RESEARCH ARTICLE

Serum Levels of Trace Elements in Patients with Prostate Cancer

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Abstract

Background: Trace elements are major components of biological structures; however, excessive levels of these elements can be toxic. Materials and Methods: In the present study, serum levels of trace elements were measured in 30 patients with newly diagnosed as prostate cancer and 32 healthy volunteer by using furnace atomic absorption spectrophotometry. Results: It was found that there was an increase in serum levels of Co, Cu, Mg and Pb ($p<0.05$), whereas a decrease in serum levels of Fe, Mn, and Zn levels in patients with prostate cancer ($p<0.05$). Conclusions: These changes may be important in the pathogenesis of prostate cancers; however, further prospective studies are needed to identify relationships between prostate cancer and trace elements.

Keywords: Prostate cancer - trace element - patient serum levels

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Introduction

In addition to being most commonly encountered cancer among men, prostate cancer is second leading cause of death among cancers, following lung cancer (Jemal et al., 2007). In recent years, increasing screening studies and use of prostate specific antigen as a marker of disease result in diagnosis at early stage. Genetic and environmental factors, dietary habits, smoking, alcohol consumption, sexual and physical activity, hormones and body size are associated to increased risk for prostate cancer. These factors play role in the development or proliferation of tumor cells either via directly by activating carcinogenic pathways or indirectly by inducing susceptibility in gene-related diseases. These indirect mechanisms indicate that carcinogenic agents are involved in either metabolic regulation or hormonal regulation (Jarup, 2003).

Several epidemiological studies showed that exposure to heavy metals have severe toxic and carcinogenic effects on both humans and animals (Vinceti et al., 2007). Epidemiological evidence confirms that heavy metals such as lead, cobalt and iron are potential carcinogens for humans (Harris and Shi, 2003; Mahata et al., 2003). It has been thought that environmental and occupational exposure to these metals is primary reason for metal-related cancers as well as increased cancer risk. It was found that cadmium has a strong contribution to prostate cancer mortality (Killielea and Downing, 2007).

Studies on concentrations of trace elements play role to improve our insight about various processes occurring within different cells. Trace elements are major constituents in biological structures; however, these elements can also be toxic when their available concentrations excess body requirements. This toxicity can also be valid for non-essential trace elements which have very similar atomic features and ability to mimic reactivity of trace elements. Thus, toxicity/duality contradiction in trace elements leads the biological system to develop ability to recognize and deliver metal compounds to its target without enabling them to involve in toxic reactions (Gecit et al., 2011; Sayır et al., 2011). It has been proven that some trace elements have major role in cancer biology; however, there is still a gap in our understanding regarding relationship between trace elements functions and initiation, advancement and inhibition of carcinogenic process in prostatic gland (Geraki et al., 2002; 2004; Naga Raju et al., 2006; Guntupalli et al., 2007; Banas et al., 2010). Thus, there is a need for trace element analysis in human tissues with or without cancer that can show relationship between cancer and these elements.

In the present study, serum trace elements levels were measured. It was found that there is an alteration in Mn, Fe, Zn, Pb, Co, Cu and Mg concentrations in the sera of the patients with prostate cancer when compared to healthy subjects.

Materials and Methods

The study included 30 men with newly diagnosed prostate cancer with a mean age of 65.4±4.2 years. All

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

	Control n=32				Patient n=30				p
	Mean	St.Dev.	Min.	Max.	Mean	St.Dev.	Min.	Max.	
Fe	2.41841	0.1909	2.0121	2.7998	0.76065	0.42755	0.1137	1.523	0.001
Mg	59.83100	4.15567	52.6500	66.3300	29.65800	4.57998	20.2400	38.880	0.001
Mn	0.74606	0.21983	0.11114	0.98991	0.09753	0.07535	0.0011	0.4378	0.001
Zn	2.94533	0.49818	2.1250	4.021	0.71272	0.33929	0.06709	1.1730	0.001
Pb	0.00121	0.00013	0.001	0.0015	0.05796	0.03062	0.02741	0.1696	0.001
Cd	0.00111	0.00011	0.00101	0.00135	0.00132	0.0015	0.00201	0.00954	0.630
Co	0.00109	0.00009	0.00101	0.00143	0.00227	0.0011	0.00122	0.0051	0.001
Cu	0.84518	0.13185	0.5222	0.9771	1.46116	0.31902	1.057	2.122	0.001

patients were lifetime non-smokers and had no history of alcohol addiction, drug abuse, antioxidant use, metabolic diseases or comorbid disease. All patients had newly diagnosed prostate cancer and preoperative blood samples. Thirty two healthy male subjects with a mean age of 62.8±5.8 were randomly selected as controls among volunteers who had no history of smoking, alcohol consumption, drug or antioxidant use, and known comorbid disease. Socioeconomic status was similar between patient and control groups.

Of the patients, 5 (16.6%) were considered as stage 1, while 4 (13.3%) as stage 2 and 20 (66.6%) as stage 3 according to PSA values, digital rectal examination findings, bone scintigraphy and biopsy results and 1 (3.3%) of the patients was metastatic.

The study was conducted in accordance to Helsinki Declaration, 1989 Revision. All participants gave written informed consent before participation to the study.

Blood samples

After 12 hours fasting, blood samples were drawn at morning hours and stored on ice at 4°C. Then, sera were separated by centrifugation at 3000 rpm for 10 minutes. Serum samples were stored at -20°C until assays.

Measurements of mineral-heavy metal levels

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

Statistical analysis

All data were analyzed by using SPSS for Windows version 13.0. Descriptive statistics of the traits evaluated were expressed as mean, standard deviation, minimum and maximum values. Mann-Whitney U test was used for intergroup comparisons. $p<0.05$ was considered as significant.

Results

Table 1 presents demographic characteristics and trace elements levels. No statistical difference was detected between patients with prostate cancer and controls regarding age and BMI.

When trace element levels were compared between groups, it was found that Co, Cu, Mg and Pb levels were significantly higher in the patient group than controls. It was also found that Zn, Fe and Mn levels were significantly lower in the patient group than controls. Cd levels were found to be higher in patients with prostate cancer compared to controls, but the difference didn't reach statistical significance.

Discussion

Trace elements are accepted as major constituents of biological structures which have a complex role in development and inhibition of cancer. However, there are raising questions whether these elements have toxic effects on human health when their available concentrations reached to a level higher than needed for biological functions, and whether these elements are essential. In this context, there are contradictory results in the literature (Piccinini et al., 1996; Zowczak et al., 2001).

In a previous study, in which distribution of trace elements was evaluated in specimens from patients with prostate cancer, increased levels of trace elements and heavy metals at hair and nails were considered to be as either reason or cause of pathological process involved in prostate cancer (Karimi, 2012). It is thought that increased levels of trace elements and heavy metals have adverse effects on DNA; thus, it is a potential cause that leads formation of free radicals or other reactive oxygen species causing prostate cancer.

In our study, it was demonstrated that there was a decrease in serum concentrations of Mn, Fe and Zn in the patients with prostate cancer when compared to the control group. Mn is an essential element involved in the activities of several enzymes. Mn protects mitochondria, endothelial cells and red blood cells against injury caused by superoxide radicals; thus, it plays a major role in the free radical defense systems such as superoxide dismutase. Therefore, it can be suggested that decreased serum Mn

concentrations with disturbance of antioxidant mechanism can make target organs susceptible to carcinogens. Decreased serum Mn concentrations were reported in patients with bladder and renal cancers (Gecit et al; 2011; Pirincci et al; 2013). It was shown that decreased Mn is potentially associated with decreased activity of superoxide dismutase in advanced stages of cancer (Gleason grade 3 or 4) when compared to group with Gleason 2 grade disease (Banas et al., 2010). In our study, we think that significant decrease in Mn levels compared controls is due to the fact that majority of the patients included had advanced disease.

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; Yaman et al., 2007; Gecit et al., 2011; Pirincci et al., 2013). It is known that Zn concentration is significantly higher in prostate gland when compared to other tissues in human body (Costello et al., 1998). Moreover, there is evidence indicating that Zn content is increased in benign prostatic hyperplasia when compared to normal prostate tissue and that there is a decrease in prostate cancer (Gyorkey et al., 1967; Brys et al., 1997); however, mechanism underlying Zn accumulation in prostate tissue and its importance is still unknown (Costello et al., 1999a; 1999b). Nevertheless, it was suggested that Zn deficiency could be a risk factor for prostate cancer (Gronber, 2003). In our study, it was demonstrated that there was significantly decreased Zn concentrations in the patients with prostate cancer compared to the controls.

Fe is an essential element involved in several biological processes ranging from electron transport to ATP production, heme and DNA synthesis (Eisenstein, 2000; Arredondo and Nunez, 2005). However, low tissue Fe isn't expected at tissues surrounding a tumor, as literature suggests that excessive Fe is associated with adverse effects resulted from oxidative stress induced (Reddy and Clark, 2004). As shown in hemochromatosis patients with excessive Fe load; it has an apparent correlation with hepatocellular carcinoma (El-Serag and Mason, 2000). Several epidemiological and clinical trials showed that low Fe levels could decrease cancer incidence including prostate cancer (Knekt et al., 1994; Mainous et al, 2005; Zacharski et al., 2008). On contrary, Kuvibidila et al. (2004) reported results indicating that increased iron stores weren't associated with prostate cancer. Taken together, it is possible that elevated iron load can predispose to prostate cancer, but cancer development may also cause decrease in iron stores or metabolically available iron. Regulation of total iron is highly complex in the body. To avoid excessive iron load, there are several metabolic control points which can eliminate minimal amounts of iron in physiological manner. In our study, results indicated that there was a significant difference in serum Fe levels between patient and control groups. Interleukin-6 (IL-6)-hepcidin axis that regulates iron metabolism is one of the mechanisms which explain our finding of low iron levels in patients with poorer prognosis. Prostate cancer patients with poorer prognosis have higher circulating IL-6 levels (Michalaki et al., 2004; George et al., 2005). It is known that the cytokine leads hepcidin generation in liver (Ganz, 2006). One of the primary roles of hepcidin is to decrease iron export to circulation from intestinal epithelial cells and iron storing macrophages (Andrews, 2008). Although this explanation seems logical, further studies are needed. One additional explanation is that low iron levels in prostatic micro-environment can already be present before onset of prostate cancer and results in more aggressive outcomes. The latter hypothesis can imply significant consequences in terms of treatment and chemoprevention.

Prostate is considered as a target organ for cadmium deposition (Lindegaard et al., 1990; Brys et al., 1997). Some experimental studies in rats demonstrated that cadmium behaves as a prostate carcinogen in tumors and hyperplastic lesions of prostate (Waalkes et al., 2003). It was shown that cadmium causes prostate cancer in rats (Goyer et al., 2004) and malign transformation of prostatic epithelial cells in humans (Achanzar et al., 2001; Nakamura et al., 2002).

The mechanisms underlying cadmium carcinogenesis aren't fully elucidated, but it has been proposed that it can occur via indirect genotoxic mechanisms, such as oxidative stress, inhibition of DNA repair, stimulation of cell proliferation, blockage of apoptosis or through epigenetic mechanisms (Hartwig, 2010). Cellular and molecular mechanisms implied in cadmium carcinogenicity include protooncogen activation, tumor suppressor gene inactivation, disrupted cell adhesion and inhibition of DNA (Waalkes, 2003; Waisberg et al., 2003). In our study, Cd levels were found to be higher in the patients with prostate cancer compared to controls, but the difference didn't reach statistical significance.

In our study, it was demonstrated that serum levels of Pb, Co, Cu and Mg were increased when compared to controls. It is well-known that Pb and Cd are toxic and carcinogenic metals (Nawrot et al., 2002). It has been suggested that Pb has a facilitating role in the carcinogenesis through inhibition of DNA synthesis and repair, oxidative injury and interaction with DNA-binding proteins and tumor suppressor proteins (Inskip et al., 1995; Wijngaarden and Dosemeci, 2006). In humans, increased carcinogenic elements may be associated to a variety of disorders. Inorganic lead exposure at early life induces teratoma and pre-neoplasm of renal and urinary bladder (Tokar et al., 2010). It was also shown that Pb levels were significantly increased in malignant glioma compared to controls (Arslan et al., 2011). In our study, Pb levels were found to be significantly higher in the patient group compared to controls.

Although copper is an essential element for animals and humans, high Cu concentrations can lead cancer by producing DNA damage via toxic free radicals (Theophanides et al., 2002). It is well-known that serum Cu levels increase in several malignancies such as

osteosarcoma, gastrointestinal tumors and lung cancer (Turecky et al., 1984). As it is suggested that copper induces angiogenesis, it can potentially cause growth in prostate cancer by improving blood supply to tumor. This can explain increased Cu levels in involved tissues (Uauy et al., 1998; Majumder et al., 2009). In a previous study, Cu levels found to be slightly higher in tissues with prostate cancer compared to those from benign prostate specimens (Yaman et al., 2005). In another study, copper levels at hair and nail were found to be significantly higher in patients with prostate cancer (Karimil et al., 2012). In our study, serum Cu levels were found to be significantly higher in the patient group compared to controls.

The known effects magnesium on either tumor transplant or chemical-induced cancers depended on the duration of Mg supplementation or deficiency (Collery et al., 1981). Optimal Mg supplementation may be associated to prophylactic effects against some neoplasms, but there is no recommendation about use of Mg alone for therapeutic purposes, as cancer cells have also high metabolic requirements (Collery et al., 1981). Recently, in rats, it was shown that Mg supplementation inhibited increased DNA synthesis at colon epithelium. In that study, this finding was suggested to be related to suppression of oncogen-induced bowel carcinogenesis by Mg (Mori et al., 1992). In a previous study, it was found that Mg levels were higher in tissue specimens obtained from patients with prostate cancer than those obtained from benign prostate hyperplasia (Yaman et al., 2005). In our study, serum Mg levels were found to be significantly higher in the patients with prostate cancer compared to controls.

In conclusion, it was seen that there was an association between prostate cancer and trace elements in the present study. We also think that increased in Co, Cu, Mg and Pb levels and decreased in Zn, Mn and Fe levels can play important roles in the induction of prostate cancers. However, future prospective studies should address reasons of alterations in the serum concentrations of trace elements in patients with prostate cancer. Further prospective studies are needed to clarify the relationship between various stages of prostate cancer and serum levels of trace elements.

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