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Serum IL-6 and TNF- α in Patients With Thyroid Disorders

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Abstract: The study was designed to evaluate IL-6 and TNF- α levels and to examine their relationship in 27 patients with hyperthyroidism, 23 with hypothyroidism, and 18 with normal thyroid functions. Mean serum levels of IL-6 and TNF- α in patients with untreated hyperthyroidism were higher than those of control group ($p < 0.001$ for both). However, these values were lower in hypothyroidism than in the controls ($p < 0.01$, $p < 0.001$, respectively). After treatment, both of the patients groups had IL-6 and TNF- α values in accordance with those of controls and these values were decreased in hyperthyroid patients ($p < 0.01$), but increased in hypothyroid ones ($p < 0.05$). There were significant correlations between before and after treatment serum IL-6 and TNF- α values in hyperthyroid patients

($r = 0.787$, $r = 0.692$, respectively) and between before and after treatment serum IL-6 and TNF- α in hypothyroid patients ($r = 0.723$, $r = 0.552$, respectively). There were significant correlations between serum IL-6 and TNF- α in control subjects ($r = 0.425$).

We concluded that serum IL-6 and TNF- α are increased in patients with hyperthyroidism, but decreased in patients with hypothyroidism subjects, and become normal by successful surgical treatment or ten or more months after medical treatment.

Key Words: Hyperthyroidism, hypothyroidism, IL-6, TNF- α

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Introduction

Most cytokines are multifunctional. It is also apparent that certain biologic functions are shared by cytokines with distinct structural properties, and that many biologic actions *in vivo* are the result of synergistic or antagonistic actions involving two or more cytokines. Cytokines are likely to play an important role in autoimmune thyroid disease. These molecules, produced by thyroid follicular cells, are essential for T and B cell growth and differentiation (1,2).

IL-6 is a 26 kD protein released by fibroblasts, T lymphocytes, endothelial cells, monocytes (3). It is a pleiotropic cytokine exerting multiple biologic activities on different types of target cells including induction of B cell differentiation (4), stimulation of myeloma, hybridoma and plasmacytoma growth (5), activation of T cells-thymocytes (6), induction of acute phase proteins (7), stimulation of hemopoietic precursor cell growth and differentiation (8), induction of myelomonocytic

differentiation (9), pyrogenic action (10), inhibition of cell growth (11) and induction of ACTH synthesis (12).

TNF- α is a multifunctional cytokine produced by macrophages and other cells during inflammatory responses (13). TNF- α can induction of acute phase proteins by hepatocytes and induction of cytokine production by T cells (14). In the present study, we report that serum levels of the cytokines IL-6 and TNF- α are increased in patients with hyperthyroidism and decreased in patients with hypothyroidism.

Material and Methods

Twenty seven hyperthyroid, 23 hypothyroid patients, and 18 normal subjects were studied. The ages (mean \pm SD) of the hyperthyroid and hypothyroid patients and normal subjects were 63 \pm 3, 55 \pm 2, and 58 \pm 4 yr, respectively. The male to female ratios of the hyperthyroid and hypothyroid and control groups were 14:13, 10:13, 9:9, respectively. Sixteen hypothyroid and

	Hyperthyroid		Hypothyroid		Control
	Before	After	Before	After	
T4 ($\mu\text{g/dl}$)	15.5 \pm 6.1	4.8 \pm 1.9	2.9 \pm 0.9	4.1 \pm 1.6	4.4 \pm 1.7
T3 (ng/dl)	227.9 \pm 69.5	117.2 \pm 22.3	44 \pm 8.5	105.2 \pm 16.3	110.1 \pm 18.6
TSH ($\mu\text{U/ml}$)	2.3 \pm 0.8	5 \pm 0.9	38.2 \pm 10.4	6.1 \pm 2.3	5.5 \pm 1.2
IL-6 (pg/ml)	14.5 \pm 4.4*	11.1 \pm 2.3*	8.2 \pm 2.4**	9.9 \pm 3.2 [#]	10.6 \pm 2.2
TNF- α (pg/ml)	18.3 \pm 5.5*	14.3 \pm 1.7*	11.4 \pm 2.4*	13.2 \pm 3.2 [#]	13.8 \pm 1.6

Table 1. Biochemical parameters of thyroid disease and normal subjects.

*p<0.001, ** p<0.01 vs. control subjects. *p<0.01, [#]p<0.05 vs. before treatment.

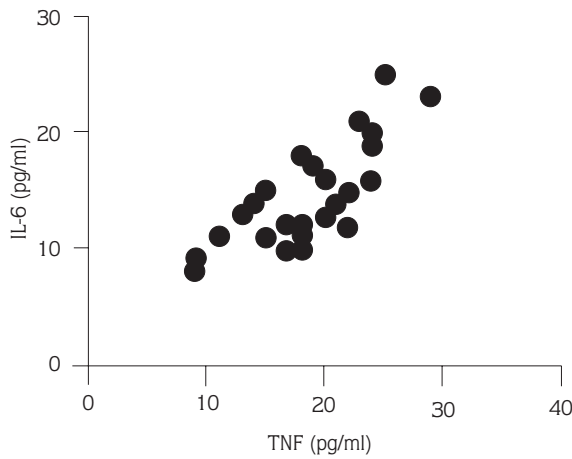


Figure 1. Linear regression analysis of the relationship between serum IL-6 and TNF- α in hyperthyroid patients before treatment. The regression equation $y=2.27+0.669x$; $r=0.787$; $p<0.001$.

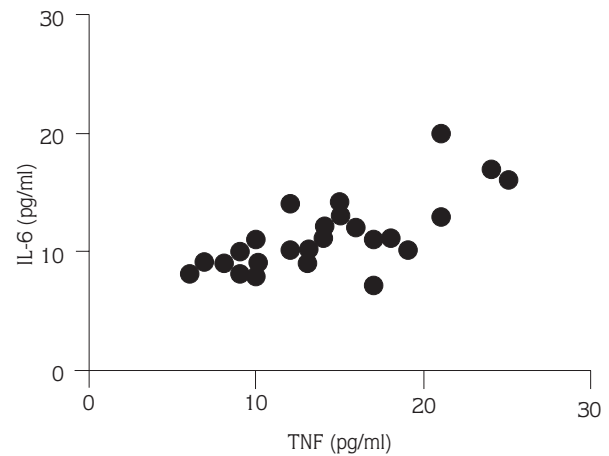


Figure 2. Linear regression analysis of the relationship between serum IL-6 and TNF- α in hyperthyroid patients after treatment. The regression equation $y=5.33+0.412x$; $r=0.692$; $p<0.001$.

22 hyperthyroid patients (10 thyroid adenectomy) were restudied when they were euthyroid after surgical treatment and 10 or more months of treatment. All of control subject and patient groups were not taking any medication known to affect thyroid metabolism.

Blood was drawn after an overnight fast, centrifuged, and serum aliquots were stored at -80°C until determination. Serum T_4 , T_3 , TSH levels were determined by automated chemiluminescence assay (Ciba Corning Diagnostics Corp. Medfield, MA 02052 USA). Serum IL-6 and TNF- α were measured by an enzyme-linked immunosorbent assay (QuantikineTM, Human TNF- α immunoassay, CN DTA 50; QuantikineTM, Human IL-6 immunoassay, CN D 6050).

Statistical analysis

The results were expressed as means \pm SD. Statistical analysis was performed by Student’s paired t-test. Linear regression analysis was used for comparison of IL-6 and TNF- α levels in thyroid disease subjects. Differences were considered significant if the P value was less than 0.05.

Results

Significant increased IL-6 and TNF- α levels in untreated hyperthyroid patients were found when compared with the healthy controls ($p<0.001$, for both). On the contrary, relatively decreased IL-6 and TNF- α levels in untreated hypothyroid patients were observed

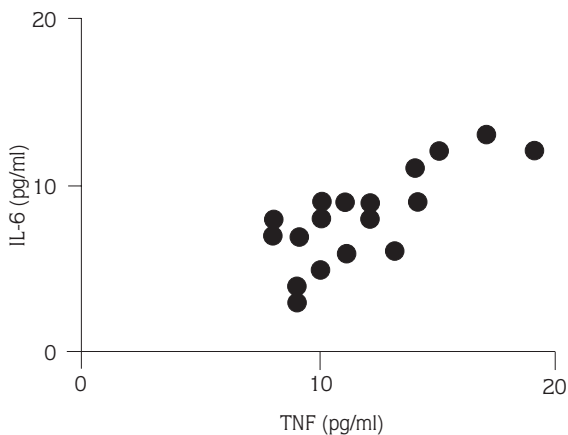


Figure 3. Linear regression analysis of the relationship between serum IL-6 and TNF- α in hypothyroid patients before treatment. The regression equation $y=1+0.63x$; $r=0.723$; $p<0.001$.

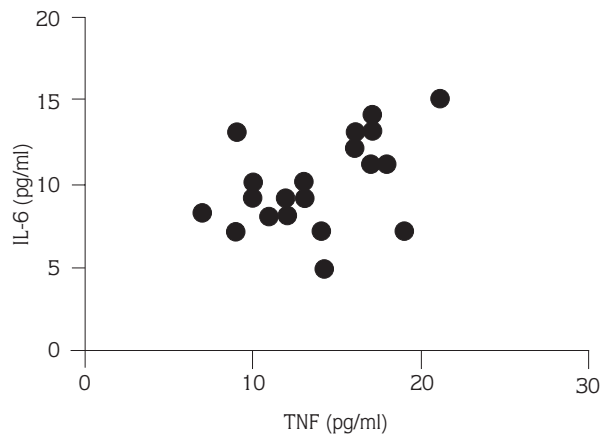


Figure 4. Linear regression analysis of the relationship between serum IL-6 and TNF- α in hypothyroid patients after treatment. The regression equation $y=5.2+0.35x$; $r=0.552$; $p<0.01$.

($p<0.01$, $p<0.001$, respectively). After treatment, serum IL-6 and TNF- α values were decreased in hyperthyroid patients ($p<0.01$), but increased in hypothyroid patients ($p<0.05$). On the other hand, serum IL-6 and TNF- α levels in hyperthyroid patients were significantly decreased after treatment ($p<0.01$), but increased ($p<0.05$) in hypothyroid patients when compared to the pretreatment values. Positive correlations between before and after treatment serum IL-6 and TNF- α levels were found in hyperthyroidism ($r=0.787$, $r=0.692$, Fig 1-2, respectively) and hypothyroidism ($r=0.723$, $r=0.552$, Fig 3-4, respectively). Additionally, a positive correlation between serum IL-6 and TNF- α levels was also found in control subjects ($r=0.425$). However, neither IL-6 nor TNF- α demonstrated correlation with T_3 , T_4 and TSH levels. After treatment, IL-6, TNF- α , T_3 , T_4 , TSH levels of hyperthyroid and hypothyroid patients did not differ statistically from control subjects ($p>0.05$; Table 1).

Discussion

Many in vivo models demonstrated the role of cytokines in pathophysiology have demonstrated that a given inflammatory stimulus results not in the generation of a single cytokine, but rather a complex cascade of cytokine release (15,16). In accordance with this, our demonstration of circulating TNF following thyroid disorders has led us to examine the production of other cytokines, in particular IL-6. We chose to study IL-6

because TNF- α has been demonstrated to be an important stimulus for IL-6 production (17)

We have shown that IL-6 and TNF- α levels are increased in the circulation in untreated hyperthyroid patients and decreased in untreated hypothyroid patients. TNF- α is polypeptide with multitudes of effects. It plays a major role in the immunological cascade leading to inflammatory response, and stimulating the release of a variety of other mediators, including IL-2, IL-6, and platelet activating factor (18,19). TNF- α is a macrophage/monocyte-derived cytokine that has been proposed as an early proximal mediator of many of the metabolic and physiologic responses. TNF- α is believed to play a central role in the development of sepsis (20) and ischemic colitis (21). IL-6 stimulates the hepatic synthesis of proteins (22,23), favors terminal differentiation of B cells into Ig-secreting cells, enhances the proliferation of multipotential hematopoietic progenitors and plays a role in the growth and differentiation of several cell types (22,24). In hyperthyroidism, increased serum IL-6 could originate from several sources including the thyroid gland, blood mononuclear cells, and bone tissue. In Graves disease (GD), although follicle cells are able to express certain cytokines, intrathyroidal lymphocytes are the main source of IL-6 production (25). Weetmann et al (26) were unable to observe any significant difference in serum IL-6 concentrations between normal subjects and hyperthyroid GD patients. Bartalena et al (27) found increased serum IL-6 concentrations in GD patients. Our finding of an increase in serum levels of IL-6, similar to

that reported in graves disease (25), again suggests that a similar effector immunological mechanism might be involved in our patients as in GD. Thus, increased intrathyroidal production of IL-6 in hyperthyroid patients is one source of elevated IL-6 levels in serum. However, because TNF- α stimulates IL-6 production by osteoblasts (28,29), elevated levels of this cytokine may contribute to the increased production of IL-6. In hypothyroidism, Because decreased intrathyroidal production of IL-6 and decreased TNF- α levels, serum IL-6 concentration might be decreased. Our results provide support for the notion

of a cascade effect of these cytokines by demonstrating a positive correlation between IL-6 and TNF- α . After treatment, serum IL-6 and TNF- α concentrations were decreased in hyperthyroid patients, and increased in hypothyroid patients.

In conclusion, the present results show that IL-6 and TNF- α levels are considerably elevated in patients with hyperthyroid, decreased in patients with hypothyroid and normalized by succesful surgical treatment or treatment of medicine. Further in vivo and in vitro experiments will be required to confirm these findings.

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