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The most effective polymorphisms of paraoxonase-1 gene on enzyme activity and concentration of paraoxonase-1 protein in type 2 diabetes mellitus patients and non-diabetic individuals: A systematic review and meta-analysis

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ABSTRACT

Introduction: Many studies have evaluated the association of paraoxonase-1 (PON1) gene polymorphisms with enzyme activity and concentration in type 2 diabetes mellitus (T2DM). However, the exact impact of these polymorphisms is not still obvious. Hence, we conducted a systematic review and meta-analysis to clarify the association of PON1 polymorphisms with its enzyme characteristics in T2DM patients and non-diabetic individuals.
Methods: We searched electronic databases including PubMed, Web of Science, Embase and Scopus for publications by April 2018. The pooled response ratio (rr) for the association and their corresponding 95% confidence intervals (CIs) were calculated using a fixed-effect model.
Results: Fifteen relevant studies fulfilled our inclusion criteria. The results showed a 1.25-fold increase in total PON1 activity in non-diabetic group against T2DM patients (p-value = 0.024). Also, only Q192R and L55M polymorphisms had sufficient studies to be included in the meta-analysis. All three genotypes of Q192R polymorphism showed significantly different activities between the study groups with the highest pooled effect size for RR genotype ($rr_{QQ} < rr_{QR} < rr_{RR}$) while this difference was seen only in LL genotype of L55M polymorphism. Therefore, Q192R polymorphism was more correlated with type 2 diabetes mellitus. In case of concentration, there was no significant differences between two groups (p-value = 0.897).
Conclusion: Current meta-analysis suggested that the observed difference of total PON1 activity was due to the different activity of various genotypes of PON1 enzyme in case of L55M and Q192R polymorphisms so that LL and RR genotypes had the most important role in the establishment of mentioned difference.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder with a final impairment of insulin secretion [1] and characterized by hyperglycemia [2]. Its growing incidence is known as a global health concern. International Federation of Diabetes (IFD) reported 378 million patients suffering from this disease in 2014 with the prediction of 600 million patients by 2035. The complications of this disease are categorized into two main groups of micro-vascular and macro-vascular consequences where it is the sixth cause of disease-related disability in the world [3]. Induction of oxidative stress and lipid peroxidation is one of the main mechanisms of such complications. Paroxonase-1 (PON1) is a 43-kDa, calcium-dependent [4], hepatic glycoprotein as a HDL-bound serum enzyme belonging to paroxonase gene family including PON1, PON2, and PON3 [5]. PON1 gene is localized at q21-q22 on the long arm of chromosome 7 in humans [6] possessing detoxification (detoxification of organophosphates [7]) and anti-oxidant functions particularly in case of modification of LDL oxidation [8–10]. It is reported that different polymorphisms of this enzyme's gene results in various function and activity levels from 10 to 40-fold among different populations [11], so that the introduction of the most effective polymorphism in the establishment of such difference may lead us to candidate the prone patients to develop T2DM. The PON1 gene has nearly 200 SNPs (single nucleotide polymorphisms) [12]. Of these, −909G/C [rs854572], −162A/G [rs705381], −108C/T [rs705379] polymorphisms located in the promoter and Q192R [rs662] and L55M [rs 854560] polymorphisms located in the coding region are the most commonly proposed SNPs.

Q192R is a substitution of Glutamine/Arginine at position 192 of amino acid sequence [6,13,14] posing a substrate-dependent manner [8] with respect to lipid peroxides [9]. The PON1 R192 isoform hydrolyses paraoxon rapidly as compared to PON1 Q192 isoform, whereas Q192 isoform hydrolyses diazoxon, sarin and soman rapidly as compared to R192 isoform [15]. However, phenylacetate hydrolysis i.e. AREase activity is not affected by Q192R polymorphism and has been shown to correspond with PON1 levels [16–18] determined by immunological methods [19,20]. This heterogeneous function results in calling Gln192 as low activity isoform and Arg192 as high activity isoform [21]. Also, the R allele of this polymorphism has been correlated with T2DM regardless of PON1 activity [22,23]. The Leucine/Methionine substitution at position 55 (L55M) is another important polymorphism of PON1 in case of enzyme characteristics [6,13,14,24]. Formerly, L55M polymorphism was believed not to affect the activity of PON1 [6,13] but recent studies claim to explore such effect [25,26]. Even there is a suggestion on the alterations of PON1 concentration by L55M polymorphism [14,27]. Nevertheless, there are studies reporting no correlation between PON1 activity and Q192R and L55M polymorphisms in diabetic patients [28,29]. A few studies have also looked at association between other mentioned polymorphisms and PON1 activity [20]. It was claimed that −108 C/T polymorphism could affect the levels of PON1 activity [30,31] and also transcriptional status and serum concentration [32–34] independent of coding Q192R and L55M polymorphisms [35]. However, literature is almost silent regarding association of promoter −909G/C, −162A/G polymorphisms and PON1 activity in type 2 diabetics [35]. With respect to remaining controversy on the impact of different polymorphisms on PON1 activity or concentration, the current meta-analysis was designated as the first and the largest study to comprehensively analyze this concept. For this aim, we evaluated the studies which had targeted the concentration and activity of PON1 based on genotypic differences of mentioned polymorphisms to elucidate the most effective polymorphism and even genotype in the establishment of desired outcome in both of diabetic and non-diabetic groups.

2. Methods and analysis:

2.1. *Search strategy and study identification*

We searched the electronic databases including PubMed, Web of Science, Embase and Scopus. The search strategy was constructed using a combination of MeSH terms and text words relating to Diabetes type 2, Polymorphism and paraoxonase 1. The electronic search was conducted by April 2018 with no language limitation. The reference lists from relevant articles were then screened for eligibility.

2.2. *Inclusion criteria*

Two independent reviewers did the primary screening of the articles and data extraction, and eligible sources were selected after discussing nonconformities and in the case of disagreement of two reviewers about the eligibility of an article, the third reviewer dissolved it by consensus. The criteria for our analysis were as follows: (1) review articles, letter to editors, short reports, conference articles, type 1 diabetes and non-human studies were excluded, (2) the studies had to consist of case (T2DM patients) and control (non-diabetic individuals) groups regardless to sample size, (3) original articles must have evaluated the levels of enzyme activity or concentration as mean ± standard deviation in both groups, (4) the polymorphism analysis should have been based on one of following methods: PCR-RFLP, RT-real time PCR, and sequencing.

2.3. *Selection, assessment and data extraction*

In order to select studies for further assessment, two independent reviewers screened the title, abstract and keywords of every retrieved record. Full articles were assessed if the given information suggested that the study was conformed to our criteria. We categorized the selected articles into two groups: (i) group with *enzyme activity* outcome (ii) group with *enzyme concentration* outcome. *Enzyme activity* group was divided upon to two aspects: (a) total PON activity (b) different polymorphisms genotype-based activity.

2.4. *Data synthesis and analysis (meta-analysis)*

The pooled effect sizes were calculated using a response ratio (rr) which is calculated by dividing the mean activity or con-

centration levels of control to case groups [36] with corresponding 95% confidence intervals (CIs). The non-diabetic individuals were considered as the control in the meta-analysis.

2.5. Statistical analysis

Effect sizes and 95% CIs were calculated using Comprehensive Meta-Analysis Software (version 2.2.064). After calculating the between –study variance [37], The pooled effect sizes were estimated using fixed-effect model [38]. Heterogeneities between studies were tested using Chi-square test. The Q test with a p-value of <0.05 and I-square >50% were indicators of inter-study heterogeneity [39]. Stratified analysis was used to explore the source of heterogeneity.

The potential publication bias was assessed using Begg's funnel plots. Also, when the funnel plot was asymmetric, possibility of publication bias was analyzed using trim and fill method. In this method, imputation of potentially missing studies (probably unpublished studies) yields a symmetric funnel plot. After imputation, if the overall effect size (adjusted effect size) was not significantly altered, publication bias was considered to be unlikely to affect the pooled estimate of effect size [40].

3. Results

The search for study involved a total of 658 studies according to the pre-defined search strategy. A total of 259 studies were excluded because of duplicate publication. The elimination of irrelevant studies resulted in 66 studies. A further 51 studies were excluded due to the lack of non-diabetic control group and major outcome data. Finally, 15 articles having all of the desired criteria were included in the meta-analysis (Fig. 1). The general characteristics of included studies are presented in Table 1.

3.1. Correlations of the levels of PON1 enzyme activity with various polymorphisms of PON1

We assessed the relevant studies in which the association of the levels of PON1 enzyme activity based on five mentioned polymorphisms with diabetes was evaluated. There were only eligible data for Q192R and L55M in the literature. The levels of PON1 activity were stated in terms of total PON1 activity and different polymorphisms genotype-based activity (QQ, QR, and RR for the Q192R polymorphism and LL, LM, and MM for the L55M polymorphism).

3.2. Total PON1 activity

The relationship between presence of diabetes and total PON1 enzyme activity is illustrated in Fig. 2. The level of total PON1 activity in non-diabetic individuals was 1.25 folds higher than that of T2DM patients (p-value = 0.024). It should be noted that no heterogeneity was seen among the studies ($I^2 = 0.00$, p-value = 0.958).

3.3. L55M polymorphism genotypes activities

As shown in Fig. 3, PON1 enzyme activities were higher in non-diabetic individuals in comparison to T2DM patients across different variants of L55M polymorphism but this difference was significant only in the case of LL genotype (rr = 1.28, p-value = 0.021). There was no significant heterogeneity in the overall meta-analysis of PON1 L55M polymorphism in LL, LM, and MM genotypes ($I^2 = 0.00$ for all genotypes and p-value = 0.9, 0.744, and 0.934 respectively).

3.4. Q192R polymorphism genotypes activities

The levels of PON1 activity due to all of Q192R polymorphism genotypes were significantly higher in non-diabetic subjects compared with T2DM patients (p-value < 0.05) with no significant heterogeneity among studies. Also, a notably elevating trend was seen about the rr related to Q192R genotypes from QQ to RR (QQ (rr = 1.33) < QR (rr = 1.39) < RR (rr = 1.48)) (as presented in Fig. 4).

3.5. Total PON1 concentration

Fig. 5 demonstrates the correlation between presence of diabetes and total PON1 enzyme concentration. There was no significant difference between the levels of total PON1 concentration in non-diabetic individuals *versus* T2DM patients (rr = 1.05, p-value = 0.897). It should be noted that no heterogeneity was seen among the studies ($I^2 = 0.00$, p-value = 0.943).

3.6. Publication bias analysis

Fig. 6 displays the funnel plot of the levels of PON1 enzyme total activity and activities based on L55M and Q192R polymorphisms genotypes with T2DM. An ideal symmetry was obtained by trim and fill imputation. After imputation of the missing studies (black circles), there was no significant difference between observed and adjusted overall effect size (Table S1). These findings showed no evidence for obvious publication bias among the included studies.

4. Discussion

To our knowledge, the exact association between the concentration and activity of PON1 as well as the polymorphisms of the PON1 gene with T2DM is not still clear. Considering this fact, we designed the current systematic review meta-analysis to address the limitation and obtain conclusive results.

Our results showed a 1.25-fold increase of total PON1 activity in non-diabetic individuals in comparison to T2DM patients. It can be partially due to the fact that chronic hyperglycemia in T2DM patients results in a heavy glycation or non-enzymatic glycosylation of PON1 [41,42], thereby leading to the inhibition of PON1 activity. This phenomenon can somehow explain the low activity of PON1 in T2DM patients [9] by alterations in conformation and/or performance of

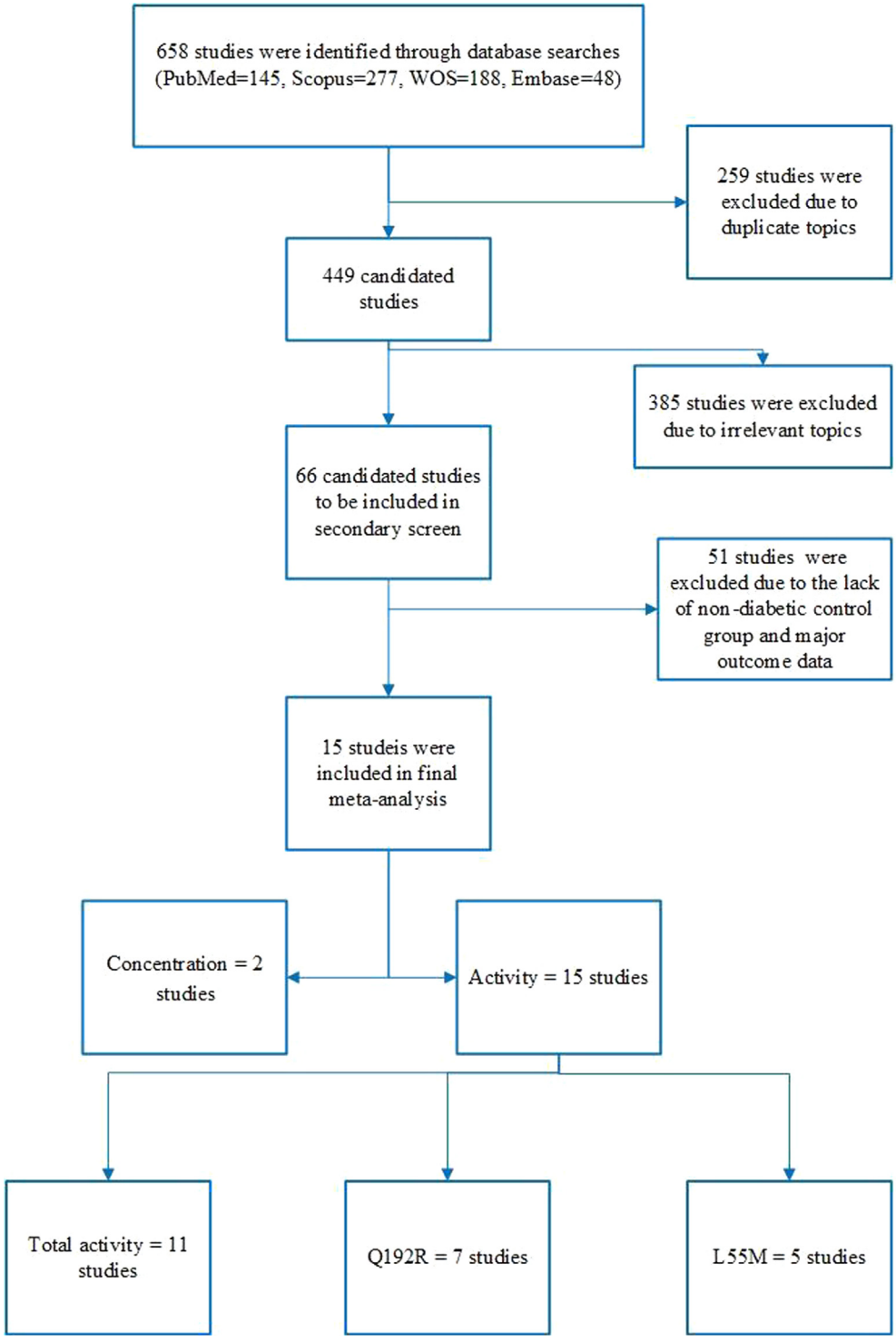


Fig. 1 – Flow chart of study selection procedure.

the enzyme itself or of HDL. Also, the lesser extent of PON1 bounding by HDL in T2DM patients in comparison to healthy persons leads to poorer stabilization of its activity [43]. In spite of total PON1 activity, the following stratified analysis of PON1 activity based on various genotypes revealed different patterns.

As mentioned before, there were five important and more common polymorphisms to be involved in the studies. There was negligible information about PON1 −909G > C, 162A > G, and −108C > T polymorphisms so that it was impossible to involve them in the meta-analysis. Hence, only studies related to PON1 Q192R and L55M genotypes were qualified to be included in the meta-analysis based on predefined inclusion criteria. No heterogeneity (Table S2) and publication bias (Fig. 6) were seen among the studies in cases of PON1 Q192R and L55M genotypes.

Table 1 – Characteristics of the included studies for meta-analysis

	Author	Year	Country	T2DM population		Non-diabetic population		Polymorphism assay technique	Total/genotype-based activity	Concentration
				Female	Male	Female	Male			
1	D. Altuner	2011	Turkey	44	56	29	21	PCR-RFLP	Total activity	—
2	M. Ali Ergun	2011	Turkey	171		80		Multiplex-PCR PCR-RFLP	Total activity	—
3	N. Gupta	2011	India	124	126	149	151	PCR-RFLP Multiplex-PCR Allele Specific Oligonucleotide (ASO) PCR	Total activity	—
4	M. Abdel-Halem Helaly	2013	Egypt	56	44	55	45	PCR-RFLP	Total activity	—
5	M. Inoue	2000	Japan	55	51	79	82	Real time PCR	Total activity	*
6	C. Letellier	2002	Bulgaria	59	108	53	52	PCR-RFLP	Total activity	—
7	B. Mackness	1998	United Kingdom	90	162	135	147	PCR-RFLP	Total activity	*
8	H. Surjit Singh	2007	India	11	46	12	51	NA	Total activity	—
9	T. Sakai	1998	Japan	74	65	61	179	PCR-RFLP	Total activity Q192R	—
10	MJ. Sampson	2005	United Kingdom	20	38	32	18	PCR-RFLP	Total activity Q192R L55M	—
11	N. Elattar	2012	Egypt	NA	NA	NA	NA	PCR-RFLP	Total activity Q192R L55M	—
12	FA. Abessolo	2012	Gabon	NA	NA	NA	NA	PCR-RFLP	Q192R L55M	—
13	B. Agachan	2004	Turkey	122	91	57	59	PCR-RFLP	Q192R L55M	—
14	M. Flekac	2007	Czech Republic	132	114	45	55	PCR-RFLP	Q192R L55M	—
15	S. Gökçen	2013	Turkey	30	20	14	16	PCR-RFLP	Q192R	—

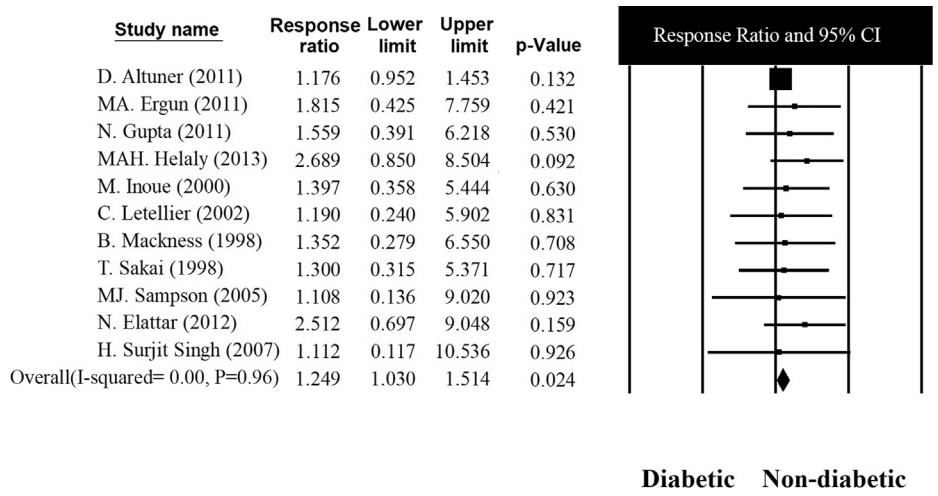
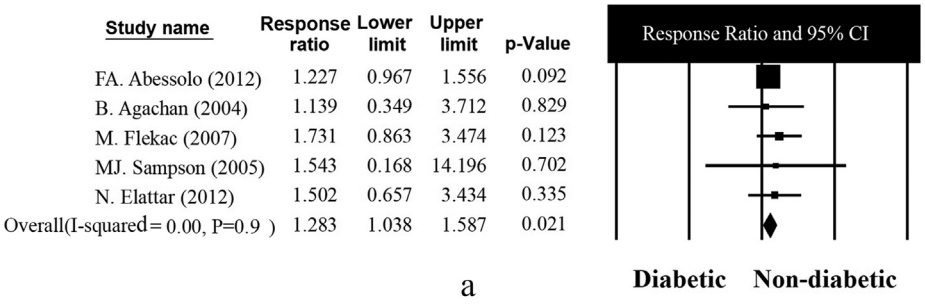
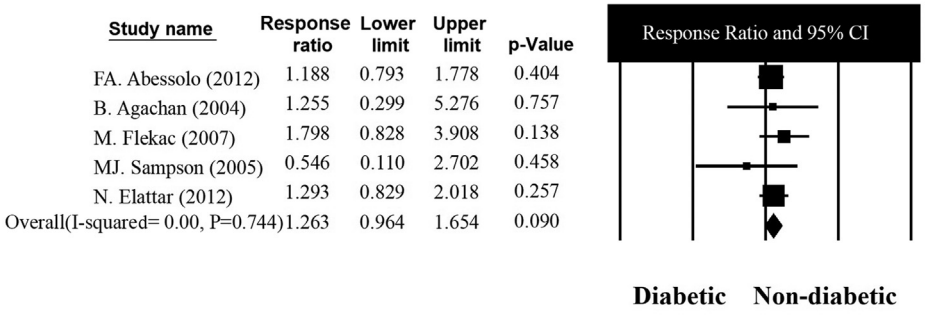


Fig. 2 – Forest plot of response ratio for the correlation of total activity of PON1 with diabetes.



a



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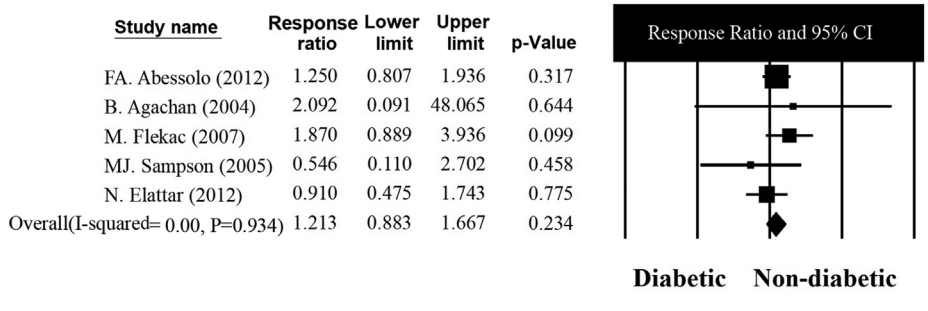
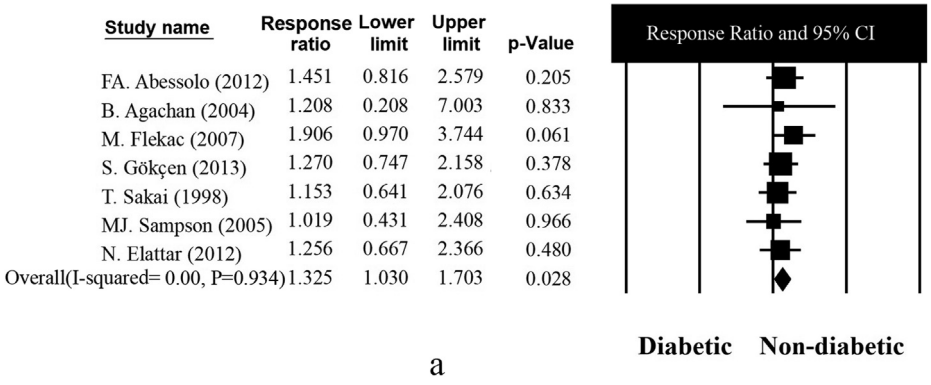
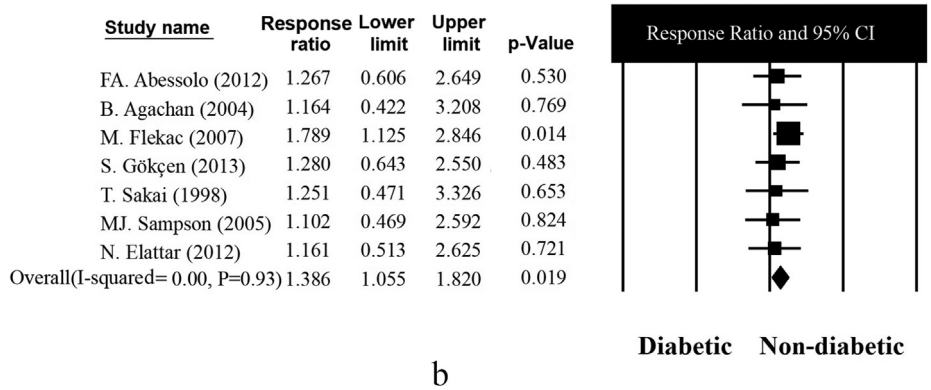


c

Fig. 3 – Forest plot of response ratios for the correlation of LL (a), LM (b), and MM (c) genotypes of L55M polymorphism with diabetes.



a



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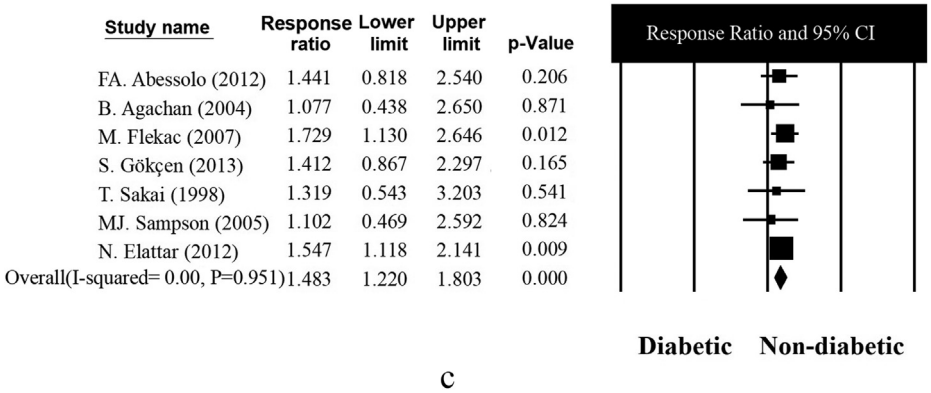

c

Fig. 4 – Forest plot of response ratios for the correlation of QQ (a), QR (b), and RR (c) genotypes of Q192R polymorphism with diabetes.

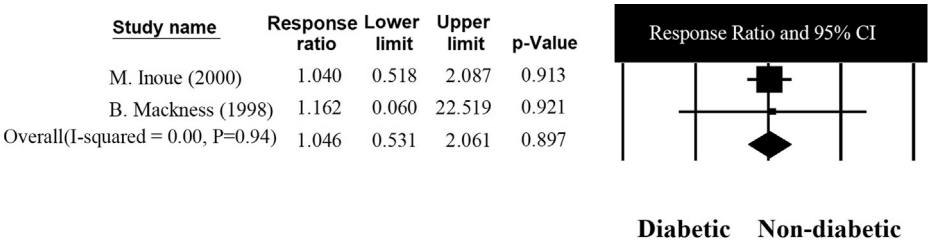

Fig. 5 – Forest plot of response ratios for the correlation of PON1 concentration with diabetes.

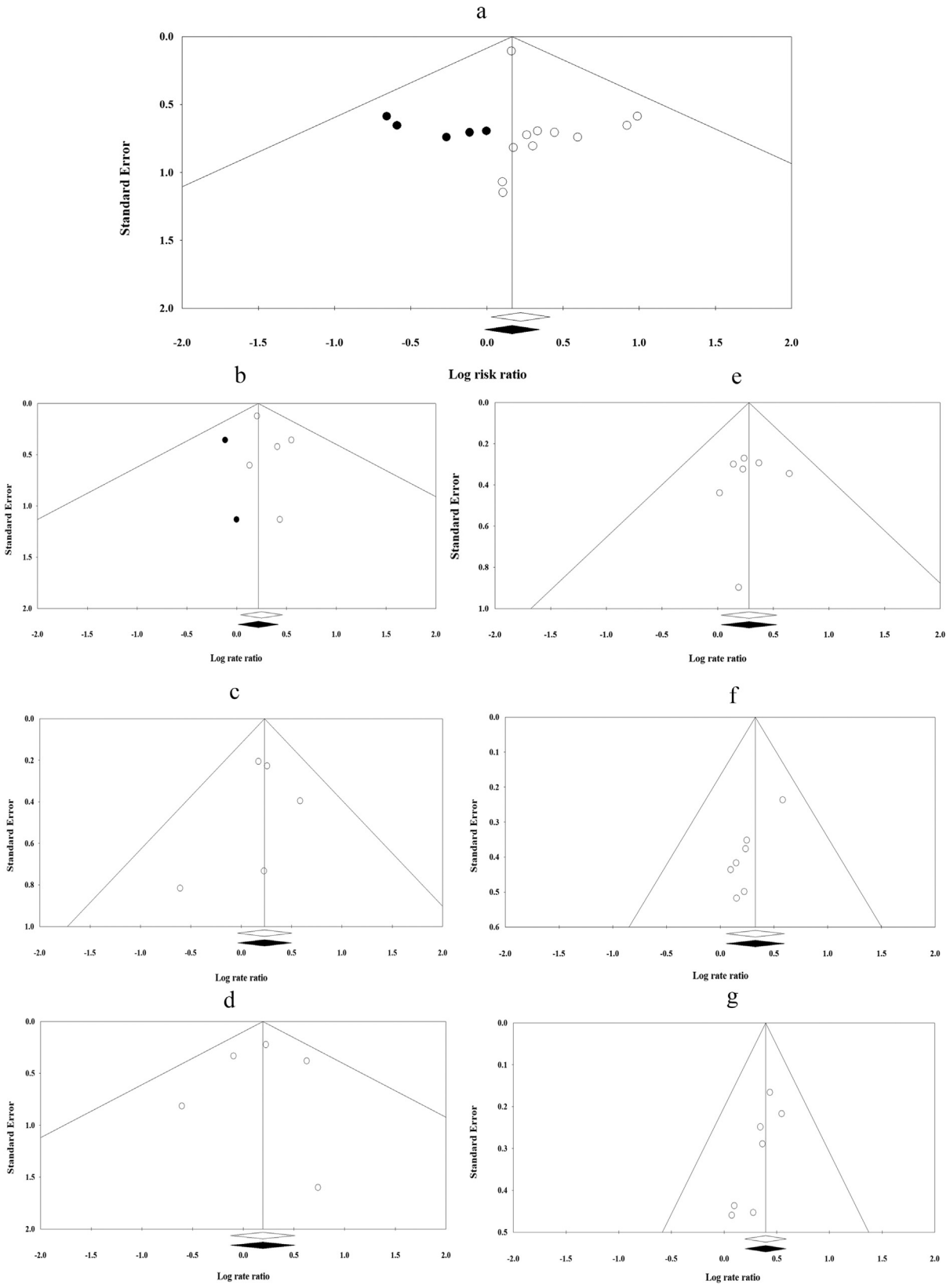

Fig. 6 – Begg's funnel plots to explore the possibility of publication bias in the pooled estimated of T2DM and (a) total PON1 activity, (b) LL, (c) LM, (d) MM, (e) QQ, (f) QR, and (g) RR genotypes-based activity of PON1 polymorphisms.

There are opposite notions about the correlation of Q192R and L55M polymorphisms in case of PON1 activity ranging from strong linkage disequilibrium between L-55 and Q-192 [14] to no correlation between them [8].

Q192R is a common polymorphism wherein glutamine is substituted by arginine, affecting the hydrolytic activity of PON1 isoenzymes with respect to certain substrates, such as paraoxon and lipid peroxides [44]. All of PON1 Q192R polymorphism genotypes revealed significant differences between T2DM patients and non-diabetic subjects (Fig. 4). Also, the comparison of the differences of PON1 Q192R polymorphism genotypes between two groups showed an elevation of pooled effect sizes with the increase of R allele portion as follows: QQ (rr = 1.33) < QR (rr = 1.39) < RR (rr = 1.48) so that this difference enlarges from QQ genotype to RR genotype. Notably, this observation proposes the probable influence of R allele in the establishment of the difference of PON1 activity between T2DM patients and non-diabetic subjects. One of the potential explanations is that polymorphisms of human PON1 can affect the hydrolytic activity of PON1 isoenzymes so that the presence of B allele at position 192 which represents the arginine (B) substitution has several-fold higher activity against A allele in case of paraoxon hydrolysis [24].The most important portion of such variance is due to the alterations of the enzyme activity toward the substrate paraoxon, whereas the hydrolysis rate for phenylacetate is almost equal for both allozymes [45].

On the other hand, it was formerly declared that the mutations in the NH_2-terminal region of the peptide may facilitate paraoxonase binding to HDL due to the changes in a highly hydrophobic sequence [46], while HDL – in the structural form of apo A-I – is needed for the maintenance of active form of paraoxonase. Now, the changes in the conformation of NH_2-terminal region because of L55M polymorphism can influence enzyme activity [14]. In the overall meta-analysis of PON1 L55M polymorphism genotypes, significant difference was only seen in case of LL genotype between T2DM patients and non-diabetic subjects while the other genotypes (LM and MM) had no significant differences. This finding suggests the lower impact of L55M polymorphism in the establishment of the observed total PON1 activity variation between T2DM patients and non-diabetic subjects.

The substitution of methionine (M)/ Leucine (L) at the position 55 does not significantly alter the hydrolysis capacity of PON1 enzyme [24] at least as much as glutamine/arginine substitution at position 192 does [47,48]. The different levels of PON1 activity in case of L55M polymorphism between the two groups in spite of no variations for two genotypes (LM and MM) suggests the cumulative effect of polymorphisms on activity levels of this enzyme [8].

According to the results of this meta-analysis, it seems that polymorphisms of PON1 coding region especially RR and LL genotype could affect serum PON1 activity levels by changing the active site of target protein through various mechanisms such as the reason which was stated about the alterations of NH_2-terminal due to L55M polymorphisms [9,14].

In addition to the influence of polymorphisms on total activity, some polymorphisms especially those of promoter region are able to alter the PON1 concentration through changing the expression of PON1 mRNA and serum concentrations of the protein [49]. However, some previous studies showed the effect of polymorphism at position 55 on enzyme concentration which is decreased from L to M allele [14]. The results of this meta-analysis did not show any difference between the concentrations of PON1 enzyme in two study groups in case of polymorphism alterations.

5. Conclusion

In conclusion, serum PON1 activity is higher in non-diabetic individuals in comparison to T2DM patients and this difference is affected by various genotypes of PON1 enzyme related to the L55M and Q192R polymorphisms. Q192R polymorphism may explain the most part of this difference in all of three genotypes while the most important genotype in case of observed difference for L55M polymorphism is only LL genotype.

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Conflict of interest

The author(s) declare no competing interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.05.007.

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