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Evaluation of trace element levels in patients with prostate cancer, benign prostatic hyperplasia and chronic prostatitis

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ÖZET

Kronik prostatit, benign prostat hiperplazi ve prostat kanserli hastalarda eser element düzeylerinin değerlendirilmesi

Giderek artan kanıtlar eser elementlerin birçoğunun enzimatik reaksiyonları engellemek veya aktive etmek suretiyle bazı biyolojik süreçlerde önemli rol oynadığına işaret etmektedir. Bu çalışmanın amacı kronik prostatit (CP), benign prostatik hiperplazi (BPH), prostat kanserli (PCa) ve sağlıklı gönüllü erkek hastaların serum örneklerindeki eser element düzeylerini araştırmaktır. Bu çalışmada PCa' lı 42 örnekten, BPH'lı 44 hastadan, 25 CP'li hastadan ve 40 kontrol grubu bireyden serum örnekleri alınmıştır. Serum örneklerinde demir (Fe), çinko (Zn), bakır (Cu), magnezyum (Mg), krom (Cr), mangan (Mn), kobalt (Co), vanadyum (V), molibden (Mo) ve selenyum (Se) düzeyleri analiz edilmiştir. PCa'lı hastalarda istatistiksel olarak anlamlı oranda artan Mn, Cu, Mo düzeyleri, daha düşük V, Se düzeyleri tespit edilmiştir. Ayrıca BPH ve CP'li hastalarda önemli oranda daha düşük V, Mg ve Se düzeyleri belirlenmiştir. Ancak BPH ve CP'li hastalarda önemli oranda artmış Mo düzeyleri bulunmuştur. Elde ettiğimiz sonuçlar eser elementlerdeki değişimin prostat kanser patogenezinde önemli olabildiğine işaret etmektedir. Buna bağlı olarak eser element düzeyleri ve prostat hastalıkları arasındaki ilişkinin aydınlatılmasında daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Prostat hastalıkları, eser elementler, kanser, benign hiperplazi*

SUMMARY

A growing body of evidence has indicated that many trace elements play an important role in a number of biological processes by activating or inhibiting enzymatic reactions. The aim of this study was to investigate the levels of trace elements in serum samples of patients with prostate cancer (PCa), benign prostatic hyperplasia (BPH), chronic prostatitis (CP) and control subjects (healthy volunteers) in men. In this study, serum samples were provided by 42 subjects with PCa, 44 patients with BPH, 25 CP patients, and 40 control subjects. The levels of iron (Fe), zinc (Zn), copper (Cu), magnesium (Mg), chromium (Cr), manganese (Mn), cobalt (Co), vanadium (V), molybdenum (Mo), and selenium (Se) in serum samples were analyzed. Significantly higher concentrations of Mn, Cu, Mo and lower levels of V, Se were found in PCa patients. Moreover, significantly lower levels of V, Mg, and Se were determined in BPH and CP patients. However, a significant increase of Mo level was found in patients with BPH and CP. The obtained results indicate that the changes of trace elements status may be important in the pathogenesis of prostate cancer. Therefore, further studies are required to identify relationships between trace elements levels and prostatic diseases.

Key words: *Prostatic diseases, trace elements, cancer, benign hyperplasia.*

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Introduction

There were an considered 10.9 million new cancer cases and 6.7 million cancer deaths worldwide in 2002 (1). In addition, prostate cancer (PCa) is considered to be one of the most commonly diagnosed tumors and the second leading cause of cancer mortality among men (2). Diet is a modifiable risk factor; non-modifiable risk factors involve age, race, and genetic/family history (3,4). Microscopic evidence of benign prostatic hyperplasia (BPH) may be found in about 50% of men by the age of 60, and over 90% by the age of 80 (2), involving the risk of acute urinary retention and the need for surgery (5,6). Chronic prostatitis (CP) is defined by lower urinary tract symptoms, predominantly with pain and management of CP symptoms is poor (7).

Trace elements are essential components of biological structures, but also they may toxic at high concentrations beyond those necessary for their biological functions (8). It has been reported that many trace elements play an important role in a number of biological processes by activating or inhibiting enzymatic reactions (9). Deficiency or excess of trace elements can induce body metabolic disorders and cellular growth disturbance, including mutation and cancer development. The limited data is available concerning the serum levels of trace elements in prostatic diseases. Therefore, the aim of this study was to evaluate variation trace elements status in patients with prostatic diseases using a case control approach.

Materials and Methods

This prospective case-control study was performed 131 patients at the age group between 46 and 85 years old referring to the Urology Department of Gulhane Military Medical Academy in Ankara, Turkey. The participants in the study were divided into four groups: PCa patients (n=42); BPH patients (n=44); CP patients (n=25) and control subjects (n=40). The study was approved by the Ethical Committee of Gulhane Military Medical Academy, protocol number 1491-258-11/1539-136, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants in the study before collection of blood specimens. None of the participants were taking antioxidant or vitamin supplements, including selenium or any mineral supplementation intake at the time of the study.

The prostatic specific antigen (PSA) level was used as an effective tumor biomarker for the early detection of prostate

cancer (10). All tumors were diagnosed histologically with specimens obtained at biopsy or surgical resection by a senior pathologist at the Department of Pathology, Ankara. The cancerous tissue from prostate biopsies was graded according to the Gleason histopathological grading system (11,12). Gleason score ≥7 was accepted as high and <7 as low grade tumors.

Venous blood (5 ml) was drawn from each patients and control subjects after overnight fasting using a plastic syringe fitted with stainless steel needle. The blood sample was collected into a metal-free plastic tube and allowed to clot at room temperature for two hour, so that clotting factors could be removed from the serum. Then the blood sample was centrifuged at 4000 rpm for 10 minutes at 4 °C to extract the serum. The serum was taken into the eppendorf tube and stand at −70°C until analysis. An Atomic Absorption Spectrometer with a Zeaman Background Correction (PerkinElmer AAnalyst 800, Shelton, CT 06484-4794 USA) was used to detect the trace element levels in serum samples. The standard solutions of trace elements were prepared in 0.2 % nitric acid at various concentrations. Standard stock solutions of iron (Fe), zinc (Zn), copper (Cu), magnesium (Mg), chromium (Cr), manganese (Mn), cobalt (Co), vanadium (V), molybdenum (Mo), and selenium (Se) (1 g/L, Sigma, USA) were prepared using corresponding spectral grade or high-purity primary standard substances and preserved in clean polyethylene bottles. The concentrations of Fe, Zn, Cu, and Mg were measured by flame atomic absorption spectrometer (the analytical conditions are listed in Table 1) and those of Cr, Mn, Co, V, Mo, and Se were determined by graphite furnace atomic absorption spectrometer (the analytical conditions are listed in Table 2).

Table I. The analytical conditions for graphite tube atomic absorption spectrometer.

	Cr	Mn	Co	V	Mo	Se
Wavelength (nm)	357.9	279.5	242.5	318.4	313.3	196.0
Pyrolysis temperature (°C)	2300	1300	2400	1200	1500	1300
Atomization temperature (°C)	2450	1900	2450	2400	2450	1900
Measurement time (sec)	5.0	3.0	4.0	6.0	7.0	4.0
Number of replicates	3	3	3	3	3	3
Standard concentrations (ng/mL)	1.5-7.5	1-10	10-50	0.5-15	10-50	30-100
Correlation coefficient	0.9996	0.9995	0.9997	0.9999	0.9996	0.9999

Table II. The analytical conditions for flame atomic absorption spectrometer.

Elements	Wavelength (nm)	Gas mixture (Flow: 16.0-7.8 L/min.)	Num.Rep.	Std.Con. (µg/mL)	Corr.Coeff.
Fe	248.3	Air- acetylene	3	1.0-5.0	0.9998
Zn	213.9	Air- acetylene	3	0.5-1.5	0.9995
Cu	324.8	Air- acetylene	3	2.0-6.0	0.9995
Mg	285.2	Air- acetylene	3	0.3-0.5	0.9996

Num.Rep: Number of replicates; Std.Con: Standard concentrations; Corr.Coeff: Correlation coefficient

Statistical analyses

SPSS 15.0 software package was used for statistical evaluations. Comparisons among the different groups were used by ANOVA tests. The values were considered statistically significant if the p value was less than 0.05.

Results

Comparison of demographic and baseline characteristics of patients groups and control subjects are given in Table 3. A total of 42 men diagnosed with primary, histologically confirmed prostate cancer, 44 patients with benign prostatic hyperplasia, 25 patients with chronic prostatitis, and 40 control

Table III. Comparison of demographic and baseline characteristics of patients groups and control subjects.

Characteristic	PCa	BPH	CP	Controls
Sample size (n, %)	42 (33.33)	44 (34.92)	25 (16.55)	40 (31.75)
Age (years)	68.2 ± 9.8*	69.9 ± 7.2*	63.7±13.3**	54.0 ± 7.5
BMI (kg/m^2)	27.5 ± 2.2	26.2 ± 3.2	25.9±3.2	26.90 ± 2.2
PSA (ng/mL)				
Total	13.2 ± 13.3*, ***	5.4 ± 3.7	11.3±6.5	1.1 ± 0.7
Free	3.3 ± 4.3	1.3 ± 0.5	1.6±0.8	0.2 ± 0.1
Tumor grading (n, %)				
Low (Gs <7)	20 (47.62)			
High (Gs ≥7)	22 (52.38)			

PCa: prostate cancer; BPH: benign prostatic hyperplasia; CP: chronic prostatitis; BMI: Body mass index; PSA: Prostate specific antigen; Values are indicated by Mean±SD; Gs:Gleason score.
* As compared with control, p<0.001
** As compared with control, p<0.05
*** As compared with BPH, p<0.05

subjects were enrolled in the study. There were no significant differences in age among patients groups, but the age of control subjects was lower than the patients. There were no significant differences in body mass index among groups. We detected the total PSA levels are significantly elevated in the prostate cancer patients compared with control subjects.

The mean serum levels of trace elements (Fe, Zn, Cu, Mg, Cr, Mn, Co, V, Mo, and Se) are demonstrated in Table 4. The levels of Fe, Zn, and Cr were not significantly different in patients groups compared to control subjects (p>0.05). The results indicated that the serum Cu, Mn, and Mo concentrations of the PCa patients were significantly higher (p<0.05) than those of the control group. However, lower levels of V, Se were found in PCa patients as compared to control subjects (p<0.05). The concentration of Mg in PCa patients was a slightly lower in comparison to controls, but it is not statistically significant. The levels of Mg, Mn, Co, and Mo were significantly increased

Table IV. The concentrations of trace elements in serum of patient groups and controls.

Parameters	Units	PCa	BPH	CP	Control
Fe	μg/mL	1.95±0.76	1.94±0.47	1.69±0.24	2.02±0.33
Zn		0.86±0.22	0.87±0.15	0.94±0.20	0.91±0.18
Cu		0.86±0.23*	0.83±0.15	0.76±0.07	0.76±0.11
Mg		17.32±1.35**, ***	16.71±1.26*	16.6±0.64*	17.43±0.66
Cr	ng/mL	0.55±0.07	0.55±0.07	0.53±0.12	0.56±0.06
Mn		0.62±0.19*, **, ***	0.25±0.07	0.28±0.06	0.22±0.08
Co		0.41±0.09c	0.32±0.04*, **	0.42±0.05	0.38±0.06
V		4.20±0.39*, ***	5.33±0.73*, **	4.45±0.57*	6.13±0.50
Mo		2.14±0.29*, **, ***	1.64±0.12*, **	1.86±0.09*	1.51±0.13
Se		68.52±6.93*, **	70.78±5.91*, **	63.49±8.25*	83.49±5.69

PCa: prostate cancer; BPH: benign prostatic hyperplasia; CP: chronic prostatitis;
Values are indicated by Mean±SD.
* As compared with controls, p<0.05
** As compared with CP, p<0.05
*** As compared with BPH, p<0.05

in PCa patients whereas the levels of V were decreased as compared to the BPH patients ($p<0.05$). Additionally, the serum concentrations of Mg, Mn, Mo, and Se were significantly elevated ($p<0.05$) in PCa patients compared with the CP patients. Significantly lower ($p<0.05$) serum levels of Mg, Co, V, and Se were determined in BPH patients as compared to control subjects. However, significantly an increase of Mo level was found in patients with BPH in comparison to control subjects ($p<0.05$). Furthermore, significantly a decreased of Co and Mo levels in serum was determined in BPH patients as compared to the CP individuals ($p<0.05$) while the levels of V, and Se were significantly increased in BPH patients. Serum Mg, V, and Se levels of CP patients were significantly lower ($p<0.05$) whereas serum Mo level was higher compared with the control subjects ($p<0.05$). Compared with the control group, all patients groups showed higher serum Mo level but lower levels of Mg, V, and Se.

Discussion

Essential elements are recognized as important constituents of biochemical reactions which have a complex role in development and inhibition of chronic disease such as cancer. These effects may show itself in very different toxicological process. However, the most proposed mechanism relationship between essential element and cancer comes from the deficiency of essential elements which may cause the failure of antioxidant defense and emerging of oxidative stress. Also, overload of these elements especially transition metals such as Cu, Zn, Co, Mn and Mo may be responsible for oxidative stress. In particular, Cu, Zn, Se, Fe, and Mn are essential components of metalloenzymes and they are important in intra-and extra cellular antioxidant defense (13). Se, Fe, Mg were essential trace elements and may be played a critical role in the process of malignant tumor incidence and progress (14). In this context, when we take into consideration conflicting available results on this subject, we need more information about the relation between essential elements and cancer.

Based on the findings of our study, the levels of Fe, Zn, and Cr were not significantly different in all patients groups compared to control subjects ($p>0.05$). Compared with the control subjects, all patients groups showed higher serum Mo level but lower levels of Mg, V, and Se. These results indicated that the higher concentrations of Mo among the patients groups might be involved in the progress of prostatic diseases. Moreover, the trace elements of Mg, V, and Se may prevent the development of prostatic diseases, including prostate cancer.

Statistically significant differences from the normal distribution of Fe, Cu, Zn, and Se have been reported to occur in cancer patients (9). Fe, Zn, and Se have a possible role in the development of prostate diseases. In addition, while Zn and Se are required for a healthy prostate, Cd shows toxic and carcinogenic effects (15). Ozmen et al (16) found that Se and Zn levels were significantly lower, and the concentrations of Co and Cu were higher ($p<0.001$) in patients with PCa (20 subjects) than in controls (21 healthy individuals). They observed the levels of Fe were not significantly different in PCa patients in comparison to controls ($p>0.05$). Also, Obiageli et al (17) evaluated the serum Se, Cu and Zn levels in PCa patients. In this study, lower levels of Se and Zn were found in PCa patients compared to control subjects although these results were not stated for Cu levels which were increased in PCa patients. These results are in agreement with our study that the serum Cu, Mn, and Mo concentrations of the PCa patients were significantly higher ($p<0.05$) than those of the control group. However, lower levels of V, Se were found in PCa patients as compared to control subjects ($p<0.05$). The concentration of Fe in PCa patients was not determined statistically significant compared to controls. Furthermore, the level of Zn also was lower, but not statistically significant in patients with PCa than in the controls. Goel and Sankhwar (18) observed that there are a strong correlation between plasma Zn concentrations and various prostatic diseases. They determined that the plasma Zn level of control subjects was 94.5+/-10.38 µg/100mL and that of prostate cancer, benign prostatic hyperplasia and chronic prostatitis patients was 59.6+/-3.08, 172.7+/-5.27, 162.4+/-2.22 µg /100mL, respectively. According to their results they suggest that the determination of Zn levels may be used as a diagnostic or screening tool and the evaluation of prostatic pathology.

Mo is an essential trace element in human nutrition, involving in the diet in very low amounts, but also potentially toxic to humans (19). We found that the concentration of Mo were higher in prostatic diseases than control subjects. There is no report about the high levels of Mo in prostatic diseases and the reference values of serum Mo concentration in healthy Turkish men. However, our result showed that the Mo level in serum was the range of 1.51-2.14 ng/mL and these values were not excessive amount.

Mg is an essential micronutrient for humans and plays many critical roles in the function of over 300 enzymes (20). In our study, a decreased level of Mg was detected in PCa patients, but it is not statistically significant. The Mg levels were lower in all patients group than in the controls. We evaluate that these findings are very important considering the information about optimal Mg supplementation may be associated with protective effects against some neoplasm. Similarly, Dai et al (21) found that the low blood Mg levels were significantly related to high-grade prostate cancer. Also, Demir et al (22) identified that the levels of Mg in leukemic patients were lower than in the controls.

Based on extensive research, V is becoming popular as an anticancer agent and it was found to reduce tumor sizes and tumor incidences in various carcinogenic models (23). However, there is lack of knowledge with respect to the effects of V on the studies of human health. We observed that the concentration of V in prostatic diseases were significantly lower than in the control subjects. Considering some positive roles of V, especially in controlling the development of diseases like cancer and diabetes (24), our results are important and valuable in terms of V and prostatic disease. In this respect controlled V supplementation in prostatic patients may be useful in the management of disease and reduce the risk of cancer development.

Some evidence demonstrated that Se can prevent the development of many types of cancer, including prostate cancer (25). Supplementing dietary Se intake has been the aim of few clinical trials in cancer development (26). Our study indicated that the levels of Se were significantly lower in PCa, BPH, and CP patients compared to control subjects. Pourmand et al (27) determined the mean serum Se level in the 62 PCa patients and 68 controls were 66.3 (SD, 17.7) ng/mL and 77.5 (SD, 22.5) ng/mL, respectively (P=0.002), consequently serum Se levels in PCa cases were lower than in controls and they suggest that Se may protect against PCa. Nozawa et al (28) examined the relationship between serum Se concentrations and risk of PCa in 47 PCa patients and 35 control subjects, finding the mean serum Se levels in the PCa patients and controls were 120.4 (SD, 14.4) ng/mL and 118.5 (SD, 16.1) ng/mL, respectively (p=0.588) and an inverse correlation between Se and PSA levels at biopsy was observed (p=0.030). According to their results they suggest that low Se levels are associated with an elevated incidence of PCa. Similarly, Brooks et al (29) found that the elevated Se levels were associated with a lower risk of PCa and they suggest that supplemental Se may reduce the risk of PCa. Brinkman et al (30) conducted one meta-analysis, suggesting that men with low Se levels are at increased risk of PCa.

The essential trace element Cu is a cofactor of many enzymes such as superoxide dismutase, ascorbate oxidase, and cytochrome c oxidase. The date of some research has indicated that both serum and tumor tissue Cu concentrations in cancer patients are significantly increased compared to control subjects. The elevated Cu concentrations in cancer patients have been demonstrated to be directly related to cancer progression (31). This was in agreement with our study that significantly an increment of the Cu level was observed in PCa patients compared with the controls ($p<0.05$). These increased Cu levels may be come from the release of cytosolic and nuclear Cu into the extra cellular compartment. Furthermore, Nayak et al (32) and Obiageli et al (17) found that the levels of Cu were increased significantly in the cancer patients as compared to controls, suggesting that the determination of trace elements like Cu may be of value in the early diagnosis of PCa.

There have been a few studies published about Co levels in cancer patients (28). In our study, we detected that the level of Co was lower in BPH patients than in the controls. But it should be noted that the interpretation of this result is very difficult with respect to BPH patient considering scientific evidence.

Deficiency or excess of trace elements can induce body metabolic disorders and cellular growth disturbance, including mutation and cancer development. In the present study, we obtained detail information about trace element status and prostatic diseases, including PCa, BPH, and CP. It was appeared that there was an association between trace elements status and prostatic diseases. As a result, the dietary supplements such as Mg, V, and Se may be beneficial in the prevention and treatment of human prostatic diseases. Two randomized clinical trials reported that the combination of minerals (Se, Mg, Cu, and Zn), antioxidants, vitamins and plant estrogens significantly decreased PSA levels compared to placebo (33). The findings in this study should be investigated with further trials especially including larger prospective study in order to obtain new insights into prostatic patients.

Conflict of interest

None declared.

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