
**PLASMA SELENIUM CONCENTRATIONS IN PATIENTS WITH EUHYROID SICK SYNDROME**

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We evaluated plasma selenium concentrations in patients with euthyroid sick syndrome express by low serum triiodothyronine (T<sub>3</sub>) concentrations. Selenium status in these patients was compared with that found in patients with both untreated and treated hypothyroidism. Selenium concentrations in plasma were significantly lower in hospitalized patients with either euthyroid sick syndrome (0.99 ± 0.37 μmol/L) or treated hypothyroidism (1.09 ± 0.25 μmol/L) than in patients with untreated hypothyroidism (1.39 ± 0.28 μmol/L). However, there was no significant, independent relationship between selenium and the thyroid function indices determined in this study. The strongest association was between serum albumin concentration and either selenium (r = 0.65), T<sub>3</sub> (r = 0.58), or the molar ratio of T<sub>3</sub> to thyroxine (r = 0.64). The decreased average selenium concentration appears to be associated with the hypercatabolic state of severely ill patients, as indicated by the serum albumin concentration; these patients should be considered for selenium supplementation and their selenium status should be monitored.

**Additional Keyphrases:** thyroid function · nutrition

Selenium is an essential trace metal for human metabolism and is required for the expression of glutathione peroxidase (GPX; EC 1.11.1.9) activity. It was shown recently that selenium is also present in Type I iodothyronine 5'-deiodinase found in mammalian tissue (2). This finding has rekindled interest in the role of selenium status in thyroid disease (2-4).

Many patients with the so-called euthyroid sick syndrome demonstrate decreased triiodothyronine (T<sub>3</sub>) concentrations in serum. Decreased peripheral conversion of thyroxine (T<sub>4</sub>) to T<sub>3</sub> in the absence of thyroid dysfunction, indicated by a normal thyrotropin (TSH) concentration, is thought to be responsible for this effect (5, 6). Many factors have been postulated to explain this inhibition of conversion, including abnormal protein binding (6).

We chose to study plasma selenium concentrations in patients with nonthyroid illness and both treated and untreated hypothyroidism who had decreased T<sub>3</sub> concentrations in serum. We evaluated the relationship of selenium concentrations to the degree of thyroxine conversion as reflected in the T<sub>3</sub>/T<sub>4</sub> ratio, in relation to other laboratory indices.

**Materials and Methods**

Sixty-seven patients having T<sub>3</sub> concentrations <1.43 nmol/L were selected for study. The patients were classified as euthyroid sick, treated hypothyroid, or untreated hypothyroid on the basis of medical and medication history, clinical diagnosis, and TSH concentrations. Reversal of the hypothyroid state was considered achieved if the TSH concentration was <10 IU/L in those patients being treated. Sixty-five apparently healthy hospital employees, ages 25-62 years, made up the healthy control group used for comparison of selenium concentrations.

T<sub>3</sub> and T<sub>4</sub> uptake (T<sub>3</sub>U) in serum were determined by fluorescence immunoassay with reagents and instrumentation obtained from Abbott Diagnostics (Abbott Park, IL) according to the manufacturer's protocol. The free thyroxine index (FT<sub>4</sub>I) was calculated as the ratio of T<sub>4</sub> to T<sub>4</sub> U; T<sub>3</sub> concentrations in serum were measured by radioimmunoassay with reagents from Diagnostic Products Corp. (Los Angeles, CA) according to the manufacturer's protocol. The molar ratio of T<sub>3</sub> to T<sub>4</sub> was calculated. The TSH concentration in serum was determined by time-resolved fluorescence immunoassay with reagents from Pharmacia (Columbia, MD). Albumin concentrations were determined by bromcresol green binding with a Boehringer Mannheim (Indianapolis, IN)
Selenium concentrations in plasma were measured with flame atomic absorption spectrometry with hydride generation (7, 8). One milliliter of plasma, separated from blood samples collected in EDTA anticoagulant tubes, was combined with 5.0 mL of concentrated nitric acid in a digestion flask and incubated at 50 °C for 1 h. We added 1 mL of 70% perchloric acid and boiled the mixture until the volume was reduced to 1.0 mL. We transferred the contents to graduated plastic tubes with rinsing and brought the volume to 2.5 mL with deionized water. We combined 0.5 mL of this solution with 10 mL of 20 mL/L HCl solution in the reaction flask of an MHS-10 hydride system (Perkin-Elmer Corp., Norwalk, CT) attached to a Perkin-Elmer 3030B atomic absorption spectrometer. Absorbance was measured at 196 nm after addition of sodium borohydride, 30 g/L, in 15 g/L sodium hydroxide reagent.

This method demonstrated a lower limit of detection of 0.06 μmol/L and an upper limit of linearity of 3.8 μmol/L. Standard curve regression correlation was 0.999. The within-run and run-to-run coefficients of variation were 3.5% and 6.3% at mean concentrations of 1.90 and 1.73 μmol/L, respectively. Recoveries varied from 98% to 103%. Average bias from target values for Standard Reference Material 2670 (National Institute of Standards and Technology, Gaithersburg, MD) and the 1990 serum selenium Quebec Interlaboratory Comparison Program was <5% for concentrations from 0.10 to 5.76 μmol/L.

The distribution of values obtained for each index was assessed with the Kolmogorov–Smirnov test and found to be not significantly different from a normal distribution (P < 0.05). Therefore, we used parametric statistics for data analysis. Differences between groups were evaluated with analysis of variance. Relationships between variables were evaluated with Pearson correlation and stepwise multiple-linear-regression procedures. Differences were considered significant at P < 0.05.

Results and Discussion

The distribution of laboratory values for the three patient groups in this study are shown in Table 1. The data for both T₃ and TSH are anticipated, because they were used as study selection and classification criteria. The total T₃/T₄ molar ratio was similar in both the treated hypothyroid and euthyroid sick groups, and both were significantly lower than those seen in either untreated hypothyroid patients or healthy control subjects (0.0203 ± 0.0082). As expected, results are consistent with the decreased conversion of T₄ to T₃ in euthyroid sick patients. Serum albumin concentrations are also clearly lower in both the treated hypothyroid and euthyroid sick groups than in the untreated hypothyroid patients. In the former two groups, 56% (28 of 50) of albumin concentrations were abnormally low (<35 g/L) at the time of sampling, whereas only 6% (1 of 17) of untreated hypothyroid patients exhibited decreased albumin concentrations.

The mean selenium concentrations were statistically different among groups (P = 0.001); both the euthyroid sick and treated hypothyroid groups exhibited selenium concentrations in plasma that were lower than those seen in patients with untreated hypothyroidism. The average selenium concentration in plasma of apparently healthy control subjects was 1.49 ± 0.32 μmol/L. There was no significant difference between selenium concentrations in plasma found in apparently healthy individuals and untreated hypothyroid patients. There is considerable overlap of selenium values among groups. The lower limit of the reference interval for plasma selenium was determined to be 0.85 μmol/L. None of the untreated hypothyroid patients had a value below this limit, whereas 20% and 31% of individuals with treated hypothyroidism and euthyroid sick syndrome, respectively, had values below the reference interval.

Table 1. Laboratory Values by Diagnosis, Mean (SD)

<table>
<thead>
<tr>
<th>No. patients</th>
<th>Hypothyroid, untreated</th>
<th>Hypothyroid, treated</th>
<th>Euthyroid sick</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. hospitalized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₄, nmol/L</td>
<td>42.2 (27.0)</td>
<td>107.2 (39.0)</td>
<td>82.6 (22.8)</td>
<td>0.049</td>
</tr>
<tr>
<td>FT₄, nmol/L</td>
<td>43.0 (28.5)</td>
<td>116.8 (41.8)</td>
<td>106.2 (23.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T₃, nmol/L</td>
<td>1.05 (0.32)</td>
<td>0.80 (0.31)</td>
<td>0.85 (0.33)</td>
<td>0.091</td>
</tr>
<tr>
<td>TSH, IU/L</td>
<td>85.8 (65.3)</td>
<td>2.3 (2.8)</td>
<td>2.3 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T₃/T₄*</td>
<td>33.2 (1.97)</td>
<td>7.3 (0.29)</td>
<td>9.9 (0.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Selenium, μmol/L</td>
<td>1.39 (0.28)</td>
<td>1.09 (0.25)</td>
<td>0.99 (0.37)</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>42.4 (0.45)</td>
<td>34.5 (4.9)</td>
<td>31.3 (8.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Analysis of variance.

** × 10³
The relationship between plasma selenium and albumin has also been described in intensive care patients (9). It is clearly a part of the overall syndrome exhibited by patients hospitalized with severe illness or after major surgery, regardless of the primary diagnosis (6). The patients in this study suffered from a variety of conditions at the time of sampling, including cardiac disease, diabetes, major surgery, organ transplantation, and sepsis.

The similarity between the patients in this study with euthyroid sick syndrome and those patients treated with levothyroxine is undoubtedly a reflection of the fact that 88% (44 of 50) of patients in both groups were hospitalized with significant illness. In contrast, 35% (6 of 17) of untreated hypothyroid patients were hospitalized and the disease expression was apparently less severe. For the indices evaluated in this study, it can be concluded that the euthyroid sick syndrome designation applies equally well to severely ill hypothyroid patients treated with levothyroxine.

We chose to measure selenium in plasma rather than in whole blood to assess the more rapid changes in selenium status that could occur in plasma when compared with erythrocyte concentrations. Plasma selenium concentrations have been shown to be responsive to dietary selenium intake or supplementation (10, 11). Although a relationship between selenium concentrations in whole blood and thyroid function indices may have been missed, it is unlikely that concentrations in the erythrocyte fraction would change more significantly than those in plasma in the time frame involved. In addition, many of these patients underwent multiple blood transfusions, which would easily obscure the initial erythrocyte selenium status. The failure to identify an independent relationship between selenium in plasma and thyroid function studies could also have resulted from the inability of plasma concentrations at a given time to reflect tissue concentrations because of a negative balance of intake and elimination during the elapsed time since the onset of hospitalization (12).

The effect of dietary intake on plasma selenium status cannot be overemphasized. The patients in this study...
exhibited a wide variation in dietary status, including tube feeding, total parenteral nutrition, and normal meal consumption. It also did not appear that the adequacy of diet corresponded just to length of hospitalization. The variation in plasma selenium concentration seen in the three patient groups could be more dependent on variation of dietary intake than on other factors, and this can only be confirmed by strictly controlled intake studies. Nonetheless, proper selenium nutrure both before and during hospitalization may be required to prevent the decreased selenium concentrations observed here. This diet dependency may exist regardless of the disease present at admission.

This study has confirmed the incidence of decreased selenium status in severely ill patients. It is interesting to note, however, that there remains overlap of selenium concentrations observed in patients with the euthyroid sick syndrome and apparently healthy control subjects. Nonetheless, there is clearly an increased incidence of abnormally decreased selenium concentrations in the hospitalized groups. Selenium is considered an important antioxidant component of plasma and tissues. Therefore, its loss could result in an increased risk of oxidative damage from oxygen-derived free radicals. Initial investigations have also demonstrated reductions of plasma glutathione peroxidase activity in patients with severe illness (13).

The implications of these findings on strategies for selenium supplementation and monitoring in severely ill patients appear obvious. Only a small number of the patients in this study had received total parenteral nutrition without selenium supplementation. Although it has proved difficult to accurately correct the decreased selenium status in critically ill patients (9), continued monitoring of the selenium status in these patients appears warranted and should be encouraged as a means to support efforts to improve treatment of these adverse changes by appropriate nutritional support.

References

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Comparison of Assay Kits for Unconjugated Estriol Shows That Expressing Results as Multiples of the Median Causes Unacceptable Variation in Calculated Risk Factors for Down Syndrome

Tim Reynolds1 and Rhys John

We compared the performance of two methods for assaying unconjugated estriol in serum: the modified Amerlex third-trimester RIA kit, as used in seminal papers on unconjugated estriol in Down syndrome screening, and the new optimized Amerlex-M second-trimester kit. The significant difference between the results of each assay could cause unacceptable changes in the detection rate and false-positive rate of Down syndrome screening programs, especially if previously published values for estriol are used in the risk calculation. It is not possible to define new calculation parameters for every assay kit because new parameters will need to be defined every time kit changes occur, which would require a large collection of samples from Down syndrome pregnancies for standardization. Possible solutions to this problem are discussed.


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