Original Article

The Association of the Altered Interleukin-17 and Interleukin-21 Serum Levels with the Occurrence of Autoimmune Thyroid Diseases

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Abstract

Background: Autoimmunity denotes the abnormal attitude where an individual defenses act against its tissues. **Objectives:** The aim of the current study was to investigate the role of interleukin-17 (IL-17) and interleukin-21 (IL-21) in the occurrence of autoimmune thyroid diseases. **Materials and Methods:** Forty-five patients and forty-five controls were selected. The candidates were those suffering thyroid gland dysfunction. Clinical investigation was performed; the ones who fulfilled the diagnostic criteria were nominated. Cobas e411 was used for measuring serum thyroid stimulating hormone, T3 and (tetraiodothyronine) T4 levels, whereas anti-thyroid peroxidase (TPO) antibodies, IL-17, and IL-21 serum levels were measured by enzyme-linked immunosorbent assay. **Results:** The mean thyroid stimulating hormone serum levels (12.04 ± 2.76) of the patients differed statistically significantly from that of the controls (1.87 ± 0.15) ($P = 0.003$). Whereas, the reported T3 and T4 mean serum levels were 2.05 ± 0.14, 100.66 ± 4.76 for the patients and 2.14 ± 0.07, 105.37 ± 2.92 for the control, respectively differed statistically non-significantly ($P = 0.57$; $P = 0.31$, respectively). The mean serum concentration of anti-TPO antibody levels of the patients (259.08 ± 59.99) was significantly different ($P < 0.001$) from that of the controls (8.71 ± 1.23). A statistically significant difference appeared when mean serum concentrations of IL-17 of the patients (44.05 ± 5.89) and the controls (29.43 ± 7.99) were compared ($P = 0.04$). Moreover, a statistically significant difference ($P = 0.02$) was observed when serum IL-21 level of the patients (57.03 ± 24.02) and controls (43.87 ± 18.48) were compared. **Conclusion:** The alterations in serum interleukins' level can be a good marker to monitor the initiation and/or the progression of autoimmune thyroid diseases.

Keywords: Anti-TPO, autoimmune thyroid diseases, IL-17, IL-21

Introduction

Autoimmune thyroid diseases (AITD) succeed due to complex interactions between environmental and genetic attributes and are manifested by responsiveness to self-thyroid antigens facilitated by autoreactive T cells and B cells escaping tolerance. Both humoral and cell-mediated response cause tissue injury in AITD.[1] Most patients of autoimmune thyroiditis[2] have detectable circulating antibodies to a variety of thyroid-specific antigens such as thyroglobulin (Tg), colloid component other than Tg, thyroid peroxidase (TPO) enzyme, Na/I symporter protein, thyroid nuclei, and thyroid stimulating hormone (TSH) receptor. Out of these, anti-TPO and anti-Tg are the most prevalent and most useful in diagnosis.

The cytokines pose a significant characteristic in the pathogenesis of AITD. The tangible originators for the disorder of the self-tolerance and the succeeding events ending in the establishment of pathogenic autoimmune responses endure to be described for the majority of the readily initiated autoimmune disorders. Researchers succeeded to investigate models of human autoimmune illnesses; the monitoring of patients revealed an overall scheme in which proinflammatory cytokines involved in

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the origination of autoimmune disorders, whereas anti-inflammatory cytokines enable the fading of inflammation and the restoration of consistent activity subsequent to the acute phase of the illness. This concept is embodied in the T helper 1/T helper 2 paradigm, which has had a serious consequence on the contemporary knowledge of the cytokine relation to autoimmunity over the last period. Remarkably, the interleukin IL-17/IL-23 axis has gradually arisen as the distinct manner of rationale that has directed experts to critically re-consider the cytokine-controlled immune phenomena in the pathogenesis and management of autoimmunity.[3]

AITD, principally including Hashimoto's thyroiditis (HT) and Graves' disease (GD), is an organ-specific autoimmune illness.[2] Former investigations have confirmed the role of a newly discovered cells for example T helper 17 (CD4+IL-17+) in the initiation of autoimmune thyroid disease.[4] T helper 17 cells are proinflammatory in nature, because they are mainly engaged in protection against fungi and bacteria. They propose a connection between innate and adaptive immunity. These cells have a decisive role in the etiology and pathogenesis of numerous autoimmune disorders, in which T helper 1 was formerly well-thought-out as a leading factor.[5] A product of T helper 17, IL-21 had gained considerable appreciation as a proinflammatory cytokine with a potential role in the pathogenesis of AITD; there are higher serum IL-21 and IL-21 mRNA levels in recently identified HT and GD cases. Though, IL-21 displays no positive link with clinical parameters, involving (free T4) FT4, (free T3) FT3, (thyroglobulin antibodies) TgAb, (thyroid stimulating hormone receptor antibodies) TRAb, and (anti-thyroid peroxidase antibodies) TPOAb.[6]

Materials and Methods

Ninety individuals, 45 patients, and 45 apparently healthy controls were included in this study. Five milliliters venous blood were aspirated from each patient and control, left to dry at room temperature for 15 min, and centrifuged to obtain the necessary amount of serum. Sample collection lasted for 6 months (November 2018 through May 2019); the candidates were those who visited Duhok Central Laboratory for routine laboratory testing. Cobas e411 was used to measuring serum TSH (Elecsys®, Mannheim, Germany) T3 (Elecsys®, Mannheim) and T4 (Elecsys®, Mannheim) levels, while anti-TPO (AESKULISA®, Wendelsheim, Germany) antibody, IL-17 (SHANGHAI YEHUA®, Shanghai, China), IL-21 (SHANGHAI YEHUA®, Shanghai) serum levels were measured by enzyme-linked immunosorbent assay. The preparation of working solutions, buffers and the procedures performed throughout this study strictly followed the manufacture's rules.

Statistical analysis

All data were analyzed by the statistical package for the social science (IBM Corporation, New York, New York) statistical package (version 25.0). Independent samples *t* test was used to compare the means in a group-wise manner. *P* value ≤ 0.05 were considered statistically significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 27112018-9 (including the number and the date in November 27, 2018) to get this approval.

Results

The results of the present study revealed that women constituted most of the participants in both patients group (88.89%) and the control group (80%) whereas men were far less than women and they were resembled by 11.1% in the patients group and 20% of the control group [Table 1].

The findings of the current work showed a mean log TSH serum level of 12.04 ± 2.76 for the patients which profoundly surpassed that of the apparently healthy controls (1.78 ± 0.15); the difference was statistically significant ($P = 0.003$), whereas, T3 and T4 mean serum levels were 2.05 ± 0.14, 100.66 ± 4.76 for the patients and 2.14 ± 0.07, 105.37 ± 2.92 for the healthy control group. The later finding indicated no significant differences between the two categories ($P = 0.57$, $P = 0.31$, respectively) [Table 2].

In the current study, the mean serum concentration of anti-TPO antibody of the patients (259.08 ± 59.99) was greater than that of the healthy controls (8.71 ± 1.23) and that difference was highly statistically significant ($P < 0.001$) [Table 3].

In the current work results, a statistically significant difference was found when mean serum concentrations of IL-17 for patients (44.05 ± 5.89) and controls (29.43 ± 7.99) were compared ($P = 0.04$). On the other hand, IL-21 serum levels of patients (57.03 ± 24.02) and healthy controls (43.87 ± 18.48) were compared and statistically significant difference ($P = 0.02$) was noticed between the two groups [Table 4].

Table 1: Gender distribution between patients and control group

Gender	Patients (%)	Controls (%)
Male	5 (11.1)	9 [4]
Female	40 (88.9)	36 (80)
Total	45	45

Table 2: The means of TSH and thyroid hormones serum levels for patient and control groups

Hormones (units)	Group	Number	Mean serum concentration ± SE	*P*-value
TSH (uIU/mL)	Patients	45	12.04 ± 2.76	0.003**
	Healthy controls	45	1.78 ± 0.15	
T3 (nmol/L)	Patients	45	2.05 ± 0.14	0.57
	Healthy controls	45	2.14 ± 0.07	
T4 (nmol/L)	Patients	45	100.66 ± 4.76	0.31
	Healthy controls	45	105.37 ± 2.92	

**Significant at $P \leq 0.01$

Table 3: Anti-TPO mean serum concentrations of patients and controls

Antibody (unit)	Group	Number	Mean anti-TPO serum concentration ± SE	*P*-value
Anti-TPO (IU/mL)	Patients	45	259.08 ± 59.99	<0.001***
	Healthy controls	45	8.71 ± 1.23	

***Significant at $P \leq 0.001$

Table 4: Mean serum of interleukin-17 and interleukin-21 for patients and controls

Interleukin	Patients (mean serum conc. ng/L ± SE)	Healthy controls (mean serum conc. ng/L ± SE)	*P*-value
Interleukin-17	44.05 ± 5.89	29.43 ± 7.99	0.04*
Interleukin-21	57.03 ± 24.02	43.87 ± 18.48	0.02*

*Significance at $P \leq 0.05$

Discussion

Nonspecific signs frequently accompany the dysfunction of the thyroid, and diagnosis is determined by laboratory testing of TSH, T3, and T4. The recent path for the detection and therapy of a malfunctioning thyroid counts on the assessment of TSH, as the most specific and perfect marker of systemic functioning of the thyroid, with test conclusions elucidated along with a standard reference rate.[7] Nevertheless, no general screening recommendations are available for thyroid disorders in adults. The American thyroid association orders screening at 35 years of age and every five years thereafter, with greater consideration to individuals who are at great hazard, for instance: pregnant females, women older than 60 years, type 1 diabetic subjects or other autoimmune illnesses, and those with a history of neck irradiation.[8]

AITD is regularly predictable by the occurrence of anti-thyroglobulin (Tg) and anti-TPO autoantibodies in combination with thyroid hormone discrepancy.[9] The results of this work were in accordance with those of other researchers who presented that anti-TPO antibodies typically found in individuals with abnormal TSH compared to those with normal TSH.[10] In the same way, it has been noticed that TSH is frequently disturbed if anti-thyroglobulin or anti-thyroid peroxidase antibodies are existing in the Saudi people.[11] Likewise, a group of researchers revealed that anti-TPO positivity is associated with a 60% incline in TSH.[12] In Iran, consistent with previous manifestations described by others who searched the correlation of T3, T4, and TSH with anti-TPO in approximately 2500 individuals. They found that the hormones' serum values suggestively altered in an autoantibody-positive group.[13]

The culmination of last century has familiarized some variations into T helper (Th) cells class. The acknowledgement of the novel subgroup of T helper cells secreting IL-17[14] revised model of Th1–Th2 paradigm and it was termed Th17.[15] The Th17 lymphocytes lineage, which was recognized and defined for the first time by a research team.[16] Their great capabilities to elicit acute and chronic inflammation render them ideal candidate for a decisive contributor in progress of autoimmune disorders.[17] Plentiful researches based on animal and human ascertain their key contribution in the pathogenesis of mankind organ-specific and systemic autoimmune disorders.[18,19] These findings nominate Th17 cells and their development and/or function-regulating pathway a good therapeutic target. Therapies focus on inactivation of Th17-dependent pathways are linked with clinical enhancement, but on the other hand are recurrently stimulating drawbacks.[15] This distinct category of CD +4 T lymphocytes secretes also IL-21[20] and IL-22.[21] Both of them are pro-inflammatory cytokines; IL-21 aids the restoration of the equilibrium between Treg cells and Th17 and IL-22 is a member of IL-10 cytokine group, which is connected to chronic inflammation and takes part in pathology of several autoimmune ailments. More recently, the existing division into non-pathogenic and pathogenic Th17 cells must be considered. The non-pathogenic

Th17 lymphocytes obviously arise in the gut, and they are in charge of sustaining the homeostatic microbiota and attacking against pathogenic microorganisms.[22] They have no autoreactive characteristics. Dissimilar to non-pathogenic cells, the pathogenic Th17 lymphocytes are activated by IL-23 and are chiefly stimulating the progression of autoimmune responses to self-antigen.[4,22]

The results of the present work were in accordance to what previously stated regarding an increased share of Th17 cells and the cytokines they secrete (mainly IL-17 family) in the course of autoimmune thyroid diseases.[5]

Generally, the results of the present study came in line with an earlier finding which emphasized the impact of Th17-associated type of cytokines such as IL-21 on the establishment of AITD, particularly in HT.[23-25]

It was confirmed that IL-21 levels uprise in the tissues and peripheral blood of subjects with rheumatoid arthritis, systematic lupus erythematosus, immune thrombocytopenia, type 1 diabetes, primary Sjogren's syndrome, psoriasis, and AITD.[26] The results of the current study are in accordance with the consensus describing Th17 lymphocytes, which produce large quantity of IL-21 are proposed to be proinflammatory effector T cells, with central functions in the induction of autoimmunity and facilitating tissue injury.[27] Compared with Th1 or Th2 cells, Th17 cells reveal almost fivefold higher levels of IL-21 mRNA and protein.[28,29] The later statement may explain the significant difference attained in the current study between patients and controls when IL-21 serum level was considered.

Of note, one of the keys to control autoimmune disease is a better comprehension of cytokine reactions in these disorders, which will aid the invention of effective immunotherapeutic approaches. This special issue encompasses molecular mechanisms of cytokines in immunopathogenesis of autoimmune diseases from bench to bedside.[30]

Conclusion

Autoimmune thyroid diseases cause a deviation of certain cytokine serum level from their normal attributes which in turn emphasizes the pivotal role of cytokines in the pathogenesis of autoimmune thyroid diseases.

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Conflicts of interest

There are no conflicts of interest.

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