The influence of single-nucleotide polymorphisms of interleukin-1β –511 and +3954 on the susceptibility to Hashimoto's thyroiditis in Egyptian women: immune-endocrine interactions

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Background
Hashimoto's thyroiditis (HT) is a T-cell-mediated autoimmune disease. Cytokines play a crucial role in modulating immune responses that affect the balance between maintenance of self-tolerance and initiation of autoimmunity. Thus, we aimed to explore the possible associations of interleukin (IL-1β) –511C/T (rs16944) and IL-1β +3954C/T (rs1143634) gene polymorphisms with susceptibility of HT, and to clarify the impact of these polymorphisms on thyroid function of Egyptian women.
Patients and methods
Polymorphisms of the IL-1β –511 and IL-1β +3954 genes were assessed in a case–control study comprising 110 HT patients and 90 controls. Genetic variants were genotyped by multiplex PCR. Polymorphisms of the IL-1β were studied by PCR-restriction fragment length polymorphism analysis.
Results
Our results revealed that the IL-1β –511 CT genotype distribution was significantly higher in HT patients than in controls. With regard to IL-1β +3954 gene polymorphisms, our results showed that there was a nonsignificant difference between the control and HT groups. Women carrying TT and CT genotype of IL-1β –511 had significantly higher values of C-reactive protein, thyroid-stimulating hormone, anti-thyroid peroxidase, and anti-thyroglobulin. As regards the IL-1β serum level, women carrying TT and TC genotype of IL-1β –511 had significantly higher values compared with patients carrying the CC genotype. Moreover, anti-thyroglobulin and free thyroxine were the only independently correlated factors with IL-1β serum level by linear regression analysis.
Conclusion
CT genotype distribution was significantly higher in patients with HT than in controls with regard to IL-1β –511 (C>T) gene polymorphisms.

Keywords:
Hashimoto', s thyroiditis, interleukin-1β, single-nucleotide polymorphisms

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Introduction

Autoimmune thyroid diseases include Hashimoto's thyroiditis (HT) and Graves' disease (GD). Many factors, such as genetic, hormonal, and environmental factors, are involved in the initiation and/or development of autoimmune thyroid disease [1]. Mounting evidence indicates that HT is a T-cell-mediated autoimmune disease that leads to clinical hypothyroidism because of thyroid destruction [2]. Interestingly, the pathophysiologic changes seen in thyroiditis are mediated by inflammatory cytokines [3].

There is compelling evidence suggesting an important role of cytokines in the pathophysiology of autoimmune disease and health [4]. Each cytokine signals by binding either to a unique or a shared receptor, triggering an intracellular signaling cascade that can cause upregulation or downregulation of transcription factors that regulate the expression of various other genes [5].

Omics studies have indeed demonstrated that interleukin-1 beta (IL-1β), which is a proinflammatory cytokine with widespread biological activities expressed by activated macrophages and several other types of cells, is thought to play a crucial role in the pathogenesis of autoimmune diseases [6], especially T-cell-mediated autoimmune diseases [7].

The IL-1β gene has two single-nucleotide polymorphisms (SNP) at position –511 in the

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promoter region (rs16944) and at position +3954 in the fifth exon (rs1143634), respectively [8,9]. The polymorphisms of the IL-1 family are involved in several autoimmune diseases such as systemic lupus erythematosus [10,11], rheumatoid arthritis [12], autoimmune hemolytic anemia [13], and GD [14].

Increasing evidence points to critical roles of proinflammatory cytokines in modulating immune responses. Although the role of cytokines is often confusing and is neither independent nor exclusive of other immune mediators, a regulatory cytokine may either favor the induction of tolerance against thyroid autoimmune disease or favor activation and/or exacerbation of autoimmune response. Therefore, we aimed to explore the possible associations of IL-1β −511C/T (rs16944) and IL-1β +3954C/T (rs1143634) gene polymorphisms with susceptibility of HT, and to clarify the impact of these polymorphisms on thyroid function of Egyptian women.

Patients and methods

This case–control study comprised 220 patients diagnosed with HT who were recruited from the Outpatient Clinics of the Endocrinology and Diabetes Unit of Internal Medicine Departments at the Zagazig University hospitals and 180 normal controls who were matched to cases by age, sex, and ethnic origin. Diagnosis of HT was obtained on the basis of clinical findings, positive serum antibodies to thyroid peroxidase (TPO-Ab) and/or thyroglobulin (TG-Ab). All participants underwent complete history taking and thorough clinical examination, and met the criterion for the diagnosis of thyroid dysfunction based on thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). We excluded patients with a history of myocardial infarction, angina, stroke, pregnancy, and diabetes. As well as those with a history of drug intake. The Ethics Committee of Faculty of Medicine, Zagazig University, approved this work. All participants signed the written informed consent before their inclusion and had a disease duration of 1 year or more.

Blood sampling

Blood samples were drawn from all participants after an overnight fast and divided into three portions: 1 ml of whole blood was collected into evacuated tubes containing EDTA, for glycated hemoglobin; 1 ml of whole blood was collected into evacuated tubes containing potassium oxalate and sodium fluoride (2 : 1) for fasting blood glucose. Serum was separated immediately from the remaining part of the sample and stored at −20°C until analysis.

Assay of thyroid function and autoantibody levels

The serum concentration of FT4 was measured with a radioimmunoassay kit (Eiken Chemical Co. Ltd, Tokyo, Japan). The normal range of serum FT4 is 1.0–1.6 ng/dl (12.9–20.6 pmol/l). The serum concentration of FT3 was measured with a radioimmunoassay kit (Japan Kodak Diagnostic Co. Ltd, Tokyo, Japan). The serum thyrotrophin (TSH) concentration was also measured with a radioimmunoassay kit (Daiichi Radioisotope Laboratories Ltd, Tokyo, Japan). Serum anti-TPO using Accu-Bind ELISA kit (Monobind Inc., Lake Forest, CA, USA) and serum anti-TG using Accu-Bind ELISA kit (Monobind Inc.).

Genotyping of interleukin-1β –511 and interleukin-1β +3954 genes' polymorphisms

Genotyping for IL-1β −511C/T and IL-1β +3954C/T polymorphisms in unrelated systemic lupus erythematosus patients and healthy controls was carried out by PCR and digested with restriction enzymes: AvaI, and a Taq, respectively. Alleles were differentiated by visual determination of size relative to known markers. The two polymorphisms studied are located on chromosome 2q14. The IL-1β gene polymorphisms IL-1β −511C/T and IL-1β +3954C/T were tested [15].

Statistical analysis

Statistical analyses were performed using the statistical package for the social sciences for Windows (version 21.0; SPSS, Chicago, Illinois, USA). Data were expressed using descriptive statistics (mean±SD) and were analyzed using ANOVA test. Genotype frequencies in cases and controls were tested for Hardy–Weinberg equilibrium, and any deviation between the observed and expected frequencies was tested for significance. Using the χ^2 test. The statistical significances of differences in the frequencies of variants between the groups were tested using the χ^2 test. In addition, the odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated as a measure of the association of IL-1β −511C/T and IL-1β +3954C/T genotypes with HT. The appropriate sample size and power of the study were determined using PAWE-3D (32). Quantitative data analysis of variance test was performed to assess the impact of IL-1β −511 rs16944 (C>T) and IL-1β +3954 rs1143634 (C>T) mutations on clinical and thyroid function in HT patients. Linear regression analyses test was performed to test the influence of the main

independent variables against IL-1β in HT patients. A difference was considered significant at *P* value less than 0.05.

Results

Clinical, anthropometric, and biochemical characteristics of the studied groups

Patients with HT had significantly higher values of systolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol, as compared with controls (Table 1). Moreover, BMI waist/hip ratio values were significantly higher in HT patients than in controls. On the contrary, patients with HT had significantly lower levels of high-density lipoprotein cholesterol compared with controls. With regard to inflammatory markers, high-sensitivity-C-reactive protein and IL-1β were significantly higher in HT group cases, as compared with controls ($P<0.05$).

Clinical and biochemical characteristics in Hashimoto's thyroiditis patients according to their thyroid state

Patients with HT were classified according to the thyroid function; there were statistically significant increases in systolic and diastolic blood pressure, fasting plasma glucose, triglycerides, total cholesterol, LDL cholesterol, anti-TPO, anti-TG, and TSH in subclinical hypothyroidism ($n=70$) and clinical hypothyroidism ($n=48$), as compared with euthyroid cases ($n=60$) ($P<0.05$). In contrast, there were significantly lower values of high-density lipoprotein cholesterol ($P<0.05$). Our results demonstrated statistically significant higher values of anti-TPO, anti-TG, total cholesterol, and LDL in patients with subclinical hyperthyroidism ($n=20$) and clinical hyperthyroidism ($n=22$) than in euthyroid patients (Table 2).

Table 1 Anthropometric and biochemical characteristics in Hashimoto's thyroiditis patients

Parameters	Healthy control group (*N*=180)	HT group (*N*=220)	*P* value
Age (years)	32.08±8.63	31.6±7.35	0.746
SBP (mmHg)	125.34±7.25	137.52±7.07	<0.001*
DBP (mmHg)	86.24±3.95	85.68±l4.182	0.466
Waist/hip ratio	0.973±0.089	1.13±0.126	<0.001*
BMI (kg/m^2)	21.93±1.98.	37.74±4.56	<0.001*
TC (mg/dl)	168.6±19.63	202.16 ±13.49	<0.001*
HDL (mg/dl)	51.58±6.8	36.77±6.06	<0.001*
LDL (mg/dl)	66.33±27.0	110.54±42.4	<0.001*
TG (mg/dl)	201.4±5.85	259.64 ±34.56	<0.001*
FPG (mg/dl)	83.9±8.35	101.96 ±13.16	<0.001*
hs-CRP (μg/ml)	2.59±0.48	5.376±0.912	<0.001*
IL-1β (pg/ml)	4.44±0.40	12.97±1.70	<0.001*

Data are presented as mean±SD. DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HT, Hashimoto thyroiditis; IL, interleukin; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides. **P* value less than 0.05 when compared with control group.

Table 2 Anthropometric and biochemical characteristics in autoimmune thyroiditis patients according to their thyroid state

Parameters	SCHT (*N*=70)	CHT (*N*=48)	Subclinical hyperthyroidism (*N*=20)	Hyperthyroidism (*N*=22)	Euthyroid (*N*=60)
SBP (mmHg)	136.2±5.7*	136.8±6.1*	128.1±2.1	133.8±5.3	121.3±5.3
DBP (mmHg)	88.1±4.7*	87.1±5.6*	83.8±4.3	82.8±2.9	80.2±3.3
Waist/hip ratio	1.446±0.11*	1.49±0.18*	1.21±0.11	1.21±0.11	1.10±0.108
BMI (kg/m^2)	39.82±2.6*	42.57±1.72*	30.9±1.7	32.0±1.58	31 ±2.47
TC (mg/dl)	234.9±11.7*	244.4±11.8*	211±18.01*	193.5±25.2	201.4±9.3
TG (mg/dl)	266.9±24.4*	301.5±33.56*	232.6±8.8*	209.6±9.9*	189.2±14.0
LDL (mg/dl)	128.9±36.8*	148.5±4.9*	85.9±30.84*	93.7±10.60*	76.5±31.8
HDL (mg/dl)	33.7±4.935*	33.78±2.15*	43±2.549	44.8±3.97	49.5±6.12
FPG (mg/dl)	102.4±9.6*	121.1±9.0*	93.4±6.80	89±7.21	94±6.86
FT3 (pg/ml)	2.81±0.52	2.12±0.35	2.44±0.33	2.01±0.416	2.11±0.34
FT4 (ng/dl)	3.01±0.52	2.32±0.811	2.64±0.733	3.22±0.45	3.32±0.34
TSH (μIU/ml)(	8.62±1.56*	18.48±10.82	0.113±0.01	0.107±0.01	2.5±0.97
Anti-TPO (IU/ml)	77.32±3.58*	85.2±2.62*	53.1±2.522*	50.4±3.03*	58.3±3.9
Anti-TG (IU/ml)	3.49±0.12*	3.75±0.46*	3.72±0.651*	3.63±0.58*	1.87±0.62
hs-CRP (μg/ml)	4.48±0.12	5.11±0.46	372±0.651	4.63±0.58	4.87±0.62
IL-1β (pg/ml)	11.62±3.56	13.48±4.82	12.1±3.01	12.14±4.01	12.5±3.97

Data are presented as mean±SD. Anti-TG, anti-thyroglobulin antibodies; anti-TPO, anti-thyroid peroxidase; CHT, clinical hypothyroidism; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; LDL, low-density lipoprotein; SCHT, subclinical hypothyroidism; TC, total cholesterol; TG, triglycerides; TSH, thyroid-stimulating hormone. **P* value less than 0.05 when compared with euthyroid group.

Distribution of genotype and allele frequencies of interleukin-1β –511 and interleukin-1β +3954 in healthy controls and Hashimoto's thyroiditis patients

Genotype and allelic frequencies of IL-1β -511C/T (rs16944) and IL-1β +3954 rs1143634 (C>T) gene polymorphisms in patients with HT and healthy volunteers are presented in Table 2. The genotype distributions were in Hardy–Weinberg equilibrium in each studied group.

Regarding interleukin-1β –511C/T (rs16944) gene polymorphisms

The CC genotype distribution was significantly lower in patients with HT (28, 13%) than in controls (52, 29%) [OR (95% CI), 0.359 (0.174–0.739); $P<0.001$], whereas the CT genotype distribution was significantly higher in patients with HT than in controls [OR (95% CI), 1.837 (1.042–3.239); $P<0.05$]. With regard to the TT genotype distribution, there were nonsignificant difference among both groups [OR (95% CI), 1.056 (0.586–1.902); $P=0.857$]. In allele distribution, the frequency of the -511C allele was 39% (172 out of 440) in the HT group compared with 48% (172 out of 360) in the controls [OR (95% CI), 0.701 (0.399–1.233); $P=0.218$], whereas the -511T allele was 61% (268 out of 440) in the HT group compared with 52% (188 out of 360) in the controls; statistical analysis indicated no difference between those groups [OR (95% CI), 1.371 (0.697–2.296); $P=0.218$] (Table 3).

Regarding interleukin-1β +3954 rs1143634 (C>T) gene polymorphisms

Our results showed that there was a nonsignificant difference between the control and HT groups. The OR (95% CI) of CC genotype distribution was [1.371 (0.697–2.296); $P=0.360$], the [OR (95% CI)] of CT genotype distribution was [0.685 (0.337–1.391); $P=0.295$] and the [OR (95% CI)] of TT genotype distribution was [1.234 (0.202–7.548); $P=0.820$]. With regard to allele distribution, the frequency of the +3954C allele was 89% (389 out of 440) in the HT group compared with 87% (312 out of 360) in the controls [OR (95% CI), 1.256 (0.535–2.950); $P=0.60$], whereas the +3954T allele was 11% (48 out of 440) in the HT group compared with 13% (48 out of 360) in the controls; statistical analysis indicated no difference between those groups [OR (95% CI), 0.796 (0.339–1.869); $P=0.60$] (Table 2).

Table 3 Distribution of interleukin-1β –511 and interleukin-1β +3954 genotypes and allele frequencies in healthy controls and Hashimoto's thyroiditis patients

	Healthy controls (*N*=180) [*n* (%)]	HT patients (*N*=220) [*n* (%)]	OR (95% CI)	*P*
IL-1β –511				
CC	52 (29)	28 (13)	0.359 (0.174–0.739)	<0.001*
CT	68 (38)	116 (53)	1.837 (1.042–3.239)	<0.05*
TT	60 (33)	76 (34)	1.056 (0.586–1.902)	0.857
C allele	172 (48)	172 (39)	0.701 (0.399–1.233)	0.218
T allele	188 (52)	268 (61)	1.425 (0.811–2.505)	0.218
IL-1β +3954				
CC	136 (76)	178 (81)	1.371 (0.697–2.296)	0.360
CT	40 (22)	36 (16)	0.685 (0.337–1.391)	0.295
TT	4 (2)	6 (3)	1.234 (0.202–7.548)	0.820
C allele	312 (87)	392 (89)	1.256 (0.535–2.950)	0.600
T allele	48 (13)	48 (11)	0.796 (0.339–1.869)	0.600

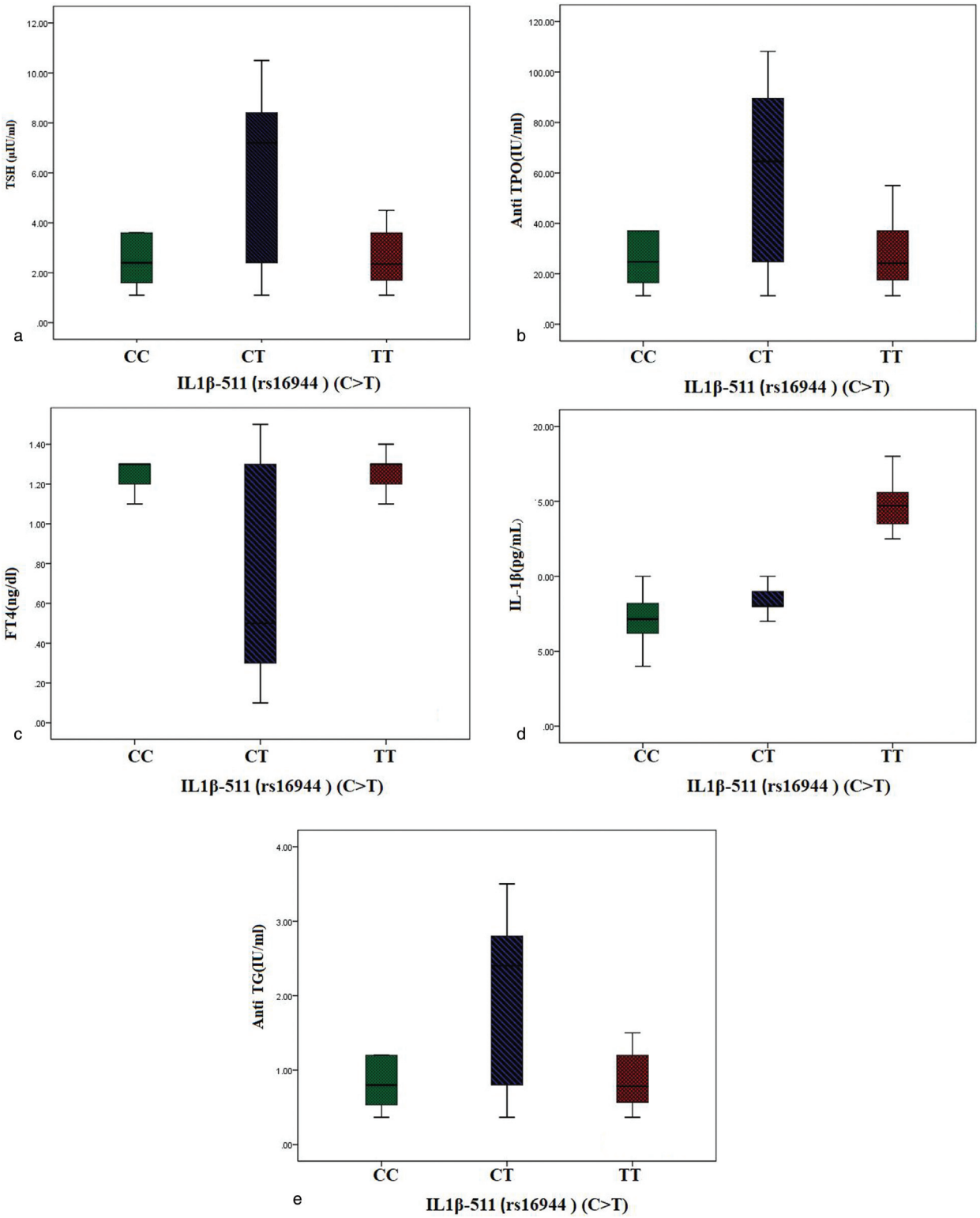
CI, confidence interval; HT, Hashimoto's thyroiditis; IL-1β, interleukin-1β; OR, odds ratios. *Statistically significant ($P<0.05$).

Table 4 Impact of interleukin-1β –511(rs16944) C>T mutations on clinical and laboratory characteristics of Hashimoto's thyroiditis patients

	IL-1β –511 rs16944 (C>T)					
	CC (*N*=28)	CT (*N*=116)	TT (*N*=76)	P_1	P_2	P_3
SBP (mmHg)	139.3 ±15.2	147.5 ±14.9	150.0 ±0.0	0.187	0.343	0.820
DBP (mmHg)	99.3 ±13.4	107.5 ±12.8	100.0 ±0.0	0.134	0.943	0.944
BMI (kg/m^2)	23.5 ±1.9	24.4 ±1.9	22.2 ±0.0	0.247	0.359	0.126
Waist/hip ratio	80.9 ±8.8	82.1 ±9.8	83.0 ±0.0	0.743	0.747	0.900
TC (mg/dl)	29.9 ±3.2	29.4 ±3.5	30.0 ±0.0	0.706	0.965	0.814
TG (mg/dl)	119.5 ±26.2	111.7 ±18.5	99.0 ±0.0	0.439	0.297	0.358
LDL (mg/dl)	257.1 ±39.8	246.3 ±28.5	210.0 ±0.0	0.481	0.115	0.090
HDL (mg/dl)	209.5 ±38.2	204.3 ±23.0	194.0 ±0.0	0.717	0.582	0.544
FPG (mg/dl)	185.3 ±32.2	196.8 ±43.3	198.0 ±0.0	0.418	0.593	0.970
hs-CRP (μg/ml)	7.87 ±1.6	10.8 ±5.6	10.5 ±3.8	<0.05*	<0.05*	0.724

Data are presented as mean±SD. DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides. P_1, significant among IL-1β –511 genotype; CT versus CC. P_2, significant among IL-1β +3954 genotype; TT versus CC. P_3, significant abetweenTT versus CT*P value less than 0.05.

Figure 1



(a) Impact of IL-1β –511 [rs16944 (C>T)] mutations on TSH (µIU/ml) serum levels. (b) Impact of IL-1β –511 [rs16944 (C>T)] mutations on FT4 (ng/dl) serum levels. (c) Impact of IL-1β –511 [rs16944 (C>T)] mutations on TSH (µIU/ml) serum levels. (d) Impact of IL-1β –511 [rs16944 (C>T)] mutations on IL-1β (pg/ml) serum levels. (e) Impact of IL-1β –511 [rs16944 (C>T)] mutations on anti-TG (IU/ml) serum levels. FT4, free thyroxine; IL, interleukin; TG, thyroglobulin; TSH, thyroid-stimulating hormone.

Table 5 Multiple linear regression analyses in Hashimoto's thyroiditis patients to test the influence of the main independent variables against interleukin-1β (dependent variable)

Model	Unstandardized coefficients		Standardized coefficients	*t*	*P*	95% CI	
	B	SE	*β*			Lower bound	Upper bound
Constant	0.963	0.118		8.128	<0.001*	0.728	1.198
anti-TG (IU/ml)	2.260	0.066	0.957	34.343	<0.001*	2.130	2.391
Constant	−1.097	0.587		−1.867	0.065	−2.262	0.068
Anti-TG (IU/ml)	2.822	0.169	1.195	16.670	<0.001*	2.487	3.158
FT4 (ng/dl)	1.271	0.356	0.256	3.573	<0.001*	0.566	1.976

Anti-TG, anti-thyroglobulin; CI, confidence interval; FT4, free thyroxine. **P* value less than 0.05.

Impact of interleukin-1β −511 rs16944 (C>T) mutations on clinical and laboratory characteristics of Hashimoto's thyroiditis patients

Women carrying TT and CT genotype of IL-1β −511 had significantly higher values of CRP compared with women carrying the CC genotype (Table 4). With regard to TSH (Fig. 1a) anti-TPO (Fig. 1c) and anti-TG (Fig. 1e), patients carrying CT genotypes had significantly higher values compared with women carrying CC and TT genotypes. On the other hand, women carrying CT genotype of IL-1β −511 had significantly lower values of FT4 compared with women carrying the CC and TT genotypes. As regards IL-1β serum level (Fig. 1d), women carrying TT (14.56±2.18) and TC (9.28 ±2.41) genotype of IL-1β −511 had significantly higher values compared with patients carrying the CC genotype (7.26±1.59). On the contrary, patients carrying CT genotypes had significantly lower values of FT4 compared with women carrying the CC and TT genotypes (Fig. 1b).

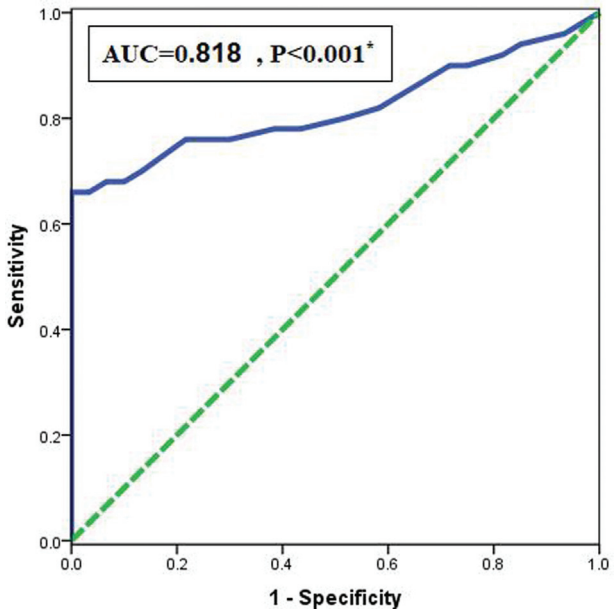
Multiple linear regression analyses in Hashimoto's thyroiditis patients to test the influences of the main independent variables against interleukin-1β (dependent variable)

Linear regression analysis test found that anti-TG and FT4 were the only independently correlated factors with IL-1β ($P<0.001$) (Table 5).

Receiver operating characteristic curve for estimating the diagnostic power of interleukin-1β serum level in differentiating patients with Hashimoto's thyroiditis from the control group

We further investigated our results by the receiver operating characteristic test; we found that the power of IL-1β serum level in differentiating patients with HT from the control group, the area under curve was 0.818 (95% CI, 0.729–0.907) with sensitivity=78%, specificity=61.7%, and the cutoff value of 3.45 (Fig. 2).

Figure 2



Receiver operating characteristic curve for interleukin-1β serum level for prediction of Hashimoto thyroiditis among Egyptian women with systemic lupus erythematous. AUC, area under curve.

Discussion

There are reports suggesting that autoimmune thyroiditis (AITD) is one of the most important autoimmune diseases in the population. However, the pathogenesis of AITD remains elusive. As we all know, the occurrence of AITD is with obvious sex tendency, and this disease is more popular in women with the ratio of female to male patients ranging from 5 : 1 to 10 : 1 [16].

There is compelling evidence suggesting an important role of family history, as about 40–50% of patients with their families were suffering from thyroid disease [17]. Current evidence indicates that environmental factors, immune elements, and genetic susceptibility are all involved in the etiology of this disease [18,19].

IL-1β has pleiotropic effects, can alter cytokine production, cell signaling, and migration. There are

several common polymorphisms that have been most frequently investigated. The IL-1β gene has two SNP at position −511 in the promoter region (rs16944) and at position +3954 in the fifth exon (rs1143634), respectively [8,15].

HT is one of the most common human autoimmune diseases responsible for considerable morbidity in women. Early diagnosis of thyroid autoimmunity deserves particular attention, because it may help us to plan preventive and therapeutic approaches. Cytokines are crucial in the regulation of immune and inflammatory responses. Hence, cytokine genes might be good candidates for HT. To our knowledge, this is the first study conducted in Egypt to explore the possible associations of IL-1β −511C/T (rs16944) and IL-1β +3954 rs1143634 (C>T) gene polymorphisms with HT, and to detect the influence of these polymorphisms and haplotypes on thyroid function.

Even more importantly, the interesting result of our study was that patients with HT had higher values of anti-TPO, anti-TG, and TSH in subclinical hypothyroidism and clinical hypothyroidism subgroups compared with the euthyroid one.

Similar results were described in the study by Khaled *et al.* [20], which found that patients with anti-TPO and anti-TG antibodies had statistically elevated TSH levels compared with those without antibodies, but, FT3 and FT4 levels showed no significant differences among patients with and without either of the antibodies.To our knowledge, this is the first study investigating the possible associations of IL-1β −511C/T (rs16944) and IL-1β +3954C/T (rs1143634) gene polymorphisms with susceptibility of HT in Egyptian women. Interestingly, we detected that the CC genotype distribution was significantly lower in patients with HT than in controls, whereas the CT genotype distribution was significantly higher in patients with HT than in controls. With regard to the TT genotype distribution, there were nonsignificant differences among both groups.

In agreement with our results, the Lacka *et al.* [21] study, which was conducted on the Polish population, the researcher found that IL-1β gene polymorphism SNP −511 was associated with the susceptibility to the development of HT among the adult Caucasian-Polish population.

In order to evaluate the associations between IL-1β +3954 (C>T) gene polymorphisms and the susceptibility of women to develop HT, our results showed that there was a nonsignificant difference between the control and HT groups.

Supporting our results, Chen *et al.* [14] found that the IL-1β −511C/T polymorphism was associated with susceptibility to GD rather than the IL-1β +3954C/T polymorphism; however, our study was conducted on HT; notwithstanding, there are some similarities between the pathogenesis of HT and GD.

Contrary to our results, Kammoun-Krichen *et al.* [22] conducted their study on the Tunisian population, and their results revealed that an association of the IL-1β +3954C/T with AITDs was found in studying the Akr family. However, IL-1β polymorphisms were found to be associated with GD in the case–control study.

In contrast, the influence of IL-1β polymorphism on susceptibility to HT was detected by Hunt *et al.* [23] who studied, in British patients with AITD, 15 polymorphisms within nine cytokine genes. The discrepancy between our results and those of others may reflect the different genetic pools represented in the different ethnicities.

Lacka *et al.* [24] demonstrated a lack of statistical correlation between the presence of two analyzed polymorphisms of IL-1β (–511, promoter and +3954, exon 5) and development of the thyroid-associated ophthalmopathy.

The interesting result of our study was the effect of IL-1β −511gene mutation on clinical and laboratory tests of patients with. We observed that women carrying TT and CT genotypes of IL-1β −511 had significantly higher values of CRP compared with women carrying the CC genotype. With regard to TSH, anti-TPO, and anti-TG, patients carrying the CT genotype had significantly higher values compared with women carrying the CC and TT genotypes. In contrast, women carrying the CT genotype of IL-1β −511 had significantly lower values of FT4 compared with women carrying the CC and TT genotypes. With regard to IL-1β serum level, women carrying TT and TC genotypes of IL-1β −511 had significantly higher values compared with patients carrying the CC genotype. On the contrary, patients carrying the CT genotype had significantly lower values of FT4 compared with women carrying the CC and TT genotypes.

In the present study, we observed that anti-TG and FT4 were the only independently correlated factors with IL-1β serum level by linear regression analysis. We tested our data by ROC curve, we found that the

power of IL-1β serum level in differentiating patients with HT from the control group, the area under curve was 0.818 (95% CI, 0.729–0.907) with sensitivity =78%, specificity=61.7%.

Conclusion

CT genotype distribution of IL-1β-511was significantly higher in patients with HT than in controls. With regard to the relation between IL-1β +3954 (C>T) gene polymorphisms and the susceptibility of women develop HT, our results showed that there was a nonsignificant difference between the control and HT groups; early diagnosis of thyroiditis decreases the health hazards related to HT. Further multicenter studies with bigger sample sizes are needed to validate our findings.

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Conflicts of interest

There are no conflicts of interest.

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