ORIGINAL RESEARCH

Immunological and hematological changes in patients with hyperthyroidism or hypothyroidism

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Abstract

Aims: Thyroid hormones have been shown to influence the immune system and haematopoiesis. The aim of this study was to evaluate some immunological and hematological parameters in peripheral blood of hypo- or hyperthyroid women.

Materials and Methods: Blood samples were collected from 50 women with hypothyroid disease, 50 women with hyperthyroid disease and a control group consisting of 50 sex - and age - matched euthyroid subjects. Thyroid function assessed according to measurement of T3, T4 and TSH levels. The complete blood count (CBC), total and differential counts of white blood cells (WBC), serum levels of immunoglobulins (IgG, IgA, IgM and IgE) and C3 and C4 complement components determined in three groups by using standard immunological and hematological methods.

Results: In hyperthyroid women the mean serum concentrations of IgG (2312.4±584 mg/dl), IgA (296± 87 mg/dl) and IgE (301± 264 IU/ml) were significantly higher than those found in the control group (1539± 974 mg/dl, P<0.0003; 234± 116 mg/dl, P<0.01; 109.8±115 IU/ml, P<0.0001, respectively) and the mean MCV was significantly lower in comparison with the euthyroid group (P<0.05). Hypothyroid patients had higher serum IgE concentrations in comparison with the euthyroid group (179.8± 218 IU/ml vs. 109.8± 115 IU/ml; P<0.047). The mean serum C3 concentration in hypothyroid patients was also significantly higher in comparison with the euthyroid group (138.7± 36.6 mg/ml vs. 117.8± 32.1 mg/dl; P<0.01). In the

hypothyroid group the mean eosinophil count was markedly higher in comparison with the hyperthyroid group (P<0.06) and the mean count of RBC and the levels of some RBC-related indices, such as hematocrit and hemoglobin, were significantly lower in comparison with the euthyroid group (P<0.05).

Conclusion: These results indicate hypergammaglobulinemia and lower MVC in hyperthyroid patients, and higher IgE levels, C3 levels and eosinophil count as well as anemia in hypothyroid patients.

List of Abbreviations

CBC	Complete blood count
CRP	C-reactive protein
Ig	Immunoglobulin
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume of erythrocytes
NF-kB	Nuclear Factor-Kappa B
PMN	Polymorphonuclear
RBC	Red blood cells
sCD23	Soluble CD23 fragments
T3	Triiodothyronine
T4	Thyroxine
TRα-/- mice	Double knockout mice targeted for disruption both thyroid hormone receptor-α isoforms

TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor
WBC	White blood cells

There is considerable experimental research on the effects of thyroid hormones on the immune system. Thyroid stimulating hormone (TSH) is a major component of the hypothalamus-pituitary-thyroid axis.¹ Although TSH is known for its important ability to control thyroid hormone production and metabolic function, it has been shown to be both produced and used by leukocytes.² Indeed, the presence of the receptor for TSH (TSHR) has been demonstrated on lymphoid and myeloid cells,^{3,4} which supports the studies demonstrating the ability of TSH to influence lymphocyte function.⁵ TSH has been shown to induce elevated antibody response⁴ and to have an enhancing effect on lymphocytes proliferation.⁶ Stimulation of splenic dendritic cells by TSH leads to more effective phagocytic activity and higher cytokine secretion.³ In the bone marrow, the TSHR is expressed on some but not all lymphocyte, granulocyte and monocyte precursors.⁷

Alternatively, TSH may also indirectly influence the immune system via triiodothyronine (T3) and thyroxine (T4), which are released from the thyroid.⁴ Impaired immune function has been demonstrated in cells with low thyroid hormones.⁴ In the TSHR-defective mouse, B-cell development in the bone marrow is diminished and administration of T4 to TSHR-defective mice increases the number of pro-B cells.⁸ Similarly, mice with gene deletion of T3 receptors have significantly reduced numbers of leukocytes in lymphoid organs, including bone marrow, thymus and spleen.⁹

In a murine model, hypo- and hyperthyroidism have been shown to impair the immune response, leading to increased tumor susceptibility.¹⁰ Disorders in the immune system, including decreased weight of lymphoid organs, decreased lymphocyte count, suppression of the immune response and metabolic activity of macrophages, have been demonstrated in experimental animals after thyroidectomy.¹¹ Increased

susceptibility to some infection diseases has been also reported in hypothyroidism patients.¹² It has been shown that the levels of thyroid hormone decrease in an animal sepsis model and thyroid hormones supplementation had a beneficial effect on the sepsis recovery and also resulted to a lower rate of mortality.¹³ The presence of a receptor for thyroid hormones has been also demonstrated on haematopoietic progenitor cells.¹⁴

The prevalence of thyroid disorders is high in the Iranian population¹⁵ and there is a higher prevalence rate of hypothyroidism in Iranian women in comparison with men,¹⁵ consistent with similar studies on other populations.^{16,17} Accordingly, only women were enrolled in this study. It should be also noted that few studies have assessed hematological and immunological parameters in patients with thyroid disorders. This study evaluated red blood cell count (RBC), the levels of RBC-related indices such as hemoglobin, hematocrit, MCV, MCH and MCHC, platelet count and also some immunological factors such as the counts of circulating white blood cells (WBC), serum concentrations of immunoglobulins (including IgG, IgA, IgM and IgE) and serum levels of complement components (C3 and C4) in hyperthyroid, hypothyroid and euthyroid women.

Materials and Methods

Subjects

In total, 100 female patients, aged 40 to 65 years, with thyroid diseases, who were admitted to Ali-e-bne-Abitaleb Hospital of Rafsanjan (a city that located in the Kerman Province in southeast Iran), were enrolled in this study. Patients were classified, according to well established criteria, as having hyperthyroidism (n=50) or hypothyroidism (n=50). The diagnosis of hyperthyroid disease was made on the basis of clinical features such as diffuse goiter, exophthalmos, tachycardia, tremor and sweating, and laboratory data such as decreased levels of serum TSH and elevated levels

of serum T3 and T4 ($T_3 > 3.6$ nmol/L; $T_4 > 160$ nmol/L; $TSH < 0.35$ mIU/L). The existence of symptoms and signs of hypothyroidism, low levels of T3 and T4 and elevation levels of TSH were accepted as sufficient criteria in diagnosing of hypothyroidism ($T_3 < 1.6$ nmol/L; $T_4 < 60$ nmol/L; $TSH > 3.5$ mIU/L).^{18,19} It should be also noted that the diagnostic accuracy of hypo- or hyperthyroidism is considered high if T4 is interpreted with the corresponding TSH.¹⁹

A third sex- and age-matched group consisted of 50 subjects who had normal thyroid functional tests and were thus registered as a euthyroid control group (T_3 : 1.8-3.6 nmol/L; T_4 : 60-160 nmol/L; TSH : 0.35-3.5 mIU/L).

We excluded patients who had been treated for hypo- or hyperthyroidism or had inflammatory or infectious diseases. Indeed any individual with a history of recurrent infections, asthma, allergy and atopic diseases, any suspected immunological disorders, cigarette smoking or use of any drugs were excluded from the study. Other exclusion criteria included malignancy, surgery and major trauma within the previous six months. The participants had not received any immunomodulating treatment within the six months prior to serum collection. All euthyroid subjects were healthy, with no acute or chronic illnesses. These control subjects were negative for C-reactive protein (CRP) latex agglutination test, had normal CBC and had normal liver and renal function tests. Blood lipids profile (including cholesterol and triglyceride) of euthyroid subjects were within normal range. All participants gave written informed consent to take part in the study. Peripheral blood (2-4 mL) were collected from the 150 subjects and the serum separated and stored at -20°C .

Thyroid hormone measurements

Serum concentrations of T3, T4 and TSH were measured by radioimmunoassay using commercial kits (Kavoshyar, Iran). The minimal detectable limits

were 0.5 nmol/L for T3, 5 nmol/L for T4 and 0.05 mIU/L for TSH.

Measurement of immunoglobulins and C3 and C4 complement components

Serum concentrations of IgG, IgA, IgM, C3 and C4 were measured by the single radial immunodiffusion method using commercial kits (Biogen, Iran). The sensitivity of the assay was 2 mg/dl. Serum IgE levels were also determined by standard sandwich enzyme-linked immunosorbent assay (ELISA) using commercial kits (Radim, Italy). The lower detection limit of the IgE was 1 IU/ml.

Blood cell count

Total and differential leukocyte counts were carried on samples obtained from peripheral blood. Total cell counts were made in hemacytometer (T-890, Culter USA). Gimsa- stained blood films were used for differential counts.

Statistical analysis

The results expressed as mean $\pm$ SD. Differences in variables were analyzed using Student t, ANOVA, Mann-Whitney U and Kruskal-Wallis as appropriate and P values of less than 0.05 were considered significant.

Results

Serum levels of immunoglobulins in euthyroid, hypothyroid and hyperthyroid groups

Hyperthyroid women had serum concentrations of IgG (2312.4 ± 584 mg/dl), IgA (296 ± 87 mg/dl) and IgE (301 ± 264 IU/ml) that were significantly higher than those found in euthyroid controls (1539 ± 974 mg/dl, $P < 0.0003$; 234 ± 116 mg/dl, $P < 0.01$; 109.8 ± 115 IU/ml, $P < 0.0001$) (Table 2).

Hypothyroid women had higher serum IgE concentration than the euthyroid group (179.8 ± 218 IU/ml vs. 109.8 ± 115 IU/ml; $P < 0.047$). The mean serum concen-

TABLE 1. The mean serum concentrations of T3, T4 and TSH in euthyroid, hypothyroid and hyperthyroid groups.

Hormone	Euthyroid subjects	Hypothyroid subjects	Hyperthyroid Subjects
T ₃ (nmol/L)	2.21 ± 0.496	1.47 ± 0.74	3.91 ± 1.89
T ₄ (nmol/L)	140.88 ± 149	55.86 ± 36.85	205.6 ± 12.1
TSH (mIU/L)	1.5 ± 0.9	136.5 ± 231.4	0.06 ± 0.03

TABLE 2. Comparison of the serum immunoglobulins, C3 and C4 concentrations between euthyroid, hypothyroid and hyperthyroid groups.

Molecule	Euthyroid subjects	Hypothyroid subjects	Hyperthyroid subjects	p.value
IgG (mg/dl)	1539 ± 974	1392.4 ± 830.6	2312.4 ± 584	*=NS, **= 0.0003
IgA (mg/dl)	234 ± 115.9	213.9 ± 121.4	295.8 ± 87	*=NS, **= 0.005
IgM (mg/dl)	140.1 ± 68.8	143.2 ± 94.7	118.8 ± 28	*=NS, **= N.S
IgE (IU/ml)	109.8 ± 115	179.8 ± 218	300.6 ± 264	*=0.047, **= 0.0001
C ₃ (mg/dl)	117.8 ± 32.1	138.7 ± 36.6	118.1 ± 33.6	*=0.01, **= N.S
C ₄ (mg/dl)	32 ± 12.1	34.3 ± 11.6	30.3 ± 11.9	*=NS, **= N.S

* Difference between hypothyroid and euthyroid groups.

** Difference between hyperthyroid and euthyroid groups.

tration of IgG and IgA was not significantly different in hypothyroid patients compared to euthyroid women (Table 2).

Serum levels of C3 and C4 in euthyroid, hypothyroid and hyperthyroid groups

The mean serum C3 levels were similar in hyperthyroid and euthyroid groups; however, serum C3 concentrations in hypothyroid patients were significantly higher in comparison with euthyroid women (138.7± 36.6 mg/ml vs. 117.8± 32.1 mg/dl; P<0.01). No significant difference was observed between three groups with respect to the mean serum C4 levels (Table 2).

WBC count in euthyroid, hypothyroid and hyperthyroid groups

Table 3 summarizes the peripheral leukocyte count in hypothyroid and hyperthyroid subjects. No significant differences were noted for total and differential leukocyte counts between euthyroid, hypothyroid and hyperthyroid groups. In euthyroid and hyperthyroid groups, the absolute counts of circulating WBC, PMN cells and lymphocytes were slightly higher than those in hypothyroid group. However, in hypothyroid group the eosinophil count was higher as compared to the euthyroid and hyperthyroid groups but the difference was not statistically significant. (P= 0.06).

TABLE 3. Comparison of total and differential circulating white blood cells between euthyroid, hypothyroid and hyperthyroid groups.

Cell papulation	Euthyroid subjects	Hypothyroid subjects	Hyperthyroid subjects	p.value
WBC [†]	7362.5 ± 1684	7067 ± 1498	7492 ± 2240	N.S
PMN	3982 ± 406	3788 ± 314	4158 ± 547	N.S
Lymphocyte	3289 ± 338	3063 ± 242	3247 ± 284	N.S
Monocyte	38 ± 3	39 ± 4	41 ± 8	N.S
Eosinophil	62 ± 8	88 ± 10	58 ± 12	***=0.06

[†] The number of cells expressed as cells/μL.

*** Difference between hyperthyroid and hypothyroid groups.

TABLE 4. Comparison of RBC-related parameters between euthyroid, hypothyroid and hyperthyroid groups.

RBC-related parameters	Euthyroid subjects	Hypothyroid subjects	Hyperthyroid subjects	p.value
Counts	$(4.8 \pm 0.4) \times 10^6$	$(4.3 \pm 0.3) \times 10^6$	$(4.9 \pm 0.5) \times 10^6$	*=0.05, **= NS
Hemoglobin (g/dL)	14 ± 0.7	13.20 ± 0.7	13.8 ± 0.8	*=0.01, **=NS
Hematocrit (%)	39.7 ± 2	38.3 ± 2.7	39.2 ± 2.6	*=0.05, **= NS
MCV (fl)	84.7 ± 6.9	85.2 ± 4.6	81.9 ± 5	*=NS, **= 0.01
MCH (fmol)	29.1 ± 3.5	29.8 ± 1.5	28.7 ± 1.6	*=NS, **= N.S
MCHC (mmol/l)	33.6 ± 1.9	33.3 ± 4.6	32.7 ± 1.3	*=NS, **= N.S

* Difference between hypothyroid and euthyroid groups.

** Difference between hyperthyroid and euthyroid groups.

MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume of erythrocytes

RBC-related parameters in euthyroid, hypothyroid and hyperthyroid groups

In hypothyroid group the mean counts of RBC was significantly lower in comparison with euthyroid group ($P < 0.05$). Some RBC-related indices, such as hematocrit and hemoglobin, were also significantly lower in hypothyroid women in comparison to euthyroid group (Table 4). Anemia has been defined by the World Health Organization (WHO) as a hemoglobin concentration < 12 g/dl in women (20). Accordingly, anemia observed in 12% of patients hypothyroidism. In the hyperthyroid group, the mean level of MCV was significantly lower in comparison with the euthyroid group ($P < 0.05$). No significant difference was found in the mean counts of RBC and some RBC-related indices such as hematocrit and hemoglobin between hyperthyroid and euthyroid groups (Table 4).

Platelet count in euthyroid, hypothyroid and hyperthyroid groups

The mean counts of platelets was 204.6 ± 49 cells/ $\mu\text{L} \times 10^3$ in euthyroid subjects, 198.2 ± 35 cells/ $\mu\text{L} \times 10^3$ in hypothyroid group and 205.6 ± 30.9 cells/ $\mu\text{L} \times 10^3$ hyperthyroid patients. No significant difference was found between hyperthyroid and euthyroid groups regarding the mean counts platelets.

Discussion

The results of the present study showed that the mean counts of circulating WBC, PMN cells and lymphocytes in hypothyroid subjects was slightly lower than those observed in hyperthyroid and euthyroid groups. Disorders in the immune system, such as decreased weight and cellularity of lymphoid organs and decreased count of lymphocytes, have been observed in experimental hypothyroid animals.¹¹ It has been demonstrated that B cell development is defective in double knockout mice targeted for disruption of both thyroid hormone receptor- α isoforms (TR $\alpha^{-/-}$ mice) and T3 and T4 administration completely corrected this deficiency. It has been reported that the frequency and the absolute number of pro-B, pre-B and B cells in the bone marrow of the hypothyroid mice are significantly reduced in comparison with their normal control group.²¹ On the other hand, higher numbers of lymphocytes in the peripheral blood and increased lymphocytes proliferative response have been reported in hyperthyroid animals.²² These experimental studies in animal models clearly indicate that thyroid hormones have profound effects on the lymphopoiesis. The studies on human lymphocytes count during hypothyroid states produced conflicting results.²³⁻²⁵ These discrepancies may be largely attributed to differences in the duration of disease, treatment of disease, age and gender of patients and hypothyroidism origin. The results of the present of the study were consistent with investigation of Christ-Crain *et al.*²⁴ In

the present study, no significant difference was observed between the absolute number of WBC in hypothyroid and euthyroid groups. In hypothyroid patients, the thyroid hormones T3 and T4 were found at lower concentrations and these lower concentrations of T3 and T4 appear to be sufficient for leukocyte differentiation. In other words, hypothyroid subjects produce thyroid hormones at lower levels but it can be argued that these concentration are sufficient for normal leukocytes differentiation. The results of this study, however, showed that in hypothyroid subjects the circulating eosinophil count was higher than that observed in hyperthyroid and control groups, although the differences was not statistically significant. It seems that lower levels of T3 and T4 or higher levels of TSH, directly or indirectly, have positive effects on eosinophil differentiation from bone marrow progenitor cells.

In the present study, lower serum concentrations of IgG and IgA were observed in hypothyroid patients in comparison with euthyroid women. Furthermore, in hyperthyroid women, the serum concentrations of IgG, IgA and IgE were significantly higher than those found in control group. A number of investigators have assessed the relationship between thyroid hormones and antibody response with inconsistent results. In animal models, it was found that the humoral immune response is positively modulated by thyroid hormones²⁶ and a thyroidectomy was shown to suppress immune response.²⁷ Furthermore, there are reports that show that thyroid hormones either had no effect on humoral immunity²⁸ or suppressed it.²⁹ One report demonstrated elevation of antibody response with anti-thyroid drug treatment.³⁰ The results of the present study regarding hypergammaglobulinemia in hyperthyroid group are consistent with results reported recently by Nandakumar *et al.*³¹ The hypergammaglobulinemia in hyperthyroid patients has been associated with the activation of NF- κ B in B lymphocytes through oxidative stress induced by thyroid hormones.³¹ It has been also reported that higher levels of sCD23 in patients with hyperthyroidism can be attributed to generalized B- cell activation.³²

In the present study, higher serum IgE levels were observed in hypo- and hyperthyroid subjects. Increased IgE levels are seen in patients with allergic diseases, parasitic infections, nonparasitic infections (such as EBV, cytomegalovirus, HIV, and Mycobacterium tuberculosis), some inflammatory diseases, hematologic malignancies, cutaneous diseases, cystic fibrosis, nephrotic syndrome and primary immunodeficiency diseases. Increased IgE levels have previously been detected after hematopoietic stem cell transplantation, in smokers (particularly male smokers), and in those with alcoholism.³³ These conditions did not influence the results of the present investigation due to the exclusion criteria used.

IgE has an important role in the immunopathogenesis of allergic disease. Clinical evidence shows worsening of asthma and chronic urticaria in hyperthyroidism. Hyperthyroidism also has been noted to increase the severity of asthma and that the control of hyperthyroidism has been shown to attenuate asthma symptoms.³⁴ The production of IgE by B lymphocytes is strongly regulated by cytokines secreted from helper T (Th) lymphocytes.³⁵ Because the lymphocytes have receptors for T3 and T4, the effects of thyroid hormones on the IgE secretion might be via T-cell subsets that, in turn, enhance IgE production by B cells. It should be noted that Th cells have been divided into two subsets based on cytokine profiles secreted upon antigen stimulation: Th1 cells secrete interleukin (IL)-2 and interferon (IFN)- γ , while Th2 cells secrete IL-4, IL-5, IL-10 and IL-13. Th2 cytokines IL-4 and IL-13 stimulate B cells to secrete IgE.³⁵ The association of hypo- and hyperthyroidism with higher levels of IgE suggests a link between hypo- and hyperthyroidism and immune responses involving Th2 cells. This may be a subject for further investigation. Ward *et al.* demonstrated that serum IL-2 and IFN- γ levels were significantly lower in a subset of hyperthyroid patients than levels found in control subjects,³⁶ suggesting a depressed Th1 pattern in the T-cell subset of hyperthyroidism. It has been also demonstrated that stimulated Th2 cells in hyperthy-

roid disease secrete excess IL-13 (37). IL-13 is the dominant IgE-inducing cytokine and also enhances the production of IgM, IgG and IgA.³⁵

The results of the present study also showed that the mean serum C3 levels in hypothyroidism group was significantly higher in comparison with the euthyroid group. It has been reported previously that some inflammatory parameters, such as C-reactive protein (CRP), were increased in hypothyroid patients.³⁸ Accordingly, the same inflammatory mediators in hypothyroid patients may inducing C3 production by hepatocytes, epithelial cells and fibroblasts. No significant difference was observed in C4 levels between hypothyroid and euthyroid groups. The reason for these apparently contradictory observations may be due to the differential inducers of C3 and C4: it has been reported that the C3 synthesis is dependent upon IL-1, IL-2 and tumor necrosis factor (TNF)- α , whereas C4 production is dependent upon IL-6 and TNF- α cytokines (39). Accordingly, the presence of a different cytokine profiles in hypothyroid patients may differentially induce C3 production.

The results of the present study showed that in hypothyroid women the count of RBC is significantly decreased in comparison with the euthyroid group. Some RBC-related indices, such as hematocrit and haemoglobin, were significantly lower in hypothyroid group. Furthermore, 12% of the hypothyroid patients were anemic, based on WHO criteria. These results indicate that thyroid hormone influences RBC-related parameters such as hematocrit and hemoglobin. The association of anemia with hypothyroidism has been also reported in other investigations.⁴⁰ The presence of receptor for thyroid hormones has been demonstrated on haematopoietic progenitor cells.¹⁴ It has been also reported that, directly or indirectly, thyroid hormones stimulate growth of erythroid colonies through erythropoietin.^{14,40} It has also been suggested that decreased erythropoietin levels may account for anemia in hypothyroidism.²⁴

The present study also showed that the mean red cell volume (MCV) is significantly decreased in the

hyperthyroid group in comparison with the hyperthyroid and euthyroid groups. The underlying mechanisms for this alteration is unknown. One possible mechanism may be premature aging of erythrocytes in the circulation of hyperthyroid patients.⁴¹ Further studies should be conducted in order to obtain a better understanding of the mechanisms that induce these alterations in peripheral blood cells of patients with thyroid disorders.

In summary, the results of the present study demonstrate important immunological and hematological alterations in thyroid disorders including hypergammabulinemia and lower levels of MVC in hyperthyroid patients and higher IgE levels, C3 concentration and eosinophil count and some degree of anemia in hypothyroid patients.

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