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Paraoxonase (PON1) 55 Polymorphism and Association with Systemic Lupus Erythematosus

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ABSTRACT

Paraoxonase-1 (PON1) is a serum HDL-bound enzyme that hydrolyzes a number of aromatic carboxylic acid esters including lipid peroxides, preventing LDL oxidation. Systemic lupus erythematosus (SLE) patients are at greater risk of oxidative stress, which is associated with abnormal plasma lipid metabolism. In this study, association of PON-55 polymorphism with serum arylesterase (ARE) activities, malondialdehyde (MDA), neopterin, lipids and lipoproteins levels in SLE patients and the development of hypertension was investigated.

The present case–control study consisted of 109 SLE patients with and without high blood pressure (BP) and 103 healthy controls from the population in the west of Iran.

PON-55 Met<Leu polymorphism was detected by restriction fragment length polymorphism (PCR-RFLP), serum ARE activity, MDA, neoptrin, lipid and apolipoprotein levels were determined by spectrophotometery and HPLC and enzyme assay, respectively. The presence of PON-55 M/M genotype was found to be associated with SLE and the development of high BP. The SLE patients with PON-M (M/L+M/M) allele had significantly lower serum ARE activity, but higher neoptrin and LDL-C than the carriers of corresponding genotypes in control group. The ARE activity was positively correlated with HDL-C and negatively correlated with LDL-C and MDA levels in SLE patients. Whereas, in SLE patients with high BP, ARE activity was only found to be negatively correlated with MDA concentration.

These data suggest that PON-55 M/M genotype is a risk factor for SLE. The carriers of this allele have high levels of MDA, neopterin and LDL-C, thus, they are more likely to develop hypertension.

Keywords: Arylesterase activity; Blood pressure; Lipid profile; Malondialdehyde; Paraoxonase 55genotype; Systemic lupus erythematosus

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INTRODUCTION

The paraoxonase (PON, aryldialkylphosphatase, EC 3.1.8.1) genes have received major attention as antioxidants that attenuate oxidation of low density lipoprotein (LDL), a key regulator in the pathogenesis of atherosclerosis leading to several cardiovascular diseases.[1] Paraoxonase family consists of PON1, PON2 and PON3. PON1 is the most investigated and best understood member of paraoxonase family. PON1 also is referred to as arylestrase (ARE), hydrolyses organophosphate substrate paraoxon and aromatic esters, such as phenylacetate.[1] PON activity is under genetic control and the variants in the PON1 gene have strong influences on PON activity.[2] One of the major polymorphisms of PON1 is L55M, where Met (M) has replaced the amino acid Leu at position 55.[3,4] The L55M have been reported to have lower paraoxonase and ARE activities than the 55 L allele isoforms. In humans, serum PON1 activity and serum HDL susceptibility to oxidation are inversely related.[5] PON1, bound to high-density lipoprotein (HDL), has been shown to inhibit low-density lipoprotein (LDL) oxidation, and low PON1 activity has been associated with increased risk of coronary artery disease.[4-6] PON1 activities is also reduced in several groups of patients with increased risk for atherosclerosis such as individuals with systemic lupus erythematosus (SLE), hypercholesterolemia, non-insulin-dependent diabetes mellitus and patients with vascular diseases, survivors of myocardial infarction and rheumatoid arthritis.[3-7,8-11] However, the exact role of PON1 in onset of diseases is still unclear.

SLE is an autoimmune rheumatic diseases.[12] SLE is characterized by diverse systemic involvement including glomerulonephritis, pericarditis, psychiatric disease and hematological disorder.[12,13] The etiology of SLE is unknown, but genetic and immunologic mechanisms as well as metabolic dysfunction have been proposed.[7,8,9,12-18] There are some evidences indicating lipid peroxidation can affect progression of atherosclerosis, cardiovascular diseases (CVD) and glomerulonephritis in SLE patients.[19,20] Hyperlipidemia, increase in lipid oxidation reactions, defects in antioxidant status and ARE activity may lead to increased oxidative stress and high frequency of cardiovascular diseases in SLE.[7-9,19-21] It has also been suggested that deficiency in function of antioxidant system and increased reactive oxygen species (ROS) may play important roles in the pathogenesis of SLE.[21-23]

No adequate knowledge exists as to whether the PON1 genotype and its ARE activity directly and/or indirectly affect the development of vascular disease, hypertension and lupus nephrites in SLE patients.

The objectives of this study was to determine whether the presence of the PON1-Met-55 allele exacerbates the risk of SLE and the development of hypertension to assess its relationship with serum PON1 ARE activity, neopterin, Malondialdehyde (MDA), lipoproteins and lipids concentrations in SLE patients from west of Iran.

MATERIALS AND METHODS

Subjects

The SLE patients (109 patients mean age of 37.3±11.3 years; range, 15–75 years; 87 females and 22 males) were recruited from Rheumatology Division of Kermanshah University of Medical Science and private clinics. All patients revealed at least four of the revised diagnostic criteria of the American College of Rheumatism (ACR) for the diagnosis of SLE.[24] Clinical and laboratory findings were defined using ACR criteria and collected from well-documented medical records during the follow-up. Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SLE activity) was calculated at the time of blood sampling.[25] Examination including chest X ray, electrocardiogram, ultrasonic cardiogram, neurological examination, urine analysis, brain computed tomography scan or magnetic resonance imaging were performed to detect any cardiovascular and renal involvement. Hypertension was defined as resting systolic blood pressure≥160 mmHg and diastolic blood pressure≥95 mmHg. SLE patients with history of proteinuria greater than 500 mg/day or renal biopsy with diffuse or focal proliferative lesion were defined with Lupus nephropathy.

The control subjects (mean age of 37.1±11.5 years; range, 15–72 years; 82 females and 21 males) were selected from healthy individuals during their annual-check-up at the Hospitals of the Kermanshah University of Medical Science. The patient and control groups were matched according to gender, age, and race. All healthy donors were interviewed and examined for coronary heart disease, RA and SLE and

no specific diseases at the medical checkup were observed. Individuals with history of rheumatic or cardiovascular diseases, hypertension, history of any autoimmune symptoms and positive related family history were excluded from the study. 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.

Chemical Analysis Measurement of Serum ARE Activity of Paraoxonase

Serum ARE activity of paraoxonase was measured spectrophotometrically using phenylacetate as substrate according to protocol previously described. [26,27] The activity was calculated as the amount of phenylacetate hydrolyzed per unit time using the molar absorption coefficient of 1310M^{-1} cm^{-1} at 270 nm and the results were expressed as U/mL. One unit of ARE activity was equal to 1 µmol of phenylacetate hydrolyzed per min.

MDA

Plasma MDA was measured by an Agilent Technologies 1200 Series HPLC system (Agilent Corp. Germany) using a fluorescence detector according to protocol previously described.[28] The column was EC 250/4.6 Nucleodur 100-5 C18ec (Macherey-Nagel, Duren, Germany). Butylated hydroxytoluene (BHT), MDA, methanol, 2-thiobarbituric acid (TBA), 1,1,3,3-tetraethoxypropane (TEP), were analytical grade and purchased from Sigma Chemical Co. (St Louis, MO, USA). All other reagents were products of Merck (Darmstadt, Germany). All analyses were conducted in duplicate and data were displayed as the mean± standard error of the mean (SEM) of duplicate treatments.

Neopterin

Serum neopterin was measured by an Agilent Technologies 1200 Series HPLC system (Agilent Corp. Germany) as described previously.[18]

Plasma Lipids

Total serum cholesterol (TC), triacylglycerol (TG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) levels were measured by the standard enzymatic method (Pars Azmon kit, Iran), using an automated Erba XL-600 (Mannheim, Germany).

DNA Analysis

Genomic DNA was extracted from peripheral blood leukocytes using phenol chloroform extraction method.[29] Genotyping of all individuals was done without knowledge of their groups or disease. The PON1-55 Met/Lue(M/L) polymorphism was detected by PCR using 5'-gaagagtgatgtataagcccca-3' and 5'-tttaatccagagctaatgaaagcc-3' as forward and reverse primers, respectively.[26,30] The 179 bp PCR products were digested with Hsp92II restriction endonuclease at 37˚C over night, the digested products were separated on a 2.5% agarose gel and visualized by ethidium bromide staining. The PON-55 Met(M) allele was identified by the presence of 126pb and 44 bp fragments in the digested PCR product. PCR products coding for heterozygotes PON-55 M and L allele produced three DNA fragments (170bp, 126bp and 44 bp) upon Hsp92II digestion.

Statistical Analysis

The allelic frequencies were calculated by the gene counting method. The $\chi 2$ test was used to verify the agreement of the observed genotype frequencies with those expected according to the Hardy–Weinberg equilibrium. The genotypes and allele frequencies of PON1 55 in SLE patients were compared to control group using $\chi 2$ test. Odds ratios (OR) were calculated as estimates of relative risk for disease and 95% confidence intervals (CI) obtained by SPSS logistic regression. The correlation values of serum activity of ARE, neoptrine, MDA, HDL-C, LDL-C and TC levels with the PON1 55 polymorphism between two groups were calculated using linear regression and an unpaired t-tests. A two-tailed Student's t test, ANOVA and nonparametric independent sample Mann-Whitney analysis were used to compare quantitative data. Statistical significance was assumed at the $p<0.05$.

RESULTS

The clinical and laboratory data for the patients and control groups are presented in Table 1.

The patients with SLE had significantly lower serum ARE activity (132480±31496 vs. 142550±26708 U/L, $p< 0.001$) and higher plasma MDA (18.4±12.7 vs. 14.1 ±6.4 µmol/L, $p= 0.003$), neopterin (25.8±38.1 vs. 6.5±2.9 nmol/L, $p< 0.001$), LDL-C (119.7±29.2 vs.

Table 1. The demographic characteristic and distribution of risk factors in SLE patients and control subjects in a population from west of Iran.

Parameter	SLE patients (n=109)	Control subjects (n=103)	*p* values
Age (years)	35.6±16.3†	37.1±11.5†	0.47
Sex (M/F)	22/87	21/82	0.87
Arylesterase activity ARE (U/L) #	132480±31496†	142550±26708†	<0.001
Neopterin (nmol/L)	25.8±38.1†	6.5±2.9†	<0.001
Malondialdehyde (MDA) (µmol/L)	18.4±12.7†	14.1 ±6.4†	0.003
LDL-cholesterol (mg/dL)	119.7±29.2†	86.4 ±37†	<0.001
HDL-cholesterol (mg/dL)	42.1±21.1†	42.7 ±11†	0.93
Total cholesterol (mg/dL)	196±37†	188±61†	0.019
Triacylglycerols (mg/dL)	179±141†	173±117†	0.76
Systemic lupus erythematosus (SLE) activity	21±12.2†	-	-

Arylesterase activity: ARE, µmol mL−1 min−1 at 37oC, substrate phenylacetate

86.4±37 mg/dL, p< 0.001) and TC concentration (196±37 vs. 188 ±61 mg/dL, *p*= 0.019) than those of control group.

PON1 55 M→L Genotypes and Alleles

Distribution of PON1 55 alleles and genotype frequencies are shown in Table 2. Distribution of the PON1 55 M/M genotype in SLE patients was significantly different from that of control group ($\chi2$=3.2, df =1, *p*=0.047), however over all distribution of PON1 55 genotypes and alleles (as calculated using the actual allele number) were not significantly different in SLE patients compared with control. The age- and sex-adjusted odds ratio (OR) for SLE patients with M/M genotype of PON 55 was 1.8 (CI=1– 4.2, *p*=0.048) (Table 3).

As shown in Table 4, the presence of the PON-55 genotypes significantly affected the ARE activity, neopterin, MDA and LDL-C levels in both groups of subjects. The SLE patients with the one and two copies of M allele of PON-55 had significantly lower serum are activity (123440±28308 vs. 135290±22715 U/L,

Table 2. The distribution of PON 55 genotypes and alleles in SLE patients and controls.

Topics	SLE patients (n=109)	Control subjects (n=103)
PON 55 genotypes		
L/L	39 (35.8%)	42 (40.8%)
L/M	50 (45.9%)	49 (47.6%)
M/M	20 (18.3%)	12 (11.7%)
	($\chi2$=3.2, df=1, *p*=0.047)	
	* ($\chi2$=2, df=2, *p*=0.37)	
PON 55 genotypes		
L/L	39 (35.8%)	42 (40.8%)
L/M+ M/M	70 (64.2%)	61 (59.2%)
	*($\chi2$=0.7, df=1, *p*=0.45)	
PON 55 allele		
L	128 (58.7%)	133 (64.6%)
M	90 (41.3%)	73 (35.4%)
	*($\chi2$=1.6, df=1, *p*=0.21)	

Control subjects

*The distribution of alleles and genotype frequencies of PON 55 in SLE patients compared with control were made using $\chi2$ test analysis

Table 3. Odd ratio of PON 55 genotypes and alleles with respect to L/L or L in SLE patients after adjustment for sex and age.

Topics	SLE patients (n=109)	Control subjects (n=101)
PON 55 genotypes		
L/L	Reference group (n=39)	Reference group (n=42)
L/M+ M/M	1.24 (0.71-2.2, *p*=0.45, n=70)	n=61
M/M	1.8 (1-4.2, *p*=0.048, n=20)	n=12
PON 55 allele		
L	Reference group (n=128)	Reference group (n=133)
M	1.28 (0.87-1.9, *p*=0.21, n=90)	n=73

Odds ratios (OR) as estimates of relative risk for disease were calculated and 95% confidence intervals obtained by using regression binary logistic analysis

p=0.01), but higher neopterin (28.3±41vs. 6.7±3.3 nmol/L, *p*<0.001), MDA (19.3±25.7 vs. 15.1±7.5 µmol/L, *p*=0.009), and LDL-C (122±32 vs. 88±33.6 mg/dL, *p*<0.001) levels compared with the carriers of corresponding genotypes in the control group. A similar trend was found in SLE patients with L/L genotype of PON-55 compared with the corresponding genotypes in control subjects. In addition, the presence of the PON-55 genotypes significantly affected the ARE activity, neopterin, MDA and LDL-C levels within each groups subjects carrier of M/L or M/M genotype compared with L/L genotype had significantly lower are activity (123440±28308 vs 149130±30579,

Table 4. Comparison of AEA activity, neoptrin, LDL-C, HDL-C, TC and TG levels between PON 55 genotypes (L/L with L/M+M/M) in SLE patients with control subjects.

Topics	SLE patients	Control subjects	**p* values
L/L	n=39	n=42	
ARE activity (U/L)	149130±30579	153450±28759	0.52
Neopterin (nmol/L)	24.4±36.8	6.3±2.4	<0.001
MDA (µmol/L)	17.7±11.1	13.8±5.7	0.035
LDL-C (mg/dL)	116±25	84±42.8	<0.001
HDL-C (mg/dL)	41.9±29.5	43.8±11.9	0.71
TC (mg/dL)	190±76.7	191±33	0.9
TG (mg/dL)	181±159	170±122	0.74
L/M+M/M	n=70	n=61	
ARE activity (U/L)	123440±28308	135290±22715	0.01
	** p=0.002	** p<0.001	
Neoptrin (nmol/L)	28.3±41	6.7±3.3	<0.001
	**p=0.19	** p=0.9	
MDA (µmol/L)	19.3±25.7	15.1±7.5	0.009
	** p=0.11	** p=0.58	
LDL-C (mg/dL)	122±32	88±33.6	<0.001
	**p=0.76	** p=0.24	
HDL-C (mg/dL)	42.2±15.2	42.2±10.3	0.98
	** p=0.94	** p=0.7	
TC (mg/dL)	199±39.7	187±51.2	0.16
	** p=0.79	** p=0.46	
TG (mg/dL)	177±131.3	175±116	0.93
	** p=0.76	** p=0.18	

*The Comparison values of serum ARE activity, neoptrin, MDA, LDL-C, HDL-C, TC and TG levels with PON-55 polymorphisms between patients and controls were calculated using t-test

**The comparative values of serum ARE activity, neoptrin, MDA, LDL-C, HDL-C, TC and TG levels between L/L genotype with M/LM/M genotypes of PON-55 within each groups.

Table 5. The distribution and odds ratio of PON 55 L/M + M/M genotypes with respect to L/L genotypes respectively in SLE patients with and without blood pressure, CVD and lupus nephropathy (LN).

	SLE patients		SLE patients		SLE patients	
	+CVD n=21	-CVD n=88	+BP n=21	-BP n=88	+LN n=32	-LN n=77
PON 55 genotypes						
L/L	6 (28.6%)	33 (37.5%)	5 (23.8%)	34 (38.6%)	13 (40.6%)	26 (33.8%)
L/M + M/M	15 (71.4%)	55 (62.5%)	16 (76.2%)	54 (61.4%)	19 (59.4%)	51 (66.2%)
	*(χ2=0.4, df=1, p=0.55)		*(χ2=1.7, df=1, p=0.2)		*(χ2=0.5, df=1, p=0.49)	
	OR=1.41 (0.5- 4.3, p=0.55)		OR=2.02 (0.7- 6, p=0.2)		OR=0.75 (0.31- 1.7, p=0.49)	
L/L	5 (55.6%)	34 (68%)	5 (50%)	34 (69.4%)	13 (68.4%)	26 (65%)
M/M	4 (44.4%)	16 (32%)	5 (50%)	15 (30.6%)	6 (31.6%)	14 (35%)
	*(χ2=0.6, df=1, p=0.46)		*(χ2=2.83, df=1, p=0.043)		*(χ2=0.1, df=1, p=0.79)	
	OR=1.7 (0.4- 7.2, p=0.47)		OR=2.27 (1.06- 9, p=0.046)		OR=0.86 (0.27- 2.7, p=0.8)	

Odds ratios (OR) as estimates of relative risk for disease were calculated and 95%
Confidence intervals obtained by using χ2 regression binary logistic analysis

p=0.002 and 135290±22715 vs. 153450±30579, *p*,0.001 within SLE and control groups, respectively). However in both groups individuals carrier of M/L or M/M genotype compared with L/L genotype had higher neopterin, MDA, LDL-C, TC, and TG levels, with no significant differences.

Distribution and odds ratio of the PON-55 genotypes in SLE patients with and without CVD, BP and LN are shown in Table 5. There was a significant difference between distribution of PON-55 MM genotype (χ2=2.83, df =1, *p*=0.043) in SLE patients with high blood pressure (BP) with those without BP. The OR of PON-55 MM genotype was found to be 2.27 (1.06- 9, *p*=0.046) in SLE patients with high BP. Our data also indicated that SLE patients with CVD had significantly higher serum neopterin level than those without CVD had significantly higher serum neoptrine levels than those without CVD (44.1±52 vs 17.7±26 nmol/L *p*=0.001)

Correlations between ARE activity with the levels of neopterin, MDA, lipids and lipoproteins for SLE patients without and with CVD, LN and blood pressure are shown in Table 6. ARE activity was negatively correlated with the levels of MDA (r=-0.25, *p*=0.011), LDL-C(r= -0.14, *p*=0.023) and positively correlated with the level of HDL-C(r=0.4, *p*<0.001), when the data from all the SLE patients were considered.

In addition, the ARE activity was also negatively correlated with the level of MDA (r=-0.23, *p*=0.024) in SLE patients with hypertension and with the LDL-C (r= -0.44, *p*=0.019) level in SLE patients with LN, but it was positively correlated with the level of TG (r= 0.61, *p*=0.033) in SLE patients with CVD.

Table 6. Correlation between ARE activity concentration with neopterin, LDL-C, HDL-C, TC and TG have been compared in SLE patients and SLE patients with CVD, LN and blood pressure.

	ARE activity SLE patients	ARE activity in SLE patients with CVD	ARE activity in SLE patients with BP	ARE activity in SLE patients with LN
Neopterin (ng/mL)	#r= -0.18	*r=-0.18	*r= 0.02	#r= 0.22
	p=0.07	*p*=0.51	p= 0.99	p=0.07
MDA (µmol/L)	#r= -0.25	*r=-0.2	#r= -0.23	*r= -0.23
	p=0.011	*p*=0.54	p=0.024	p=0.06
LDL-C (mg/dL)	#r= -0.14	*r=-0.18	*r= -0.025	*r=-0.44
	p=0.023	*p*=0.57	p=0.9	p=0.019
HDL-C (mg/dL)	*r= 0.4	*r= -0.19	*r= 0.17	*r= 0.5
	p<0.001	*p*=0.56	p=0.53	p=0.007
TC (mg/dL)	*r= -0.07	*r=0.23	*r=-0.07	*r= 0.02
	p=0.53	*p*=0.47	p 0.8	p=0.9
TG (mg/dL)	*r= 0.04	*r= 0.61	*r= 0.13	*r= 0.09
	p=0. 7	*p*=0.033	p=0.64	p=0.64

* Pearson correlation coefficient # Spearman correlation coefficient

DISCUSSION

In the present study, we found a strong association between the PON1 55 M/M genotype and the risk of SLE and the development of hypertension in patients with SLE. We found that the presence of PON1 55 M/M genotype increases the risk of SLE and the development of high blood pressure by 1.8 (1-4.2) and 2.27 (1.06-9) fold compared to PON 55 L/L genotype, respectively.

The distribution of the PON1 55 M/M genotype in the SLE subjects was significantly different from that of the control group. In addition, SLE patients with hypertension had significantly higher frequency of the PON1 55 M/M genotype than those without hypertension.

In addition, as shown in Table 4, SLE patients who carry one or two copies of PON 55 M allele (M/L+M/M) had significantly lower serum ARE activity and higher serum levels of neopterin, MDA and LDL-C than control groups carrying the corresponding PON 55 L allele. Also within each group carriers of M/L or M/M genotypes of PON-55 compared L/L genotype had significantly lower ARE activities.

These findings support the notion that PON 55 M allele increases the risk of SLE in individuals. [7] The contribution of PON 55 M allele to induction of SLE is apparently due to decrease arylesterase activity of PON 55 also ARE activity is affected by this polymorphism [17] The ARE activity of PON is affected by PON-55 polymorphism. If, the protection of LDL against oxidation by PON1 is indeed a meaningful phenomenon, then the M allele should confer increased complication of SLE protection compared to L allele. The L allele coding for a protein displays significantly higher activity towards phenylacetate and paraoxon hydrolysis than the M allele.[2]

The risk of diseases (such as SLE) related to oxidative damage and lipid peroxidation has been suggested to be greater in people with low PON1 activity than in those with high activity. [4,7,8,9,19-22] Interestingly, we found that serum ARE activity was negatively correlated with MDA and LDL-C levels and positively correlated with HDL-C level in SLE patients. Patients with SLE had significantly lower serum ARE activity and higher plasma MDA and LDL-C concentrations than those of control group. In addition, there was a significant negative correlation between the level of serum ARE activity and MDA in SLE patients with high BP. These results are consistent with previous studies suggesting that increase in the levels of LDL-C and MDA concentrations and decrease in the serum level of PON1 activity interfere with anti-oxidant and anti-inflammatory functions of HDL, favoring atherogenesis.[7-9,19,20] Together, these data suggest that SLE is associated with oxidative stress.

Mechanisms against oxidative stress are very important in protection and tapering down the rate of progression in SLE and its associated complication. It has been suggested that deficient function of antioxidant systems activities and increased ROS and MDA production may play a role in the pathogenesis of SLE.[19-23,31,32] Serum PON1 also hydrolyzes proinflammatory oxidized lipids (such as MDA) which present in oxidized LDL-C and ruins their potentially atherogenic characteristics.[7-9]

Our results indicated that SLE patients had significantly higher levels of MDA, neopterin and lower ARE activity in sera compared with control groups. Elevated LDL-C, TC, TG, neopterin, MDA, and decreased ARE activity and HDL-C are risk factors for BP and CVD.[18-21,33-37]

Recent studies indicated that serum MDA levels in SLE patients have a positive correlation with severity of disease [9,19-21] Tripi et al. and Van Lenten et al. suggested that reduced PON1 activity could be due to inflammation in SLE patients.[7,38]

Morbidity and mortality due to coronary artery disease is increased in SLE.[39] The mechanisms underlying this increase is unclear, but inflammation is thought to play a role. Rho et al have shown neopterin was more robustly with atherogenic mediators of inflammation rather than homocysteine in SLE. They suggested that neopterin has been considered as a candidate biomarker for monitoring SLE activity.[40]

Although the underlying cause of SLE is not fully known, altogether, these findings suggest that oxidative stress contributes to the accelerated atherogenesis in SLE. This, however, needs further investigation.

In the present study, we demonstrated that the distribution M/M genotype of PON 55 M→L polymorphism was significantly different between subjects with and without SLE. The carriers of M allele have distinctly reduced serum ARE activity and elevated serum levels of MDA, neopterin and LDL-C, suggesting that these individuals may be more susceptible to oxidative stress, impairment of

antioxidant system, abnormal lipid metabolism, high blood pressure, cardiovascular disease and myocardial infarction. This study also indicated that carriers of the PON 55 MM genotype had 2.2-fold higher risk of developing hypertension than LL homozygote carriers.

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