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Selenium and thyroid health in NZ European women

Ljiljana Jowitt*

Faculty of Health and Environmental Sciences, School of Interprofessional Health Studies, AUT University, New Zealand

Abstract

The primary aim of the study was to determine differences in the hormonal status (TSH, T3, and T4) between healthy participants and participants with Hashimoto's thyroiditis. The secondary aim of the study was to assess plasma selenium nutritional status and its relationships with the serum levels of thyroid hormones in both of the groups. This study is a pilot and a cross-sectional. Study participants were assigned into two groups, the control group with healthy participants (n=13) and a group of women with Hashimoto's thyroiditis (n=8). Any change in the participants' daily routine was not required. For the measurement of plasma selenium, thyroid stimulating hormone, tetra iodothyronine, and triiodothyronine, creatinine, and glomerular filtration rate, participants' non-fasting blood samples were taken. Two women with subclinical hypothyroidism were excluded from the statistical data analyses. Women with Hashimoto's thyroiditis were older, had higher tetra iodothyronine level, low triiodothyronine/tetra iodothyronine ratio, higher plasma selenium levels, and similar triiodothyronine plasma levels to women in the control group. Significant relationships between triiodothyronine and selenium, triiodothyronine were identified in the group of women with Hashimoto's thyroiditis. There was a moderate selenium deficiency in both of the groups that affected more women with hypothyroidism. Compromised peripheral deiodination in women with hypothyroidism required increased L-thyroxine dosing, which in turn increased the level of tetra iodothyronine, and decreased pituitary thyroid stimulating hormone, in order to achieve the desired level of the triiodothyronine. In order to increase plasma selenium level, recent research has suggested that selenium supplementation with selenomethionine or selenium selenite, might also slow down the process of thyroid destruction by thyroid autoantibodies in Hashimoto's thyroiditis. In the past, the process of selenium supplementation had variable success rates. Therefore, further research is warranted.

Abbreviations: TSH: Thyroid stimulating hormone; T3: Triiodothyronine; T4: Tetraiodothyronine; SeMet: Selenomethionine; SeCys: selenocysteine

Introduction

Prevalence estimates of primary hypothyroidism worldwide range from 1% to 10.3%, and for hyperthyroidism from 0.5% to 2.5% [1]. There are limited data on the prevalence and type of thyroid disease (TD) in New Zealand community. Hamilton study, which included 662 patients in general practice, estimated the overall prevalence of TD in women of about 4.8%, and about 1.1% in men. Hence, women were 4.5 times more likely than men to have TD. New Zealand European ethnic group had the greatest prevalence of TD of 3.5%, then the Maori ethnicity of 2.1%, Pacifica peoples of 1.8%, Asians 1.8%, and other ethnic groups of 2.0%. Of those with TD, hypothyroidism diagnosed in 2.5% in the Hamilton study population, while in general practice hypothyroidism accounted for 78.9% of diagnosed thyroid diseases. These data are comparable (with 3.1% of TD in adults) with national and international literature, with TD being more prevalent in women and in elderly.

Thyroid hormone secretion is regulated by the hypothalamic-pituitary-thyroid axis ic (HPT axis), through stimulatory actions of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) [2]. TSH stimulates the thyroid gland to synthesize tetra iodothyronine (T4) and triiodothyronine (T3). T4 is synthesized entirely by the thyroid gland and acts as a prohormone to generate T3, which is required for normal growth and development, and energy homeostasis, and O2 consumption in tissue cells. Conversion of T4 to T3 in body tissues provides negative feedback at the level of both anterior pituitary and the hypothalamus [3].

The thyroid gland has a high tissue concentration of the essential nutritional trace element selenium (Se), more than the liver or any other organ or a tissue in the body [4]. Selenium plays a crucial role in the maintenance of metabolic, immune-endocrine, and cellular homeostasis, owing to its antioxidant and anti-inflammatory properties [5]. Biological actions of selenium are mostly mediated through the expression of at least 30 selenoproteins, coded by 25 genes that have 21st amino acid selenocysteine at their active centre [6]. The essential role of selenoproteins is in their involvement in peroxide degradation, cellular redox and transcription regulation, thyroid hormone deiodination, and spermatogenesis [7, 8]. The major selenoproteins, expressed in the thyroid gland are glutathione peroxidases (GPXs), thioredoxin reductase (TRs), and deiodinases (Ds)[9, 10]. The process of thyroglobulin (Tg) iodination is catalyzed by selenoenzyme thyroid peroxidase (TPO), which requires higher hydrogen peroxide (H2O2) concentration generated by the thyrocytes [11, 12]. Selenoenzymes GPXs prevent lipid peroxidation and protect the cell membranes from oxidative damage. The GPX1 is one of the most abundant selenoenzyme and is highly sensitive to selenium deficiency [13, 14].

Selenoenzymes deiodinases are present in the thyroid gland and all body tissues [15]. At the cellular level, thyroid hormone signalling can change, owing to local activation and inactivation of thyroid hormone via deiodination pathways inside the target cells [16-18]. The type 1

Correspondence to: Ljiljana Jowitt, Faculty of Health and Environmental Sciences, School of Interprofessional Health Studies, AUT University, 90 Akoranga Drive, North Shore Campus, AF 416, PO Box 92006, 1142, Auckland, New Zealand, Tel: +649 9219999 extension 8096; Email: ljowitt@aut.ac.nz

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deiodinase (D1) and type 2 deiodinase (D2) increase cellular thyroid activity by converting prohormone T4 to the activeT3, whereas the type 3 deiodinase (D3) reduces cellular thyroid activity by converting T4 to reverse T3, and of T3 to 3, 3'-diiodothyronine (T2)[19, 20]. These pathways control thyroid hormone bioavailability and bioactivity at various levels of cellular organization, and their effects are far less understood [21].

Selenium acts as an antioxidant in plasma and extracellular fluids, where selenium as amino acid selenocysteine is incorporated into selenoprotein P and is carried bound to albumin as selenomethionine (SeMet) [22, 23]. The liver secretes the most of the selenoproteins, and is the main site of selenium metabolism and homeostasis.

Selenoprotein P (SEPP1) and GPX3 are present in human plasma and can be used as a biomarker of selenium nutritional status [24]. Measurements of SEPP1 and GPX3 in plasma can identify the risk of selenium nutritional deficiency. According to Xia and co-authors [25], SEPP1 is the best plasma biomarker, because its optimization required a larger selenium intake than did a GPX3 activity. In selenium deficiency, the synthesis of some selenoenzyme such as glutathione peroxidase is prioritized over that of others [26, 27]. Changes in selenium status may affect immune response, neurodegeneration, cardiovascular disease, and cancer [28].

Selenium intake in New Zealand population

According to the 2008/09 New Zealand Nutrition Survey (NZANS) which collected information from 4721 adults New Zealanders aged 15 years and over, selenium intakes increased from 1997 to 2008/09. Se intakes were still inadequate for about one-third of males (31.5%) and over half (58.2%) of females [29]. The median usual daily selenium intake was 67.0 μg for males, and 47.1 μg for females. Elderly population, both males and females aged 71+ years (52.0 μg and 39.5 μg, respectively), and females aged 15–18 years (38.7 μg) had lower selenium intakes than 31-50-year-old males and females (78.0 μg and 51.9 μg, respectively). In New Zealand, the recommendation for selenium intake should be on average 60 μg per day for men and 53 μg per day for women, to achieve the maximal activity of GPXs in plasma or erythrocytes [30].

The major source of selenium in New Zealand is bread (15%), followed by fish and seafood (12%), and poultry (10%). Intakes of Se in New Zealand have improved after increased importation of high-Se Australian and other imported wheat. Fruit, vegetables, and grains are grown in New Zealand have lower selenium levels than plant foods from other countries with a soil higher in selenium levels [31, 32].

The primary aim of the study was to determine differences in the hormonal status (TSH, T3, and T4) between healthy participants and participants with Hashimoto's thyroiditis. The secondary aim of the study was to assess Se nutritional status and its relationships with the serum levels of thyroid hormones in both control and hypothyroid group on medication with L-thyroxine.

Patients and method

This study is a pilot study, crossectional, and observational study. Participants in the study were self - assigned into two groups, control group with healthy participants, and a group of women with Hashimoto's thyroiditis (HT) on medication with L-thyroxine. Any change in the participants' daily routine was not required. The plasma selenium, TSH, T4, T3, creatinine and e-GFR (Glomerular Filtration Rate) was determined in women in both groups, and compared with gold standards. Plasma TSH, T3, and T4 were measured using competitive immunoassays technique by the LabTests Laboratories in Auckland. Serum selenium was measured using inductively coupled plasma –dynamic reaction cell mass spectrometry by the Canterbury Health Laboratories in Christchurch, New Zealand. Data on the anti-thyroperoxidase (anti-TPO) antibodies were not available in women with HT.

Statistical analyses

Data were analysed by the SPSS for windows (version 22.0, SPSS Inc., Chicago, Illinois, USA). Owing to the small sample size, non-parametric tests were used for data analysis. Descriptive statistics and correlation analyses were used in order to determine relationships among variables. The results of plasma contents concentrations were expressed as the mean ± standard deviation. Values with a $p < 0.05$ were taken as significant.

Results

The study sample consisted of eight women with HT on medication with L-levothyroxine, and 12 women in a good health in the control group. Two women, diagnosed with subclinical hypothyroidism, were excluded from statistical data analysis. Women with HT were older, had lower plasma TSH levels, lower T3/T4 ratio, and higher T4 and selenium levels (Table 1). Plasma T3 levels were almost identical in both groups. The values of creatinine and e-GFR were within the optimal range in both groups.

There was a significant positive relationship between age and T4 ($p<0.01$, Spearman's rho = 0.926**), and T3 and selenium ($p<0.02$, Spearman's rho = 0.778*) in hypothyroid women. In addition, there was a positive relationship between T3 and the T3/T4 ratio ($p<0.01$, Spearman's rho = 0.794*). Significant negative relationship between creatinine and e-GFR ($p< 0.007$, Spearman's rho = - 0.851**) was identified in hypothyroid group and control group ($p<0.000$, Spearman's rho = -0.843**).

In the control group, there was a significant positive relationship between T3 and the T3/T4 ratio ($p< 0.008$, Spearman's rho = 0.701**) and significant positive relationship between T4 and the T3/T4 ratio ($p<0.03$, Spearman's rho = 0.600*) (Table 2).

The values of the variables for both, the control group and hypothyroid group on medication, were distributed into 10th, 25th, 50th and 75th percentiles (Table 3).

Discussion

In this study, with a relatively small sample size (n= 23), participants were European women with the mean age of 53.50 ± 7.76 in the control

Table 1. Descriptive statistics (mean ± SD).

		Control group n=13		Group on medication n=8	
		Mean ±SD	**Range**	**Mean ±SD**	**Range**
Age		52.69 ± 7.39	37- 64	58.00±6.74	48-65
Reference range					
TSH	0.30 - 4.00 mIU/L	2.06 ± 0.41	1.40 - 2.90	1.55 ±1.02	0.63-3.30
T4	10.0 -20.0 pmol/L	14.61 ± 1.44	12.00-17.00	15.50 ±1.41	14.00-18.00
T3	3.0 – 6.5 pmol/L	4.76 ± 0.58	3.90 - 6.10	4.46 ± 0.72	3.50 – 6.00
T3/T4 ratio	0.30 – 0.325	0.33 ± 0.05	0.26 -0.44	0.29 ± 0.06	0.23-0.43
Selenium	0.45 – 1.40 umol/L	1.28 ± 0.15	1.00 -1.52	1.35 ± 0.17	1.16 – 1.69
Creatinine	45 – 90 umol/L	67.69 ± 8.66	51.00 - 82.00	66.37 ± 10.36	49.00-84.00
e-GFR	>90 mL/min/1.73m^2	85.69 ± 6.55	69.00 - 90.00	84.37 ± 9.47	64.00-90.00

Table 2. Relationships between variables in the hypothyroid group (Spearman's rho).

	Age	TSH	T3	T4	Selenium	Creatinine	GFR
TSH	-.491						
	.217						
T3	-.066	.228					
	.876	.588					
T4	.926**	-.442	-.173				
	.001	.273	.682				
Selenium	.156	.381	.778*	.147			
	.713	.352	.023	.728			
Creatinine	-.476	-.120	-.313	-.395	-.395		
	.233	.778	.450	.333	.333		
GFR	.000	.518	.535	-.070	.546	-.851**	
	1.000	.188	.172	.869	.162	.007	
T3T4ratio	-.606	.422	.794*	-.671	.398	.085	.331
	.111	.298	.019	.069	.329	.842	.423

*Significant findings
**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

group and 56.33 ± 7.16 in the group of women with a long-standing HT (Table 1). Two women identified with subclinical hypothyroidism were excluded from data analysis. Plasma T3 and T4 levels were within optimal range, whereas plasma TSH levels were 10mIU/L and 4.7mIU/L respectively. Accordingly, subclinical hypothyroidism is characterized with normal T3 and T4 plasma levels and elevated TSH [33, 34]. Among the experts, there is agreement that subclinical hypothyroidism is an early mild failure of thyroid function [35,36]. The hormonal pattern associated with the subclinical hypothyroidism is a compensated state in which high plasma TSH serves to maintain normal thyroid hormone levels. The standard medication for subclinical hypothyroidism and life-long management of hypothyroidism is a hormone replacement therapy of a single daily dose of L-thyroxine [37]. According to the American Thyroid Association (ATA), the goal of therapy with L-thyroxine is to restore clinically and biochemically a euthyroid state in patients. The usual dose of levothyroxine is 1.6 to 1.8μg/kg per day, while elderly patients require a smaller dose of 1μg/kg per day or even less, in relation to age, weight and cardiac status.

The results of the study demonstrated that plasma TSH, T4, and T3 levels, and T3/T4 ratios between the two groups differed. Mean plasma TSH levels were slightly lower in women with HT, being 1.55 ±1.02 and 2.06 ± 0.41 respectively, although the recommendation by ATA was to aim for a TSH in the lower half of the normal range (0.4 -4.5 mIU/L.), around 2.5 mIU/L in patients with primary hypothyroidism [38]. The two study participants' TSH levels were closer to the lower end of the normal range, being 0.63 mlU/L and 0.81 mlU/L respectively (less than 0.1mIU/L.), which were attributed to the L-thyroxine overtreatment. Studies proved, that chronic maintenance of TSH below the optimal reference range might be associated with atrial fibrillation, osteoporosis, and bone fractures [39-41]. On the other hand, TSH levels maintained above the normal range might cause the development of metabolic dysfunction [42]. The initial treatment with L-thyroxine in hypothyroidism requires TSH level monitored every six to eight weeks with adjustment of the L-thyroxine dosing [43]. Once the TSH has stabilized, semi-annual or annual testing is required [44].

Further, the mean plasma T3 levels were almost identical in both groups, being 4.76 ± 0.58 and 4.46 ± 0.72 respectively, whereas plasma T4 levels were significantly higher in the hypothyroid group than in the control group (15.50 ±1.41 and 14.61 ± 1.44 respectively). Increased T4, and a slight decrease in plasma TSH (1.55± 1.02), and the T3/T4 ratio (0.29 ± 0.06 and 0.33 ± 0.05 respectively) in the hypothyroid group indicated that in order to achieve normal T3 levels, higher doses of L-thyroxine should be given to patients [45]. In support of these findings, the study by Mortoglou and Candiloros (2004) demonstrated a similar case scenario, where hypothyroid patients were given a higher dose of L-thyroxine in order to maintain average plasma T3 levels [46].

In women with HT, there was a significant positive relationship between plasma selenium and T3 ($p< 0.05$, and Spearman's rho was 0.778). In this relationship, both variables have a tendency of rising, meaning that T3 production will increase if selenium plasma levels increase. Selenium deficiency inhibits the conversion of T4 to T3 by both selenoenzyme, type I and type II deiodinases. During the process of deiodination, selenium in the form of SeCys has a dominant role, which underlines the dependency of type 1 and types 2 deiodinases' activity on plasma selenium levels [47]. However, in the present study baseline plasma selenium levels were higher in women with HT (1.35 ± 0.17), than in the control group (1.28±0.15), and also were higher than the baseline selenium levels recommended by Thomson and co-authors [48]. According to Thomson *et al.* plasma selenium levels of 0.82 – 0.90 μgmol/L should be adequate for optimal function of deiodinases. However, Karunasinghe *et al.* [49] have suggested that the basic selenium requirement may vary with genotype for a number of variations in selenoprotein genes, suggesting that an effective dietary selenium intake for one person may be different from that for others. In the absence of this information, recommended plasma selenium levels should be in the range of 1.27 – 1.90 μmol/L.

Selenium plasma levels were based on the measurement of SEPP1 which is the most reliable biomarker of selenium status, and its full expression requires a significantly higher selenium dose [50]. SEPP1 and selenoenzyme deiodinases rank high in the hierarchy of selenium supply, and cannot be affected by marginal selenium deficiency like GPx [51]. Maximal activity of selenoenzyme is reached at blood selenium levels above 1.27 μmol/L, or according to the recent research by Rayman [52], plasma selenium levels in the range of 1.6 to 1.9 μmol/L are considered optimal for thyroid and overall good health. However, in relation to optimal plasma selenium levels, there is an agreement between those two studies by Rayman (2012) and Karunasinghe and co-authors (2012). Plasma selenium levels were slightly higher in the hypothyroid group than in the control group, with the mean plasma selenium levels closer to the lower end of the optimal range (1.28 ± 0.15 and 1.35 ± 0.17 respectively), which might be explained by different diet in those affected.

Hashimoto's thyroiditis is part of the spectrum of autoimmune thyroid diseases which cluster in families [53]. It displays an organized lymphocytic infiltration that leads to thyrocytes apoptosis, and to thyroid fibrosis with age [54]. This draws attention to hypothyroid women in the study, who were older than women in the control group were, and who had TSH, T3, and the T3/T4 ratio (due to high T4), and selenium levels less than 10% ($<10^{th}$) of women in the control group. This finding indicated that in order to maintain adequate levels of T3, higher doses of L-thyroxine (T4) should have been given as a replacement therapy (Table 3). Poor selenium status at the 10^{th} percentile of 1.16 μmol/L, lower than recommended, is associated with a diminished process of the peripheral deiodination, increased T4, and lower T3/T4 ratio. Selenium supplementation, with either selenium

Table 3. The values of variables distributed in percentiles in both groups.

Percentiles	10th	25th	50th	75th	90th
Hypothyroid group on medication with L-thyroxine					
Age	48.00	51.00	59.50	64.00	
TSH	0.63	0.71	1.25	2.57	
T3	3.5*	4.10	4.35	4.72	
T4	14.00*	14.25	15.00	16.75*	
T3/T4 ratio	0.23	0.24	0.28*	0.31*	
Selenium	1.16*	1.23	1.29	1.46	
Control group					
Age	40.60	46.50	54.00	58.50	62.80
TSH	1.44	1.70	2.10	2.22	2.74
T3	4.02	4.20	4.90	5.10	5.74
T4	12.40	14.00	14.00	16.00*	16.60
T3/T4 ratio	0.26	0.28	0.34*	0.35*	0.41
Selenium	1.04	1.14	1.29	1.38	1.51

selenite or SeMet, might be effective in slowing the progression of autoimmune thyroiditis (AIT), as reflected by the reduction of serum autoantibodies, with more or less success [55-59].

In regards to the relationship between creatinine and GFR which is purely physiological, estimates of GFR that are based on serum creatinine are routinely used for the assessment of kidney function, and/or creatinine excretion [60]. However, there is a link between serum creatinine and GFR genes to chromosome 2, meaning this region harbours a gene influencing phenotypic variation in serum creatinine and GFR [61].

Conclusions

This study had a relatively small sample size and provided important findings. Significant relationships between T3 and selenium, and age and T4 were identified in women with Hashimoto's thyroiditis. There was a moderate selenium deficiency in both of the groups that affected more women with hypothyroidism. Compromised peripheral deiodination in women with hypothyroidism required increased L-thyroxine dosing, which in turn increased the level of T4, and decreased pituitary TSH, in order to achieve the desired level of T3. To increase plasma selenium level, recent research has suggested that selenium supplementation with selenomethionine (SeMet) or selenium selenite might slow down the process of thyroid destruction by thyroid autoantibodies in Hashimoto's thyroiditis, through a decrease in autoimmune inflammation. The process of selenium supplementation has variable success rates in New Zealand and worldwide. Hence, further research is warranted.

Expert panels do not recommend screening of TSH for subclinical hypothyroidism of the general population, although ATA recommended screening in all adults beginning at the age of 35 years, including women of fertile age, and every 5 years thereafter, in order to postpone development of overt hypothyroidism and its morbidity.

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