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Relation between selenium plasma levels and different prostatic pathologies

C.M. López Fontana[a,*], R.F. Pérez-Elizalde[a], M.C.M. Vanrell[a,◆], G.M. Recalde[a,◆], A.L. Uvilla[a,◆], and J.D. López-Laur[a,b]

[a]Laboratory of Metabolic Diseases and Cancer, Faculty of Pharmacy and Biochemisty, Universidad Juan Agustín Maza, Mendoza, Argentina

[b]Department of Clinical Urology, Faculty of Medical Sciences, Universidad Nacional de Cuyo, Mendoza, Argentina

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Several studies have demonstrated an inverse relation between serum selenium levels (Se) and advanced prostate cancer (PCa).

Objective: To determine and compare selenium plasma levels in patients with different prostatic pathologies.

Material and methods: It is a transversal, descriptive and comparative study. A sample of 64 men between 50 and 80 years old were selected for the study between 2007 and 2009. All volunteers underwent a digital rectal examination, prostate specific antigen level, ultrasound and transrectal prostate biopsy (12-14 chips). Prostate cancer was subclassified according to Gleason Score. Selenium was determined indirectly by serum Glutathione peroxidase (Kit Ransel, Randox SRL, Crumlin, UK). Statistical analysis was performed using ANOVA I ($p<0.05$).

Results: Glutathione Peroxidase level was 33.75±2.36mg/ml in control patients. A decrease of 31.6% was observed in patients with BPH (23.08±1.57mg/ml) and of (63.6%) in subjects with prostate cancer (12.28±1.03mg/ml) ($p<0,0001$). There was no correlation with the Gleason Score.

Conclusion: Serum selenium is lower in patients with prostatic pathologies being even more important in cancer patients regardless of the Gleason Score.

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*Corresponding author.
E-mail: investigacioncap@yahoo.com.ar (C.M. López Fontana).
◆Trainees

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Relación entre los niveles plasmáticos de selenio y las diferentes enfermedades prostáticas

Palabras clave:
Selenio
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R E S U M E N

Diversos estudios han demostrado una relación inversa entre los niveles séricos de selenio (Se) y la detección de cáncer de próstata (CaP) avanzado.

Objetivo: Determinar y comparar los niveles plasmáticos de Se en pacientes con diferentes enfermedades prostáticas.

Materiales y métodos: El estudio fue transversal, descriptivo y comparativo. La población estuvo constituida por 64 hombres de entre 50-80 años, seleccionados luego de una consulta urológica de rutina durante el período 2007-2009. Se realizó una historia clínica detallada, tacto rectal, determinación de PSA y concentración plasmática de Se mediante una técnica espectrofotométrica para glutatión peroxidasa en sangre entera (Kit Ransel, Randox SRL, Crumlin, UK). Las afecciones prostáticas se establecieron por biopsia transrectal ecodirigida (12-14 tomas) y el grado tumoral por score de Gleason. El análisis estadístico se realizó mediante ANOVA I ($p < 0,05$).

Resultados: La concentración media de Se en los individuos controles ($n = 10$) fue de 33,75 ± 2,36 mg/ml, en los pacientes con enfermedad benigna ($n = 41$) de 23,08 ± 1,57 mg/ml y en los casos con CaP ($n = 13$) de 12,28 ± 1,03 mg/ml ($p < 0,0001$). Se observó una disminución del 31,6% en los pacientes con enfermedad prostática benigna y de un 63,6% en aquellos con CaP en relación con los controles. No se observaron diferencias estadísticamente significativas entre el score de Gleason y los valores de glutatión peroxidasa.

Conclusión: Los sujetos con enfermedad prostática, tanto benigna como maligna, tienen niveles de Se en sangre menores que los individuos sanos.

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Introduction

Selenium (Se) is an oligoelement found in the body in the form of selenomethionine and selenocysteine. It is an essential component of cellular glutathione peroxidase, thereby acting as an important antioxidant. In addition, selenium complements the antioxidant effect of vitamin E by protecting cell membrane integrity.

At present, there is evidence that Se is related to prostate carcinogenesis. In recent years, many studies have been carried out in an attempt to clarify the relationship between this element and prostate cancer (PCa). In the double-blind study published by Clark et al.,[1] involving the administration of 200 µg of Se daily in patients with a history of skin cancer, such supplementing had no effect upon the development of recurrent skin tumors, though the incidence of PCa was seen to decrease by two-thirds. Yoshizawa et al.[2] have explored the association between the risk of PCa and high prediagnostic Se levels in laboratory mice. High Se levels were found to be related to a lessened risk of PCa. Both studies[1,2] reported a reduction of over 60% in the incidence of PCa between the groups that consumed larger doses of Se versus those administered lower doses.

The present study determines and compares the blood Se values in patients with different prostate gland disorders.

Materials and methods

Study population

The study population consisted of 64 males between 50-80 years of age selected on occasion of routine urological consultation and/or population-based educational campaigns in the period 2007-2009. We excluded those patients with a family history of PCa, as well as those in which the biopsy revealed atypical small acinar proliferation (ASAP) or high-grade prostatic intraepithelial neoplasm (PIN), obese patients, and those individuals who had participated in a clinical nutrition trial in the last 6 months.

The subjects were then divided into three groups:

- *Control group (n=10):* normal individuals with no apparent risk of developing PCa, and without chemically or biochemically detectable disease. Individuals without evidence of prostatism (lower urinary tract symptoms, LUTS) as evaluated by the IPSS/AUA score, with normal rectal digital exploration findings, PSA < 4 ng/ml, and a prostate gland of under 30 g as assessed by transrectal ultrasound.
- *Benign prostatic hyperplasia (BPH) and/or chronic prostatitis (CrP) (n=41):* individuals with LUTS, an IPSS/AUA score compatible

with BPH, normal rectal digital exploration findings, PSA = 4 ng/ml, a prostate gland of under 30-50 g as assessed by transrectal ultrasound, and an ultrasound-guided puncture biopsy of the prostate gland. Of the total 41 cases, 31 presented BPH and 10 had BPH with a CrP component.

- *Cancer group (n=13):* patients with prostate adenocarcinoma diagnosed on the basis of the ultrasound-guided puncture biopsy findings, and presenting a histopathological report.

Study design

A cross-sectional, descriptive and comparative design was adopted, with the compilation of a detailed clinical history, rectal digital examination and the determination of PSA levels. We also determined the plasma Se concentration indirectly using a spectrophotometric technique for glutathione peroxidase in whole blood (Kit Ransel, Randox).

The diagnosis of prostate disease was established from the ultrasound guided transrectal biopsy findings, with the obtainment of 12-14 cores, depending on the weight of the gland. Prostate size was established by transrectal ultrasound using a classical transducer, while tumor grading was based on the Gleason score. All subjects signed the informed consent document approved by the Ethics Committee of the Faculty of Medical Sciences of Universidad Nacional de Cuyo (Argentina).

Statistical analysis

The statistical analysis was performed using the SPSS version 15.0 statistical package (SPSS, Inc., Chicago, IL, USA). The following statistical descriptors were used: arithmetic mean and standard deviation of the mean. The data were compared by analysis of variance (ANOVA) and *post hoc* Bonferroni testing. Statistical significance was accepted for $p<0.05$ in all cases.

Results

The study population consisted of 64 male Latin American volunteers with a mean age of 60.5±5.59 years. Weight, height and body mass index (BMI) did not differ significantly among the three groups, as can be seen in table 1. Energy consumption (kcal/day) and macronutrient distribution in the different groups were in line with the recommendations for the general population. The intake of Se and vitamin E showed no statistically significant differences among the groups, though vitamin E consumption in general was lower than that recommended for this age range (15 mg/day).

The mean Se concentration among the controls was 33.75±2.36 mg/ml (35.24≥μ≤32.08 mg/ml; 95% confidence interval), versus 23.08±1.57 mg/ml among those with benign disease (23.56≥μ≤22.6 mg/ml; 95% confidence interval), and 12.28±1.03 mg/ml in the subjects with PCa (12.84≥μ≤11.72 mg/ml; 95% confidence interval)($p<0.001$). A 31.6% decrease in these levels was observed in the patients with benign prostate disease, versus 63.6% in those with PCa, with respect to the controls.

The mean prostate gland weight among the controls was 28.7±1.95g (29.9≥μ≤27.5 g; 95% confidence interval), versus 41.4±2.36 g in the subjects with BPH and/or BPH with CrP (42.12≥μ≤40.67 g; 95% confidence interval), and 42.2±1.8 g among the individuals with PCa (43.18≥μ≤41.22 g; 95% confidence interval). No statistically significant differences were recorded among the three groups, and no correlation with the blood Se levels was observed ($p>0.05$). The Gleason score was 7 (4+3) in 10 patients with PCa, while in three cases the score was 8 (4+4). Likewise, no variations were observed in the glutathione peroxidase values according to this tumor aggressivity marker.

Table 1 – General characteristics of the study population

Group				
Parameter	Control (n=10), mean±SD	BPH-CrP (n=41), mean±SD	Cancer (n=13), mean±SD	p[a]
Age, years	58.93±6.13	60.53±5.04	62.2±5.42	0.284
Prostate weight, g	28.7±1.95	41.4±2.36	42.2±1.8	0.04[b]
PSA, ng/ml	1.5±1.4	5.4±3.15	7.4±11.7	0.073
Weight, kg	98.8±18.15	89.15±17.54	95.25±10.91	0.346
Height, m	1.74±0.06	1.71±0.06	1.74±0.06	0.356
BMI, kg/m2	32.39±5.51	30.18±4.19	31.52±3.86	0.437
Energy, kcal	2145.2±738.44	2198.8±553.15	2444.8±614.37	0.442
Carbohydrates, %	44.07±7.1	42.8±8.9	47.6±8.08	0.674
Proteins, %	17.36±3.03	17.36±2.92	15.8±2.62	0.328
Lipids, %	30.0±5.5	28.9±5.8	28.57±7.2	0.863
Selenium, μg/d	122±35	115±27	114±27	0.755
Vitamin E, mg/d	9.39±3.52	9.36±2.83	9.41±2.99	0.883

SD: standard deviation; BPH: benign prostatic hyperplasia; BMI: body mass index; CrP: chronic prostatitis; PSA: prostate specific antigen.
[a]ANOVA I. Statistical significance $p>0.05$.
[b]*Post hoc* Bonferroni test findings: control ≠ BPH-CrP; control ≠ cancer; BPH-CrP = cancer.

Discussion

The high incidence, morbidity and mortality of prostate cancer (PCa) underscores the need for new strategies to control this disease. Chemical prevention, particularly with Se compounds, is a promising option for neoplastic diseases.

Selenium is a micronutrient, since only small amounts are required (recommended daily allowance, RDA = 50 µg/day). Ingestions in excess of 400 µg/day can have toxic effects (selenosis). This element preferentially accumulates within the prostate gland, with only a very small presence in the seminal vesicles. Selenium deficiency is relatively rare, but can be found in patients with severe intestinal disorders, or in subjects receiving only parenteral nutrition, as well as in populations dependent upon crops grown in low-selenium soils. The main sources of Se are shellfish, kidneys and meat. However, the element is found in greater proportions in foods of plant origin and in cereals when these crops are grown in selenium-rich soil. Selenium is found in organic and in inorganic form. Plants take up Se in inorganic form and transform it into organic Se – this being the active and most useful form for the body. The consumption of foods containing abundant antioxidant micronutrients, supplemented with a daily dose of Se and vitamin E, together with early diagnosis, appear to be very important factors for reducing the incidence and mortality of PCa. A varied diet containing animal and plant foods is a good way to supply the body with Se.

A study known as the Nutritional Prevention of Cancer Trial, including 1312 men and women with a history of non-melanoma skin cancer, showed no benefit derived from Se supplementing in terms of the prevention of new tumors. However, a 60% reduction in the number of new cases of PCa was observed among the males that received the mineral supplement during 6.5 years, compared with those administered placebo.[3]

Different studies have shown that patients with low serum Se levels are at a two-fold greater risk of being diagnosed with PCa than those with normal Se values,[4] while high levels of this mineral appeared to confer no protection against this type of neoplasm.[4]

The accumulation of Se within the prostate tissue, and local selenoprotein activity, have been analyzed as a potential mechanism for the prevention of PCa. Collaborative studies[5] have been able to determine Se derivatives *in vitro*, such as selenite, selenomethionine and selenocysteine, which possess protective effects. However, to date, it is not known whether these *in vitro* effects can be extrapolated to living organisms. Other clinical studies in PCa patients have found that high Se concentrations could lead to cell apoptosis and thus exert a cancer preventive effect.[6] Studies in mice with PC3 strain prostate cells have found that a high Se dose appears to play a role in preventing the progression and in reducing angiogenesis in animal models.[7]

Different studies have shown that prostate tumor cells previously treated with Se become more sensitive to gamma irradiation.[8] It has also been shown that increased blood Se levels can delay tumor progression in males that develop prostate malignancies.[8]

In contrast, other studies that have analyzed daily dietary Se consumption have recorded no correlation among the latter, the serum Se levels and the risk of PCa.[9] In fact, a study known as the European Prospective Investigation into Cancer and Nutrition, investigating the relationship between plasma Se and the risk of PCa in 959 males with incidental prostate carcinoma, found no relationship between plasma Se and PCa risk, grade or stage.[10] In addition, one of the more recent studies (SELECT), designed with the main objective of clarifying the role of vitamin E and Se in PCa, concluded that supplementation with both of these micronutrients did not reduce the incidence of PCa by 25% as had been postulated in the working hypothesis.[9]

Paradoxically, different preclinical and epidemiological studies, such as that published by Klein et al.[9] (in phase III), continue to indicate that vitamin E and Se exert a potential beneficial effect in relation to PCa. In addition, similar positive results have been published on this micronutrient, and on the need to combine it with vitamin E in order to enhance its action.

In sum, selenium as a chemical protective agent against PCa requires additional and more rigorous studies, placing emphasis on two fundamental aspects: a non-toxic protective dose, and the risk of certain associated diseases, since the most important difficulties reported in relation to Se supplementing have been neurological and liver toxicity associated with high doses of Se, and a high risk of developing type 2 diabetes in smokers.[9]

Conclusion

The results of our study suggest that patients with benign and malignant prostatic diseases, regardless of the Gleason score, have lower blood selenium concentrations than healthy individuals, and that supplementing with adequate doses of this element may be effective as chemical prevention against prostate cancer.

Conflicts of interest

This study was financed by Universidad Juan Agustín Maza and the Fundación Allende. These institutions only supplied financial aid, and exerted no influence upon the study.

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