Increased transforming growth factor-β1 plasma concentration is associated with high plasma 3,3′,5′-tri-iodothyronine in elderly patients with nonthyroidal illnesses

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Abstract

Objective: To study transforming growth factor-β1 (TGF-β1) plasma concentrations in elderly patients with nonthyroidal illnesses (NTI).

Design: Case-control study.

Methods: We measured plasma concentrations of tri-iodothyronine (T₃), reverse T₃ (rT₃), thyroxine (T₄), free T₃ (fT₃) and free T₄ (fT₄) estimates, TSH, and TGF-β1 in 48 elderly NTI patients consecutively admitted in our Division of Internal Medicine and Metabolic Diseases, and in 11 healthy age- and sex-matched controls.

Results: The data on thyroid hormones enabled us to identify three groups: Group A, subjects (8 patients) with T₃ and fT₃ levels comparable to those in controls; Group B, subjects (30 patients) with T₃ and fT₃ levels lower than controls but rT₃ levels comparable to those of controls; Group C, subjects (10 patients) with T₃ and fT₃ levels lower than those of controls and higher rT₃ levels. The patients of Group C showed higher plasma levels of TGF-β1 compared with controls. Moreover, we found a positive correlation between TGF-β1 and rT₃ (rₛ = 0.38, P < 0.01) in the whole group of NTI patients.

Conclusions: Our data seem to confirm the hypothesis that TGF-β1 could play a role in the pathogenesis of some modifications of thyroid function observed in patients with nonthyroidal illnesses.

European Journal of Endocrinology 138 47–50

Introduction

In elderly patients with nonthyroidal illnesses (NTI), decreased plasma tri-iodothyronine (T₃) and free T₃ (fT₃), and increased plasma reverse T₃ (rT₃) levels are frequently observed, while thyrotropin (TSH) usually remains normal. These changes in thyroid hormone metabolism are referred to as the ‘sick euthyroid syndrome’. The lower T₃ and higher rT₃ plasma values are determined by a lower T₃ production rate and a decreased rT₃ clearance rate due to diminished iodothyronine 5′-deiodinase activity (1).

Cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interferon-γ (IFN-γ), have recently been shown to have an inhibitory influence on the hypothalamic–pituitary–thyroid axis in vivo and in vitro. In particular these cytokines inhibit [¹²⁵I]iodide transport and organification and type I deiodinase in rat thyroid cells (2–5). Several authors have indicated TNF-α, IL-1, IL-6, and acid and basic fibroblast growth factor as putative mediators of the modifications in thyroid function observed in NTI patients (6–9). Elsewhere we reported on the links between the low T₃ syndrome and erythropoietin and TNF-α plasma concentrations in NTI patients (10).

Transforming growth factor-β1 (TGF-β1) is a cytokine that inhibits in vitro growth, differentiation and 5′-deiodinase activity in thyroid cells (5, 11). These findings allowed us to hypothesize that TGF-β1 could play a role in the pathogenesis of the thyroid dysfunction of NTI patients. In order to verify this hypothesis, we evaluated TGF-β1 plasma concentrations and thyroid function tests in elderly patients with a variety of nonthyroidal illnesses.

Subjects and methods

Our series consisted of 60 elderly informed consent patients with nonthyroidal illnesses consecutively admitted in our division. Patients with thyroidal, hypophsyal or hypothalamic disease (n = 7), those on drugs affecting the metabolism or regulation of thyroid and pituitary hormones (i.e. glucocorticoids,
propranolol, amiodarone, estrogens and antiepileptics) 
\((n = 3)\), and those treated with cytokines (i.e. IL-2 or 
IFN-α in malignant tumors) \((n = 2)\), were excluded 
from the study. The remaining 48 patients (23 females, 
25 males; mean age 73.1 ± 5.4 years) were not on 
dopamine and/or drugs known to interfere with thyroid 
hormone assays, and presented with the following 
diagnoses: 10 congestive heart failure (CHF), 14 
diabetes mellitus in a poor metabolic control (NIDDM), 
10 chronic liver disease (CLD), 8 chronic renal 
failure (CRF), and 6 neoplasia. The control group 
consisted of 11 age- and sex-matched healthy subjects. 
Nutritional status was evaluated in all subjects by 
the measurement of the following parameters: body 
mass index, lymphocytes, serum iron, hemoglobin, 
plasma albumin, transferrin and cholesterol. Plasma 
mass index, lymphocytes, serum iron, hemoglobin, 
thyroid function and plasma TGF-β1 levels.

Plasma T3, thyroxine (T4), TSH, fT3, and free T4 (fT4) 
estimates were evaluated with an ELISA kit (Enzy-
mun Test, Boehringer Mannheim Immunodiag-
nostics, Milan, Italy). The interassay variation for the 
TGF-β1 method was 5.2% at 1.44 ng/ml and 4.8% at 
3.1 ng/ml. The intraassay variation was 5.2% and 4.8% 
respectively.

Statistical analysis was performed using the Kruskal– 
Wallis nonparametric test because data did not involve 
distributional assumptions. Spearman’s correlation 
coefficient was used for evaluation of the relationship 
between TGF-β1 and thyroid function parameters. Data 
were expressed as mean ± s.d. or median with 25th and 
75th percentiles when appropriate. Values of 
P < 0.05 were considered significant.

Results

The data on thyroid hormones allowed us to identify 
the following groups: Group A, subjects (8 patients) 
with T3 and fT3 estimate levels comparable to those 
in controls; Group B, subjects (30 patients) with T3 and 
fT3 estimate levels lower than controls but rT3 levels 
comparable to those of controls; Group C, subjects (10 
patients) with T3 and fT3 estimate levels lower than 
those of controls, and higher rT3 levels (Table 1).

Diagnoses of patients’ illnesses in the groups studied 
were: Group A: three NIDDM, one CHF, two CLD, one 
CRF and one neoplasia; Group B: ten NIDDM, seven 
CHF, four CLD, six CRF and three neoplasia; Group C: 
one NIDDM, two CHF, four CLD, one CRF and two 
neoplasia.

The patients of Group C showed significantly higher 
TGF-β1 levels with respect to controls (Table 1). Data 
values for plasma TGF-β1 in the groups studied are 
shown in Fig. 1.

No statistically significant difference was found, 
amongst the groups studied, as regards the nutritional 
status.

Spearman’s correlation analysis performed on the 
whole group of NTI patients showed a positive correla-
tion between TGF-β1 and rT3 \((r_5 = 0.38, P < 0.01)\) 
(Fig. 2). This correlation was not found within each 
group. No correlation was detectable between TGF-β1 
and T3, T4, fT3 and fT4 estimates, and TSH.

Furthermore, when we divided NTI patients in 
subgroups according to their diagnoses, in order to 
investigate whether any of the underlying illnesses 
could affect plasma TGF-β1 levels regardless of the 
thyroid status, no statistically significant differences 
were found amongst the subsets of NTI patients for both 
thyroid function and plasma TGF-β1 levels. Moreover, 
within the diagnosis subgroups, no correlation was 
found between TGF-β1 plasma concentrations and rT3, 
T3, T4, fT3 and fT4 estimates, and TSH.

Table 1 General characteristics, thyroid function and TGF-β1 plasma levels in 48 consecutive elderly patients with nonthyroidal illness and in 11 healthy subjects. Data are expressed as median, with 25th and 75th percentiles (the interquartile range) in parentheses (Kruskal–Wallis test). Group A: T3, fT3 and rT3 levels comparable to those of controls. Group B: low T3 and fT3 levels but normal rT3 compared with controls. Group C: low T3 and fT3, and high rT3 levels compared with controls.

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Controls ((n = 11))</th>
<th>Group A ((n = 8))</th>
<th>Group B ((n = 30))</th>
<th>Group C ((n = 10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± s.d.)</td>
<td>–</td>
<td>72.3 ± 6.5</td>
<td>71.9 ± 6.3</td>
<td>73.1 ± 5.3</td>
<td>73.8 ± 5.3</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/5</td>
<td>5/3</td>
<td>14/16</td>
<td>6/4</td>
<td></td>
</tr>
<tr>
<td>rT3 (ng/ml)</td>
<td>0.09–0.35</td>
<td>0.19 (0.12–0.21)</td>
<td>0.16 (0.14–0.20)</td>
<td>0.15 (0.13–0.21)</td>
<td>0.48±0.1 (0.37–0.65)</td>
</tr>
<tr>
<td>T3 (nmol/l)</td>
<td>1.20–2.70</td>
<td>1.40 (1.30–1.40)</td>
<td>1.50 (1.35–1.55)</td>
<td>1.20±0.1 (1.10–1.20)</td>
<td>1.20±0.1 (1.00–1.20)</td>
</tr>
<tr>
<td>T4 (nmol/l)</td>
<td>50.0–151.0</td>
<td>90.0 (71.2–102.9)</td>
<td>89.4 (77.2–96.5)</td>
<td>84.9 (77.2–95.2)</td>
<td>91.4 (87.5–95.2)</td>
</tr>
<tr>
<td>fT3 estimate (pmol/l)</td>
<td>5.40–9.30</td>
<td>7.40 (6.91–7.68)</td>
<td>6.83 (6.45–7.68)</td>
<td>6.30±0.1 (6.00–6.45)</td>
<td>6.00±0.1 (5.53–6.30)</td>
</tr>
<tr>
<td>fT4 estimate (pmol/l)</td>
<td>11.8–24.6</td>
<td>16.1 (12.3–20.1)</td>
<td>15.4 (14.4–15.8)</td>
<td>15.7 (13.2–17.2)</td>
<td>15.8 (14.5–16.6)</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>0.23–4.00</td>
<td>1.05 (0.61–2.00)</td>
<td>1.05 (0.86–1.40)</td>
<td>1.00 (0.70–1.90)</td>
<td>0.98 (0.55–1.50)</td>
</tr>
<tr>
<td>TGF-β1 (ng/ml)</td>
<td>28.0–157.0</td>
<td>42.5 (25.0–80.0)</td>
<td>47.5 (35.0–57.5)</td>
<td>34.0 (22.5–59.0)</td>
<td>112.5±19.1 (80.0–157.0)</td>
</tr>
</tbody>
</table>

\(^a\) \(P < 0.001\), \(^b\) \(P < 0.05\) vs controls; \(^c\) \(P < 0.001\), \(^d\) \(P < 0.01\), \(^e\) \(P < 0.05\) vs group A; \(^f\) \(P < 0.001\), \(^g\) \(P < 0.01\) vs group B.
Discussion

Our findings confirm that elderly NTI patients have an altered endocrine thyroid function. In fact, 40 of the 48 subjects examined had reduced $T_3$ concentrations, and 10 of these had a typical ‘low $T_3$ syndrome’, with an increase in $rT_3$ concentrations.

The main findings in our study were the higher TGF-$\beta_1$ levels in patients with low $T_3$ syndrome and the direct correlation between TGF-$\beta_1$ and $rT_3$ found in the whole group of NTI patients. This could lead us to hypothesize a causative role for TGF-$\beta_1$ in mediating some of the alterations in thyroid function observed in NTI patients.

Although TGF-$\beta_1$ shows a regulatory action on the growth and differentiation of thyroid cells (12), and a powerful inhibitory action on type I deiodinase in vitro (5, 11), little is known about the effect of this cytokine on thyroid function in vivo. Moreover, only the NTI patients with low $T_3$ syndrome (Group C), in which a reduced $5'$-deiodinase activity was generally shown, had higher TGF-$\beta_1$ plasma levels. The lower $T_3$ and higher $rT_3$ levels found in this group could represent, at least in part, a consequence of an inhibitory effect of TGF-$\beta_1$ on type I deiodinase in vivo, as also suggested by the direct correlation found between TGF-$\beta_1$ and $rT_3$ in the whole group of NTI patients. On the other hand, the lack of correlations when the groups are considered separately apparently rules out the possibility that the peculiar endocrine status of the patients of each group could affect TGF-$\beta_1$ plasma concentrations. The direct correlation found only in the whole group of NTI patients seems to indicate a major influence of chronic diseases on TGF-$\beta_1$ plasma concentrations. The direct correlation found only in the whole group of NTI patients seems to indicate a major influence of chronic diseases on TGF-$\beta_1$ plasma levels. Regarding the high concentrations of TGF-$\beta_1$ in Group C patients, it cannot be ruled out that this may depend on the greater severity of the disease in these subjects. This could have caused an increase in the plasma concentrations of TGF-$\beta_1$, which could in turn have determined the particular endocrine pattern of ‘sick euthyroid syndrome’ found by us.
Moreover, the recent finding that TGF-β1 expression is induced by TNF-α and IL-1β in rat pulmonary arterial endothelial cells (13) suggests that TGF-β1 expression could be stimulated by these cytokines also in other cell lines. This hypothesis has been confirmed in vitro in aged FRTL-5 rat thyroid cells, in which TNF-α-induced TGF-β expression is increased at the transcriptional level (14). These findings suggest another interpretation of our data. Since several authors have indicated TNF-α, IL-1, and other cytokines as putative mediators of the modifications in thyroid function observed in NTI patients (6–9), and higher TNF-α levels were found in NTI patients with alterations of thyroid function (8), one could hypothesize that the inhibitory action of TNF-α on thyroid function is not only a direct one, but could also be mediated by other cytokines, such as TGF-β1.

Norr can it be ruled out that the effect of TGF-β1 on thyroid hormones may be mediated by other cytokines, such as IL-6, which are known to affect thyroid function (7). Stouthard et al. (15), for example, have shown in humans that chronic IL-6 administration triggers a reduction in the plasma T1 concentrations and increases rT3 and T4. As TGF-β1 can induce IL-6 expression (16, 17), it appears likely that the effects of TGF-β1 on thyroid function are, at least in part, mediated by IL-6; anyway, findings obtained under different experimental conditions led us to hypothesize a more complex modulatory effect of TGF-β1 on IL-6 expression (18).

Our observations, together with the previously reported in vitro findings, suggest that some of the alterations in thyroid function parameters in nontoxic thyroidal illnesses may be related to higher TGF-β1 plasma concentrations.

References

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Received 15 May 1997
Accepted 26 August 1997