DOI: 10.2478/10004-1254-60-2009-1901

Scientific Paper

PROSTATE-SPECIFIC ANTIGEN (PSA) IN SERUM IN RELATION TO BLOOD LEAD CONCENTRATION AND ALCOHOL CONSUMPTION IN MEN

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Received in July 2008
Accepted in October 2008

The combined influence of age, smoking, alcohol, blood lead and cadmium concentrations, and serum copper, zinc, and selenium concentrations on prostate-specific antigen (PSA) in serum was investigated in a group of 57 men aged 21 years to 40 years. The subjects had no occupational exposure to metals and no other known reasons suspected of influencing prostate function or metal metabolism. No significant correlation was found between PSA and any of the explanatory variables considered. Nevertheless, when taking into account all of the above-mentioned potentially explanatory variables, the results of stepwise multiple regression showed a significant increase in PSA with respect to an increase in blood lead, and a decrease in PSA with respect to an increase in intensity of alcohol consumption. The median and range values of blood lead concentration in the 57 men were 26.0 μg L^{-1} and (10.1 to 108.0) μg L^{-1}, respectively. These results suggest that even a low-level environmental lead exposure, common for general populations worldwide, may contribute to the risk of prostate cancer in men. The influence of lead as well as cadmium, zinc, and selenium on prostate damage and PSA should be further investigated in relatively young men for the purpose of disease prevention.

KEY WORDS: *cadmium exposure, human environmental lead exposure, lifestyle factors, prostate damage, toxic and essential metals interaction.*

Prostate-specific antigen (PSA), combined with digital rectal examination of the prostate, is used as an aid in the detection of prostate cancer in men. PSA is mainly synthesised in and secreted from epithelium of prostate tissue, and it correlates positively with age and prostate volume (1).

Prostate cancer is one of the most frequently diagnosed cancers in men worldwide. In Croatia in 2005, it was diagnosed in 13 % of all newly diagnosed cancers in men (2). Malignant transformation of prostate and progression of carcinoma appear to be the consequence of a complex series of initiation and promotional events under genetic and environmental influences. The most important risk factors are age, family history of disease, race and country of residence. The possible role of environmental and lifestyle factors, including smoking, alcohol consumption, and diet, has been suggested and is widely debated (3-6).

Lead (Pb) and cadmium (Cd) are toxic metals, both are pervasive in the human environment and accumulate in the human body over a lifetime. In spite of a decreasing trend of Pb exposure in Croatia (7-11) and worldwide, Pb toxicity remains a significant public health problem. Recent evidence has indicated that even low-to-moderate blood lead (BPb) levels can significantly reduce human semen quality (8, 10, 12). Pb compounds have been classified by the International Agency for Research on Cancer (IARC) as possible human carcinogens (Group 2B)

on the basis of sufficient evidence of carcinogenicity in experimental animals, but inadequate evidence of carcinogenicity in humans (13-15). Based on the published data, Pb can induce DNA damage as a consequence of complex biological events, which follow one another. It is likely that the Pb-related depletion of glutathione (GSH) and/or increased production of reactive oxygen species (ROS) may be the trigger in the induction of oxidative stress that causes specific responses, depending also on the functional cellular characteristics. The lymphocytes of Pb-exposed workers seem to respond to a chronic state of oxidative stress by mechanisms that involve downregulation of protein kinase Cα, an effect that is commonly seen with other tumor promoters (16). Evaluating the possible role of environmental exposure to Pb as a risk factor for prostate pathology in men suffering from prostate cancer and benign prostate hyperplasia (BPH), Siddiqui et al. (17) found that BPb was significantly higher in prostate cancer and BPH cases than in control subjects. Blood levels of zinc (Zn) and copper (Cu) were significantly lower in prostate cancer and BPH cases than in controls. In all the three groups, a statistically significant positive correlation between BPb and thiobarbituric acid reactive substances (TBARS), measured as malondialdehyde, and inverse correlation between BPb and the antioxidant GSH level were observed after adjusting for age as a possible confounder. However, positive association between BPb and TBARS was relatively more pronounced in prostate cancer patients than in BPH and controls. These results suggest that environmental exposure of men to Pb may be a risk factor for prostate cancer and/or benign prostate hyperplasia, possibly through the generation of ROS and/or reducing the level of Zn which acts as a cellular growth protector (17). Cd has been designated as a human carcinogen (Group 1) based on its carcinogenicity to the lung (18). In several studies, Cd is indicated as a potential carcinogen for the human prostate (15, 19, 20), although other studies did not find any significant association between occupational exposure to Cd and prostate cancer (21, 22). In a study of men from a Cd-polluted area in China, Zeng et al. (23) found a significant dose-response relationship between urinary Cd concentration and the prevalence of cases with abnormal PSA, while blood Cd concentration in subjects with abnormal findings on digital rectal examination of the prostate was significantly higher than in subjects with normal findings. Results of a study by van Wijngaarden et al. (24) suggest the protective effect of an increased Zn intake on Cd-induced prostatic injury. Namely, these authors observed a significant positive correlation between urinary Cd concentration and PSA levels (after the interaction with Zn was taken into account) only when dietary Zn intake levels were low. Further investigation is needed to provide better insight into those Pb-related and Cd-related mechanisms of prostate cancer in men.

Zn and selenium (Se) are essential elements for male reproductive function (15, 25, 26). Epidemiological studies and randomised intervention trials suggest that the risk of prostate cancer in men can be reduced by an increased intake of Se (27-29) or Zn (24). Furthermore, Cu, Zn, and Se are the co-factors essential for optimal activity of the antioxidant enzymes Cu,Zn-dependent intracellular superoxide dismutase (SOD) and Se-dependent glutathione peroxidase (GPx), that play a key role in protecting cells against oxidative damage. It is known that oxidative stress is implicated in the pathogenesis of over 100 human diseases, including cancer. A deficiency of Zn and Se, and to a lesser extent of Cu, can have adverse consequences for disease susceptibility and maintenance of optimal health (26, 30, 31). Pb and Cd can interfere with the metabolism of Cu, Zn, and Se by affecting their absorption, distribution, and bioavailability in the body; can contribute to oxidative stress; and can inhibit DNA repair (11, 15, 32-35). On the other hand, Zn and Se may act as Pb and Cd antagonists and thus mask the Pb-related and/or Cd-related adverse health effects (33). In the human general population, the most important sources of each of the above-mentioned metals are food, water, and air. The levels of blood Pb (BPb), blood Cd (BCd), serum Cu (SCu), serum Zn (SZn) and serum Se (SSe) are commonly used as biomarkers of metal body burden in humans, and are known to depend on age, sex, stress, dietary habits, smoking, and alcohol consumption.

Alcohol consumption has been extensively studied in relation to prostate cancer, yet findings on the direction of the association are equivocal (6). Overall results, however, indicate that alcohol may be predicted to have both adverse and beneficial effects on prostate carcinogenesis. The oxidative stress hypothesis implies that alcohol would act early in the prostate carcinogenesis pathway, and thus alcohol consumption would adversely affect the overall incidence of prostate cancer. The hormone hypothesis implies that alcohol would reduce hormonal promotion of the growth of prostate tumors.

Namely, alcohol intake alters sex hormone levels into profiles that would be predicted to decrease the risk of prostate cancer. Whether men who drank every day (i.e. regularly) did not have an increased risk of prostate cancer because they have sustained depression of testosterone relative to oestrogen, needs further evaluation (6).

This study considers the combined influence of age, smoking, alcohol consumption, BPb, BCd, SCu, SZn, and SSe on the serum concentration of PSA in men with no occupational exposure to metals.

SUBJECTS AND METHODS

Study population

The study was carried out in 57 male subjects who had never been occupationally exposed to metals. The subjects were randomly selected among those reporting for examination in the andrology unit of the Vuk Vrhovac Clinic in Zagreb. The group contained subjects from couples with suspect infertility (who were not necessarily abnormal themselves) and voluntary candidates for semen donation for artificial insemination (who were not necessarily normal or accepted for this purpose), examined in random order under identical conditions. In order to ensure optimal methodological conditions for each subject, the examination was carried out on particular days of the week when each of the patients and semen donor candidates was equally considered for possible selection and inclusion in the study. The selection criteria were age (20 to 40) years; absence of a disease, condition, or exposure to physical and/or chemical factors that affect or are suspected to affect spermatogenesis or semen quality; and the absence of acute disease, or high body temperature during the preceding 4 months [period that exceeds the duration of one spermatogenesis cycle of approximately (72 ± 9) days]. None of the selected subjects had been occupationally exposed to thermal, ionizing or microwave irradiation, pesticides, herbicides, organic solvents, anesthetics and vinyl chloride, or used dietary supplements containing Cu, Zn, Se, Mg and Fe, which could influence male reproductive parameters or metal metabolism. All subjects gave informed consent before inclusion in the study. The study was performed in accordance with the ethical principles for medical research involving human subjects (the World Medical Association Declaration of Helsinki, revised in October 2000) and was approved by the ethical committee of each of the two collaborating institutions in Zagreb.

A questionnaire including data on age, dietary habits, smoking, alcohol consumption, and professional and medical history was completed by a physician for each of the 57 subjects. The structured interview included questions on exposure to physical and chemical agents (based on an exposure checklist, with the names of the present and all previous organisations of employment and job titles, which were used for the individual exposure validation by a specialist in occupational health), use of dietary supplements, etc. The question with regard to dietary habits consisted of 3 options: mixed food, vegetarian with fish, or vegetarian without fish. All 57 subjects declared mixed food consumption. There were 23 smokers and 34 nonsmokers, and 24 consumers and 33 nonconsumers of alcohol. The questions with regard to the habits of smoking and alcohol consumption each consisted of 3 options: never, former, or current, including the time of cessation (year), duration period, and the habit intensity for the latter two options. For the calculations, data on the intensity of smoking (average number of cigarettes per day) and alcohol consumption (average number of "drinks", i.e. units of alcohol per week) in the previous 4 months were used, by assuming the value of zero cigarettes per day and zero "drinks" per week for nonsmokers and nonconsumers of alcohol, respectively (see Table 1).

Sampling and analyses of biological specimens

For each subject, venous blood was sampled at the Vuk Vrhovac Clinic between 08:00 h and 10:00 h. All subjects were required to fast in the preceding 10 h, abstain from alcohol in the preceding 24 h, and avoid any sexual activity in the preceding 4 days. Special care was taken to avoid any contamination with metals during the blood sampling, storage, and analyses. The chemicals used for metal analyses were of analytical grade for spectroscopy (Merck, Darmstadt, Germany).

In all 57 subjects, the following measurements were performed for assessment of the metal body burden: BPb, BCd, SCu, SZn and SSe. The BPb and BCd measurements were performed by electrothermal-atomic absorption spectrometry (AAS) method, essentially the same as the one described for seminal plasma Pb and Cd determination (36), controlled daily for accuracy by analyzing three reference blood samples with certified BPb and BCd values: BCR

no. 194 to 196 (Community Bureau of Reference, European Commission, Brussels, Belgium). The accuracy of both BPb and BCd measurements was also controlled by the laboratory's regular participation in the National External Quality Assessment Scheme (Birmingham, UK) and our mean running variance index score (MRVIS) was consistently lower than the average MRVIS for all participants. The SCu and SZn measurements were performed by flame-AAS method (37), controlled daily for accuracy by analyzing two reference serum samples with certified SCu and SZn values: Seronorm (Nycomed Pharma, Oslo, Norway) and Second Generation (J. Versieck, Gent, Belgium). SSe was measured by electrothermal-AAS method (38), controlled daily for accuracy by analyzing two reference serum samples with certified SSe values: Seronorm (Nycomed Pharma, Oslo, Norway) and Second Generation (J. Versieck, Gent, Belgium). The accuracy of SCu, SZn, and SSe measurements was also controlled by the laboratory's regular participation in the Trace Elements External Quality Assessment Scheme (Guildford, UK) and our results were consistently categorized as being Acceptable (as opposed to Borderline or Unacceptable as the remaining two options).

PSA concentration in serum was measured by automated method using a chemiluminescence immunoassay Advia Centaur system (Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA).

Statistical methods

Because of the skewed distribution of most of the measured parameters, the results are presented as range, and the 5th, the 50th (median), and the 95th percentile values. The significance of the difference in BCd and BPb between the subgroups of smokers and nonsmokers was calculated using the Mann-Whitney *U*-test (*z, p*). Spearman's rank correlation (*r, p*) was calculated for associations between each of the measured parameters. Forward stepwise linear multiple regression was used to calculate the interrelationship of all the parameters considered possible explanatory variables (which were simultaneously introduced in the model) with respect to PSA.

RESULTS

Table 1 shows data for the variables measured in the study population. The BPb values indicate a low-level exposure to Pb in all of the 57 subjects. Exposure to Cd was mostly through smoking and thus the difference in BCd between the 23 smokers and 34 nonsmokers was highly significant (z=5.970, p<0.0001). The median and range BCd values in these subgroups were 4.01 μg L^{-1} (0.25 to 6.83) μg L^{-1} and 0.25 μg L^{-1} (0.03 to 0.97) μg L^{-1}, respectively. Smokers also had a significantly higher BPb than nonsmokers (z=2.424, p<0.02); the median and range BPb values were 37.0 μg L^{-1} (10.1 to 108.0) μg L^{-1} and 23.8 μg L^{-1} (10.1 to 58.0) μg L^{-1}, respectively.

The results of Spearman correlation between each of the variables measured in the 57 subjects showed no significant association between PSA and any of the possible explanatory variables considered (age, smoking, alcohol, BPb, BCd, SCu, SZn, and SSe). A significant positive correlation was found between SCu and SZn (r=0.424, p=0.001), between BPb and BCd (r=0.417, p<0.002), between smoking

Table 1 *Descriptive data for the variables measured in 57 men with no occupational exposure to metals*

Variable	Range	Percentile		
		5th	50th Median	95th
PSA / μg L^{-1}	0.2 to 1.7	0.3	0.5	1.4
Age / years	21.6 to 40.2	23.5	32.4	38.7
Smoking / cigarettes per day	0 to 40	0	0	35
Alcohol / drinks[a] per week	0 to 35	0	0	30
BPb / μg L^{-1}	10.1 to 108.0	11.0	26.0	70.0
BCd / μg L^{-1}	0.03 to 6.83	0.11	0.33	5.94
SCu / μg L^{-1}	698 to 1275	770	970	1232
SZn / μg L^{-1}	611 to 1266	688	962.5	1158
SSe / μg L^{-1}	53 to 95	54	73	91

BPb = blood lead; BCd = blood cadmium; SCu = serum copper; SZn = serum zinc; SSe = serum selenium
[a]*One drink = 3 dL of beer, 1 dL of wine, or 0.3 dL of brandy.*

and alcohol (r=0.621, p<0.0001), smoking and BCd (r=0.820, p<0.0001), and smoking and BPb (r=0.344, p<0.009), and between alcohol and BCd (r=0.614, p<0.0001), and alcohol and BPb (r=0.473, p=0.0002). These significant correlations indicate a complex association among all these variables, suggesting the possibility that certain variables may mask a causal effect of other variables on PSA.

Table 2 shows the results of forward stepwise linear multiple regression in 57 subjects when PSA, as a dependent variable, was considered with respect to all of the following independent (explanatory) variables: age, smoking, alcohol, BPb, BCd, SCu, SZn, and SSe. The explanatory variables were simultaneously introduced in the model, and none of them was removed from the model throughout the stepwise procedure. Beta (β) is the standardised regression coefficient, whereas the coefficient B value relates to the units of measurement actually used for the dependent variable and independent (explanatory) variables in the equation. The advantage of β coefficients (as compared to B coefficients which are not standardised) is that their magnitude allows for a direct comparison of the relative contribution of each independent variable in the prediction of the dependent variable, even for variables measured on disparate ranges or expressed in noncomparable units of measurement. The p-value of β is equal to the p-value of B.

After adjusting for potentially confounding variables by multiple regression, the results (Table 2) showed a significant association between an increase in BPb and an increase in PSA (β=0.333, p=0.030), and between an increase in intensity of alcohol consumption (drinks per week) and a decrease in PSA (β=-0.327, p=0.033). Exactly the same results were obtained when, in separate regression models, the multiplicative interaction term BPb*BCd or BPb*alcohol was introduced together with all of the remaining potentially explanatory variables considered (age, smoking, alcohol, BPb, BCd, SCu, SZn, and SSe), indicating that neither BCd nor alcohol had modified the observed significant effect of BPb on PSA. However, an independent effect of alcohol on PSA was observed (Table 2) that was in the opposite direction to that of BPb on PSA.

Essentially the same results were obtained when data for the dependent variable (PSA) included in the regression model were logarithmically (log) transformed in order to produce their normal (Gaussian) distribution. This resulted in the same explanatory variables that entered the regression equation (i.e. BPb and alcohol), although the corresponding β- and p-values showed a slightly greater relative contribution to the effect on PSA, and a better level of significance for the given explanatory variable, as compared to those shown in Table 2. These results were β=-0.397, p=0.009 for alcohol, and β=0.381, p=0.012 for BPb. Exactly the same results were obtained when either BPb*BCd or BPb*alcohol was introduced in the regression model together with all of the remaining potentially explanatory variables, confirming that neither BCd nor alcohol interacted with BPb and thus did not modify the observed significant effect of BPb on PSA.

All of the 57 men in this study had normal findings on digital rectal examination of the prostate; the absence of prostatitis and any significant increase in estimated prostate volume were found.

DISCUSSION

The BPb level in the study population (Table 1) is comparable to the levels found in adult male general population groups in many countries worldwide. In general, men have commonly higher BPb levels than women (15). The reported geometric mean BPb values for the general population groups, comprising men

Table 2 *Summary of the multiple regression results for associations between prostate-specific antigen (PSA), as the dependent variable, considered with respect to all of the potentially explanatory variables (age, smoking, alcohol, BPb, BCd, SZn, SCu, and SSe)[a] in 57 male subjects*

Variable	Beta	Coefficient (B)	Standard error of B	p
PSA				
Intercept		0.4459	0.0836	0.0000
BPb	0.333	0.0058	0.0026	0.0305
Alcohol	-0.327	-0.0109	0.0050	0.0335

*[a]Exactly the same results were obtained when, in separate regression models, the multiplicative interaction term BPb*BCd or BPb*alcohol was introduced together with all of the above-mentioned explanatory variables.*

and women, from the United States and Japan were 28 μg L^{-1} (39) and 23.2 μg L^{-1} (40), respectively.

The BCd level in the study population (Table 1) is comparable to the levels found in general population groups in many other countries. Increased BCd levels in our study population can mainly be ascribed to smoking, and the relatively high Cd content in Croatian cigarettes. In Croatian heavy smokers, BCd levels of up to 13 μg L^{-1} were commonly found (7, 8, 41, 42). The geometric mean BCd values reported for 10 countries, including Belgium, China, India, Israel, Japan, Mexico, Peru, Sweden, USA and Croatia (in former Yugoslavia), ranged from 0.2 μg L^{-1} (Sweden) to 1.5 μg L^{-1} (Belgium) for nonsmokers, and from 0.6 μg L^{-1} (India) to 2.8 μg L^{-1} (Croatia) for smokers (7), whereas those of a meta analysis in Italian subjects were 0.52 μg L^{-1} for nonsmokers and 1.47 μg L^{-1} for smokers (43). The BCd levels for nonsmokers in this study [median: 0.25 μg L^{-1}, range: (0.03 to 0.97) μg L^{-1}] and in our previous studies (7, 8, 41, 42, 44) are comparable to or even lower than those in other countries.

The levels of SCu, SZn, and SSe in the study population (Table 1) are comparable to those for healthy adult general population groups in many other countries, although the range of published values is relatively wide. For example, the reported range for SCu was (600 to 1760) μg L^{-1} in Italian subjects (45) and (585 to 2027) μg L^{-1} in German subjects (46), and that for SZn was (540 to 1510) μg L^{-1} in Italian subjects (45) and (608 to 1510) μg L^{-1} in German subjects (46). Variations in SSe levels are particularly pronounced, both between different countries and within some countries such as the United States and China, which is mainly because of the large differences in Se concentration in soil (47); among 20 countries considered, the lowest average SSe values (<80 μg L^{-1}) are found in New Zealand and generally in the eastern European countries, whereas the highest average SSe values have been reported from the seleniferous regions in the United States (198 μg L^{-1}) and China (490 μg L^{-1}).

Epidemiological studies of combined exposure to various metals that may influence individual susceptibility to adverse health effects are generally lacking. Similarly to our previous findings in men (9-11, 42, 44), significant correlations were found between smoking habits, alcohol consumption, BPb, and BCd in the group of men in this study. With regard to the hypothesis that Pb and/or Cd adversely affect prostate function and may also influence PSA level in men, these variables may be both potential confounders and risk factors.

After adjusting for a possible influence on PSA of each of the explanatory variables considered in the study population, the multiple regression results (Table 2) showed a small, albeit significant BPb-related increase in PSA. It is important to note that the study population consisted of relatively young men [age median: 32 years, range: (21 to 40) years] known to be at lower risk of prostate cancer compared to elderly men. Furthermore, the BPb values in the study population indicate a low-level exposure to Pb (Table 1) with regard to the currently acceptable BPb limit of 100 μg L^{-1} for the general population, including children, who are particularly susceptible to Pb toxicity (15).

In addition to direct toxicity of Pb on the prostate secretory function in men, as indicated by a significant Pb-related decrease in seminal plasma concentrations of Zn, acid phosphatase, and citric acid (8, 10, 25, 48), there are two plausible mechanisms for Pb-induced prostate damage that may ultimately progress into prostate cancer. One is related to the role of Pb through oxidative stress (15, 17, 33, 35, 49, 50). The other concerns a significant Pb-related increase in serum testosterone, observed at low-to-moderate levels of chronic exposure to Pb in men (8, 10). This may have implications on the initiation and development of prostate cancer, because testosterone is known to augment the progress of prostate cancer in its early stages. It is interesting to note that the highest prevalence of prostate cancer in the general population of men has been reported for African Americans, known to commonly have relatively higher BPb levels than other ethnic groups in the United States.

Published evidence on the possible association between an increased risk of prostate cancer and Pb and/or Cd in occupationally exposed men is inconclusive (15). This may partly be explained by the fact that in many circumstances an increased exposure to these toxic metals is combined. Furthermore, occupational and environmental exposures to each of these metals are usually combined with exposure to the essential metal Zn that can act as an antagonist of the Pb-related and Cd-related reproductive toxicity (15, 25, 33). Thus it is important to simultaneously measure biomarkers of Pb, Cd, and Zn body burden and to control and adjust for each other, when evaluating the effect of any of these metals on PSA and prostate function in men.

With regard to the observed significant inverse association between PSA and intensity of alcohol consumption (drinks per week) after adjusting for potentially confounding variables by multiple regression (Table 2), it is important to note that alcohol consumption significantly positively correlated with BPb in the study population (r=0.473, p=0.0002). This association between alcohol consumption and BPb is common in humans (9-11, 44, 51) because alcoholic beverages contain an appreciable amount of Pb, and also because ethanol metabolism alters redox potential in the body and thus can mobilise the biologically inert fraction of accumulated Pb from the bones into the peripheral blood. Therefore, it seems possible that some of the reported alcohol-induced adverse effects on prostate carcinogenesis in men, reviewed by Platz et al. (6), may in fact be causally related to Pb, since those studies did not address Pb as a possible confounder. Furthermore, the oxidative stress hypothesis related to the effect of alcohol on prostate carcinogenesis (6) seems not to be plausible in view of decreased (rather than increased) erythrocyte lipid peroxidation in alcohol drinkers compared to controls, which was particularly evident in subjects who consumed more than 140 g of alcohol per day (52). However, the influence of alcohol consumption on PSA and prostate cancer in men still appears equivocal. For further elucidation, more studies on a large number of men should be done by performing a thorough control and adjustment for many potential confounders, including BPb in particular.

In conclusion, after adjusting for potentially confounding variables by multiple regression, this study has shown a significant positive association between PSA and BPb. This was observed in relatively young men at a low-level environmental Pb exposure common for general populations worldwide. With regard to the possibly related risk of prostate cancer, the influence of Pb, Cd, Zn, and Se on prostate damage and PSA should be further investigated in relatively young men for the purpose of disease prevention.

Acknowledgement

This study is a part of the research project "Reproductive health effects of toxic and essential metals in men" sponsored by the Croatian Ministry of Science, Education and Sports (grant no. 022-0222411-2408).

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Sažetak

PROSTATNI SPECIFIČNI ANTIGEN (PSA) U SERUMU U ODNOSU NA KONCENTRACIJU OLOVA U KRVI I KONZUMIRANJE ALKOHOLA U MUŠKARACA

Zajednički utjecaj dobi, pušenja, alkohola, koncentracija olova i kadmija u krvi te koncentracija bakra, cinka i selenija u serumu na prostatni specifični antigen (PSA) u serumu istražen je u skupini od 57 muškaraca dobi od 21 do 40 godina. Ispitanici nisu bili profesionalno izloženi metalima niti su imali druge poznate razloge za sumnju o mogućem utjecaju na funkciju prostate ili na metabolizam metala. Nije nađena značajna korelacija između PSA i bilo koje od razmatranih uzročnih varijabla. Međutim, nakon što su uzete u obzir sve navedene potencijalno uzročne varijable, rezultati postupne višestruke regresije pokazali su značajan porast PSA u odnosu na porast olova u krvi, kao i značajno sniženje PSA u odnosu na porast intenziteta konzumiranja alkohola (broj jedinica alkohola na tjedan). Vrijednosti medijana i raspona koncentracije olova u krvi u toj skupini muškaraca bile su 26,0 μg L^{-1} te 10,1 μg L^{-1} do 108,0 μg L^{-1}. Rezultati upućuju na mogućnost da čak i niska razina izloženosti olovu iz okoliša, uobičajena za opće populacije diljem svijeta, može pridonijeti opasnosti od raka prostate u muškaraca. Potrebno je daljnje istraživanje utjecaja olova i također kadmija, cinka i selenija na oštećenje prostate i na PSA u relativno mladih muškaraca u svrhu prevencije bolesti.

KLJUČNE RIJEČI: *interakcija toksičnih i esencijalnih metala, čimbenici načina života, čovjekova izloženost olovu iz okoliša, izloženost kadmiju, oštećenje prostate*

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