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Estimation of Serum Level and rs17855750 A/C Genetic Polymorphism of Interleukin-27 in Hashimoto Thyroiditis Patients

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Abstract

Background. Hashimoto's thyroiditis (HT) is a prevalent autoimmune disorder characterized by lymphocytic infiltration and thyroid destruction, leading to hypothyroidism. Cytokines, particularly IL-27, are essential mediators that balance self-tolerance and the initiation of autoimmune responses. **Aim.** The objective of this study is to evaluate serum IL-27 levels in HT patients versus healthy controls and investigate the $rs17855750$ A/C polymorphism's association with genetic susceptibility to HT. **Methods**. Serum IL-27 was measured using ELISA, and thyroid function (FT3, FT4, TSH) was assessed. Genetic analysis identified AA, AC, and CC genotypes for the rs17855750 polymorphism to compare frequencies between study groups. **Results**. IL-27 was significantly elevated in HT patients ($p < 0.0001$). The AA genotype was significantly more frequent in the HT group ($p = 0.03$). **Conclusion.** Findings suggest IL-27 serves as a potential biomarker, and the AA genotype contributes to HT susceptibility.

Keywords: Interleukin-27, *rs17855750*, polymorphism, SNPs, Hashimoto's illness.
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Introduction

Hashimoto's thyroiditis (HT) is an autoimmune illness occurs when the immune system mistakenly targets healthy cells and organs in the body. This disorder happens when the thyroid gland is attacked by the immune system, leading to inflammation and a decrease in its hormone production capabilities. (1,2). The thyroid is the site of an accumulation of lymphocytes, or large quantities of white blood cells.

The antibodies that initiate the autoimmune response are produced by lymphocytes. Chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis are alternative terms for the same medical illness. One problematic aspect of the illness is the antibodies production that attack thyroid tissue, resulting in progression fibrosis. It can take some time till later in the illness process to make the diagnosis, which is typically difficult. The most common findings from these tests are elevated values of antithyroid peroxidase (TPO) antibodies resulting in increase of values of free thyroxine (fT4) and thyroid-stimulating hormone (TSH). Nevertheless, in the early stages of the condition, some individuals may have signs and laboratory results that are comparable to hyperthyroidism. This is due to the fact that the thyroid gland is susceptible to random cell death (3,4). When the immune system mistakenly targets and destroys thyroid cells, a condition known as Hashimoto thyroiditis. It accounts for the vast majority of cases in industrialized nations (5).

A variety of indicators play a part in HT illness; interleukins is one of them. Contrary to popular belief, a wide variety of cells in the body produce interleukins (IL), a kind of cytokine, and involved in different clinical cases (6–9). This cytokine is essential for immune cell activation and differentiation, as well as for cell motility, adhesion, maturation, and proliferation. Moreover, they have the ability to either reduce or increase inflammation (10). One of these interleukins, IL-27, is a recent addition to the IL-12 family. It is significantly influencing how the immune system and CD4 + T cell differentiation are regulated. Several signaling cascades, including as the p38 MAPK and JAK-STAT pathways, are triggered by IL-27. When p38 MAPK is active, it phosphorylates a number of downstream targets, some of which are transcription factors, which allows it to alter gene expression. In addition, STAT (signal transducers and activators of transcription) proteins are phosphorylated by active JAKs, resulting in dimerize, translocate to the nucleus, and regulate gene expression (11). Macrophages, monocytes and dendritic cells (DCs), are all examples of antigen-presenting cells (APCs) that, when activated by microbes or other immunological stimuli, mainly produce IL-27 (12).

It has been demonstrated that IL-27 is crucial in a number of autoimmune illnesses (13). IL-27 activates many signaling pathways and has pro- and anti-inflammatory characteristics. In general, IL-27's pro- or anti-inflammatory effects depend on the specific human illness, the animal model, and the analyzed tissue or cell type. However, studies from animal models of autoimmunity have mostly been used to infer the likely function of IL-27 in the illness processes due to the clear difficulties in identifying the specific role of this cytokine from blood or urine values in humans with autoimmunity (11,14).

Therefore, the work goaled to estimate the role of sera level of IL-27 and its SNP in incidence of HT.

Materials and Methods

This research was conducted at the Diabetes Illness Center on patients with Hashimoto's illness after receiving clearance from the Ethics Committee of Biotechnology, Collage of Science, University of Baghdad. The purpose was to assess changes in several biomarkers associated with this condition. Fifty individuals having a historical diagnosis of Hashimoto's illness were included in the research. They were comprised of 36 women and 14 men, with ages ranging from 16 to 57. In addition, 50 individuals who seemed to be in good health were included as the control group. There were 32 women and 18 men, and their ages varied from 18 to 62. Samples were collected during the period from June to July 2023. Each patient was requested to fill out a full questionnaire that included basic demographic information (age, sex, medication history, etc.) and more specific measurements (sera Anti Tg, Anti TPO, TSH, FT4, FT3, etc.). Each patient without HT, suffered from different autoimmune diseases, its age out of the range (15-65 years), pregnant, or had concomitant other conditions, was excused from the study. Each control individual was no suffered from HT or other autoimmune diseases.

Blood sample collection

Under aseptic conditions, 6ml of venous blood were taken from each subject. A sterile EDTA tube was used to collect two milliliters of peripheral venous blood for the eosinophil count test, a sterile gel tube was used to collect two milliliters of peripheral venous blood for DNA extraction, and a centrifuge was used to separate the sera from the blood in the gel-tube. The sera were then dispensed into two sterile Eppendorf tubes, each of which held tightly closed and kept at -20°C until the sample was tested.

Immunological method

The amount of IL-27 in the blood was measured using an ELISA kit manufactured by SunLong Biotech Co., LTD of China. The steps outlined by the manufacturer were adhered to. This kit has a detection range of 3.3-200 pg/ml.

Molecular study

Samples of DNA were extracted from peripheral blood utilizing the kit of ReliaPrep™ DNA extraction kit (Promega/ U.S.A), based on the instructions of manufacturer. Single nucleotide polymorphisms (SNPs) in the *IL-27* gene (*rs17855750*) were evaluated via the amplification in qPCR in High resolution melting (HRM) assay. The sequence of forward primer is: (5′-CTGGGGGGCAAGGTCTGTTA GT-3′) and reverse primer is: (5′-GCTCCTGGTTCAAGCTGGTGTC-3) with product size (232 bp) according to Pang *et al.* (15), followed by an HRM analysis with ramping by 0.2 °C from 60 to 95 °C. The EVA-Green in master mix component was used, and the polymorphism detected by High Resolution Melt (HRM) analysis. Normalized melting curves (NMCs) and differential curves (DCs) were generated using the HRM Tool that was incorporated into the program, and qPCR-HRM was used for polymorphism detection. The cycling protocol was programed for the following optimized cycles and according to the thermal profile is enzyme activation at 94ºC for 10 sec, denature at 95ºC for 15 sec, Annealing at 60.6ºC for 1 minute, Extension at 72ºC for 20 sec and HRM 65-95ºC 0.2 sec for 1 degree.

Statistical Analysis

The substantial variations in the identified allele between gene collections were evaluated using SPSS statistical analysis. Probability measures such as odds ratios (ORs) and 95% CIs were computed using a logistic regression model.

Results

The results indicated that there were significant variations in Mean ± SD of age among patients with HT and health controls (HCs) $(41.2 \pm 11.6\ vs.\ 36.7 \pm 11.6\ years, respectively)$ with $(p < 0.05)$. No significant variations were observed in sex of patients and controls with $(p > 0.05)$, as in table 1.

There were highly significant variations in Mean ±SD of immunological values of FT3, FT4 and TSH among patients with HT and HCs (1.70 ± 0.60 vs. 4.70 ± 0.95 ng/dL, 0.81 ± 0.30 vs. 16.35 ± 1.97 µg/dL and 7.36 ± 3.42 vs. 1.57 ± 1.00 IU/mL, respectively) with p < 0.0001, as showed in table 2.

Table 1: The Demographic of the studied groups.

Parameter	Patients HT (n=50)	HCs (n=50)	p-value
Age (years)	No. (%)	No. (%)	
<30	10 (20.0)	16 (32.0)	0.079 NS
30-39	9 (18.0)	16 (32.0)	
40-49	12 (24.0)	7 (14.0)	
≥50	19 (38.0)	11 (22.0)	
Mean ±SD (Range)	41.2 ± 11.6 (16-56)	36.7 ± 11.6 (16-59)	0.052 NS
Sex			
Male	15 (30.0)	23 (46.0)	0.099 NS
Female	35 (70.0)	27 (54.0)	

Table 2: Immunological parameters of Individuals with HT and HC.

Parameter	patients HT (n=50)	HCs (n=50)	p-value
FT3 (ng/dL)	1.70 ± 0.60	4.70 ± 0.95	0.0001*
FT4 (µg/dL)	0.81 ± 0.30	16.35 ± 1.97	0.0001*
TSH (IU/mL)	7.36 ± 3.42	1.57 ± 1.00	0.0001*
Anti TPO (IU/mL)	221.45 ± 143.66	-	-
Anti Tg (IU/mL)	190.72 ± 54.08	-	-

There was significant variations in Mean ±SD sera values of IL-27 among Individuals with HT and HCs (458.12 ± 117.94 vs. 0.60 ± 0.10 ng/m, respectively) with p < 0.0001, as displayed in figure 1. The IL27 gene was observed single nucleotide polymorphism SNP (rs17855750 A/C).

Three genotypes (AA, AC and CC) were detected, AA was significantly varied with p-value = 0.030, AC and CC were non-significantly varied with (OR: 0.319 vs. 0.962 and 95% CI: 0.03-3.73 vs. 0.08-11.6 respectively) among groups, as displayed in table 3. The genotype frequencies of AA, AC and CC in rs17855750 polymorphism were 4, 46 and 50% in Individuals with HT, 2, 72 and 26% in HCs, respectively. These frequencies were significantly variations in females with HT and health females, with p < 0.05, as displayed in table 3.

Table 3: genotypes and allele frequencies of IL27 gene rs17855750 SNP in Individuals with HT and HCs.

IL-27 *rs17855750*	Hashimoto's Illness (n=50)		Control (n=50)		OR (95%CI)	*p*-value
	No.	%	No.	%		
AA	2	4.0	1	2.0	-	0.030*
AC	23	46.0	36	72.0	0.319 (0.03-3.73)	0.340
CC	25	50.0	13	26.0	0.962 (0.08-11.6)	0.975
A	27	27.0	38	38.0	0.330(0.0 4-12.0)	0. 060
C	73	73.0	62	62.0	0.971(0.09- 15.0)	0.080

Discussion

In corresponding with this study, Ahmed and Mohammed (16) reported that the mean age of patients was 40.72 years, and females constituted 60.7% of cases. In addition, it has been reported that the incidence of HT was greater percentage in females (17,18) and the male to female ratio was around 1:3.8 (18). Women have a more vigorous immune response than men, which unfortunately makes them more prone to autoimmune diseases, including Hashimoto's thyroiditis and Graves' disease, leading causes of hypothyroidism and hyperthyroidism (19). Though little information is now available on their potential function in conditioning the aggregation of autoimmune illnesses, it is known that growing older and being female are linked to an increased risk of acquiring autoimmune disorders, Women have up to a fourfold increase in risk for autoimmune disease compared to men. Many explanations have been proposed, including sex hormones, the X chromosome, microchimerism, environmental factors, and the microbiome (20).

The result in the recent work confirms the effect of the HT illness on the values of thyroid hormones FT3, FT4 and TSH directly. One of the most noticeable endocrine glands on the human body is the thyroid gland. Produced by the thyroid gland on thyroglobulin (Tg), the hormones thyroxine (T4) and triiodothyronine (T3) regulate metabolism, enhance protein synthesis, facilitate the development of the central and peripheral nervous systems, and increase oxygen consumption by all cells in the body with the exception of those in the retina, adult brain, spleen, and red blood cells (21). A thyroid-stimulating hormone (TSH), which is pituitary hormone, results in the gland of thyroid to release the hormones thyroxine (T4) and triiodothyronine (T3). TSH regulate the metabolic rate of almost every single cell in the body (22). It is well-known that anti-TPO affects around 10% of the general population and 30% of the elderly. Hypothyroidism in old age is a possible diagnosis prompted by this illness. Additionally, several investigations have demonstrated that sub-clinical hypothyroidism can progress to clinical hypothyroidism if anti-TPO is present (23). A blood test measuring your hormone levels is the only accurate way to find out whether there's a problem (24). A study on the correlation of various thyroid antibodies, such as anti-TPO and antiTg, with the different thyroid hormones, such as TSH, T3, and T4, revealed the presence of anti-TPO and antiTg had strong correlations. On the other hand, a moderate to low correlations were observed when the two were in comparison with T3 (25). pproximately 64.45% of the individuals who had elevated TSH values and underwent antiTPO testing were found to have elevated values of antiTPO. It was determined by the study that individuals with this illness should undergo testing for autoimmune thyroiditis (26). There were significant variations in Mean ±SD sera values of IL-27 among Individuals with HT and HCs (458.12±117.94 vs. 0.60±0.10 ng/m, respectively) with $p<0.0001$, as displayed in figure 1.

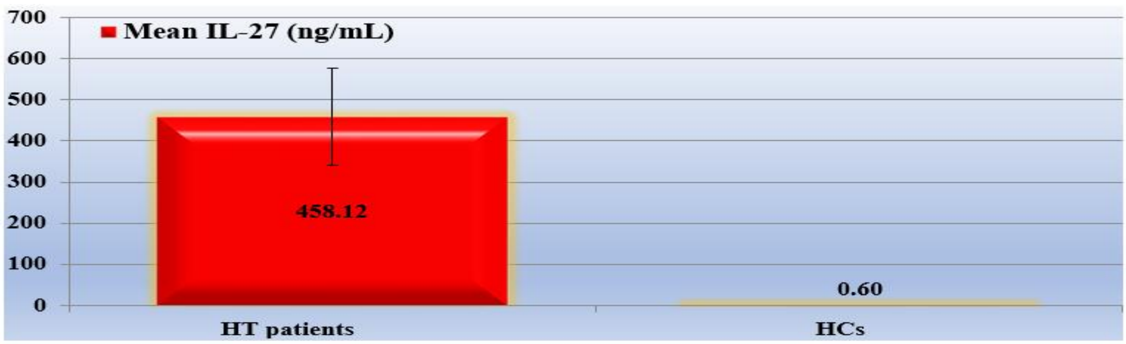

Figure 1: Sera values of IL-27 in patients with HT and HCs.

The appearance of a highly significant variation in the level of interleukin 27 in Individuals with HT proves the existence of a relationship between IL-27 and this illness, as displayed in the figure 1 above. Since Hashimoto’s illness is an autoimmune condition marked via inflammations of the thyroid glands (27). The function of IL-27 in Hashimoto’s illness has been a subject of research interest due to its involvement in regulating immune responses and inflammation. Hypothyroidism develops when the system of immune wrongly attacks and cause damage in the gland of thyroid. The cytokine IL-27 is essential for controlling inflammation and immunological responses. Patients with Hashimoto's thyroiditis may have greater values of IL-27 compared to healthy persons, according to research (28).

The inflammatory and anti-inflammatory actions of IL-27 are mediated by antigen-presenting cells. It has the ability to control the actions of several types of immune cells, such as T cells, B cells, and natural killer cells. Dysregulation of IL-27 values may have functions in the development of autoimmune illnesses like HT (29). A number of research have looked at how IL-27 values relate to Hashimoto's thyroiditis. According to their research, IL-27 values are greater in Hashimoto's thyroiditis patients than in HCs. People suffering from Hashimoto's thyroiditis may have elevated IL-27 values due to persistent immune system activation and inflammation (28,30). The precise mechanisms underlying the elevation of IL-27 in Hashimoto’s thyroiditis are not fully understood. However, it is hypothesized that dysregulation of immune responses, genetic factors, and environmental triggers may contribute to the upregulation of IL-27 in this autoimmune condition (31).

The IL-27 is a gene on chromosome 16p11 that belongs to the IL-12/IL-6 family (32). It is among the essential potential genes for T cell growth and differentiation.

Polymorphisms of the IL27 gene are now known to be important in a number of inflammatory and autoimmune illnesses, including rheumatoid arthritis (33), Behcet's illness (34), inflammatory bowel illness (35), and systemic lupus erythematosus (36). Prior research has demonstrated a noteworthy correlation between HT and IL27 rs17855750 (37). The molecular mechanisms underpinning the involvement of IL27 rs17855750 in autoimmune disorders remain unknown, but the rs17855750 locus is a sensitive factor to HT (38,39). The IL-27 gene rs17855750 single nucleotide polymorphism (SNP) observed a genetic variation in the human genome, the genotype AA, AC and CC. The mutant genotype CC (50%) is highly frequency in patients more than wild type compared with heathy control. This specific SNP may has been affected in diseas..

Studies have investigated the association between the rs17855750 SNP and Hashimoto’s thyroiditis, was closely related to the abnormal activation of T lymphocytes, and IL27 is a proinflammatory cytokine that plays an essential role in transcriptional activation and regulation of T lymphocytes

(28). IL27 was viewed as a proinflammatory cytokine before, due to its support to the development of interferon (IFN)-secreting T helper cells (Th). However, IL27 has recently been shown to act as a negative regulator of ongoing immune responses during infection and autoimmune inflammation because it can limit the production of proinflammatory cytokines by CD4 T cells including IFN and resist the role of IL-6 (43).Studied examined the association of IL27 gene with several autoimmune and inflammatory diseases, analyzed the contribution of potentially functional SNPs of IL27 and demonstrated a clear association between IL27 polymorphisms and disease susceptibility. Previous studies showed that rs153109, rs17855750 and rs181206 of IL27 gene displayed significant associations with dilated cardiomyopathy , atrial fibrillation , allergic rhinitis , pre-eclampsia and renal cell carcinoma and Thyroid autoimmunity (40,41.42. The pathogenesis of autoimmune illness is not well-understood, but complex interactions between genetic, environmental, immunological, and gut microbiome factors have been suggested (44,45).

Many studied demonstrated cytokine (particularly pro-inflammatory cytokines) formation have an essential function in the chronic illnesss (46,47). Changes in immune status can disrupt this balance and excessive cytokines which causes several disorders such various autoimmune illnesss (48–50).

Conclusion

The identifications of the associations of IL27 *rs17855750* with HT, genotypes significant with some ages. HT effects on immunological parameters patients, further more sera values 458.12 of IL-27 is highly increased in patients compare to healthy. Our findings proven genetic contribution susceptibilities and proved the crucial function of IL27 in pathogenesis of HT and concede as a biomarker in HT illness.

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