Arch Clin Exp Med 2018;3(3):138-142. e-ISSN: 2564-6567

DOI:10.25000/acem.421521 Araştırma makalesi / Research article

VCAM1 (T-1591C and T-833C) and E-selectin S128R polymorphisms are not risk factors for Hashimoto's thyroiditis.

VCAM1 (T-1591C ve T-833C) ve E-selektin S128R polimorfizmleri Hashimoto tiroiditi için risk faktörleri değildir.

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Abstract

Aim: The etiopathogenesis of Hashimoto's thyroiditis (HT) has not been clearly elucidated although the role of chronical inflammation and endothelial dysfunction has been established. Adhesion molecules such as vascular cell adhesion molecule1 (VCAM1) and E-selectin are secreted from vascular endothelium and promote accummulation of leukocytes in damaged endothelial areas. This study examined the possible association of VCAM1 (T-1591C and T-833C) and E-selectin S128R single nucleotide polymorphisms (SNPs) with the occurence of HT for the first time.

Methods: VCAM1 (T-1591C and T-833C), and E-selectin S128R SNPs in DNA from peripheral blood leukocytes of 189 patients with HT and 247 healthy controls were investigated by real-time PCR combined with melting curve analysis using fluorescence-labeled hybridization probes.

Results: We did not find significant differences in the distributions of studied polymorphisms between patients with HT and healthy controls.

Conclusions: The results of present study suggest that VCAM1 (T-1591C and T-833C) and E-selectin S128R SNPs may not be risk factors for HT. For all that; further studies with a larger cohort, analyzing other polymorphisms in VCAM1 and E-selectin genes are necessary to support our observations.

Key words: Hashimoto's thyroiditis, VCAM1, E-selectin, polymorphism

Öz

Amaç: Hashimoto tiroiditinin (HT) etyopatogenezi tam olarak aydınlatılamamış olmakla birlikte kronik inflamasyon ve endotel disfonksiyonunun önemli olduğu bilinmektedir. Vasküler hücre adezyon molekülü 1 (VCAM1) ve E-selektin gibi adezyon molekülleri endotel tarafından salgılanırlar ve hasarlı endotel bölgesine lökositlerin migrasyonunu düzenlemektedirler. Bu çalışmada ilk kez VCAM1 (T-1591C ve T-833C) ve E-selektin S128R tek nükleotid polimorfizmleri (SNPs) ile HT arasında bir ilişki olup olmadığı araştırılmıştır.

Metod: HT'li 189 hasta ve 247 sağlıklı kontrol kişinin periferik kan lökositlerinden izole edilen DNA örneklerinde VCAM1 (T-1591C ve T-833C) ile E-selektin S128R polimorfizmleri floresan boya-işaretli problar kullanan ve erime eğri analizine dayanan "real-time" PCR yöntemi ile incelendi.

Bulgular: Çalışmamızda kontrol grubu ve HT hastalarında araştırılan polimorfizmlerin dağılımlarında anlamlı bir fark bulunmadığı saptandı.

Sonuç: Bu çalışmanın bulgularına göre VCAM1 (T-1591C ve T-833C) ve E-selektin S128R polimorfizmleri HT için bir risk faktörü olmayabileceğini düşündürmektedir. Bununla birlikte, bulgularımızın desteklenmesi için örnek sayısının arttırılması, ayrıca VCAM1 ve E-selektin genlerin farklı polimorfik lokuslarının da incelenmesi gerektiği kanısındayız.

Anahtar kelimeler: Hashimoto tiroiditi, VCAM1, E-selektin, polimorfizm

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Ethics Committee Approval: The study wass approved by the local ethical authority.
Etik Kurul Onayı: Çalışma lokal etik komite tarafından onaylanmıştır.

Conflict of Interest: No conflict of interest was declared by the author.
Çıkar Çatışması: Yazar çıkar çatışması bildirmemiştir.

Financial Disclosure: This study was supported by Scientific Research Projects Coordination Unit of Istanbul University. (Project number: 5843).
Finansal Destek: Bu çalışma İstanbul Üniversitesl Bilimsel Araştırma Projeleri Koordinasyon Birimi tarafından 5843 numaralı proje ile desteklenmiştir.

Geliş Tarihi / Received: 07.05.2018
Kabul Tarihi / Accepted: 06.08.2018
Yayın Tarihi / Published: 30.11.2018

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Introduction

Hashimoto's thyroiditis is the most common organ-specific autoimmune disorder characterized by diffuse lymphocytic infiltration of the thyroid gland, elevated levels of the serum anti-thyroid antibodies, evidence of goitrous or atrophic gland, and frequent thyroid dysfunction in varying degrees [1]. The precise pathophysiologic mechanism of HT remains still unclear. The most relative evidence suggests that ongoing immune intolerance and low-grade chronic inflammation with subsequent endothelial damage are included in the pathogenesis [2, 3]. The damage of the vascular endothelium plays a significant role in the extravasation of blood leukocytes infiltrating of thyroid gland, thus leading to an autoimmune response. [4-6]. Vascular cell adhesion molecule 1 (VCAM1) and E-selectin are significant biomarkers of endothelial dysfunction, mediating the recruitment and transendothelial transmigration of inflammatory cells from the circulation during autoimmune and atherosclerotic process. Patients with in autoimmune thyroid disorders, increased expression and serum levels of adhesion molecules are found [7-9]. VCAM1(T-1591C and T-833C) and E-selectin S128R single nucleotide polymorphisms (SNPs) are among the main polymorphisms of VCAM1 and E-selectin genes, implicated as risk factors in some autoimmune conditions [11-12]. To our knowledge, there is no any literature regarding for the association between above mentioned loci and susceptibility to HT. Therefore, in the present study we aimed to investigate whether VCAM1 (T-1591C and T-833C) and E-selectin S128R SNPs could affect tendency to HT.

Material and methods

One hundred and eighty nine patients with the specification of HT and 247 healthy participants as control were inclusive in this prospective case-control study. The study was confirmed by the Institutional Review Board at Şişli Etfal Research and Training Hospital. The study complied with the principles of the Declaration of Helsinki. Informed consent was obtained from each subject.

Symptoms or findings in hypothyroiditis including mild stiffness of the enlarged thyroidal gland, increased or normal thyroid stimulating hormone (TSH) value, decreased or normal free tri-iodo-thyronine (FT3) or free thyroxine (FT4) values, and high levels of autoantibodies (anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-Tg)) in screening tests were diagnosed as HT. Damage of echogenity in parenchyma and fibrotic separations and pseudo nodular view in Doppler ultrasonography of the thyroid gland were also found. Fine needle aspiration was only performed to score the patients having a thyroid nodule ≥1cm in diameter (n=17). All HT patients were subjected to thyroxine therapy until euthyroid state has been achieved. The thyroxine dose was arranged according to TSH concentrations checked regularly in three month gaps. The control group occurred of 247 individuals matched for age and sex. None of the controls had personal or family history of thyroid disease and goiter on examination; they had normal thyroid functions and were negative for thyroid autoantibodies. Exclusion criteria were the existence of any co-morbid cardiac, autoimmune, infectious, musculoskeletal or malignant disease and a recent history of operation or trauma.

Blood samples were taken in the morning subsequent to an overnight (12 h) fast. Peripheral venous blood samples were collected in plain tubes for routine biochemical analysis, and in EDTA-K3 for genotype analysis. Serum cholesterol, triglyceride, very low density lipoprotein (VLDL)-, low density lipoprotein (LDL)- and high density lipoprotein (HDL)-cholesterol measurements were performed on ISE 1800 DPP Roche autoanalyzer (Roche Diagnostics, Germany). Serum TSH, freeT3, free T4, anti-Tg and anti-TPO were measured on Modular EEE Electrod Elecsys Roche autoanalyzer (Roche Diagnostics, Germany). Serum soluble VCAM1 (sVCAM1) and serum soluble E-selectin (sE-selectin) levels were measured by commercially available ELISA kits (Diaclone, Besançon, France) according to the manufacturer's instructions. The normal reference ranges for laboratory parameters were: anti-TPO < 5.61 IU/mL, anti-TG < 4.11 IU/mL, TSH 0.35-4.94 mI/mL, free T3 2.63-5.7 pmol/L, free T4 9.01-18.02 pmol/L, cholesterol 130-200 mg/dL, triglyceride <150 mg/dL, HDL-C > 40 mg/dL, LDL-C 100-130 mg/dL. Body mass index (BMI) was calculated as the ratio between body weight and height (kg/m2).

Genomic DNA was isolated from peripheral blood leukocytes by using High Pure Polymerase Chain Reaction (PCR) Template Preparation Kit (Roche Diagnostics, Germany). Detection of polymorphisms was made by rapid capillary PCR with melting curve analysis using fluorescence-labeled hybridization probes in a LightCycler (Roche Diagnostics, Germany). PCR primers and probes for melting point analyses are given in Table 2. Primers and probes were designed by Tib MolBiol (Berlin, Germany). Analysis was done in 20 □l volumes using glass capillaries. The PCR mix contained 2 µl of the genomic DNA, 2 µl of LCTM FastStart DNA Master HybProbe kit (Roche Diagnostics), 0.5-1 µM of each primer, 0.2-0.4 µM of each probe and 1.5-2.5 mM total MgCl2. Reaction conditions were as follows: initial denaturation at 95 °C for 10 min, then 45 cycles of denaturation at 95 °C for 1 s, annealing (due to primers), and elongation at 72 °C for 12 s. Melting curve analysis was done with an initial denaturating step at 95 °C for 5 s and 20 s at 40-45 °C, slow heating to 70-80°C, with a ramping rate of 0.1-0.15 °C/s and continuous fluorescence detection. Melting curves were evaluated by two independent observers who were blinded to the analysis of the clinical data. In addition, 10% of randomly selected samples were repeated independently to verify genotyping results and 100% concordance was found. SNP genotypes were tested for departures from HWE for controls and patients, and all polymorphisms were in HWE.

Statistical analysis

Statistical analyses were performed with SPSS 15.0 for Windows (Chicago, IL, USA). In addition, the NCSS 2000 statistical package (Kaysville, Utah, USA) was used to evaluate the power analysis. We had a 97% power to detect an effect size (W) of 0.20 using a 2 degrees of freedom (α= 0.05). Differences in genotype distributions and allele frequencies in the patients and the controls were compared for statistical significance using the chi-square (χ^2) test. The statistical significance for deviations from Hardy-Weinberg Equilibrium (HWE) was determined using the Pearson χ^2-test. Odds ratios (ORs) were calculated and given with 95% confidence intervals (CIs). The wild-type genotype/allele served as a reference category. Mann-Whitney U, Kruskal-Wallis and Spearman correlation tests were used for the evaluation of clinical and biochemical parameters. The differences were considered significant if the value of probability (p) did not exceed 0.05.

Results

A total of 436 subjects were included in this case-control study. The mean age of HT patients was 40.99±12.96 years (range 16-78 years) (21 male, 168 female), and of controls was 37.9±9.96 years (range 18-67 years) (32 males, 215

females). Clinical characteristics and thyroid hormonal status of controls and HT patients are shown in Table 1. TSH, cholesterol, LDL-C, sVCAM levels and BMI were significantly increased in HT patients according to controls (p= 0.001 for all).

The genotypic and allelic distributions of the polymorphisms in the studied genes for patients and the controls are shown in Table 3. In this study, no statistically significant differences were found in genotype or allele distributions of all evaluated polymorphisms between the patients with HT and the controls (Table 3). With respect to plasma levels of adhesion molecules, sVCAM1 concentrations were higher and sE-selectin levels were unchanged in patients with HT according to controls (Table 1). When sVCAM and sE-selectin concentrations in HT patients were evaluated according to studied polymorphisms, no significant differences between genotypes were found (Table 4-6).

Table 1: Characteristics of controls and patients with Hashimoto's thyroiditis (HT).

	Control (n=247)	HT (n=189)	p
Age (years) ¥	37.9±9.96 (18-67)	40.99±12.96 (16-78)	0.705
HT onset$^{\mu}$			
< 40 year	-	98 (51.9)	-
>40 year	-	90 (47.6)	-
Gender$^{\mu}$			
Male	32 (13.0)	21 (11.1)	0.719
Female	215 (87.0)	168 (88.9)	0.488
Familial history$^{\mu}$	-	99 (52.4)	-
Smoking$^{\mu}$	107 (43.3)	97 (51.3)	0.070
BMI (kg/m^2)$^{\beta}$	24.7±4.89	27.55±5.70	0.001
Systolic BP (mmHg)$^{\beta}$	118.2±10.4	115.2±11.9	0.209
Diastolic BP (mmHg)$^{\beta}$	73.5±7.9	71.8±10.3	0.215
Anti-TPO (IU/mL)$^{\beta}$	-	625.4±370.4	-
Anti-Tg (IU/mL)$^{\beta}$	-	560.4±380.0	-
TSH (mIU/L)$^{\beta}$	1.66±0.8	4.0±2.7	0.001
FreeT_3 (pmol/L)$^{\beta}$	3.2±0.3	3.3±0.4	0.315
FreeT_4 (pmol/L)$^{\beta}$	13.2±2.7	13.5±3.9	0.235
Cholesterol (mg/dL)$^{\beta}$	177.24±36.80	192.71±35.00	0.001
Triglyceride (mg/dL)$^{\beta}$	102.86±55.89	113.18±52.98	0.113
HDL-C (mg/dL)$^{\beta}$	56.38±12.56	59.25±12.20	0.116
LDL-C (mg/dL)$^{\beta}$	100.35±32.09	115.81±30.12	0.001
sVCAM1 (ng/mL)$^{\beta}$	1,477.7±491.9	2,733.5±880.6	0.001
sE-selectin (ng/mL)$^{\beta}$	69.11±35.49	66.88±31.81	0.250

¥: mean±SD (range), μ: n (%), β: mean±SD.
BP: blood pressure, BMI: body mass index, HT: Hashimoto's thyroiditis, HDL-C: high density lipoproteine-cholesterol, LDL-C: low density lipoproteine-cholesterol, sVCAM1: soluble vascular cell adhesion molecule 1, TSH: thyroid-stimulating hormone

Table 2: Sequences of primers or probes employed in this study

VCAM1 T -1591C (rs1041163)
Primer 1 5'-TGATGATGACACAAACACTGT-3'
Primer 2 5'-GAAAAATAAGTTGGAGATGCT-3'
Probe 1 5'-GGGATCAGAAAAATTGATTCAGG-FL
Probe 2 5'-LC640-CTAGCTTATAAACAAGTAACCCAGAGGTCCT-3'
VCAM1 T-833C (rs3170794)
Primer 1 5'-CAGATGGATTCCATACACTTTCATT-3'
Primer 2 5'-GGACTGTAACTGAAATTGCTGC-3'
Probe 1 5'-AAGTTACCAATAATTTGGTTAAATTGCTGGA-FL
Probe 2 5'-LC640-TTGGAATTTTTTTGCATACTTAAATG-3'
E-Selectin S128R (rs5361)
Primer 1 5'-TGCTGATGTCTCTGTTGC-3'
Primer 2 5'-GGTCTCTACACATTCACCG-3'
Probe 1 5'-GCTTTGTATTTTCCGTAGCTGCCTGTACC-FL
Probe 2 5'- LC640-ATACATCCTGCCGTGGCC-3'

HT: Hashimoto's thyroiditis, VCAM1: vascular cell adhesion molecule1

Table 3. Distribution of genotypes and allele frequencies for Hashimoto's thyroiditis (HT) and control group.

	Controls n (%)	HT n (%)	OR (95 % CI)	p
VCAM1 T-1591C				
TT$^{\mu}$	169 (68.4)	121 (64.0)	1.0*	-
CT$^{\mu}$	68 (27.5)	61 (32.3)	1.25 (0.83-1.90)	0.288
CC$^{\mu}$	10 (4.1)	9 (3.7)	0.98 (0.36-2.64)	0.964
CT+CC	78	70	1.22 (0.82-1.82)	0.334
T allele frequency	0.82	0.80	1.0*	-
C allele frequency	0.18	0.20	1.14 (0.81-1.61)	0.446
VCAM1 T-833C				
TT$^{\mu}$	234 (94.7)	179 (94.7)	1.0*	-
CT$^{\mu}$	13 (5.3)	10 (5.3)	1.01 (0.43-2.35)	0.989
CC$^{\mu}$	0 (0)	0 (0)	1.31 (0.03-66.16)	1.00
CT+CC	13	10	1.01 (0.43-2.35)	0.989
T allele frequency	0.97	0.97	1.0*	-
C allele frequency	0.03	0.03	1.00 (0.44-2.32)	0.989
E-selectin S128R				
SS$^{\mu}$	205 (83.0)	147 (77.8)	1.0*	-
SR$^{\mu}$	40 (16.2)	40 (21.2)	1.40 (0.86-2.27)	0.179
RR$^{\mu}$	2 (0.08)	0 (0)	1.40 (0.19-10.01)	0.739
SR+RR	42	40	1.40 (0.87-2.25)	0.170
S allele frequency	0.91	0.89	1.0*	-
R allele frequency	0.09	0.11	1.35 (0.87-2.09)	0.184

*: Reference values for OR, $^{\mu}$: n (%), CI: Confidence interval, OR: Odds ratio, HT: Hashimoto's thyroiditis, VCAM1: Vascular cell adhesion molecule 1

Table 4: sVCAM1 (vascular cell adhesion molecule 1) and sE-selectin levels in patients with Hashimoto's thyroiditis in accordance with their genotypes of the VCAM1 T-1591C gene polymorphism.

	TT	CT + CC	p
sVCAM (ng/mL)$^{\beta}$	2,780.7 ± 891.1	2,673.3 ± 871.0	0.549
sE-selectin (ng/mL)$^{\beta}$	69.84 ± 32.32	60.24 ± 30.74	0.149

$^{\beta}$: mean±SD

Table 5: sVCAM1 (vascular cell adhesion molecule 1) and sE-selectin levels in patients with Hashimoto's thyroiditis in accordance with their genotypes of the VCAM1 T-833C gene polymorphism.

	TT	CT	p
sVCAM (ng/mL)$^{\beta}$	2,747.4 ± 862.1	2,373.7 ± 801.0	0.286
sE-selectin (ng/mL)$^{\beta}$	66.15 ± 32.27	78.99 ± 22.50	0.250

$^{\beta}$: mean±SD

Table 6: sVCAM1 (vascular cell adhesion molecule 1) and sE-selectin levels in patients with Hashimoto's thyroiditis in accordance with their genotypes of the E-selectin S128R gene polymorphism.

	SS	SR + RR	p
sVCAM (ng/mL)$^{\beta}$	2,584.8 ±788.1	3,007.8 ± 997.2	0.065
sE-selectin (ng/mL)$^{\beta}$	68.87 ± 31.68	61.89 ± 32.43	0.387

$^{\beta}$: mean±SD

Discussion

The present study was conducted to investigate whether VCAM1 (T-1591C and T-833C) and E-selectin S128R SNPs could affect tendency to HT. The variant allele frequencies of the studied polymorphisms in our control group were consistent with previous studies [12-14].

Low-grade chronic inflammation and endothelial damage with subsequent endothelial dysfunction, have been increasingly recognized as having a central role in hypothyroidism [2, 3]. Cellular adhesion molecules are well accepted as markers of low-grade inflammation and endothelial dysfunction [15]. Some clinical studies as well as our results indicate that plasma levels of VCAM1 are elevated in patients with HT [7, 8]. Additionally, enhanced expression of VCAM1 has been observed in immunocytological analyses of tissue from thyroid glands in patients with HT [9]. VCAM1 is expressed on the surface of several cell types, including leukocytes, endothelial cells, macrophages, myoblasts, and dendritic cells [15]. VCAM1, facilitating the adhesion of leukocytes and monocytes to and their transmigration through the activated endothelium, plays an important role in the early stages of vascular disease in conditions with chronic inflammation [15]. It has been suggested that increased expression of VCAM1 on activated endothelium may facilitate transmigration of monocytes and T lymphocytes across the endothelium [16] with subsequent release of inflammatory cytokines by endothelial cells and monocytes [17]. In turn, cytokines induce VCAM1 expression, which binds adjacent endothelial cells (via its ligand very late antigen-4), therefore potentiating autoimmune process [17]. VCAM1 -1591 and -833 SNPs are among the main polymorphisms in the promoter region of VCAM1 gene described in the literature, regarding for association with various diseases [18-20]. Idelman et al. [20] demonstrated that -1591 and -833 loci of VCAM1 gene are biologically active and could influence the progression of some diseases. However, in our study, there is no any significant difference in the allele and genotype frequencies of studied VCAM1 polymorphisms between HT and controls. Neither -1591 nor -833 genotypes didn't influence the plasma VCAM1 concentrations.

E-selectin is expressed on endothelial cells after activation by pro-inflammatory cytokines [21]. The most studied polymorphism of E-selectin gene is S128R (or A561C) SNP found to be an important risk factor for development of endothelial dysfunction [13, 22, 23]. The substitution of serine (S) to arginine (R) has been shown to decrease importantly binding specificity and capacity to carbohydrate molecules on leukocyte surface, leading to an increase in cellular adhesion two- to three-fold in comparison with wild-type gene [24]. The 128R allele may thus increase leukocyte adherence to endothelium contributing to the progression of endothelial dysfunction. Additionally, Mlekush et al. [25] demonstrated that E-selectin plasma levels in 128R allele carrying subjects were significantly higher than S128S homozygous ones. It has been previously shown that 128R allele is associated with an increased risk for systemic lupus erythematosus in Spanish and English populations [12]. In addition, Chen et al. has been demonstrated that some common variants of E-selectin gene (not including S128R polymorphism) are related with increased risk for Graves' disease in Chinese population [11]. It is seen from the results that there is not any association between S128R polymorphism of E-selectin gene and susceptibility to HT in our population, and that S128R polymorphism does not have impact serum E-selectin levels.

Interpretation of our findings, as in the case of all genetic studies, meets with certain limitations. The biological effects of studied polymorphisms remain to be elucidated. Further studies investigating the mechanisms of genetic control of VCAM -1591 / – 833 and E-selectin 128 expressions are needed to clarify the possible relationship between VCAM /E-selectin genes and autoimmune disorders.

As a conclusion, VCAM1 (-1591 and -833) and E-selectin 128 polymorphisms seem to be not related with HT, although this cannot be definitively excluded without further analysis in a larger study group combined with analysis of further polymorphisms in the VCAM1 and E-selectin genes.

Acknowledgement

This study was supported by Scientific Research Projects Coordination Unit of Istanbul University. (Project number: 5843).

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