Biol Trace Elem Res (2015) 167:194–199
DOI 10.1007/s12011-015-0310-y

Plasma Selenium Levels in First Trimester Pregnant Women with Hyperthyroidism and the Relationship with Thyroid Hormone Status

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Received: 21 January 2015 / Accepted: 10 March 2015 / Published online: 22 March 2015

Abstract The thyroid gland has the highest selenium (Se) concentration per unit weight among all tissues. The aims of the present study were to evaluate the Se levels in the plasma of hyperthyroidic pregnant women and to investigate the association between maternal plasma Se concentrations and thyroid hormone levels. The study population consisted of 107 pregnant women, 70 healthy pregnant women (group 1) and 37 pregnant women with hyperthyroidism (group 2). The plasma free triiodothyronine (fT3) and free thyroxine (fT4) levels were significantly higher, and the plasma thyroid-stimulating hormone (TSH) and Se levels were significantly lower in group 2 than in group 1 ($p<0.05$). A correlation analysis showed a positive correlation between Se and fT4 in group 1 and with TSH in group 2 ($p<0.05$). Decreased maternal serum antioxidant trace element Se in hyperthyroidic pregnant women compared with normal pregnant women supported the hypothesis that hyperthyroidism was associated with decreased antioxidant response.

Keywords Hyperthyroidism · Pregnancy · Selenium

Introduction

Selenium (Se), from the Greek *selene* (meaning moon), is a chemical element with the atomic number 34. It was discovered by Berzelius as early as 1817 and is a well-known essential trace element that is important for human health [1]. Studies of Se typically begin with the characterization of the first mammalian enzyme containing the unusual amino acid selenocysteine (SeCys) in its catalytic center and cellular glutathione peroxidase (GPx) [2, 3]. The main selenoprotein families are the GPx genes (seven genes), the thioredoxin reductase (TRx) genes (three genes), and the iodothyronine deiodinases (IDIs) (three genes) [2–5]. After the identification of type-1 5′-deiodinase (DI) as a SeCys-containing enzyme and the confirmation of the same connection in all three IDIs, Se was associated with thyroid functioning [6, 7]. During the iodination process and the conversion of thyroxine (T4) to triiodothyronine (T3), SeCys has a dominant role that underlines the dependency of DI activity on Se levels. The key step in the activation of thyroid hormones is the monodeiodination of T4 to 3,3′,5-T3 by Se-containing DIs (DI-1, DI-2) [8, 9]. Based on the evidence, the pathological expression of DIs has been found in several severe disorders of thyroid hormone metabolism, such as Graves' disease and hypothyroidism [10, 11].

The thyroid gland has the highest Se concentration per unit weight among all tissues. Selenium is incorporated into key enzymes that are involved in several metabolic pathways [12]. It is hypothesized that the GPx and the TRx genes participate in a complex defense system that maintains normal thyroid function by protecting the gland from hydrogen peroxide (H_2O_2), which is produced by the thyrocytes, and reactive oxygen intermediates [13, 14].

Recent studies have elucidated the role of Se deficiency in the pathogenesis of endemic myxedematous cretinism [15, 16] and in regulating thyroid function [9, 17]. Reduced Se levels have been reported in patients who have been newly diagnosed with autoimmune thyroid disease and endemic myxedematous cretinism [18, 19]. It was also found that Se is effective in improving quality of life and reducing the

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progression of mild active Graves' orbitopathy in a randomized trial by the European Group on Graves' Orbitopathy [2]. The mechanisms involved in the improvement of Graves' orbitopathy remain unclear, but one possibility is an effect mediated by a reduction in oxidative stress because the selenoproteins protect against damage caused by reactive oxygen species (ROS) [12]. This hypothesis has currently been proven by Khong et al. [20], who found lower serum Se levels in Graves' disease patients with orbitopathy compared to Graves' disease patients without orbitopathy.

Bacic-Vrca et al. [21] found that adding a set combination of antioxidants (vitamin E, vitamin C, beta-carotene, and Se at the dose of 60 lg/day) to methimazole was more effective than methimazole alone in subjects with Graves' disease. More recently, a study found statistically similar Se levels in Graves' disease patients in remission compared to those with persistent or recurrent disease following the discontinuation of treatment with antithyroid drugs. The Se levels were highest in the remission group, and a negative correlation was found between thyroid-stimulating hormone (TSH) antireceptor antibodies and plasma Se levels in this group [22]. Because the balance between intracellular and extracellular oxidants and antioxidants appears to be disturbed and the Se supplementation is effective in Graves' disease [21], I hypothesized that Se levels should be lower in hyperthyroidic pregnant women compared to normal pregnant women. To my knowledge, there has been no study thus far on the correlation between Se status and hyperthyroidism in pregnancy.

The aims of the present study were to evaluate the Se levels in hyperthyroidic pregnant women in the first trimester and to investigate the association between maternal plasma Se concentrations and thyroid hormone levels.

Materials and Methods

This cross-sectional study included 107 pregnant women in the first trimester of pregnancy. They were recruited among patients treated at the antenatal clinics of the Department of Gynecology and Obstetrics of the Medical Faculty of Kahramanmaras Sutcu Imam University. Research ethics approval was obtained from the Ethics Committee of Kahramanmaras Sutcu Imam University before the initiation of the study, and signed informed consent was obtained from all patients and volunteers. The study population consisted of 107 pregnant women who were divided into two groups. The first group consisted of 70 healthy pregnant women (group 1), and the second group consisted of 37 pregnant women with hyperthyroidism (group 2).

The diagnosis of hyperthyroidism was made according to the guidelines of the standard of the National Academy of Clinical Biochemistry (NACB), first trimester, TSH 0.4–4.2 uIU/ml and free-T4 (fT4) 0.8–2.7 ng/dl. Overt and subclinical hyperthyroidism were defined as decreased TSH, and increased fT4 or normal fT4 levels, respectively [23]. Women with overt hyperthyroidism were included, whereas subclinical hyperthyroidism was an exclusion criterion.

The pregnant women in both groups were carefully matched for maternal age, gestational age, and body mass index (BMI). Gestational age was calculated based on menstrual history or, in the case of irregular cycles, from ultrasound data obtained during the first trimester of pregnancy. The BMI was calculated as weight (kg)/height squared (m^2). All participants were nonsmokers, had not received any medication before becoming pregnant, and had no clinical evidence of cardiovascular, metabolic, or inflammatory diseases. Exclusion criteria were multiple gestation, confirmed diabetes mellitus, chronic hypertension, connective tissue disease, inflammatory or infective disorders, heart disease, and pregnant women with hyperemesis gravidarum, as well as treatment with aspirin, warfarin, lipid-lowering drugs, nonsteroidal anti-inflammatory drugs, or antibiotics.

Blood Sampling

A blood sample was taken from each participant before administration of any medication and before any medical or surgical intervention. The blood samples were taken when the pregnant women were applied during the first trimester aneuploidy-screening test. The blood samples, which were obtained from the antecubital area, were collected between the hours of 08:00 and 09:00 following 10–12 h of fasting. Fasting venous blood specimens were drawn from the antecubital vein and collected in No Additive Vacutainer (Becton-Dickinson, Franklin Lakes, NJ) blood-collecting tubes according to standard hospital guidelines for venipuncture and sample collection. The serum separator tube specimens were allowed to clot and then centrifuged for 10 min at 3000*g* to separate the serum. Serum TSH, fT4, and free-T3 (fT3) levels were analyzed with an automatic hormone analyzer (Advia Centaur XP, Siemens, Germany), using radioimmunoassay kits (Advia Centaur XP, Germany).

Plasma samples were stored and frozen at −70 °C until analysis of Se levels. Selenium measurement was performed in a graphite furnace atomic absorption spectrophotometer (PerkinElmer Analyst 800) using Zeeman background correction. Matrix modifiers were palladium (4 mg in a 20-ml sample) and magnesium sulfate (3 mg in a 20-ml sample). Samples and calibration standards were diluted 1:3 with 0.05 % Triton X-100 to improve the sample viscosity and the reproducibility of the results. Selenium levels in all groups were evaluated according to a standard curve as micrograms per liter, and Se calibration standards were prepared from the commercial Se standard (1000 mg/l) by serial dilutions [24]. According to the Se tests of the control and patient groups, a sensitivity of 72 % and a specificity of 55.5 % were found.

Statistical Analyses

All data were analyzed using the Statistical Package for the Social Sciences for Windows version 17.0 (SPSS, Chicago, IL). The data were initially tested for normal distribution by Kolmogorov-Smirnov test and found abnormal ($p<0.05$). The one-way ANOVA test was used for statistical significance of differences in variables among groups, and the Mann-Whitney *U* test was used for multiple comparisons when a significant result was obtained. Correlations between variables were evaluated using Spearman's rho correlation tests. Data are presented as mean±SD, minimum-maximum, and median. Statistical significance was defined as $p<0.05$.

Results

The clinical characteristics of the groups are given in Table 1. The demographic features (median maternal age, gestational age at sampling, and BMI) in both groups were similar ($p>0.05$). The plasma fT3 and fT4 levels were significantly higher in group 2 (the hyperthyroidic group) than in group 1 (the healthy control group) ($p<0.05$) (Table 2). A significant decrease in the TSH and Se levels was found in group 2 ($p<0.05$) compared to group 1. A correlation analysis showed a positive correlation between Se and fT4 in group 1 and with TSH in group 2 ($p<0.05$) (Table 3).

Discussion

In the present study, for the first time, I found that serum Se levels were lower in hyperthyroidic pregnant women in the first trimester compared to maternal age-, BMI-, and gestational age-matched healthy pregnant controls in a Turkish population. The studies performed in two iodine-deficient areas, one with prevalent myxedematous cretinism and the other without, showed that the trace elements involved in GPx and superoxide dismutase enzyme activities (i.e., Se, magnesium, copper, and zinc) were lacking [25]. The thyroid gland produces H_2O_2 for thyroid hormone synthesis, and if H_2O_2 is not properly reduced to H_2O by intracellular defense mechanisms or during the hormone synthesis process, the thyroid gland will be exposed to free radical damage [26]. Vitamins C and E and enzymes such as catalase, superoxide dismutase, and Se-containing enzymes protect the thyroid gland against H_2O_2. The only identified selenoenzyme is the GPx [2, 27, 28].

Recently, the benefits of Se treatment for autoimmune thyroid diseases, particularly for Hashimoto's thyroiditis and Graves' disease, have been reported in several studies. Selenium substitution may improve the inflammatory status in patients with autoimmune thyroiditis, especially in those with high activity [28–30]. There must be different ways to explain the effect of Se on thyroid pathologies. If Se supplementation is effective in hypothyroidism conditions, how can it also be effective in hyperthyroidism conditions?

Therefore, for the first time, I investigated the Se levels in hyperthyroidic pregnant women and found that they were low. A study of a Danish population found lower Se levels in patients who were newly diagnosed with Graves' disease and autoimmune hypothyroidism [31]. However, in contrast to my study, no association between Se level and the thyroid function status of the patients was found [32]. Similar to my study, the study of Khong et al. [20] found lower serum Se levels in Graves' disease patients with orbitopathy compared to Graves' disease patients without orbitopathy. Wertenbruch et al. [33] found similar serum Se levels in Graves' disease patients who were in remission or who had a relapse; however, they noted that the highest level of Se was in Graves' disease patients in remission. Also, they found a positive effect of Se on Graves' disease outcomes [33].

There are a number of potential molecular mechanisms underlying the thyroid pathologies in subjects with a lower Se status. The likely enzymes responsible for the observed interrelation are the SeCys-containing active selenoproteins,

Table 1 The clinical characteristics of groups

	Healthy pregnancies (group 1) ($n=70$)		Hyperthyroidic pregnancies (group 2) ($n=37$)		*p*
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Age (years)	26.54±4.68	26.00 (19.00–43.00)	26.32±4.63	26.00 (18.00–37.00)	>0.05
BMI (kg/m^2)	25.55±4.55	24.99 (16.26–38.87)	26.01±4.37	25.85 (16.65–38.05)	>0.05
Gestational age at sampling (weeks)	12.84±0.75	13.00 (11.00–14.00)	12.57±0.87	13.00 (11.00–14.00)	>0.05

All parameters are given as mean±standard deviation, median, and range values. *p* values statistically evaluated as $p>0.05$ are not significant and as $p<0.05$ are significant

n subject number, *BMI* body mass index

Table 2 Laboratory results of groups

	Healthy pregnancies (group 1) (n=70)		Hyperthyroidic pregnancies (group 2) (n=37)		p
	Mean±SD	Median (range)	Mean±SD	Median (range)	
fT3 (pg/ml)	4.18±0.68	4.25 (2.79–5.54)	5.83±2.34	5.50 (3.51–18.60)	<0.05
fT4 (ng/ml)	1.29±0.23	1.25 (0.80–2.00)	3.51±0.68	3.37 (2.76–6.00)	<0.05
TSH (μIU/ml)	1.26±0.80	1.11 (0.13–3.99)	0.11±0.09	0.08 (0.00–0.36)	<0.05
Se (μg/l)	91.89±15.89	89.01 (60.74–164.00)	70.72±9.60	70.98 (54.71–101.20)	<0.05

All parameters are given as mean±standard deviation, median, and range values. p values statistically evaluated as $p>0.05$ are not significant and as $p<0.05$ are significant

n subject number, *fT3* free triiodothyronine, *fT4* free thyroxine, *TSH* thyroid-stimulating hormone, *Se* selenium

such as IDIs, that are presumably converting the effects of Se into biological processes [3, 4, 34]. In contrast to my study, other studies have found a weak negative correlation between serum Se concentration and T4 or fT4 [9, 35, 36].

It has been accepted that a state of oxidative stress is present in hyperthyroid patients. However, the literature reveals contradictory results regarding the activity of the antioxidant defense system in hyperthyroid patients. Although most studies have shown an increase in the antioxidant defense enzymes in hyperthyroidic patients [37, 38], some have not [39]. Some studies have even found decreased levels [40]. Despite the discrepancies, the restoration of euthyroidism through medical treatment and the correction of intra- and extracellular antioxidant defense system abnormalities are necessary [37–41]. The discrepancies regarding the antioxidant activity in patients with hyperthyroidism may be due to differences in the assessment methods used in the various studies or to the duration of the hyperthyroid status at the time of evaluation [13].

There are some limitations in the current study. Although beta-human chorionic gonadotropin (β-hCG) is known to interfere with TSH especially during the first trimester of pregnancy, my data does not include β-hCG levels. Hence, it is not known whether the correlation between serum Se and TSH is independent of the serum β-hCG levels. Because this study is cross sectional in design and primarily focuses on trace element levels, there are no follow-up data through the midtrimester and postpartum periods.

In conclusion, this study indicated a decrease of Se levels in sera from pregnant women with hyperthyroidism compared with normal pregnant women, supporting the hypothesis that hyperthyroidism was associated with increased oxidative status. Also, I found a positive correlation between Se and TSH in hyperthyroidic pregnant women. The results of the present study, as well those of some previous studies, suggest that sufficient Se intake is one of the environmental factors that may help prevent hyperthyroidism. Although my data indicate a disturbance in the antioxidative balance during hyperthyroidism, prospective intervention studies are needed to evaluate the potential role of Se in patients suffering from hyperthyroidism.

Table 3 Correlations of Se with the levels of T3, T4, and TSH of hyperthyroidic pregnant and healthy pregnant women

Parameters	Healthy pregnancies (group 1) (n=70)		Hyperthyroidic pregnancies (group 2) (n=37)	
	Se		Se	
	r	p	r	p
Gestational age	0.06	0.62	0.17	0.31
BMI	0.04	0.73	−0.12	0.49
fT3	−0.13	0.29	0.22	0.19
fT4	0.25	0.035*	−0.22	0.81
TSH	−0.01	0.90	0.42	0.01*

p values statistically evaluated as $p>0.05$ are not significant and as $p<0.05$ are significant

n subject number, *Se* selenium, *BMI* body mass index, *fT3* free triiodothyronine, *fT4* free thyroxine, *TSH* thyroid-stimulating hormone, *r* Spearman's rho correlation coefficient

Conflict of Interest The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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