Clin Rheumatol (2018) 37:971–977
https://doi.org/10.1007/s10067-017-3859-3

ORIGINAL ARTICLE

Synergism between apolipoprotein E Ɛ4 allele and paraoxonase (PON1) 55-M allele is associated with risk of systemic lupus erythematosus

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Received: 24 January 2017 / Revised: 19 August 2017 / Accepted: 27 September 2017 / Published online: 22 December 2017

Abstract Evidences indicate that abnormal lipid metabolism and lipid peroxidation can affect the progression of complications in systemic lupus erythematosus (SLE) patients. Apolipoprotein E (ApoE) and paraoxonase-1 (PON1) play important role in lipid metabolism and protection of lipid peroxidation. The polymorphisms of ApoE and paraoxonase (PON1) L55M (Met < Leu) allele genes lead to disorders in lipid metabolism and are related to atherosclerosis. This study is the first investigation to examine the possible association between ApoE and PON1-L55M polymorphisms and correlation with serum arylesterase (ARE) activities of PON, levels of malondialdehyde (MDA), neopterin, and lipid lipoprotein in SLE patients from Iranian western population. The present case-control study consisted of 107 SLE patients and 101 gender- and age-matched, unrelated, healthy controls from Iran's western population. The ApoE and PON1-L55M genotypes were identified using PCR-RFLP method. The serum level of MDA, neopterin, lipid levels, and ARE activity were determined by HPLC, commercial kits, and spectrophotometry, respectively. Our results showed that ApoE ε4 and PON1-55M alleles act synergistically to increase the risk of SLE by 1.47 times ($p = 0.038$). We found that the frequency of ApoE 3/ 4 genotype was higher in SLE patients (11.2%) compared with control subjects (5%), although the difference was not significant ($p = 0.087$). This study for the first time not only demonstrates that ApoE 4 and PON-55M alleles synergistically increase the risk of SLE but also reveals that serum levels of MDA, neopterin, and LDL-C are high in SLE patients. This information may be in value for evaluating SLE progression and in the elucidation of the mechanisms of the disease pathogenesis.

Keywords Apolipoprotein E genotypes · Arylesterase activity of paraoxonase · Malondialdehyde · Neopterin · Paraoxonase (PON1)-55 polymorphism · Systemic lupus erythematosus

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Abbreviations

SLE	Systemic lupus erythematosus
MDA	Malondialdehyde
ROS	Reactive oxygen species
CAD	Coronary artery disease
LDLR	Low-density lipoprotein receptor

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies against self-antigens and loss of immunological tolerance [1, 2]. The

clinical symptoms of SLE are widespread and one of the most important manifestations is chronic inflammation [1]. Genetics and environmental effects are involved in the etiology of SLE [3]. Lipid peroxidation is the one of the main molecular mechanisms involved in the oxidative damage to cell structures leading to atherosclerosis in SLE patients [4–6]. Atherosclerosis appears to be a major cause of morbidity and mortality in SLE patient [7].

Paraoxonase-1 (PON1; aryldialkylphosphatase, EC 3.1.8.1) and apolipoprotein E (ApoE), the two serum major bioscavengers, have recently received a lot of attention as antioxidants that attenuate oxidation of low-density lipoprotein (LDL), a key regulator in the pathogenesis of atherosclerosis leading to several cardiovascular diseases (CVDs) [8].

Apolipoprotein E is a glycoprotein, which plays an important role in human lipoprotein metabolism, in T lymphocyte proliferation, and in regulating immune reactions [9]. The gene encoding ApoE is located on chromosome 19q 13.2 and has three polymorphic alleles, ε2, ε3, and ε4 [10]. Homozygous ApoE genotypes include ApoE ε2ε2, ApoE ε3ε3, and ApoE ε4ε4, and heterozygous genotypes are ApoE ε2ε3, ApoE ε3ε4, and ApoE ε2ε4. The most common genotypes (approximately 60%) between different populations are ApoE ε3ε3. Single-nucleotide polymorphisms (SNPs) at positions 112 and/or 158 in APO protein molecule are responsible for ApoE ε2 and ApoE ε4 isoforms, which have a low and high affinity for their receptors, respectively [11]. It has been suggested that ApoE specific isoforms protect neuronal and other tissue cells against free radicals and oxidative cell death. These effects are correlated with in vitro ApoE antioxidant activity (ranked E2 > E3 > E4) [12].

We have previously demonstrated that single-nucleotide polymorphism of PON-55M/M genotype is a risk factor for SLE. The carriers of this allele have high levels of MDA, neopterin, and LDL-C and lower serum ARE activity; thus, they are more likely to develop hypertension [8].

In this study, we examined possible association between ApoE and PON1-L55M polymorphisms with susceptibility to SLE and with the markers of lipid peroxidation, inflammation, and oxidative stress.

Subjects and methods

Subjects

The study protocol was approved by the Ethics Committee of the Kermanshah University of Medical Sciences and was in accordance with the principles of the Declaration of Helsinki II and all subjects provided written informed consent.

For this case-control study, we collected a total of 208 blood samples from 107 SLE patients and 101 control healthy volunteers. SLE patients (mean age, 37.3 ± 11.3 years; range, 15–75 years; 88 females and 19 males) were recruited from Imam Reza Hospital of the Kermanshah University of Medical Sciences. Clinical and laboratory findings were in line with the American College of Rheumatology (ACR) criteria for SLE and were collected with respect to age, gender, and involved organs [13].

One-hundred-one control healthy volunteers (mean age, 37.1 ± 11.5 years; range, 15–72 years; 81 females and 20 males) without any history of autoimmune disease, coronary heart disease, SLE, or specific diseases at their annual medical checkup were selected from individuals hospitalized at the Kermanshah University of Medical Sciences' Hospitals.

Clinical and laboratory assessments

The ARE activity and levels of MDA and neopterin in the serum samples were determined by spectrophotometer and by HPLC (Agilent Technologies 1200 Series, Agilent Corp., Germany) using EC 250/4.6 Nucleodur 100-5 C18ec column (Macherey-Nagel, Düren, Germany), respectively, as previously described [8].

Serum lipids

Serum lipids and lipoproteins profile were measured by the standard enzymatic method (Pars Azmon Kit, Iran), using an automated Erba XL-600 (Mannheim, Germany).

Genotyping analysis of ApoE and L55M polymorphisms

Blood samples were collected in tubes containing EDTA anticoagulant, and DNA was extracted using phenol chloroform extraction method according to the standard protocol [14].

Apolipoprotein E gene was amplified by polymerase chain reaction (PCR) using forward 5′-TCCAAGGAGCTGCA GGCGGCGCA-3′ and reverse 5′ACAGAATTCGCCCC GGCCTGGTACACTGCCA-3′ primers. In order to determine the different ApoE alleles, Cfo1 restriction enzyme was used to digest the PCR product and PCR fragments were electrophoresed in a 12% non-denaturing polyacrylamide gel and visualized by ethidium bromide. The size of full-length PCR product was 227 bp, and ε3, ε2, and ε4 digested PCR fragments were 91, 81, and 71 bp, respectively [15, 16].

Genotypes and allele of PON1-55Met > Leu (M > L) were detected by PCR-RFLP, as previously described [17]. Genotyping of all individuals was performed without knowledge of their groups or disease.

Statistical analysis

The allelic frequencies were calculated by the gene counting method. The χ^2 test was used to verify the agreement of the observed genotype frequencies with those expected according

Table 1 Laboratory parameter distribution level of serum lipids, neopterin, malondialdehyde, and other risk factors in SLE patients and control groups in a population from Kermanshah Province

Parameter	SLE patients (n = 107)	Control subjects (n = 101)	p values
Age (years)	35.6 ± 16.3	37.1 ± 11.5	0.74
Sex (M/F)	19 (17.7%)/88 (86.3%)	20 (19.8%)/81 (80.2%)	0.38
Arylesterase activity (ARE) (U/L)[a,b]	127,670 (118,700–1,450,400)	147,470 (137,200–164,490)	<0.001
Neopterin (nmol/L)[b]	10.2 (5.1–23)	5.9 (4.73–7.54)	<0.001
Malondialdehyde (MDA)[b] (μmol/L)	1.75 (1.28–2.59)	1.02 (0.84–1.28)	<0.001
LDL-cholesterol (mg/dL)[b]	114 (101–132)	77 (63–108)	<0.001
HDL-cholesterol (mg/dL)	42.1 ± 21.1	42.7 ± 11	0.067
Total cholesterol (mg/dL)[b]	189 (172–213)	176 (143–212)	0.017
Triacylglycerols (mg/dL)	179 ± 141	173 ± 117	0.76

SLE systemic lupus erythematosus, *M* male, *F* female, *ARE* arylesterase, *MDA* malondialdehyde, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TGs* triacylglycerols

[a] μmol L^{-1} min^{-1} at 37 °C, substrate phenylacetate

[b] Non-parametric two independent sample Mann-Whitney test

to the Hardy-Weinberg equilibrium. ApoE, PON-55 genotypes, and allele frequencies in SLE patients were compared to controls using the χ^2 test. Odds ratios (ORs) were calculated as estimates of relative risk for disease and 95% confidence intervals (CIs) obtained by SPSS logistic regression. The interaction between ApoE 4 allele and PON-55M was determined using a logistic regression model. The correlations of serum levels of neopterin, MDA, HDL-C, LDL-C, total cholesterol (TC), triglyceride (TG), and aryl esterase activity with the ApoE and PON-55 polymorphisms between studied groups were calculated using linear regression and unpaired t test (Pearson). A two-tailed Student's t test, analysis of variance (ANOVA), and non-parametric independent-sample Mann-Whitney analyses were used to compare quantitative data. Statistical significance was assumed at $p < 0.05$. The SPSS statistical software (SPSS for Windows 16; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Clinical, demographic features, and laboratory test results for the SLE patients and control group are shown in Table 1. Details of parameters have been described previously [8, 18,

Table 2 The distribution and odd ratio (OR) 95% confidence interval (95% CI) of ApoE genotypes and alleles in patients with SLE and control subjects

	SLE patients (n = 107)	Control subjects (n = 101)
ApoE genotypes		
E3/E3	84 (78.5%)	89 (88.1%)
E3/E2	11 (10.3%) (χ^2 = 2.1, df = 1, p = 0.15) OR = 1.67 (95% CI = 0.83–3.4, p = 0.16)	7 (6.9%)
E3/E4	12 (11.2%) (χ^2 = 3, df = 1, p = 0.087) OR = 1.59 (95% CI = 0.94–2.7, p = 0.096) (χ^2 = 3.6, df = 2, p = 0.1)	5 (5%)
ApoE allele		
3	191 (89.3%)	190 (94%)
2	11 (5.1%) (χ^2 = 0.95, df = 1, p = 0.33) OR = 1.63 (95% CI = 0.6–4.4, p = 0.34)	7 (3.5%)
4	12 (5.6%) (χ^2 = 2.7, df = 1, p = 0.099) OR = 1.55 (95% CI = 0.9–2.6, p = 0.1) (χ^2 = 2.4, df = 2, p = 0.29)	5 (2.5%)

Detailed distribution of genotypes and alleles of PON-55 has previously been described

19]. Overall distribution of ApoE genotypes and alleles in SLE patients compared to control group were not significant (Table 2). Frequency of ApoE ε3/ε4 genotypes in SLE patients were higher than the control group (χ^2 = 3.1, *df* = 1, p = 0.087), suggesting that ApoE ε3/ε4 genotype may have trend to increase the risk of SLE although not reaching, significance (OR = 1.59, p = 0.09).

Present study analyzed relevance of ApoE genotypes with serum levels of neopterin, ARE activity, MDA, LDL-C, HDL-C, TC, and TG. SLE patients with ApoE ε3/ε3 and ε3/ε4 genotypes had significantly higher neopterin ($p < 0.001$, p = 0.027) and MDA ($p < 0.001$, p = 0.02) and lower ARE activity ($p < 0.001$, p = 0.027) compared with same genotypes of control subjects (Table 3). All three groups of SLE patients that have been classified according to Table 4 have a significantly higher levels of neopterin (nmol/L), MDA (μmol/L), and LDL-C (mg/dL) and lower level of ARE (U/L) in comparison with healthy subjects.

Logistic regression analysis was used to identify interaction between ApoE 4 and PON-55M alleles in SLE patients. The result demonstrated a strong and significant interaction between ApoE 4 and PON-55M alleles (χ^2 = 3.1, *df* = 3, p = 0.037). This interaction increased the risk of SLE by 1.47 times (1.03–2.6, p = 0.038).

In addition, as shown in Table 4, SLE patients carrying both ApoE 4 and PON-55M alleles had significantly lower ARE activity compared to SLE patients carrying both negative ApoE 4 and PON-55M allele subjects.

Discussion

SLE is an inflammatory, multisystem, and autoimmune disease with an unknown etiology and widespread clinical and laboratory manifestations [3, 20]. According to evidences, one of the genes involved in the risk of SLE and its complications is ApoE. ApoE is associated with plasma chylomicron, VLDL, IDL, and HDL [21] and playing pivotal roles as a ligands for receptor-mediated clearance of chylomicron and VLDL remnants (Apo E receptor and LDL-receptor (Apo B/E receptor)) [22]. ApoE and PON are two major bioscavengers that are involved in inflammation and lipid metabolism [8]. They attenuate oxidation of LDL, a key regulator in the pathogenesis of atherosclerosis leading to several CVD [8]. However, at present, no information about the clinical significance of the relationship between the concomitant presence of the PON-55M and ApoE 4 alleles and susceptibility to SLE is available. In addition, their involvement in lipid peroxidation and inflammatory markers, i.e., MDA, neopterin, lipid, and lipoprotein concentrations, are unclear. Because of lack of study concerning with PON1 and ApoE polymorphism associated with SLE disease, we were interested to evaluate this new subject.

Table 3 Cardiovascular parameters in SLE patients and control subjects carrying various ApoE genotypes

	E3/E4 genotype			E3/E2 genotype			E3/E3 genotype			
	SLE patients, n = 84	Control subjects, n = 89	[a]p values	SLE patients, n = 11	Control subjects, n = 7	[a]p values	SLE patients, n = 12	Control subjects, n = 5	[a]p values
ARE (U/L)	126,770 (117, 120–144,590)	147,940 (131, 480–167,400)	[a]<0.001	127,670 (121, 130–147,400)	145,040 (137, 400–150,300)	0. 09	122,550 (107, 460–1,452,500)	140,300 (130, 090–152,730)	0.027
Neopterin (nmol/L)	10.8 (4.7–20.3)	5.5 (4.7–7.7)	[a]<0.001	10 (5.2–17)	5.4 (3.5–7.3)	0.1	13.2 (8.3–49.6)	5.8 (4.3–7.2)	[a]0.027
MDA (μmol/L)	1.76 (1.31–2.6)	0.98 (0.85–1.28)	[a]<0.001	1.68 (1.43–2.41)	0.87 (0.81–1.16)	0.013	2.4 (1.18–2.84)	1.03 (0.86–1.4)	0.02
LDL-C (mg/dL)	114 (101–132)	74 (63–96)	[a]<0.001	110 (83–125)	83 (45–58)	0.47	119 (96–148)	108 (96–147)	0.16
HDL-C (mg/dL)	42.4 ± 11	43.3 ± 23	0.75	38.3 ± 8.3	49.3 ± 13.5	0.065	36 (32–49)	39 ± 10.3	0.51
TC (mg/dL)	189 (172–211)	176 (145–212)	[a]0.02	179 (131–200)	178 (153–211)	0.53	191 (153–232)	180 (143–232)	0.81
TG (mg/dL)	178 ± 122	168 ± 120	0.61	244 ± 284	154 ± 68	0.4	191 ± 122	133 ± 133	0.42

Statistical analyses were done using *t* test

[a] Non-parametric two independent sample Mann-Whitney test

Table 4 Laboratory parameters compared in SLE patients carrying various interactions between PON-55M allele and ApoE 4 allele

	Both negative ApoE 4 allele and PON-55M allele (n = 36)	Negative ApoE 4 allele and positive PON-55M allele (n = 60)	Both positive ApoE 4 allele and PON-55M allele (n = 11)
ARE (IU/L)	139,830 (122,450–160,280)	122,770 (99,236–137,400), p = 0.004	136,940 (102,980–1,470,800), p = 0.038
Neopterin (nmol/L)	14.4 (4.7–31.5)	9.3 (5.2–14.9), p = 0.079	10.1 (7.3–29.6), p = 0.25
MDA (μmol/L)	1.94 (1.2–2.8)	1.75 (1.29–2.447), p = 0.13	1.03 (0.83–1.3), p = 0.23
LDL-C (mg/dL)	113 (97–128)	114 (101–136), p = 0.91	118 (105–158), p = 0.3
HDL-C (mg/dL)	41 ± 20.2	42.5 ± 10.2, p = 0.73	39 ± 8.8, p = 0.27
TC (mg/dL)	192 ± 33	197 ± 38, p = 0.69	200 ± 49.5, p = 0.43
TG (mg/dL)	1.94 (1.2–2.8)	1.75 (1.29–2.447), p = 0.13	1.03 (0.83–1.3), p = 0.23

Statistical analyses were done using t test

The present case-control study is the first investigation demonstrating that both PON-55M and ApoE 4 alleles act in synergy to increase the risk of SLE in a sample of a Kermanshah population in western Iran.

The ApoE 4 and PON-55M alleles independently increased the risk of SLE by 1.14- and 1.1-fold, respectively. The concomitant presence of both ApoE 4 and PON-55M alleles in individuals increased their susceptibility to SLE by 1.47-fold. The association between PON-55M/M genotype with high levels of MDA, neopterin, LDL-C, and SLE disease has been confirmed with Bahrehmand et al. They also referred that carriers of mentioned genotypes were more exposed to developing hyper blood pressure (HBP) [23]. This paper presents new results concerning with PON1 and ApoE polymorphism associated with SLE disease, and we could not find any study that evaluate the effect of these SNPs in SLE trigger or pathogenesis. One study comprising 377 SLE patients and 482 healthy subjects from US whites and blacks revealed that genetic variation in the PON3 gene significantly was associated with serum PON1 activity [24].

Consistent with our results, Ibrahim et al. demonstrated that PON1-L55M SNP correlated with SLE and the frequency of M allele was higher in patients (90%) compared with controls (78.3%, p = 0.04) from Cairo of Egypt [25]. The role of PON2 genetic variants in serum PON activity and increase risk of lupus nephritis and SLE-related immunologic disorder had been indicated in one case-control study by Dasgupta et al. in population from Caucasian [26]. It has been mentioned that ApoE ε4 allele is an important risk factor for various disorders, and also has been involved in the pathogenesis of multiple autoimmune diseases [27, 28].

Also, previous studies showed that SLE patients with ApoE ε4 allele were more exposed to cardiovascular diseases [29, 30]. ApoE allele ε4 is associated with susceptibility risk/clinical manifestations of SLE, and ε2 may increase its severity while ε3 is protective for SLE in Saudis cited by Al-Rayes et al. [31]. One study revealed that carotid intima-media thickness (IMT) in SLE patients strongly is associated with IDL fraction, which is affected by ApoE genotype [32].

In another study that was performed by Orlacchio in population from Canada, SLE patients carrying E2 allele developed CAD after a mean ± SD of 6.0 ± 1.9 versus 14.5 ± 5.4 years in those with E3/3 (p < 0.01) [33]. Zurnic's et al. detected that Serbian patients with carotid atherosclerosis and ApoE ﻩ2 allele are less predisposed to carotid plaque formation. Moreover, these patients had a lower level of LDL-C in circulation [34].

Results of this study also demonstrated that the serum levels of neopterin, MDA, and LDL-C are significantly elevated and PON-activity is lower in SLE patients compared with controls. This is consistent with our previous studies indicating that the SLE patients who carry M allele of PON-55 have distinct elevated serum levels of neopterin, MDA, and LDL-C and reduced serum ARE activity, suggesting that these individuals may be more susceptible to SLE [8].

Studies suggest that elevated oxidative stress and lipid peroxidation play important roles in SLE progression and may exacerbate pathogenesis [1, 20]. MDA is the product of lipid peroxidation associated with inflammatory diseases [35]. Neopterin is produced by macrophages after stimulation with interferon secreted by activated T cells and is associated with activation of cell-mediated immunity [36]. Our results showed that levels of neopterin and MDA are higher in serum of patients carrying ApoE ε3/ε4 and ε3/ε3 genotypes compared to controls with same genotypes. Song et al. have shown that serum ApoE concentration has a positive correlation with SLE disease activity, and conversely, it has a negative correlation with the concentration of TC and TG in SLE patients [9]. Shah's review also cited a positive association of lipid oxidation in the development of lupus [37]. In addition, we have previously found that subjects with ApoE ﻩ4 allele have a distinct plasma lipid profile and may be more susceptible to Alzheimer's disease (AD) because of low levels of apoA1 and HDL-C [14]. Al Harthi et al. investigated ApoE gene variants and serum lipid concentration relevance with psoriasis risk.

They reported that serum cholesterol and LDL levels were considerably higher in psoriasis patients and these patients had ApoE 훼4 alleles, whereas carriers with 훼2 alleles had higher HDL cholesterol and triglycerides [38].

Conclusions

We found for the first time that the concomitant presence of both ApoE 4 and PON-55M alleles synergistically increase the risk of SLE. There was a significant association between Apoε3/ε4 genotypes and increase risk of SLE. In addition, we found that SLE patients have low PON activity and high MDA, neopterin, and LDL-C levels in serum, suggesting that the reduced antioxidant defense in carriers of ApoE ε4 and PON-55M alleles may contribute to atherosclerosis, inflammation, and other complications in SLE patients. Thus, a therapeutic modality should be considered for these subjects. Further studies with larger sample sizes and different ethnicities are necessary to verify our findings.

Acknowledgments This work was performed in partial fulfillment of requirements for a M.Sc by degree in Clinical Biochemistry, Kermanshah University of Medical Sciences, Kermanshah, Iran (Ali Miri). All authors contributed equally to this study.

Source of Funding This study was funded by Kermanshah University of Medical Sciences, Kermanshah, Iran, Grant No. 90324.

Compliance with ethical standards

Disclosures None.

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