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Thyroid dysfunction due to trace element deficiency—not only selenium but also zinc

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Abstract

Introduction: Levels of serum selenium (Se) and zinc (Zn) decrease when total parental nutrition (TPN) is administered without trace element supplementation for just a few weeks. These trace elements are involved in thyroid hormone metabolism, and their deficiencies cause thyroid dysfunction. However, there have been few reports on the details of its clinical course.

Case presentation: A 50-year-old man presented with thyroid dysfunction due to Se and Zn deficiency. He had an approximately 70-cm residual small intestine after undergoing intestinal resection and he received TPN without trace element supplementation for one and a half months. Blood tests revealed high levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) and low levels of free triiodothyronine (FT3). An abnormal pattern of thyroid function led to suspicion of Se deficiency. Se supplementation raised FT3 levels and lowered FT4 levels to within their respective reference ranges; however, subclinical hypothyroidism persisted with transient TSH elevation. We suspected that Zn deficiency also contributed to the hypothyroidism and, therefore, initiated Zn supplementation, which resulted in normalization of thyroid function.

Discussion: Although thyroid dysfunction has been reported in many studies conducted on Se and Zn deficiencies, hormonal patterns vary between reports. Further accumulation of cases, including detailed data on nutritional status, would be of benefit to elucidate the clinical reality.

Conclusion: It is important to consider Se and Zn deficiencies when TSH and FT4 levels are elevated. It should also be noted that transient TSH elevation may be observed with Se supplementation.

Keywords: Selenium, Zinc, Thyroid, Trace element, Total parenteral nutrition

Statements and declarations

Competing interests

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Consent to participate

The patient has given written informed consent for the use of clinical information.

Author contributions

All authors contributed to the article and approved the submitted version.

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Introduction

Trace elements are vital to human health and essential to metabolism [1]. It has been reported that blood selenium (Se) and zinc (Zn) levels decrease after only a few weeks of receiving total parental nutrition (TPN) without trace element supplementation [2, 3].

It is well known that Se deficiency causes whitened nails, muscle weakness, cardiac myopathy, and liver dysfunction, while Zn deficiency causes skin symptoms, weakened immune system, and taste disturbances [4, 5]. Additionally, Se affects thyroid hormone metabolism by disrupting iodothyronine deiodinases (DIOs) [4] and weakening the resistance of thyroid cells to oxidative stress [6]. Zn is not only involved in the synthesis of thyrotropin-releasing hormone and thyroid-stimulating hormone (TSH), but also in the activation of DIOs and resistance to oxidative stress [7, 8]. Zn is also a component of the thyroid hormone receptor and affects its activity [7, 8]. Se and Zn deficiencies are thought to cause thyroid dysfunction through various pathways and not only through these mechanisms [9]. To the best of our knowledge, no studies have documented the detailed restoration process of thyroid function after supplementation with trace elements.

We present a patient with short bowel syndrome (SBS) who received TPN and developed thyroid dysfunction due to Se and Zn deficiencies. Intriguingly, alterations in thyroid function exhibited, such as elevated levels of transient TSH during the clinical course. This report could be informative as regards distinctive features of trace element supplementation in patients receiving TPN and those with atypical thyroid abnormalities associated with trace element deficiencies.

Case presentation

A 50-year-old man was referred to our department because of thyroid dysfunction (Table 1) with a high TSH level of 6.58 μIU/mL (reference range: 0.61–4.23) and free thyroxine (FT4) level of 1.88 ng/dL (reference range: 0.90–1.70) and a relatively low free triiodothyronine (FT3) level of 2.6 pg/mL, reference range: 2.3–4.0), indicating a relatively low FT3/FT4 ratio of 1.38. Tests for antithyroglobulin and antithyroid peroxidase antibodies yielded negative results.

The medical history of the patient was as follows. He underwent surgery and retroperitoneal irradiation for a testicular tumor without recurrence at the age of 1 year. At 38 years of age, the patient was diagnosed with fatty

liver disease. At 39 years of age, he developed bilateral ureteral stenosis, and ureteroileal anastomosis was performed the following year. Blood tests at 42 years of age revealed no apparent thyroid dysfunction. At 50 years of age, he underwent ileal resection because of adhesive intestinal obstruction due to abdominal incisional hernia, while the remaining small intestine measured approximately 70 cm. After oral intake was initiated postoperatively, malabsorption and dehydration occurred due to the SBS. The patient was discharged from the hospital on TPN. The trace element-containing high-calorie infusion is standard for patients receiving long-term TPN. Se is among the trace elements whose supplementation is recommended. However, since this patient also received oral intake and the risk of Se deficiency was considered low, transvenous Se supplementation was not administered. Three days after discharge, he was readmitted to our hospital because of an elevated white blood cell count (16,100 /μL) during a regular surgical visit. Blood tests also revealed elevated liver enzyme levels (aspartate aminotransferase [AST], 183 U/L; alanine aminotransferase [ALT], 200 U/L). Blood tests to investigate the cause of elevated liver enzyme levels revealed abnormal thyroid function and the patient was referred to our department.

The patient's height, body weight, and body mass index were 154.3 cm, 53.5 kg, and 22.5 kg/m^2, respectively. Goiter was not palpable and hair changes and nail whitening or deformity were not observed. The patient experienced lower extremity muscle pain. He had no symptoms consistent with Zn deficiency, such as dermatitis, stomatitis, alopecia, bedsores, or dysgeusia. Electrocardiography showed a normal sinus rhythm with no abnormal ST changes, T-wave inversions, or low voltage.

The unique abnormal pattern of thyroid function (low FT3 despite high FT4 and elevated TSH levels), clinical history of short bowel length, and requirement of TPN indicated trace element deficiencies, including Se and Zn. Blood tests revealed low levels of serum Se (7.2 μg/dL, reference range: 10.5–17.3) and Zn (69 μg/dL, reference range: 80–130).

Considering the elevated FT4 level relative to FT3 level, we suspected that the dysfunction of DIOs due to Se deficiency was more significant than that due to Zn deficiency. We first initiated intravenous administration of 100 μg/day of sodium selenite on day 23 after referral to our department (Fig. 1). Muscle pain in the lower extremities improved a few days after Se supplementation. On day 51, Se levels improved to 13.2 μg/dL and liver function improved. During Se supplementation, FT3 levels increased with the suppression of FT4 levels, leading to an increase in the FT3/FT4 ratio. Surprisingly, TSH levels transiently increased to a maximum of 18.3 μIU/mL on

day 42 and then slightly decreased to 5.23 μIU/mL on day 55. Se supplementation was continued until discharge on day 55. After discussion with the surgeon and nutritionist, we discontinued Se supplementation because we considered intestinal absorption and Se concentration to have improved. On day 181, serum Se levels remained within the reference range of 11.4 μg/dL after the withdrawal of Se supplementation.

Although serum Se levels were maintained, laboratory findings remained indicative of subclinical hypothyroidism (TSH: 12.6 μIU/mL, FT3:2.8 pg/mL, FT4:1.67 ng/dL, and FT3/FT4 ratio, 1.68). Thus, we considered the possibility that Zn deficiency was involved in the development of subclinical hypothyroidism. Zn supplementation was initiated on day 65 and serum Zn level reached 100 μg/dL on day 181. In the meantime, TSH concentration decreased to a reference range and thyroid function reached a euthyroid state on day 181 (TSH: 2.66 μIU/mL, FT3: 3.5 pg/mL, FT4: 1.18 ng/dL, and FT3/FT4: 2.97). In this case, thyroid function was recovered only with supplementation of trace elements, without thyroid hormone supplementation therapy.

Subsequently, his serum Se and Zn levels remained within the reference ranges. However, because of irregular diet and Zn supplementation, his serum Se and Zn levels dropped to 9.9 μg/dL and 79 μg/dL on day 377, respectively, below the reference ranges. Interestingly, on the same day, TSH level increased again, while FT3/FT4 ratio decreased (TSH: 4.94 μIU/mL, FT3: 3.3 pg/mL, FT4: 1.23 ng/dL, and FT3/FT4: 2.68). This suggests that trace element supplementation was important for maintaining thyroid function in this patient.

Discussion

We present a case of SBS and the use of TPN that caused abnormal thyroid function (low FT3 despite high FT4 and elevated TSH levels). This abnormal thyroid function, different from subclinical hypothyroidism, non-thyroidal illness, and syndrome of inappropriate TSH secretion, led us to suspect Se and Zn deficiencies.

Se and Zn deficiencies can develop in about 10–20 days and 2 weeks, respectively, in cases of insufficient trace element intake [2, 3]. Se and Zn are quickly depleted compared with other trace elements, even with relatively short-term inadequate intake [10, 11]. Despite the clinical importance of these trace element deficiencies, the frequency of Se and Zn deficiencies in patients on TPN remains unclear. Particular attention should be paid to Se deficiency in patients on TPN, as common multi-trace element products and some parenteral or enteral nutrition formulas do not contain Se. Se deficiency has been reported in patients with SBS owing to reduced intestinal Se

absorption [12]. In addition to the use of TPN and SBS, the following have also been reported as instances where Se and Zn deficiencies occur: Se deficiency occurs in dialysis, cirrhosis, anorexia nervosa, and inflammatory bowel disease [13–16]; Zn deficiency occurs in malnutrition, inflammatory bowel diseases, and cirrhosis [5].

In this case, postoperative malabsorption was observed and withdrawal from TPN took longer than 2 months. Oral Se supplementation via diet and medication was considered insufficient; therefore, transvenous Se supplementation was initiated. However, in this case, the length of the remaining small intestine was 70 cm; if it was shorter than 60 cm, withdrawal from TPN would be difficult [17]. After some time had elapsed since surgery and intestinal tract function had become stable, it was possible to supplement trace elements only with oral medications and food. Indeed, after discontinuing transvenous Se supplementation and starting oral Zn supplementation, serum Se and Zn levels were maintained provided that the diet and medications were adequate. Therefore, we plan to continue oral Se and Zn supplementation in this patient. It may be useful to conduct periodic interviews (for trace element deficiency symptoms, including muscle pain in the lower extremities, which was initially observed) and blood tests (for Se and Zn levels as well as abnormal thyroid hormone patterns) to monitor the patient's trace element sufficiency status.

Se functions as a selenoprotein, and there are 25 types of selenoproteins, such as glutathione peroxidase, thioredoxin reductase, and DIOs [18]. Thyroid dysfunction is also one of the outcomes of Se deficiency, as it decreases the expression of DIOs. The DIOs consist of types 1, 2, and 3 (D1, D2, and D3, respectively). D1 and D2 have a predominant effect on the conversion of thyroxine (T4) to triiodothyronine (T3) in peripheral tissues [4] and D3 inactivates T4 irreversibly. D1 synthesis is more sensitive to serum Se levels than D2 and D3 [19].

In an animal model, Se deficiency inhibited the conversion of T4 to T3 by decreasing the expression of DIOs, resulting in high T4, low T3, and high TSH levels [20]. A report showed that, when Se is supplemented in patients with Se deficiency, TSH and FT4 levels decrease, and FT3 and FT3/FT4 ratios increase, similarly to the findings in our patient [4]. These changes were consistent with several previous reports; however, there were no reports of clinical courses that documented transient elevations of TSH, as in our case. It has been reported in an animal study that DIO subtypes differ in their affinity for thyroid hormones and in the degree of inhibition caused by Se deficiency, which may account for this inconsistent trend [20]; however, further investigation is needed to elucidate this mechanism.

In this case, abnormal thyroid function persisted after Se sufficiency, which led to the suspicion of thyroid dysfunction due to Zn deficiency. Zn supplementation in Zn-deficient patients has been shown to decrease TSH and increased FT3 and FT4 levels [21]. The clinical course of our patient's subclinical hypothyroidism after Se sufficiency improved after Zn supplementation, suggesting that the thyroid abnormality may have also been caused by Zn deficiency.

Several studies have been conducted to investigate the relationship between Se and Zn supplementation and thyroid function (Table 2). However, the outcomes related to changes in thyroid function after Se supplementation remain controversial [22–24]. These results may have occurred because various factors such as nutritional status (including other trace elements), medications, and smoking modulate thyroid function [25, 26]. One reason the conclusions are controversial may be that some groups have included data collected at the time of transient TSH elevation, as in this case. In any case, it is important to have a comprehensive assessment of thyroid function and trace element sufficiency status.

In the present case, there were no symptoms suggestive of Se deficiency except for muscle pain in the lower extremities. If Se supplementation is further delayed, lethal cardiac problems, such as idiopathic dilated cardiomyopathy, might have occurred [27]. When patients with SBS or those receiving TPN exhibit thyroid dysfunction, especially in a unique abnormal pattern (low FT3 despite high FT4 and elevated TSH levels), it is important to suspect trace element deficiencies. In such high-risk patients, regular measurements of trace elements should be considered even when asymptomatic.

This study has some limitations. First, because this is a single case report, the effects of comorbidities and other confounding factors on trace elements and thyroid function cannot be excluded; therefore, it cannot be concluded that only the Se and Zn supplementation improved thyroid function. Second, the course of the disease after long-term follow-up was unclear. To solve this problem, it is necessary to accumulate cases of trace element deficient patients from multiple centers, with detailed follow-up of thyroid function data.

Conclusion

Herein, we report a case of unique abnormal thyroid function with Se and Zn deficiencies and the detailed restoration process of thyroid function after supplementation. Se and Zn deficiencies are important differential diagnostic indicators of thyroid dysfunction with short bowel syndrome or use of TPN.

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283 **Table 1. Clinical data**

	Patient's data	Reference range for male adults
White cell count (/μL)	10,100	3,300–8,600
Differential count (%)		
Neutrophils	77.1	40–71
Lymphocytes	15.2	26–47
Eosinophils	2.1	<7
Basophils	0.6	<1
Hemoglobin (g/dL)	12.7	13.6–17.0
Hematocrit (%)	37.9	39–52
Platelet count (/μL)	266,000	158,000–348,000
Sodium (mmol/L)	138	138–145
Potassium (mmol/L)	3.7	3.6–4.8
Chloride (mmol/L)	98	101–108
Urea nitrogen (mg/dL)	14.7	8–20
Creatinine (mg/dL)	0.89	0.65–1.07
Glucose (mg/dL)	107	73–109
Total protein (g/dL)	6.3	6.6–8.1
Albumin (g/dL)	2.9	4.1–5.1
Aspartate aminotransferase (U/L)	122	13–30
Alanine aminotransferase (U/L)	108	10–42
γ-glutamyl transpeptidase (U/L)	395	13–64
Alkaline phosphatase (U/L)	111	38–113
Total bilirubin (mg/dL)	7.5	0.4–1.5
Direct bilirubin (mg/dL)	5.1	<0.2
TSH (μIU/mL)	6.58	0.61–4.23
FT3 (pg/mL)	2.6	2.3–4.0
FT4 (ng/dL)	1.88	0.9–1.7
FT3/FT4	1.38	
Thyroglobulin (ng/mL)	19.6	<33.7
Antithyroglobulin antibody (IU/mL)	12	<28
Antithyroid peroxidase antibody (IU/mL)	<9	<16
Se (μg/dL)	7.2	10.7–17.1
Zn (μg/dL)	69	80–130

284 Abbreviations: Se, selenium; Zn, zinc; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free
285 thyroxine

Table 2. Thyroid function with Se and Zn supplementation

	Study type	Country	Age	Sex (M/F)	The number of patients	TSH	FT4	FT3	FT3/FT4	Ref
-	Case report (Se and Zn supplementation)	Japan	50	Male		↓	↓	↑	↑	This case
Thyroid function with Se supplementation										
1	Case report	Australia	76	Male	1	↑	→	↑	↑	[28]
2	Case report	Germany	1, 3, 6	Female	3	↓	↓	↓ ~ ↑	↓ ~ ↑	[29]
3	Interventional study	Japan	3–42	10/12	22	↓	↓	↑	↑	[4]
4	Observational study	Japan	1–24	4/11	15	→	↓	→	-	[22]
5	Interventional study	Brazil	53.3±16.1	17/23	40	→	↑	↑ [a]	↑ [a]	[23]
6	Interventional study	Italy	-	-	36	-	↓ [b]	-	-	[30]
7	Interventional study	Congo	-	-	52	→	↓	→[a]	-	[31]
8	RCT	Denmark	60–74	-	491	↓	↓	→	→	[32]
9	Meta-analysis	New Zealand	18–65	111/185	296	-	↓ ~→[b]	-	→[a, b]	[33]
10	RCT	UK	60–74	1:1	368	→	→	→	→	[34]
Thyroid function with Zn supplementation										
11	Case report	USA	female college students		2	↓ ~ ↑	↓ ~ ↑	↓ ~ ↑	↑	[35]
12	Interventional study	Pakistan	16–30	60/72	132	↓	↑	↑	-	[21]
13	Interventional study	Japan	-	-	9	-	-	↑	-	[36]
14	Meta-analysis	Various countries	1–65	-	629	↓ ~ ↑	↓ ~ ↑ [c]	→~ ↑ [d]	-	[7]

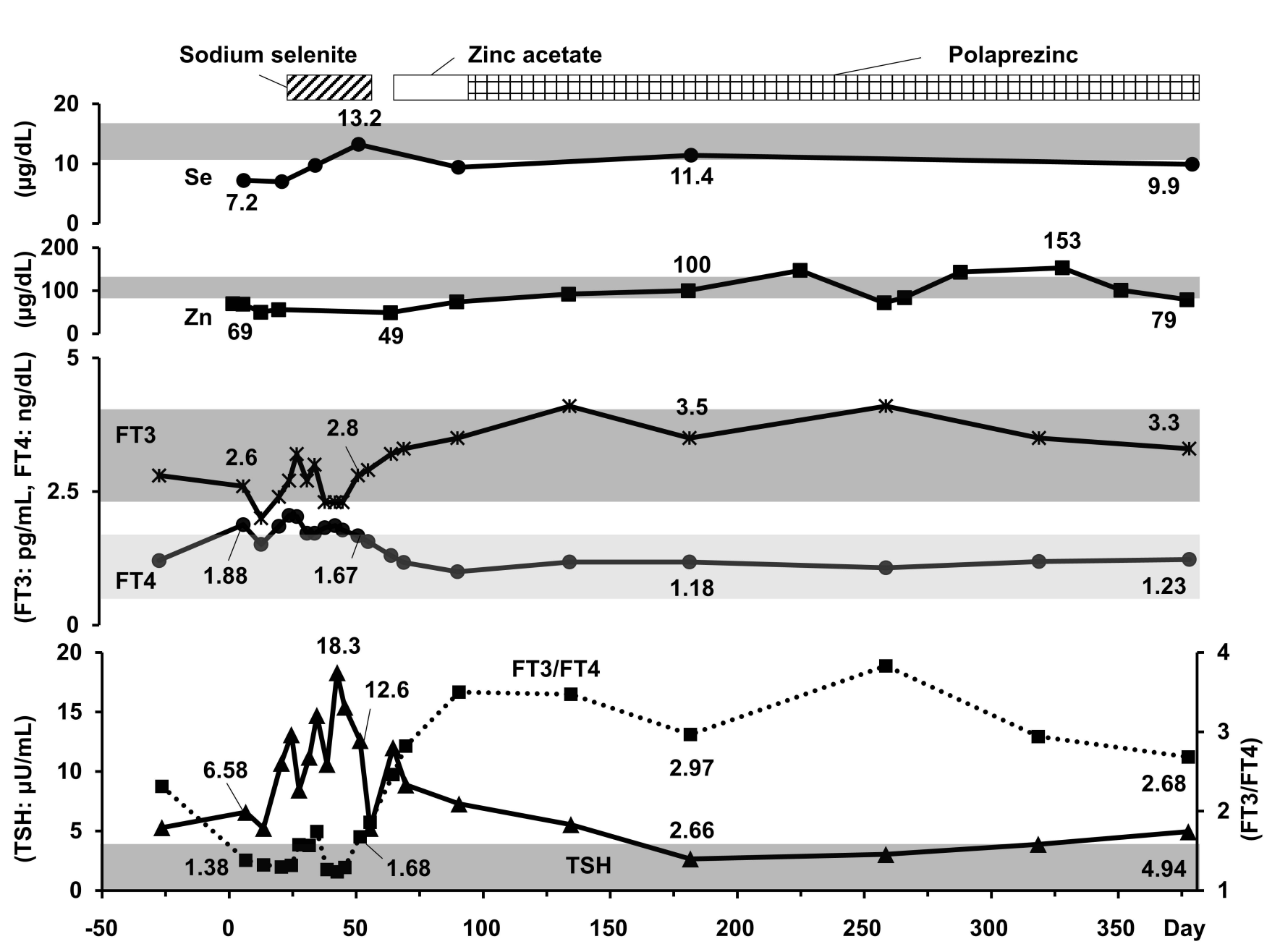
Abbreviations: UK, United Kingdom; USA, United States of America; M, male; F, female; Se, selenium; Zn, zinc; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; Ref, reference; RCT, randomized controlled trial

290 [a] Total T3 is measured instead of free T3. [b] Total T4 is measured instead of free T4. [c] Total T4 is measured instead of free T4 in six studies. [d] Total T3 is measured

291 instead of free T3 in six studies.

Fig. 1: Clinical course

The clinical course of this case has been described. Day 0 is the date of referral to our department. The upper part of the Figure shows the progress of trace element supplementation and the lower part shows the progress of thyroid hormone and TSH levels. The highlighted areas indicate the Se, Zn, FT3, FT4, and TSH reference ranges as follows: Se: 10.7–17.1 µg/dL, Zn: 80–130 µg/dL, FT3: 2.3–4.0 pg/mL, FT4: 0.9–1.7 ng/dL, and TSH: 0.61–4.23 µU/mL. Abbreviations: Se, selenium; Zn, zinc; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine


Sodium selenite
Zinc acetate
Polaprezinc
(μg/dL)
Se
13.2
7.2
11.4
9.9
Zn
153
100
69
49
79
(FT3: pg/mL, FT4: ng/dL)
FT3
3.5
2.8
2.6
3.3
FT4
1.88
1.67
1.18
1.23
(TSH: μU/mL)
(FT3/FT4)
18.3
FT3/FT4
12.6
6.58
2.97
2.68
2.66
1.38
1.68
TSH
4.94
-50
0
50
100
150
200
250
300
350
Day