Turk J Endocrinol Metab. 2021;25:193-201

Serum Paraoxonase-1 Activity and Paraoxonase Q192 Gene Polymorphism in a Young, Healthy Population

Sağlıklı Genç Popülasyonda Serum Paraoksonaz-1 Aktivitesi ve Paraoksonaz Q192 Gen Polimorfizmi

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Abstract

Objective: Paraoxonase-1 (PON1) enzyme and PON Q192R gene polymorphism are associated with atherosclerosis in many middle-aged individuals and high populations at risk of cardiovascular disease. This study aimed to determine serum PON-1 and arylesterase (ARE) activities, PON Q192R polymorphism, and their association with gender, lipoprotein levels, and carotid intima-media thickness (CIMT) among young healthy individuals. **Material and Methods:** Four hundred fifteen healthy volunteers (F/M: 213/202, 19-25 years) were included in the study. Serum lipoprotein levels and PON1, ARE activities were measured using spectrophotometric methods. PON 192Q polymorphism was evaluated by polymerase chain reaction, and CIMT was measured using Doppler ultrasonography. **Results:** Serum PON1 activity and PON Q192R polymorphism frequencies were similar between men and women, while ARE activity was significantly higher in women. PON1 activity was considerably higher in RR carriers than in QQ and QR carriers among both men and women. Serum high-density lipoprotein level was lower, and CIMT was higher in men compared to women. **Conclusion:** PON1 enzyme activities did not differ according to gender, and ARE activity was higher in women. High PON1 activity is associated with PONQ192 RR polymorphism carriers. PON Q192 gene polymorphism could be a determinant of PON activity.

Keywords: Paraoxonase-1; paraoxonase Q192R gene; arylesterase; gender; high-HDL cholesterol

Özet

Amaç: Paraoksonaz-1 (PON1) aktivitesi ve Q192R gen polimorfizminin kardiyovasküler riskii yüksek ve yaşlı popülasyonlarda ateroskleroz ile ilişkisi gösterilmiştir. Bu çalışmanın amacı, sağlıklı genç popülasyonda serum PON-1 ve arilesteraz (ARE) aktivitelerini ölçmek ve bu düzeylerin cinsiyet, lipoprotein düzeyleri, PON Q192R gen polimorfizmi ve karotis intima medya kalınlığı ile (KIMK) ilişkisini değerlendirmektir. **Gereç ve Yöntemler:** Dört yüz on beş sağlıklı gönüllü (K/E: 213/202, minimum-maksimum 19-25 yaş) çalışmaya dâhil edildi. Serum lipoprotein düzeyleri PON-1 ve ARE aktiviteleri spektrofotometrik yöntem ile ölçüldü. PON Q192R gen polimorfizmi polimeraz zincirleme reaksiyonu, KIMK Doppler ultrasonografi ile değerlendirildi. **Bulgular:** Serum ARE aktivitesi kadınlarda erkeklere göre daha yüksek bulundu, ancak PON1 aktiviteleri her 2 grupta benzerdi. PON Q192R gen polimorfizm sıklıkları ve dağılımları kadın ve erkeklerde benzerdi. Tüm çalışma grubunda PON1 aktivitesi, PON Q192R RR taşıyıcılarında QQ ve QR taşıyıcılarından daha yüksek izlendi. Erkeklerde, kadın grubuna göre serum yüksek yoğunluklu lipoprotein düzeyi düşük, KIMK ölçümü yüksek tespit edildi. **Sonuç:** PON1 enzim aktivitesi cinsiyete göre farklılık göstermemiş olup, ARE aktivitesi kadınlarda daha yüksek izlenmiştir. PONQ192 RR polimorfizm "Yüksek PON1 aktivitesi, PONQ192 RR polimorfizm taşıyıcıları ile ilişkilidir." PON Q192R gene polimorfizmi PON aktivitesinin belirleyicisi olabilir.

Anahtar kelimeler: Paraoksonaz-1; paraoksonaz Q192R geni; arilesteraz; cinsiyet; yüksek HDL kolesterol

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Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 05.12.2020 **Received in revised form:** 14.04.2021 **Accepted:** 04.05.2021 **Available online:** 04 Jun 2021

DOI: 10.25179/tjem.2020-80427

Introduction

Paraoxonase-1 (PON1) is well-known as a free-radical scavenging system bound to high-density lipoprotein (HDL) molecule, providing anti-oxidant properties (1). PON1 catalyzes the hydrolysis of aryl esters, lactones, and hydroperoxides. It plays a crucial role in anti-atherosclerotic activity by inhibition of lipoprotein oxidation and inactivation of toxic peroxidation products, also preventing their accumulation. Also, the arylesterase (ARE) activity of PON1 is involved in the detoxification of lipid peroxides, which are related to endothelial dysfunction and coronary artery disease (CAD) (2).

HDL cholesterol is inversely correlated with CAD development; the protective effect is attributed to enzymes, such as PON (3,4). HDL-associated PON1 inhibits low-density lipoprotein (LDL) oxidation, stimulates cholesterol efflux from macrophages, and confers atheroprotective activity to HDL particles. CAD prevalence is higher in patients with the lowest PON1 activity. Carotid intima-media thickness (CIMT) is considered a sign of cardiovascular (CV) disease in the early stages and is inversely related to PON1 activity in several studies (5-7).

PON1 enzymatic activity is substrate-dependent and varies with different ethnic backgrounds. Although PON1 activity differs extensively from one case to another, the action remains relatively stable for a given person (3). The PON1 gene has nearly 200 different single nucleotide polymorphisms. The most frequent polymorphisms in the PON1 gene coding region are leucine/methionine substitution at position 55 and glutamine/arginine substitution at position 192 (8). Q192R is more widely recognized and studied in subjects with atherosclerosis compared to L55M polymorphisms. PON1 gene polymorphisms independently influence the ability of the enzyme to protect LDL oxidation or alter PON1 activity (9). Although people with PON1 gene Q192R polymorphism are expected to be at an increased risk of CAD, literature reports conflicting data on the relationship of this polymorphism with endothelial dysfunction or coronary heart disease (8,10-14).

Serum lipid fractions and lipoprotein-related enzyme activities might differ between the populations. The Turkish Heart Study (15) reported that HDL-C levels in healthy Turkish people tended to be lower than the U.S. and European populations. If so, this may be associated with a decline in PON1 activity and an increment in atherosclerotic markers. Studies performed on the middle-aged Turkish population have reported that HDL cholesterol in women and non-HDL cholesterol in men are determinants of CV disease (15,16). Yet, the distribution of lipid profile and its reflection on atherosclerotic markers in healthy Turkish youth is not clear.

This study aimed to determine serum PON and ARE activities and their relationship with gender, lipoprotein levels, PON1 gene Q192R polymorphism frequencies, and CIMT in a group of the healthy, young Turkish populace.

Material and Methods

Study Population

The study protocol was announced to all the volunteering participants on the university campus. Eligible 213 women and 202 men were included in the study. General physical examination (weight, height, and blood pressure measurements), routine biochemical, blood, and urine tests were used to identify healthy subjects.

A questionnaire collected the family and medical history, smoking, and alcohol habits of the subjects. Weight, height, waist and hip circumference, systolic blood pressure and diastolic blood pressure (SBP and DBP) were measured using standard techniques. Body mass index (BMI) was calculated as body weight (kilograms)/(height in meters)^2. Waist-hip ratio (WHR) was calculated as waist circumference (centimeters)/hip circumference (centimeters). Blood and urine samples were collected after 8 h of fasting in the morning for PON1 and ARE activity and lipid profile determination. CIMT was defined using high-resolution B-mode ultrasonography non-invasively by an experienced operator.

Participants with diabetes mellitus, hypertension, CV diseases, renal or hepatic diseases, inflammation, smokers, alcohol or drug abusers were excluded from the study.

The local ethics committee of the Marmara University Medical School approved the study protocol (MAR-YC-2002-0056), and procedures were applied according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was obtained from all the subjects before the tests and procedures.

Genotyping of DNA

DNA was extracted from peripheral blood samples using a High Pure PCR Template Preparation Kit (Roche Diagnostics Mannheim Germany). Previously published polymerase chain reaction (PCR) protocol for PON1 192 polymorphism was applied. A 99-bp fragment amplification was done using the following primers: 5′ TAT TGT TGC TGT GGG ACC TGA G-3′ and antisense primer 5′-CAC GCT AAA CCC AAA TAC ATC TC-3′. The contents of the PCR mixture used were: 1.5 mM MgCl2, 0.2 mM/l dNTP, 1U Taq DNA polymerase, 100 ng DNA template, and 0.2 μM/L of each primer (MBI Fermentas, Ukraine). The PCR product was digested with 8U Bsp PI at 37 °C for 12 h, and 3% agarose gel electrophoresis was used for separation. Ethidium bromide staining of gel was visualized under ultraviolet light. Alleles were assigned as Q (glutamine) and R (arginine) based on the presence of undigested (99bp) and digested (66 and 33bp) fragments, respectively (17).

Serum Paraoxonase and Arylesterase Activity Determinations

Serum PON1 activity was measured by the kinetic method. Enzymatic hydrolysis of paraoxon at 37 °C for 3 min was monitored, and the formation of 4-nitrophenol at 405 nm was determined. The optimal paraoxon concentration that provided a linear reaction rate was determined [0.1 M Tris-HCl buffer (pH 8) with 2 mmol/L $CaCl_2$, 1 mol/L NaCl]. Serum ARE activity was measured by the kinetic method. Enzymatic hydrolysis of phenylacetate at 25 °C for 3 min was monitored, and the formation of phenol at 270 nm was determined. The optimal phenylacetate concentration that provided a linear reaction rate was determined in a 0.1 M Tris-HCl buffer (pH 8) containing 2 mmol/L $CaCl_2$. A Tecan Infinite M200 microplate reader was used for the measurements, enabling simultaneous analysis of multiple samples (18).

Serum Lipid Measurements

An enzymatic colorimetric test that uses cholesterol oxidase in a Roche 917 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany) measured the serum cholesterol levels. The intra-assay precision was 0.8% for a mean concentration of 231 mg/dL while inter-assay precision was 1.7% for a mean concentration of 210 mg/dL. An enzymatic colorimetric test determined serum triglyceride levels in a Roche 917 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany). The intra-assay precision was 1.5% for a mean concentration of 201.4 mg/dL, while the inter-assay precision was 1.8% for a mean concentration of 224 mg/dL. Serum HDL concentrations were analyzed by a direct method using PEG-modified enzymes and dextran sulfate (Roche Diagnostics GmbH, Mannheim, Germany). The intra-assay precision was 0.58% for a mean concentration of 46.9 mg/dL and inter-assay precision was 1.3% for a mean concentration of 63.7 mg/dL.

Measurements of Carotid Intima-Media Thickness

A single vascular sonographer, who did not know the clinical or laboratory profile of the participants, performed the imaging studies. IMT was measured using a 10 MHz linear array transducer with GE Vingmed, System Five (Horten, Norway). Measurements were done in a supine position. The common carotid artery IMT measurements were done at 2 cm distal to the proximal surface of its bifurcation. A longitudinal B-mode image was used. The distance between two interfaces of the lumen at end-diastole indicated the IMT. Three points from the right and left common carotid arteries were measured manually, and the mean value was calculated (19).

Statistical Analysis

All statistical calculations were carried out using SPSS (Statistical Package for Social Sciences) for Windows 15.0 software (SPSS, Chicago, IL, USA). The chi-square test was used to check the Hardy-Weinberg equilib-

rium (HWE) and differences between the distributions of PON polymorphisms. Student t-test was used for the parametric variables, and chi-square (c^2) test was used for the comparison of categorical data. The level of statistical significance was set at $p<0.05$. All results are expressed as mean±standard deviation.

Results

Anthropometric Features, Lipid Profile, and Serum Paraoxonase-1 Activity of the Study Population

The general anthropometric features, lipid profiles, serum PON1, and ARE activities of the study population have been summarized in Table 1. The mean age of the study population was 23.6±1.4 years. BMI, waist to hip ratio, LDL cholesterol, triglyceride levels, SBP and DBP were significantly higher in males. In contrast, HDL levels were significantly lower in men compared to that in women. The serum PON1 activity did not differ between men and women, while the ARE activity was considerably higher in women (p=0.008) (Table 1).

Paraoxonase-1 Polymorphisms and Distribution of Genotypes

The distribution of the genotypes and alleles for PON1 exonic 192QR polymorphism is shown in Table 2. In this study, genotypes were similar to HWE (p>0.05). PON 192 QR genotype frequencies were 26%, 56.3%, and 17.6% for QQ, QR, and RR, respecitively. Allele frequency for major and minor alleles was 0.55:0.45 (chi-square for HWE=1.96, p>0.05). PON gene 192 polymorphism frequencies and distribution of the genotypes and alleles were similar between men and women (Table 2).

PON1 activity was significantly higher in the RR carriers (p<0.01) compared to QR and QQ genotypes (Table 3). ARE activity did not differ between the groups. LDL cholesterol was lower in RR carriers, significantly among women (p=0.02 vs. QR). SBP and DBP was considerably lower in RR carriers in males (p=0.01 and p=0.03). There was no significant difference between the groups according to polymorphism differences in terms of CIMT.

Carotid Intima-Media Thickness Measurements

Although CIMT measurements were not in the atherosclerotic range, it was significantly higher in the males (0.46±0.001 cm) compared to the females (0.45±0.01 cm) (p=0.006).

Correlations

Serum PON1 activity was positively correlated to ARE activity (r: 0.32; p<0.0001), HDLc (r: 0.26 p=0.01) and negatively correlated to CIMT (r: -16; p=0.01). A positive correlation between PON1 activity and ARE

Table 1. Demographic characteristics, lipid parameters, and paraoxonase and arylesterase enzyme activities of the study groups.

Parameters	All subjects n=415	Men n=202	Women n=213	p value
Age (years)	23.6±1.4	23.7±2.0	23.5±2.0	NS
BMI (kg/m^2)	22.3±1.1	22.9±2.3	21.6±2	<0.0001
Waist/Hip ratio	0,79±0.08	0.85±0.08	0.73±0.06	<0.0001
SBP (mmHg)	116.5±12.4	123.2±12.7	110.7±12.2	<0.0001
DBP (mmHg)	74.3±7.4	75.9±7.0	72.2±8.1	<0.0001
Total cholesterol (mg/dL)	156.8±32	156.2±36.5	157.4±28.3	NS
LDL (mg/dL)	89.2±26	92.9±29.7	85.3±22.8	0.007
HDL (mg/dL)	54.3±14.6	48.5±14.3	60.2±15.0	<0.0001
Triglyceride (mg/dL)	76.5±29.6	85.7±34.2	68.4±25.1	<0.0001
Paraoxonase activity (U/L)	246.4±156	236.9±154	256±159	NS
Arylesterase activity (KU/L)	96.6±29.3	90.8±30.2	102.7±28.4	0.008

BMI: Body mass index; DBP: Diastolic blood pressure; NS: Nonsignificant; SBP: Systolic blood pressure; HDL: High-density lipoprotein.

Table 2. Paraoxonase gene 192 polymorphism frequencies in young, healthy men and women.

	Frequencies n (%)		X^2 for HWE
Women	QQ	55 (25.8)	
	QR	120 (56.3)	3.8 p=0.055
	RR	38 (17.8)	
	Allele frequencies R 0.46 Q 0.54		
Men	QQ	53 (26.2)	
	QR	114 (56.4)	3.8 p=0.52
	RR	35 (17.3)	
	Allele frequencies R 0.46 Q 0.54		

HWE: Hardy-Weinberg equilibrium.

and HDLc was observed. However, a negative correlation was noted with CIMT in men and women, respectively (r: 0.20; p=0.01) and (r: 0.32; p<0.0001) for ARE activity, (r: 016; p=002) and (r: 0.18, p=0.007) for HDLc, (r:-0.32; p=9.001) and (r: -0.18; p=0.03) for CIMT.

ARE activity was negatively correlated to BMI (r: -0.20; p=0.01) and CIMT (r: -0.27; p=0.02) in males. No significant correlation in women was observed. Multiple regression analysis (stepwise selection) was performed. PON activity was taken as a dependent parameter, and PON 192Q polymorphism, ARE activity, HDL, total cholesterol, LDL, and triglyceride, BMI was included in the model. PON1 activity was strongly associated with PON192Q genotype and ARE activity in the whole group (R^2: 31.9, p<0.0001).

Discussion

This study did not find a possible gender effect on PON activities and PON 192Q polymorphism genotype frequency in a healthy young Turkish population. PON Q192R gene polymorphism was a determinant of PON activity in this young population. It was observed that total cholesterol, LDLc, and triglyceride levels were higher, whereas HDLc levels and ARE activities were significantly lower in men compared to women. Nevertheless, serum PON1 activities were similar between men and women.

Mahley et al. reported that education and socioeconomic status might positively affect HDLc levels because they found higher HDLc levels in the university-educated subjects than primary school-educated subjects (20). While the sample size in the present study was smaller than the Turkish Heart Study cohort, it mainly involves healthy young, 20-26 years, college students. The present study groups' HDLc levels were higher than that of the previous studies conducted in Turkish populations (15,20). This may be attributed to the normal BMI and high education level of this study group. Lower HDL

Table 3. Paraoxonase activity, lipid levels, blood pressure, and CIMT measurements in PON192 Q gene polymorphism among women and men.

	Women			Men		
	RR	QR	QQ	RR	QR	QQ
Paraoxonase activity (U/L)	349±219†	244±132‡	158±94	525±191†	266±159§	192±112
Arylesterase activity (U/L)	95.7±28.2	92.7±24.3	86.3±24.6	94.4±14	95.0±24	101.2±24
Total cholesterol (mg/dL)	153.6±26.9	159.0±25.8	153.6±30.6	151.8±42.7	159.5±34.8	152.3±35.6
HDLc (mg/dL)	65.3±12.5	55.2±16.1	58.5±15.5	48.6±14.5	48.6±15.5	48.1±11.6
LDLc (mg/dL)	78.1±21.4¶	89.3±21.6	82.2±24.9	87.3±36.0	93.5±27.7	91.4±23.2
Triglyceride (mg/dL)	71.6±28.1	66.3±21.9	67.6±24.1	83.7±52.7	81.6±43.6	80.9±37.8
BMI (kg/m^2)	19.8±4.2	20.8±3.4	20.9±2.7	24.3±3.3	23.5±3.7	23.6±3.1
SBP (mmHg)	110.7±10.7	112.3±12.1	108.6±13.7	119.0±15.1*	126.4±9.7	123.0±10.6
DPB (mmHg)	70.0±9.2	72.9±7.5	72.4±9.1	73.4±8.1**	78.4±9.2	78.0±7.1
CIMT (cm)	0.44±0.05	0.45±0.05	0.45±0.04	0.46±0.05	0.46±0.06	0.45±0.05

†p<0.01 vs. QR and QQ; ‡p<0.01 vs. group QQ in women; §p<0.05 vs. QQ group in men; *p=0.01 vs. group QR in men; **p=0.03 vs. QR group in men; ¶p=0.02 vs. group QR in women; CIMT: Carotid intima-media thickness; HDLc: High-density lipoprotein cholesterol; LDLc: Low-density lipoprotein cholesterol; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

levels in men can be explained by a significantly higher BMI and waist to hip ratio.

While serum levels of PON1 activity remained constant for an individual, it varies widely among people. PON gene polymorphisms may affect PON1 activity, but they can also be affected by other factors. Serum PON1 activities for phenylacetate and paraoxon showed a positive correlation with HDLc in the present study, which seems to be one factor explaining the diversity in serum PON1 activity consistent with previous studies (18,21). On the other hand, lower ARE activity was found in men than women, although there was no statistical significance between the female and male subjects in terms of PON1 activity. HDLc levels were lower, whereas BMI, LDL, and triglyceride were higher in men than in women. These metabolic differences may cause a decrease in ARE activity. Agirbasli et al. (22) included a healthy adolescent Turkish population in their study and determined that HDLc level was the most considerable predictor of PON1 activity in the lean control group.

In contrast, BMI was found to be the strongest predictor in subjects with obesity or IR. Sepahvand et al. (23) reported that age and sex did not influence PON1 activity, while another study reported that ARE activity was affected by gender to a limited extent (24). Those studies indicate a possible gender influence on PON1 and ARE activity. CIMT is an early sign of atherosclerotic vessel diseases and is inversely related to PON1 activity (4,6,7,25,26). A large body of literature shows that PON1 activity decreases significantly in patients with an apparent CAD than healthy people. Some of these have reported that low PON1 activity can predict the severity of CAD (4). Studies in hypertensive patients with no overt CAD have shown that PON1 activity is negatively related to CIMT (27). Chen X et al. (6) have claimed that the anti-oxidant effect of HDLc is influenced by gender. Several studies have reported the relationship of low PON1 and ARE activity with an increase in CIMT (12,27,28).

PON gene polymorphisms affect PON1 activity. Also, PON1 activity and PON gene polymorphisms were associated with CAD (27,29). On the other hand, Mackness et al. (8), Godbole et al. (30), and Gupta et al. (31) showed that PON1 activities were lower in subjects with CAD than in control subjects regardless of the PON1 genotype.

PON gene polymorphisms were also associated with carotid arterial wall thickness in subjects with familial hypercholesterolemia (28). Frequencies of PON1 alleles extensively alter across human populations. Genetic polymorphism at position 192 of the PON1 molecule confers low (homozygous for a glutamine substitution) or high activity (homozygous for arginine) against the substrate paraoxon (27). PON1 Q192R allelic frequencies in the present study population were different from those reported in various Caucasian subjects. Studies conducted on American, English, Finnish, German and French population reported PON 192 gene Q allele frequencies between 71-76% (8,9,13). Studies from Chilean and Mexican populations were reported to have Q allele frequencies of 56% and 51%, respectively (32,33). In the present study, Q allele frequency was 54% in a healthy young Turkish population, while a previous study reported 67% Q allele frequency in different case-control studies (34).

Some studies show that Q192R polymorphism of PON seems to be associated with atherosclerotic stages (9,12,29), but there are conflicting data in this regard. Scherrer et al. (5) reported that the p.192Q variant of PON1 is not associated with carotid atherosclerosis in 584 asymptomatic healthy Brazilian populations. The HUMPONA study (13) confirmed that Gln-Arg 191 polymorphism of PON is not related to the risk of CAD in Finns. Another study on the Turkish population (35) showed no significant difference in the distribution of PON1 Q192R polymorphism. A correlation with atherosclerosis between angiographically documented CAD compared to healthy control people was noted. They concluded that serum PON activity might be a more appropriate marker than the PON1 genotype in assessing the extent and severeness of atherosclerosis. Similarly, the present study could not find any relation between PON1 polymorphism and CIMT but RR polymorphism carriers showed higher PON1 activity compared with QR and QQ carriers in both young men and women. In another study, a 4.33-fold incre-

ment in the risk of acute coronary syndrome (ACS) in participants with the PON1 192 RR genotype than those with the QQ genotype was reported, and authors concluded the PON1 192 RR genotype was more prevalent in ACS patients than healthy subjects (36). The relationship between PON polymorphism and atherosclerotic disease may vary according to the genetic makeup of the populations and environmental factors.
Contrary to the literature, the present study found higher HDL levels in subjects with PON1 192 RR genotype; this may be attributed to the differences in PON2 and PON3 activities or the presence of L55M polymorphisms. Also, the present study included only young, healthy subjects without any chronic diseases; this could be one reason for the different outcomes of this study compared to the previous reports (8,12,37).

Conclusion

The study indicated that PON1 enzyme activities did not differ according to gender. ARE activity was higher in women. High PON activity was associated with PON Q192R gene RR polymorphism carriers. PON Q192R gene polymorphism was a determinant of PON activity.

Acknowledgement

Special thanks to Kaysu Ozaltun for technical assistance for measuring Paraoxonase activities and PON1 genotyping.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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.

Authorship Contributions

Idea/Concept: Dilek Gogas Yavuz, Önder Şirikçi; Design: Özlem Üstay; Control/Supervision: Dilek Gogas Yavuz, Tuğçe Apaydın; Data Collection and/or Processing: Palmet Gün Atak, Ahu Telli; Analysis and/or Interpretation: Tuğçe Apaydın, Dilek Gogas Yavuz; Literature Review: Özlem Üstay, Dilek Gogas Yavuz; Writing the Article: Dilek Gogas Yavuz, Tuğçe Apaydın; Critical Review: Özlem Üstay; References and Fundings: Önder Şirikçi; Materials: Ahu Telli, Palmet Gün Atak.

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