THE PAST AND PRESENT OF PARAOXONASE ENZYME: ITS ROLE IN THE CARDIOVASCULAR SYSTEM AND SOME DISEASES

PROŠLOST I SADAŠNJOST ENZIMA PARAOKSONAZE: NJENA ULOGA U KARDIOVASKULARNOM SISTEMU I NEKIM BOLESTIMA

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Summary: Although paraoxonase is synthesized in many tissues including the heart, colon, kidneys, lungs, small intestines and brain, its major locus of synthesis is the liver. PON1 is in close association with apolipoproteins and protects LDL against oxidation. It was reported that PON1 quantities dropped to 40 times lower than normal in cardiovascular diseases and diseases like diabetes, ulcerative colitis, Crohn’s disease, chronic renal failure, SLE, Behçet’s disease, cancer, hepatitis B, obesity, metabolic syndrome, Alzheimer’s and dementia. It is speculated that the concerning decline in serum PON1 amount results from single nucleotide polymorphism in the coding (Q192R, L55M) and promoter (T-108C) sites of the PON1 gene. Additionally, circulating amounts of PON1 are affected by vitamins, antioxidants, fatty acids, dietary factors, drugs, age and lifestyle. This collection attempts to review and examine the past and present studies of paraoxonase and its relation with the cardiovascular system and some relevant diseases.

Keywords: paraoxonase, polymorphism, cardiovascular system diseases

Introduction

Paraoxonase is an ester hydrolase enzyme belonging to the class of group A aryl dialkyl phosphatases. It has been referred to by a host of names including A-esterase-1, serum aryl dialkyl phosphatase-1, aromatic esterase-1, esterase B1, esterase E4, phosphoryl esterase, organophosphate acid anhy-
Paraoxon (OPA), organophosphate esterase, organophosphate hydrolase, organophosphorus acid anhydrase, organophosphorus hydrolase, paraoxon esterase, paraoxon hydrolase, pirimiphos-methyl-oxon esterase and organophosphate paraoxon (1). As it usually uses paraoxon as its substrate (O,O-diethyl, O-p-nitrophenyl phosphate), it has been widely accepted to refer to this enzyme family as »paraoxonase«.

Esterases remove the toxic substances in the organism by breaking down their ester and ester-like bonds. Esterases were numbered by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB). The number, subgroup and substrate samples of esterases are presented in Table I. Of the two substrates of esterases, one is water (H₂O) and the other are specific substrates compatible with enzyme subgroups. The committee, known shortly as the Enzyme Committee (EC), refers to hydrolases as EC 3, and to ester hydrolases (esterases) as EC 3.1. Accordingly, esterases are enzymes which hydrolyze the ester bonds of substrate molecules.

Paraoxon is the paraoxonase substrate most commonly used to determine the enzyme activity of paraoxonase, which is primarily synthesized in the liver. Paraoxon is the active metabolite of parathion, an organophosphate compound synthesized in the liver. Spectrophotometric measurement of phenol or p-nitrophenol that arises from the hydrolytic activity of paraoxonase is commonly used to determine the enzyme activity. Measurement of the amount of phenyl acetate, an aromatic carboxylic acid ester, using a similar method, is used to find out the arylesterase (AE) activity of the enzyme (2–5). It has been argued that, although the similarities between their active sites are not evident, PON and AE enzymes, whose isoelectrical point is 5.1, use the same active centers competitively and, therefore, are competitors (6).

PON and AE enzymes, which are two different hydrolase enzymes, were both numbered EC 3.1.1.2 by the NC-IUBMB, as they were initially in the same group. However, it was understood by the 1990s that, as opposed to AE, PON could hydrolyze phosphoric and phosphinic acid esters, in addition to phenolic acid esters. After that, PON was re-numbered by the NC-IUBMB (EC 3.1.8.1).

Paraoxonase enzyme shows a high affinity to paraoxon, methyl paraoxon and chlormethyl paraoxon (7). The enzyme was demonstrated to detoxify some organophosphate derivatives like diazoxon, sarin and soman, and various aromatic carboxylic acid esters (8–10).

<table>
<thead>
<tr>
<th>Number</th>
<th>Subgroup</th>
<th>Name</th>
<th>Substrate</th>
</tr>
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<tbody>
<tr>
<td>3.1.1</td>
<td>Carboxylic Ester Hydrolase</td>
<td>Arylesterase</td>
<td>Phenyl acetate</td>
</tr>
<tr>
<td>3.1.2</td>
<td>Thioester Hydrolase</td>
<td>Acetyl-CoA hydrolase</td>
<td>Acetyl-CoA</td>
</tr>
<tr>
<td>3.1.3</td>
<td>Phosphoric Monoester Hydrolase</td>
<td>Glucose 6-phosphatase</td>
<td>Glucose 6-phosphate</td>
</tr>
<tr>
<td>3.1.4</td>
<td>Phosphoric Diester Hydrolase</td>
<td>Glycerophosphodiester phosphodiesterase</td>
<td>Glycerophosphodiester</td>
</tr>
<tr>
<td>3.1.5</td>
<td>Triphosphoric Monoester Hydrolase</td>
<td>dGTP triphosphohydrolase</td>
<td>Deoxyguanosine triphosphate (dGTP)</td>
</tr>
<tr>
<td>3.1.6</td>
<td>Sulfuric Ester Hydrolase (Sulfatase)</td>
<td>Choline sulfatase</td>
<td>Cholin sulphate</td>
</tr>
<tr>
<td>3.1.7</td>
<td>Diposphoric Monoester Hydrolase</td>
<td>Monoterpenyldiphosphatase</td>
<td>Monoterpenyldiphosphate</td>
</tr>
<tr>
<td>3.1.8</td>
<td>Phosphoric Triester Hydrolase</td>
<td>Paraoxonase</td>
<td>Paraoxon</td>
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<tr>
<td>3.1.11</td>
<td>Exodeoxyribonuclease</td>
<td>Exodeoxyribonuclease I</td>
<td>DNA</td>
</tr>
<tr>
<td>3.1.13, 3.1.14</td>
<td>Exoribonuclease</td>
<td>Yeast ribonuclease</td>
<td>RNA</td>
</tr>
<tr>
<td>3.1.15, 3.1.16</td>
<td>Exonuclease</td>
<td>Spleen exonuclease</td>
<td>—</td>
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<tr>
<td>3.1.21, 3.1.22, 3.1.25</td>
<td>Endodeoxyribonuclease</td>
<td>Deoxyribonuclease</td>
<td>DNA</td>
</tr>
<tr>
<td>3.1.26, 3.1.27, 3.1.30, 3.1.31</td>
<td>Endoribonuclease</td>
<td>Ribonuclease</td>
<td>RNA</td>
</tr>
</tbody>
</table>
History

Paraoxonase enzyme was discovered by Abraham Mazur (11) in 1946 and was then more extensively studied by W. Norman Aldridge starting in 1953. In his study, Aldridge described paraoxonase as an A-esterase that hydrolyzes p-nitrophenyl, propionate and butyrate (12). In 1961, Jose Uriel (13) identified the presence of PON in the immunoprecipitates of high-density lipoprotein (HDL) after electrophoresis in the human serum. In 1973, Geldmacher-Von Mallinck et al. (14) demonstrated the presence of PON in the human serum genetically. Various polymorphisms of paraoxonase were found in the ensuing years (3). In 1983, it was revealed that PON activity was dependent on Ca²⁺ (15). Mackness et al. (16) demonstrated in 1985 that PON binds to different areas of HDL in sheep and humans. Then, it was suggested that PON was carried via apolipoprotein A1 (Apo A1) on HDL (17). After this development, it was suggested that PON could be involved in the atherogenesis and lipid metabolism (19). Besides, it was reported that HDL could protect low-density lipoprotein against the oxidation induced by copper ions through PON, which is one of the lipoproteins and enzymes that HDL carries in its structure (18).

Structure and Functions

Paraoxonase is an enzyme family composed of three members: PON1, PON2, and PON3. Human and rat studies showed that paraoxonase acted on three different substrates (paraoxon, chlorpyrifos-oxon and diazoxon) on the same chromosome (7q21-22 area in humans and the 6th chromosome in rats). Localizations of Single Nucleotide Polymorphisms (SNPs) and the binding areas of the transcription factors of PON1 gene were modified (40) and are shown in Figure 1. Paraaxon destruction in the blood is an indicator of the PON1 enzyme. The activity of the enzyme gives an idea about the PON1 concentration of 192Q>R polymorphism.

![Figure 1](image-url)
Human PON enzyme displays two polymorphisms that vary as Met (M) ↔ Leu (L) and Arg (R) ↔ Gln (Q) between the 55th and 192nd amino acid groups, respectively. Those carrying arginine have high activity (RR), and those carrying glutamine have low activity (QQ) in the 192nd position. The enzyme with moderate activity is expressed with the RQ genotype. Promoter and coding regions that affect PON1 expression and activity are presented in Table II.

The distribution of PON1 192 allele was examined according to races, and it was found to be 30% in Eskimos, 40% in American Indians, 32–64% in African Americans, 27–31% in Caucasian Americans, 44% in Hispanic Americans, 32–52% in Mexicans, 52% in African Brazilians, 31% in Caucasian Brazilians, 24–31% in Caucasian Europeans, 31% in Caucasian Turks, 17–54% in Indians, 56–62% in the Chinese, 30–60% in Koreans, 29–61% in the Taiwanese, 59% in Malaysians and 59–66% in the Japanese (41–45).

Similarly, the distribution of the 52M allele of PON1 was examined according to races, and it was found to be 4% in Eskimos, no data for American Indians, 18–20% in African Americans, 35–36% in Caucasian Americans, no data for Hispanic Americans, 0–16% in Mexicans, 21% in African Brazilians, 33% in Caucasian Brazilians, 26–38% in Caucasian Europeans, 28% in Caucasian Turks, 4–21% in Indians, 0–5% in the Chinese, 3–6% in Koreans, 5–6% in the Taiwanese, 6% in Malaysians and 4–10% in the Japanese (41–45).

Individually different in vitro responses of PON to different substrates are explained by genotype (46). Additionally, optimal stability and activity of the enzyme depend on the presence of Ca^{2+}. Although Ca^{2+} is not needed in the hydrolysis of lipid peroxides, the presence of two Ca^{2+} at the center of the enzyme is important for the hydrolysis of organophosphates. Calcium plays a critical role in the activity of the enzyme, either by directly participating in catalytic reactions or by ensuring that the active center of the enzyme is kept in the appropriate configuration. When Ca^{2+} improves the nucleophilic property of phosphorus by polarizing the phosphate-oxygen double bond (P=O), it becomes easier to draw diethyl phosphate away from the active region of the enzyme. That PON is dependent on Ca^{2+} for its activity distinguishes this enzyme from other A-esterases which function through cobalt (Co^{2+}), manganese (Mn^{2+}) and magnesium (Mg^{2+}). PON1, which is found in almost all mammalian organs and tissues, performs its maximum activity in the plasma and liver (47). Similarities of PON members with antioxidant capacity at the amino acid level range between 79 to 90% among mammalians, while the similarities of the genes in terms of their nucleotides are in the 81 to 90% range (48).

Rat PON enzyme which weighs 39,496 kDa is composed of 355 amino acids. When compared in terms of their amino acid numbers, rat PON is seen to have one amino acid more than the human PON. Table III shows the rat PON amino acid numbers. Human and rat PON structures are similar to a great extent in the amino acid numbers. Two out of the three cysteine amino acids found in the human PON enzyme structure are bound by a disulfide bond between them. Bioactivity of the enzyme depends upon its free cysteine amino acid forming a conjugation with its substrate. The enzyme inhibited by sulphydryl compounds is re-activated by cysteine. Rat PON enzyme possesses four cysteine amino acids in its structure. For the enzyme to react, one or two of the cysteine amino acids must bind to the substrate.

<table>
<thead>
<tr>
<th>Position</th>
<th>Variants</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>192</td>
<td>Glutamine / Arginine</td>
<td>No effect</td>
</tr>
<tr>
<td>Coding area 55</td>
<td>Leucine / Methionine</td>
<td>L &lt; M</td>
</tr>
</tbody>
</table>

Table II: Promoter and coding regions that affect PON1 expression and activity.

<table>
<thead>
<tr>
<th>Position</th>
<th>Variants</th>
<th>The effects of promoter activity</th>
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</thead>
<tbody>
<tr>
<td>Promoter -907</td>
<td>Cysteine / Glutamine</td>
<td>C &lt; G</td>
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<tr>
<td>-824</td>
<td>Arginine / Glutamine</td>
<td>No effect</td>
</tr>
<tr>
<td>-162</td>
<td>Arginine / Glutamine</td>
<td>A &gt; G</td>
</tr>
<tr>
<td>-126</td>
<td>Arginine / Glutamine</td>
<td>No effect</td>
</tr>
<tr>
<td>-107</td>
<td>Cysteine / Thymidine</td>
<td>C &gt; T</td>
</tr>
</tbody>
</table>

Table III: Rat PON amino acid numbers.
The paraoxonase enzyme was first studied in toxicology due to its ability to hydrolyze organophosphate compounds. Its ability to hydrolyze organophosphate neurotoxins, insecticides and carboxylic acid esters was the first known protective function attributed to the PON1 enzyme (25, 49). PON is also a potent inhibitor of cholinesterases that break down acetylcholine. Since many of the enzymes that can detoxify thiones and oxons (paraoxonase, glutathione, transferase, monooxygenase, etc.) are found in the lungs, it is believed that that is where most of the reaction takes place (50). As the body of knowledge about the antioxidant properties of paraoxonase grows, it becomes an increasingly popular molecule in the research carried out for the diagnosis and treatment of diseases (51, 52).

Data obtained from the human PON studies demonstrate that 15.8% of PON1, which has a glycoprotein structure, consists of three carbohydrate chains. The expressions and distributions of PON proteins in the tissues of humans vary. PON1 and PON3 are found in the liver and plasma, while PON2 was established by the IHC method to be present in the liver, kidney, heart, brain, testes, the endothelial layer, as well as the smooth muscle cells of the aorta. Although PON1 has the lysine amino acid in the 106th place, PON2 and PON3 do not. Since they do not have a lysine residue in the 105th position, PON2 and PON3 cannot hydrolyze paraaxon. PON1 and PON3, which are heavily expressed in the liver and kidneys, are bound to HDL and carried in the circulation (53, 54). PON2, which is expressed in many tissues, is an intracellular enzyme and is not present in the plasma (55). Since paraaxon is not used as a substrate in the studies involving PON2 and PON3, data about these enzymes are limited, while there is more information on PON1.

Serum PON1 activity in full-term neonates and premature infants is half of that in adults, but it is known to reach adult levels within the first year (6). PON activity is reduced in aging, various diseases and malnutrition. Apart from that, the differences between an individual’s serum PON1 activities were attributed to the polymorphisms in the structure of the enzyme. When the effects of proatherogenic diet on serum PON1 activity were analyzed, a significant decrease was noted in the enzyme activity, while flavonoid antioxidants were seen to elevate enzyme activity by as much as 20%. Serum PON1 levels decrease irreversibly with smoking. In addition to acute phase reactants, pregnancy and disorders that influence the Apo A1 metabolism affect the serum PON1 levels (56, 57).

PON1, which is not found in invertebrates, fish and birds, is bound to HDL and is carried in the serum of mammals. Thanks to its hydrophobic property in the N-terminal site, PON can easily bind to phospholipids and lipoproteins (HDL). The strong binding of PON to HDL has been demonstrated in human and rabbit serum PON trials. Since the HDL sub-units interacting with PON contain Apo A1 and Apo J proteins, Apo A1 and Apo J are thought to be involved in the PON-HDL binding. It was shown in immune-affinity chromatography studies that the part of HDL that contains PON1 is a small fraction of the total HDL (58).

PON1 and PON3, bound to high density lipoprotein (HDL), and PON2, which is not carried via HDL, serve in the oxidation of LDL. Furthermore, PON2 inhibits the monocyte chemotaxis stimulated by oxidized LDL (55). PON1, found together with HDL in the circulation, takes part in the preclusion of the oxidation of plasma lipoproteins. Prevention of the accumulation of lipid peroxides in HDL and LDL depends on their being metabolized through PON1 as a result of peroxidation. Thanks to this property, PON1 is more effective than vitamins A and E in helping HDL protect LDL against oxidation. It is believed that HDL realizes its antioxidant capacity through the enzymes associated with it such as PON1, LCAT and PAF-AH. PON protects LDL cholesterol particularly against the oxidation that can be induced by the cop-

<table>
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<th>Amino acid</th>
<th>Amount</th>
</tr>
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<tbody>
<tr>
<td>Leucine</td>
<td>44</td>
</tr>
<tr>
<td>Valine</td>
<td>32</td>
</tr>
<tr>
<td>Serine</td>
<td>27</td>
</tr>
<tr>
<td>Glycine</td>
<td>23</td>
</tr>
<tr>
<td>Threonine</td>
<td>22</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>21</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>21</td>
</tr>
<tr>
<td>Alanine</td>
<td>20</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>19</td>
</tr>
<tr>
<td>Proline</td>
<td>19</td>
</tr>
<tr>
<td>Lysine</td>
<td>18</td>
</tr>
<tr>
<td>Asparagine</td>
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<td>Phenylalanine</td>
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<tr>
<td>Tyrosine</td>
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</tr>
<tr>
<td>Histidine</td>
<td>11</td>
</tr>
<tr>
<td>Arginine</td>
<td>9</td>
</tr>
<tr>
<td>Methionine</td>
<td>6</td>
</tr>
<tr>
<td>Glutamine</td>
<td>4</td>
</tr>
<tr>
<td>Cysteine</td>
<td>4</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>4</td>
</tr>
</tbody>
</table>
per ion (Cu+2) and free radicals (59). Mackness et al. (18) showed in 1991 that PON was involved in the protection of LDL phospholipids against oxidation during the onset of the atherosclerosis process. It was demonstrated in the study that lipid peroxide formation incubated by copper in LDL was inhibited by HDL at around the rate of 90%, and that the levels of the substances that reacted with thiobarbituric acid (Thiobarbituric Acid-Reacting Substances; TBARS) as well as lipoperoxide formation were prevented by PON1 isolated from HDL. PON2 has recently become a focus of attention due to its antioxidant capacity and its expression in endothelial cells and vascular wall cells. PON2, whose molecular weight is 44 kDa, fulfills its antiatherogenic function by reducing the production of intracellular hydroperoxides and by inhibiting cell-mediated LDL oxidation (55).

Although PON3 is synthesized in the liver and carried by HDL, it does not display any enzyme activity. It does have limited arylesterase (AE) activity and can hydrolyze lactones such as statin. PON3 was seen to be more effective than PON1 in preventing the LDL oxidation induced by copper in rabbits. Since it is known that PON1 mRNA expression is suppressed throughout the acute phase response period, when PON3 mRNA expression is different in rabbits, it is believed that PON1 and PON3 can act differently in the prevention of atherosclerosis (35).

Like ghrelin, paraoxonase is carried in the plasma by binding to HDL. In a relevant study carried out by Beaumont et al. (60) in 2003, it was shown that there was a significant interaction between ghrelin and HDL in fasting individuals, and that this interaction was associated with a correlation between appetite, growth hormone secretion and lipid transfer. However, the authors stated that they did not know how the changes in HDL and ghrelin levels altered pathophysiology. De Vriese et al. (61) reported that butyrylcholinesterase and other esterases in the human serum and carboxylesterase in rats led to ghrelin des-octanoylation. Apart from the serum, they also showed ghrelin breakdown through des-octanoylation in the N-terminal end of the stomach, liver or kidney homogenates. Independent of the detoxification function of PON, it was argued that the bioactive ghrelin found in the organism broke down the ester bond between the octanyl group and thus converted acylated ghrelin to the desacyl ghrelin form (62).

**Antioxidant Properties**

Shih et al. (63) suggested in their mouse study that PON3 might have a critical role in protecting from obesity and atherosclerosis. Besides hydrolyzing organophosphate neurotoxins, aromatic carboxylic acid esters and organic toxins like insecticides, PON1 has an antioxidant activity. PON1 which is co-present with HDL in the plasma prevents the oxidation of plasma lipoproteins. By re-metabolizing the broken down lipids, it prevents accumulation of lipid peroxides in HDL and LDL. Thus, HDL indirectly protects LDL from oxidation. Dietary factors that affect PON1 expression in *in vitro* and *in vivo* conditions are briefed in *Figure 2* (64–70).

PON1 and PON3, which have antioxidant properties, inhibit LDL oxidation (71). Mackness et al. (16) established through ultracentrifugation of the human serum that PON1 is carried by HDL in the blood. The level of PON1-bound HDL in the blood constitutes only a small amount of the total HDL (58). PON2 which is not bound to HDL also has antioxidant characteristics and inhibits LDL oxidation. Besides, it inhibits the monocyte chemotaxis activated by oxidized LDL.

![Figure 2](image-url) Dietary factors that affect the expression of PON1.
Measurement of PON1 activity

Phenyl acetate is the most commonly used substrate in the determination of arylesterase activity. It hydrolyzes PON1 paraoxon, which results in the formation of a yellow colored parainitrophenol, and the increased absorbance of this yellow color is measured spectrophotometrically at 412 nm (2). PON1 is now measured with autoanalyzers (72). Measurements using calcium-binding samples with EDTA should not be employed. Samples with heparin or serum samples are ideal for the analysis of PON1. The factors which affect PON1 amounts include genetic factors, smoking, some drugs (hypolipidemic agents, statins, anti-diabetics), diet (polyphenols, antioxidants), lifestyle and lipid metabolism (73).

Clinical Significance

PON1 activity is reduced in ulcerative colitis and Crohn’s disease, and the 192Q (74–75) and 55L (75) allele were found frequently in these patients. It was speculated that the decrease in PON1 activity in these diseases was in response to elevated cytokines (76). This hypothesis has been confirmed by experimental evidence, as it was reported that interleukin-6, interleukin-β and Tumor Necrosis Factor (TNF-α) reduced PON1 mRNA expression in hepatocyte cell cultures (77, 78).

PON1 activity was curbed in patients with metabolic syndrome. This curbed PON1 activity was shown to be associated with HDL oxidation in in vitro experiments (79–81). Oxidation of HDL in diabetic patients causes a change in the PON1 protein and an ensuing drop in PON1 activity (79). PON1 activity was shown to decrease in type 1 and type 2 diabetes patients in several studies, while some other studies reported that PON1 activity was not related to type 1 and type 2 diabetes (82–83). Apart from that, it was noted in some studies that diabetes was correlated with PON1 polymorphism, although other studies failed to confirm this correlation (84–86). Gupta et al. (87), for instance, noted that the 192R allele and (-907)C allele had a high prevalence in type 2 diabetes patients. Flekac et al. (88) reported that the 192Q allele and 55M allele were more common in diabetic cases. Kao et al. stated that the 55L allele was more prevalent in patients with diabetic retinopathy (89). It was reported in many other studies that the 55M allele and 192R allele were prevalent and common in patients with diabetic retinopathy (84, 88, 90).

Patients who developed dementia were found to have a higher frequency of the 55M allele (91–92). Although Helpecque et al. reported that the -107T allele meant high risk of dementia (93), it was concluded in another study that this observation was a contradiction (94). It was noted in several studies that there was no relation between dementia and PON1 (95–98). Similarly, PON1 activity was reported to drop in Alzheimer’s patients, although the results are contradictory (99–101). Dantoine et al. argued that the 192 PON1 polymorphism might be a critical marker in distinguishing Alzheimer’s patients from patients with vascular dementia and healthy individuals (96). PON1 activity was also reported to decrease in major depression by Barim et al. (102). It was argued that environmental neurotoxins that are metabolized by PON1 in sporadic idiopathic cases might contribute to neurodegeneration, that is, they might pave the way for genetic predisposition to Parkinson’s disease (103). PON1 activity also declines in schizophrenic conditions (104–105). It was noted that PON1 activity decreased in patients with chronic renal failure (106–110) and that it was restored following kidney transplantation (106).

Klic et al. (111) and Aslan et al. (112) reported in their respective studies that PON1 activity decreased in patients with hepatitis B. They stated that PON1 activity decreased because of the lack of PON1 production, which resulted from the destruction of PON1-producing hepatocyte cells due to hepatitis B.

Horoz et al. noted that PON1 activity lessened in patients with hepatitis C and in those on hemodialysis treatment (113). Selek et al. (114) reported that PON1 activity subsided in beta thalassemia patients. PON1 activity was stated to decrease in the serum of cement factory workers who are exposed to cement dust (115).

It was shown in several studies that there might be a correlation between paraoxonase concentrations and cancer. As it is well-known, oxidative stress is a major etiological factor in carcinogenesis. Since PON1 is an endogenic free radical scavenger, the decrease in its amount may be involved in the etiopathology of cancer. For example, serum paraoxonase levels were found reduced in gastric, pancreas, epithelial and lung cancer cases. There is also a correlation between cancer and the PON1 polymorphism. For example, the PON192 polymorphism distribution was found lower in glioma and meningioma patients, relative to the control group. Stevens et al. (116) reported an increase in L55M polymorphism in cases with invasive breast cancer with the MM genotype. Decreases in PON1 were also established in many other diseases including: rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus (SLE) and Behcet’s disease. The decrease in PON1 activity in these diseases suggests that it has an antioxidant character.

Effects on Cardiovascular System

Due to the antiatherogenic effect of HDL, it is believed that PON1 and atherosclerosis are correlated (117). PON1 which breaks down biologically active LDL can mediate the elimination of a fatty streak by preventing lipid peroxidation (118). In other
words, by inhibiting LDL oxidation, PON1 can reduce the risk of vascular atherosclerotic disease. To do this, it requires the presence of the N-terminal hydrophobic signal peptide (117).

Several studies reported a correlation between the cardiovascular system and PON1 (118). For instance, it was shown that the 192R polymorphism was associated with a high risk of cardiovascular system disease in Punjabis of northwestern India (119) and also that the same polymorphism also posed a risk for Italians (120), Egyptians (121) and the Taiwanese (122). Carotid abnormalities of the 192R allele are correlated with high plasma HDL levels, but not with a low HDL plasma concentration (123, 124). In contrast to the cited studies, the 192Q allele was found in a higher frequency and was associated with the risk of cardiovascular system diseases in the German (125) and Polish (126) population. It was noted that the Q192R polymorphism of PON1 was not related to carotid intima thickness (127). A similar result was reported for Sicilian hypercholesterolemic patients in whom early carotid atherosclerosis and polymorphism were found unrelated (128). These results were confirmed by the findings of the EPIC Norfolk study group who did not find any correlation between the cardiovascular system and Q192R variants (129). Similar to the contradicting results obtained with the Q192R allele, the results concerning the relation between L55M polymorphism and cardiovascular system are inconsistent as well. For instance, while the 55M allele was found to be in high frequency in the Portuguese (130), Germans (125) and Taiwanese (122), the L variant was found more common in Italians (120, 127) and Brazilians (131). Despite all these findings, Campo et al. (128) reported that there was no correlation between the L55M polymorphism and the cardiovascular system. Studies conducted on the Turkish population demonstrated that there might be a relation between PON1, Q192R gene polymorphism and coronary artery diseases (132). Plasma PON1 activity was reported to be lower in those with familial hypercholesterolemia and those who had myocardial infarction (19).

**Conclusion**

Paraoxonase, an enzyme synthesized mainly in the liver, is bound to HDL in the blood circulation. High levels of PON1 in the circulation reduce cardiovascular risk. Single nucleotide polymorphism (SNP) affects the PON1 concentration. Its circulatory levels are affected by genetic factors, lifestyle, age and drugs (for instance, statins, fats and fatty acids, antioxidant vitamins, nutrients rich in polyphenols content). Although there is no general consensus, it has been reported to decrease in many diseases, including ulcerative colitis, Crohn’s disease, chronic renal failure, SLE, Behçet’s disease, cancer, Hepatitis B, obesity, metabolic syndrome, Alzheimer’s and dementia.

**Conflict of interest statement**

The authors stated that there are no conflicts of interest regarding the publication of this article.

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