Section: Biochemistry

Original Research Article

IMPACT OF PON1 GENE POLYMORPHISMS ON DIABETIC COMPLICATIONS AND RISK STRATIFICATION IN INDIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder frequently accompanied by microvascular and macrovascular complications. Oxidative stress plays a pivotal role in the pathogenesis of these complications. Paraoxonase 1 (PON1), an antioxidant enzyme associated with HDL, is influenced by gene polymorphisms—especially Q192R and L55M—which affect enzymatic activity and vulnerability to oxidative damage. The objective is to evaluate the association between PON1 gene polymorphisms and the prevalence of diabetic complications (retinopathy, nephropathy, cardiovascular disease) in T2DM patients in a central Indian cohort. **Materials and Methods:** A cross-sectional study was conducted among 192 T2DM patients. Genotyping for Q192R and L55M polymorphisms was performed using PCR-RFLP. Diabetic complications were documented based on clinical and diagnostic criteria. PON1 enzyme activity was assessed spectrophotometrically. Statistical analysis was conducted using SPSS v26. **Result:** Patients carrying the RR genotype of Q192R and the MM genotype of L55M showed significantly higher prevalence of nephropathy ($p = 0.01$), retinopathy ($p = 0.03$), and cardiovascular events ($p = 0.02$). Lower PON1 activity levels were independently associated with higher rates of complications. Logistic regression confirmed the predictive value of these polymorphisms and enzyme activity in identifying high-risk patients. **Conclusion:** PON1 polymorphisms Q192R and L55M are significantly associated with increased risk of diabetic complications in T2DM patients. Assessing these genetic markers, along with enzyme activity, may enhance risk stratification and guide personalized interventions in clinical practice.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a progressive disease characterized by chronic hyperglycemia, insulin resistance, and β-cell dysfunction. Over time, sustained metabolic disturbances lead to serious complications such as diabetic nephropathy, retinopathy, and cardiovascular diseases, which significantly impact morbidity, quality of life, and healthcare costs.

Among the key drivers of these complications is oxidative stress—a biochemical imbalance between reactive oxygen species (ROS) and antioxidant defenses. One of the critical enzymes involved in combating oxidative stress is Paraoxonase 1 (PON1), which is bound to high-density lipoprotein (HDL) and hydrolyzes lipid peroxides in oxidized LDL. Genetic polymorphisms in the PON1 gene, especially Q192R (rs662) and L55M (rs854560), are known to alter enzymatic activity, affecting individual susceptibility to oxidative damage.

Patients with low PON1 activity, often associated with RR and MM genotypes, may be at higher risk for vascular and microvascular injury. In the Indian population, where genetic background, dietary habits, and disease burden present unique challenges, limited data exist regarding the association between PON1 polymorphisms and diabetic complications.

This study aims to assess the relationship between Q192R and L55M polymorphisms and the prevalence of common diabetic complications in T2DM patients. Understanding these genetic influences can support the development of personalized diagnostic and therapeutic strategies.

MATERIALS AND METHODS

Study Design and Population: A cross-sectional observational study was conducted from 2022 to 2025 at a tertiary care hospital in central India. A total of 192 patients with confirmed T2DM were included.

Inclusion/Exclusion Criteria

- Inclusion: Age 30–65 years, diagnosed with T2DM per ADA guidelines.
- Exclusion: Patients with type 1 diabetes, chronic infections, malignancy, or on antioxidant therapy.

Clinical Assessment of Complications

- Nephropathy: Assessed using urinary albumin-to-creatinine ratio and serum creatinine.
- Retinopathy: Diagnosed via fundoscopic examination by an ophthalmologist.
- Cardiovascular disease: Documented history of coronary artery disease, ECG changes, or relevant diagnostic imaging.

Genotyping and Enzymatic Assays: Genomic DNA was extracted from peripheral blood. Q192R and L55M polymorphisms were identified using PCR-RFLP. PON1 activity was measured by spectrophotometry using paraoxon and phenyl acetate substrates.

Statistical Analysis: Chi-square test was used for genotype-complication associations. Logistic regression assessed the independent predictive value of genotypes and enzyme activity. $p < 0.05$ was considered statistically significant.

RESULTS

Genotype Distribution and Complication Prevalence: Patients with RR and MM genotypes had a significantly higher prevalence of complications:

Table 1: Distribution of PON1 Genotypes and Diabetic Complications

Genotype	Nephropathy (%)	Retinopathy (%)	CVD (%)
QQ/LL	18.2	12.1	9.0
QR/LM	27.6	21.3	15.5
RR/MM	43.7	36.2	31.0

Enzyme Activity and Complications: Lower PON1 activity was significantly associated with increased rates of complications.

Table 2: Mean PON1 Activity in Patients With and Without Complications

Complication Status	Paraoxonase Activity (U/mL)	Arylesterase Activity (U/mL)
No Complications	148.6 ± 19.2	112.3 ± 18.5
≥1 Complication	96.4 ± 17.7	78.1 ± 15.2
p-value	<0.001	<0.001

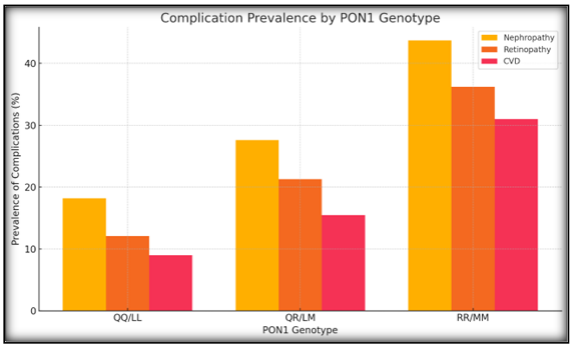

Figure 1: Complication Prevalence by PON1 Genotype – showing increasing prevalence of nephropathy, retinopathy, and cardiovascular disease (CVD) across genotypes from QQ/LL to RR/MM.

Correlation between Enzyme Activity and Number of Complications: A significant inverse correlation was observed between number of complications and PON1 activity.

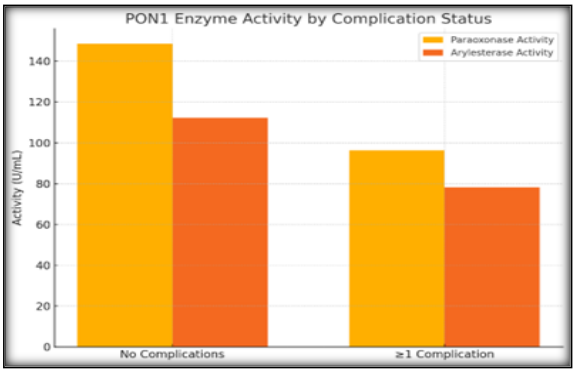

Figure 2: PON1 Enzyme Activity by Complication Status – showing significantly reduced paraoxonase and arylesterase activity in patients with ≥1 complication.

Table 3: Correlation between Number of Complications and PON1 Activity

Number of Complications	Mean Paraoxonase Activity (U/mL)	Mean Arylesterase Activity (U/mL)
0	149.1 ± 18.7	113.0 ± 17.9
1	112.8 ± 16.3	89.4 ± 14.5
≥2	87.5 ± 15.9	69.6 ± 13.8
p for trend	<0.001	<0.001

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Table 4: Logistic Regression for Risk of Any Diabetic Complication

Variable	Adjusted OR	95% CI	p-value
RR Genotype	2.84	1.56–5.18	0.001
MM Genotype	2.42	1.32–4.45	0.004
Low PON1 Activity	3.76	2.11–6.69	<0.001

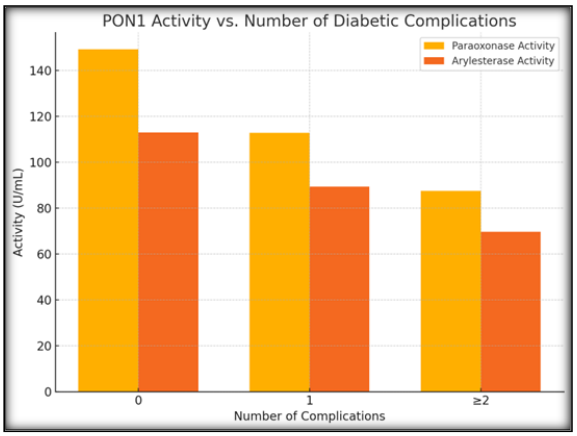

Figure 3: Correlation between Number of Complications and PON1 Activity

Logistic Regression Analysis: Multivariate logistic regression was used to assess the predictive value of genotypes and enzyme activity.

DISCUSSION

Our study confirms a significant association between PON1 gene polymorphisms—particularly the RR genotype of Q192R and MM genotype of L55M—and an increased prevalence of diabetic complications in T2DM patients. These findings are consistent with prior studies, such as those by Tsimihodimos et al. (2012) and Zaki et al. (2011), which showed that, reduced PON1 activity due to these polymorphisms contributes to heightened oxidative stress and vascular dysfunction.[1,2]

The inverse relationship observed between PON1 activity and the number of complications aligns with research by Deakin et al (2013),[3] who demonstrated that reduced paraoxonase and arylesterase activities are associated with the development of nephropathy and atherosclerotic burden in diabetes. Similarly, El-Said et al,[4] (2015) showed that diabetic patients with nephropathy had significantly lower PON1 activity than those without complications.

Importantly, our results suggest that the RR and MM genotypes are independent predictors of complications, as confirmed by logistic regression analysis. These findings are in agreement with Costa et al (2013),[5] who emphasized that individuals with such genotypes are more susceptible to LDL oxidation and subsequent atherosclerosis, especially in the presence of poor glycemic control.

Furthermore, the significant decrease in PON1 activity among patients with multiple complications [Table 3] supports the oxidative stress hypothesis in diabetes pathogenesis. This trend mirrors the conclusions of Ceriello (2005) and Jialal and Devaraj (2005),[6,7] who proposed that oxidative stress acts as a mediator linking hyperglycemia to endothelial injury and inflammation.

The high prevalence of RR and MM genotypes in our central Indian cohort also suggests possible ethnic or regional influences. Elatar et al. (2012) previously observed regional variability in PON1 polymorphism distribution, and our findings underscore the need for population-specific genetic studies in India.[8]

Compared to global literature, our findings reinforce the broader pattern that genetic and enzymatic impairments in PON1 play a central role in diabetic complications. However, the inclusion of both HbA1c and glycated albumin (in the parent study) allows us to capture both long-term and short-term glycemic fluctuations, potentially providing a more nuanced risk prediction model.

This study has limitations, including its cross-sectional design, which limits causal inference. Moreover, other oxidative and inflammatory markers were not assessed. Future longitudinal studies should include these markers and explore the efficacy of antioxidant interventions tailored to genotype.

CONCLUSION

This study demonstrates that PON1 polymorphisms Q192R and L55M, particularly the RR and MM genotypes, are significantly associated with increased risk of diabetic complications in T2DM. Lower PON1 enzyme activity further amplifies this risk. Genetic and enzymatic profiling may enhance clinical decision-making by enabling earlier identification of vulnerable individuals.

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