

# A Study of Serum Zinc, Iron, Selenium, and Copper levels in patients with bladder cancer

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## Abstract:

**Back ground:** The association of serum trace elements like Zinc, Iron, Selenium, and copper has been found in different types of cancer. Many authors observed direct association between micronutrient deficiency and the cancer mortalities. Many of essential trace element are required for growth “ play an important role in the suitable biochemistry of the body “ and they could also stimulate the growth of tumors.

**Objectives :** Assessment the level of trace element ( Zn, Fe, Se, and Cu ) in serum of patients with bladder cancer.

**Patients & Methods:** Serum samples of (40) male and female patients with bladder cancer and (20) healthy controls were enrolled in this study. Bladder cancer patients were undergo cystoscopy and diagnosed clinically by consultant urologist as newly diagnosed for primary bladder tumor. Tumor characterized by 2 independent pathologists according to the criteria of WHO . Trace element were determined by Atomic Absorption Spectrophotometer.

**Results :** Significant increase in serum (Cu) levels and significant decrease in serum (Zn, Fe, and Se) levels in bladder cancer patients when compared with normal group.

**Conclusion :** Low serum ( Zn, Fe, and Se) and high Cu levels in bladder cancer patients when compared with control indicates the role of bladder cancer disorders in trace elements metabolism.

**Key words:** Trace elements, bladder cancer.

## Introduction :

Bladder cancer is one of most common urologic malignancies world wide with approximately 300,000 new cases occurring each year[1,2].Bladder cancer is well-known condition that affects men more than women. One reason for its higher incidence in men is that the androgen receptor, which is much more active in men than in women, plays a major part in the development of the cancer (3).

The incidence is higher in industrialized countries, such as, the United States, Canada, and France, than developing countries, such as, Asia and Africa [4].

In Iraq, bladder cancer is the third most common malignant tumor(6.6%) in both males and females. It is the second most common tumor in men ( 10.3% ) and the eighth in women ( 3% ) (5) .

Bladder cancer refers to several types of malignant growth of the urinary bladder. It is a disease in

which abnormal cells multiply without control in the bladder (1).

Many studies suggested that bladder cancer is influenced by environmental factors including cigarette smoking, fluid consumption, schistosomal infection, exposure to industrial chemicals ( aromatic amines ) , diet, having along-term bladder infection or other irritation, and older age (over 55 years old) (1, 3) .

Smoking causes about half of the death from bladder cancer in men and more than one-third in women (6, 7) .

A number of nutrients including dietary; energy intake macro and micro nutrients (minerals and vitamins) have been hypothesized to influence bladder cancer risk (8, 9) .

Many authors observed direct association between micronutrient deficiency and the cancer mortalities

(10), and many studies suggest that the need of some essential elements has been diminished in cancer cell proliferation (9). The role of trace minerals in etiology of cancer :-

**Copper (Cu)** is a biologically essential trace element that is required for the synthesis of hemoglobin, white blood cells maturation, bone strength and as an integral component of certain metallo enzymes and proteins that help biochemical reactions occur in every cell. Copper enzymes play a role in oxygen free radical metabolism and in certain amino acid conversion (11, 12, 13).

Copper plays an essential role in the expression or function of many angiogenesis factors, including fibronectin; collagenase; angiogenin; etc...which works as inhibitors might be useful cancer chemotherapeutic (14,15). Copper has a protective role to prevent cancer and this may be due to its anti-oxidant properties as part of Cu-Zn superoxide dismutase (13, 15).

**Zinc (Zn)** functions are varied and numerous, including synthesis of cholesterol, proteins, and fats, releasing vitamin A from the liver, assisting the immune system and cell growth being required for vision, taste perception, prostate reproduction health and insulin function, metabolizing alcohol, and protecting against copper and heavy metal toxicity, such as cadmium and lead (16,17, 18). Several studies have proven the success of Zn supplementation by protecting against free radical damage, but may also be necessary for tumor growth due to its role in gene transcription and cell proliferation (19).

**Iron** Many workers have revealed a higher rise of cancer in individuals with larger Fe stores than those with small Fe stores (20, 21). Some studies have shown that iron can inhibit tumor development while others have shown that it might enhance it. Iron may increase the risk of cancer through its effect on free radical formation (19, 21).

**Selenium** is an essential trace element required for normal function, growth, and reproduction. It is suggested that selenium may protect against cancer particularly, because of its antioxidant properties, and appears to play a key role in reducing the risk of some cancers, cardiovascular disease, and diabetes (22).

Several hypotheses have been proposed to explain the inhibition of tumorigenesis by selenium, including its effect on carcinogen metabolism, effect on the endocrine and immune system, production of cytotoxic selenium metabolites, inhibition of protein synthesis, specific enzymes, and tumor growth; Stimulation of apoptosis, and protection against oxidative stress (22,23,24).

This study is aimed to assess the level of trace elements (Zn, Fe, Se, and Cu) in bladder cancer patients for both sexes and indicate which element in terms of concentration, is more affected by the underlying pathology of patients.

## Patients and methods :

### Subjects :

This study encompassed (40) subjects (13 women, and 27 men) with an age range between (20-90) years, and the average age (55) years. Patients under suspicion for bladder cancer who were to undergo cystoscopy over the period of study from

(Sep.,2007 to Nov., 2008) were enrolled in this study. They were diagnosed clinically by consultant Urologists as newly diagnosed patients at Al-Yarmook teaching hospital. Also (20) healthy subjects were enrolled in this study as a control.

### Collection of Samples :

#### Blood samples :

Blood samples of 3-5 ml were collected by venipuncture, using plastic disposable 5 ml syringes, from all patients and control groups. Blood samples were allowed to clot at room temperature, then centrifuged for 15 minutes at approximately 500 rpm to obtain at least 0.5 ml of un-hemolyzed cell-free serum. Serum samples were stored in aliquots at -20 °C until used for the measurement of trace element levels.

#### Tissue samples :

Tissue samples from 40 cases of bladder cancer (newly diagnosed cases) fixed in 10% buffered formalin and embedded in paraffin wax, were stained with hematoxylin-eosin (25). Tumors were characterized by 2 independent pathologists according to the criteria of WHO (26).

**Measurement of Minerals :**

Minerals concentration were determined in diluted serum comparing with working standard of these minerals by using Atomic Absorption Spectrophotometer .

**Statistical analysis :**

The results were presented as mean + standard deviation (SD) and range .

**Results:**

Table ( 1) observed significantly reduction in serum Se, Fe, and Zn levels of bladder cancer patients ( mean + SD :  $0.34 + 0.05$ ;  $1.45 + 1.01$ ;  $3.59 + 35$  )  $\mu\text{mol/L}$ , when compared with control groups ( mean + SD:  $1.03 + 0.15$ ;  $17.27 + 1.25$ ;  $15.51 + 2.21$  )  $\mu\text{mol/L}$ , (P value:  $< 0.0001$  ), while highly significantly serum levels of Cu was demonstrated in our results for bladder cancer patients ( mean + SD:  $31.76 + 1.90$   $\mu\text{mol/L}$  ) respectively when compared with control groups ( mean + SD:  $19.17 + 1.78$   $\mu\text{mol/L}$  ) (Pvalue  $< 0.0001$  ).

**Discussion:****Effect of bladder cancer on trace elements :****Selenium ( Se ) :**

A significant decrease was observed in serum Se level in patients with bladder cancer ( mean + SD ;  $0.34 + 0.05$   $\mu\text{mol/L}$ ), when compared with control group  $1.03 + 0.15$   $\mu\text{mol/L}$  ) Table(1),Figure(1), and that was agree with several other researches [22,23,24] . Selenium is important in the active centre of the Se-dependent GSH-PX. This enzyme has four subunits and each contain one Se atom. This enzyme important for protecting lipids in polyunsaturated membrane from oxidative degradation. It was suggested that Se protects cell by inhibiting free oxygen radical production .Moreover, an important antioxidant ( vit. E ) is transport by selenoproteins. There is evidence for a direct relationship between GSH-Xp activity and carcinogenesis (27,28) .

Other study found a reduction in serum Se as a useful parameter for the diagnosis and treatment of those patients and attributed this reduction as a

result of protective migration of Se from blood to the cancer tissue. Some human epidemiologic studies showed that low Se concentration in serum increase the risk of human cancer (23,29) .

**Iron ( Fe ) :**

Serum Iron levels in patients with bladder cancer were found to be significantly lower compared with control group ( Table 1 )( Figure 1), and that was agree with several researchers [30,31,32]. Serum Iron levels are considered as biochemical indicators for nutritional assessment. Utilization of Iron in collagen synthesis by the hydroxylation of proline and lysine leads to decreased serum Iron level in cancer patients . In most cases, clinical anemia may be a contributing factor (31) .

Inadequate intake of food due to burning sensation might also be an important factor. Reduction in serum Iron level may be due to malnutrition caused by the tumor burden in cancer patients (33) .

**Zinc(Zn) :**

In our study ,difference of serum Zinc level between the bladder carcinoma group and control group was statistically significant ( P value  $< 0.0001$  )(Table 1) (Figure 1), and that was correlated by many researcher which reported that Zinc inhibits the development of cancer and that low serum Zinc is associated with several forms of cancer (34,35,36) .

Zinc may prevent cancer via the metabolism of high density lipoprotein ( HDL ), vitamin A, and DNA synthesis . Zinc may exert prophylactic anti-cancer effect by preventing elevation of (HDL). Zinc is an essential component of the enzyme involved in DNA synthesis and repair , and it's essential nutrient for axonal transport. Both functions contribute to the prevention of cancer. It has been hypothesized that Zn could be operating at several different levels and influencing lymphocyte monoclonal proliferation (37) .

The decrease in serum Zn level can be also attributed to the high urinary excretion of Zn and shifting of Zn from serum to the liver as a protective mechanism against the spread of cancer (34) .

**Copper(Cu):**

Our study showed significant hypercupremia which observed in cases of bladder cancer when compared with healthy control group (Table 1)(Figure 1), and

that agree with several studies (38,39). Copper are important microelements which not only regulate the physiological functions of various organs, but are also associated in the production of pathological changes in these organs. Serum copper values are significantly elevated in many diseases e.g. chronic obstructive pulmonary disease (COPD), malignancy, and psychosis (39). The Cu in serum exists largely in the form of ceruloplasmin (more than 90%) containing 6 atoms of Cu molecules, hypercuperemia may be due to increased ceruloplasmin in blood induced by the disease process. In malignancies there is an increased rate of tissue destruction and there by increase abenzidine oxidase activity and release of copper into the circulation (38).

Zinc is known to be a physiological antagonist of copper and this may be responsible for hypozincaemia observed with hypercuperemia in malignant process (39). A direct interference of Zn with intestinal absorption of Cu and as a result of that Cu could displace Zn from metallothionein, because of copper's high affinity toward this protein, a mechanism explains the decrease observed in serum Zn level, that accompanied with an increase in serum Cu level measured in this study. Malignancies in general are invariably accompanied by anemia and hypoproteinemia, two conditions which on their own are associated with low serum Zinc level and high serum Copper level (38,33).

In conclusion, we observed a statistically significant association between serum trace elements concentrations and risk of bladder cancer. Low mean serum Zn, Fe, Se, and high Cu levels in bladder

cancer patients as compared with controls indicate the strong association with bladder cancer in our country. Further studies are needed to confirm our findings.

Table 1: Show significant difference in serum (Cu, Se, Fe, and Zn) levels in bladder cancer patients

Trace element	Bladder cancer	Control	P value
Copper ( $\mu\text{mol/L}$ )	3190.76 $\pm$ 1, (2830.90-35.)	1978.17 $\pm$ 1, (1520.60-22.)	0.0001*
Selenium ( $\mu\text{mol/L}$ )	034.4 $\pm$ 005, (044.30-0.)	115.03 $\pm$ 0, (030.90-1.)	0.0001*
Iron ( $\mu\text{mol/L}$ )	101.45 $\pm$ 1, (010.45-5.)	1725.27 $\pm$ 1, (1410.30-19.)	0.0001*
Zinc ( $\mu\text{mol/L}$ )	335.59 $\pm$ 0, (350.02-4.)	1521.51 $\pm$ 2, (1290.00-18.)	0.0001*

\*Significant using t-test for two independent means at 0.05 level of significance

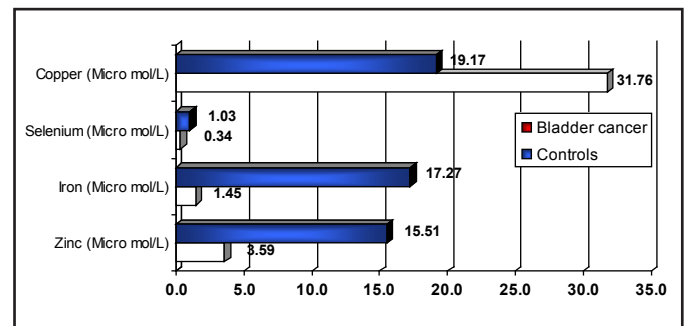


Figure 1: Comparison of serum Cu, Se, Fe, and Zn in control and bladder cancer patients

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## دراسة معدلات كل من الزنك،الحديد،السيلينيوم،والنحاس في مصول سرطان المثانة

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### الخلاصة:

تم إيجاد تصاحب كل من العناصر الضئيلة مثل الزنك، الحديد، السيلينيوم، والنحاس في مختلف حالات السرطان. كثير من الباحثين اظهروا تصاحب مباشر بين عوز العناصر الضئيلة ومعدلات الوفاة لمرضى السرطان. كثير من العناصر الضئيلة الأساسية مطلوبة للنمو وتلعب دور مهم في كفاءة الكيمياء الحياتية في الجسم وكذلك يمكن ان تحفز النمو السرطاني .

الغاية:تقدير معدلات العناصر الضئيلة (الزنك، الحديد، السيلينيوم، والنحاس) في مصول عدد من مرضى سرطان المثانة . الطريقة: جمعت عينات من مصول مرضى سرطان المثانة وعددها (40) عينة من الرجال والنساء، و(20) عينة تمثل مصال الاصحاء كمجموعة سيطرة، حيث خضع جميع المرضى للفحص والتشخيص السريري لمرض سرطان المثانة، ودعم هذا التشخيص بالفحص النسيجي .

تم قياس العناصر الضئيلة بواسطة الطرق الكيمياوية باستخدام جهاز (Atomic Absorption Spectrophotometer)، وتحليل النتائج ومقارنتها مع نتائج الدراسات السابقة .

النتائج: اظهرت نتائج الفحص وجود ارتفاع في مستوى النحاس، وانخفاض ملحوظ في كل من (الزنك، الحديد، والسيلينيوم) لدى مرضى سرطان المثانة مقارنة مع الاصحاء .

الاستنتاج : انخفاض معدلات كل من الزنك، الحديد، والسيلينيوم، وارتفاع معدل النحاس في مرضى سرطان المثانة عند المقارنة مع مجاميع الاصحاء دل على دور اضطرابات سرطان المثانة في العمليات الايضية للعناصر الضئيلة.