The Role of Selenium in Iodine Metabolism in Children with Goiter

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Possible interactions between selenium and iodine metabolism were investigated in 7- to 16-year-old children with goiter (n = 136) living in southeastern Poland in iodine-deficient areas influenced by a sulfur industry. The Se–iodine interactions in these children were compared to the interactions in children from outside of that region (n = 38). Blood selenium (BSe) concentration and plasma glutathione peroxidase activity were much lower in the study group (64.1 ± 15.7 µg/L; 111.0 ± 27.6 U/L) than in the control group (85.3 ± 19.6 µg/L; 182.4 ± 35.6 U/L). Almost all of the data [plasma thyroid-stimulating hormone (TSH) concentration, plasma free thyroxine (fT_4) concentration] fell within the reference limits. There was no statistically significant difference between the control and the study groups with respect to fT_4 and TSH. However, statistically significant differences of fT_4 and TSH in the study group were revealed between females belonging to the lower (n = 21; fT_4, 16.1 ± 3.3 pmol/L; TSH, 1.83 ± 1.05 mU/L) and upper Se quartiles (n = 24; fT_4, 14.5 ± 2.2 pmol/L; TSH, 1.26 ± 0.90 mU/L), $p < 0.05$. Neither group differed in iodine in urine concentration, age, and body mass index. The difference in fT_4 concentrations can be attributed to an Se deficiency. The relationship exists only for females, which suggests a sex-linked hormonal response to concomitant Se and iodine deficiencies. *Key words*: **fT_4, glutathione peroxidase, goiter, iodine, selenium, sulfur, thyroid, TSH.** *Environ Health Perspect* **108:67–71 (2000). [Online 14 December 1999]**
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Selenium is an integral component of the active center of glutathione peroxidase and type I 5′-iodothyronine deiodinase. It plays an indispensable role in thyroid hormone synthesis. The synthesis of physiologically active triiodothyronine (T_3), in particular, is largely dependent on the Se status. Concurrent Se and iodine deficiencies may result in a modified thyroid hormone metabolism in animals (*1–2*). In humans this essential trace element is a highly probable cofactor in myxoedematous cretinism (*3–5*). However, the administration of Se to iodine- and Se-deficient schoolchildren and myxedematous cretins in Northern Zaire resulted in a decompensation of the thyroid hormone synthesis that was particularly apparent in the cretin subjects (*6–9*). In cretins, Se supplementation caused a decrease in the already low level of thyroid hormones (T_3 and thyroxine) accompanied by an increase of thyroid-stimulating hormone (TSH), which was elevated even before the trial. On the other hand, excessive Se administration to subjects with subtly impaired thyroid hormone synthesis did not cause any symptoms of hypothyroidism (*10*). Se investigations and supplementation trials were also carried out in patients suffering from phenylketonuria. Because of protein restrictions in their diet, these patients have an extremely low Se intake, which can influence thyroid hormone metabolism (*11–16*). Selenium intake is moderate in Poland, and a tendency toward time-decreasing blood Se levels in children was observed (*17*). In areas where an excess of one of the two elements is present, the antagonism between sulfur and Se also must be taken into account. We have known since the 1960s that the use of sulfur-containing fertilizers can cause a 30–80% reduction in forage Se concentrations, a magnitude which, to some degree, is independent of the Se concentration in the soil. This Se reduction has been explained by a dilution effect caused by a growth response (increase in dry matter yields) to the higher concentration of sulfur in the soil. A mechanism of the direct inhibition of selenate and selenite uptake by plants must also be taken into account. The latter effect has been used in many attempts to reduce Se toxicity to plants and animals in seleniferous soils (*18–20*).

Materials and Methods

Subjects. The study population resided in four small towns in southeastern Poland: Janów Lubelski, Nowa Dęba, Rudnik, and Sandomierz (Tarnobrzeg region). We assumed that the population studied was nearly uniform in socioeconomic and hygienic factors as well as in exposure to possible Se and iodine in food, air, and water, because the study population was drawn from the same relatively small geographical location. The total goiter frequency among schoolchildren in the study area was 32.0–55.4%; the mean concentration of iodine in urine (IU) was 54.6–93.1 µg/L (*21*) and the percentage of neonates with TSH level > 5 mU/L was 8.37–10.28% for 1995–1997 (*22*).

There are no extant detailed studies available for the whole of southeastern Poland on the Se content in soil and plants. The prevalent cultivated types of soils in this region are loess and silts (*23*). The Se content in the soils depends on their properties (e.g., the amounts of fraction < 0.02 mm in different areas and the amount of organic matter of humic origin). The Se content in soils like those in the Tarnobrzeg region (soils that are common in Poland) ranges from 0.16 to 0.46 mg/kg (*24*). As compared to other countries these soils are rather poor in total Se. Low levels of Se (below 0.2 or 0.3 mg/kg) in Tarnobrzeg region were confirmed by Dutka (*23*). The environment of the Tarnobrzeg region is heavily influenced by the sulfur industry: sulfur exploitation and processing and sulfur levels in soils in this region are relatively high (summarized in Table 1).

One hundred thirty-six subjects were surveyed (mean age, 11.1 ± 2.1 years; mean weight, 39.0 ± 10.8 kg; 90 females and 46 males). Subjects were selected on the basis of previously published epidemiologic data from this region (*21,26–27*). The parents of the subjects gave written consent for their children's examinations. The study protocol was submitted and approved by the Ethical Committee of Collegium Medicum of the

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Jagiellonian University (Cracow, Poland). The control group consisted of 38 subjects (mean age, 11.5 ± 3.0 years; 19 females and 19 males) who were hospitalized in an orthopedic unit of the Polish–American Children's Hospital, Collegium Medicum of the Jagiellonian University, for minor surgical ailments but who were otherwise healthy with no clinical signs of thyroid disorders.

Analytical methods. We measured the following parameters: blood selenium (BSe) and plasma glutathione peroxidase (plGSHPx) activity as the biochemical markers for Se status and IU, TSH in plasma, free thyroxine (fT_4) in plasma, and thyroid volume (TV) as indicators of iodine status (fT_4 was also used as parameter reflecting variation in iodothyronine deiodinase type I activity). The set of parameters was completed by some anthropometric measurements (weight, height, and age) and sonographic screening of thyroid gland. Sonography of the thyroid was performed only on the individuals from the study group. Heparinized whole blood samples (sodium-heparine, Vacutainer; Beckton Dickinson, Rutherford, NJ) were obtained from 136 (study group) and 38 (control group) individuals and urine samples were obtained from 136 and 17 individuals, respectively. Blood samples taken from the cubital vein were immediately aliquoted and preprocessed. The first aliquot was frozen and the second was carefully centrifuged at 4°C at 1500*g* for 10 min to obtain supernatant plasma, which was transferred with a pipette to the propylene Eppendorf tubes and then frozen. Samples were kept frozen until determinations. All steps were performed using metal-free disposable plastic syringes, centrifuge tubes, and transfer pipettes. Urine samples were collected in plastic cups and were kept frozen until analysis.

Electrothermal atomic absorption spectrometric measurements of BSe concentrations were performed on a Perkin Elmer model 5100 ZL (Perkin-Elmer, Norwalk, CT) with longitudinal Zeemen-effect background correction equipped with an AS-70 automatic sampler and an Se hollow cathode lamp. Absorption readings, measured as peak area, were determined at the wavelength of 196 nm and at the slit width of 0.70 nm. We used the purge gas argon and pyrolytically coated graphite tubes with stabilized temperature platform furnace throughout.

The blood samples were first thawed and then diluted (1:2) with a 0.1% nitric acid solution containing 0.1% Triton X-100. This solution was then mixed thoroughly and 20 µL was injected into the graphite furnace for analysis. We used palladium nitrate (0.4%) as a modifier. To offset the effect of matrix interferences, calibration was made against standards based on human whole blood (method of additions calibrate). Seronorm reference human blood was purchased to assess the quality of Se measurements (batch no. 205053; Nycomed Pharma AS, Oslo, Norway). The mean analyzed value was 80.3 ± 1.3 mg/L (certified value 82 µg/L, range 76–88 µg/L), and within-batch precision was 1.6–8.0%.

We evaluated plGSHPx activity with *t*-butyl peroxide as the acceptor substrate according to the method of Paglia and Valentine (*28*) and modified by Günzler (*29*). The reaction was carried out either in a Cobas Fara centrifugal spectrophotometer (Roche Products Ltd., Welwyn Garden City, Herts, UK) or a Spekol 11 spectrophotometer (Carl-Zeiss, Jena, Germany). Both instruments were equipped with constant temperature cell housing. One unit of plGSHPx activity was expressed as 1 µmol NADPH oxidized/min; within-batch precision was 7.6%.

We measured plasma TSH by a sensitive immunoradiometric method with materials from Orion Diagnostica, Espoo, Finland, and we measured plasma fT_4 concentration with a radioimmunoassay kit manufactured by Immunonotech, Marseille, France. The declared intraassay coefficients of variation were 1.5% (for mean level of 1.72 mU/L) for TSH and 4.41% (for mean level of 11.7 pmol/L) for fT_4.

IU samples were analyzed by a catalytic method using the Sandell-Kolthoff reaction with minor modifications; details have been reported by Dr̀dż (*30*). We used an ultrasonographic device, Siemens Sonoline SI 400 (Siemens Medical Systems, Inc., Issaquah, WA) with a linear transducer at 7.5 MHz, for sonography of the thyroid. The subjects' nutritional status in the study group was roughly assessed by measuring the height and weight of each individual and calculating the body mass index (BMI) from them. The variability in sample sizes is due to a shortage of materials or to the inability to obtain blood or urine from some participants.

Statistical approach. We checked the normality of the parameter distribution by Kolmogorov-Smirnov and chi-square tests. To compare the studied and control groups and to assess the effects of Se concentration and glutathione peroxidase activity on iodine metabolism in both groups, parameters showing a gaussian distribution in both populations were compared using analysis of variance; parameters with a nongaussian distribution were compared by the Kruskal-Wallis test. Pearson's or Spearman's coefficient was applied to bivariate normal distributions and to nonbivariate normal distributions, respectively. A probability level of $p < 0.05$ was considered statistically significant. Statistical analyses were carried out using the statistical package STATISTICA (StatSoft, Tulsa, OK).

Results

The main descriptive characteristics of both the study and the control group parameters are summarized in Table 2. Two parameters in the study group (TSH and IU) and two in the control group parameter sets (fT_4 and IU) had a nongaussian distribution. There were statistically significant differences between the levels of Se, plGSHPx, and IU. Almost all of the data (TSH and fT_4) fell within the reference limits. The control and study groups did not differ in these parameters. Within the study group we found no differences with respect to Se and plGSHPx when domicile, sex, and age were taken into account. However, when the study group was divided in subgroups according to BSe levels, we found statistically significant differences were between females belonging to the lower (n = 21; fT_4, 16.1 ± 3.3 pmol/L; TSH, 1.83 ± 1.05 mU/L) and upper Se quartiles (n = 24; fT_4, 14.5 ± 2.2 pmol/L; TSH, 1.26 ± 0.90 mU/L), $p < 0.05$ (Figures 1 and 2). Neither group differed in IU, age, or BMI.

We calculated either Pearson's or Spearman's correlation coefficients for all Se and iodine parameters. In addition, in the

Table 1. Sulfur content in the Tarnobrzeg region versus mean values in Poland.

	Tarnobrzeg region	Mean value in Poland
Sulfur in soil	0.01–0.32%	0.012%
Sulfates in surface waters	25–400 mg/L	58 mg/L
Sulfur in water sediments	0.1–4%	0.047%

Data from Lis and Pasieczna (*25*).

Table 2. Main descriptive statistics of Se and iodine parameters in the study and control groups.

		Study group				Control group				
Parameter	Unit	*n*	Mean	Min	Max	*n*	Mean	Min	Max	*p*
BSe	µg/L	136	64.4	30.3	111.5	37	85.3	52.6	128.4	< 0.001
plGSHPx	U/L	135	111.0	49.4	207.8	38	182.4	115.8	283.0	< 0.001
fT_4	pmol/L	135	14.9	1.2	24.4	38	15.0	8.50	20.6	NS
TSH	IU/L	134	1.57	0.17	6.01	37	1.99	0.26	4.86	NS
IU	µmol/L	136	0.60	0.08	2.87	17	0.92	0.28	1.84	< 0.005

Abbreviations: max, maximum; min, minimum.

study group, we assessed the correlations between these parameters and the TV, as well as the normalized TV. A normalization of TV was made by dividing the TV of each subject by the age-adjusted upper limit of normal TV given by Delange (*31*), Gołkowski et al. (*32*), and Gutekunst et al. (*33*) or by body surface area [BSA (in square meters) BSA = $W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4}$, where W = body weight (in kilograms) and H = height (in centimeters)] (*34*). The correlations found in the study group are summarized in Table 3. The only correlations in the control group were between Se and TSH (r = -0.385, $p < 0.05$) and Se and IU (r = -0.549, $p < 0.05$). No correlation between Se or plGSHPx and age was found for any group.

Discussion

The levels of BSe and plGSHPx are higher in the control group as compared to the study group. Se levels in the study group were similar to those reported for New Zealand, Austria, Turkey, and Hungary (Table 4). They ranged from the highest normal values to deficiencies. The mean Se level was 75% of the mean Se concentration in the control group. Lower Se levels have rarely been reported from Poland, except in children with malignant diseases of the hematopoetic system (*40*) or with secondary malabsorption (*44*). Drastically lower plasma Se levels (35 ± 11 µg/L) were found for mothers at delivery in Poland (*45*).

The low plGSHPx was comparable to levels in other countries with relatively low Se values, for example, Hungary and Germany (mean plGSHPx of the study group was 61% of the mean activity in the control group).

In the present study, BSe and plGSHPx demonstrated a wide range of levels in the control group. This range probably reflects the wide range of Se intake. Control group BSe and plGSHPx levels were comparable to results reported by various authors for healthy children from other parts of Poland or from other countries such as Italy, Scotland, and Finland (Table 4). However, the comparison of results from different laboratories has limited meaning because of the lack of standardized methods used to determine plGSHPx activity. It seems more plausible to compare relative plGSHPx activity, i.e., the ratio of plGSHPx activity in the study and control groups versus the BSe ratio in the corresponding groups. Table 5 shows results calculated in this way. BSe and plGSHPx ratios obtained in the present work are similar to those of Wąsowicz et al. (*44*) and Popadiuk et al. (*40*) but differ from those obtained for children with phenylketonuria (*14,15*).

The results for BSe, plGSHPx, and IU show that the study group is both Se and iodine deficient. In contrast, Se and iodine concentrations in the control group are much higher. The low BSe and plGSHPx activities are presumably caused by decreased absorption. Using an algorithm given by Longnecker et al. (*46*) or a regression curve

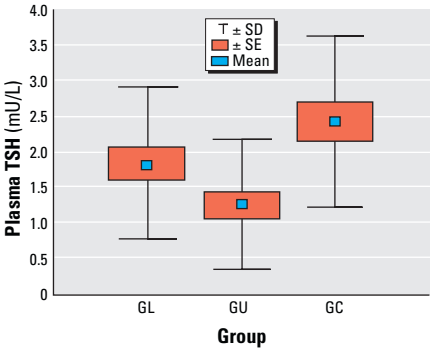

Figure 1. f_{T4} parameter, box plot by groups. Abbreviations: GL, girls belonging to lower Se quartile; GU, girls belonging to upper Se quartile; GC, girls belonging to control group. The significance of difference between GL and GU and between GL and GC is $p < 0.05$.

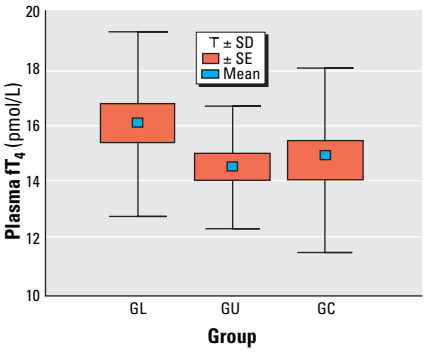

Figure 2. TSH parameter, box plot by groups. Abbreviations: GL, girls belonging to the lower Se quartile; GU, girls belonging to the upper Se quartile; GC, girls belonging to the control group. The significance of the difference between GL and GU is $p < 0.05$; the significance of difference between GC and GU is $p < 0.001$.

Table 3. Linear correlation coefficients for Se indices, thyroid metabolism parameters, and thyroid volume.

	plGSHPx	fT_4	TSH	IU	TV	TV/D	TV/GO	TV/GU	TV/BSA
Se	0.282[a,#]	NS	NS	NS	NS	NS	NS	NS	NS
plGSHPx		NS	NS	NS	NS	-0.261[a,**]	-0.234[b,**]	-0.234[b,**]	-0.180[b,*]
fT_4			NS	NS	-0.330[b,#]	-0.299[a,#]	-0.356[b,#]	-0.253[b,**]	-0.306[b,#]
TSH				NS	NS	-0.211[b,*]	NS	-0.233[b,**]	NS
IU					NS	NS	NS	NS	NS

Abbreviations: TV/D, thyroid volume divided by age-adjusted upper limit of normal thyroid volume, as given by Delange (*31*); TV/GO, thyroid volume divided by age-adjusted upper limit of normal thyroid volume, as given by Gołkowski et al. (*32*); TV/GU, thyroid volume divided by age-adjusted upper limit of normal thyroid volume, as given by Gutekunst et al. (*33*); TV/BSA, thyroid volume divided by body surface area.
[a]Pearson's. [b]Spearman's. *$p < 0.05$. **$p < 0.01$. #$p < 0.001$.

Table 4. BSe concentration and activity in various populations of healthy children.

Study location	Population studied	BSe (µg/L)	plGSHPx (U/L)	Reference
New Zealand	7 ± 3 years, n = 63	48–60	–	(*35*)
Styria, Austria	5 years	58.8 ± 11	–	(*36*)
Turkey	n = 11	61	–	(*37*)
Hungary	–	64.0 ± 11.1	87 ± 19	(*38*)
Styria, Austria	10–19 years, n = 26	66.3 ± 25	-	(*36*)
Hungary	5–19.5 years, n = 38	67.9 ± 11.9	95 ± 16	(*39*)
Poland	8–10 years, n = 21 (studied 1986–1988)	77 ± 9	183 ± 21	(*17*)
Poland	7–16 years, n = 70 (control group)	85.8 ± 18.6	194 ± 26	(*40*)
Germany	4.5–17 years, n = 16	88.5 ± 17.4	126 ± 29	(*39*)
Poland	8–10 years, n = 20 (studied 1981–1983)	93 ± 14	201 ± 29	(*17*)
Italy	12–13 years n (M) = 312, n (F) = 352	104.9 ± 12.6 (M) 102.2 ± 13.7 (F)	–	(*41*)
Scotland	3–14 years, n = 50	118.5 ± 17.4	–	(*42*)
Finland	9–15 years, n = 322	129 ± 14	–	(*43*)

Abbreviations: F, females; M, males.

Table 5. BSe concentration and plGSHPx activity ratios in different study and control groups.

Populations	Se ratio	plGSHPx ratio	Reference
Children with phenylketonuria/healthy children	1:2.92	1:2.46	(*15*)
Children with phenylketonuria/healthy children	1:2.55	1:2.87	(*14*)
Children with malignant diseases of the hematopoetic system/healthy children	1:1.34	1:1.30	(*40*)
Children with secondary malabsorption/schoolchildren	1:1.26	1:1.35	(*44*)
Study group/control group	1:1.33	1:1.64	This work

calculated by Haldimann et al. (*47*), we estimate that the daily intake of this element was 19–25 µg. The Haldimann et al. (*47*) regression curve shows the relationship between dietary Se intake and blood or plasma Se. We speculate that inadequate diet, the consumption of food with a low Se content, and the competition between Se and sulfur, which is a widely spread contaminant in the Tarnobrzeg region, presumably contribute to the lower Se intake. No other explanation for the disparate results is evident.

The incidence of low IU in the study group is in agreement with our expectations. In the late 1980s it was discovered that the discontinuation of iodine supplementation in common salt in 1980 had led to an increase in iodine deficiency in the area investigated (*26*). As a consequence, approximately 50% of the children excreted < 50 µg iodine/L. Even in the control group of the present study, 18% of the children had IU below normal values. Poland is considered a region of mild or moderate iodine endemy; therefore, cases of iodine deficiency cannot be excluded in advance in any group investigated.

Despite the apparent differences in Se and iodine indices, no significant changes could be demonstrated in the concentration of TSH or fT_4 between control and study groups. This could be caused by the overlapping of two processes: decreased T_4 secretion caused by an iodine deficiency and reflected by a lower fT_4 concentration in the plasma, and an increase of fT_4 associated with reduced iodothyronine deiodinase activity caused by an Se deficiency.

The positive correlation between BSe and plGSHPx in the study group is essentially in agreement with the observations of other authors (*17,39,40*). The lack of such a correlation in the control group confirms the absence of an association between these parameters at higher levels of BSe. Contrary to our expectations, we did not find an inverse correlation between BSe and fT_4. We based our expectations on the assumption that an Se deficiency impairs T_4 deiodination to T_3. There are little data to confirm this effect in human populations with marginal deficiencies of both elements. Such a correlation (r = -0.173, $p < 0.01$) was shown by Kvicala et al. (*48*). However, the Kvicala et al. (*48*) study group included more subjects of both sexes that ranged in age from 6 to 65. In more narrow age ranges, the authors did not find this correlation. This correlation was also absent in a study conducted by Dohán et al. (*49*) on hospitalized geriatric patients. Similarly, studies regarding the relationship between serum Se and TSH yielded conflicting results. Our data showed a negative correlation between BSe and TSH only in the control group. A negative correlation was also mentioned by Napolitano et al. (*50*). A positive correlation between serum Se and serum TSH was observed in the Kvicala et al. (*48*) study, although only in boys under 18 years of age and in women 50–65 years of age. In other groups, the correlations were positive, negative, or there was no association (*48*). Thus, the diversity of the results preclude firm conclusions as to whether Se metabolism is relevant for the regulation of TSH release in humans. Further studies need to be carried out to clarify the role of Se in the modulation of TSH secretion.

We found a negative correlation between fT_4 and TV in the whole study group and in the females studied (r = -0.346, $p < 0.005$, n = 86). In the Kvicala et al. study (*48*), a similar correlation was detected only in boys under 18 years of age. There was a lack of correlation between BSe or plGSHPx and TV. However, when TV was normalized, a negative correlation was found among plGSHPx and TV divided by the age-adjusted upper limit of normal TV given by Delange (*31*), the TV divided by age-adjusted upper limit of normal TV given by Gołkowski et al. (*32*), the TV divided by age-adjusted upper limit of normal TV given by Gutekunst et al. (*33*), or the TV divided by BSA. Such results suggest a relationship between the lowering of an antioxidant barrier and the function of the thyroid, which is physiologically exposed to high hydrogen peroxide concentrations.

We found more visible differences when the study group was classified according to BSe concentrations. An Se deficiency influences the thyroid metabolism in female subjects in the study group by slightly increasing plasma fT_4 and TSH levels, although all of the subjects in the study group were euthyroid. Statistically significant higher fT_4 concentrations in females belonging to the lower Se quartile as compared to females belonging to the upper Se quartile (or control group) can be attributed to an Se deficiency. This hypothesis is supported by results obtained in studies of children with phenylketonuria or those living in areas deficient in Se and iodine (*7,14–15*). However, the shift in TSH values should be viewed with caution because the coincidence with the pubertal growth spurt (approximately 70% of the females) and some additional factors confounding the neuroendocrine regulation of TSH secretion cannot be excluded. One of these factors is unidentified goitrogens in the environment.

Our results obtained only for females suggest a sex-linked hormonal response to concomitant Se and iodine deficiencies. This concept is reinforced by observations made by Podoba et al. (*34*), who showed that the TV increases differ between males and females older than 9–10 years of age. On the other hand, the prevalence of thyroid dysfunction is greater in women than in men. For these reasons possible different impacts of Se, iodine, or Se and iodine deficiencies on thyroid function in females and males should be thoroughly studied.

In conclusion, it is premature to speculate about the causal relationships among Se status, ovarian sex steroids, thyrotropin, and thyroid hormones. These relationships remain to be fully clarified. However, the results of the present study indicate that in iodine-deficient females, changes in Se concentrations may be involved in the covariation of fT_4 and TSH.

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