Relation between Thyroid Function and Serum Interleukins-6 and -10 in Systemic Lupus Erythematosus and Rheumatoid Arthritis

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Abstract: Alterations in the circulating thyroid hormone concentrations constituting the euthyroid sick syndrome (ESS) is frequently associated with systemic non-thyroidal diseases such as a systemic connective tissue disease (SCTD). **Aim**: to elucidate the possible relation between interleukins (IL6 and IL-10) and any changes in thyroid hormone level in patients with SCTD. **Subjects and Methods**: Thirty patients with systemic lupus erythematosus (SLE) and thirty rheumatoid arthritis (RA) patients in addition to 30 healthy age- and sex- matched controls were recruited from the Internal Medicine Department of Ain Shams University Hospital. Serum level of IL-6 and IL-10, thyroid stimulating hormone (TSH), thyroid hormones, including T3 and T4, antithyroglobulin antibodies (ATGAb), thyroid peroxidase antibodies (TPOAb), ESR, RF, ANA, and CRP were determined. **Results**: A significant reduction in the circulating T3 levels compared to the healthy controls (0.938±0.477 vs 1.345±0.44 nmol/L and p=0.001) with a significant reduction in the circulating total T4 level (47.9±28.41 vs 108±19.49 nmol/L and p=5.546E-06) with a serum TSH level within the normal reference value. IL-6 and IL-10 concentrations rose to a high significant level compared to the controls. By subgroup analysis, we have noticed a high significant reduction in T3 and T4 concentration among the two subgroups of patients and their controls (p=3.294E-05 and =9.816E-05 respectively), they differ significantly as well, in both IL-6 and IL-10 elevations (p=5.864E-34 and = 2.110E-18 respectively). **Conclusions**: the proportion of patients with subnormal serum T3, total T4 and TSH levels was highest in SLE patients, and they displayed the highest mean IL-6 and IL-10 concentrations (192.5±45.1 ng/L &122.95±46.1 ng/L, respectively) compared with the RA patient subgroup (82.95±28.9 ng/L & 69.05±44.0 ng/L, respectively). [Journal of American Science 2010; 6(9):924-931]. (ISSN: 1545-1003).

Keywords: Systemic Lupus Erythematosus- Rheumatoid Arthritis- serum cytokines-thyroid functions

1. Introduction

Autoimmune diseases are clearly associated with many factors, such as genetic, hormonal and environmental as well as immune defects [1]. These factors, referred to as the mosaic of autoimmunity, can interact in diversity of autoimmune diseases and the association of these diseases in the same patients [2]. Autoimmune thyroid disease, marked by the presence of antibodies directed against thyroid antigens, has been associated with a number of non-organ specific rheumatological disorders [3]. These associations include SLE [3, 4, and 5], RA [6, 7], Sjogren syndrome [8], scleroderma and vasculitides [9, 10]. Patients with non-thyroidal illness (NTI) frequently have changes in serum thyroid hormone measurements that may suggest thyroid dysfunction, they have been very low circulating concentrations of total and absolute free triiodothyronine (T3), low-normal concentrations of total thyroxin (T4), elevated concentrations of absolute free T4, and circulating concentrations of thyroid stimulating hormone (TSH) that are either normal or subnormal [11]. Hesch [1981] has reported that these low levels are commonly compensated for by simultaneous elevation in the thyroid stimulating hormone level. Consequently, the patients are usually clinically euthyroid [12]. This is referred to as the euthyroid sick syndrome (ESS) [13]. Inflammatory cytokines are influential in systemic disease mediation [14]. More precisely, the cytokine tumor necrosis factor-α (TNF- α) and interleukin-1β (IL-1 β) resulted in similar changes in the thyroid hormone concentrations when given systematically to experimental animals [15] as well as to human volunteers [16]. However, none of the two cytokines were detectable in patients with NTI [17, 18]. In contrast to IL-1 and TNF- α, IL-6 is usually detectable in serum during illness and acts as a systemic hormone [19].

IL-6, an inflammatory cytokine, is characterized by pleiotropy and redundancy of action. Apart from its haematologic, immunologic and hepatic effects, it has many endocrinal as well as metabolic actions. Specifically, it is a potent stimulator of the hypothalamic-pituitary- adrenal axis and is under the tonic negative control of glucocorticoids [20]. It acutely stimulates the secretion of growth hormone, inhibits thyroid-stimulating hormone secretion and decreases serum lipid concentrations. Furthermore, it is secreted

during stress and is positively controlled by catecholamine [21]. In contrast to IL-6, IL-10 is one of the most potent anti-inflammatory cytokines [22, 23], that is produced by macrophages as well as other cell types although was primarily thought of as T cell derived cytokine [24].

In the case of ESS, there has so far been no investigation linking between thyroid function and the cytokines; IL-6 as well as IL-10 in patients with variable NTI. So in order to evaluate the possible role of IL-6 and IL-10 in the development of altered thyroid hormone concentrations in patients with ESS, we carried out this study.

2. Material and Methods

This study included thirty patients with systemic lupus erythematosus (SLE),(25 female (83%)&5 males (17%); aged 35.1±1.6) and thirty patients with rheumatoid arthritis (RA),(20 females (66.6%)&10 males(17.4%); aged 26.8±1.7) in addition to 30 healthy age- and sex- matched controls(50% female &50% male), were recruited from the Internal Medicine Department of Ain-Shams University Hospital. Patients fulfilled the American Rheumatism Association criteria of RA [25] and SLE [26]. The duration of the disease was 22.9±0.3 months for SLE patients and 33±2.3 months for RA patients. Exclusion criteria were any patient with known or clinically suspected thyroid dysfunction. All patients in this study were free of immunosuppressant or corticosteroid medications. RA patients were on low dose of methotrexate (10mg/week) and SLE patients on hydroxychloroquine (250mg/day).The patients displayed no exacerbation of their disease activity at least 4weeks prior to the onset of blood sampling. In addition, all subjects were free of other medications during the study.

All patients and controls gave informed consent to participate in the study according to the protocol approved by the local ethics Committee in accordance with the ethical standards of the Helsinki declaration.

All patients and controls were subjected to complete history taking, through clinical examination and to the following investigation:

1. Erythrocyte sedimentation rate (ESR) using Westergreen method.
2. C-reactive protein (CRP) measured by Humatex latex agglutination slide for the qualitative and semi quantitative determination of CRP.
3. Rheumatoid factor (RF) measured by using a Stanbio RA factor latex agglutination slide for the qualitative and semi quantitative determination of RF in serum.
4. Antinuclear antibodies (ANA) done by ANAFIDR test, which is an indirect fluorescent antibody test. The kit was supplied by Diasorin, Minnesota, USA.
5. The ultra sensitive human thyroid stimulating hormone (hTSH II) was measured using a Microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of TSH in the human serum on the AxSYM system (Abbott Laboratories, Abbot Park, USA). [27]
6. The free serum T3 level was determined using the MEIA method for quantitative estimation of free triiodothyronin in human serum on AxSYM system (Abbott Laboratories, Abbot Park, USA).[28]
7. The total serum T4 level was measured using the Fluorescence Polarization Immunoassay (FPIA) method for the quantitative determination of thyroxin (T4) in human serum on AxSYM system (Abbott Laboratories, Abbot Park, USA)[29].
8. Antithyroglobulin antibodies (ATGAb) using an indirect solid phase enzyme immunometric assay (ELISA) kit from Organteck [28].
9. Thyroid peroxidase antibodies (TPOAb) using Immulite analyzer kit supplied by Diagnostic Product Corporation, CA, USA [28].
10. Serum IL-6 was measured using a commercially obtained immunoassay (IL-6 Quantikin assay, R&D Systems, Abingdon, UK), Enzyme –linked immunosorbent assay (ELISA) was used to measure the serum level of IL-10 (Human IL-10 Quantikin ELISA immunoassay, R&D Systems Inc, Minneapolis, Minnesota, USA).

Both interleukins were assessed by competitive enzyme-linked immunosorbent assay (ELISA) in the serum of both patients and controls samples using recombinant human cytokine as standard [30].

Statistical Analysis

Variables are given as mean and standard deviation (SD) unless stated otherwise. Differences between 3 or more variables were analyzed by ANOVA single- factor test (Kruskal-Wallis Test). The significance of difference between 2 sets of variables was assessed by the student t-test. Correlation coefficient test (r-test) was used to detect the significance for correlation between two quantitative variables (Pearson correlation). All analysis was performed using the Statistical Package for Social Science (SPSS) version 10.0.

3. Results

We have detected as seen in table 1, a reduction in the circulating T3 levels in the serum of all patients compared to the control group (0.936±0.47 vs. 1.343±0.45nmol/L) and it was noted to be a statistically significant one (t test p=0.001). Also there was a significant reduction in the circulating level of T4 in all patients compared to the control group (74.9±2804 vs. 108.3±14.5 nmol/L, p=5.546E-06). As noticed in the same table, while the serum TSH level was significantly lower in patients than the control, we have observed that the serum level was within the normal reference values of the employed immunoassay (0.49±4.67µIU/L).

IL-6 concentration was highly significantly elevated in all patients compared to the control group (105.18±72.01 vs. 3.34±1.18ng/L, t test p=1.648E-08).

IL-10 concentration was very highly significantly elevated in all patients compared to the control group (74.13±52.98 vs. 2.65±0.94ng/L, t test p=5.668E-08).

We have detected as seen in table 2 and figure 1, serum levels of T3, T4 and TSH that was found to be below the normal range was highest in the systemic lupus patients (70%, 70% and 72%, respectively) and these patients displayed the highest mean concentration of the circulating IL-6 as well as of IL-10 (192.55±15.12 ng/L & 122.94±46.05 ng/L, respectively) compared with the corresponding figures seen in rheumatoid arthritis patients (82.95±18.90 ng/L & 69.06±44.04ng/L, respectively).The mean titers of both antibodies (TPOAb & ATGAb) were insignificantly higher in SLE and RA patients versus controls.

Table 3, shows a negative correlation between serum IL-6 and serum T3, and it was statistically significant, similarly between T4, while TSH showed a non significant positive correlation with the serum IL-6 concentration. Likewise, IL-10 was found to be negatively and significantly correlated with serum T3, while there was no significant with T4 and TSH. Interestingly, both interleukins were positively correlated with each other, and this association was statistically significant ($p<0.001$).

Table (1): Comparison between the Lab parameters in patients and control

Tested parameters	NTI-patients	Healthy controls	p-value
T3 (n mol/L)	0.936±0.47	1.343±0.45	0.001
T4(n mol/L)	74.90±28.41	108.3±14.5	5.546E-06
TSH (µ IU/L)	1.078±0.52	1.921±0.93	2.651E-06
IL-6 (n g/L)	105.18±72.01	3.34±1.18	1.648-08
IL-10 (n g/L)	74.132±52.98	2.65±0.94	5.668E-08

Table (2): Prevalence and concentrations of Lab parameters in subgroups of patients

subgroups	T3	T4	TSH	IL-6	IL-10	ATGAb	TPOAb
SLE	0.63±0.12 (70%)	75.65±37.57 (70%)	1.23±0.64 (72%)	192.55±15.12	122.94±46.05	15.12±11.5 5%	121±65.4 15%
RA	1.07±0.47 (35%)	70.85±22.68 (25%)	0.96±0.32 (18%)	82.95±18.90	69.06±44.04	59.4±24.5 30%	56.9±48.4 5%
controls	1.343±0.45	108.3±14.5	1.921±0.93	3.34±109	2.65±0.94	13.38±7.72	9.7±4.78

TPOAb = Thyroidperoxidase antibody
ATGAb = Antithyroglobulin antibody
SLE= systemic lupus erythematosus
RA= rheumatoid arthritis

Normal ATGAb = 20-50 ng/ml
Normal TPOAb< 35 IU/ml
Normal TSH =0.49- 4.67 µ IU/L
Normal T3 = 0.68- 2.1 n mol/L
Normal T4 = 58- 154 n mol/L
Normal IL-6 < 20 ng/l
Normal IL-10 < 5 n g/L

Table (3): Correlation matrix for the investigated thyroid hormone levels and serum concentrations of both IL-6 & IL-10 in patients with NTI

Tested parameters	Correlation Coefficient	T3	T4	TSH	IL-6	IL-10
T3	Pearson Correlation Sig(2-tailed)	1 -	-0.276 NS	-0.278 NS	-0.620 <0.001**	-0.512 <0.001**
T4	Pearson Correlation Sig(2-tailed)	-0.276 NS	1 -	-0.245 NS	-0.276 NS	-0.166 NS
TSH	Pearson Correlation Sig(2-tailed)	-0.278 NS	-0.245 NS	1 -	0.278 NS	0.141 NS
IL-6	Pearson Correlation Sig(2-tailed)	-0.620 <0.001**	-0.276 NS	o.278 NS	1 -	0.770 <0.001**
IL-10	Pearson Correlation Sig(2-tailed)	-0.620 <0.001**	-0.166 NS	0.141 NS	0.770 <0.001**	1 -

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.001 level (2-tailed).

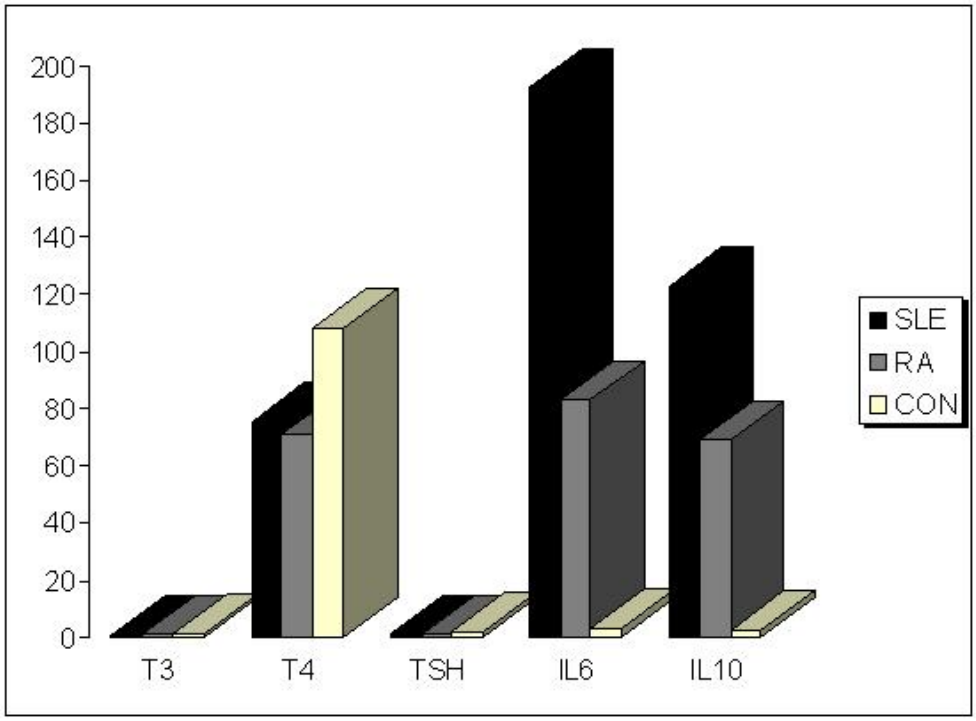

Figure (1): Prevalence and concentrations of Lab parameters in subgroups of patients

4. Discussions

In the current study, we have detected in the whole group of patients with NTI, significant reduction in the circulating T3 and total T4 concentrations signifying thyroid dysfunction, table (1). By subgroup analysis, the mean titers of antithyroglobulin (ATGAb) and thyroid peroxidase antibodies (TPOAb) were insignificantly higher in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) patients versus controls, table (2). In SLE patients ATGAb and TPOAb were detected in 5% and 15%, respectively compared to 10% for both antibodies in controls. Pyne and Isenberg [3] showed that the prevalence of TPOAb was 3.7% and of ATGAb was 1% in SLE patients. Park et al [1] reported TPOAb and ATGAb to be 20.6% and 27%, respectively in SLE patients'. RA patients, we found that ATGAb was detected in 30% while TPOAb was detected in 5%, Chan et al [7] reported that the prevalence of TPOAb was 10.9% in RA patients.

The mechanisms for coexistence of both autoimmune thyroid diseases and the two non-organ specific autoimmune disease, SLE and RA are unknown; however several mechanisms may contribute. Auto reactive T cells which can cause primary thyroid destruction as well as polyclonal B cell activation in the two autoimmune rheumatic diseases may induce autoimmune thyroiditis and SLE or RA in the same patient. It is also possible that autoimmune thyroid disease is secondary to the production of thyrotropin by activated lymphocytes or auto antibodies against the thyroid, its hormone, or receptors. Other factors such as genetic and environmental factors may be involved [1, 15].

Kochi et al (2005) [31], found associations between the SNP and susceptibility to autoimmune thyroid disease and systemic lupus erythematosus. FCRL3 may therefore, have a pivotal role in autoimmunity; on the other hand, a genetic linkage effect in a region of D5S1462 on the chromosome 5q14.3-15 It was already demonstrated between two related autoimmune condition – SLE and thyroid disease [32], These results suggest that stratifying SLE pedigrees by the presence of other autoimmune disorders may facilitate the discovery of genes related to SLE and that 5q14.3-15 harbors a susceptibility gene shared by SLE and AITD [32].

Our patients, who are clinically euthyroid, are bio chemically abnormal defining the euthyroid sick syndrome (ESS) as was reported by Wartofsky & Burman (1982)[13] to accompany many NTI and to be characterized by altered thyroid hormone changes, particularly low T3 and elevated rT4 [13 ,33]. Serum TSH levels, the key factor which stimulates thyroid hormone production and release by thyroid cells, showed a mean value in patients that was not significantly different from that in normal controls. Our findings were in concordance with others [13, 33 &34].

Speculations as to the value of ESS development in patients with NTI have long been heard. Some investigators reported that these hormone responses might represent part of the adaptive response, which lowers tissue energy requirements in the face of systemic illness or a maladaptive response, which induced damaging tissue hypothyroid [35].

In our study, we have detected a considerably elevated level of the pro-inflammatory as well as the anti-inflammatory cytokines, IL-6 and IL-10, respectively in the patients as a whole compared to the control subjects, table (3). The increased IL-6 concentration in our patients with NTI who displayed thyroid dysfunction consistent with ESS accords with the observation of its possible role as an endocrine cytokine because of its regulatory effect on many endocrine systems [36] including the thyroid gland [37] with subsequent suppression of thyroid peroxidase gene production and T3 secretion [38,39]. In addition this is supported by the earlier recognition of inflammatory cytokines as mediators of disease activity [40] and this has further suggested their possible involvement in the pathogenesis of the ESS [41]. We have as well, detected a considerably elevated level of the anti-inflammatory cytokine, IL-10 in the whole group of patients compared to the healthy controls. Dehoux and associates (2000), agreed with our results [42], as well as Lacki et al (2006)[43], who, concluded that the elevation of IL-10 serum levels in SLE and RA and the correlation between IL-10 and IL-6 in SLE may suggest that IL-10 may play a central role in inflammatory connective tissue diseases.

Further, we have noticed the positive association between the increases of both IL-6 and IL-10 in NTI patients as a whole. This could be attributed to the fact that the secretion of both interleukins is stimulated by the same cytokines as a tumor necrosis factor-α (TNF- α) [44,45].such elevation of IL-10 levels was hoped to minimize the deleterious effect of the raised concentration of IL-6 in these patients through suppression of the activated macrophages by the released IL-10. This is because one of the unique actions of IL-10 is its ability to inhibit the production of activated macrophage-derived pro-inflammatory cytokines [46, 47, 48 and 49]. Tangiuchi and colleagues (1999) highlighted this potential predictive effect of IL-10 in their patients with systemic inflammatory states [50]. Disease activity in SLE, in contrast to RA, appears to be associated with high-level production of IL-10 [Emanule& Ilia, 2006] [51].

In this study the suppressed thyroid hormone levels were negatively associated with the elevated serum level of IL-6. This correlation does not exist for the serum level of TSH and IL-6 and this was not surprising since TSH level was maintained within the normal reference value to keep the patient's euthyroid clinically. Boelen and colleagues (1993) have observed similar correlation in their patients [19].

It is observed also that the highest level of IL-6 along with the lowest measurements of both T3, as well as T4, was present in SLE patients, while lower changes in the level of thyroid hormones were noticed in RA patients. The proportion of patients with subnormal serum T3, total T4 and TSH levels was highest in SLE patients, and they displayed the highest mean IL-6 and IL-10 concentrations.

(192.5±45.1 ng/L &122.95±46.1 ng/L, respectively) compared with the RA patient subgroup (82.95±28.9 ng/L & 69.05±44.0 ng/L, respectively). Others agreed with our results [19, 42, 50 & 51].

Welby et al, (2001) [52] reported that no significant correlations between serum concentration of IL-6 and any of the thyroid hormones were demonstrated for any of the RA patient groups.Interleukin-6 might induce the synthesis of an acute phase protein, in vivo which in turn would be responsible for the changes seen in thyroid hormone transport and metabolism. This was supported by the fact that the liver is the best characterized target for IL-6, where it induces an acute phase response in response to a variety of non-thyroidal illnesses [53].

5. Conclusion

Alterations in thyroid function tests are very common in patients with NTI. Euthyroid sick syndrome occurs in many patients with a wide range of non-thyroidal illnesses in association with appreciable perturbation in the circulating IL-6 as well as IL-10 concentrations. We recommend assessment of thyroid function as a part of a biochemical and immunological profile of SLE and RA patients.

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Abbreviations

ESS: Euthyroid sick syndrome
SCTD: Systemic connective tissue disease
SLE: systemic lupus erythematosus
RA: rheumatoid arthritis
IL-6: interleukin-6
IL-10: interleukin-10
TSH: thyroid stimulating hormone
T3: triiodothyronine
T4: tetraiodothyronine
ATGAb: antithyroglobulin antibodies
TPOAb: thyroid peroxidase antibodies
ESR: erythrocytic sedimentation rate
RF: rheumatoid factor
ANA: antinuclear antibody
CRP: C-reactive protein
NTI: non-thyroidal illness
TNF- α: tumor necrosis factor-α

8/9/2010