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Evaluation of Paraoxonase1 Polymorphisms in Hypothyroid Patients and Their Relationship with Paraoxonase Activity and Serum Lipids

Hipotiroidili Hastalarda Paraoksonaz1 Polimorfizmlerinin Değerlendirilmesi ve Bu Polimorfizmlerin Paraoksonaz Aktivitesi ve Serum Lipidleri ile İlişkisi

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Abstract

Objective: The risk for atherosclerosis increases in hypothyroidism, although its associated mode of pathogenesis has not been determined yet. Paraoxonase1 (PON1) is an enzyme that is antioxidative and antiatherogenic. This study was planned to determine distributions of PON1 192 and 55 gene polymorphisms in hypothyroid patients and healthy individuals and to investigate the effects of these polymorphisms on PON1 activity and serum lipids.

Material and Methods: Seventy-five primary hypothyroid patients and 45 healthy volunteers were recruited into the study and PON1 192 and 55 gene polymorphisms, serum PON1 activity, and lipid profiles were measured in them.

Results: The activity of PON1 declined in the recruited patients compared to that in the control group ($p<0.05$). No significant difference was observed in PON1 192 Q/R and 55 L/M genotype distributions and allele frequencies between patients and the control group. Moreover, these polymorphisms affected PON1 activity ($p<0.05$) but had no effect on serum lipids.

Conclusion: PON1 192 and 55 polymorphisms cause significant changes in paraoxonase activity. PON1 activity was lower in hypothyroid patients and was independent of these polymorphisms, thus does not create any genetic risk for increased atherosclerosis in these patients.

Keywords: Hypothyroidism; paroxonase1 activity; polymorphism; paroxonase1 192; paroxonase1 55

Özet

Amaç: Hipotiroidizmde ateroskleroz riskinin arttığı bilinmesine rağmen, hipotiroidizmdeki aterosklerozun patogenezi henüz tam olarak açıklanamamıştır. Paraoksonaz1 (PON1), antioksidan ve antiaterojenik etkileri olduğu bilinen bir enzimdir. Bu çalışma, hipotiroidili hastalarda ve sağlıklı bireylerde PON1 192 ve 55 gen polimorfizmlerinin dağılımını belirlemek ve bu polimorfizmlerin PON1 aktivitesi ve serum lipidleri üzerine etkilerini araştırmak için planlandı.

Gereç ve Yöntemler: Çalışmaya 75 primer hipotiroidi hastası ve 45 sağlıklı gönüllü dâhil edildi. PON1 192 ve 55 gen polimorfizmleri, serum PON1 aktivitesi ve lipid profilleri ölçüldü.

Bulgular: Hastalarda PON1 aktivitesi kontrol grubuna göre düşüktü ($p<0.05$). Hasta ve kontrol grubu arasında PON1 192 Q/R ve 55 L/M genotip dağılımlarında ve allele frekanslarında anlamlı bir fark gözlenmedi. Ayrıca, bu polimorfizmlerin PON1 aktivitesini etkilediği ($p<0,05$) ve serum lipidleri üzerinde etkisinin olmadığı görülmüştür.

Sonuç: PON1 192 ve 55 polimorfizmleri paraoksonaz aktivitesinde önemli değişikliklere neden olmaktadır. Bununla birlikte, hipotiroidi hastalarında PON1 aktivitesi bu polimorfizmlerden bağımsız olarak düşük bulunmuştur ve bu hastalarda artmış ateroskleroz için genetik risk oluşturmamaktadır.

Anahtar kelimeler: Hipotiroidizm; paroksonaz aktivitesi; polimorfizm; paroksonaz1 192; paroksonaz1 55

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Introduction

Hypothyroidism is a clinical condition that occurs as a result of thyroid hormone deficiency and affects several systems in the body (1). Its prevalence is high in the general population, especially in females (2) and is associated with an increased risk of atherosclerosis and ischemic heart disease. Hypercholesterolemia, hypertension, and impaired endothelial function have been suggested for atherosclerosis. However, the pathogenesis of atherosclerosis related with hypothyroidism is confusing and has not been clarified yet (3).

Atherosclerosis has an important role in the pathogenesis of cardiovascular diseases. It is also one of the most common causes of mortality and morbidity in the whole world. High plasma cholesterol levels (especially low-density lipoprotein cholesterol, LDL-C) and triglycerides, low levels of high-density lipoprotein cholesterol (HDL-C), smoking, hypertension, diabetes mellitus, male gender, lack of exercise, obesity, and stress are among the risk factors of atherosclerotic cardiovascular diseases (4).

Paraoxonase1 (PON1) is an enzyme that is associated with HDL-C and has antioxidant and antiatherogenic effects. It participates in the protection of HDL-C and LDL-C against oxidation (5). The activity of PON1 is affected by various environmental factors, such as lifestyle, diseases (e.g., coronary heart disease, diabetes, dementia), smoking, diet, in addition to another important factor, genetic polymorphism. PON1 has two common polymorphisms in the coding region of its respective gene. Polymorphism at position 192 occurs with glutamine (Q) to arginine (R) substitution (PON1 192 Q/R), and polymorphism at position 55 occurs with leucine (L) to methionine (M) substitution (PON1 55 L/M) (6). The polymorphisms in the PON1 gene have been implicated as potential risk factors for atherosclerosis (7,8).

Low activity of PON1 has been observed in hypothyroid patients and some experimentally created hypothyroid rat models (9-12). However, PON1 polymorphisms in hypothyroid patients has not been studied.

In this study, we investigated the distribution of PON1 192 and 55 gene polymorphisms among hypothyroid patients and healthy population and evaluated the relationship of these polymorphisms with PON1 activity and serum lipid levels.

Material and Methods

A total of 120 adult individuals were included in this study. These included primary hypothyroid patients (n=75) and healthy controls (n=45). The individuals diagnosed with untreated subclinical or clinical hypothyroidism were selected for the patient group. Subclinical patients (n=12) had elevated TSH levels (>4 mU/L) and normal (many times at the lower limit of normal range) free-T4 and free-T3 levels. On the other hand, free-T4 and/or free-T3 levels of clinical patients (n=63) were low whereas TSH levels were elevated (>10 mU/L) (13). Patients with positive anti-TPO or anti-TG levels were considered as patients with hypothyroidism associated with Hashimoto's thyroiditis (n=59). Others from the patient group (n=16) were evaluated as cases of hypothyroidism related to postoperative, idiopathic or radioactive iodine therapy. The control group consisted of 45 individuals who were healthy and without any systemic disease.

The study design was descriptive and data were collected prospectively. The characteristics of the groups (hypothyroid patients and healthy controls) were compared for analyses. Informed consent was taken from the participants. The study protocol and procedures were approved by local ethical committee and were in accordance with the Helsinki Declaration.

Systolic and diastolic blood pressure (SBP, DBP) were measured as recommended by the American Heart Association (14). The body mass index (BMI) was calculated using the formula BMI=weight/height^2 (kg/m^2). Venous blood samples were collected between 8:00 and 9:00 am after overnight fasting and serum samples were stored at –40 °C until the analysis. All laboratory measurements were performed at the research laboratory of Medical Faculty. Glucose, total cholesterol, triglycerides, HDL-C were measured using commercially available enzymatic reagents on Olympus AU 640 autoanalyzer (Olympus, Japan). The LDL-C value was calculated using the Friedewald equation when the triglyceride level was less than 400

mg/dL. Free T3, free T4, TSH, anti-TPO, and anti-TG levels were measured by electrochemiluminescence immunoassay on Roche COBAS E601 autoanalyzer (Roche Diagnostics, USA).
Serum PON1 activity was measured by screening for an increase in yellow-colored paranitrophenol which occurs after the hydrolysis of paraoxon by PON1 and measuring the absorbance at 412 nm (15).

Isolation of DNA

For DNA isolation, blood samples were taken in the tubes including EDTA. DNA was isolated from peripheral blood leucocytes by using MagNa-pure LC DNA isolation kit 1 (Roche, REF 03 003 990 001) on the MagNa-pure LC automatic DNA RNA isolation system (Roche Diagnostics GmbH, Germany).

Determination of PON1 genotype

DNA was extracted from the white cells and the PON1 genotype for the 192 and 55 polymorphisms which determinated using PCR amplification and restriction enzyme digestion. PON1 192 and 55 polymorphisms were detected using *Alw*I digestion and *Nla*III digestion, respectively, as described (16).

Statistical Analysis

Numeric variables with normal distributions are shown as means±SD and numeric variables with non-normal distributions are shown as median (25-75% percentile). The comparisons between categorical variables were made using the Chi-squared test. The comparisons of numerical variables with normal distribution were made using independent samples t-test and one-way ANOVA. When a significant difference was seen in variance analysis, Tukey's posthoc test was performed as a multiple comparison test. The comparisons of numerical variables with non-normal distribution were made using the Mann-Whitney U test and Kruskal Wallis analysis. The relationships between numerical variables were examined using Spearman's Correlation analysis. A value with $p<0.05$ was accepted as significant.

Results

The demographic data of controls and the patients are shown in Table 1. The patient group comprised 63 women (84.0%), 12 men (16.0%) with the mean age of 42.4±11.2 years. The control group com-

Table 1. Clinical and biochemical data of hypotyhroid patients and controls.

Parameter	Patients(n=75)	Controls(n=45)	p
Age (year)*	42.3±11.2	40.6±5.2	0.257
Gender (male/female)	12 (16.0%)/63 (84.0%)	5 (11.1%)/40 (88.9%)	0.592
BMI (kg/m2)**	29.3 (25.9-33.7)	24.9 (21.8-27.7)	<0.001
Smoking, n (%)	9 (12.0%)	0 (0.0%)	0.026
Diabetes, n (%)	7 (9.3%)	0 (0.0%)	0.044
Hypertension, n (%)	11 (14.7%)	0 (0.0%)	0.007
SBP (mmHg)**	120 (110-130)	110 (100-120)	0.003
DBP (mmHg)**	70 (60-80)	70 (60-70)	0.002
Glucose (mg/dL)**	94 (87-100)	82 (78.5-88.5)	<0.001
Total Cholesterol (mg/dL)**	228 (183-272)	171 (159-193.5)	<0.001
Triglyceride (mg/dL)**	170 (108-224)	101 (74-130.5)	<0.001
HDL-C (mg/dL)**	46 (39-53.2)	47 (42-59)	0.251
LDL-C (mg/dL)**	144 (107-188)	100 (89-119.5)	<0.001
TSH (µU/mL)**	28.8 (12.1-67.2)	1.6 (1.1-2.1)	<0.001
Anti-TPO (IU/mL)**	415.5 (45.3-1300)	9.47 (5.9-17.3)	<0.001
PON1 activity (U/L)**	43 (23.4-76.9)	66.4 (32-91.1)	0.033

*Data is givenin means±SD.
**Data are given in median (25-75% percentile).

prised 40 women (88.9%), 5 men (11.1%) with the mean age of 40.6±5.2 years. There was no significant difference in age and gender distribution between the groups. BMI, SBP, DBP, glucose, total cholesterol, triglyceride, LDL-C, TSH, and Anti-TPO were significantly higher in the patient group compared with those in the control group. PON1 activity was significantly lower in the patients than in the controls ($p<0.05$).

There were 9 smokers (12.0%), 7 diabetics (9.3%), and 11 hypertensives (14.7%) in the patient group, while there were no such cases in the control group.

Genotype distributions and allele frequencies of PON1 192 and 55 polymorphisms in both groups are presented in Table 2. However, polymorphism analysis of one of the participants in the control group failed, thus, genetic analysis results were evaluated in 44 people. There was no significant difference in genotype distributions and allele frequencies between the two groups ($p>0.05$).

The patient group was divided into two subgroups as Hashimoto and others. These groups were compared with controls to assess PON1 192 and 55 genotype distributions and no statistically significant difference between the groups was observed ($p>0.05$). Concurrently, the patient group was also divided into two subgroups as subclinical and clinical hypothyroid cases and compared with the control group to assess PON1 192 and 55 genotype distributions; no significant difference was observed between the groups ($p>0.05$)

The distributions of PON1 activity and lipid levels in patient and control groups considering PON1 192 genotypes are presented in Table 3. In both groups, serum PON1 activities of the individuals with QR and RR genotypes were significantly higher when compared to those with QQ genotypes ($p<0.05$). Although, PON1 activity was higher in patients and controls with the RR genotype than in the patients with QR genotype, the difference was not statistically significant ($p>0.05$).

Likewise, no statistically significant difference in terms of total cholesterol, triglyceride, HDL-C, and LDL-C levels was observed between patient and control groups regarding PON1 192 genotype distribution ($p>0.05$).

Distributions of PON1 activity and lipid levels in patient and control groups considering PON1 55 genotype are presented in Table 4. Serum PON1 activity of the individuals with LL genotype was significantly higher when compared to the individuals with MM genotypes, in the patient group ($p<0.05$) as well as those with the LM genotype, although this was not statistically significant ($p>0.05$). Likewise, while the serum

Table 2. Genotype distributions and allele frequencies of PON1 192 and 55 polymorphisms in patient and control groups.

	Patients (n=75)	Controls(n=44)	p
Q/R 192 genotypes			
QQ	38 (50.7%)	16 (36.4%)	0.338
QR	29 (38.7%)	22 (50.0%)	
RR	8 (10.7%)	6 (13.6%)	
Allele frequency			
Q	70.0%	61.0%	
R	30.0%	39.0%	
L/M 55 genotypes			
LL	38 (50.7%)	25 (56.8%)	0.355
LM	25 (33.3%)	16 (36.4%)	
MM	12 (16.0%)	3 (6.8%)	
Allele frequency			
L	67.0%	72.0%	
M	33.0%	28.0%	

Table 3. Distributions of PON1 activity and lipid levels according to PON1 Q/R 192 genotypes in patient and control groups.

	Patients (n=75)				Controls (n=44)			
Q/R 192	**QQ (n=38)**	**QR (n=29)**	**RR (n=8)**	**p**	**QQ (n=16)**	**QR (n=22)**	**RR (n=6)**	**p**
PON1 (U/L)	23.4 (18.5-29.3)[a]	64.3 (55.2-84)[b]	90.8 (76.1-98.1)[b]	<0.001	26.2 (22.4-34.1)[a]	78.3 (65-93)[b]	119.3 (89.2-137.8)[b]	<0.001
Total Cholesterol (mg/dL)	240.7±56.7	223.1±56.2	234±64.7	0.464	170.6±23.8	176±25.9	175.5±27.3	0.805
Triglyceride (mg/dL)	165.5 (101-215)	187 (124.7-229.5)	135.5 (94-161.5)	0.215	109±47.7	106.5±48.6	104.5±46.7	0.977
HDL-C (mg/dL)	46 (41-54)	45 (36.7-53)	42 (39.5-54.5)	0.575	49.3±15	48.5±10.1	51.5±6.4	0.860
LDL-C (mg/dL)	153±45.3	140.4±57.8	157.3±58.4	0.547	101.1±17.3	105.8±24.1	102.8±23	0.802

[a,b]: There aren't any differences between the groups which contain the same letter.

Table 4. Distributions of PON1 activity and lipid levels according to PON1 L/M 55 genotypes in patient and control groups.

	Patients (n=75)				Controls (n=44)			
L/M 55	**LL (n=38)**	**LM (n=25)**	**MM (n=12)**	**p**	**LL (n=25)**	**LM (n=16)**	**MM (n=3)**	**p**
PON1 (U/L)	61.5 (36.3-90.2)[a]	39.8 (23.1-64.6)[ab]	21.7 (16.8-23.4)[b]	<0.001	68.9 (38.1-82.5)	70.6 (24.3-93.3)	31.4 (27.8-38.1)	0.235
Total Cholesterol (mg/dL)	239.4±63.6	221.6±42	237.8±65	0.464	173±22.6	174.8±30.3	177.6±15.6	0.944
Triglyceride (mg/dL)	158.5 (106-211)	170 (114.5-216.7)	220 (101.5-288)	0.485	97 (72-127.5)	94.5 (73.5-120)	119 (119-149.7)	0.249
HDL-C (mg/dL)	47 (41-58)	43 (37.7-46.7)	43.5 (35-51.5)	0.102	46 (43-56)	49 (42.5-61.5)	37 (34-45.2)	0.290
LDL-C (mg/dL)	148 (98-203)	137 (113.5-171.5)	138.5 (97.5-187.5)	0.56	103.3±19	102.8 ±25.6	111.6±20	0.804

[a,b]: There aren't any differences between the groups which contain the same letter.

PON1 activity in the individuals with the LM genotype was higher than those with the MM genotype, this difference was not statistically significant (p>0.05).
PON1 activity in controls with LL and LM genotype was higher than those with MM genotypes; however, no statistically significant differences were observed (p>0.05).
Concurrently, no statistically significant difference was observed in terms of total cholesterol, triglyceride, HDL-C and LDL-C levels among individuals with PON1 55 genotype in patient and control groups (p>0.05).

Discussion

The risk of atherosclerotic cardiovascular disease increases in hypothyroidism. However, the pathogenesis of atherosclerosis in relation to hypothyroidism may be multifactorial, although it has not been fully elucidated (3). Hypothyroid patients have a lipid profile that may initiate atherosclerosis. While some studies (17) reported an increase in total cholesterol, LDL-C, HDL-C, and triglyceride levels, others showed (18) no difference in HDL-C and triglyceride levels. Likewise, varying levels of lipid have been observed in hypothyroid patients. A recent cross-sectional study reported gender-specificity and the effect of age on the relationship between hypothyroidism and lipid profile (19). In this study, total cholesterol, LDL-C, and triglyceride levels were high in hypothyroid patients, while HDL-C levels were the same in both the patient and the control groups, in accordance with previous reports (20-22). Hypothyroid patients have an atherogenic lipid profile, but this is not enough for enlightening atherosclerosis, alone (23).

PON1 is an enzyme that is mainly synthesized in the liver and found in structure of HDL-C and exerts antioxidative and antiatherogenic effects. PON1 hydrolyzes oxon metabolites of organophosphates, nerve agents like sarin, soman (esters like phenylacetate), lactones, cyclic carbonates, and phospholipid hydroperoxides. It also hydrolyzes hydrogen peroxide. Activity and concentration of PON1 vary between populations. The quantity and the quality of this enzyme are important in determining the risk of vascular disease development (24). The studies on PON1 activity in hypothyroid patients have given varying results. In some studies, no significant difference was found between hypothyroids and controls in terms of PON1 activity (25,26). Lower PON1 activity was observed in hypothyroid patients when compared with healthy controls, consistent with a few other studies (9-12,27).

The causes of lower PON1 activity have not been clarified yet. Among several suggested mechanisms, oxidative stress plays a significant role. Aviram et al. (28,29) stated that PON1 has an important role in the protection of both HDL and LDL from oxidation. This effect occurs by PON1 mediated hydrolysis of lipid peroxides and cholesterol lineate hydroperoxides. Moreover, PON1 is inactive during the hydrolysis of lipoprotein related peroxides. Some studies have highlighted that LDL-C is more tended to oxidation and oxidised LDL-C levels in blood circulation were elevated in hypothyroid patients (22,30,31). In this study, we did not observe any significant difference between the patient and the control groups in terms of HDL-C levels, and also, LDL-C levels were significantly increased in the patient group. Therefore, this indicates the existence of potential factors that lower PON1 activity independent of HDL-C level in hypothyroid patients.

The results of studies conducted on oxidative stress in hypothyroid patients are conflicting. Ateş et al. (32) investigated total antioxidant status in euthyroid, subclinical and clinic patients secondary to Hashimoto's thyroiditis, and observed it to be lowered in clinical hypothyroid patients when compared to healthy controls and other groups. However, oxidative stress index and total oxidant status were significantly higher in clinic hypothyroid patients than in the other groups and higher in euthyroid and subclinical patients than the controls. Although in a few studies (9,11) have shown increased oxidative stress in hypothyroidism, no difference has found in another study (26). It is obvious that more exhaustive studies are needed to assess the role of oxidative stress in the tendency of atherosclerosis in hypothyroidism.

Another important cause of lower PON1 activity is polymorphism. In PON1 192 polymorphism, serum paraoxonase activity in homozygote people who have R in 192nd position is high, while in individuals with Q is low, and in heterozygote people with QR, medium activity was observed (16,33). Concurrent with earlier studies, PON1 activities of the patients and the controls in this study, with RR and QR genotypes, were significantly higher than those with QQ genotype, and those with RR genotype exhibited higher PON1 activity than those with QR genotype, although, it was not significant statistically. We hypothesize that this may be due to the small number of recruited people exhibiting RR genotyped.

Considering PON1 55 polymorphism, some studies report higher paraoxonase activity in the people with LL and LM alleles than those harboring MM allele, while no difference between LL and LM alleles in terms of paraoxonase activity was observed (34). Consistent with the study of Altuner et al. (35), in this study, we found that PON1 activity in patients with LL genotype was higher than those with MM and in LM genotypes but not statistically significant, and there was no difference between LL and LM genotypes in terms of PON1 activity. In control group, while the activities of LL and LM genotypes were higher than MM genotypes, these differences could not have been found statistically significant, probably because the number of people with MM genotype was only 3.

Until now, PON1 polymorphisms have been evaluated in many disorders like metabolic syndrome, diabetes, Alzheimer's disease, stroke, urolithiasis, and coronary heart disease. However, no such study has evaluated PON1 polymorphism in hypothyroid patients. In a study by Lambrinoudaki et al. (36), the porters of the PON1 R allele in

postmenopausal women was associated with lower T3 levels. Our study is the first to investigate PON1 polymorphism in hypothyroid patients. These results led us to hypothesize the effect of PON1 192 and 55 polymorphisms on PON1 activity. We observed that these polymorphisms do not have any effect on PON1 activity in hypothyroid patients and also are not an important genetic predisposition for increased atherosclerosis.

In this study, the levels of total cholesterol, triglyceride, HDL-C, and LDL-C were investigated in terms of PON1 192 and 55 genotypes, both in patients and controls. The relationship between PON1 polymorphisms and serum lipid levels has been investigated in different patient groups except in hypothyroidism. Hegele et al. (37) found lower triglyceride and LDL-C levels and higher HDL-C levels in QQ genotyped people than in the other genotypes. Furthermore, in another study, the total cholesterol level of QQ genotyped people was found to be low (8). In a study that included Systemic Lupus Erythematosus patients, LDL-C levels were estimated to be higher in individuals carrying 55 MM and ML genotypes than those carrying LL genotype (38), although varying results were observed. In line with a few earlier studies (39-41), we found that PON1 192 and 55 polymorphisms do not affect serum lipid levels.

Study Limitations

An important limitation of this study was the low number of subjects in patient and control groups. Furthermore, it might have been better to exclude situations that increase the risk of oxidative stress and cardiovascular disease such as diabetes, hypertension, and smoking in the patient group.

Conclusion

In conclusion, PON1 192 and 55 polymorphisms were found to cause important changes in PON1 activity, while allele frequencies and genotype distributions of these polymorphisms showed no difference between the hypothyroid patients and controls. Furthermore, independent of these polymorphisms, PON1 activity was low, and thus may not be a genetic risk for increased atherosclerosis in hypothyroid patients.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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Authorship Contributions

Idea/Concept: Gülden Başkol, Fahri Bayram; Design: Ayşen Caniklioğlu; Control/Supervision: Gülden Başkol; Data Collection and/or Processing: Fahri Bayram, İlkay Çakır, Meral Mert, Ayşen Caniklioğlu, Nahide Ekici Günay; Analysis and/or Interpretation: Gülden Başkol, Ferhan Elmalı; Literature Review: Ayşen Caniklioğlu; Writing the Article: Ayşen Caniklioğlu; Critical Review: Fahri Bayram, Gülden Başkol; References and Fundings: Erciyes University Scientific Research Projects Commission; Materials: Ayşen Caniklioğlu.

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