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Correlation between Selenium Concentrations and Glutathione Peroxidase Activity in Serum and Human Prostate Tissue

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Abstract

Background—Low serum selenium concentration has been associated with increased risk of prostate cancer. A possible mechanism is through the antioxidant activity of selenoenzymes. However, the effect of selenium intake on selenoenzymes at target tissues is not well established. Hence, we investigated the correlation between serum and prostate tissue selenium concentrations and prostate tissue activity of glutathione peroxidase (GPX), a major selenoenzyme with antioxidant properties.

Methods—In an ongoing study investigating gene expression in prostate tissue, we measured serum selenium concentration in 98 men using atomic absorption spectrometry. Of these men, we selected 12 men with the highest and 12 men with the lowest serum selenium concentrations and measured selenium concentration and GPX activity in fresh frozen prostate tissue using the cyclic neutron activation analysis and a direct spectrophotometric procedure, respectively.

Results—The mean serum selenium concentrations among low and high selenium groups were 123.7 ± 5.9 μg/l and 196.7 ± 16.6 μg/l ($p < .0001$), respectively. The corresponding mean prostate tissue selenium concentrations were 1.39 ± 0.28 μg/g and 1.65 ± 0.42 μg/g ($p = 0.08$), resulting in a positive correlation between serum and prostate tissue selenium concentrations ($r = 0.56$, $p = 0.02$). The mean prostate tissue GPX activity was non-significantly greater in the low serum selenium group (32.2 ± 8.4 U/g protein) than in the high serum selenium group (29.6 ± 5.9 U/g protein) ($p = 0.39$) and it was not correlated with serum or prostate tissue selenium concentrations ($r = -0.22$, $p = 0.37$ for serum and $r = -0.33$, $p = 0.18$ for prostate tissue).

Conclusion—Serum and prostate tissue selenium concentrations were moderately correlated. In this population with relatively high selenium concentration, neither prostate tissue nor serum selenium concentrations were associated with prostate tissue GPX activity.

Keywords

selenium; glutathione peroxidase; serum; prostate tissue

Introduction

While most observational studies have shown an inverse association between serum selenium and prostate cancer risk [1–10], results from two clinical trials are mixed [11, 12].

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The Nutrition Prevention of Cancer Trial (NPCT) showed a strong protective effect, limited to men with low baseline serum selenium concentrations, while the Selenium and Vitamin E Trial (SELECT), one of the largest cancer prevention trials conducted to date, found no effect of selenium supplementation on prostate cancer. One of the arguments for the null finding in SELECT is that the selenium concentrations of the participating men were already relatively high at baseline, beyond which selenium supplementation may have no further beneficial effect on the activity of selenoenzymes [12]. Selenium is critical for the activity of selenoenzymes which prevent oxidative damage to DNA and other biomolecules and modulate inflammation [13], relevant risk factors for prostate cancer [14]. To further explore the impact of circulating selenium as a measure of selenium intake on selenoenzyme activity in the prostate, we examined the correlation between serum and prostate tissue selenium concentrations and prostate tissue activity of glutathione peroxidase (GPX), a key selenoenzyme. To our knowledge, this is the first study that examined the correlation in human prostate tissue. Overall our finding of no correlation between serum or prostate tissue selenium concentrations and GPX activity in prostate tissue in a study population with relatively high selenium concentrations is consistent with the null finding in the SELECT.

Methods

Study population

Serum and prostate tissue samples were collected from men who were recruited as part of an ongoing study to investigate associations between hormones, nutrients, and gene expression in prostate tissue conducted at the Veteran Affairs Medical Center in Seattle. In brief, this study included men who were between the ages of 45–74 years, who were referred for prostate biopsy for prostate specific antigen (PSA) level of greater than 4.0 ng/ml and/or suspicious digital rectal exam, were able to comprehend the procedure of prostate biopsy, and had a life expectancy of at least 5 years. Furthermore, men were excluded if they had an active serious infection or immunosuppression, history of bleeding disorders, or a need for anticoagulation drugs. Only men with no indication of prostate cancer based on pathological evaluation of the diagnostic biopsy were included in this study. Blood samples were collected before the biopsy procedure. After standard diagnostic biopsies were obtained, additional biopsy samples from the peripheral zone were collected for research purposes. Participants also filled out the questionnaire on their demographics, health, medical history, medication use such as non-steroidal anti-inflammatory drugs (NSAIDs), lifestyles including physical activity, and supplement use (i.e., multivitamin, vitamins C and E, Saw Palmetto, fish oil/omega-3 and others). The PSA level closest to the date of biopsy was extracted from the participants' medical records. All study participants signed an informed consent and the study was approved by the Institutional Review Board. In order to maximize the difference in selenium concentration, we measured serum selenium concentrations in 98 men and selected those 12 men with the highest and those 12 men with the lowest serum selenium concentrations for prostate tissue analysis (selenium concentration and GPX activity).

Laboratory analysis

Selenium concentration in serum was measured by atomic absorption spectrometry (Perkin-Elmer 5000; Perkin-Elmer Corp., Norwalk, CT) as described elsewhere [10]. The coefficient of variation (CV) of the quality control (QC) pool of the National Institutes of Standards and Technology (NIST) certified sample was 7.7%. The GPX activity was measured with the total GPX assay kit (ZeptoMetrix Corp., Buffalo, NY) by applying a direct spectrophotometric procedure and protein concentration was measured to normalize GPX activity per gram protein. The CV of the QC samples for the GPX activity varied from 0.8% to 4.8% with a mean of 2.4%. Protein concentration in tissue was measured in duplicate with

a microplate BCA procedure on the SpectraMax Spectrophotometer (Molecular devices, Sunnyvale, CA) and was used to normalize GPX activity per gram protein. The CV for duplicate protein values ranged from 1.0 to 4.3%. The prostate tissue selenium concentration was quantified through cyclic neutron activation analysis using a modification of a previously described method [15]. To monitor the quality, we measured selenium concentrations in three Bovine Liver (SRM 1577) samples provided by the NIST (Washington, D.C.). The CV was 2.0% and the mean value (1.11 μg/g dry weight) was in agreement with the NIST certified selenium concentration (1.1 ± 0.1 μg/g dry weight).

Statistical analysis

The characteristics of 24 participants were compared between the low and high serum selenium groups by applying the *t*-test for continuous variables and χ^2-test for categorical variables. The Pearson correlations between serum or prostate tissue selenium concentration and prostate tissue GPX activity were estimated with and without adjustment for covariates [i.e., age at prostate biopsy, body mass index (BMI, kg/m^2), alcohol use (current, former, or never), PSA level, NSAID use including aspirin and ibuprofen (yes or no), and physical activity (usual number of days of exercise per week)]. Furthermore, the analysis was repeated for those who were not taking selenium from single supplement based on self-reporting. The adjusted correlations were reported as a partial correlation coefficient. All statistical analyses were performed by SAS version 9.1 (SAS Institute, Inc., Carey, NC).

Results

The serum selenium concentrations of 98 men who enrolled in the ongoing study ranged from 112.5 to 232.8 μg/l. We selected 12 men with the highest serum selenium concentrations (mean: 196.7 ± 16.6 μg/l, range: 178.2–232.8 μg/l) and 12 men with the lowest serum selenium concentrations (mean: 123.7 ± 5.9 μg/l, range: 112.5–129.3 μg/l). Men in the high serum selenium group tended to be older and have higher BMI and lower PSA level, although these differences were not significant (Table 1). Mean prostate tissue selenium concentration was higher in the high selenium group (1.65 μg/g) than in the low selenium group (1.39 μg/g) ($p = 0.08$). GPX activity did not differ between the high selenium group (29.6 U/g protein) and the low selenium group (32.2 U/g protein; $p = 0.39$).

There was a significant, although modest, positive correlation between serum and prostate tissue selenium concentrations ($r = 0.49$, $p = 0.02$ without adjustment; $r = 0.56$ $p = 0.02$ with adjustment; Table 2 and Figures 1–3). In contrast, there were non-significant inverse associations of serum selenium concentration with prostate tissue GPX activity ($r = -0.25$, $p = 0.24$ without adjustment; $r = -0.22$, $p = 0.37$ with adjustment) and prostate tissue selenium concentration and GPX activity ($r = -0.19$, $p = 0.38$ without adjustment; $r = -0.33$, $p = 0.18$ with adjustment).

When the analysis was restricted to men who were not taking selenium either from single or multivitamin supplement ($n = 16$), the adjusted correlations between prostate tissue selenium and serum selenium ($r = 0.49$, $p = 0.15$), between prostate tissue selenium and prostate tissue GPX activity ($r = 0.07$, $p = 0.85$) and between serum selenium and prostate tissue GPX activity ($r = -0.08$, $p = 0.83$) were slightly attenuated and became non-significant for serum and tissue selenium, probably due to smaller sample size.

Discussion

In this study of 24 men prescreened for low and high serum selenium concentrations, there was a moderate positive correlation between serum and prostate tissue selenium

concentrations. There were, however, no significant associations between serum or prostate tissue selenium and GPX activity.

Measured serum selenium concentrations in this study are within the range, although on the high end, of selenium concentrations observed in previous studies for prostate cancer [1, 9, 10, 16, 17]. Furthermore, the difference in selenium concentrations between the low and high selenium groups (124 to 197 μg/l) in our study is similar to the difference in the post-intervention concentrations in the NPCT, in which mean serum selenium concentrations were approximately 115 μg/l in the placebo and 180 μg/l in the supplementation group after nine years [11]. In the SELECT, the mean serum selenium concentrations were 140 μg/l in the placebo and 252 μg/l in the selenium groups at 4th annual visit [12]. Accordingly, our study was able to investigate the impact of serum selenium on prostate tissue measurements for a similar wide range as observed in the two trials.

The prostate tissue selenium concentrations observed in this study are comparable, although again on the higher end, to those from previous studies among healthy men [18, 19]. A study conducted in Kansas reported that the mean tissue selenium concentration in five healthy men was 1.32 ± 0.09 μg/g [18] and another study using autopsy samples from 41 men who had died suddenly or unexpectedly reported a mean concentration of 1.3 ± 0.4 μg/g [19]. In three other studies, including men predominately with prostate cancer or benign prostatic hyperplasia, prostate tissue selenium concentration ranged from 0.20 to 1.47 μg/g [20–23].

We found a positive correlation between serum selenium as a measure of selenium intake and prostate tissue selenium concentrations among all men ($r = 0.56$, $p = 0.02$). Although there has been no study among men without prostate cancer examining a correlation between serum and prostate tissue selenium, there are two studies conducted among prostate cancer patients. A study among 15 prostate cancer patients reported a weak, non-significant positive correlation between serum and prostate tissue selenium concentrations ($r = 0.27$, $p = 0.33$) [20]. A trial among 66 prostate cancer patients [22] showed that selenium supplementation (200 μg/day as selenomethionine) for 14 to 31 days increased the serum selenium concentration by 15% ($p = 0.001$) and the prostate tissue selenium concentration by 22% ($p = 0.003$) comparing the supplementation group ($n = 34$) with the non-supplemented group ($n = 32$). In contrast to our study, these two previous studies measured selenium concentration in cancer tissue, which may affect the selenium concentration. However, all these studies found a positive association between circulating and prostate tissue selenium concentrations, supporting the use of circulating selenium concentration as a surrogate for prostate tissue selenium concentration.

To our knowledge, no study has investigated the association between selenium concentration and GPX activity in human prostate tissue, a potentially important target tissue for a chemopreventive effect of selenium. Animal studies have found positive correlations between prostate tissue selenium concentration and GPX activity ($r = 0.30$–0.96) [24, 25] in various tissues (prostate tissue was not investigated). However, it should be pointed out that these studies included a wide range of selenium concentration starting with very low selenium concentrations. While there is no other human tissue study, several studies investigated circulating concentrations, which may be used as surrogate for tissue measurements. These studies showed that selenium supplementation increases circulating selenium concentrations (Table 3) [26–37]. Furthermore, selenium supplementation increased GPX activity in blood components in some studies [30–35], especially in the population with low selenium status, but in not all studies [26–28, 36, 37]. Based on these blood-based studies, circulating GPX activity was estimated to plateau at about 90 to 100 μg/l [32, 34]. In our study serum selenium concentration in the low selenium group was between 112.5 and 129.3 μg/l and hence, above the concentration at which circulating GPX

activity plateaus. If we can extrapolate from concentration in blood to prostate tissue, it is possible that selenium concentrations in this study population were above the range where a positive correlation could have been observed. Consistent with these findings is the NCPT observation that the preventive effect of selenium supplementation on prostate cancer risk was limited to men with low baseline selenium concentration, particularly those in the first tertile (<106 μg/l) [38], which are below the concentrations observed in our study or in the SELECT. Hence, these results may further suggest that beneficial effects of selenium are limited to population where selenoenzyme activity has not reached a plateau.

Strength of this study includes prostate tissue samples from men without an indication of prostate cancer; however, it should be noted that biopsies were taken because of their elevated PSA levels or abnormal digital rectal examination. Hence, our findings might be more generalizable than studies among patients undergoing prostatectomy for their cancer treatment. Another strength includes the measurement of selenium and GPX activity in the target tissue of interest, instead of using a blood compartment as a surrogate. Although this study collected important baseline characteristics, we may have missed to adjust for additional factors that might have influenced our measurements, including genetic variations in *GPX* genes. Measurements of selenium and GPX activity at different time points would have likely reduced measurement error; however, such study is less feasible since this would require multiple biopsies. A further potential limitation is lack of a measurement of GPX at protein level, which may be important, owing to the unique feature of selenoenzyme translation and biosynthesis process [39]. We focused on GPX, an important selenoenzyme expressed in the prostate tissue [40], and hence, we cannot rule out the possibility that tissue selenium may be correlated with other selenoenzymes also expressed in the prostate, such as selenoprotein P or selenoprotein 15 [40–42]. While our study included a relatively small number of men, our approach of prescreening men for high and low serum selenium concentrations is an efficient way to increase the statistical power, given that it is less expensive and invasive to measure serum concentrations than to measure the selenium concentration and GPX activity in tissue.

Conclusion

In conclusion, in this study of 24 men without prostate cancer, we found a positive correlation between serum and prostate tissue selenium concentrations. This suggests that serum selenium can be considered a reasonable surrogate marker for prostate tissue selenium concentration in large epidemiologic studies. In contrast, there was no correlation of serum and prostate tissue selenium with prostate tissue GPX activity, which may be due to relatively high selenium concentrations in this population. This is consistent with the finding from the SELECT where selenium supplementation did not affect the risk of prostate cancer in a population with relatively high selenium concentrations. Future studies are needed in men with low serum selenium concentrations.

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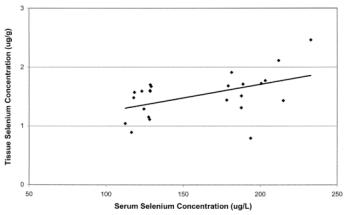

Figure 1.
Correlation between Serum and Tissue Selenium Concentrations

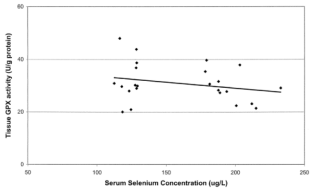

Figure 2.
Correlation between Serum Selenium Concentration and Tissue GPX Activity

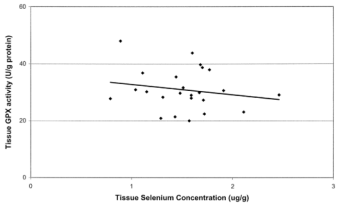

Figure 3.
Correlation between Tissues Selenium Concentration and GPX Activity

Table 1

Characteristics of the Study Population*

	Low selenium	High selenium	P for difference**
Number	12	12	-
Age at biopsy (years)	60.8 ± 6.4	62.2 ± 5.6	0.59
PSA level (ng/ml)	6.12 ± 4.51	4.12 ± 3.24	0.23
Body mass index (kg/m^2)	27.9 ± 4.7	29.3 ± 6.7	0.58
Alcohol use (N)			0.15
Current	8	7	
Former	4	2	
Never	0	3	
Tobacco use (N)			1.00
Former	12	12	
Selenium supplement use***	4	4	0.67
NSAID use			1.00
Yes	4	4	
No	8	8	
Physical activity			0.48
less than 1 day a week	9	5	
≥ 1 day a week	3	7	
Serum selenium concentration (μg/L)	123.7 ± 5.9	196.7 ± 16.6	<.0001
Tissue selenium concentration (μg/g)	1.39 ± 0.28	1.65 ± 0.42	0.08
GPX activity (U/g protein)	32.2 ± 8.4	29.6 ± 5.9	0.39

* Mean (standard deviation) or the frequency is provided.

** The difference between the two groups was tested by the *t*-test for continuous variables and χ^2-test for categorical variables.

*** Selenium supplement use from single or multivitamin supplements is provided; the use is unknown for one participant in high selenium group.

Table 2

Correlations of Serum Selenium Level (μg/l) with Prostate Tissue Selenium Level (μg/g) or GPX Activity (U/g protein) (n = 24)*

Correlation	Unadjusted		Adjusted**	
	r	p-value	r	p-value
Serum selenium and tissue selenium	0.48	0.02	0.56	0.02
Serum selenium and tissue GPX activity	−0.25	0.24	−0.22	0.37
Tissue selenium and tissue GPX activity	−0.19	0.38	−0.33	0.18

* Pearson correlation coefficients were calculated.

** The partial correlation coefficients were adjusted for age, BMI, alcohol use, PSA level, NSAID use, and physical activity.

Table 3

Previous Studies Investigating Effect of Selenium Supplementation on Circulating Selenium Concentration and GPX Activity

Author Year (ref)	Location	N	Supplementation or Controls/Placebo			Seleniumμg/l[1]			GPX[2]		
			Duration	μg/day	Form	Baseline	End	p-value[3]	Baseline	End	p-value[3]
Ravn-Haren 2008 [36] (cross-over design)	Denmark	20	4×1 week with 8-week washout periods in between	0	Milk and placebo tablets	113	113	-	82.7	82.7	-
				300	Selenate and milk	108	127	p=0.01	82.2	81.8	N.S.
				300	Se-enriched yeast and milk	115	146	p<0.0001	77.6	82.3	N.S.
				480	Se-enriched milk and placebo tablets	107	154	p<0.0001	81.5	82.0	N.S.
Bibow 1993 [26]	Norway	7	6 weeks	-[4]	Low-Se bread[4]	107	104	-	0.57	0.45	-
		7		60	Se-enriched bread	112	126	p<0.005	0.52	0.48	N.S.
van Dokkum 1992 [27]	Netherlands	6	6 weeks	-[4]	Low-Se bread[4]	78	77	-	4.9	5.0	-
				200	Se-enriched bread	79	143	p<0.05	4.3	4.5	N.S.
Neve 1988 [28]	Belgium	6	60 days	0	Placebo pills	84[6]	84[6]	-	7.3[6]	7.4[6]	-
		10		100	Selenomethionine	87	123	p<0.05	7.6[6]	8.0[6]	N.S.
van der Torre 1991 [29][5]	Netherlands	4	9 weeks	-[4]	Low-Se bread[4]	74	74	-	240	250	-
		8	9 weeks	215	Se-enriched bread or meat	65	138	p<0.05	218	340	Not reported
		7		135	Se-enriched bread or meat	72	122	p<0.05	209	300	Not reported
Levander 1983 [30;31]	Finland	12	11 weeks	-	-	70	77	-	208[6]	254[6]	-
		10		200	Enriched in yeast	69	171	p<0.05	240[6]	377[6]	p<0.05
		10		200	Enriched in wheat	70	167	p<0.05	234[6]	414[6]	p<0.05
		10		200	Selenite	70	113	p<0.05	240[6]	424[6]	p<0.05
Alfthan 2000 [32]	China	10	12 weeks	0	Placebo pills	12	12[6]	-	7.2	7.2[6]	-
		10		200	Selenite	13	78	p<0.05	7.4	28.0[6]	p<0.05
		10		200	Se-enriched yeast	13	102	p<0.05	7.3	25.9[6]	p<0.05
Alfthan 1991 [31;33]	Finland	15	16 weeks	0	Placebo pills	113	111	-	185	178	-

Author Year (ref)	Location	N	Supplementation or Controls/Placebo			Seleniumμg/l[1]			GPX[2]		
			Duration	μg/day	Form	Baseline	End	p-value[3]	Baseline	End	p-value[3]
		10		200	Se-enriched yeast	110	166	p<0.05	173	184	N.S.
		10		200	Selenite	108	120	p<0.05	168	222	p<0.05
		10		200	Selenate	105	107	N.S.	166	232	p<0.05
Duffield 1999 [34]	New Zealand	10	20 weeks	0	Placebo tablets	62	64	-	330	373	-
		10		10	Selenomethionine	63	72	N.S.	331	364	N.S.
		11		20	Selenomethionine	66	82	p<0.05	339	400	N.S.
		10		30	Selenomethionine	68	86	p<0.05	335	412	N.S.
		11		40	Selenomethionine	64	90	p<0.05	352	444	p<0.05
Thomson 1993 [35]	New Zealand	10	32 weeks	0	Placebo yeast	56	61[6]	-	27	27	-
		11		200	Selenomethionine	53	109[6]	p<0.001	24	34	p<0.01
		12		200	Selenate	53	191	p<0.001	22	34	p<0.01
Ravn-Haren 2008 [37]	Denmark	28	5 years	0	Placebo yeast	Not measured	92	-	Not measured	92.7	-
		27		100	Se-enriched yeast	Not measured	165	p<0.05	Not measured	98.8	N.S.
		23		200	Se-enriched yeast	Not measured	221	p<0.05	Not measured	104	N.S.
		27		300	Se-enriched yeast	Not measured	260	p<0.05	Not measured	98.8	N.S.

[1] Selenium concentration was measured in plasma [27–35;37] or serum [26;36].

[2] GPX activity was measured in red blood cells [28;29;31–33;35–37], platelet [26;27;29–31], or whole blood [34]. The unit used was U/g protein [26;29;30;33] or U/g Hb [27;28;32;34–37].

[3] P-value compares selenium supplement group with the placebo group at the end of supplementation period and “N.S.” indicates no statistically significant difference between supplementation and placebo group.

[4] Received normal or non-enriched bread, which contains some selenium.

[5] Within the two intervention group of study [29], half of subjects received bread and the other half received meat, however the separate results for bread vs. meat were not provided

[6] Values were derived from figures and, therefore, may be less precise.