Section: Biochemistry

Original Research Article

ASSOCIATION OF PARAOXONASE 1 (PON1) GENE POLYMORPHISMS (Q192R AND L55M) WITH ENZYME ACTIVITY AND GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is characterized by chronic hyperglycemia, insulin resistance, and oxidative stress. Paraoxonase 1 (PON1), an antioxidant enzyme associated with high-density lipoprotein (HDL), is modulated by genetic polymorphisms, notably Q192R and L55M. These polymorphisms influence enzymatic activity and may affect glycemic control and oxidative burden. The objective is to investigate the association between PON1 gene polymorphisms (Q192R and L55M), PON1 enzymatic activity, and glycemic control markers—HbA1c and glycated albumin (GA)—in Indian patients with T2DM. **Materials and Methods:** A cross-sectional study involving 384 participants (192 T2DM patients and 192 matched controls) was conducted. Genotyping for Q192R and L55M was performed using PCR-RFLP. PON1 activity was measured spectrophotometrically. HbA1c and GA levels were evaluated using standardized methods. Statistical analysis was performed using SPSS v26. **Result:** The RR and MM genotypes were more prevalent in the T2DM group and were associated with significantly lower PON1 activity ($p < 0.001$). A significant inverse correlation was observed between PON1 activity and both HbA1c ($r = -0.38$, $p < 0.001$) and GA ($r = -0.42$, $p < 0.001$). **Conclusion:** PON1 polymorphisms Q192R and L55M are significantly associated with reduced enzyme activity and poorer glycemic control. PON1 genotyping and enzyme activity may serve as additional tools for glycemic assessment and risk stratification in T2DM.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic, multifactorial metabolic disorder characterized by insulin resistance, relative insulin deficiency, and persistent hyperglycemia. It accounts for more than 90% of all diabetes cases globally and is associated with a high burden of morbidity and mortality due to its long-term microvascular and macrovascular complications. The increasing prevalence of T2DM, particularly in developing countries like India, underscores the urgent need to understand its pathophysiological mechanisms and identify novel biomarkers for early diagnosis and effective disease management.

Oxidative stress has emerged as a critical factor in the pathogenesis of T2DM and its complications. Hyperglycemia induces overproduction of reactive oxygen species (ROS), which damages pancreatic β-cells, impairs insulin signaling, and accelerates endothelial dysfunction. Antioxidant defense mechanisms are compromised in T2DM, exacerbating oxidative injury and contributing to complications such as nephropathy, retinopathy, and atherosclerosis.

Paraoxonase 1 (PON1), a calcium-dependent enzyme synthesized in the liver and bound to high-density lipoprotein (HDL), plays a central role in mitigating oxidative stress by hydrolyzing lipid peroxides in oxidized low-density lipoproteins (LDL). This activity is critical for maintaining vascular integrity and reducing atherogenesis. PON1 also exhibits anti-inflammatory properties and is considered a protective factor in various oxidative stress-related diseases, including T2DM.

Genetic polymorphisms in the PON1 gene significantly influence its enzymatic activity and expression. Among these, the Q192R (rs662) and L55M (rs854560) variants have been extensively studied. The Q192R polymorphism involves a substitution of glutamine (Q) with arginine (R) at position 192, while L55M denotes a leucine (L) to

methionine (M) substitution at position 55. These allelic variations result in significant inter-individual differences in PON1 catalytic efficiency, substrate specificity, and antioxidant capacity.

Studies have demonstrated that individuals with the RR genotype tend to have lower antioxidant protection despite higher hydrolytic activity against certain substrates, whereas those with the MM genotype also exhibit reduced overall PON1 activity. These genetic differences may influence an individual's susceptibility to oxidative stress and diabetic complications.

In addition to HbA1c, which reflects long-term glycemic control, glycated albumin (GA) has gained prominence as a short-term glycemic biomarker, particularly useful in conditions where HbA1c may be unreliable (e.g., anemia, hemoglobinopathies). Unlike HbA1c, GA reflects glucose levels over a 2–3 week period and is more sensitive to acute glycemic fluctuations.

Emerging evidence suggests a link between PON1 gene polymorphisms, PON1 enzyme activity, and glycemic markers such as HbA1c and GA. However, limited studies have addressed this relationship in Indian populations where genetic diversity and environmental factors may yield distinct metabolic profiles.

This study aims to evaluate the distribution of PON1 Q192R and L55M polymorphisms, their influence on enzyme activity, and their association with glycemic control markers (HbA1c and GA) in patients with T2DM. Understanding this relationship could aid in the identification of high-risk individuals and the development of personalized approaches to diabetes management.

MATERIALS AND METHODS

Study Design and Setting: This observational, cross-sectional study was conducted between 2022 and 2025 at the Department of Biochemistry, Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, India. The protocol was approved by the Institutional Ethics Committee prior to data collection.

Study Population: A total of 384 participants were enrolled, including 192 patients diagnosed with Type 2 Diabetes Mellitus based on American Diabetes Association (ADA) criteria and 192 age- and sex-matched non-diabetic healthy controls.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Adults aged 30–65 years
- Confirmed diagnosis of T2DM (for patient group)
- No known chronic illness in controls

Exclusion Criteria

- Type 1 diabetes or gestational diabetes
- Chronic inflammatory, hepatic, or renal disorders
- Use of antioxidant supplements or lipid-lowering medications
- History of recent infection or acute illness

Sample Collection: Venous blood (5 mL) was collected from each subject after overnight fasting.

- 3 mL was collected in a plain tube for serum separation (PON1 enzyme activity, DNA extraction).
- 2 mL was collected in an EDTA tube for glycated albumin and HbA1c estimation.

Genomic DNA Extraction and Genotyping

Genomic DNA was extracted using a commercial spin-column kit from leukocyte-rich buffy coat. Genotyping of PON1 Q192R and L55M polymorphisms were performed by PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) technique, followed by gel electrophoresis for visualization.

Biochemical Analyses

- PON1 Enzyme Activity: Measured using paraoxon (for paraoxonase activity) and phenyl acetate (for arylesterase activity) via spectrophotometry. Results were reported in U/mL.
- HbA1c: Measured using HPLC-based standardized assay as per NGSP/DCCT protocol.
- Glycated Albumin (GA): Quantified using an enzymatic colorimetric method (Lucica GA-L, Asahi Kasei Pharma) on serum samples.
- Other Parameters: Fasting plasma glucose and lipid profile were assessed using an automated biochemical analyzer.

Statistical Analysis: Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± SD and compared using t-tests or ANOVA. Genotype and allele frequencies were compared using Chi-square test. Pearson correlation was used to evaluate associations between PON1 activity and glycemic parameters. A p-value < 0.05 was considered statistically significant.

RESULTS

Genotype Distribution: The frequencies of RR and MM genotypes were significantly higher in the T2DM group compared to controls ($p < 0.01$). Hardy-Weinberg equilibrium was maintained in the population.

Table 1: Distribution of PON1 Q192R and L55M Genotypes Among Study Groups

Genotype	T2DM Patients (n=192)	Controls (n=192)	p-value
QQ	58 (30.2%)	89 (46.4%)	<0.01
QR	79 (41.1%)	71 (37.0%)	0.42
RR	55 (28.6%)	32 (16.6%)	<0.01
LL	51 (26.6%)	78 (40.6%)	<0.01
LM	84 (43.8%)	79 (41.1%)	0.61
MM	57 (29.7%)	35 (18.2%)	<0.01

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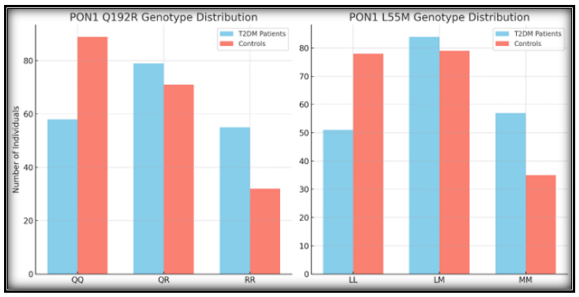

Figure 1: The graph shows the distribution of PON1 Q192R and L55M genotypes among T2DM patients and controls.

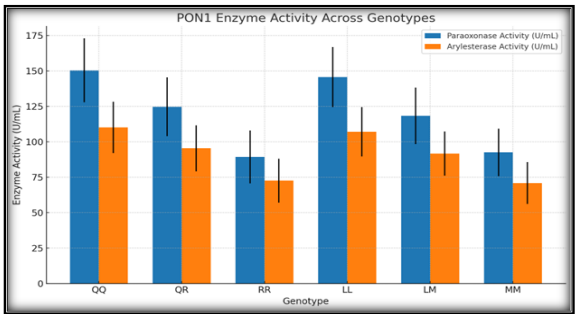

Figure 2: The graph shows PON1 enzyme activity across genotypes with error bars for standard deviation.

PON1 Activity and Genotype Correlation

PON1 enzymatic activity was significantly lower in individuals with RR and MM genotypes compared to QQ and LL genotypes, respectively. RR individuals showed 40% lower paraoxonase activity than QQ genotype ($p < 0.001$).

Association with Glycemic Control

HbA1c and GA levels were significantly higher in RR and MM carriers. PON1 activity inversely correlated with HbA1c ($r = -0.38$, $p < 0.001$) and GA ($r = -0.42$, $p < 0.001$).

Table 2. PON1 Enzyme Activity Across Genotypes

Genotype	Paraoxonase Activity (U/mL)	Arylesterase Activity (U/mL)	p-value
QQ	150.4 ± 22.5	110.2 ± 18.1	Ref
QR	124.7 ± 20.8	95.4 ± 16.2	<0.05
RR	89.3 ± 18.7	72.6 ± 15.5	<0.001
LL	145.6 ± 21.2	107.1 ± 17.4	Ref
LM	118.3 ± 19.9	91.7 ± 15.6	<0.05
MM	92.5 ± 16.8	70.9 ± 14.8	<0.001

Table 3: Correlation of PON1 Activity with Glycemic Markers

Parameter	r-value	p-value
HbA1c (%)	-0.38	<0.001
Glycated Albumin (%)	-0.42	<0.001

DISCUSSION

The findings of this study demonstrate a significant association between PON1 gene polymorphisms (Q192R and L55M), enzyme activity levels, and glycemic control in patients with Type 2 Diabetes Mellitus (T2DM). The RR and MM genotypes were significantly more prevalent among T2DM patients and were associated with markedly lower paraoxonase and arylesterase activities. These results align with those reported by El-Said et al. (2015),[1] who found decreased PON1 activity in T2DM patients, particularly among individuals carrying the RR genotype. Similarly, Adiga et al. (2022),[2] noted reduced PON1 activity in Indian T2DM subjects, reinforcing the role of genetic variation in modulating oxidative stress defenses.

The observed negative correlation between PON1 activity and both HbA1c and glycated albumin (GA) further supports its potential as a biomarker for glycemic status. Previous studies by Harshad and Shetty,[3] (2024) and Zhang et al,[4] (2024) have demonstrated that lower PON1 activity corresponds to increased oxidative burden, resulting in poor glycemic regulation. Our data substantiate these findings, showing that individuals with RR and MM genotypes not only exhibit lower enzyme activity but also elevated HbA1c and GA levels, which are indicators of suboptimal glucose control.

Comparatively, Deakin et al,[5] (2013) and Tsimihodimos et al,[6] (2012) also reported that specific PON1 polymorphisms were associated with increased risk of diabetic complications, such as nephropathy and cardiovascular disease. While our current study did not focus on complications, the association of polymorphisms with poor glycemic markers may infer an elevated risk for such outcomes.

Notably, the inverse correlation with GA—a sensitive marker of short-term glycemic fluctuation—echoes findings by Koga et al. (2020),[7] suggesting that PON1 activity could serve as a dynamic measure of glucose variability. This becomes particularly important in patients where HbA1c is confounded by conditions like anemia or hemoglobinopathies, which are not uncommon in the Indian context.

Moreover, our observation of the genotype distribution in an Indian population provides a valuable addition to global data. It supports prior assertions by Elatar et al,[8] (2012) and Costa et al,[9] (2013) that ethnic variations in PON1 polymorphism frequencies can influence disease susceptibility and prognosis. Thus, this study reinforces the need for

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population-specific genetic data in tailoring diabetes management strategies.

The limitations of the present study include its cross-sectional design, which precludes causal inference, and the lack of direct assessment of diabetic complications. Future studies should incorporate longitudinal designs and evaluate the predictive value of PON1 polymorphisms in the development of complications.

In summary, our findings affirm that PON1 Q192R and L55M polymorphisms significantly affect enzyme activity and are associated with markers of poor glycemic control in T2DM. Routine genotyping and activity assessment of PON1 may serve as useful adjunct tools for risk stratification and personalized diabetes care.

CONCLUSION

Q192R and L55M polymorphisms of the PON1 gene significantly influence enzymatic activity and are linked to poorer glycemic outcomes in T2DM. PON1 genotyping and enzyme activity measurement can serve as useful adjuncts in diabetes management and risk stratification.

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