RESEARCH ARTICLE

Levels of Serum Trace Elements in Renal Cell Carcinoma Cases

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Abstract

Trace elements which are essential components of biological structures may also be toxic when present at levels above the amounts required for biological function. In our study, trace element levels were measured with furnace atomic absorption spectrophotometry in 33 newly diagnosed renal cell carcinoma cases (preoperative) and 32 healthy controls. When compared with the control group, it was found that the levels of cadmium (Cd), lead (Pb) were higher and the levels of zinc (Zn), iron (Fe) and manganese (Mn) were lower in the patient group. These changes may be important in the formation of renal cell carcinoma, a question which should be explored with postoperative comparative studies.

Keywords: Renal cell cancer - serum trace elements - cadmium - iron - lead - zinc

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Introduction

In the US, roughly 30,800 new cases and 12,000 deaths from renal cancer take place annually, making renal cancer the sixth largest cause of cancer deaths. Renal cell carcinoma is responsible for 90-95% of all kidney malignancies (Curti, 2004). The incidence of renal cell carcinoma has increased in the US and worldwide by roughly 2-4% per year for the last 20 years (Chow et al., 1999; Dhote et al., 2000). Advances in diagnostic imaging and early detection do not fully account for this trend (Chow et al., 1999). Rates of renal cancers are higher among males and have increased more rapidly among African-Americans than Whites (Chow et al., 1999). Established risk factors for renal cancer contain smoking, use of phenacetin containing drugs, hypertension, obesity, and end-stage renal disease (ESRD) (McLaughlin et al., 1996). Of the patients who present with local disease and are considered for surgery with curative intent, roughly one-third will go on to develop metastatic disease. Metastatic kidney cancer is resistant to all "standard" forms of radiation therapy, chemotherapy, and hormonal therapies used in the treatment of other kinds of carcinomas.

Although the trace elements are the essential components of biological structures, they may show toxic effect when they are more concentrated than the amount that are required for biological functions. In addition, the toxicity can be spread to other non-essential elements of very similar atomic characteristics that can mimic the reactivity of a trace element. To cope with this essentiality/toxicity duality, biological systems have developed the ability to recognize a metal, and bring it to the target without allowing the metal to participate in toxic reactions (Gecit et al., 2011; Sayır et al., 2011). Proteins are primarily account for such recognition and transport, and most of the associations of trace element with other biomolecules lead to undesirable chemical modifications of these molecules.

Oxidative processes take place most intensively in the background of an imbalance of trace elements incorporated into the structure of enzymes accounting for antioxidant protection (Hoekstra et al., 1974). Both an increase and a decrease of trace element ion content can influence the activity of the antioxidant enzymes (Yelinova et al., 1996). Some of these trace elements contain: iron (Fe), copper (Cu), and zinc (Zn). Statistically significant differences from the normal distribution of Fe, Cu, and Zn have been reported to occur in patients with various forms of cancers (Spartz et al., 1992). In some studies, the Cu/Zn ratio in serum samples has been utilized as chemoprophylaxis (Li et al., 2004) and also as a way of evaluation and prognosis assessment in cancer patients (Kumar et al., 2003; Mazdak et al., 2010).

In the present study, the levels of serum trace element in patients with renal tumor were evaluated and the concentrations of Mn, Cd, Pb, Fe and Zn were changed in the serum of patients with renal cell carcinoma in comparison to the healthy subjects.

Materials and Methods

33 male patients with renal cell cancer with a mean age of 58.3±2.6 were included in the study. All of the patients

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Table 1. Descriptive Statistics and Comparison Results According to the Groups for Specifications

	Control					Patient					p
	Medyan	mean	St. dev.	Min.	Mak.	Medyan	mean	St. dev.	Min.	Mak.	
Co(μgdl)	0.013	0.02	0.02	0	0.05	0.025	0.02	0.006	0.01	0.03	0.623
Mg(μgdl)	10.074	10.16	3.19	6.06	15.01	9.295	9.77	2.904	6.02	15.58	0.725
Cu(μgdl)	0.614	0.65	0.147	0.44	0.86	0.79	0.77	0.194	0.31	0.99	0.089
Cd(μgdl)	0.027	0.02	0.016	0	0.04	0.091	0.09	0.017	0.01	0.1	0.001
Zn(μgdl)	0.897	1.03	0.427	0.61	1.65	0.295	0.3	0.071	0.18	0.45	0.001
Fe(μgdl)	1.144	1.18	0.508	0.51	2.38	0.36	0.35	0.125	0.12	0.53	0.001
Mn(μgdl)	0.056	0.08	0.047	0.04	0.18	0.044	0.04	0.01	0.02	0.06	0.001
Pb(μgdl)	0.02	0.03	0.025	0	0.07	0.098	0.1	0.007	0.09	0.12	0.001

have not smoked during their life, they have not had alcohol addiction, have not used the supportive antioxidant and they did not any drug abuse and any metabolic disorders. There was not any other major diseases or cancers in any of the patients except for the kidney tumor. All of the patients have newly been diagnosed and they consisted of the patients whose blood samples were received in the preoperative period. 32 male patients who made up the control group (mean age 57.4±3.2) were randomly selected among the volunteers who did not have any known important disease and who did not use cigarettes, alcohol, drugs and additional antioxidant. Patient and control group had a similar socio-economic status.

According to the results of radiological and postoperative histopathological evaluation, 25 (75.8%) of our patients were stage 1, 5 (15.1%) of them were stage 2 and 3 (9.1%) of them were metastatic renal tumor of stage 4.

The study protocol was carried out in accordance with the Helsinki Declaration as revised in 1989. All participants were informed about the study protocol and the written consent was taken from each one.

Blood collection

Following 12 h of fasting period, blood samples were taken in the morning, collected into empty tubes and immediately kept on ice at 4°C. The serum was then isolated from the cells by centrifugation at 3000 rpm for 10 min. Serum samples for measurement of trace element levels were kept at -20°C until they were used.

Measurements of Mineral-Heavy Metal Levels

Exactly 2.0 mL of the mixture of HNO_3/H_2O_2 (2:1) was attached to 0.7 g of the serum samples. The mixture was placed into the water bath at 70˚C for 30 min and mixed occasionally. Then, 1.0 mL of the same acid mixture was attached, and the mixture was transferred into a Teflon vessel bomb for the microwave oven. The bomb was closed, and the solution was inserted inside the microwave oven. Radiation was applied for 3 min at 450 W. After addition of 0.5 mL of the same acid mixture, radiation was repeated for 3 min. After cooling for 5 min, 2.0 mL of 0.1 mol/L HNO_3 was added, and the solution was transferred into a Pyrex tube. After centrifugation, the clear solution was used for the determination of Mn, Cd, Cu, Pb, Fe Mg, Co and Zn (11, 12). They were measured by Atomic Absorption Spectrophotometer measurements using a UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK).

Statistical analysis

Descriptive statistics for the studied traits were expressed (reported) as median, mean, standard deviation, minimum and maximum values. Mann-Whitney U test was used for comparison of groups. In the study, 5% level was taken into account to statistically significant differences between groups and SPSS Statistical package program (Ver.13) was used for the all statistical computations.

Results

Demographic characteristics of the group with renal tumors and the control group and the levels of trace element were shown in Table 1. There were no statistically significant differences between renal cancer patients and controls in respect to age and BMI.

The levels of trace element in both groups were compared. Cd and Pb levels in patients with renal tumors were statistically higher according to the control group. Zn, Fe and Mn levels in patients with renal tumors were statistically lower according to the control group. When compared with the control group, the levels of Cu in patients with renal tumors were higher, but the levels of Mg were lower. However, this difference was not statistically significant.

Discussion

Trace elements are important components of biological structures, but their roles in the development and inhibition of cancer is complex and have raised many questions because of their essential and toxic effects at concentrations beyond those necessary for their biological functions on human health. Literature on this subject showes conflicting results (Piccinini et al., 1996; Zowczak et al., 2001).

Our study showed that concentrations Mn, Fe and Zn in the serum the patients with renal cancer decreased compared to the control group. Mn is an essential element that is needed for the activity of several enzymes. Mn is one of the essential trace elements that plays an important role in antioxidant defense and forms a part of SOD enzyme (Johnson et al., 2001). So, low serum concentration of Mn with the mechanism of antioxidant disturbance can make the target organs sensitive to the carcinogens. The data of the present study indicated that the Mn concentration in the serum of the patients with renal cancer was lower than that of the control group. According to our hypothesis, and Mn as the trace elements affecting the oxidation status can result in this oxidant/antioxidant imbalance in renal cancer patients.

Zinc plays an anticarcinogenic role by stabilizing the structure of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and ribosome. Zinc is also essential to the function of several transcription factors and proteins that recognize certain DNA sequences and regulate gene transcription. Zinc protects cells from free-radical injury (Wu et al., 2004). Zn may protective as potent lung cancer. In addition, it is suggested that low levels of zinc can induce the pathogenesis of lung cancer (Cobanoglu et al., 2010). Lower serum Zn concentrations in patients with ovarian and cervical cancers have been reported (Cunzhi et al., 2003; Yaman et al., 2007). It seems that determination of zinc levels in ovarian cancer patients and comparison with a normal controls without ovarian pathology is necessary to fully elucidate the relationship between the Zn level and ovarian cancer. Additionally, normal or elevated concentration of zinc in blood serum identifiable only in cases of primary cancer of the liver (matched by a decrease in blood serum zinc level in the remaining cases) supplies a differential diagnosis sign suggesting transformation of hepatocirrhosis into primary cancer of the liver (Karlinskiĭ et al., 1985). Our study indicated decrease Zn concentrations in the renal cancer patients with control patients, the differences were statistically significant.

Iron is an essential trace element that is crucial to normal cell functioning and its deficiency or excess is associated with several disease states (Dayani et al., 2004). The most common hematologic abnormality is anemia (Chisholm et al., 1982), which occurs in approximatly one third of cases with equal frequency in patients with renal cell carcinoma with and without hematuria. İt is generally normocitic and normochromic (Melocow et al., 1960). Although anemia has not been fully characterized, it appears to be associated with malignancy and secondary either to bone marrow suppresion or to interference of ferrokinetics (Loughlin et al., 1984). The iron level were significantly elevated in the malignant glioma patients as a whole compared to controls (Arslan et al., 2011). Dayani et al. showed that the mechanisms of pathogenesis could be mediated by direct effect of iron overload on the formation of hydroxyl-free radicals from hydrogen peroxide and superoxide via the Fenton and Haber-Weiss reaction (Dayani et al., 2004). In their studies in which Chia-Cheng et al. (1991) compared the preoperative and postoperative serum iron levels of 82 patients with renal cell carcinoma; they have suggested that the preoperative serum iron levels of the patients with renal cell carcinoma were low and by showing that this value returned to the normal postoperatively, the serum iron levels could be used as a tumor marker in patients with renal celled-carcinoma. Our study, the performed analysis showes that patients having renal cancer were significantly different compared to the control group.

Our study also indicated that concentrations Cd and Pb in the serum the patients with renal cancer increased compared to the control group. Pb and Cd are established toxic and carcinogenic metals (Nawrot et al., 2002).The elevated levels of carcinogenic elements may be associated with a number of physiological disorders in humans. Early life inorganic lead exposure induces testicular teratoma and renal and urinary bladder preneoplasia (Erik et al., 2010). Serum level of Cd was increased in patients with bladder cancer (Geçit et al., 2011). Zinc is an essential metal required for the synthesis of DNA, RNA, and protein as well as for enzymatic activity of Zn-containing enzymes (Cousins et al., 2003). Conversely, there is no biological requirement for cadmium. In animal models, zinc reduces the carcinogenic effects of cadmium, which supports the antagonistic relationship between cadmium and zinc (Waalkes, 2003). The cellular and molecular mechanisms implicated in cadmium carcinogenicity include activation of proto-oncogenes, inactivation of tumor suppressor genes, disruption of cell adhesion, and inhibition of DNA repair (Waalkes, 2003; Waisberg et al., 2003).It has been reported that Cd is a mutagen in mammalian (Snow et al., 1997; Hayes et al., 2007) and enhanced concentration of Cd may result in prostate, renal and lung cancers (Drasch et al., 2005). Moreover, in the last decade, injection of cadmium metal powder and various cadmium compounds has been reported to produce sarcomas locally and interstitial cell testicular tumors systemically (WHO, 2000) in experimental animals. Our study suggests that individuals with increased exposure to cadmium have an increased risk of renal cancer. Recent research seems to indicate that a low level of lead (Pb) exposure has a number of negative consequences for health. Among these consequences are impairment of the function of renal tubular cells, inhibition of sperm formation, damage to the fetus, slowing of motor nevre velocity, dysfunction of the central nervous system, and hypertension and other cardiovascular diseases (Landrigan, 1989; 1990; Meller et al., 1992). The Cd and Pb levels were significantly elevated in the malignant glioma patients as a whole compared to healtly controls (Arslan et al., 2011).

We have been investigating the role of copper as an essential trace element that is required for angiogenesis. It has been demonstrated that copper is required for angiogenesis and tumor growth in several murine tumor models. Serum Cu level was significantly lower with lung cancer compared to healthy human (Cobanoglu et al., 2010). In our study, Cu levels were in higher levels in tumor patients. However, this difference was not statistically significant.

In conclusions, the presence of an association between renal cancer and trace elements is observed in the present study. We also suggest that a increase Cd and Pb levels and decrease Zn, Mn and Fe levels may play an important role in renal cancer induction. However, further prospective cohort studies concerning the causes of changes in trace elements concentration in blood serum of patients with renal cancer seems to be well ground. Further studies are required to clarify the association between the different stages of renal cancer and serum trace element levels.

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