Selenium substitution has no direct effect on thyroid hormone metabolism in critically ill patients

Matthias W A Angstwurm, Jochen Schopohl and Roland Gaertner

Departments of Endocrinology and Intensive Care, Faculty of Medicine, Ludwig Maximilians Universität, Standort Innenstadt, Medizinische Klinik, München, Germany

(Correspondence should be addressed to M Angstwurm, Medizinische Klinik, Ziemssenstrasse 1, 80336 Munich, Germany. Email: Matthias.angstwurm@med.uni-muenchen.de)

Abstract

Background: In severe illness, plasma selenium levels are decreased; a decreased activity of the selenoenzyme 5'-deiodinase has been hypothesized to contribute to low tri-iodothyronine (T3) levels in non-thyroidal illness (NTI) syndrome in these patients.

Objective: To analyse the influence of selenium substitution on thyroid hormone metabolism in patients with severe sepsis.

Design: A prospective, randomized, controlled study at the medical internal intensive care unit of the University of Munich. Results are for 41 consecutive patients with severe sepsis with an APACHE II score >15. Patients received either sodium selenite (500 µg/day for the first 3 days, reducing to 250 and then 125 µg/day every 3 days) or a placebo.

Results: At study entry, APACHE II score and demographics were identical in both groups. The mean levels of TSH, free tri-iodothyronine and total T3, as well as plasma selenium and selenium-dependent peroxidase (GSH-Px) activity, were decreased. Plasma selenium and GSH-Px activity were normalized on days 3, 7 and 14 in patients receiving selenium (n = 21), but remained below normal in the control patients. Patients receiving selenium had a better clinical outcome and thyroid hormone levels normalized earlier. Thyroid hormone levels increased in patients who showed clinical improvement, independent of selenium levels or selenium substitution.

Conclusions: Selenium substitution in patients with NTI improves morbidity, but has no direct effect on the free and total thyroid hormones. In severely ill patients, decreased deiodinase activity due to low plasma selenium levels seems unlikely. After clinical revival, TSH and then the thyroidal hormones normalize independently of selenium substitution.

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Introduction

The importance of the essential trace element selenium for human health has been recognized for many years (1). The most important role of selenium is the formation of selenocystein, the 21st amino acid, which is located in the catalytic centre of all selenoenzymes. One important role of the selenoenzymes is the maintenance of nearly all redox systems in cellular and extracellular compartments. One of the best-known and -characterized redox systems is the glutathione complex consisting of a selenium-dependent peroxidase (GSH-Px). The activity of GSH-Px is linked to available selenium. Furthermore, selenium plays a major role in thyroid hormone metabolism. The activity of all three known deiodinases, D1–D3, is dependent on selenium (2–4). The importance of selenium in thyroid hormone metabolism is also reflected by the fact that the thyroid is the organ with the highest selenium content (5–7); selenium levels remain higher in the thyroid compared with other tissues such as liver, kidney and skin, even when deficiency occurs (8).

In patients with severe illness, significant changes of peripheral thyroid hormone metabolism as well as thyroid-stimulating hormone (TSH) are observed. This so-called non-thyroidal illness (NTI) syndrome is characterized by altered thyroid hormone metabolism as well as depressed TSH secretion. Only a few hours after the onset of an acute illness, tri-iodothyronine (T3) levels decrease. Depending on the severity and duration of the illness (9), this is followed by a fall in thyroxine (T4) and TSH. The decrease in plasma T3 levels is accompanied by an increase in reverse T3; therefore, the decline had been explained by a decrease in the activity of 5'-D1 within the liver. The precise aetiology and the therapeutic consequences of these changes remain controversial (10–14).

Plasma selenium levels are low in patients with severe illness and sepsis (15) leading to low GSH-Px activity and a redistribution of selenium occurs away
from the liver to the muscles, at least in rats (8); therefore, a decreased production and activity of the selenium-dependent deiodinases has been supposed (11), leading to impaired T4 and T3 metabolism.

It has already been shown that in critically ill patients, selenium substitution leads to an earlier normalization of plasma T3 levels compared with controls (16) and that low plasma selenium levels correlate with low T3 levels (17). From these studies, it has been concluded that the main cause of low T3 levels might be the decreased activity of the selenoenzyme 5'-D1.

In the rat anterior pituitary, the negative feedback regulation of TSH production and secretion depends on the local production of T3 from T4 by the activity of 5'-D1 and 5'-D2 (18–20). By analogy, in critically ill patients the decreased hypothalamic 5'-D1 activity is supposed to be involved in the decreased TSH release. In the central nervous system, the local production of thyroid hormone, mainly by the 5'-D2 enzyme, determines thyrotrophin-releasing hormone (TRH) release. Therefore low plasma selenium levels may lead to low deiodinase activity implicating a role of selenium in the pathophysiology of the NITI syndrome.

We have recently demonstrated in a prospective, randomized and placebo-controlled trial, that selenium substitution in patients with severe sepsis improves outcome and reduces morbidity in the most severely ill patients (21). In addition, the reduced GSH-Px activity could be restored by selenium substitution. In this study, we examine the thyroid hormone and TSH levels in these patients, to show whether selenium substitution has any influence on the typical changes seen in NITI syndrome.

**Methods**

**Subjects and study design**

Forty-two patients with severe sepsis or systemic inflammatory response syndrome (SIRS) (22) and an APACHE II score (23) of greater than 15 (APACHE II score used as a tool for measurement of morbidity) were prospectively randomized alternately into two groups in the first 24 h after admission. The influence of selenium substitution on mortality and organ failure in these patients has been published previously (21). We now present the thyroid hormone metabolism data which were collected prospectively during the study. Patients with known thyroid disease were excluded; one patient had to be excluded because of newly discovered hypothyroidism. No patient received any thyroid medication, thyroid hormones or amiodarone- and iodine-containing agents. In addition, patients were excluded if they were aged under 18 years or if they refused to participate in the study. The following were also indicators for exclusion: resuscitation, pancreatitis, major burns, trauma or surgery, gastrointestinal bleeding, pregnancy or known kidney failure with creatinine levels above 2 mg/dl.

Patients received either placebo (Se-) or sodium selenite (Se+) at 500 µg/day for the first 3 days, reducing to 250 and 125 µg every 3 days. All patients received additional 35 µg sodium selenite in the commercial trace element solution. The dose of substitution was chosen to normalize diminished serum selenium levels. The recommended dosage of selenium in patients on parenteral nutrition is between 70 and 200 µg/day. In patients with proven selenium deficiency, up to 1000 µg sodium selenite per day had been used. In our patients with severe SIRS, acute renal failure is a common complication. We used selenium in a smaller dose and for only a limited time to prevent potentially harmful serum selenium levels because selenium is excreted in the urine. However, this dose is nowhere near the toxic selenium intake (more than 3000 µg/day over weeks). Because the aim was to restore the selenium deficiency and no pharmacological therapy was performed, no written informed consent was required, according to our investigational review committee.

As a measure of morbidity during the course of stay, the APACHE III score (24, 25) was determined at days 1, 3, 7 and 14 after admission using the worst value within 24 h. The APACHE III score was necessary to determine morbidity as other scores are not validated for follow-up measurements. Patients with an increasing APACHE III score (>5 points) between days 1 and 14, or those dying before day 14, were judged to be clinically worsening; those patients with a decreasing score (>5 points) between days 1 and 14 were judged to be clinically improving.

**Treatment**

All patients were treated according to good clinical practice with standard care including appropriate antimicrobial agents, catecholamines including a continuous dopamine infusion at low dose (200 µg/min) during their stay, continuous venovenous haemofiltration in patients with renal failure, ventilation and sedation in patients with respiratory insufficiency. Hydrocortisone at a dose of 200 mg/24 h was substituted without cortisol measurements in all patients. No patient received thyroid hormones. The analysis of thyroid hormones was done after all patients had finished the study. Therefore, the treatment of patients was blinded and independent of thyroid hormone results; selenium substitution had no impact on any treatment modalities. All patients received nutrition at the time of admission to the study, primarily parenteral including vitamins (Intralipid and Soluvit; Pharmacia, Upsala, Sweden), glucose, lipids and gluten-free-amino acids (total calories, 2400 kcal/day).
Laboratory and technical investigations

Blood samples were drawn from indwelling catheters at days 1, 3, 7 and 14 for analysis of total selenium concentrations and GSH-Px activity before the selenium substitution of the day. All blood samples were centrifuged within 1 h of withdrawal and were stored at −20°C until assayed in series. Selenium in plasma was determined by the hybrid atom absorption method (26). To convert conventional units to international units, multiply 1 μmol selenium by 78.96 to achieve 1 μg/l. The normal range for selenium is 52–95 μg/l. GSH-Px was measured as described previously (27). In addition, free T3 (normal range, 2.3–4.3 μg/dl), free T4 (normal range, 0.8–1.8 ng/dl) and TSH (normal range, 0.4–4.0 μU/ml) were determined by commercial enzyme immunometric assays (BykSangtec, Dietzenbach, Germany). Total T4 (normal range, 77–142 nmol/l and 4.5–10 μg/l) and T3 (normal range, 1.4–2.2 nmol/l and 0.8–1.8 μg/l) were determined by chemoluminescence assays (ACS).

Statistics

The statistical analysis was done using the commercially available software package SPSS, version 10.0 (SPSS, Inc., Chicago, IL, USA). All data are presented as means ± S.E.M. unless otherwise stated. Wilcoxon and Mann–Whitney non-parametric tests were used for one-time comparisons within and between the groups for paired and unpaired data respectively. The course of a variable within a specific group of patients was compared using the Wilcoxon test for paired samples. Pearson’s correlation coefficients were calculated. P values are two-sided; a difference between groups was classified as significant if P < 0.05.

Boxplots show median, 25th and 75th percentile as boxes, and 5th and 95th percentile as error bars; extreme values are shown as circles.

Table 1 Characterization of patients at admission.

<table>
<thead>
<tr>
<th></th>
<th>Se− (n = 21)</th>
<th>Se+ (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>8/13</td>
<td>5/16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.5±5.2</td>
<td>54.3±4.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24±1.4</td>
<td>21±1.5</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19±1.1</td>
<td>17±1.3</td>
</tr>
<tr>
<td>Multiple organ dysfunction score</td>
<td>4±0.6</td>
<td>4±0.6</td>
</tr>
<tr>
<td>Patients with pneumonia</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Patients with peritonitis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>T4 (norm, 77–142 nmol/l)</td>
<td>47±4.65</td>
<td>59±7.29</td>
</tr>
<tr>
<td>Free T4 (norm, 0.8–1.8 ng/dl)</td>
<td>1.0±0.06</td>
<td>1.1±0.07</td>
</tr>
<tr>
<td>T3 (norm, 1.4–2.8 nmol/l)</td>
<td>0.8±0.06</td>
<td>0.9±0.08</td>
</tr>
<tr>
<td>Free T3 (norm, 3.5–8.0 pg/ml)</td>
<td>1.95±0.14</td>
<td>2.12±0.18</td>
</tr>
<tr>
<td>TSH (norm, 0.4–4.0 μU/ml)</td>
<td>0.29±0.05</td>
<td>0.30±0.10</td>
</tr>
<tr>
<td>Selenium (norm, 70–140 μg/ml)</td>
<td>35.8±3.2</td>
<td>42.6±5.3</td>
</tr>
</tbody>
</table>

Results are number of patients and means with standard error. BMI, body mass index.

Results

Characterization of patients at admission

All patients were suffering from severe sepsis/SIRS; the median APACHE II score at admission was 20±1.1 in controls and 20±1.2 in the selenium-treated group; there were no significant differences in gender, age, other scores for the severity of disease or underlying disease (Table 1).

Thyroid hormones

At admission, the levels of total T4 were already low (52.6±4.3 nmol/l) and the levels of free T4 (1.03±0.52 ng/dl) were also in the low normal range, with no significant differences between the Se− and Se+ groups. Both total T3 (0.86±0.05 nmol/l) and free T3 (2.06±0.11 pg/dl) levels were below the normal range, with no significant differences between the Se+ and Se− groups (Table 1 and Fig. 1). At admission, the serum selenium levels were not correlated with T3 (r = 0.08, P = 0.615) or T4 levels (r = 0.13, P = 0.424), or with APACHE III score (r = 0.095, P = 0.560). During follow-up (Fig. 1), the levels of total thyroid hormones were identical in the Se− and Se+ groups. In addition, there were no differences in free thyroid hormone levels between the groups, either at admission or during the course of the illness.

In contrast, the TSH concentrations were low and identical (P = 0.178) in both groups at admission; however, whereas the levels of TSH remained constantly low between days 1 and 14 in the Se− group, the TSH levels significantly increased in the Se+ group at day 14 compared with day 1 (P = 0.035) and day 3 (P = 0.013) (Fig. 1). There was a trend of higher TSH levels at day 14 in the Se+ than in the Se− group (P = 0.078 using Wilcoxon log rank test for unpaired samples).

Selenium and plasma GSH-Px activity

At admission, the mean serum selenium concentration was 39.5±3.07 μg/l with no differences between groups. This level is about 40% lower than normal. In the Se+ group selenium plasma levels significantly (P < 0.001) increased at day 7 to 79.0±6.68 μg/l, but remained low (40.7±4.02 μg/l) in the Se− group.

Plasma GSH-Px activity was also decreased in all patients at admission and was correlated with serum selenium level, increasing significantly after selenium substitution (21). GSH-Px activity was only associated with the ratio of T4 to T3 in the Se− patients (r = 0.583 and P = 0.036 in the Se− group, compared with r = 0.371 and P = 0.179 in the Se+ group).
Correlation between selenium and T4/T3 ratio

The plasma selenium levels at admission ($r = 0.017$ for all patients at day 1) or during the course ($r = 0.011$ in Se− and $r = 0.124$ in Se+ at day 7) were not correlated with the ratio of T4 to T3. The ratio of T4 to T3 was within the normal range, independent of the treatment group, at day 1 and during the follow-up. Between days 1 and 7, changes in T3 levels were highly correlated with changes in T4 levels independent of selenium substitution (Fig. 2: Se+, $r = 0.799$; Se−, $r = 0.693$).

Morbidity and thyroid hormones

The morbidity of the patients was evaluated using the APACHE III score. The APACHE III score was negatively correlated with the levels of total T4 ($r = -0.462$, $P < 0.001$) or total T3 ($r = -0.514$, $P < 0.001$) at admission. In the Se+ group the APACHE III scores at days 7 ($P = 0.018$) and 14 ($P = 0.028$) were significantly lower compared with the Se− group. In total, changes of the levels of TSH ($r = -0.422$, $P = 0.035$), T3 ($r = -0.474$, $P = 0.015$) and T4 ($r = -0.444$, $P = 0.022$) were significantly correlated with the APACHE III score.
Figure 2 Correlation between the change in T4 and T3 levels between days 1 and 7. Correlation coefficient between T4 and T3 in Se+ \( (r = 0.799) \) and Se− \( (r = 0.693) \) patients.

\( P = 0.023 \) were negatively correlated with changes in APACHE III score between days 1 and 14. We separated those patients who clinically improved between days 1 and 14, evaluated by a decrease of more than five APACHE III score points, from patients without a decrease or with even an increase in their APACHE III score; independently of whether they received selenium or not. In patients whose condition improved, the total T3 \( (P = 0.046) \) and TSH \( (P = 0.016) \) significantly increased, whereas T4 remained constantly low \( (P = 0.245) \). These changes in T3 and TSH were identical in the Se+ and Se− groups (Fig. 3). In Se+ patients whose APACHE III score did not improve, T3 decreased between days 1 and 14 \( (P = 0.043) \), while the TSH levels decreased significantly in both Se+ \( (P = 0.043) \) and Se− group \( (P = 0.028) \) when APACHE III score did not improve. TSH levels significantly increased in Se+ when APACHE III score decreased between days 1 and 14 \( (P = 0.023) \).

Taking both selenium groups together, in patients whose condition improved, total T3 increased \( (P = 0.043) \) and APACHE III score decreased \( (P < 0.0001) \); in contrast, in patients whose condition did not improve, total T3 remained constant over the time period.

Discussion

In this prospective, randomized clinical intervention trial we showed that the characteristic changes in thyroid hormone metabolism are associated with the clinical course of the disease, but are not associated with either serum selenium levels or selenium-dependent GSH-Px activity. Overall, patients supplemented with higher doses of selenium had a better outcome in subgroups (21) and earlier normalization of thyroid hormone levels, but those patients who did not recover under selenium substitution also showed no recovery from NTI syndrome.

In our patients, total T4 and T3 levels were already low at admission to the intensive care unit and they are inversely correlated with the severity of the disease, as shown previously (29). TSH levels are also low, and are inversely correlated with the APACHE II score and mortality (30). Patients had a mortality rate of 40% as expected by the median APACHE II score of 18 (23). The selenium concentrations in the serum were also decreased to 60% compared with the normal, in agreement with previous studies (31, 20, 32).

In animal models, severe selenium deficiency or severe sepsis leads to a decreased activity of the selenoenzyme 5’-deiodinase type I in the liver (11, 28, 33, 34). A correlation between low selenium and low T3 has also been found in critically ill patients (17). Therefore, it has been concluded that low selenium might also lead to a decreased 5’-deiodinase activity followed by low T3 production in humans. This was supported by an interventional trial in trauma patients where it was shown that a substitution with sodium selenite normalizes total T3 levels earlier compared with controls (16). No correlation between low T3 and selenium levels, however, was found in other studies in critically ill patients (35, 36) or in the healthy population (37). In patients with subacute thyroiditis, selenium substitution had no influence on serum free T3, T4 or TSH levels (38, 39).

Selenium substitution might be beneficial to the patient, leading to a significantly lower incidence of renal failure, improved clinical outcome and reduced mortality in severely ill patients or patients with pneumonia (21). The majority of patients showing clinical improvement had received selenium; also thyroid hormone parameters normalized earlier in Se+ patients than in those who did not receive selenium. However, those patients who improved despite not receiving selenium also showed a normalization in thyroid hormones. In addition, the changes of T4 and T3 levels are closely linked to each other. Independent of selenium substitution (Fig. 2); the ratio of T4 and T3 also remained unchanged after selenium substitution. This clearly implicates that the low thyroid hormone levels are a consequence of the underlying condition and not of the low selenium level. Therefore, the influence of cytokines like interleukin-1, tumour necrosis factor or interferon, and glucocorticoids or drugs – and not the influence of diminished selenium levels – on 5’-deiodinase type I or II activity might be responsible for the low T3 levels in patients with low selenium levels.
severe sepsis (40, 41). All drugs including low-dose dopamine or hydrocortisone, however, were used in a similar way in both groups of patients. Therefore selenium substitution has no clinically important role as a parameter influencing thyroid hormone levels.

The selenium in human plasma is bound to selenoprotein P, GSH-Px and albumin (42). The activity of plasma GSH-Px is an indicator only for the availability of selenium in the kidney, because the extracellular GSH-Px is synthesized in the proximal tubular cells and depends on renal function. Circulating plasma selenium levels and GSH-Px activity may not reflect the total amount of selenium in the body; changes in tissue distributions and a hierarchy of availability for selenoenzymes exists (43). In selenium-deficient rats, GSH-Px activity declines first (44). A normal amount of type I 5'-deiodinase is expressed at selenium concentrations 10-fold below the minimal level necessary for GSH-Px expression (45). This is also supported by our study: despite diminished plasma selenium levels and diminished GSH-Px activity, the levels of T4 and T3 and the ratio of T4 to T3 remained unchanged even

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**Figure 3** Change of T3 and TSH with clinical course and selenium substitution. The difference in APACHE III score was calculated between days 1 and 14: patients who died are included in the group with increasing APACHE III score. T3 levels are significantly different at days 7 and 14 between patients with decreasing and increasing APACHE III scores (day 7, $P = 0.004$ in Se+ and $P = 0.055$ in Se-; day 14, $P = 0.031$ in Se+ and $P = 0.037$ in Se-).
in the control group whereas in the selenium substitution group of patients the plasma GSH-Px activity (as a measure of biologically available selenium) increased within 3 days of selenium substitution and the ratio of T4 to T3 remained constant. Therefore sufficient selenium in plasma leading to increased GSH-Px synthesis in the kidney did not lead to a change 5'-deiodinase activity in the liver.

The low TSH levels, despite low thyroid hormones in patients with non-thyroidal illness reflect an insensitivity of the TSH release. This insensitivity is also confirmed by the fact, that TSH response to TRH is lower in severely ill or fasting patients. The gene expression of TRH in the paraventricular nucleus is decreased in critically ill patients (13). Changes in thyroid hormone metabolism in the brain, cortisol or cytokines might be responsible for the low TRH mRNA expression (46). Thyroid hormones exert a negative feedback on the TRH expression. The 5'-deiodinase type II activity in the arcuate nucleus is increased in hypothyroidism; as 5'-deiodinase type II is also a selenium-dependent enzyme, low selenium could theoretically be responsible for a decreased activity. This would lead to decreased T3 production locally in the arcuate nucleus and an increase in TRH and TSH response. Therefore, low selenium cannot be responsible for the low TSH levels seen in critically ill patients. This is also supported by our findings that the change in TSH level is independent of selenium supplementation but follows clinical improvement.

As a consequence of clinical recovery, demonstrated by decreasing APACHE III score, the initially low TSH levels subsequently raise. This rise in TSH level is seen again in both Se+ and Se− patients, but only if the clinical condition improves. Therefore selenium substitution improves the clinical outcome and secondarily leads to normalization of thyroid hormone levels.

Subtle effects, however, might be missed by the influence of treatment. The treatment was identically in both groups of patients but included dopamine or hydrocortisone, which are known to have some influence on thyroid hormones.

In conclusion, we could not find significant results supporting the concept that selenium substitution in severe septic patients influences deiodinase activities or improves thyroid function directly. Selenium substitution ameliorates the clinical condition. As a consequence of the better clinical condition thyroid function normalizes.

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