composition is described above was taken.
- Two test tubes were taken and labeled as Zinc standard and Zinc standard.
- In zinc standard test tube add Reagent 1 500µl with micropipette. Add reagent 2 500µl with micropipette. Violet color appeared. Add Reagent 3 25µl with the micropipette. Color change to dark violet.
- In zinc sample test tube add Reagent 1 500µl with micropipette. Add reagent 2 500µl with micropipette. Violet color appeared. Add blood serum 25µl with the micropipette. Color change to dark violet.
- Incubate the zinc standard and zinc sample in water bath for 10 minutes at 37°C.
- Clinical chemistry analyzer METROLAB1600 was used for further assay.
- Read water absorbance of distilled water.
- Read reagent blank (distilled water), note the reading.
- Read standard (zinc standard as sample), note the reading.
- Read sample (zinc sample blood), note the reading.
- Read the reading on the screen which varies between 70-115µg/dl.

2.9 Sensitivity/ limit of detection

The method is able to discriminate until 3(µg/dl).

2.10 Linearity

The method is linear up to 100(µg/dl).

2.11 Precautions

- Highly lipemic serum samples can sometimes interfere in the analysis. It should be cleared by centrifugation of filtrate before use. For a seminal fluid assay, centrifuge the sample for 10 minutes, at 3000 RPM. Dilute the supernatant 1+99 with normal saline before use.
- Chelating agent such as EDTA, Oxalate and citrate, present even in traces, prevent the formation of color complex, hence necessary care should be taken during the assay.
- Use the glassware surely without zinc traces.
- The volume could be proportionally changed.
- If the results are incompatible with a clinical presentation, they have to be evaluated within a total clinical study.
- Only for IVD use.

3. Results and Discussion

Cancer is wide spread disease nowadays. Patients of cancer are increasing day by day. Many trace elements have their impact on this disease one of them is zinc. To check the level of zinc in serum of cancerous patients, the blood samples of cancer patients were collected from MAYO HOSPITAL. The patients were suffering from different types of cancer such as; breast cancer, oral cavity cancer, esophageal cancer, lung cancer, uterus cancer, blood cancer, urinary bladder and brain tumor cancer patient. The basic parameters which were studied in cancer patients other than the zinc level in serum patients are the age of patients, weight of patients, effect of chemicals on patients, effect of radiation on cancer patients, effect of smoking on cancer patients, dramatic change in weight of cancer patients, the infection of chest and skin and infection of eyesight and taste change.

The male have greater chance of cancer than female. The cancer causing factors may be changed according to gender. In this study female have uterus and breast cancer, males have lung cancer, oral cavity cancer, esophageal cancer, urinary bladder cancer, blood cancer, and brain tumor.

Cancer can be considered an age related disease because the incidence of most cancers increases with age, rising more rapidly beginning in midlife. Elder ones have lesser immunity against the disease have high chance of cancer. Cancer may occur in adults or mid age male and female, many factors are the cause of cancer in childs, adults or olders. These may be due to DNA damage and mutation, imbalance of diet and minerals, exposure to chemicals and radiations and many others. The age of patients whose serum was taken to study the level of zinc in cancer patient fall in age between 35-60 years. Most of females lie between 40-45 years. Most of males lie above 45 years. The patients of age 40-45 years of both male and female have more frequent chance of cancer.

The range of weight of cancer patients whose serum is taken to check the level of blood is 50-80kg. Males lie in range of 50-60kg more frequently while female have weight above 60 kg. The weight of male cancer patients is reduced below to normal range while the female weight is more than normal level of height/ weight scale. The fat is deposited in female body and causes the increase in their weight and is the cause of barest cancer.

Obesity is main cause of cancer in females. Breast cancer is caused by the premenopausal obesity in females. Many female gain weight during chemotherapy. Obesity has not equal influence on all the tissues as a causative factor of cancer, but in case of breast cancer all the females are overweight. In males weight is reduced in cancer disease, weight having no role as causative agent of cancer in males. In male patients of esophagus cancer, oral cavity cancer, lung cancer and urinary bladder cancer weight is dramatically decreased.

The effect of smoking is more frequently seen in the male persons who are used to smoke daily. Some persons use smokeless tobacco which has harmful effect and cause oral, esophageal and lung cancer. Almost 66% of male persons use tobacco and are suffering from severe type of cancer.

Smoking also increases the risk of at least 14 other cancers including cancers of the mouth, pharynx (upper throat), nose and sinuses, larynx (voice box), oesophagus (gullet or food pipe), liver, pancreas, stomach, kidney, bowel, ovary, bladder, cervix, and some types of leukemia Smoking could increase the risk of breast cancer, but any increase in risk is likely to be small.

The exposure to chemicals has greater influence as cancer causing agent. 65% of cancer patients has been exposed to many chemicals in routine life, which lead them to disease of cancer. There is a list of chemicals to which patients has been exposed these are arsenic compounds found in herbicides, alloys, medications, fungicides, and contaminated water. Some chemicals are asbestos and benzene which are found in paint, dyes, roof papers, printing rubber and vinyl chloride use in refrigerators. Patients are exposed to these chemicals in daily life routine numerous time, these causative agents cause cancer of various type. Vinyl chloride, from which PVC is manufactured, is a carcinogen and thus a hazard in PVC production. This chemical that does not necessarily cause cancer on their own, but promote the activity of other carcinogens in causing cancer. Exposure to MBT, PBN, ortho-toluidine or aniline is the cause of urinary bladder cancer. Patient exposed to these chemicals in manufacturing factory has urinary bladder cancer. These chemicals are used in dye manufacturing factories.

40% of cancer patients were exposed to radiation in daily life activities. These radiations are carcinogenic and cause various types of cancer. 40% of cancer patients were exposed to radiation in daily life activities. These radiations are carcinogenic and cause various types of cancer. These radiations are emitting out from various instruments use in daily routine. These are following radiation emitting compounds to which patients have been exposed, cadmium found in metal painting, preservatives, paints, and nuclear fuel processing.

41% males were exposed to radiation in various ways, 58.8% of male cancer patients were not exposed to radiations. 37.5% of female were exposed to radiations,62.5% of female cancer patients were not exposed to radiations.

The weight of cancer patients may dramatically change. Weight of patients may be increased, decreased or

may not change significantly. Table 1 shows that 25% cancer patients have dramatically increase weight. 60% cancer patients have dramatically loss of weight. 15% cancer patients have no significant change in their weight.

Weight of male cancer patients is dramatically decrease, male loss their weight. 25% of female have dramatically increase weight and 15% female have no significance change in their weight. Females gain weight during chemotherapy. In cancer patients the loss of appetite is main cause of the dramatically weight loss. Many males loss their weight during chemotherapy, in lung cancer patients loss of appetite is main cause of lung cancer. oral cavity and esophageal cancer patients are unable to intake and chew food and loss weight because they are unable to take diet.

The infections from which cancer patients are suffering. Theirs infections are of cold, cough, chest infections which are severe in lung cancer, oral cavity cancer, blood cancer and esophageal cancer patients. Skin cancers are found in breast and osteosarcoma cancer patients. In this study 55% of cancer patients are infectious to cold, cough, chest and skin infections, while 45% of cancer patients are not infected.

58.3% of males are infected, 41.6% are not infected from these infections. 50% of females are infected from infections, 50% of females are not infected from infections. Immune system of cancer patients is unable to fight against microorganisms; infectious causing agents are more frequently attack on these patients and cause secondary infections.

Cancer patients may suffer from problem of vision, speaking, taste, difficulty in balance and hearing. 15% of patients are suffered from these physiological problems, 80% of patients are unaffected whose serum is taken to check zinc level in cancer patients. The brain tumor cancer patients are having these problems.

Zinc level in blood of cancer patients is lower than the normal individuals. In male the zinc level is much reduced than female, therefore male are more susceptible to cancer. The level of zinc must be maintained in normal range to prevent from cancer.

Table 1: The level of zinc in cancer patients having different type of cancer.

Sr. No	Patients	Gender	Type of cancer	Zinc concentration normal range (72.6-127.0)
1	A	Female	Breast cancer	75.43
2	B	Female	Breast cancer	71.67
3	C	Male	Oral cavity cancer	54.24
4	D	Female	Breast cancer	66.98
5	E	Male	Lung cancer	63.34
6	F	Male	Urinary bladder cancer	55.45
7	G	Female	Uterus	70.34
8	H	Male	Oral cavity	66.78
9	I	Male	Esophageal cancer	56.98
10	J	Female	Endometrium (uterus cancer)	80.67
11	K	Female	Breast cancer	78.90
12	L	Female	Breast cancer	87.23
13	M	Male	Lung cancer	67.98
14	N	Female	Breast cancer	73.67
15	O	Male	Brain tumor	57.91
16	P	Male	Urinary bladder cancer	51.40
17	Q	Male	Blood cancer	49.63
18	R	Male	Oral cavity cancer	67.24
19	S	Male	Urinary bladder cancer	55.26
20	T	Male	Lung cancer	60.23

This table illustrates the level of zinc in cancer patients which is lower than the normal person blood. The persons whose zinc level is reduced than optimum value are more susceptible to cancer.

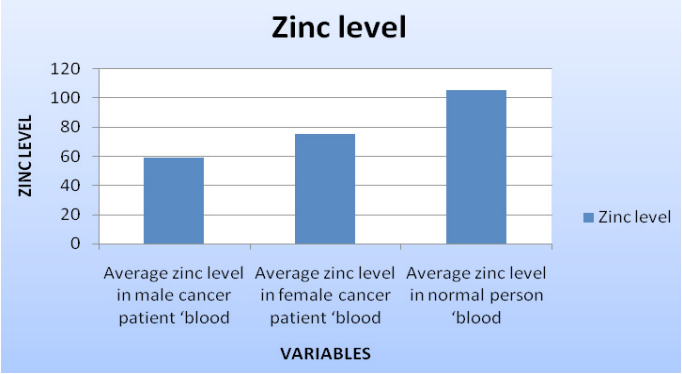

Figure 1: Level of zinc in blood.

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. In this study, the male cancer patients were more frequent than female. In cancer, susceptibility is generally higher in males although some cancers are more common in women. Breast cancer and uterus cancer are most common types in female, while male have lung cancer, oral cavity

cancer, esophageal cancer, and urinary bladder cancer. In this research 60% were male and 40% were female. In male the zinc level is much lower than female, and male have greater chance of cancer. Zinc is an important antioxidant factor, when its concentration is lower than optimum value the chances of cancer are increased. Testosterone can cause oxidative stress and the greatest weight as life-shortening factor among men has been given susceptibility to oxidative stress and its contribution to diseases in general. Estrogen, on the other hand, is protective against oxidative stress, and the fact that women live longer than men has been linked to estrogen's antioxidant properties (Barrett, 2011).

In this study, patients were fall in mid age and old age. The chance of cancer is higher in older than younger because immune system efficiency is reduced. The frequent patients in this study lie between 45-60 years. Age related conditions may be related to Zn deficiency by the alteration of intracellular Zn homeostasis, because metallothioneins are unable to release zinc, and transporting proteins (ZIP families) are defective resulting in a low content of intracellular Zn (Nishida, 2013).

In present study it is concluded that weight has its impact as cancer causing agent in female. Female were overweight and male have lower BMI. A low plasma zinc level is associated with obesity (Marreiro *et al.*, 2002). Zinc may regulate serum leptin concentration (Mantzoros, 1998) and appetite control. Zinc (Zn), an essential micronutrient and a component of many enzymes, is involved in the synthesis, storage and release of insulin (Song, 2005). Studies have reported that Zn has been implicated in altered lipid markers, insulin resistance, oxidative stress, inflammatory markers (Kelishadi, 2010) adiposity and serum leptin level (Tallman *et al.*, 2013). In this study 66.6% male were smokers and suffered from lung cancer oral cavity cancer and esophageal cancer. Non smokers were 33.3% and the cause of cancer in them are many other factors. Nicotine adductors usually have the risk of deficiency in important nutrients and minerals including zinc. Trace elements, such as iron, zinc, and vitamin E were found to be deficient among smokers compared to non-smokers. Many studies have looked at the effects of cigarette smoking on tumor genesis, yet very little research has investigated the effects of cigarette smoking in cancer patients (Sobus *et al.*, 2014). Increased cell proliferation following cigarette smoke component exposure has been seen in esophageal, breast, and lung cancer cells (Dasgupta *et al.*, 2009). In addition to cell proliferation, cigarette smoke can induce migration in cancer cell (Hanahan *et al.*, 2011).

In this study 65% cancer patients were exposed to chemicals, and 35% were not exposed to chemicals. Excess risk of cancer associated with exposure to chlorinated hydrocarbon solvents and nickel, as well as suggested increased risk of exposure to other substances including chromium and organochlorine pesticides. These chemicals reduce the zinc level (Fritschi *et al.*, 2015).

In this study some cancer patients are exposed to radiations which cause cancer. 40% patients wrere exposed to chemicals and 60% were non exposed to chemicals. High energy radiation include x-rays and gamma rays and some higher energy ultraviolet (UV) rays, these have enough energy to remove an electron from (ionize) an atom. Ionizing radiation can damage the DNA inside cells, which can lead to mutations and the uncontrolled cell growth we know as cancer. Zinc protect the DNA from damage and prevent mutation (Leone *et al.*, 2006).

In this study the 55% of cancer patients were having infections such as cold, cough, chest infections, skin rashes and 45% patients were non infectious. Minor zinc deficiencies may cause poor digestion, infections, skin problems, and fatigue and many other diseases may occur along the way. Primary and secondary antibody responses are reduced in zinc deficiency, particularly for those antigens that require T-cell help, such as those in heterologous red blood cells. In addition, antibody response and the generation of splenic cytotoxic T cells after immunization are reduced (Viscoli *et al.*, 2005).

In this study 15% of cancer patients were having vision, taste, speaking, hearing and balance problems, while 80% patients were not facing these problems. Reduced zinc level has influence on cancer patients in causing these problems. Zinc functions in more enzymatic reactions than any other mineral. Enzymes need minerals and vitamins in order to work properly. If an enzyme is lacking the necessary mineral, it cannot fulfill its appropriate action no matter how much of the vitamin is available.

Conclusions and Recommendations

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Cancer is caused by many factors, one of them is the decreased level of some minerals, such as zinc. Zinc is an important antioxidant factor which reduces the chance of cancer in patients. The zinc level of cancer patients is reduced below the optimum value. In male the zinc level is much reduced than female, therefore male are more susceptible to cancer. The level of zinc must be maintained in normal range to prevent from cancer.

Novelty Statement

The zinc level is actually one of the indicator for the diagnosis of cancer. Most of the patients who have lower zinc level have associated risk factor with cancer. This is actually a smart study to analyze risk factor associated with cancer so the patients should careful in future

Conflict of interest

The author have declared no conflict of interest.

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