Přehledový článek | Review article

Serum Paraoxonase-1 and Atherosclerotic Cardiovascular Disease

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SOUHRN

Díky svému umístění chrání hydrofobní lipidová doména paraoxonázy-1 (PON-1) lipoproteiny o vysoké hustotě (high-density lipoprotein, HDL), lipoproteiny o nízké hustotě (low-density lipoprotein, LDL) a buněčné membrány na vnější straně před oxidací. Nezastavuje se tím tvorba konjugovaných dienů, ale mění se tak produkty lipoperoxidace na neškodné karboxylové kyseliny místo aldehydů, které by se mohly navazovat na apolipoprotein B. Paraoxonáza-1 v séru negativně ovlivňuje nové příhody u diabetu a aterosklerotického kardiovaskulárního onemocnění (ASKVO). Diabetes, dyslipidemie a zánět snižují aktivitu PON-1. Ablace lidského genu pro PON-1 nebo nadměrná exprese tohoto genu u zvířat posiluje nebo tlumí vnímavost k rozvoji aterosklerózy. Na rozdíl od apolipoproteinu AII zvyšují sérová koncentrace amyloidu A a myeloperoxidáza, apolipoprotein AI a poměr lecitin : cholesterol acyl transferáza antioxidační účinek PON-1. Strava a již užívané léky měnící hodnoty lipidů mohou účinnost PON snížit, je však třeba provádět specifickou léčbu zvyšující hodnoty PON-1.

Keywords:
Atherosclerotic cardiovascular disease
High-density lipoprotein
Paraoxonase-1

ABSTRACT

Due to where paraoxonase-1 (PON-1)'s hydrophobic lipid domain is located, high-density lipoprotein (HDL) protects low-density lipoprotein (LDL) and the cell membranes on the outside from oxidation. It doesn't stop the formation of conjugated dienes, but it changes the products of lipid peroxidation into harmless carboxylic acids instead of aldehydes that could link to apolipoprotein B. Serum PON-1 inversely affects new events in diabetes and atherosclerotic cardiovascular disease (ASCVD). Diabetes, dyslipidemia, and inflammation decrease PON-1 activity. Human PON-1 gene ablation or overexpression in animals enhances or reduces atherosclerosis susceptibility. Unlike AII, serum amyloid A, and myeloperoxidase, apolipoprotein AI and lecithin : cholesterol acyl transferase boost PON-1 antioxidant activity. Diet and pre-existing lipid-modifying drugs may impact PON-1 activity, but specific PON-1-raising therapy is required.

Introduction

Aldridge discovered serum paraoxonase in 1953. Diethyl-para-nitrophenyl phosphate, an organophosphate, inhibits "B" esterases like acetylcholinesterase and butyrylcholinesterase; therefore, it was initially called "A" esterase. Diethyl-para-nitrophenyl phosphate, or paraoxon, is a potent neurotoxin generated by parathion metabolism. Hydrolyzing paraoxon needs "A" enzymes. Paraoxonase-1 (PON-1) protects organophosphate toxins like insecticides and military nerve weapons. Due to its importance in toxicology, PON was nearly solely on high-density lipoprotein (HDL) in the mid-1980s, according to Reading University toxicologist Mackness. Due to atherosclerotic cardiovascular disease (ASCVD)-related decreased HDL, myocardial infarction (MI) survivors reported lower serum activity.[1]

HDL-C inversely and independently affects atherosclerotic ASCVD. HDL stimulates cholesterol efflux from artery wall macrophages, is an antioxidant, anti-inflammatory, antithrombotic, and maintains endothelial cells. PON-1, an

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antioxidant liver-produced HDL-bound esterase enzyme, inhibits low-density lipoprotein (LDL) oxidation through lipperoxide hydrolysis. According to rodent and human research, PON-1 activation makes HDL anti-atherogenic and cardioprotective. Stable coronary artery disease, post-MI, hypercholesterolemia, the metabolic syndrome, and type 2 diabetes decrease blood PON-1 activity.[2–4]

A few general population studies revealed inverse associations. PON-1 activity's connection with CVD risk in general population settings is unclear.[5,6] PON-1 may be a better atherosclerotic CVD risk factor than HDL-C. So, long-term data from the general population are needed to look into the link between PON-1 activity at the start and future CVD. We aimed to conclude a review of baseline PON-1 activity and CVD risk.

PON-1 polymorphisms and gene family

PON-1, the primary serum paraoxonase, has two more family members whose genes cluster on chromosome.[7] Paraoxonase-3 (PON-3), another paraoxonase family member on HDL, is substantially less abundant than PON-1. It lacks organophosphatase and arylesterase. PON-1 and PON-3 are lactonases, whereas PON-3 prefers higher molecular mass lactones. Even before gene sequencing, paraoxonase 1 was observed to vary substrate activity.[8]

Unlike paraoxon, phenyl acetate hydrolyzes quicker. Nevertheless, half of Europid paraoxon PON-1 activity was low, 8–9% high, and the rest intermediate. Early 1990s sequencing of PON-1 revealed that this difference in activity was primarily due to the substitution of arginine (R) for glycine (Q) at position 192R, resulting in a low-activity 192Q isoenzyme and a high-activity 192R isoenzyme. 192R and Q alloenzymes' hydrolytic activity towards paraoxon varies by population.[1] Anti-atherosclerotic PON-1 hydrolyzes paraoxon less efficiently. At high concentrations, the 192R isoenzyme may protect more than the 192Q polymorphism.

Epidemiology: Mendelian randomization, serum PON-1 activity

PON-1 activity may predict atherosclerosis; however, prospective studies are required. Serum PON-1 independently predicted ASCVD, resulting in a risk variation equivalent to HDL cholesterol. The Caerphilly Heart Study of middle-aged men gave the first prospective data.[9] Kunutsor et al.[10] meta-analyzed these results and five more. There were 15,064 participants and 2,958 ASCVD cases. Three paraoxon-substrate experiments and three phenyl acetate-substrate experiments. The age-adjusted pooled ASCVD relative risk per 1 SD of increased PON-1 activity was 0.87, extremely significant.[11] Kunutsor et al.[10] say that PON-1 activity was not a part of a multivariate equation that could predict future cases of ASCVD. HDL cholesterol is favourably affected by regression dilution bias because serum PON-1 activity changes more than HDL cholesterol. PON-1 activity was decreased in early ASCVD patients with elevated HDL cholesterol, highlighting its biological relevance.[12]

PON-1 activity predicted future events in ASCVD patients who had coronary revascularization. Bhattacharyya et al.'s[13] work was very relevant. They evaluated 1,399 Cleveland Clinic coronary angiography patients. PON-1 aryl esterase and paraoxonase activity were significantly adversely linked with new ASCVD occurrences after a minimum 3-year followup. In 150 individuals matched for the PON-1 192 polymorphism (equal numbers with the QQ, QR, and RR), blood PON-1 activity was significantly related (p 0.001) with fatty acid oxidation products.

Due to its lactonase structure, PON-1 may predict lactone substrate activity.[14,15] PON-1 lactonase activity does not enhance ASCVD risk prediction in prospective epidemiology.[16] PON-1 lactonase activity and disease are growing concerns.[17] Homocysteine thiolactone, which binds to apoB like glucose and lipid peroxides, may increase the ASCVD risk of atherosclerosis.[18] Low serum PON-1 increases urine homocysteine thiolactone, particularly in PON-1-192R carriers.[14]

Bioplausibility and evolution

Polymorphisms of PON-1, which extend organophosphate neurotoxic resistance, enhance the lifespan of exposed populations without detoxifying mutations but at the cost of those with the less favourable form. Evolutionary extinction may precede mutation. Farm workers who dip sheep in diazinon (the active metabolite diazinoxon) with the 192Q PON-1 genotype and greater blood PON-1 (dazoxonase activity) are less likely to acquire neuropsychiatric symptoms.[19] PON-1 synthetic organophosphates created by cyanobacteria (blue-green algae) may create vast amounts of neurotoxic organophosphates, threatening early hominids on Africa's big lakes.[20] PON-1 presumably originated from PON-2, its intracellular twin.

Cholinesterases and acetylcholine responses predate metazoa and the neurological system. Organophosphate poisoning was inevitable. Anaerobic, deep-sea hydrothermal vent organophosphates were the first lifeforms. Organophosphate metabolism proteins may have become paraoxonases. DFPase (eukaryotic squid), organophosphate hydrolase, acid anhydrolase, phosphotriesterase (bacteria), and SsoPox (archea) are additional organophosphatases.[21] RePON-1 resembles squid DFPase. Six-bladed propellers feature four sheets. Both core tunnels contain two calcium ions.[22]

Oxidative respiratory chain phosphorylation metabolism was faster than glycolysis in oxygen-rich photosynthetic life. Oxygen toxicity needs protection. Paraoxonases are antioxidant enzymes.[23] Elias and Tawfik propose that paraoxonases developed as promiscuous esterase lactonases in an interesting study.[24] Despite structural variations, their active site resembles lactonases more than esterases. Single-celled organisms create lactones such as N-acylhomoserine lactones to modify gene expression for bioluminescence, biofilm growth, virulence factor expression, and motility at quorum sensing thresholds. Lactonases can sense quorums like hormones (ironically, acetylcholine and acetylcholinesterase). PON-1 metabolises atherogenic homocysteine thiolactone.[25]

HDL and PON-1 prevent lipid peroxide buildup

With the help of oxygen free radicals (myeloperoxidase, NADPH oxidase), tissue fluid or inflammatory cells can peroxidize polyunsaturated fatty acyl groups in polyunsaturated fatty acids. Linoleate is the most common polyunsaturated fatty acid (C18:2). Hydrogen abstraction causes lipid peroxidation. UV detects conjugated dienes. Between its double C-C bonds, linoleate has two single C-C bonds, with outer orbitals occupied by electrons from two hydrogens. As a double bond flips over, hydroxyl radicals (OH•, produced by O_2• with water) attach one hydrogen atom to its unpaired electrons, forming a conjugated diene (**Fig. 1**). A conjugated diene, which resonates with ultraviolet light, separates the new double bond from the next. Vitamin E, β-carotene, and ubiquinol-10 inhibit early lipid peroxidation by transferring electrons instead of linoleate. PON-1 doesn't alter this phase. HDL PON-1 reduces conjugated diene free radical-induced LDL lipid peroxides in late linoleate oxidation.[1]

Clinical trials of vitamin E failed, proving the LDL oxidation hypothesis of atherosclerosis false.[26] Conjugated diene production chemically alters LDL, permitting arterial wall macrophages and smooth muscle cell receptor-mediated absorption. Oxygen reacts with linoleate to form 9-hydroperoxy-10,12-octodecadienoic acid (9-HPODE), aldehydes (propandial, hexanal, nonanal), unsaturated aldehydes (hexenal, nonenal), and their hydroperoxy derivatives. These aldehydes degrade apoB into a ligand for macrophages and altered smooth muscle cell scavenger receptors like SCARB1. Oxidised polyunsaturated fatty acids resemble lactones.[27–29]

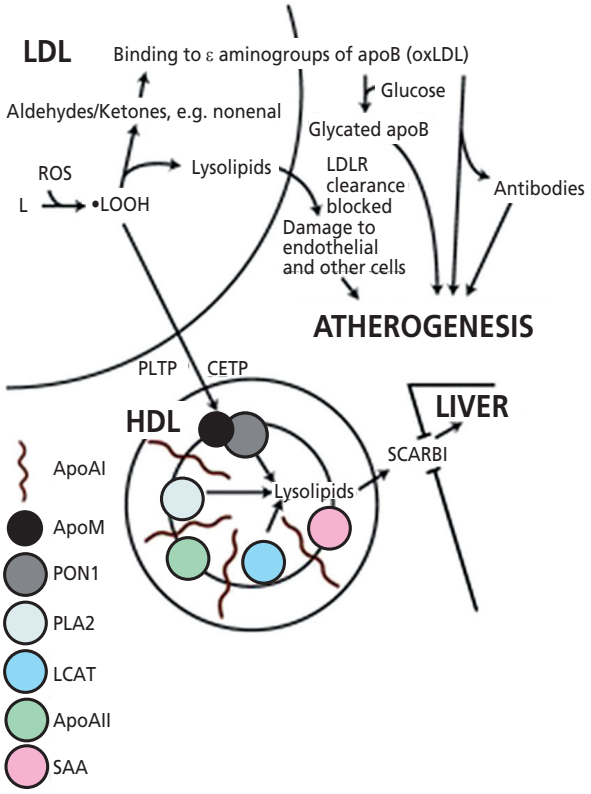

Fig. 1 – Biological role of paraoxonase-1.

PON-1 must contact LDL or cell membrane phosphatidyl choline and cholesteryl ester components to inhibit aldehyde adduction. HDL particles may contact cell membranes in tissue fluid.[30,31] HDL and apoB-containing lipoproteins exchange plenty of phospholipid and cholesterol, notably in humans when lecithin cholesterol acyltransferase (LCAT) esterifies HDL. Cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) aid this. By esterifying cholesterol, LCAT generates lysophosphatidyl choline. HDL shields lysophosphatidyl choline until it hits the hepatic sinusoids and is released to hepatocytes for re-esterification.[32,33]

Diabetes and metabolic syndrome

Diabetes types 1 and 2 are more likely to have problems with their large and small blood vessels when PON-1 activity is low.[34] Reduced PON-1 may cause type 2 diabetes. In vitro, high glucose glycation lowers PON-1 function. Metabolic syndrome (prediabetes) before hyperglycemia cannot explain low serum PON-1 activity. Diabetics exhibited 8% glycated serum apoB, non-diabetics 4%. FH elevates LDL and glycated apoB without diabetes. Glycated apoB outnumbers oxidatively modified apoB in diabetics and non-diabetics. Subfractions of LDL (SD-LDL) contained more glycated apoB than VLDL and LDL. SD--LDL may circulate longer or expose apoB to glucose. Ketones and lipid peroxidation glycate apoB-arginine and proline residues. Glycated and oxidised apoB produces macrophage foam cells.[35,36] In vitro, apoB in LDL is glycation-resistant. High glucose concentrations boost normal LDL, although not as much as in diabetes.[36] HDL from those with above-median blood PON-1 activity protects LDL apoB from glycation better in vitro.[37] HDL may protect against atheroma and diabetes through this mechanism, but further study is needed.

MI

MI may be caused in part by PON-1, according to research. Some studies have found a link between low PON-1 activity and a higher risk of heart disease and MI, while others have found no link. We don't fully understand how PON-1 may affect the risk of MI, but it is thought that the enzyme may help protect against oxidative stress and inflammation, which are both thought to contribute to the development of atherosclerosis. Even though more research is needed to fully understand the link between PON-1 and MI, measuring person's PON-1 activity levels may be a good way to figure out how likely they are to get heart disease and could be used to help plan preventative and treatment measures.[38]

Pulmonary embolism (PE)

There hasn't been a lot of research on the link between PON-1 and PE, but some studies suggest that low levels

of PON-1 activity may be linked to a higher risk of getting PE. Also, some studies have shown that the levels of PON-1 activity are lower in people with PE than in healthy people. We don't fully understand how PON-1 may affect the risk of PE, but it is thought that the enzyme may help protect against oxidative stress and inflammation, both of which are thought to lead to the formation of blood clots. Measuring PON-1 activity levels may be a useful tool for assessing an individual's risk of developing the condition and could potentially be used to guide preventative measures and treatment strategies.

Ischemic stroke

PON-1 is an enzyme that is mostly made by the liver. It is attached to high-density lipoprotein (HDL) particles and travels through the blood. PON-1 has been shown to have antioxidant and anti-inflammatory properties, and low levels of PON-1 have been associated with various health conditions, including ASCVD and stroke. Several studies have investigated the relationship between serum PON-1 levels and ischemic stroke. It has been suggested that low levels of PON-1 may increase the risk of ischemic stroke, while others have not found a significant association.[39]

Patients with type 2 diabetes who had lower serum PON-1 levels were more likely to have an ischemic stroke. Low levels of PON-1 were linked to a higher risk of recurrent ischemic stroke in people who had already had a stroke or trans-ischemic attack (TIA). But it's important to keep in mind that the link between serum PON-1 levels and ischemic stroke is complicated and may be affected by age, gender, lifestyle, and other health conditions. So, more research is needed to fully understand what role PON-1 plays in the start and spread of an ischemic stroke.[40]

Therapeutic and diagnostic possibilities

PON-1-related nutritional studies abound. Data may be inconsistent because of the varied substrates used to assess PON-1 activity, their small size, and their poor design. Obesity lowers PON-1 activity, particularly with lipids or diabetes.[41] HDL cholesterol and PON-1 activity vary. A Mediterranean diet and pomegranate juice may increase PON-1 activity.[42] Family dysbetalipoproteinaemia decreases PON-1 activity the most.[43] Statins, fibrates, ezetimibe, probucol, niacin, and metformin raise serum PON-1, whereas sulphonamides decrease it.[44]

Nevertheless, enzymes are simpler to stop than activate. CETP inhibition reduced LDL, not atherosclerosis. CETP may transfer oxidised phospholipid and cholesteryl ester to HDL for PON-1 to act on, however, HDL particles are too big for cholesterol efflux. PON-1-rich HDL infusion is unlikely because quickly generated repon-1 may lack antioxidant ability (see earlier). Oral HDL mimetics may increase HDL-like particle PON-1 activity. LDL and triglyceride antisense oligonucleotides affect PON-1 growth. Increasing its gene or creating a gain-of-function mutant lacking a polar tag for HDL absorption may also increase PON-1 activity.[45,46]

PON-1 may predict ASCVD. Its anti-atherosclerotic properties are unknown. Should long-chain fatty acid peroxide or lactone replace phenyl acetate or paraoxon as test substrates? PON-1's atherosclerosis prevention method requires determining its primary substrate(s); however, it may not be necessary for therapeutic application. Clinical biochemical tests sometimes use alkaline phosphatase; however, its physiological function is unknown, and its substrate is artificial. Diabetes changes PON-1 hydrolytic activity, which is more connected to ASCVD than protein concentration. PON-1 hydrolyzes phenyl acetate quicker than paraoxon. PON-1 affects paraoxon hydrolysis. If PON-1's physiological function includes lactonase activity, dihydrocoumarin or homocysteine thiolactone may be good test substrates. Some PON-1 activity assays confuse the issue by using plasma instead of serum and including B esterase and non-specific hydrolysis.[47]

Serum PON-1 activity indicates whether HDL is pro- or anti-inflammatory and atherosclerotic. Cholesterol efflux capability is more difficult and error-prone. As lower PON-1 activity is associated with higher serum amyloid A (SAA), the ratio of SAA to PON-1 activity is a better indication of HDL type than either test alone.[48]

Recent studies

Pentraxin 3 **(**PTX3) may prevent obese or severe psoriatic patients from developing cardiometabolic disorders. PON-1 may signal psoriasis-related liver issues.[49] All cells produce toxic, reactive homocysteine thiolactone (HCTL). PON-1 effectively hydrolyzes it extracellularly. In vitro, HCTL decreased paroxonase and aryl esterase activity, indicating it may affect this enzyme's protein structure. In vivo tests showed lower PON-1 activity in hyperhomocysteinemia patients.[50] PON-1 paraoxonase activity may predict non-ST-segment elevation myocardial infarction (NSTEMI) prognosis.[51] S-nitrosylation of repon-1 boosts biological activity and may delay atherosclerosis.[52] PON1 prevents LDL oxidation and atherosclerosis, whereas TiO_2 nanoparticles (NP) may reduce these advantages.[53]

Thymus atlanticus decreased high-fat diet (HFD)-induced hyperlipidemia, insulin resistance, and PON-1 activity. Thymus atlanticus biomolecules may treat HFD-related metabolic problems. Thymus atlanticus supplementation for metabolic diseases may result from this study.[54] Coronary artery disease (CAD) patients had low plasma PON-1 and HDL, increased LDL, total cholesterol, and triglycerides. Q192R polymorphism was more common in CAD patients.[55] The main topic points of recent studies are shown in **Table 1**.

Conclusion

PON-1 is an enzyme that is primarily synthesized in the liver and secreted into the bloodstream, where it circulates bound to HDL particles. PON-1 has been shown to play a role in protecting against ASCVD. PON-1 has been shown to have antioxidant and anti-inflammatory properties that may help to prevent the development of atherosclerosis. Studies have shown that individuals with

Table 1 – The main topic points of recent studies

Reference no.	Authors	Subjects	Main theme
Ref. 12	Corsetti et al.	ASCVD patients	PON-1 activity was decreased in early ASCVD patients with elevated HDL cholesterol, highlighting its biological relevance
Ref. 15	Murillo-González et al.	Cardiac patients	Due to its lactonase structure, PON-1 may predict lactone substrate activity
Ref. 16	Petric et al.	Health states and common complex diseases such as atherosclerosis, dementias, obesity, and diabetes	PON-1 lactonase activity does not enhance ASCVD risk prediction in prospective epidemiology
Ref. 18	Borowczyk et al.	Coronary artery disease patients	Homocysteine thiolactone, which binds to apoB like glucose and lipid peroxides, may increase the ASCVD risk of atherosclerosis
Ref. 28	Poznyak et al.	Review	Oxidised LDL may help explain the atherogenic process
Ref. 29	Gilad et al.	Mouse resistance arteries	EDHF 5,6-DHTL regulates Ca^{2+} influx and vascular dilation through endothelial PON-1 lactonase activity
Ref. 39	Xu et al.	Acute ıschemic stroke patients	It has been suggested that low levels of PON-1 may increase the risk of ischemic stroke, while others have not found a significant association
Ref. 49	Baran et al.	Psoriatic patients	Pentraxin 3 (PTX3) may prevent obese or severe psoriatic patients from developing cardiometabolic disorders. PON-1 may signal psoriasis-related liver issues.
Ref. 50	Moshtaghie et al.	Hyperhomocysteinemia patients	All cells produce toxic, reactive homocysteine thiolactone (HCTL). PON-1 effectively hydrolyzes it extracellularly. In vitro, HCTL decreased paraoxonase and aryl esterase activity, indicating it may affect this enzyme's protein structure. In vivo tests showed lower PON-1 activity in hyperhomocysteinemia patients.
Ref. 51	Leocádio et al.	NSTEMI patients	PON-1 paraoxonase activity may predict non-ST-segment elevation myocardial infarction (NSTEMI) prognosis
Ref. 52	Hajouj et al.	Nitrosylated human serum albumin (cellular)	S-nitrosylation of repon-1 boosts biological activity and may delay atherosclerosis
Ref. 53	Mortazavi et al.	Rats	PON1 prevents LDL oxidation and atherosclerosis, whereas TiO_2 nanoparticles (NP) may reduce these advantages
Ref. 54	Khouya et al.	High-fat diet-fed hamsters	Thymus atlanticus decreased high-fat diet (HFD)-induced hyperlipidemia, insulin resistance, and PON-1 activity. Thymus atlanticus biomolecules may treat HFD-related metabolic problems. Thymus atlanticus supplementation for metabolic diseases may result from this study.
Ref. 55	Nasreen et al.	CAD patients	Coronary artery disease (CAD) patients had low plasma PON-1 and HDL, increased LDL, total cholesterol, and triglycerides. Q192R polymorphism was more common in CAD patients.

low levels of PON-1 activity have an increased risk of developing ASCVD. Overall, PON-1 is an important enzyme in the prevention of ASCVD, and further research may lead to new therapeutic strategies for preventing and treating this condition.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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