

Relation Between Thyroid Hormone Concentration and Serum Levels of Interleukin-6 and Interleukin-10 in Patients With Nonthyroidal Illness Including Chronic Kidney Disease

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Keywords. thyroid hormones, interleukins, chronic kidney disease, thyroid stimulating hormone, congestive heart failure, myocardial infarction

Introduction. We evaluated relations between interleukins (IL) IL-6 and IL-10 and euthyroid sick syndrome (ESS) in patients with nonthyroidal illness (NTI).

Materials and Methods. Sixty patients and 20 healthy volunteers were recruited. The patients had either chronic kidney disease (CKD), congestive heart failure (CHF), or acute myocardial infarction (MI), distributed equally in 3 subgroups. Serum levels of IL-6 and IL-10, thyroid stimulating hormone (TSH), total T4, and T3 were determined.

Results. In the 60 patients with NTI, we detected a significantly lower T3 and T4 levels compared to controls, while TSH level was within the reference range. Also, IL-6 level was substantially higher than that in controls ($P < .001$) and correlated with T3 ($r = -0.620, P < .001$) and T4 ($r = -0.267, P < .001$). Similarly was IL-10 level ($P < .001$) that correlated with T3 ($r = -0.512, P < .001$), but not with T4. The ILs correlated positively with each other ($r = 0.770, P < .001$). Only IL-6 was a predictor of low T3 ($P = .001$). The proportion of patients with subnormal T3, T4, and TSH levels was highest in those with MI along with greatest IL-6 and IL-10 levels compared to patients with CHF and CKD. Patients with CKD showed the least disturbance in IL-6 and IL-10 despite the lower levels of T3, T4, and TSH in a higher proportion of them compared to patients with CHF.

Conclusions. The high frequency of ESS in patients with NTI may be linked to IL-6 and IL-10 alterations. Perturbation of IL-6, and not IL-10, might be involved in the pathogenesis of ESS along with other key players as suggested by our findings in CKD.

IJKD 2008;2:16-23
www.ijkd.org

INTRODUCTION

Despite the absence of thyroid disease, patients with nonthyroidal illness (NTI) frequently have changes in serum levels of thyroid hormones that may suggest thyroid dysfunction. The clinical impression of euthyroidism is supported by normal serum thyroid stimulating hormone (TSH) in most of these patients.¹ Many of the clinically euthyroid patients with NTI have low circulating concentrations

of total and absolute free tri-iodothyronine (T3), low or normal concentrations of total thyroxine (T4), elevated concentrations of absolute free T4, and normal or subnormal levels of TSH.² However, Hesch reported simultaneous elevation of TSH to compensate for these low levels.³ Consequently, patients are usually clinically euthyroid. This has been named "euthyroid sick syndrome" (ESS) which was first described about 4 decades earlier.^{4,5}

Patients with chronic kidney disease (CKD) as an example of the NTIs may be in an ESS state although they are clinically euthyroid, and the degree of this thyroid dysfunction matches the severity of kidney damage.⁶⁻⁸ Recently, impact on the thyroid gland was noticed not only by chronic but also by acute renal failure.⁹ The combination of an impaired immune response coupled with persistent immune stimulation may have a role in the low-grade systemic inflammation and altered cytokine balance that characterizes the uremic state. The mechanisms accounting for such alterations in the thyroid hormone levels in association with NTI have remained unknown despite extensive investigations. However, interleukin-6 (IL-6) is usually detectable in serum during the disease course and acts as a systemic hormone that may mediate the well-documented inhibitory effect of IL-1 on thyroid cell functions.^{10,11} Interestingly, Shalaby and colleagues¹² suggested IL-6 as a potential factor in the pathogenesis of the ESS. Interleukin-6 acts by inducing competition for limiting amounts of co-activators, decreases hepatocyte thyroxine 5'-deiodinase enzyme expression, and inhibits thyroid function through binding of IL-6-sIL-6R complex to gp130.^{13,14} In contrast to IL-6, IL-10 is one of the most potent anti-inflammatory cytokines and is produced by macrophages as well as other cell types.^{15,16} Interestingly, pro-inflammatory stimuli like IL-1-beta and tumor necrosis factor-alpha enhance its secretion without any influence of IL-6.¹⁴

We carried out this cross-sectional study to evaluate the potential link between thyroid function and the cytokines, IL-6 and IL-10, in a group of patients with ESS associated with variable NTIs including CKD.

MATERIALS AND METHODS

Patients

We investigated serum samples collected from 60 patients (46 men and 14 women; mean age, 45 ± 19 years) who were hospitalized because of a wide variety of NTIs. The patients were recruited to the planned study consecutively except for those with known or clinically suspected thyroid dysfunction. Additional exclusion criteria were the use of thyroid hormones or thyrostatic drugs. The patients comprised of 3 equal subgroups reflecting the nature of their NTI including those

with CKD, congestive heart failure (CHF), and acute myocardial infarction (MI). None of the patients with CKD was on dialysis treatment as their mean estimated glomerular filtration rate, using the abbreviated 4-variable MDRD formula, was 27.6 ± 3.0 mL/min/1.73 m². The leading cause of their kidney disease was diabetes mellitus (30%), hypertension (25%), glomerular disease (15%), obstructive nephropathy (10%), and unknown (20%). The severity of MI was assessed clinically as well as by the degree of elevation of creatine kinase myocardial band (CK-MB) isoenzyme.

Twenty healthy volunteers (15 men, 5 women; mean age, 39 ± 5 years) were recruited among the hospital staff as the control group. Because of the consecutive method of recruitment, there was unequal distribution of sex in the patients and consequently in the control groups.

Methods

Samples from both patients and controls were collected for measurement of serum IL-6, IL-10, TSH, T3, and total T4 levels. Blood samples were taken between 7 AM and 9 AM after an overnight fasting. After centrifugation (1500 g) for 10 minutes, aliquots of serum were stored at -20°C until the time of sample analysis. Both, the ultrasensitive human TSH and free T3 were measured by a microparticle enzyme immunoassay on AxSYM System (Abbott Laboratories, Abbott Park, USA),^{17,18} while total serum T4 was measured by the fluorescence polarization immunoassay on AxSYM System using the standard laboratory methodologies.¹⁹

Serum IL-6 was measured using a commercially obtained immunoassay (IL-6 Quantikin assay, R & D Systems, Abingdon, UK) with sensitivity of 0.7 ng/L and an intra-assay and interassay coefficients of variation of 3.2% and 5.7%, respectively. The reference value for IL-6 in fresh samples of healthy individuals ranged from 12.5 ng/L to 20 ng/L. The serum level of IL-10 (Human IL-10 Quantikin enzyme-linked immunosorbent assay, R & D Systems Inc, Minneapolis, Minnesota, USA) was measured with an expected value below 5 pg/mL and no cross-reactivity with other ILs including IL-6. The maximum intra-assay and interassay coefficients of variation were 9.8% and 5.6%, respectively. Both ILs were assessed by competitive enzyme-linked immunosorbent assay in the sera of patients and controls according to a method described by Helle

and colleagues using recombinant human cytokine as standard.²⁰

For the patients with MI, CK-MB isoenzyme was measured as a rough indicator of myocardial damage severity. The estimated glomerular filtration rate was calculated based on the 4-variable abbreviated MDRD formula:

$$\text{GFR} = 186 \times [(\text{serum Cr})^{-1.154}] \times \text{age}^{-0.203} (\times 0.742 \text{ if female, } \times 1.21 \text{ if black})$$

in which Cr is indicative of serum creatinine concentration (mg/dL).

In accordance with our institutional guidelines, the protocol was approved by Medical Research and Ethics Committee. All participants were fully informed of the investigational nature of this study as well as its aim, and provided written consent.

Statistical Analyses

Variables are given as mean \pm standard deviation unless otherwise indicated. The *t* test, single-factor analysis of variance and Pearson correlation test were used as indicated. Multivariate linear regression analysis was employed to determine the predictive value of quantitative parameters. A *P* value less than .05 was viewed significant. All data analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 10.0, SPSS Inc, Chicago, Ill, USA).

RESULTS

Thyroid Hormones

We noted, as seen in Table 1, significantly lower T3 levels in the patients with NTI compared to the corresponding levels in the control participants. Likewise were the serum T4 concentrations. While TSH was significantly lower in the patients with NTI, it was well within the reference range of the employed immunoassay (0.49 μ IU/L to 4.67 μ IU/L).

Serum Interleukins

In the patients with NTI, serum level of IL-6 was significantly higher than that in the controls (Table 1). Overall, this level is considerably greater than the sensitivity of the used immunoassay kit and greater than the upper limit of reference value (< 20 pg/mL), as well. Similarly, serum level of IL-10 was significantly higher than the measurements observed in the controls. We noticed that such concentrations are significantly greater than the upper limit of reference level of the used kit (< 5 pg/mL). Of note, in order to verify the validity of the data in view of the high level of the investigated ILs and to assess the linearity of the assay, we diluted the samples with the appropriate calibrator diluents to produce samples with values within the dynamic range of the used immunoassay.

Relation Between Thyroid Hormones and Interleukins

In the patients with NTI, we observed a significant inverse correlation between serum IL-6 and T3 levels (Pearson correlation; $r = -0.620$, $P < .001$; Figure 1). There was also a significant correlation between serum IL-6 and total T4 levels ($r = -0.267$, $P < .001$). Likewise, IL-10 inversely correlated with T3 ($r = -0.512$, $P < .001$; Figure 1), but not with T4 or TSH. Interestingly, there was a significant correlation between IL-6 and IL-10 ($r = 0.770$, $P < .001$; Figure 2).

By linear regression analysis, IL-6 was found to be a potential risk factor that could predict the observed lower circulating level of T3 (nonstandardized coefficient [B] \pm standard error [SE] = $-3.72 \text{ E-}03 \pm 0.001$, $R^2 = 0.338$, $P = .001$), but IL-10 was not a predictor ($B \pm SE = -7.512 \text{ E-}04 \pm 0.001$, $R^2 = 0.338$, $P = .63$). However, only a borderline degree of significance was seen for IL-6 as a potential predictor

Table 1. Serum T3, T4, TSH, IL-6, and IL-10 Levels in Patients With NTI Controls*

Parameters	Patients With NTI (n = 60)	Healthy Controls (n = 20)	<i>P</i>
T3, nmol/L	0.94 \pm 0.47	1.34 \pm 0.45	.001
T4, nmol/L	74.90 \pm 28.41	108.30 \pm 14.50	< .001
TSH, μ IU/L†	1.08 \pm 0.52	1.92 \pm 0.93	< .001
IL-6, ng/L	105.18 \pm 72.01	3.34 \pm 1.02	< .001
IL-10, ng/L	74.33 \pm 52.99	2.64 \pm 0.92	< .001

*T3 indicates tri-iodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; IL, interleukin; and NTI, nonthyroidal illness.

†Out of the investigated 60 patients, 4 showed a TSH serum level that was below the sensitivity of the used assay (0.06 μ IU/L). These patients were assumed to have a TSH concentration of (0.06 μ IU/L) in order to calculate the mean TSH value.

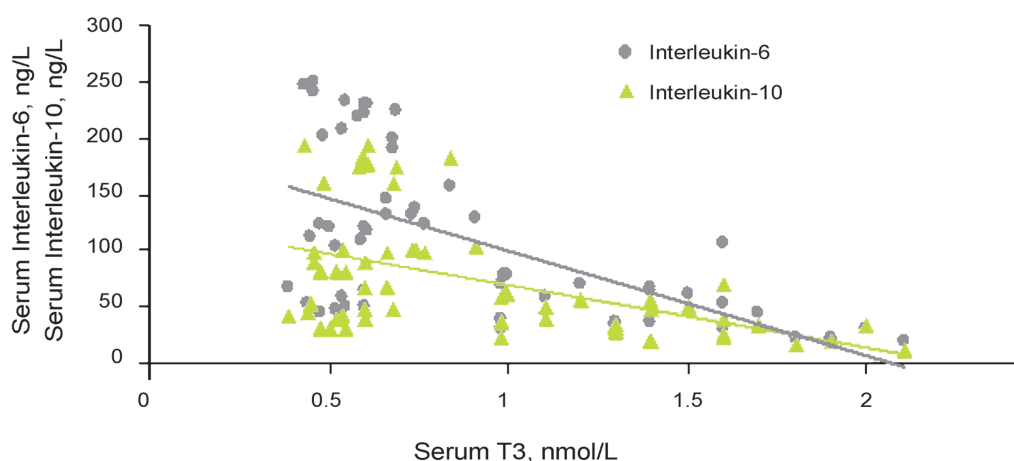


Figure 1. Correlations between serum T3 and both IL-6 and IL-10 in all patients with nonthyroidal illness. The correlation coefficient was -0.62 for IL-6 ($P < .001$) and -0.51 for IL-10 ($P < .01$). IL indicates interleukin and T3, tri-iodothyronine.

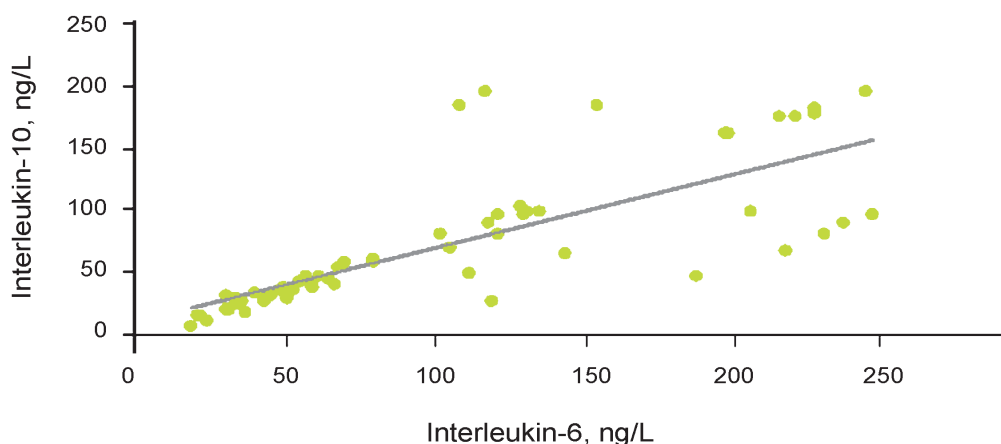


Figure 2. Correlation between IL-6 and IL-10 in the 60 patients with nonthyroidal illness ($r = 0.77$, $P < .001$). IL indicates interleukin.

of T4 reduction in NTI ($B \pm SE = -0.144 \pm 0.079$, $R^2 = 0.082$, $P = .07$). Importantly, IL-10 was not a potential predictor for the lower thyroid hormone concentrations.

Subgroup Analyses

Using the single-factor analysis of variance, we detected significant differences in serum T3 alterations between the 3 subgroups of patients with NTI and their controls ($P < .001$). Approximately, more or less similar level of significance did exist for total T4 ($P < .001$). Interestingly, differences in both IL-6 and IL-10 between the 4 subgroups were significant too ($P < .001$). Mean values of the measured parameters in each group are demonstrated in Table 2.

Furthermore, the proportion of patients with

T3, total T4, and TSH levels below the reference ranges was highest in the patients with MI (Table 2) who displayed the greatest mean concentrations of both IL-6 and IL-10 (192.5 ± 45.1 ng/L and 122.95 ± 46.1 ng/L, respectively) compared to those with CHF and CKD (Table 2). Of note, the changes in the serum levels of the ILs matched with the severity of myocardial damage in the patients of MI subgroup as inferred from the significant correlations observed between the CK-MB isoenzyme and both IL-6 ($r = 0.498$, $P = .02$) and IL-10 ($r = 0.467$, $P = .04$).

Surprising was our observation that the patients with CKD showed the least disturbance in IL-6 and IL-10 despite the exhibition of levels lower than the reference limits of T3, T4, and TSH in a higher proportion of them compared with the patients

Table 2. Serum T3, T4, TSH, IL-6, and IL-10 in Subgroups of Patients With NTI*

Parameters	CKD (n = 20)	CHF (n = 20)	MI (n = 20)
T3, nmol/L	1.14 ± 0.57 (40.0)	1.07 ± 0.47 (35.0)	0.63 ± 0.13 (70.0)
T4, nmol/L	78.2 ± 23.47 (45.0)	70.85 ± 22.68 (25.0)	75.65 ± 37.57 (70.0)
TSH, μ IU/L	1.04 ± 0.54 (25.0)	0.96 ± 0.32 (15.0)	1.23 ± 0.63 (75.0)
IL-6, ng/L	40.50 ± 14.38	82.95 ± 18.90	192.55 ± 15.12
IL-10, ng/L	30.4 ± 10.57	69.05 ± 44.04	122.95 ± 46.06

*Values in parentheses are the percentages of patients with values lower than normal for the corresponding parameters. T3 indicates triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; IL, interleukin; NTI, nonthyroidal illness; MI, myocardial infarction, CHF; congestive heart failure; and CKD, chronic kidney disease.

with CHF (40%, 45%, and 26% versus 35%, 25%, and 18%, respectively; Table 2).

DISCUSSION

In the current study, we observed a considerably lower serum T3 and total T4 concentrations, signifying thyroid dysfunction, in patients with variable NTIs, while serum TSH showed a mean value that was not significantly different from that in the healthy controls. Our findings are in concordance with that noted by Horimoto and coworkers,²¹ but in contrast with the results of a study undertaken by Kayima and associates.²² Clinically euthyroid patients are biochemically abnormal, defining the previously described ESS.^{4,23}

Speculations as to the value of ESS development in patients with NTI have long been considered. Some investigators reported a protective function of this phenomenon,^{4,24} while others viewed it either as an adaptive response to reduce tissue energy requirements in face of systemic illness, or as a maladaptive one that induces damaging tissue hypothyroid.²⁵ In this study, we detected a substantially high level of the pro-inflammatory cytokine, IL-6, in patients with NTI, supporting its possible role as an endocrine cytokine with a regulatory effect on many endocrine systems including the thyroid gland.^{26,27} We also detected a considerably high level of the anti-inflammatory cytokine, IL-10 in the patients with NTI. Likewise, Dehoux and associates reported IL-10 release in response to stressful situations such as cardiopulmonary bypass.²⁸ Interestingly, we noticed a direct association between IL-6 and IL-10 which accords with a previous notion and could be attributed to the fact that secretion of both ILs is stimulated by the same cytokines such as tumor necrosis factor-alpha.²⁹⁻³¹ Therefore, within the cytokine network, activation of pro-inflammatory

mediators such as IL-6 is followed by increased production of endogenous inhibitory molecules including the antagonistic cytokine IL-10 in an attempt to suppress release of pro-inflammatory cytokines. This dimorphic response may be related to macrophages resistance to the suppressive effect of IL-10 as a result of down-regulation of the expression of soluble IL-10 receptors.³² The high IL-10 levels was hoped for to minimize the deleterious effect of the raised IL-6.³³ Taniguchi and colleagues highlighted this potential protective effect of IL-10 in their 25 patients with systemic inflammatory states.³⁴

In this study, the suppressed thyroid hormones were inversely associated with serum IL-6 elevations. Boelen and colleagues observed a similar correlation in their 100 patients with NTI during their first day of hospitalization.¹⁰ However, such correlations did not exist for TSH and IL-6. This was not surprising since TSH was maintained within the reference values. Also, we observed an inverse association between the high serum level of IL-10 and the suppressed thyroid hormone levels, in contrast to the findings of Guillen and associates.³⁵ Dissimilar to IL-6, IL-10 was not an indicative of the observed thyroid hormones' alterations. Hence, our results did not support any role for IL-10 in the pathogenesis of ESS. This is in concordance with what noticed by Boelen and colleagues.³⁶

We observed a highest level of IL-6 along with lowest measurements of both serum T3 and serum T4 in the patients with MI, while the least changes were noticed in patients with chronic illness exemplified by CHF. This is in accordance with the hypothesis that the magnitude of thyroid hormones' alteration parallels the severity of the associated NTI.^{37,38} Similarly, the considerably increased IL-10 in our patients with MI was found

to be linked, at least statistically, to the detected ESS. Such increase in IL-10 was reported to be beneficial to patients admitted to ICU through improving their outcome.³⁹ In fact, Kimur and coworkers correlated the increased IL-6 and IL-10 with thyroid hormones' alterations in their 20 patients with acute MI, and the time course of both ILs and T3 seemed to be tightly linked.⁴⁰

The least disturbance in serum T3, T4, and TSH levels concomitant with the lowest levels of IL-6 and IL-10 were observed in patients with CHF, yet higher than those in control subjects. This is more or less similar to the findings of Nishino and associates,⁴¹ as well as those of Davies and colleagues; however, the latter have not tested IL-10.⁴² On the other hand, we observed that T3 and T4 were considerably low in an appreciable proportion of patients with CKD, whilst their serum IL-6 (and IL-10) levels were of lesser elevations compared to other two subgroups. This might simply mean that while a probable contributory role for IL-6 is suggested, it is not the only factor involved in the pathogenesis of ESS encountered in some specific forms of NTI such as CKD. Our view is supported by a study done on 28 patients with CKD in 1994 and another by Boelen and colleagues who found that only 28% of T3 levels variability was accounted for by the circulating IL-6 concentrations.^{10,43}

From our observations in chronic forms of NTI, we can suggest that an acute rather than a long-lasting perturbation of IL-6 may be involved in development of ESS. In accordance with our suggestion was the work carried out by Stouthard and colleagues who tested the influence of acute compared to chronic administration of IL-6 on thyroid hormone homeostasis.⁴⁴ This was further supported by Hashimoto and associates who demonstrated an inverse association between IL-6 and thyroid hormones in their pediatric patients with short-lived illness,⁴⁵ but not in longer-lasting diseases.⁴⁶ The same holds true for IL-10 that seems to be only partly involved in this process.²⁸ The continuation of the ESS state, as has been postulated by Docter and associates,⁴⁷ would, however, be attributed to yet unidentified factors.

CONCLUSIONS

We can conclude that ESS occurs in many patients with a wide range of NTIs in association with an

appreciable perturbation in IL-6 as well as IL-10, and that its pathogenesis might be regulated by IL-6 with possible involvement of some other, yet unrecognized, key players in some specific forms of NTI such as CKD.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The authors as well would like to thank Miss Linda Dudgale who improved the quality of the written English by her assistance with language fluency and grammar checking for of this paper.

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Received July 2007
Revised October 2007
Accepted October 2007