Involvement of circulating interleukin-6 and its receptor in
the development of euthyroid sick syndrome in patients with
acute myocardial infarction

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Abstract

Objective: In patients with acute myocardial infarction (AMI), low triiodothyronine (T3) levels with
normal or subnormal levels of thyrotropin (TSH), the euthyroid sick syndrome (ESS), have been
reported, however, the mechanism of altered thyroid hormone metabolism is unknown. Recent reports
have shown that interleukin-6 (IL-6) plays a key role in the pathogenesis of AMI and ESS. This
preliminary study investigates the relationship between thyroid states and plasma levels of IL-6, the
soluble IL-6 receptor (sIL-6R), and the soluble transducing 130 kDa glycoprotein (sgp130) in AMI.

Design and methods: We measured the concentration of TSH, free T3 (FT3), free thyroxine (FT4), IL-6,
sIL-6R and sgp130 in plasma from 24 patients with AMI and 20 normal controls.

Results: All 24 AMI patients showed significantly lower concentrations of FT3 with normal or
subnormal levels of TSH, and higher concentrations of IL-6 and sIL-6R than controls. IL-6 level
was correlated with creatine phosphokinase (CPK) and FT3 levels but not with FT4 or TSH levels in
patients with AMI. The time course of IL-6 and FT3 concentration seemed to be closely linked. sIL-6R
level was correlated with CPK and sgp130 levels, but not with FT3, FT4 or TSH levels. FT4 level was
 correlated with sgp130 level.

Conclusion: Patients with AMI develop ESS through activation of IL-6 and its receptor system.

Introduction

Alterations in thyroid hormone metabolism occur in
patients with acute myocardial infarction (AMI) (1–5).
This phenomenon, called euthyroid sick syndrome
(ESS), is observed in patients with systemic diseases
and may have a protective function (6, 7). It has
recently been hypothesized that interleukin-6 (IL-6), a
pleiotropic cytokine, has a causal role in the develop-
ment of ESS in patients with systemic diseases (8–15).
There is also increasing evidence to support IL-6
induction in AMI (16–19), and myocardial ischemia–
reperfusion-induced IL-6, IL-6 receptor and gp130
expression in rats (20). These data suggest that the
low triiodothyronine (T3) syndrome in AMI may partly
be explained by an elevation of circulating IL-6. Binding
of IL-6 to the soluble IL-6 receptor (sIL-6R) inhibits
thyroid function, however, gene expression of IL-6 and
gp130 but not IL-6R has been shown in human thyroid
follicles (21). Thus, IL-6 may exert an inhibitory effect
on thyroid function mainly through binding of the IL-
6–sIL-6R complex to gp130. Recent data suggest that
sIL-6R potentiates the antagonistic activity of soluble
gp130 (sgp130) on IL-6 responses (22). In the case of
ESS, there has so far been no investigation of the
relationship between thyroid function, IL-6, and its
receptor system, sIL-6R and sgp130. This preliminary
study is the first report of close linking between thyroid
function and the IL-6 binding system in patients with
AMI.

Materials and methods

Patients and specimens

Twenty-four patients (20 men, 4 women; 45–79 years)
admitted to Fujioka Hospital within 6 h of the onset of
AMI symptoms and 20 healthy controls (16 men, 4
women; 45–55 years) were enrolled after informed
consent was obtained. In patients with AMI, informed
consent was obtained on admission and percutaneous
transluminal coronary angioplasty (PTCA) was per-
formed immediately. Subjects were free of collagen
diseases, liver disease, renal failure, malignancy.
Measurement of plasma contents

IL-6 concentration was measured by a chemiluminescent enzyme immunoassay kit (Fujirebio, Tokyo, Japan). Soluble IL-6 receptor concentration was measured by an enzyme-linked immunosorbent assay (Bender Medsystems, Vienna, Austria). Soluble gp130 concentration was measured by an immunoenzymometric assay (Medgenix Diagnostics S.A., Fleurus, Belgium). Normal ranges were as follows: IL-6, <1.5 pg/ml; sIL-6R, 25–91 ng/ml; and sgp130, 280–620 ng/ml. Thyrotropin (TSH), free T3 (FT3), and free thyroxine (FT4) concentrations were measured by enzyme immunoassays (Sanyokasei, Kyoto, Japan). CPK and LDH concentrations were measured by autoanalyzer.

Statistical analysis

Data are presented as means ± s.d. Statistical analysis was performed using Student's unpaired t-test or linear regression. A level of P < 0.05 was accepted as significant.

Results

In all 24 patients with AMI the mean overall plasma levels of CPK, IL-6 and sIL-6R were significantly increased, while the FT4 level was significantly decreased compared with controls (Table 1). TSH and FT3 levels were decreased after onset of AMI, and both subsequently recovered to the normal range. In patients with AMI, the minimum levels of TSH were significantly decreased (P<0.05, 0.64±0.15 μU/ml; 25±11 h after onset of AMI) compared with controls. Circulating levels of IL-6 were already elevated at admission, then increased to the maximum level. The time course of IL-6 and FT3 concentration seemed to be closely linked (Fig. 1A). IL-6 concentration had increased maximally (50±24 pg/ml) 75±46 h after onset of AMI, while FT3 concentration had decreased minimally (1.4±0.4 pg/ml) 76±43 h after onset of AMI. Two patients showed subnormal levels of FT4, but no overall significant decline was observed compared with controls. The plasma levels of sIL-6R and sgp130 gradually decreased from admission to the end of the study. In AMI patients, the FT3 level was subnormal, but both TSH and FT4 levels were within the normal or subnormal range (Table 1). This hormonal state was characteristic of ESS.

The CPK level was positively correlated with IL-6 (Fig. 2A) and sIL-6R (Fig. 2D) levels. IL-6 concentration was inversely related to FT3 concentration (Fig. 2B) and FT3/FT4 ratio (Fig. 2C), but not to FT4 or TSH levels in AMI. The sIL-6R level was negatively correlated with sgp130 level (Fig. 2E), but not with TSH, FT3, or FT4 levels in AMI. Plasma levels of sgp130 were the same as control levels (Table 1), and a significant relationship was detected between sgp130 and FT4 levels in AMI (Fig. 2F). These significant relationships were obtained by analysis of overall data from admission to 120 h after onset of AMI. Then we analyzed these data according to the time after onset of AMI (group 1: 12 h and 24 h after onset of AMI; group 2: 36 h and 48 h after onset of AMI; group 3: 60 h and 72 h after onset of AMI; group 4: 84 h and 96 h after onset of AMI; group 5: 108 h and 120 h after onset of AMI). The IL-6 level was negatively related to TSH level (Fig. 1B) in group 1, but no significant relationship was detected between IL-6 and TSH levels in other groups. On the other hand, the IL-6 level was negatively correlated to FT3 level and FT3/FT4 ratio in all groups (P<0.05, respectively; total data are shown in Fig. 2B and C). Similarly significant relationships between sIL-6R and sgp130 levels, and between sgp130 and FT4 levels were detected in all groups (P<0.05, respectively; total data are shown in Fig. 2E and F).

Discussion

This preliminary study indicates that IL-6 and sIL-6R may be pathogenic factors in the development of ESS in AMI.
Recent reports have shown a negative correlation between T3 and T4 levels and the level of IL-6 (8, 13–15). IL-6 given to cancer patients decreases serum T3 and TSH levels, but not T4 level (23). Production of IL-6 is induced by IL-1 or tumor necrosis factor α (TNFα) (24), and a direct effect of IL-1 and TNFα on thyroid function has been reported (25–30). Administration of IL-1 and TNF to rodents or humans causes ESS (25, 26, 31). These cytokines may assist in the onset of ESS in AMI, although we did not determine plasma levels of them. IL-6 is produced by many cell types, including monocyte/macrophages, fibroblasts, endothelial cells, mast cells, neutrophils, keratinocytes, and osteoblasts (32). Expression of IL-6 mRNA has been confirmed in cultured thyroid follicles (21) and ventricular myocytes (19). Recently, induction of IL-6, IL-6R, and gp130 expression in rats cardiomyocytes after reperfusion from brief ischemia has been shown (20). In patients with AMI significant correlation between levels of CPK and both IL-6 and sIL-6R on thyroid function has been reported (25–30). Administration of IL-1 and TNF to rodents or humans causes ESS (25, 26, 31). These cytokines may assist in the onset of ESS in AMI, although we did not determine plasma levels of them. IL-6 is produced by many cell types, including monocyte/macrophages, fibroblasts, endothelial cells, mast cells, neutrophils, keratinocytes, and osteoblasts (32). Expression of IL-6 mRNA has been confirmed in cultured thyroid follicles (21) and ventricular myocytes (19). Recently, induction of IL-6, IL-6R, and gp130 expression in rats cardiomyocytes after reperfusion from brief ischemia has been shown (20). In patients with AMI significant correlation between levels of CPK and both IL-6 and sIL-6R suggest that both IL-6 and sIL-6R in AMI patients are released from both inflammatory cells and cardiomyocytes. In addition, the time course of IL-6 and FT3 seemed to be closely linked and a strong relationship between IL-6 and FT3 was detected in AMI. These findings suggest involvement of IL-6 and its receptor system in the pathogenesis of ESS in patients with AMI. Thus acute cardiac damage may affect thyroid states through activating IL-6 and its receptor system in AMI.

Yamazaki et al. (1996) could not detect IL-6 receptor mRNA in cultured human thyroid follicles, and they indicated that sIL-6R exerted the inhibitory effects of

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**Figure 1** (A) Time course of interleukin-6 (IL-6) and free triiodothyronine (FT3) concentration in patients with acute myocardial infarction (AMI). Presented data are mean (±S.D.) values of IL-6 and FT3 concentration. ○: circulating IL-6 concentration; ●: circulating FT3 concentration. (B) Relationship between IL-6 and FT3 within 24 h after onset of AMI. Presented points show respective values of 48 blood samples obtained from 24 patients with AMI at first 12 and 24 h after onset of AMI.

\[ Y = -0.021x + 1.1 \]

\[ r^2 = 0.1 \]

\[ P < 0.05 \]
IL-6 on thyroid cells (21). All of our patients with AMI showed elevated levels of sIL-6R, yet no significant correlation between sIL-6R and TSH, FT₃, or FT₄ was detected. In this regard, elevated sIL-6R levels may be necessary but insufficient alone to exert the inhibitory effects of IL-6. Further study is required to determine the role of sIL-6R in the pathogenesis of ESS.

The IL-6–sIL-6R complex affects thyroid function in cultured human thyroid follicles through binding to gp130 (21). Muller-Newen et al. (1998) reported that sgp130 antagonizes the effect of the IL-6–sIL-6R complex and that this antagonistic effect is enhanced by sIL-6R in cells lacking membrane-bound IL-6R (22). Thus sgp130 may antagonize the inhibitory effects of IL-6 binding to sIL-6R on thyroid function in thyroid follicles that lack IL-6R (21). This hypothesis is supported by the result that elevation of IL-6 and sIL-6R and normal levels of sgp130 were detected in AMI. The negative relationship between sIL-6R and sgp130 also supports the hypothesis. In this regard, the positive relationship between sgp130 and FT₄ might be caused by an inhibitory action of sgp130 on the IL-6–sIL-6R complex. Two questions remain unanswered. Does sgp130 antagonize the inhibitory effects of the IL-6/sIL-6R complex? And does sIL-6R enhance the antagonistic effects of sgp130 on thyroid cells?

Administration of IL-6 briefly but significantly decreased TSH levels in cancer patients (23). In our study, the plasma level of TSH was significantly decreased after the onset of AMI and then recovered, similar to the findings of Stouthard et al. (1994). Additionally, TSH level was negatively correlated to IL-6 level in the first 24 h after onset of AMI. These facts suggest that the decline in plasma TSH was also associated with an elevated IL-6 level. The gradual recovery of plasma TSH, however, occurred whilst plasma IL-6 was still elevated. This may suggest that circulating TSH is affected by IL-6 and other factor(s) in AMI. TSH is a key factor which stimulates thyroid hormone production and release by thyroid cells. The low circulating level of FT₃ cannot be explained by the negative correlation between FT₃ and sgp130 level.
changes in TSH alone in patients with AMI. Thus, IL-6 may affect thyroid metabolism at both pituitary and thyroid levels.

Patients with a decrease in serum T₄ alone, representing the mildest form of ESS, do not show clinical signs of hypothyroidism (7). IL-6 inhibits thyroid hormone conversion of T₄ to T₃ by blocking 5'-deiodinase activity or mRNA expression (9, 33, 34), suggesting that the development of ESS in AMI is induced by an effect of IL-6 on both the pituitary–thyroid axis and peripheral conversion of thyroid hormone. Altered thyroid hormone homeostasis in ESS is related to an increase in reverse T₃ (rT₃) levels (7, 8, 23). We did not determine circulating levels of rT₃, however, the fact that FT₃, but not FT₄, decreased significantly might suggest an increase in rT₃ levels in AMI. In this regard, the negative relationship between IL-6 level and FT₃/FT₄ ratio represents the mildest form of ESS in AMI. In some conditions, there is a gradual progression from a low T₃ level to an advanced illness with extremely low T₃ and T₄ levels, which can be associated with high mortality (7). Similarly excessive decreases of T₄ are linked with increasing mortality in AMI (4, 35). In this study two patients with subnormal levels of FT₄ were graded Killip IV (Killip’s classification). Circulating levels of FT₃ and FT₄ in patients with AMI classified Killip IV were significantly lower than those of Killip I (Table 2), and those patients received catecholamine treatment. These findings support the idea that excessive decreases of T₄ are linked with seriousness of AMI. In this regard, catecholamine administration might affect circulating levels of FT₄ in AMI, similar to findings of former investigations (36, 37). Previous reports have not defined a role for IL-6 in progression to low circulating levels of T₄. In this regard, the positive relationship between sgp130 and FT₄ levels may reflect a self-protective action for providing progression of low FT₄ in AMI. This raises the question of whether circulating levels of FT₄ relate to sgp130 in severe cases of AMI.

In conclusion, our results suggest that acute cardiac damage leads to development of ESS through activation of IL-6 and its receptor system.

Table 2 Circulating levels of thyroid hormone, interleukin-6 and its receptor, and Killip’s classification on admission in patients with acute myocardial infarction.

<table>
<thead>
<tr>
<th>Killip I</th>
<th>Killip II</th>
<th>Killip III</th>
<th>Killip IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (μU/ml)</td>
<td>1.1 ± 0.5</td>
<td>1.0 ± 0.5</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td>FT₃ (pg/ml)</td>
<td>2.4 ± 0.4</td>
<td>2.3 ± 0.5</td>
<td>2.4 ± 0.5</td>
</tr>
<tr>
<td>FT₄ (ng/dl)</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>12.5 ± 10.1</td>
<td>13.2 ± 9.2</td>
<td>15.2 ± 13.0</td>
</tr>
<tr>
<td>sIL-6R (pg/ml)</td>
<td>146.6 ± 78.2</td>
<td>133.2 ± 62.2</td>
<td>141.2 ± 87.3</td>
</tr>
<tr>
<td>sgp130 (pg/ml)</td>
<td>869.2 ± 180.1</td>
<td>702.4 ± 193.8</td>
<td>583.6 ± 184.4</td>
</tr>
</tbody>
</table>

Data are presented as means ± s.d. * P < 0.05, Killip I vs Killip IV. Values for respective parameters were evaluated by measurement of plasma content on admission in patients with AMI.

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T Kimura and others

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