http://rjdnmd.org
Rom J Diabetes Nutr Metab Dis. **25**(2):171-180
doi: 10.2478/rjdnmd-2018-0020

EVALUATION OF ASSOCIATION BETWEEN Q192R AND L55M GENETIC POLYMORPHISMS OF PON1 AND SERUM PARAOXONASE-1 ACTIVITY IN HEALTHY INDIVIDUALS, A META-ANALYSIS

Mostafa Saadat ✉

Department of Biology, College of Sciences, Shiraz University, Shiraz, Iran

received: December 12, 2017 *accepted*: May 19, 2018
available online: June 15, 2018

Abstract

Background and Aims: *Several studies have reported the alteration of the paraoxonase 1 (PON1) enzyme activity in various diseases, including diabetes mellitus. The Q192R and L55M are two genetic variations in the coding region of PON1. To evaluate the relationship between these polymorphisms and the alteration in serum paraoxonase activity, the present meta-analysis was carried out.* ***Material and Methods:*** *Eligible studies published before October 2017 was identified in several databases. The paraoxonase activity in subjects with variant alleles of the study polymorphisms were normalized using the activity of the QQ or LL genotypes. The pooled mean effect of alterations in activity level and its 95% confidence intervals (95% CI) was calculated.* ***Results:*** *Thirty-two studies including 11532 healthy participants were used for the present meta-analysis. The paraoxonase activity was increased in the QR and RR genotypes. This elevation was greater among Caucasians than those among Asians and Africans. The activity in the LM and MM genotypes compared with the LL genotype were decreased, this reduction in Caucasians was greater than Africans.* ***Conclusions:*** *At least in part other PON1 polymorphisms and environmental factors may accounts for heterogeneity between studies.*

key words*: heterogeneity, paraoxonase, genetic polymorphism*

Background and aims

Paraoxonase 1 (*PON1*, OMIM: 168820) is synthesized by liver and secreted into blood [1]. It has both paraoxonase and aryl esterase activities. Although its physiological role in detoxification and in intermediary metabolism is uncertain [2], it may play an important role against chronic exposure to some toxic environmental chemicals [1]. Deficient mice for Pon1 are sensitive to the toxic effects of chlorpyrifos oxon and are more susceptible to atherosclerosis compared with the wild type mice [3].

The *PON1* gene is polymorphic and its variant alleles occurring at a relatively high frequency in human populations. The Q192R (rs662) and L55M (rs854560) are two missense substitutions in the coding region [1]. The associations between these two genetic variations and the risks of several multifactorial traits have been investigated [4-9]. Several

✉ Department of Biology, College of Sciences, Shiraz University, Shiraz 71467-13565, Iran. Tel: +98-71-36137432
corresponding author e-mail: saadat@shirazu.ac.ir

studies have reported the alteration in PON1 activity in a variety of diseases [1,10-12]. It has been reported that PON1 and other enzymes or proteins involved in detoxification or transporter of xenobiotics are associated with risk of diabetes mellitus [13-16].

It has been reported that the rs662 and rs854560 *PON1* genetic variations are associated with serum paraoxonase activity [2,12]. According to site directed mutagenesis at position 192 of the PON1, the mutant 192R enzyme compared to the 192Q wild-type, show an enhanced (about 1.7-fold) paraoxonase activity [17].

Serum paraoxonase activity shows highly variability between individuals [10-12,17]. Numerous studies indicated that the paraoxonase activity in healthy participants significantly is associated with the Q912R and L55M polymorphisms [18-47]. The RR and LL genotypes showed higher paraoxonase activity compared to the QQ and MM genotypes, respectively. However, the amounts of the elevations were not similar between studies for genotypes. To evaluate the relationship between the *PON1* polymorphisms (Q912R and L55M) and relative changes of the paraoxonase activity under *in vivo* condition, the present meta-analysis was carried out.

Materials and methods

Search strategy

Literature databases, including PubMed, Scopus, DOAJ, Index Copernicus, Academic Journals Databases, Serbian citation index, and KoreaMed were searched for relevant studies (before September 2017). The following search terms were used: (PON1 paraoxonase activity, enzyme activity, rs854560, rs669, polymorphism, L55M, and Q192R. The search was limited to studies published in English. In addition the bibliographies of the retrieved studies were screened to identify relevant publications.

Inclusion and exclusion criteria

The eligible published association studies had to meet all the following criteria: useful data including sample size, genotypes distributions and mean (SD) of paraoxonase enzyme activity in serum of healthy control subjects were given in tables. Accordingly, the exclusion criteria were as follows: reviews, meta-analysis, editorial articles, abstracts, comments, and studies with same or overlap data. The application of the above-mentioned criteria yielded 30 reports [18-47]. Study of Tripi et al., reported paraoxonase activity in two healthy subjects based on the ethnicity of their participants [26]. In another study, authors reported the paraoxonase activity in males and females, therefore, considered as two studies [21]. Therefore 32 studies were eligible for meta-analysis.

Data extraction

The following data were extracted from each study: first author's name, publication year, country, and ethnicity of the individuals involved, frequencies of the genotypes for each polymorphisms, average and SD of the serum paraoxonase activity for each genotype of the study polymorphisms. The genotypes of the *PON1* polymorphisms were evaluated by RFLP-PCR or high resolution melting curves by real time PCR methods. In all studies the serum PON1 activity was measured with spectrophotometric assay using paraoxon as substrate.

Statistical analysis

Comparison between observed and expected (based on the Hardy-Weinberg equilibrium) frequencies for each genotype was tested by a chi-square test. The enzyme activities of the

genotypes of both polymorphisms were normalized against the activity of the reference genotypes. The LL and QQ genotypes were considered as reference genotypes for L55M and Q192R polymorphisms, respectively.

The pooled effect size as the mean difference and its 95% confidence intervals (95% CI) was calculated. The heterogeneity between studies was evaluated with the Q statistics and the I^2 statistics. If no significant heterogeneity was found between the studies (I^2<50% and P>0.10 for Q statistics), the pooled mean difference of the enzyme levels was calculated by using the fixed effects model [48]. Otherwise, the random effects model was applied [49]. Two comparisons were performed in our meta-analysis: LM *vs* LL and MM *vs* LL (for L55M polymorphism) and QR *vs* QQ and RR *vs* QQ (for Q192R polymorphism). We also performed subgroup analysis according to ethnicity (Caucasians, Africans, and Asians) and sample size (less than and more than 100 subjects). Using the QUANTO (http://biostats.usc.edu/software) software, assuming a power of 0.80, α=0.05, 25% frequency for the variant alleles, and R^2_G=0.10, a minimum of 74 subjects would be necessary to detect a real difference in the serum paraoxonase activity between genotypes. Therefore, we stratified the studies based on the sample size: less than and more than 100 subjects.

By sequential removal of each study, the sensitivity analysis was performed to evaluate the stability of the findings. To investigate the evidence for publication bias, the funnel plot and Egger's test were used. In the Egger's test, statistical significance was assumed with P<0.05 [50].

Results

In total, 32 independent studies including 11532 participants were used in the present study [18-47]. The studies were published between 2000 and 2016. The studies were conducted on different ethnic populations: 18 studies included a Caucasian population, 7 studies included an Asian population (Table 1), and 6 studies included an African population. The genotyping frequencies in the participants showed significant differences with the expected frequencies in five studies [24,25,33,36,45]. These studies were excluded from meta-analysis.

Table 1. Study characteristics of published studies on the association between the *PON1* polymorphisms and serum paraoxonase activity in healthy individuals.

Study	Year	Country	Ethnicity	Q192R polymorphism					L55M polymorphism				
				QQ	QR	RR	R*	P**	LL	LM	MM	M*	P**
Kujiraoka	2000	Japan	Asian	13	34	40	0.655	0.207	-	-	-	-	-
Brophy	2000	USA	Mix	155	131	31	0.304	0.666	128	156	33	0.350	0.147
Yamada	2001	Japan	Asian	28	116	93	0.637	0.367	-	-	-	-	-
Senti-1	2002	Spain	Caucasian	320	274	62	0.303	0.762	-	-	-	-	-
Senti-2	2002	Spain	Caucasian	342	307	75	0.315	0.619					
Nakanishi	2003	Japan	Asian	12	56	59	0.685	0.805	-	-	-	-	-
Campo	2004	Italy	Caucasian	97	93	18	0.310	0.516	92	90	26	0.341	0.586
Agachan	2004	Turkey	Caucasian	36	61	10	0.378	0.028	51	51	7	0.298	0.218
Kotur-Stevuljevic	2006	Serbian	Caucasian	60	30	15	0.285	0.002	-	-	-	-	-
Tripi-1	2006	USA	Caucasian	246	161	20	0.235	0.325	157	195	58	0.379	0.837
Tripi-2	2006	USA	African	9	22	7	0.473	0.320	22	14	2	0.236	0.905
Hofer	2006	Australia	Caucasian	87	49	14	0.256	0.077	57	72	20	0.375	0.714
Browne	2007	USA	Caucasian	41	31	7	0.284	0.743	-	-	-	-	-
Sepahvand	2007	Iran	Caucasian	63	56	13	0.310	0.914	23	63	46	0.587	0.858
Unur	2008	Turkey	Caucasian	25	22	6	0.320	0.730	28	20	5	0.283	0.609
Garces	2008	Spain	Caucasian	624	524	118	0.300	0.598	482	600	184	0.382	0.901
Birjamohun	2009	UK	Caucasian	1640	1262	269	0.283	0.236	1293	1418	403	0.357	0.644
Chia (Eng)	2009	Singapore	Asian	14	97	49	0.609	<0.001	138	21	1	0.071	0.837

Table 1. *Continued.*

Study	Year	Country	Ethnicity	Q192R polymorphism					L55M polymorphism				
				QQ	QR	RR	R*	P**	LL	LM	MM	M*	P**
Kanamori-Kataoka	2009	Japan	Asian	6	29	28	0.674	0.700	-	-	-	-	-
Zafiropoulos	2010	Greece	Caucasian	237	161	21	0.242	0.339	155	207	63	0.391	0.650
Altuner	2011	Turkey	Caucasian	38	9	3	0.150	0.093	21	25	4	0.330	0.355
Eom	2011	Korea	Asian	19	65	69	0.663	0.546	-	-	-	-	-
Helaly	2013	Egypt	African	44	49	7	0.315	0.175	50	44	6	0.280	0.361
Gokcen	2013	Turkey	Caucasian	8	14	8	0.500	0.715	-	-	-	-	-
Zhang	2014	China	Asian	37	98	85	0.609	0.338	193	25	2	0.065	0.252
Kresanov	2015	Finland	Caucasian	1071	707	117	0.248	0.982	-	-	-	-	-
Ahmed	2015	Egypt	African	20	36	24	0.525	0.381	40	24	16	0.350	0.002
AnandBabu	2016	India	Caucasoid	8	16	2	0.384	0.126	19	7	1	0.166	0.729
Fridman	2016	Argentina	Caucasian	116	62	25	0.275	<0.001	88	98	17	0.325	0.153

*Allelic frequency, **P value for Hardy-Weinberg equilibrium.

Table 2. Summary of meta-analysis of studies investigating the relationship between the Q192 R *PON1* polymorphism and serum level of paraoxonase activity in healthy individuals.

Comparisons	Number of Studies	Heterogeneity between studies				Mean difference between LM and LL			
		Q	df	P	I^2 (%)	Difference	Lower	Upper	P
QR vs QQ									
All studies	32	5164.3	31	<0.001	99.4	+0.980	+0.751	+1.210	<0.001
All studies expect 5 studies*	27	5008.4	26	<0.001	99.4	+1.016	+0.767	+1.266	<0.001
Caucasians	15	2030.5	14	<0.001	99.3	+1.130	+0.844	+1.417	<0.001
Africans	5	184.3	4	<0.001	97.8	+0.452	-0.08	+0.984	0.096
Asians	6	245.8	5	<0.001	97.9	+0.988	+0.654	+1.323	<0.001
Small studies (≤100 subjects)	10	231.5	9	<0.001	96.1	+0.845	+0.542	+1.149	<0.001
Large studies (>100 subjects)	17	3699.5	16	<0.001	99.5	+1.113	+0.790	+1.437	<0.001
RR vs QQ									
All studies	32	6903.1	31	<0.001	99.5	+2.182	+1.705	+2.659	<0.001
All studies expect 5 studies*	27	6462.2	26	<0.001	99.5	+2.222	+1.703	+2.740	<0.001
Caucasians	15	3252.4	14	<0.001	99.5	+2.455	+1.833	+3.076	<0.001
Africans	5	220.2	4	<0.001	98.1	+1.196	+0.408	+1.985	<0.001
Asians	6	364.1	5	<0.001	98.6	+2.014	+1.325	+2.703	<0.001
Small studies (≤100 subjects)	10	238.9	9	<0.001	96.2	+2.002	+1.488	+2.517	<0.001
Large studies (>100 subjects)	17	6033.5	16	<0.001	99.7	+2.334	+1.649	+3.020	<0.001

*Excluded studies showing significant difference between observed number and expected values of genotypes base on Hardy-Weinberg equilibrium.

The associations between the genotypes of the Q192R polymorphism and alterations in serum paraoxonase activity were investigated (Figure 1). The QR and RR genotypes showed higher activity. The paraoxonase activity were increased +1.016 (95% CI: +0.767 to +1.266, P<0.001) and +2.222 (95% CI: +1.703 to +2.740, P<0.001) in the QR and RR genotypes, respectively. After studies were stratified by ethnicity of their participants and the sample size, the similar findings were observed. Elevations of the enzymes activity in both QR and RR genotypes among Caucasians were greater than the activity among Asians and Africans (Table 2). Asians revealed intermediate values compared with Caucasians and Africans.

The associations between the genotypes of L55M polymorphism and alterations in serum paraoxonase activity were shown in Figure 2. The paraoxonase activities in serum of the LM

and MM genotypes compared with the LL genotype were significantly decreased -0.250 (95% CI: 0.195 to -0.304, P<0.001) and -0.578 (95% CI: -0.490 to -0.666, P<0.001), respectively (Table 3). Reduction in the enzyme activity among Caucasians was greater than Africans.

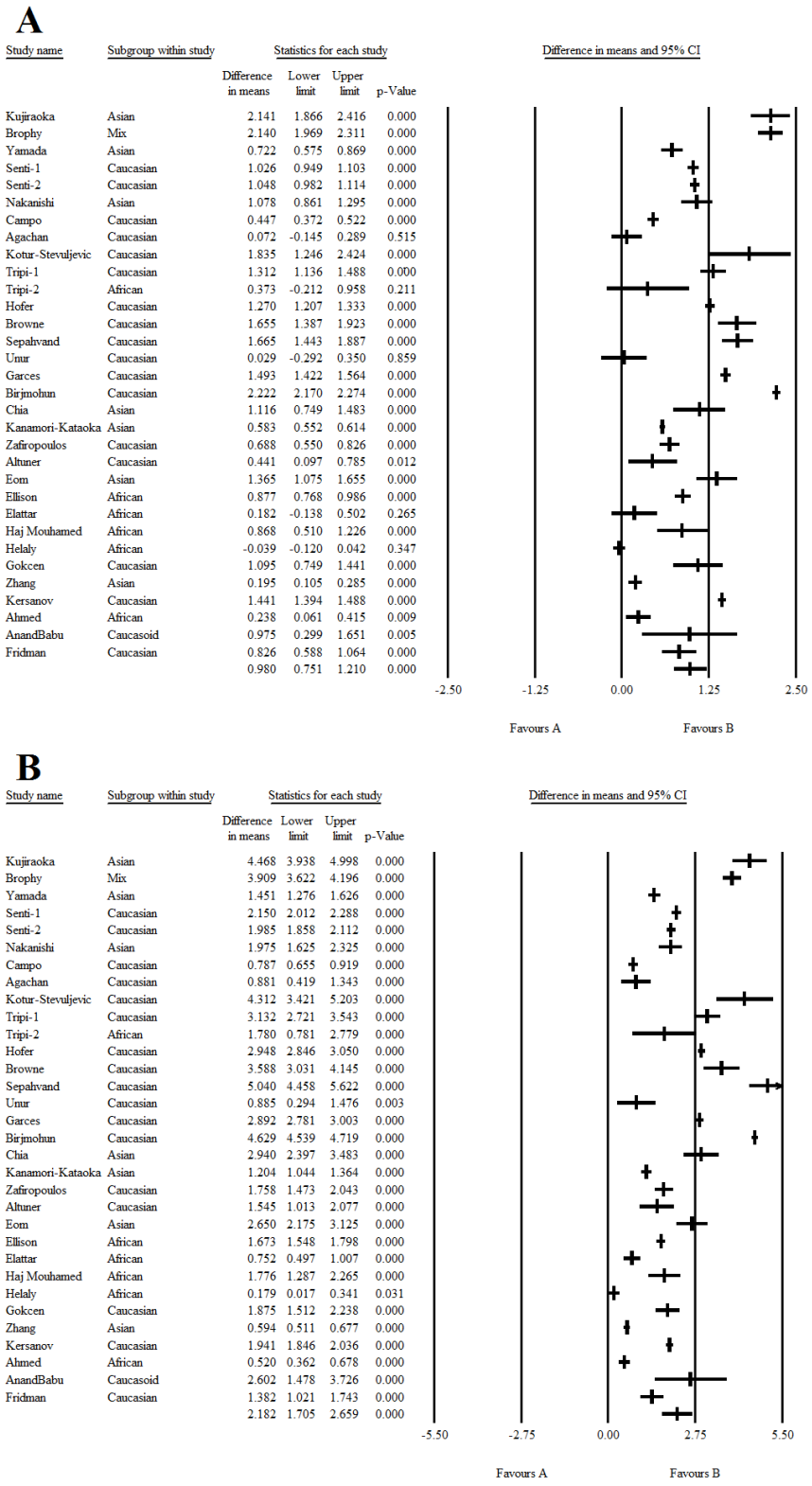

Figure 1. *Forest plots of the relationship between the PON1 Q192R polymorphism (A: QR vs QQ; B: RR vs QQ genotypes) and serum paraoxonase activity in healthy individuals*

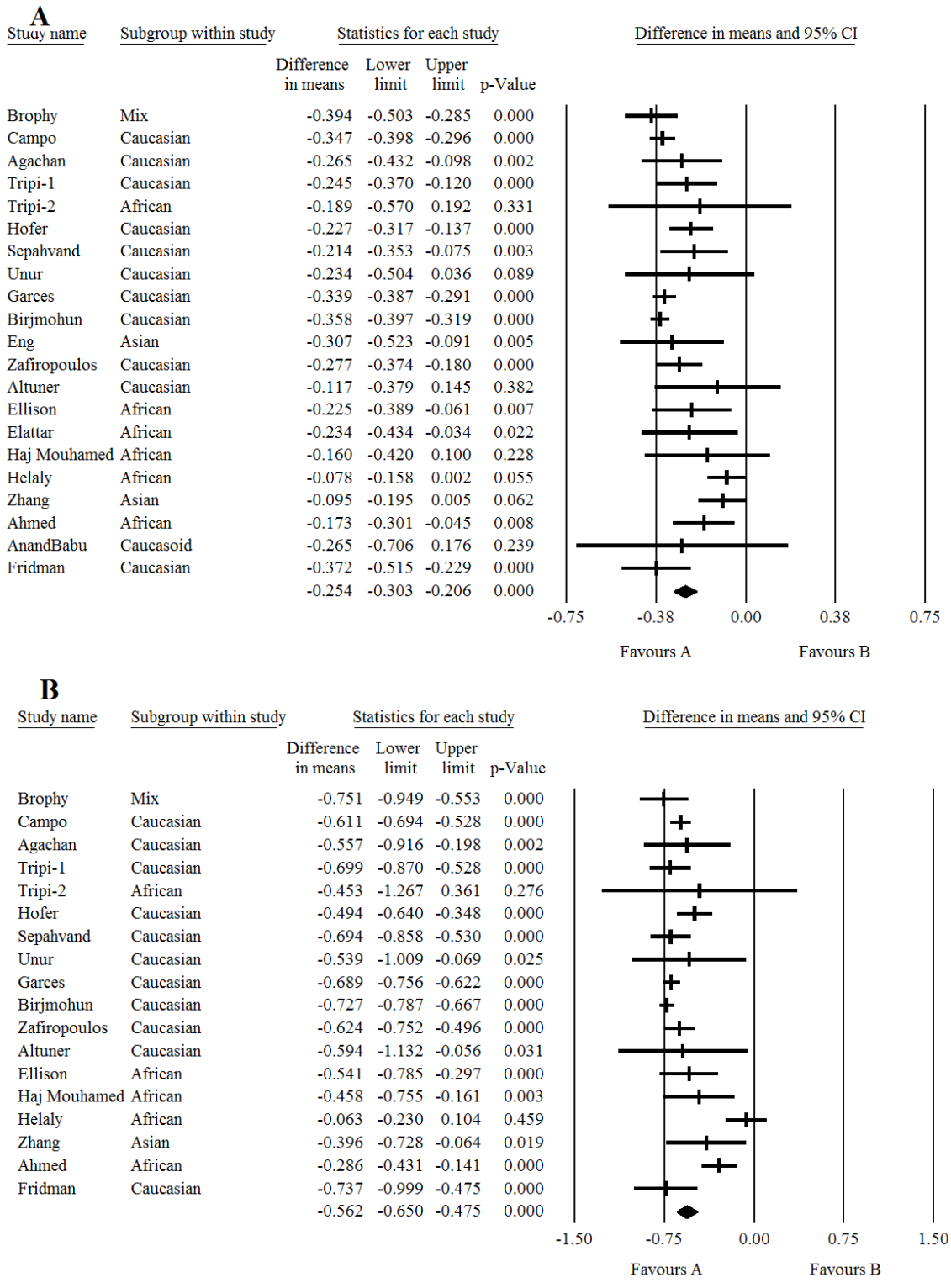

Figure 2. *Forest plots of the relationship between the PON1 L55M polymorphism (A: LM vs LL; B: MM vs LL genotypes) and serum paraoxonase activity in healthy individuals*

Table 3. Summary of meta-analysis of studies investigating the relationship between the L55M *PON1* polymorphism and serum level of paraoxonase activity in healthy individuals

	Number of Studies	Heterogeneity between studies				Mean difference between LM and LL			
		Q	df	P	I^2 (%)	Difference	Lower	Upper	P
LM vs LL									
All studies	21	77.7	20	<0.001	74.2	-0.254	-0.206	-0.303	<0.001
All studies expect 5 studies*	17	72.9	16	<0.001	78.0	-0.250	-0.195	-0.304	<0.001
Caucasians	10	16.25	9	0.062	44.6	-0.305	-0.267	-0.343	0.096
Africans	5	4.09	4	0.394	2.2	-0.125	-0.061	-0.189	<0.001
Small studies (≤100 subjects)	6	0.67	5	0.985	0.0	-0.213	-0.114	-0.311	<0.001
Large studies (>100 subjects)	11	69.2	10	<0.001	85.5	-0.258	-0.195	-0.321	<0.001
MM vs LL									
All studies	18	73.4	17	<0.001	76.8	-0.562	-0.475	-0.650	<0.001
All studies expect 3 studies*	15	62.2	14	<0.001	79.1	-0.578	-0.490	-0.666	<0.001
Caucasians	9	12.3	8	0.135	35.4	-0.658	-0.608	-0.708	<0.001
Africans	4	12.4	3	0.006	75.8	-0.351	-0.054	-0.648	0.021
Small studies (≤100 subjects)	4	0.08	3	0.994	0.0	-0.543	-0.348	-0.737	<0.001
Large studies (>100 subjects)	11	66.0	10	<0.001	84.8	-0.582	-0.485	-0.679	<0.001

*Excluded studies showing significant difference between observed number and expected values of genotypes base on Hardy-Weinberg equilibrium.

There was heterogeneity between studies for both polymorphisms. The source of heterogeneity was assessed by ethnicity (Caucasian/Asian/Africans) and sample size (≤100 / >100 subjects). The subgroup analyses did not reveal any sources contributing to the substantial heterogeneity (Tables 2,3). There was no evidence for publication bias (P>0.90). Sensitivity tests indicated that the present findings were stable.

Discussions

Several association studies indicating that serum paraoxonase activity was associated with numerous diseases [3,11,12,17-19]. Site directed mutagenesis revealed that the missense substitutions Q192R (rs662) and L55M (rs854560) were associated with alteration in paraoxonase activity. In the present meta-analysis we tried to reveal the relationship between genotypes and alteration levels in enzyme activity. Using several search engines, 32 studies were included in the study. The paraoxonase activity in serum of subjects with variant alleles of the polymorphisms were normalized with the activity of the QQ and LL genotypes, respectively. The most important findings of the present meta-analysis are:

1. The R- and M- genotypes are significantly associated by increased and decreased in enzyme activity, respectively.

2. Elevation and reduction in enzyme activity are correlated with the number of R and M alleles, respectively. This is consistent with co-dominant autosomal inheritance patterns.

3. There is significant heterogeneity between studies and we failed to find the source of the heterogeneity (Tables 2,3). It has been well established that several environmental factors (such as diet, and life-style) and physiological and pathological states have significant effect on PON1 enzyme activity [1,10-12]. At least in part some unknown environmental factors may accounts for heterogeneity between studies.

Using site directed mutagenesis at position 192 of PON1 indicated that the mutant enzyme

(192R) has 1.7-fold more activity compared with the wild type (192Q) protein [17]. It is well established that several genetic variations at the *PON1* promoter region are correlated with the gene expression level [12,37]. These polymorphic sites have strong linkage-disequilibrium with each other [26,37]. The frequency of the polymorphic alleles and haplotypes varies with ethnicity [26,37]. In articles used for the present meta-analysis, no data on distributions of the haplotypes among populations and their association with enzyme activity was reported.

Some limitations of the present study should be acknowledged. Environmental factors including some of life style (such as smoking habit) may be associated with the enzyme activity [1,10-12]. Studies which were included in the present meta-analysis did not report these factors. Further well-designed large studies are required to investigate gene-environment interactions and combinations of genetic polymorphisms.

Conclusions

The paraoxonase activity was increased in the QR and RR genotypes. This elevation was greater among Caucasians than those among Asians and Africans. The activity in the LM and MM genotypes compared with the LL genotype were decreased, this reduction in Caucasians was greater than Africans. There was significant heterogeneity between studies for both polymorphisms and subgroup analyses did not reveal sources contributing to the heterogeneity. At least in part other *PON1* polymorphisms and environmental factors may accounts for heterogeneity between studies.

Acknowledgements. This study was supported by Shiraz University, Iran.

Disclosure. The author declares no conflict of interest.

REFERENCES

1. Mackness M, Mackness B. Human paraoxonase-1 (*PON1*): Gene structure and expression, promiscuous activities and multiple physiological roles. *Gene* 67: 12-21, 2015.

2. La Du BN. The human serum paraoxonase/arylesterase polymorphism. *Am J Hum Genet* 43: 227-2279, 1988.

3. Shih DM, Gu L, Xia YR et al. Mice lacking serum paraoxonase are susceptible to organophosphate toxicity and atherosclerosis. *Nature* 394: 284-287, 1998.

4. Wei LK, Au A, Menon S et al. Polymorphisms of *MTHFR*, *eNOS*, *ACE*, *AGT*, *ApoE*, *PON1*, *PDE4D*, and ischemic stroke: Meta-analysis. *J Stroke Cerebrovasc Dis* 26: 2482-2493, 2017.

5. Gu HF, Mou M, Liang ZG, Sun C, Ren XY, Xiao YB. The association between paraoxonase 1 gene polymorphisms and polycystic ovarian syndrome. *Cell Mol Biol (Noisy-le-grand)* 62: 44-47, 2016.

6. Hernández-Díaz Y, Tovilla-Zárate CA, Juárez-Rojop IE et al. Effects of paraoxonase 1 gene polymorphisms on heart diseases: Systematic review and meta-analysis of 64 case-control studies. *Medicine (Baltimore)* 95: e5298, 2016.

7. Chen L, Lu W, Fang L et al. Association between L55M polymorphism in paraoxonase 1 and cancer risk: a meta-analysis based on 21 studies. *Onco Targets Ther* 9: 1151-1158, 2016.

8. You T, Lv J, Zhou L. *PON1* Q192R and L55M polymorphisms and organophosphate toxicity risk: a meta-analysis. *DNA Cell Biol* 32: 252-259, 2013.

9. Saadat M. Paraoxonase 1 genetic polymorphisms and susceptibility to breast cancer: a meta-analysis. *Cancer Epidemiol* 36: e101-103, 2012.

10. Camps J, Iftimie S, García-Heredia A, Castro A, Joven J. Paraoxonases and infectious diseases. *Clin Biochem* 50: 804-811, 2017.

11. Seres I, Bajnok L, Harangi M, Sztanek F, Koncsos P, Paragh G. Alteration of PON1 activity in adult and childhood obesity and its relation to adipokine levels. *Adv Exp Med Biol* 660: 129-142, 2010.

12. Costa LG, Cole TB, Jarvik GP, Furlong CE. Functional genomic of the paraoxonase (*PON1*) polymorphisms: effects on pesticide sensitivity, cardiovascular disease, and drug metabolism. *Ann Rev Med* 54: 371-392, 2003.

13. Allen Crow J, Meek EC, Wills RW, Chambers JE. A case-control study: The association of serum paraoxonase 1 activity and concentration with the development of type 2 diabetes mellitus. *Diabetes Metab Res Rev* doi: 10.1002/dmrr.2967, 2017.

14. Femlak M, Gluba-Brzózka A, Ciałkowska-Rysz A, Rysz J. The role and function of HDL in patients with diabetes mellitus and the related cardiovascular risk. *Lipids Health Dis* 16: 207, 2017.

15. Mousavi S, Kohan L, Yavarian M, Habib A. Pharmacogenetic variation of *SLC47A1* gene and metformin response in type2 diabetes patients. *Mol Biol Res Commun* 6: 91-94, 2017.

16. Saadat M. Null genotypes of glutathione S-transferase M1 (*GSTM1*) and T1 (*GSTT1*) polymorphisms increased susceptibility to type 2 diabetes mellitus, a meta-analysis. *Gene* 532: 160-162, 2013.

17. Aggarwal G, Prajapati R, Tripathy RK et al. Toward understanding the catalytic mechanism of human paraoxonase 1: Site-specific mutagenesis at position 192. *PLoS One* 11: e0147999, 2016.

18. Kujiraoka T, Oka T, Ishihara M et al. A sandwich enzyme-linked immunosorbent assay for human serum paraoxonase concentration. *J Lipid Res* 41: 1358-1363, 2000.

19. Brophy VH, Jarvik GP, Richter RJ, Rozek LS, Schellenberg GD, Furlong CE. Analysis of paraoxonase (*PON1*) L55M status requires both genotype and phenotype. *Pharmacogenetics* 10: 453-460, 2000.

20. Yamada A, Shoji T, Tahara H, Emoto M, Nishizawa Y. Effect of insulin resistance on serum paraoxonase activity in a nondiabetic population. *Metabolism* 50: 805-811, 2001.

21. Senti M, Tomás M, Elosual R, Sala J, Masiá R, Marrugat J. The paraoxonase-1 codon 192 polymorphism is associated with fasting total cholesterol and LDL-cholesterol concentrations only in postmenopausal women. The REGICOR study. *Clin Chem Lab Med* 40: 677-683, 2002.

22. Nakanishi M, Takanami Y, Maruyama T et al. The ratio of serum paraoxonase/ arylesterase activity using an improved assay for arylesterase activity to discriminate PON1 (R192) from PON1 (Q192). *J Atheroscler Thromb* 10: 337-342, 2003.

23. Campo S, Sardo MA, Trimarchi G et al. The paraoxonase promoter polymorphism (-107)T>C is not associated with carotid intima-media thickness in Sicilian hypercholesterolemic patients. *Clin Biochem* 37: 388-394, 2004.

24. Agachan B, Yilmaz H, Karaali Z, Isbir T. Paraoxonase 55 and 192 polymorphism and its relationship to serum paraoxonase activity and serum lipids in Turkish patients with non-insulin dependent diabetes mellitus. *Cell Biochem Funct* 22: 163-168, 2004.

25. Kotur-Stevuljevic J, Spasic S, Stefanovic A et al. Paraoxonase-1 (PON1) activity, but not *PON1*(Q192R) phenotype, is a predictor of coronary artery disease in a middle-aged Serbian population. *Clin Chem Lab Med* 44: 1206-1213, 2006.

26. Tripi LM, Manzi S, Chen Q et al. Relationship of serum paraoxonase 1 activity and paraoxonase 1 genotype to risk of systemic lupus erythematosus. *Arthritis Rheum* 54: 1928-1939, 2006.

27. Hofer SE, Bennetts B, Chan AK et al. Association between *PON1* polymorphisms, PON activity and diabetes complications. *J Diabetes Complications* 20: 322-328, 2006.

28. Browne RW, Koury ST, Marion S, Wilding G, Muti P, Trevisan M. Accuracy and biological variation of human serum paraoxonase 1 activity and polymorphism (Q192R) by kinetic enzyme assay. *Clin Chem* 53: 310-317, 2007.

29. Sepahvand F, Rahimi-Moghaddam P, Shafiei M, Ghaffari SM, Rostam-Shirazi M, Mahmoudian M. Frequency of paraoxonase 192/55 polymorphism in an Iranian population. *J Toxicol Environ Health A* 70: 1125-1129, 2007.

30. Unür M, Demirez E, Ağaçhan B et al. The relationship of oral disturbances of diabetes mellitus patients with paraoxonase gene polymorphisms. *Cell Biochem Funct* 26: 870-873, 2008.

31. Garcés C, López-Simón L, Rubio R et al. High-density lipoprotein cholesterol and paraoxonase 1 (PON1) genetics and serum PON1 activity in prepubertal children in Spain. *Clin Chem Lab Med* 46: 809-813, 2008.

32. Birjmohun RS, Vergeer M, Stroes ES et al. Both paraoxonase-1 genotype and activity do not predict the risk of future coronary artery disease; the EPIC-

Norfolk Prospective Population Study. *PLoS One* 4: e6809, 2009.

33. Chia SE, Mohamed Ali S, Yap PH, Gan L, Ong YB, Chia KS. Distribution of *PON1* polymorphisms PON1Q192R and PON1L55M among Chinese, Malay and Indian males in Singapore and possible susceptibility to organophosphate exposure. *Neurotoxicology* 30: 214-219, 2009.

34. Kanamori-Kataoka M, Seto Y. Paraoxonase activity against nerve gases measured by capillary electrophoresis and characterization of human serum paraoxonase (PON1) polymorphism in the coding region (Q192R). *Anal Biochem* 385: 94-100, 2009.

35. Zafiropoulos A, Linardakis M, Jansen EH, Tsatsakis AM, Kafatos A, Tzanakakis GN. Paraoxonase 1 R/Q alleles are associated with differential accumulation of saturated versus 20:5n3 fatty acid in human adipose tissue. *J Lipid Res* 51: 1991-2000, 2010.

36. Altuner D, Ates I, Suzen SH, Koc GV, Aral Y, Karakaya A. The relationship of PON1 QR 192 and LM 55 polymorphisms with serum paraoxonase activities of Turkish diabetic patients. *Toxicol Ind Health* 27: 873-878, 2011.

37. Eom SY, Kim YS, Lee CJ, Lee CH, Kim YD, Kim H. Effects of intronic and exonic polymorphisms of paraoxonase 1 (*PON1*) gene on serum PON1 activity in a Korean population. *J Korean Med Sci* 26: 720-725, 2011.

38. Ellison CA, Crane AL, Bonner MR et al. PON1 status does not influence cholinesterase activity in Egyptian agricultural workers exposed to chlorpyrifos. *Toxicol Appl Pharmacol* 265: 308-315, 2012.

39. Elatar N, Swelam EE, Hamed E, Elnahal S, Mostafa E. Paraoxonase 1 gene polymorphism relationship with type 2 diabetes mellitus. *Life Sci J* 9: 1742-1751, 2012.

40. Haj Mouhamed D, Ezzaher A, Mechri A et al. Effect of cigarette smoking on paraoxonase 1 activity according to *PON1* L55M and *PON1* Q192R gene polymorphisms. *Environ Health Prev Me*d 17: 316-321, 2012.

41. Helaly MA, Abdel-Khalek EE, Abdel-Hafez HA et al. Paraoxonase1 55 and 192 gene polymorphisms in an Egyptian population with diabetic complications. *Eur J Basic Med Sci* 3: 9-16, 2013.

42. Gökçen S, Cengiz M, Özaydın A. Serum paraoxonase levels and *PON1* (192) polymorphism in type 2 diabetes mellitus patients. *Gazi Med J* 24: 70-73, 2013.

43. Zhang X, Sui H, Li H, et al. Paraoxonase activity and genetic polymorphisms in northern Han Chinese workers exposed to organophosphate pesticides. *Exp Biol Med (Maywood)* 239: 232-239, 2014.

44. Kresanov P, Vasankari T, Ahotupa M et al. Paraoxonase-1 and oxidized lipoprotein lipids. The cardiovascular risk in young Finns study. *Atherosclerosis* 241: 502-506, 2015.

45. Ahmed NS, Shafik NM, Elraheem OA, Abou-Elnoeman SE. Association of paraoxonase-1 (Q192R and L55M) gene polymorphisms and activity with colorectal cancer and effect of surgical intervention. *Asian Pac J Cancer Prev* 16: 803-809, 2015.

46. AnandBabu K, Bharathidevi SR, Sripriya S et al. Serum Paraoxonase activity in relation to lipid profile in age-related macular degeneration patients. *Exp Eye Res* 152: 100-112, 2016.

47. Fridman O, Gariglio L, Riviere S, Porcile R, Fuchs A, Potenzoni M. Paraoxonase 1 gene polymorphisms and enzyme activities in coronary artery disease and its relationship to serum lipids and glycemia. *Arch Cardiol Mex* 86: 350-357, 2016.

48. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22: 719-748, 1959.

49. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials* 7: 177-188, 1986.

50. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 315: 629-634, 1997.