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# A Brief Review: PON1 Activity in Type 2 Diabetes Complications

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## Abstract

*This review investigates the relationship between Human Serum Paraoxonase 1 (PON1) activity and complications in Type 2 Diabetes Mellitus (T2DM). Recognizing the critical role of PON1 as an antioxidant enzyme associated with HDL. A comprehensive literature review spanning from 2013 to 2023 was conducted, utilizing PubMed, Scopus, and Web of Science databases. The search strategy incorporated relevant keywords and medical subject headings (MeSH) related to "Paraoxonase 1," "Type 2 Diabetes Mellitus," and associated complications. To enhance search precision, Boolean operators were used.*

*Compromised PON-1 activity was consistently identified in T2DM, showing correlations with dysregulated lipid markers, cardiovascular complications, atherosclerosis, diabetic nephropathy, and diabetic retinopathy. Gender-specific variations in PON-1 activity, particularly pronounced in women, were also observed. There is a bidirectional relationship between diabetes and PON-1 and it can be used both as a diagnostic and prognostic marker, assessing risk and complications in T2DM. Further research is necessary to validate these findings and pave the way for targeted therapeutic interventions, encompassing diverse populations.*

*Index Terms* - PON-1(Paraoxonase-1), Metabolic disorder, Type-2 Diabetes Mellitus (T2DM), Diabetes Complications, Risk assessment, Predictive Marker

## 1. INTRODUCTION:

Type 2 diabetes, the most prevalent form of diabetes, arises when blood glucose levels are excessively high due to insufficient insulin production or ineffective insulin utilization. Risk factors include age, family history, being overweight or obese, and belonging to certain ethnic groups like Asian pacific islanders. Physical inactivity, high blood pressure, prediabetes, and gestational diabetes also increase susceptibility to type 2 diabetes (CDC and National Institutes of Diabetes and Digestive and Kidney Diseases).

In this sedentary metabolic disorder, elevated blood glucose leads to microvascular and macrovascular complications. Diabetic nephropathy, retinopathy, neuropathy, macroangiopathy, and cardiovascular disorders are common complications of untreated diabetes (Farmaki.,2020). When blood sugar levels remain high for an extended period, it can cause oxidative stress in the body, this stress is attributed to Reactive Oxygen Species (ROS) which can damage essential cellular components such as proteins, lipids, and DNA. Concurrently, hyperglycemia-induced mitochondrial dysfunction and specific pathway activation contribute to heightened ROS production (Khalid et al.,2022; Volpe et al.,2018; Giacco et al.,2010). To counteract the damage caused by ROS, our body has free radical scavenging systems, like PON1 (Erdem et al.,2010).

Human serum paraoxonase 1 (PON1) is an esterase enzyme that is physically associated with high-density lipoproteins (HDL). It plays a crucial role in the protective function of HDL, safeguarding lipoproteins and biological membranes from oxidative damage. The enzyme's potential protective effect against atherosclerosis stems from its ability to hydrolyze lipid peroxides, thereby preventing the accumulation of phospholipids in oxidized low-density lipoprotein (LDL) (Primo-Parmo

et al.,1996; van et al.,2006). PON1's ability to hydrolyze different substrates contributes to its diverse biological functions, particularly its role in protecting against oxidative stress by preventing the accumulation of oxidized lipids. Various substrates known to be hydrolyzed by PON1 include Phosphotriesters, Esters, and Lactones (Khersonsky et al.,2005).

PON1enzyme was first identified for its capability to hydrolyze and thereby neutralize organophosphorus compounds extensively employed in pesticides and nerve gases like sarin, soman, and VX. Still, PON1 is a subject of research due to its crucial role in safeguarding humans from both the acute and chronic adverse impacts of these compounds (Costa et al.,2013; Costa et al.,2003; Chistiakov et al.,2017; Costa et al.,2020). Monitoring trends in cardiovascular complications through PON1 holds critical importance in the management of patients with T2DM. In the context of diabetes, serum PON1 activity experiences a decrease even before the onset of clinical cardiovascular disease (CVD), as evidenced in animal models of diabetes (Durrington et al.,2011; MACKNESS et al.,200). Even though studies have been undertaken and are currently ongoing in this arena, more focused research on the multifaceted influence of PON1 in diabetes and its acute and chronic complications needs to be addressed. Cases of genetic polymorphism in the PON1 gene have been reported in some studies, and their influence on the disease pathogenesis, prognosis, and development of complications need to be explored through extensive research in this area.

This comprehensive review focused on exploring the nuanced relationship between PON1 enzyme activity and the multifaceted landscape of complications associated with Type 2 Diabetes. Studies have revealed a bidirectional relationship between PON1 enzyme activity and diabetes and this review will focus exclusively on examining published studies that illuminate the nuanced connection between PON1 enzyme activity and diabetes, particularly its diverse complications. A concerted effort has been made to explore the predictive value of PON1 as a potential marker for complications in individuals with diabetes.

A detailed literature search was conducted to identify relevant articles from the past decade, utilizing reputable databases such as PubMed, Scopus, and Web of Science. The search criteria included keywords; "PON1," "type 2 diabetes," and "complications," ensuring a comprehensive retrieval of recent and significant studies. The selected articles underwent meticulous review, focusing on their methodology, key findings, and contributions to understanding the complex interplay between PON1, diabetes, and associated complications.

## 2. Materials and Methods

This review employed a systematic search strategy to identify pertinent studies from reputable scholarly databases, including Google Scholar, PubMed, Scopus, and Web of Science. The search encompassed the period from 2013 to 2023, with a primary focus on exploring the intricate role of PON1 in T2DM, specifically emphasizing case studies, case-control studies, and cohort studies. The search strategy incorporated relevant keywords and medical subject headings (MeSH) related to "Paraoxonase 1," "Type 2 Diabetes Mellitus," and associated complications. To enhance search precision, Boolean operators such as "AND" and "OR" were judiciously employed, allowing for the refinement and expansion of search terms. This systematic approach ensured a comprehensive retrieval of pertinent articles, thereby bolstering the thoroughness and inclusiveness of the review's findings.

## 3. PON-1 with Type-2 Diabetes Mellitus

### 3.1. Atherosclerosis-related diseases in T2DM and role of PON-1:

PON1 is an enzyme associated with HDL and plays a crucial role in the protective function of HDL against atherosclerosis. In individuals with type 2 diabetes, the impact of hyperglycemia-induced oxidative stress is notable, significantly influencing the qualitative functions of HDL. This underscores the potential relationship between diabetes, oxidative stress, and the qualitative attributes of HDL, emphasizing the need to explore and understand these interactions for potential therapeutic interventions (Dhanunjaya et al.,2015), according to a study conducted in the caucasian population aimed to explore relationships between high-density lipoprotein cholesterol (HDL-c) and lipid-related oxidative stress markers (paraoxonase-1) in the context of hyperglycemia and oxidative stress in T2DM. The analysis included 67 T2DM patients and 40 healthy subjects, and the results of the study showed elevated levels of triglycerides, LPO, non-HDL/HDL, and ApoB/ApoA1, along with decreased levels of HDL-c, ApoA1, and PON1 in T2DM subjects compared to controls. According to this study, there was a lack of relationship among PON1, HDL-c, and ApoA1 in T2DM patients, whereas, in control groups, PON1 activity positively correlated with these parameters. Strong correlations between non-HDL-c and ApoB, as well as LPO and TG, were observed in both study groups. These findings suggest that compromised anti-oxidant and anti-atherogenic HDL properties, associated with weakened PON1 function and lipid peroxidation, may contribute to the development of atherosclerosis-related diseases in T2DM (Viktorinova et al.,2018).

### 3.2. Cardiovascular complications in T2DM and the role of PON-1

Research suggests that analyzing the genotypic and phenotypic activity of PON-1 can be a reliable marker for assessing cardiovascular complications in diabetic patients (Shokri et al.,2020). A case-control study conducted in North Indian patients aimed to assess serum PON-1 activity and its correlation with the duration of T2DM. The study included 80 participants, encompassing individuals with T2DM and healthy controls. PON-1 concentration was measured using ELISA and western blotting, and its activity was determined spectrophotometrically. The diagnostic accuracy of serum PON-1 in

identifying T2DM was evaluated through ROC (Receiver Operating Characteristic) analysis. Results revealed significantly elevated levels of LDL, VLDL, TG, A1C, FBS, and TC in patients with T2DM compared to healthy controls. Serum PON-1 concentration and activity demonstrated a decreasing trend with the duration of diabetes, with higher levels observed in patients with shorter diabetes durations (<1 year) compared to those with longer durations (>7 years). Notably, PON-1 levels were further reduced in individuals with habits such as smoking and alcohol consumption. The study suggests that serum PON-1 levels decrease in conditions characterized by high oxidative stress, including metabolic syndrome, obesity, uncontrolled diabetes, and dyslipidemia (Wamique et al.,2018). The incidence of diabetes is comparatively higher among the Indian population (Gupta et al.,2023). To mitigate complications and predict adverse events, risk assessment is a crucial step and the findings of the study show the predictive value of PON-1 as a risk marker.

A study conducted to investigate the influence of PON-1 and lipid abnormalities in the development of cardiovascular complications revealed that decreased salt-stimulated activity of PON-1-salt in individuals with T2DM is negatively correlated with atherogenic indices such as total cholesterol (TC)/HDL-C, LDL-C/HDL-C, and the atherogenic index of plasma (AIP). Genetic variants PON-1-L55M and PON-1-Q192R significantly influence these associations. AIP, in particular, demonstrates a more substantial negative impact on PON-1-salt, indicating its potential as an independent risk factor for atherosclerosis in T2DM. Understanding these relationships could aid in identifying increased cardiovascular risk, emphasizing the importance of assessing both PON-1 salt status and atherogenic indices in individuals with T2DM (Qujeq et al.,2018). According to published research, PON-1 has predictive value in coronary artery disease (CAD). In an investigation of the association between apolipoprotein A (apoA)-I glycation, PON-1 activities, and the severity of CAD in patients with T2DM, the findings revealed that diabetic patients with significant CAD exhibited higher apoA-I glycation intensity and lower activities of high-density lipoprotein (HDL)-associated PON1 and PON3 compared to those without CAD. The study suggested that elevated apoA-I glycation and reduced HDL are associated with the presence and severity of CAD in individuals with T2DM (Dhanunjaya et al.,2015).

Lipid profiling is a technique used to evaluate changes in lipid metabolism which is common in diabetes. Two key markers, HDL and LDL are used to gain insight into the health of lipid metabolism in the body (He et al.,2018). HDL-c (High-Density Lipoprotein-c) has anti-atherogenic, antioxidant, anti-inflammatory, and anti-thrombotic properties, which could be influenced by enzymes and proteins associated with it, such as cholesteryl ester transfer protein (CETP) and PON-1. The CETP gene regulates the exchange of lipids between circulation and tissues, promoting the transfer of cholesterol esters between lipoprotein particles. Changes in CETP synthesis, structure, and function can alter susceptibility to CVDs. In T2DM, altered CETP activity could increase the risk of CVDs by reducing HDL-c content, increasing small dense LDL particles, and subsequent cardiovascular complications. In a study aimed to explore the relationship between the TaqIB polymorphism in CETP, lipoprotein profile, oxidant/anti-oxidant status, and PON-1 activity in individuals with T2DM. The results indicated that diabetes is associated with heightened oxidative stress, as evidenced by increased thiobarbituric acid-reactive substances (TBARS) and catalase activity. As in the previous studies, PON-1 activity was notably lower in diabetic individuals (Siewert et al.,2015). In support of the findings of this study, an observational case-control study conducted by Patra et al.,2013, also stated that PON-1 may be a better predictor than HDL for atherosclerotic risk in T2DM patients. The study involved 30 patients diagnosed with T2DM and 30 age and sex-matched controls. PON-1 levels were measured by ELISA and the results showed that both HDL and PON-1 were negatively correlated with various atherogenic indices, but the strength of the negative correlation was always greater for PON-1. In multiple linear regression analysis, the regression coefficient (β) was always higher for PON-1 than for HDL when taking the atherogenic indices as an outcome variable. More studies concur with these findings, like a similar study conducted by Dullaart et al.,2014; showed that PON-1 activity, HDL cholesterol, and apoA-I were decreased in T2DM patients, while HDL particle concentration remained unaltered. PON-1 was more closely related to HDL cholesterol than to apoA-I and the positive relationship of PON-1 with HDL particle concentration and with large HDL particles was stronger than that with HDL cholesterol. According to the study, the inverse relationship of PON-1 with T2DM was only modestly attenuated by HDL cholesterol or HDL particle characteristics.

According to a case-control study conducted on Egyptian patients, to assess the serum PON-1 levels in patients with T2DM, both with and without hypertension, to identify PON-1 as a potential predictor marker for atherogenesis. The study included 90 participants, and results indicated elevated levels of blood glucose, serum cholesterol, serum triglycerides, serum LDL, and serum Hs CRP, along with decreased serum PON-1 and serum HDL in the diabetic group compared to healthy individuals. Correlation analyses revealed a positive association between reduced serum PON-1 and decreased serum HDL, while negative correlations were observed with increased serum glucose, cholesterol, triglycerides, LDL, and Hs CRP (Elbawab et al.,2020). The potential role of PON-1 in modulating antioxidant functions associated with HDL may contribute to preventing cardiovascular complications in individuals with T2DM (Namitha et al.,2015). The activity of PON-1 has been observed to decrease not only in T2DM but also in other diseases like Alzheimer's and obesity. Both clinical evidence and molecular mechanisms indicate a strong association between PON-1 and T2DM (Öztaş et al.,2022).

### 3.3. PON 1 and Diabetic Nephropathy:

Diabetic nephropathy is a major complication in chronic diabetic patients, and in untreated cases, leads to end-stage kidney failure and even death (Min et al.,2012). A prospective study aimed to investigate the relationship between serum PON-1 activity, and the risk of incident T2DM, conducted within the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, involving 5947 predominantly Caucasian participants without pre-existing diabetes, the analysis revealed a positive correlation between serum PON-1 and HDL cholesterol. However, after adjusting for conventional diabetes risk factors and potential confounders, the study found no significant association between PON-1 activity and incident T2DM. In contrast, serum HDL cholesterol concentration was independently and inversely associated with the risk of T2DM in the same cohort, questioning the importance of PON-1 activity in diabetes development (Kunutsor et al.,2017). A similar study aimed to assess PON-1 activity in patients with T2DM, both with and without diabetic nephropathy, and explore its correlation with lipid profiles, disease duration, and glycemic status. The study included 30 participants with T2DM, comprising 20 with diabetic nephropathy, 10 without nephropathy, and 15 healthy age-matched controls. The results show that PON-1 activity was significantly reduced in both diabetic groups, with and without nephropathy. In diabetic patients with nephropathy, PON-1 activity correlated negatively with HDL ($r = -0.496$, $P = 0.026$). These findings point to the potential link between reduced PON-1 activity and the presence of diabetic nephropathy in individuals with T2DM.

### 3.4. PON-1 and Diabetic retinopathy:

Diabetic retinopathy is another major chronic complication that needs to be addressed. A study conducted by Budak et al.,2013, aimed to assess PON-1 activity, lipid profile, and high-sensitivity C-reactive protein (hs-CRP) in T2DM with and without retinopathy, sharing a common 10-year disease duration. A total of 54 subjects with type 2 diabetes, including those with proliferative diabetic retinopathy (PDR) and without retinopathy (nonDR), were included in the study along with a control group of 24 healthy subjects. This study revealed that the group with proliferative diabetic retinopathy (PDR) had lower paraoxonase activity and higher hs-CRP levels compared to the healthy control group. Specifically, paraoxonase activity in the DM + PDR group was positively associated with HDL cholesterol and negatively associated with serum glucose, total cholesterol, and LDL cholesterol levels in patients with diabetes. In recent years, there has been an increase in the number of published studies focusing on vascular complications in diabetes. A study published in the "International Journal of Diabetes in Developing Countries" involved 80 T2DM patients, categorized as those without complications (n=40) and those with vascular complications (n=40), and compared them with 40 healthy age- and sex-matched controls. Results indicated that PON-1 arylesterase (ARE) and lactonase (LACT) activities were significantly decreased in T2DM patients with complications compared to those without complications. Both were also significantly lower in DM patients (with or without complications) compared to the control group. Logistic regression analysis was employed to assess the predictive utility for diabetic complications, revealing a significant contribution of PON1 lactonase and arylesterase activities. The study concludes that decreased PON-1 lactonase and arylesterase activities may be considered additional risk factors for the development of vascular complications in T2DM (Mogarekar et al.,2016).

### 3.5. PON1 Polymorphisms in T2DM :

Recent advancements in genomics have shown that genetic polymorphisms in the PON-1 gene also play a crucial role in the development of complications. A case-control study aimed to explore the association between single-nucleotide polymorphisms (SNPs) in PON-1 and some related genes with T2DM susceptibility included 250 patients and 250 healthy controls. The study identified a significant association of C and R alleles with T2DM susceptibility, indicating odds ratios of 1.42 ($p < 0.005$) and 1.40 ($p < 0.007$), respectively. The CC and RR genotypes were found to be more prevalent in T2DM patients, and these genotypes were associated with higher levels of LDL and low HDL. The study suggests that PON-1 gene polymorphisms could serve as potential biomarkers for T2DM susceptibility (Wamique et al.,2015). Similarly, another case-control study on the Iranian population investigated the association between three PON-1 polymorphisms (Q192R, L55M, and −108C>T) and T2DM. The analysis involved 340 individuals, including 171 documented T2DM patients and 169 healthy controls. Genotyping for L55M and Q192R polymorphisms in the coding region and −108C>T in the promoter sequence of PON-1 was conducted. Statistical analysis revealed no significant association between Q192R and −108C>T polymorphisms with diabetes. However, the allelic frequency of methionine (M) in the PON1 55 gene polymorphism was significantly higher in T2DM patients than in controls (37% vs. 28%, $P < 0.05$). Moreover, a strong association was found between the LM+MM group and diabetes ($P = 0.006$). Haplotype analysis indicated a significantly lower frequency of the L-T-R haplotype in patients compared to controls, suggesting a protective effect. The study suggests that the Met allele of the PON-1 55 gene polymorphism is an independent risk factor for T2DM, and the L-T-R haplotype may confer protection in the south Iranian population. The observed frequency differences in PON-1 polymorphisms highlight the ethnic variability and contribute valuable data for further epidemiological studies.

### 3.6. Other Diabetic Complications and PON-1

The complications of diabetes are diverse and cannot be viewed through a narrow lens. A simple infection in a diabetic can have unpredictable long-term consequences for the patient. Periodontitis; an infection of soft tissue around the teeth is common nowadays (Lakschevitz et al.,2011). The researchers at the Dresden University of Technology investigated the possible correlation between decreased PON-1 activity and the association between impaired glucose metabolism or diabetes mellitus and periodontitis. They found that patients with T2DM had an increased risk of generalized periodontitis and reduced PON-1 activity compared to controls. However, patients with pre-diabetes showed neither an increased periodontitis risk nor impaired paraoxonase status and PON-1 was not associated directly with periodontitis, but poor oral

hygiene, male sex, and PON-1 phenotype were found to be significant predictors for periodontitis extent. The study concluded that T2DM, but not a prediabetic state, increases the risk of generalized periodontitis. PON-1 status in patients with T2DM may contribute to this association (Noack et al.,2013).

Similarly, a case-control study at Mississippi State University assessed serum PON-1 activity and concentration over a 20-year period. The study found no difference with age in PON-1 activity assessed using three substrates, paraoxon, phenyl acetate, and dihydrocoumarin, or PON-1 serum concentration. C-reactive protein concentration increased 0.7 mg/L over the 20-year interval. Lower PON-1 activity assayed with phenyl acetate was associated with an increased risk of developing T2DM as was a lower PON-1 serum concentration. PON-1 activity assayed with paraoxon or dihydrocoumarin was not associated with the development of T2DM. The study concluded that lower PON-1 activity and concentration were associated with an increased risk of developing T2DM when adjusted for many of the common risk markers for T2DM previously identified (Crow et al.,2018).

Several other studies also concur with the predictive value of PON-1 as an indicator of complications in diabetes. Another cross-sectional study conducted to compare serum PON-1 activity between individuals with T2DM and non-diabetic controls and assess the association between PON-1 activity and various insulin resistance (IR) models in diabetics revealed significantly higher PON-1 activity in diabetics compared to controls, accompanied by notable hyperinsulinemia and lower C-peptide levels in diabetic cases. Insulin resistance models, including HOMA B cell, HOMA 1% B cell, and C-peptide–based IR (CIR), were significantly lower in diabetic cases. Receiver operating characteristic analysis suggested PON-1 as a potential marker for diabetes, and the odds ratio indicated a threefold higher risk of T2DM in subjects with elevated PON-1 levels. Significant negative correlations were observed between PON-1 activity and quantitative insulin sensitivity check index as well as CIR (HOMA-IR C). The study concluded that elevated PON-1 activity could serve as a beneficial marker for T2DM (Bansal et al.,2013).

### 3.7. Gender Basis:

Investigating the correlation between gender and the differential functionality of physiological systems is imperative for a comprehensive understanding of sex-specific variations in biological processes. A study by the University of Ferrara in Italy found that the onset and progression of T2DM are linked to sex. The study assessed the activity of PON-1 enzyme bound to HDL, in 778 patients, including controls and diabetics. The results showed that PON-1 activity decreased in both women and men with T2DM compared to controls, but the change was 50% larger in the female cohort. The enzyme activity was associated with serum glucose levels only in women, and lower PON-1 activity was independently associated with increased odds of being diabetic. The study suggests that PON-1 deficiency in T2DM is a gender-specific phenomenon, with women being more affected than men (Rosta et al.,2020). With concurring results a study by Trentini et al.,(2019) indicates a significant influence of sex on serum PON-1 activities and their relationship with cardiovascular disease risk factors. Arylesterase and lactonase activities of PON-1 were found to be significantly higher in women compared to men, regardless of confounding factors such as high-density lipoprotein-cholesterol, age, smoking, and body mass index or waist circumference. The interplay between PON-1 and fat measures was also strongly influenced by sex, with arylesterase showing a significant and independent inverse correlation with overall obesity in women, but not in men. Interestingly, this association between arylesterase and BMI in women was particularly significant among those younger than forty-five years. However, neither of the PON-1 activities remained associated with waist circumference in men or women after full adjustment. These preliminary findings suggest that sex may play a crucial role in influencing PON-1 activity and its potential contribution to other risks.

Indeed, further research involving larger populations and diverse ethnic groups is essential to validate and provide more clarity on the observed findings. The current studies, while preliminary, contribute valuable insights into our understanding of PON-1 enzyme activities and their association with diabetes mellitus. These findings underscore the importance of considering sex-specific differences, PON-1-polymorphism, and other potential confounding factors in the assessment of PON-1 activity and its implications for risk assessment in diabetes. As the field advances, ongoing investigations will help refine our understanding and potentially lead to more targeted interventions and therapeutic strategies.

## 4. Results and Discussion:

This comprehensive review explores the multifaceted role of PON-1 in T2DM across various complications and aspects. From multiple studies and a detailed search across databases, this review reveals significant insights into the relationship between PON-1 and lipid markers, cardiovascular complications, atherosclerosis, PON-1 polymorphism, diabetic nephropathy, diabetic retinopathy, and other complications. The reviewed studies collectively confirm that, in individuals with T2DM, PON-1 experiences compromised anti-oxidant properties of HDL, and PON-1 activity shows a lack of correlation with HDL-c and ApoA1, emphasizing weakened PON-1 function and lipid peroxidation as potential contributors to atherosclerosis-related diseases in T2DM. Decreased PON-1 activity was not only associated with T2DM but also with other diseases and conditions including Alzheimer's and obesity. There is a decreasing trend in PON-1 levels with the duration of diabetes with elevated apoA-I glycation and reduced HDL-associated PON-1 with the severity of CAD in T2DM. Moreover, this negative correlation between PON-1-salt and atherogenic indices indicates its role as an independent risk factor for atherosclerosis in T2DM. This reduced PON-1 activity is linked to the development of diabetic nephropathy, retinopathy, and other vascular complications. Therefore these studies propose PON-1 as a reliable marker for assessing complications in diabetic patients. In an attempt to associate between gender and PON-1 activity, it was found that PON-1

deficiency in T2DM is a gender-specific phenomenon, more pronounced in women with higher arylesterase and lactonase activities in women, highlighting sex-specific variations in PON-1 activity.

Future research endeavors should prioritize investigating PON-1 activities in diverse ethnicities and populations to validate and extend the current understanding. Studies are imperative to establish the potential of PON-1 as a reliable marker in both the diagnosis and management of diabetes. So as, advanced research is needed to delve into the phenotypic and genotypic diversities of the PON-1 gene, elucidating how genetic mechanisms contribute to the complications associated with T2DM. In the future, the integration of PON-1 as a routine marker in the diagnosis and management of diabetes appears to be promising. Continued research efforts in this arena will offer deeper insights, paving the way for a more nuanced understanding of PON-1's role and potential clinical applications in the context of diabetes and its complications.

## Conclusion:

This review highlights the potential role of Paraoxonase-1 in type 2 diabetes mellitus (T2DM). Examining studies from 2013 to 2023 across major databases, the review reveals that in T2DM, compromised anti-oxidant properties of HDL associated with PON-1 contribute to atherosclerosis-related diseases. PON-1 emerges as a potential marker for assessing complications in diabetic patients, showing its relationships with lipid markers, cardiovascular complications, and coronary artery disease severity. Noteworthy is the decreasing trend in PON-1 levels with diabetes duration and its gender-specific deficiency, particularly pronounced in women. This link between reduced PON-1 activity in T2DM underscores broader implications in diabetic complications.

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