

Original Article

Thyroid hormone status in patients with severe selenium deficiency

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Abstract. Selenium (Se) is an essential trace element that is involved in numerous biological processes in the form of a selenoprotein such as iodothyronine deiodinase (DIO). Se deficiency may prevent the conversion of T4 to T3 through reducing DIO expression and thereby affecting thyroid hormone status. However, this has not been well documented in humans. In this study, to clarify the association between Se and thyroid hormone status, we investigated the thyroid hormone levels in patients with severe Se deficiency (< 2 µg/dl). Severe Se deficiency was associated with increases in free T4 levels, but not with decreases and increases in free T3 and thyroid stimulating hormone (TSH) levels, respectively. Increases in free T4 levels during Se deficiency were reduced with Se supplementation; however, neither free T3 nor TSH levels were affected. Taken together, these findings indicate that free T4 may be a useful biomarker for Se status when serum Se levels are severely low.

Key words: selenium, thyroid hormone, deiodinase

Introduction

Selenium (Se) is an essential trace element involved in numerous biological processes including the antioxidant defense system (1, 2), and the biological functions of Se are achieved in the form of selenoproteins. Se deficiency is clinically associated with the development of nail whitening, hair loss, hair color change, muscle weakness, and cardiomyopathy, and Se status is also associated with the development of cancer,

cardiovascular disease, diabetes mellitus, and thyroid disease (1, 3, 4); however, the precise molecular mechanisms through which Se status affects the pathogenesis of these diseases are not fully understood (1). The various forms of Se ingested from the diet are converted to selenide. Selenide is then added to tRNA^{[Ser]Sec} in the form of selenophosphate to produce Sec-tRNA^{[Ser]Sec}, and selenocysteine (Sec) is incorporated into selenoproteins during translation with other interacting factors such as SBP2 (selenocysteine insertion sequence-binding protein) (2, 5). Twenty-five selenoproteins, including glutathione peroxidase (GPx) and iodothyronine deiodinases (DIO) (6) have been identified in humans, and decreases in their synthesis have been linked to Se deficiency (7). Se intake differs markedly among countries and is based on the Se content in the environment (8). Se deficiency therefore rarely occurs in countries such as Japan where Se content in the environment is sufficient. However,

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Se deficiency can be common in certain clinical settings where patients are exclusively nourished through parenteral nutrition or enteral formula that may not include Se supplementation (9).

DIO is one of the selenoproteins involved in thyroid hormone metabolism. DIO1 and DIO2 catalyze the synthesis of the active thyroid hormone T3 from T4 (10). Therefore, Se deficiency may result in increases and decreases in T4 and T3 levels, respectively, through reducing the expression and/or activities of DIO1 and DIO2. This has been demonstrated in a study in which rodents that had been fed a low Se diet showed increased T4 levels with decreased T3 levels (7). Furthermore, mutations in the *SBP2* gene, which are critical for the incorporation of Se during translation, have been reported to increase and decrease T4 and T3 levels, respectively, in humans (11). Consistent with these observations, the inverse relationship between Se concentration and T4 levels have been reported (12); however, there is also evidence that demonstrates a lack of association between these two parameters (13). These findings suggest that the effect of Se deficiency on thyroid hormone status remains in dispute, especially in humans. To clarify the association between Se status and thyroid hormone levels in humans, we retrospectively analyzed the thyroid hormone status in patients with Se deficiency and found that Se deficiency was associated with increases in free T4 levels.

Methods

Study design and patients

We retrospectively evaluated the medical records of 15 patients (ranging from 6 mo to 24 yr old) who presented with severe Se deficiency. Severe Se deficiency was defined as Se levels below the detection limit (less than 2.0 µg/dl). All patients had visited the Osaka Women's and Children's Hospital prior to December 2015, and their clinical characteristics are summarized in Table 1. Serum levels of TSH (thyroid stimulating hormone), FT3 (free T3), FT4 (free T4), and MCV

(mean corpuscular volume) were evaluated based on medical records. Serum TSH, FT3, and FT4 levels were analyzed based on competitive enzyme immunoassay (Tosoh AIA Automated Immunoassay System, Tosoh Bioscience, Inc., Japan), and serum Se levels were determined using an atomic absorption spectrometry-based method. The study was approved by the Ethical Review Board of Osaka Women's and Children's Hospital.

Statistical analysis

All data were expressed as the mean ± standard deviation (SD). Results were analyzed for significant differences using the paired Student's *t*-test. Pearson's correlation coefficients were used to analyze associations. Significance was set at $p < 0.05$.

Results

Clinical characteristics of the patients

The clinical characteristics of 15 patients with severe Se deficiency are summarized in Table 1. Eleven patients were exclusively nourished through enteral feeding and 4 were nourished through total parenteral nutrition. Se content in the enteral formula is summarized in Table 2. Se supplementation was provided through a normal diet, Se-containing enteral supplements (V-ACCEL®, NUTRI Co., Ltd. Mie, Japan), and/or intravenous Selenic acid (H₂SeO₄) administration, and the duration of Se supplementation ranged from 3 months to 18 months, as shown in Table 1.

Free T4 levels were elevated in patients with severe selenium deficiency

To investigate the association between Se deficiency and thyroid hormone status, the serum concentrations of TSH, FT3, and FT4 levels in the patients were retrospectively determined based on their medical records. The TSH and FT4 levels were measured in all patients, while the FT3 levels were only available in 9 patients. As shown

Table 1. Clinical characteristics of patients

Case	Age	Gender	Underlying disease	Mode of nutrition	Clinical symptoms	Se supplementation	Duration of Se supplementation	Serum Se levels after supplementation (µg/dl)	TSH (µU/ml) pre/post	FT3 (pg/ml) pre/post	FT4 (ng/dl) pre/post
1	6 mo	F	CIPO	TPN	ND	Ordinary foods	NA	NA	0.462/NA	2.08/NA	1.52/NA
2	1 yr 4 mo	F	Down Syndrome Short bowel syndrome	Elemental diet (Elemental-P®)	Hair color change	Enteral Se supplement	NA	NA	2.776/NA	NA/NA	2.43/NA
3	1 yr 6 mo	M	Short bowel syndrome	TPN	ND	Ordinary foods	8 mo	11.2	1.29/2.05	3.36/3.12	1.94/1.01
4	1 yr 8 mo	F	Esophageal hiatus hernia Intestinal malrotation	Elemental diet (Elemental-P®)	ND	Enteral Se supplement	3 mo	2.3	5.557/4.1	4.15/3.49	1.43/1.32
5	2 yr 1 mo	M	Kabuki Syndrome	Elemental diet (Elemental-P®)	ND	Enteral Se supplement	18 mo	7.2	4.041/4.463	NA/NA	2.71/1.63
6	5 yr 4 mo	F	HIE, CP, Epi	Elemental diet (Elemental-P®) Highly hydrolyzed milk (New MA-1®)	Hair color change	Enteral Se supplement	15 mo	6.1	1.121/2.091	NA/NA	2.37/1.59
7	5 yr 6 mo	F	HIE, CP	Elemental diet (Elemental-P®)	ND	Ordinary foods	7 mo	3.2	1.01/1.301	2/4.03	2.59/1.16
8	6 yr 2 mo	F	HIE, CP	TPN	Hair color change Nail whitening	Enteral Se supplement	3 mo	7.5	1.829/1.619	NA/NA	2.3/1.62
9	7 yr	M	CIPO	TPN	ND	Enteral Se supplement	13 mo	3.9	1.299/5.137	NA/NA	1.56/0.84
10	8 yr 2 mo	F	Ohtahara Syndrome	Oligomeric formula (Twinline®)	ND	NA	NA	NA	0.954/NA	NA/NA	1.21/NA
11	9 yr 8 mo	F	HIE, CP, Epi	Elemental diet (Elemental-P®)	Hair color change Nail whitening	Enteral Se supplement	NA	NA	1.175/NA	2.41/NA	1.51/NA
12	12 yr 3 mo	F	Down Syndrome Short bowel syndrome	TPN	Nail whitening	Enteral Se supplement	6 mo	9.2	5.675/6.796	NA/NA	1.47/1.12
13	18 yr	F	22q11.2 deletion syndrome, Epi	Elemental diet (Elemental-P®)	Hair color change	Enteral Se supplement	15 mo	8.1	1.895/2.03	NA/NA	1.08/0.61
14	20 yr	M	HIE, CP	Elemental diet (Elemental-P®)	Hair color change	Enteral Se supplement	9 mo	8.8	1.589/1.381	NA/NA	2.34/1.66
15	24 yr 4 mo	F	Sturge-Weber syndrome	TPN	Hair color change Nail whitening	IV	5 mo	11.6	0.887/1.974	2.66/3.22	4.18/1.1

CIPO: chronic intestinal pseudo-obstruction, HIE: hypoxic-ischemic encephalopathy, CP: cerebral palsy, Epi: epilepsy, TPN: total parenteral nutrition, IV: intravenous, NA: data not available, ND: not described in the medical records. Elemental-P®, Elelental®; EA Pharma Co., Ltd., Tokyo, Japan. Twinline®, Otsuka Pharmaceutical factory, Inc., Tokushima, Japan. New MA-1®, Morinaga Milk Inc. Co., Ltd., Tokyo, Japan.

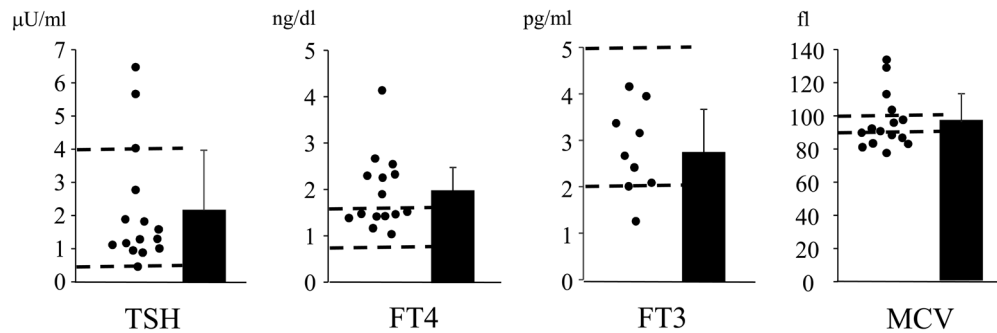


Fig. 1. FT4 levels are elevated in patients with severe Se deficiency. Serum levels of TSH (N = 15), FT3 (N = 9), FT4 (N = 15), and MCV (N = 15) were evaluated in patients who displayed severe Se deficiency. Broken lines indicate the upper and lower limits of the institutional normal range. Closed circles represent the values of each patient. The mean value and standard deviation are shown on the right.

Table 2. Se content in enteral formula

Products	Se content ($\mu\text{g}/100 \text{ kcal}$)
Elental-P®	0
Elental®	0
Twinline®	1.2
New MA-1®	0.86

Elental-P®, Elental®; EA Pharma Co., Ltd., Tokyo, Japan. Twinline®; Otsuka Pharmaceutical factory, Inc, Tokushima, Japan. New MA-1®; Morinaga Milk Inc. Co., Ltd., Tokyo, Japan.

in Fig. 1, the mean FT4 levels were elevated (institutional normal range, 0.82–1.63 ng/dl). Seven of 15 patients showed FT4 levels above the normal range, and 5 of 9 patients showed either low or low-normal levels of FT3 with the average levels of FT3 within the institutional normal range (2.0–4.9 pg/ml). The TSH levels were slightly elevated in 2 patients, but the average levels fell within normal values (institutional normal range, 0.41–4.01 $\mu\text{U}/\text{ml}$). The average levels of MCV, which are known to be elevated in patients with Se deficiency, were within the normal range (89–99 fl), and only 4 of 15 patients showed increases in MCV levels.

Supplementation of Se was associated with decreases in FT4 levels

To determine whether elevation of the

FT4 levels was due to Se deficiency, changes in thyroid hormone levels were analyzed after Se supplementation. The thyroid hormone levels were compared in the 11 patients receiving Se supplementation (Table 1). Although the serum Se levels were elevated due to Se supplementation, the levels still met the Se deficiency criteria, as set by the Japanese Society of Clinical Nutrition, in 5 patients (0–5 yr, $\leq 6.0 \mu\text{g}/\text{dl}$; 6–14 yr, $\leq 7.0 \mu\text{g}/\text{dl}$; 15–18 yr, $\leq 8.0 \mu\text{g}/\text{dl}$; and >19 yr, $\leq 10.0 \mu\text{g}/\text{dl}$). The reason the increase in Se levels differed among participants may be due to the distinct mode, amount, and duration of Se supplementation, as intravenous Se supplementation rapidly achieved the normalization of Se concentration compared to the other mode of Se supplementation. In response to the increased Se levels, the FT4 levels decreased significantly, and all the patients showed normal levels of FT4; however, the levels of TSH and FT3 did not alter with Se supplementation (Fig. 2 and Table 1).

No association was observed between serum Se and FT4 levels in patients after Se supplementation

We determined whether Se concentration was associated with FT4 levels in patients who had displayed detectable Se levels after Se supplementation. As shown in Fig. 3A and B,

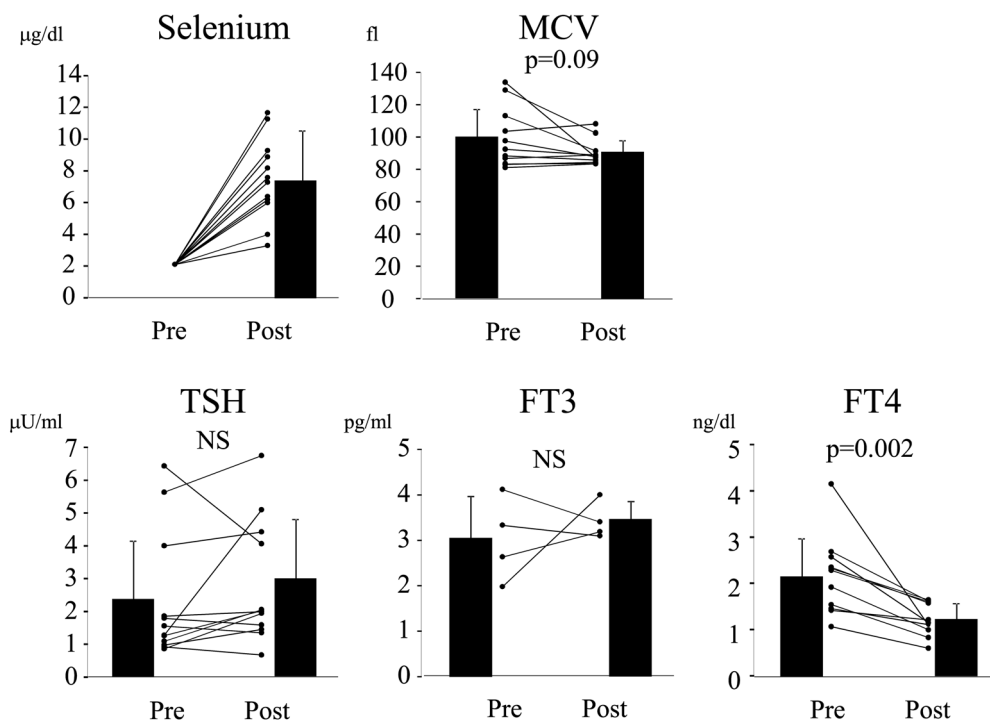


Fig. 2. FT4 levels are decreased after Se supplementation. Serum levels of TSH (N = 11), FT3 (N = 4), FT4 (N = 11), and MCV (N = 11) were compared before and after Se supplementation. Closed circles represent the values of each patient. Values from the same patient are connected in a straight line.

neither FT4 nor MCV correlated with Se levels. In addition, increases in Se levels were not associated with changes in FT4 levels (Fig. 3C). These findings suggest that FT4 does not reflect the state of Se sufficiency when the Se content is mildly decreased.

Discussion

In this study, we showed that decreases in Se levels were associated with increased T4 levels in patients with severe Se deficiency. DIO1 and DIO2 are selenoproteins, and they have been shown to be decreased in conditions of Se deficiency. The mechanism through which Se deficiency elevates FT4 levels most likely involves the suppression of DIO1 and DIO2 expressions that catalyze the conversion of T4 to T3. Similar findings have also been reported in elderly people (12), and in patients with phenylketonuria (14) and cystic fibrosis (15). However, a randomized

controlled trial involving 368 euthyroid participants who exhibited low-to-moderate Se deficiency demonstrated no association between Se status and the T4/T3 ratio (13). Therefore, the role of Se in thyroid hormone metabolism has demonstrated inconsistency between studies and remains unclear.

As parenteral nutrition or enteral formula may not include Se supplementation, Se deficiency can occur in given clinical settings. Indeed, Se levels have been shown to be decreased in many of the patients nourished through parenteral nutrition (16, 17), but no clinical symptoms have been reported in patients with Se deficiency (16), suggesting that Se deficiency-associated clinical symptoms occur more frequently as Se deficiency extends in duration. However, there is also evidence that Se deficiency-associated symptoms emerged shortly after Se became deficient (9); therefore it is still unclear whether there is an association between the duration of Se deficiency

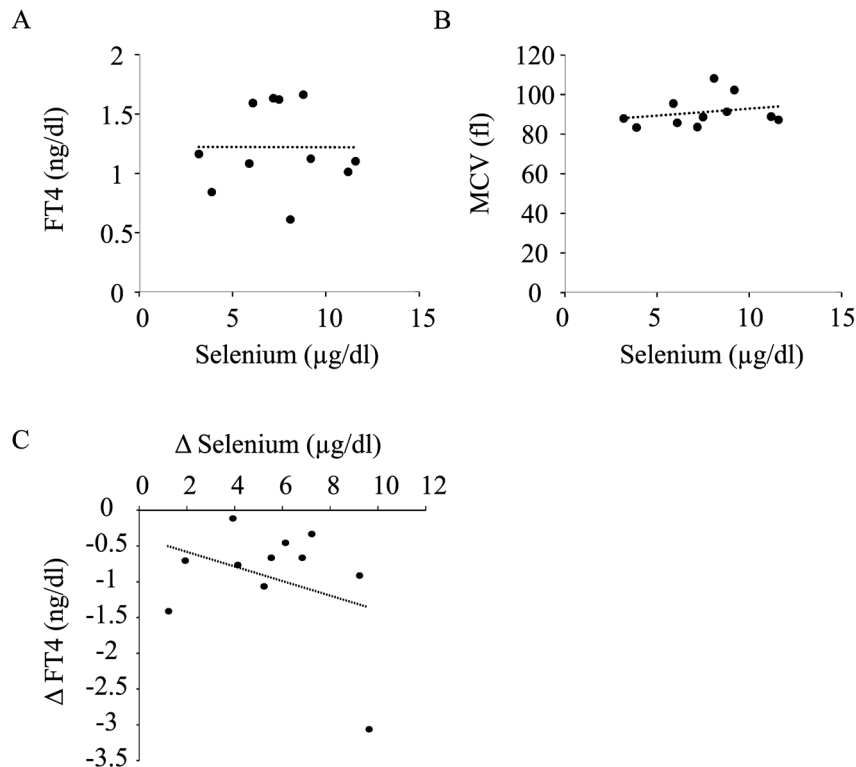


Fig. 3. No association is observed between Se and FT4 levels after Se supplementation. (A) Correlation between serum Se and FT4 levels were analyzed. Pearson's correlation coefficient $r = -0.0025$, $p = 0.99$. (B) Correlation between serum Se levels and MCV was determined. Pearson's correlation coefficient $r = 0.24$, $p = 0.42$. (C) Correlation between increases in serum Se levels (Δ Selenium: subtracting 2.0 from the values obtained after Se supplementation) and the changes in FT4 levels (Δ FT4) was determined. Pearson's correlation coefficient $r = -0.36$, $p = 0.20$.

and the development of clinical symptoms.

Animal studies have revealed that Se content differs significantly within tissues during a state of Se deficiency. For example, the Se content in the cerebrum, pituitary, and thyroid is maintained compared to the liver and kidney (7, 18). Consistent with this, the DIO activity is also preserved in the former tissues (18). These findings indicate that physiologically important tissues are protected from Se deficiency; however, the underlying mechanisms that cause the uneven distribution of Se during Se deficiency remain to be elucidated. Since DIO activity is minimally affected when Se intake is moderately reduced (7), T4 levels and/or the T4/T3 ratio are unlikely to be affected in a state of moderate Se deficiency. This hypothesis was supported in

the previously mentioned randomized controlled study (13). In contrast, when Se intake is severely reduced, impaired DIO activity seems to cause the elevation of T4 and/or the T4/T3 levels through blocking the T4 conversion to T3. This suggests that differences in the definition of Se deficiency among studies may have led to different conclusions regarding the association between Se and the thyroid hormone status.

Our findings have shown that Se status does not affect TSH levels, which may also indicate that Se deficiency is not associated with hypothyroidism. However, caution should be taken when interpreting the association between thyroid hormone status and TSH levels because the Se content differs among the tissues during Se deficiency. As described above, the Se content

is greater in the cerebrum and in the pituitary gland where a negative feedback system is operative, implying that T3 conversion from T4 in these tissues is maintained compared to the other tissues. These findings suggest that the serum concentration of TSH levels may not reflect the peripheral thyroid hormone status, and it is possible that TSH levels are inappropriately low despite the presence of peripheral thyroid hormone deficiency.

Se deficiency causes growth retardation in both rodents and humans; however, the underlying mechanisms are not fully understood. Since Se deficiency has been shown to reduce GPx activity, the accumulation of oxidative damage may explain the mechanisms of Se deficiency-associated growth retardation (19, 20). It is possible that hypothyroidism due to Se deficiency is responsible for Se deficiency-associated growth retardation; however, further studies are required to confirm this hypothesis.

In conclusion, we found that serum FT4 levels were elevated in patients with severe Se deficiency but were reduced with Se supplementation. Therefore, these findings highlight the use of FT4 levels as a possible biomarker for severe Se deficiency. Understanding the alterations in thyroid hormone levels in conditions of Se deficiency is important to allow for early intervention concerning Se deficiency prior to the development of Se deficiency-associated clinical symptoms. Since mutations in the *SBP2* gene also cause inhibition in the conversion of T4 to T3, this disorder should be considered as a differential diagnosis when increases in FT4 levels are associated with decreases in FT3 and marginal increases in TSH levels (11, 21–24). Since the TSH levels did not decrease with Se supplementation, it is still unclear whether Se deficiency can cause the development of hypothyroidism. Further investigations are required to clarify the association between Se deficiency and hypothyroidism.

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