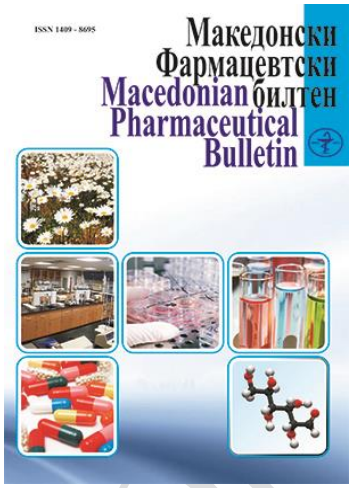
This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo, copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

Accepted Manuscript



Title: Paraoxonase enzymes - paraoxonase 1 and its role in HDL functionality and prediction of the development of cardiovascular disease

Authors: Katerina Krsteva Jakimovska*,
Sonja Topuzovska

Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, str.50 Divizija no. 6, 1000 Skopje, North Macedonia

DOI:
Received date: October 2025
Accepted date: January 2026
UDC:
Type of paper: Review paper
Mac. Pharm. Bull. 72 Vol. (2) 2026

Please cite this article as:

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

doi: *Review paper*

Paraoxonase enzymes - paraoxonase 1 and its role in HDL functionality and prediction of the development of cardiovascular disease

Katerina Krsteva Jakimovska*, Sonja Topuzovska

Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, str.50 Divizija no. 6, 1000 Skopje, North Macedonia

Abstract

Serum paraoxonase enzymes (PONs) are found in mammals. Initially, PON1 was discovered as an enzyme that is responsible for hydrolyzing organophosphate compounds in tissues. PON1 is a structurally defined glycoprotein synthesized in the liver. After its synthesis, the enzyme is first positioned at the cell surface and is later secreted into the bloodstream, where it becomes primarily associated with high-density lipoprotein particles. The functionality of HDL in preventing the oxidation of lipoproteins, particularly LDL, is due to PON1 and HDL associated proteins. Many studies show that the assessment of HDL proteome, especially the enzymes - including PON1, may have important clinical significance in predicting adverse cardiovascular events.

PON1 activity is influenced by both genetic and environmental factors. Several single-nucleotide polymorphisms have been identified in the gene encoding PON1, although only a few significantly affect enzyme activity and concentration and are associated with reduced plasma PONase activity.

The prevalence of PON1 gene–associated polymorphisms in the Macedonian population has not yet been investigated. Such a study would help elucidate the relationship between these polymorphisms and variations in PON1 activity and concentration, as well as their association with HDL functionality. This knowledge could contribute to improved prediction of cardiovascular risk in the Macedonian population.

Keywords: PON1, HDL, cardiovascular, PON1 polymorphisms

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

Paraoxonase enzymes

Paraoxonase enzymes (PON) as a family of enzymes are found in mammals. Three paraoxonases are known and those are the isoenzymes (PON1, PON2 and PON3). They were initially identified based on their role in the enzymatic hydrolysis of organophosphates. (Mackness and Mackness, 2013).

The nomenclature of this enzyme family derives from early *in vitro* assays of PON1, which demonstrated its ability to hydrolyze paraoxon, the toxic metabolite of parathion. PON1 was first described in 1940 by Mazur, who identified its enzymatic activity in mammalian tissues to be able to hydrolyze organophosphate compounds. (Mackness and Mackness, 2013).

Subsequently, Aldridge classified organophosphate hydrolases into A- and B-esterases, based on whether they catalytically hydrolyze organophosphate compounds (A-esterases) or are irreversibly inhibited through binding to these compounds (B-esterases). According to this classification PON1 was assigned to the A-esterase group, as it was identified to be able to catalytically hydrolyze the toxic paraoxon 0.

In 1990, with the discovery of the genes related to PON1, the other two enzymes part of the family of paraoxonase enzymes- PON2 and PON3, were also named paraoxonases, even though not one of them is able to hydrolyze the paraoxon. Following discussions regarding the appropriate nomenclature of PON enzymes, it was decided to defer their naming until their natural physiological substrates were identified. However, the spectrum of physiologically relevant substrates for these two enzymes remains unresolved 0

The three genes involved in encoding paraoxonases are located in tandem – one next to the other, on the long arm of chromosome 7 at position 7q21-22. Between the three genes there is 70% similarity in nucleotide sequences and about 60% similarity in amino acid sequences. PON1, PON2 and PON3 have nine exons. The only difference is that PON1 has an extra codon at position 106 (lyzine) in exon 4, not present in the other two. Based on structural homology, the PON2 enzyme evolutionary is the oldest, followed by the PON3 enzyme and finally PON1. The expression of the mRNA of the PON1 enzyme is mostly observed in the liver, while the mRNA of the PON3 enzyme is primarily found in the liver, but also in the kidney. On the other hand, mRNA for the PON2 enzyme is present in a variety of tissues, including kidney, liver, lung, small intestine, placenta, spleen, stomach, testis, and cells of the arterial wall, including endothelial cells, smooth muscle cells, and macrophages (Ng et al., 2005; Rajkovic et al., 2011).

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

PON1 enzyme

Paraoxonase-1 is a glycoprotein composed of 354 amino-acid residues and has a relatively small molecular mass of about 43 kDa. Its primary site of production is the liver, with smaller amounts formed in the kidneys. Immunohistochemical analyses demonstrate that PON1 is distributed across multiple mammalian tissues (Mackness and Mackness, 2013; Rodrigo et al., 2001). After synthesis, the enzyme first associates with the cell surface and is subsequently released into circulation, where it predominantly attaches to high-density lipoproteins (HDL) (Mackness et al., 2010).

The structure of the PON1 enzyme is organized in the shape of a six-bladed propeller, where each blade is composed of four beta sheets. Two calcium ions are located in the central tunnel of the enzyme. The calcium ion located deeper in the tunnel has a structural role that is critical for the conformational stability of PON1. The other calcium ion lying at the bottom of the enzyme's active site has a catalytic role and is important for substrate positioning and activation of the ester bond. Three helices are located above the active site of PON1: H1, H2 and H3 and they have a function in the binding interactions between PON1 and HDL (Shunmoogam et al., 2018). The enzyme is N- glycosylated and contains disulfide bridges. The protein includes three cysteine residues: two participate in forming an internal disulfide bonds, whereas the remaining residue (cys-284) is essential for maintaining full paraoxonase and arylesterase activity in serum. This cysteine residue cys-284 participates in the orientation and binding of PON1 to its substrate and is important for the shielding role of PON1 in preventing LDL oxidation (Harel et al., 2004).

Although PON1 can be detected in multiple tissues, in the bloodstream it is found almost entirely bound to HDL particles. The interaction with HDL requires the enzyme’s N-terminal helical region, which includes helices H1 and H2. Phospholipids on the HDL surface facilitate this binding. When HDL interacts with hepatocyte membranes, it removes PON1 from the cell surface, allowing the enzyme to relocate from the membrane to the outer layer of the lipoprotein. The hydrophobic N-terminal sequence of PON1 enables it to interact with phospholipids on both lipoproteins and cell membranes. As HDL matures, it further enhances the functional activity of PON1.

PON1 is able to move between HDL and very-low-density lipoproteins (VLDL), and it can also be transferred to endothelial cells that interact with HDL. This exchange is facilitated

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

by scavenger receptor class B type 1 (SR-BI). The enzyme can likewise be delivered to macrophages, which subsequently internalize it. Once bound to macrophages through sites that overlap with HDL-binding regions, PON1 accumulates within the cytoplasm, where it localizes to areas similar to those occupied by PON2. It has also been proposed that macrophage phospholipids may enhance the attachment of PON1, supporting both its stabilization and enzymatic function. This cellular association likely accounts for the enzyme's detection within atherosclerotic plaques, where it may contribute to local protection (Khalil et al., 2021).

PON1 requires calcium ions for its catalytic function. Chelating agents such as ethylenediaminetetraacetic acid (EDTA) and ethylene glycol tetraacetic acid (EGTA) bind calcium and, as a result, irreversibly inhibit PON1 and decrease its structural stability. (Getz and Reardon, 2004; Shunmoogam et al., 2018). The structure of PON1 is shown in Figure 1.

This enzyme functions is as an esterase/lactonase. PON1 is a multifunctional enzyme capable of degrading oxidized phospholipids and hydrolyzing lactones present on lipoproteins. The antioxidant properties of HDL - particularly its ability to prevent oxidation of LDL - are largely attributed to PON1 and other proteins associated with HDL.

Animal studies support this protective role: human PON1 transgenic mice develop significantly fewer atherosclerotic lesions, and in these animals, murine HDL shows an enhanced capacity to protect LDL from oxidation (Variji et al., 2019).

In patients with coronary artery disease, the increased levels of malondialdehyde formation in endothelial HDL, occur as a result of reduced PON1 activity, and may have a negative effect on endothelial HDL functionality. Many studies have shown that assessment of the HDL proteome, especially of its associated enzymes, including PON1, may have notable clinical significance in predicting adverse cardiovascular events, rather than assessing HDL cholesterol levels/concentrations alone (Variji et al., 2019).

Fig. 1.

HDL lipoprotein, reversible cholesterol transport and PON1

A significant number of epidemiological studies have associated higher levels of HDL cholesterol (HDL-C) with a reduced risk of cardiovascular disease. However, recent attempts to therapeutically increase HDL cholesterol levels have failed to demonstrate clinical benefit, despite increasing HDL concentrations in the body. As a result, this lipoprotein is currently in

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

a paradoxical situation. This paradoxical situation in which HDL finds itself may be a result of the nature of the information it provides. HDL-C levels alone do not directly indicate how effectively cholesterol will be transported from vascular macrophages to the liver. The efficiency of this efflux pathway is determined by multiple factors, and not just by the total mass or concentration of cholesterol itself (Variji et al., 2019).

As a result of its biological complexity, several studies have suggested that HDL- C concentration alone does not provide a true picture of its functionality and therefore may not provide significant clinical benefits, in contrast to HDL proteins, especially the enzymatic components, which may be more important in obtaining useful clinical information (Variji et al., 2019).

HDL particles enriched with the enzyme PON1 are associated with antioxidant activity, anti-inflammatory activity and the lipid -carrying function of HDL itself. PON1 helps HDL prevent the buildup of lipid peroxides in oxidized LDL, inactivate bioactive oxidized phospholipids, and stimulate HDL-mediated, eNOS-dependent nitric oxide (NO) production. It also enhances the efflux of cholesterol from cholesterol-laden macrophages (Huang et al., 2013).

PON1 carries out multiple biological functions, including the prevention of lipid oxidation, modulation of reactive nitrogen species metabolism, stimulation of nitric oxide (NO) production, and enhancement of cholesterol efflux from cholesterol-loaded macrophages (Bacchetti et al., 2020).

In addition, several animal studies have directly demonstrated that apoA-I, a component of HDL, has an antiatherogenic function. Transgenic mice engineered to express higher levels of human PON1 show greater protection against atherosclerosis compared with wild-type mice. On the contrary, mice lacking PON1 display an increased susceptibility to atherosclerosis compared to wild-type controls. However, findings from animal studies have limitations and cannot be directly extrapolated to humans. However, they are certainly useful for the transition from *in vitro* studies to clinical studies (Shunmoogam et al., 2018).

This observation leads to the need for a better understanding of HDL and its constituent components (enzymes, proteins). HDL is essentially a general term for a highly heterogeneous group of particles composed of a large number of proteins, including apolipoprotein A-I (Apo A -I), which is the major structural protein of HDL, as well as additional proteins involved in hemostasis, thrombosis, the immune and complement systems, growth factor, receptor, and

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

hormone-associated proteins. Current evidence suggests that certain subpopulations of HDL particles composed of unique clusters of specific HDL-associated proteins also perform specific biological functions. HDL particles containing the enzyme PON1, as previously shown as an atheroprotective protein, exhibit enhanced antioxidant, anti-inflammatory, and lipid- carrying functions. PON1 is a circulating esterase and lactonase that is carried on HDL. Circulating PON1 is mainly associated with HDL, but small amounts are found in VLDL and chylomicrons. It has been suggested that PON1 may use VLDL as a vehicle to transfer the enzyme to HDL (Harel et al., 2004).

Reverse cholesterol transport - the process by which cholesterol is removed from peripheral tissues and returned to the liver for elimination via bile and feces - represents the primary mechanism for regulating excess cellular cholesterol and constitutes the major anti-atherogenic function of HDL. The first step in this pathway, having both rate-controlling purpose, is cholesterol efflux from macrophages. It begins when apolipoprotein A-I (apoA-I) interacts with the ATP-binding cassette transporter ABCA1, leading to the transfer of phospholipids and cholesterol and the formation of nascent pre-β HDL. These particles are then progressively enriched with cholesterol to generate mature HDL subclasses (HDL3 and HDL2).

Interestingly, *in vitro* studies have demonstrated that cholesterol efflux mediated by the ABCA1-apoA-I interaction can be notably enhanced in the presence of PON1. Although the cholesterol efflux is initiated specifically through ABCA1-apoA-I interaction, purified PON1 appears capable of interacting with ABCA1 transporter via a similar mechanism to ABCA1-apoA-1, thereby promoting cholesterol efflux. PON1 further stimulates this process by up-regulating ABCA1 transporter expression and increasing the binding affinity between HDL and ABCA1 (Khalil et al., 2021).

Evidence from animal models confirms this effect *in vivo*. Administration of recombinant PON1, as well as studies in mice that overexpress human PON1 (hu-PON1-Tg), show enhanced antioxidant properties of HDL and a greater capacity to promote cholesterol efflux. In these transgenic mice, both HDL-mediated efflux and overall reverse cholesterol transport are significantly increased. Macrophages from hu-PON1-Tg animals display elevated expression of ABCA1 and ABCG1 transporters, supporting the view that PON1 facilitates cholesterol removal and transport by inducing membrane cholesterol-transport proteins (Khalil et al., 2021).

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

Taken together, both incubation of macrophages with PON1 and transfection with human PON1 lead to overexpression of the ABCA1 and ABCG1 transporters, and the injection of these macrophages into mice notably enhances reversible cholesterol transport.

These findings indicate that, beyond its well-recognized antioxidant properties, PON1 plays a direct role in regulating the principal anti-atherogenic function of HDL and its ability to mediate reversible cholesterol transport, as demonstrated by consistent evidence from both *in vitro* and *in vivo* studies.

PON1 and statins

It is therefore not surprising that PON1 activity is further regulated by statin therapy (Bacchetti et al., 2020). Statins help protect against atherosclerosis by reducing LDL-C, total cholesterol, and triglycerides, while also increasing HDL-C levels (Christidis et al., 2007; Ferretti et al., 2015). Treatment with statins increases PON1 enzymatic activity, thereby contributing to their overall atheroprotective potential (Christidis et al., 2007).

By being statin regulated, PON1 prevents lipid accumulation, peroxides in lipoproteins and biological membranes leading to reduced lipid content peroxides in the coronary arteries as well as reduced atherosclerotic lesions in the carotid blood vessels (Bacchetti et al., 2020).

Several mechanisms have been proposed to explain the statin-induced increase in PON1 activity. One explanation is that higher PON1 activity after statin therapy may result from reduced oxidative stress, because PON1 becomes partially inactivated in the presence of oxidized LDL particles (Tomás et al., 2000).

Some studies have shown that PON1 activity increases significantly following statin therapy, and that this rise occurs independently of any changes in HDL-C levels (Godbole et al., 2023).

Evidence from a systematic review and meta-analysis of 25 clinical trials indicates that statin therapy is associated with significant increase in PON1 paraoxonase and arylesterase activities, but not in PON1 protein concentration. The analysis further showed that the PON1-enhancing effects of statins remained robust across sensitivity analyses and appeared to be independent of statin dose, treatment duration, and changes in plasma LDL-cholesterol levels (Ferretti et al., 2015).

In addition, several studies have reported that specific statins - including atorvastatin, simvastatin, and fluvastatin - can effectively increase serum paraoxonase activity while

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

reducing triglyceride levels. However, this effect appears to be more significant in individuals with certain PON1 phenotypes. These findings suggest that the human PON1 genotype may influence, and potentially determine, the therapeutic response to statin treatment (Mirdamadi et al., 2008).

PON1 polymorphisms

The activity of the PON1 enzyme is regulated by both genetic and environmental factors that vary between individuals and populations. Based on this, a large number of single-nucleotide polymorphisms have been identified. Eight of them have been identified in the promoter region of the gene of PON1 enzyme and 176 polymorphisms have been identified in the genetic sequence. These polymorphisms may influence the risk of developing the disease and on the severity of the disease. It is well established that low PON1 enzyme activity is associated with an increased risk of cardiovascular disease, thus implying that PON1 is a physiologically important enzyme (Shunmoogam et al., 2018).

The activity and concentration of the PON1 enzyme in the human population was determined that can vary up to 40-fold. Some of the enlisted polymorphisms can have an impact on the activity or on the concentration of the PON1 enzyme. Part of this variability in activity and concentration can be explained by the presence of genetic polymorphisms of this enzyme that are associated with the substitution of amino acids in the protein at position 55 (methionine or leucine) - PON1 55M or 55L, and position 192 (arginine or glutamine: PON1 192Q or 192R). It has been established that the PON1 192QQ/55MM polymorphism has the lowest PON- ase activity in plasma (Khalil et al., 2021).

Furthermore, the distribution of PON1 polymorphisms varies among different ethnic populations. These differences may also lead to large differences in the activity of this enzyme among different populations (McDaniel,2014).

UNEDITED PROOF

Discussion and perspectives in research

From the above, it can be concluded that in the last few decades a large amount of research has been done, and great progress has been made regarding the understanding of HDL cholesterol and its functionality. At the same time, it is out of great interest that the

*Corresponding author e-mail: katekr@yahoo.com

understanding of the functionalities of proteins related to this lipoprotein - HDL has made brake trough.

The enzyme PON1, with its structure and activity, contributes to the regulation of the main antiatherogenic properties of HDL. Epidemiological and animal studies have shown that PON1 is a physiologically important enzyme that may play an important role in the protection against coronary vascular diseases. The atheroprotective role of PON1 is due to its antioxidant, anti-inflammatory role and its ability to regulate the reversible cholesterol transport. The lowering of the PON1 activity can be considered as an important factor contributing to HDL dysfunction.

In addition, the prevalence of single-nucleotide polymorphisms of the PON1 enzyme gene in the world population are relatively well researched and already known, while in the Macedonian population they are unknown and have not been researched so far.

From that point of view, it is of interest to conduct research that would approach the determination of genotypic variations of the gene of PON1 enzyme in a population where coronary artery disease has been confirmed by angiography , where the degree of association of different genotypes and mutations with the degree of change in PON1 activity and concentration could be defined , as well as the probability of the association and prediction of the risk of cardiovascular disease, because it is not yet known whether the resulting cardiovascular condition leads to a decrease in the activity of the PON1 enzyme or whether the cardiovascular condition is a product of the decreased PON1 activity.

Of course, future studies will be needed to further elucidate the physiological functions and mechanisms by which the PON1 enzyme exerts its antiatherogenic effects and its role in cardiovascular protection, to determine a narrow range of genetic and biochemical tests that would find their rightful place in early diagnosis of cardiovascular diseases and thus predict the risk of cardiovascular complications.

UNEDITED PROOF

Conclusion

Paraoxonase enzymes, particularly PON1, represent an important focus of current biomedical research due to their close association with HDL lipoprotein and cardiovascular health. The presented, clearly indicate that PON1 is one of the key components in mediating

*Corresponding author e-mail: katekr@yahoo.com

the antiatherogenic properties of HDL, primarily through its antioxidant and anti-inflammatory functions and its involvement in the regulation of reverse cholesterol transport.

Current evidence demonstrates that HDL lipoprotein functionality cannot be adequately assessed solely by measuring HDL-cholesterol concentration, but rather depends significantly on its proteomic composition and enzymatic activity, with PON1 playing a central role. Reduced PON1 activity is associated with increased oxidative stress, HDL dysfunction, and a higher risk of atherosclerosis and coronary artery disease. Furthermore, statin therapy has been shown to enhance PON1 activity, representing an additional mechanism by which statins increase their cardioprotective effects beyond lipid-lowering.

Genetic polymorphisms of the PON1 gene greatly influence the variability of the enzyme activity. While these polymorphisms have been extensively studied worldwide, their distribution and clinical relevance in the Macedonian population remain unexplored. This highlights the need for population-specific studies aimed at identifying PON1 genotypic variations and explaining their relationship with enzyme activity, concentration, and cardiovascular disease risk.

Future research should therefore focus on further clarifying the physiological functions and mechanisms of PON1 antiatherogenic effects, as well as on defining a targeted panel of genetic and biochemical markers that could be implemented in early diagnosis, risk stratification, and prediction of cardiovascular complications. Such an approach would contribute to improved understanding of cardiovascular pathophysiology and support the development of more effective and personalized preventive and therapeutic strategies.

UNEDITED PROOF

References

Bacchetti, T., Ferretti, G., Carbone, F., Ministerini, S., Montecucco, F., Jamialahmadi, T., Sahebkar, A., 2020. Dysfunctional high-density lipoprotein: the role of myeloperoxidase and paraoxonase-1. Current Medical Chemistry 28(14), 2842-2850. doi:10.2174/0929867327999200716112353.

Christidis, D.S., Liberopoulos, E.N., Kakafika, A.I., Miltiadous, G.A., Liamis, G.L., Kakaidi, B., 2007. Effect of paraoxonase 1 polymorphisms on the response of lipids and lipoprotein-associated enzymes to treatment with fluvastatin. Arch. Med. Res. 38, 403–10. doi:10.1016/j.arcmed.2007.01.006.

*Corresponding author e-mail: katekr@yahoo.com

Ferretti, G., Bacchetti, T., Sahebkar, A., 2015. Effect of statin therapy on paraoxonase-1 status: A systematic review and meta-analysis of 25 clinical trials. Prog. Lipid Res. 60, 50–73. doi:10.1016/j.plipres.2015.08.003.

Furlong, C.E, Marsillach, J., Jarvik, G.P., Costa, L.G, 2016. Paraoxonases-1, -2 and -3: What are their functions?. Chem. Biol. Interact. 259(B), 51-62. doi:10.1016/j.cbi.2016.05.036

Getz, G.S., Reardon, C.A., 2004. Paraoxonase, a cardioprotective enzyme: continuing issues. Curr. Opin. Lipidol. 15, 261-267.

Godbole, C., Thaker, S., Salagre, S., Shivane, V., Gogtay, N., Thatte, U., 2023. A prospective study to assess the role of paraoxonase 1 genotype and phenotype on the lipid-lowering and antioxidant activity of statins. Indian J. Pharmacol. 55(3), 179-184. doi:10.4103/ijp.IJP_215_20.

Harel, M., Aharoni, A., Gaidukov, L., 2004. Structure and evolution of the serum paraoxonase family of detoxifying and anti-atherosclerotic enzymes. Nat. Struct. MolBiol. 11, 412-419.

Huang, Y., Wu, Z., Riwanto, M., Gao, S., Levison, B.S., Gu, X., Fu, X., Wagner, M.A., Besler, C., Gerstenecker, G., Zhang, R., Li, X.M., DiDonato, A.J., Gogonea, V., Tang, W.H., Smith, J.D., Plow, E.F., Fox, P.L., Shih, D.M., Lusis, A.J., Fisher, E.A., DiDonato, J.A., Landmesser, U., Hazen, S.L., 2013. Myeloperoxidase, paraoxonase-1, and HDL form a functional ternary complex. J. Clin. Invest. 123(9), 3815-2828. doi:10.1172/JCI67478.

Khalil, A., Fulop, T., Berrougui, H., 2021. Role of Paraoxonase1 in the Regulation of High-Density Lipoprotein Functionality and in Cardiovascular Protection. Antioxid. Redox. Signal. 34(3), 191-200. doi:10.1089/ars.2019.7998.

Mackness, B., Beltran-Debon, R., Aragones, G., 2010. Human tissue distribution of paraoxonases 1 and 2 mRNA. IUBMB Lif. 62, 480-482.

Mackness, M., Mackness B., 2013. Targeting paraoxonase-1 in atherosclerosis. Expert OpinTher. Targets 17, 829-837.

McDaniel, C.Y., Dail, M.B., Wills, R.W., Chambers, H.W., Chambers, J.E., 2014. Paraoxonase 1 polymorphisms within a Mississippi USA population as possible biomarkers of enzyme activities associated with disease susceptibility. Biochemical Genetics 52(11–12), 509–523. doi:10.1007/s10528-014-9663-8.

Mirdamadi, H.Z., Sztanek, F., Derdak, Z., Seres, I., Harangi, M., Paragh, G., 2008. The human paraoxonase-1 phenotype modifies the effect of statins on paraoxonase activity and lipid

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

parameters. Br. J. Clin. Pharmacol. 66(3), 366-374. doi:10.1111/j.1365-2125.2008.03213.x.

Ng, C.J, Shih, D.M., Hama, S.Y., Villa, N., Navab, M., Reddy, ST, 2005. The paraox nase gene family and atherosclerosis. Free Radic BiolMed.38, 153-63.

Rajkovic, M.G., Rumora, L., Barisic, K., 2011. The paraoxonase 1, 2 and 3 in humans. Biochem. Med (Zagreb) 21(2), 122-30. doi:10.11613/bm.2011.020.

Rodrigo, L., Hernandez, A.F., Lopez-Caballero, J.J., Gil, F., Pla, A., 2001. Immunohistochemical evidence for the expression and induction of paraoxonase in rat liver, kidney, lung and brain tissue. Implications for its physiological role. Chem. Biol. Interact. 137, 123-137.

Shunmoogam, N., Naidoo, P., Chilton, R., 2018. Paraoxonase (PON)-1: a brief overview on genetics, structure, polymorphisms and clinical relevance. Vasc. Health Risk Manag. 14, 137-143. doi:10.2147/VHRM.S165173

Tomás, M., Sentí, M., García-Faria, F., Vila, J., Torrents, A., Covas, M., 2000. Effect of simvastatin therapy on paraoxonase activity and related lipoproteins in familial hypercholesterolemic patients. Arterioscler. Thromb. Vasc. Biol. 20, 2113–2109. doi:10.1161/01.atv.20.9.2113.

Variji, A., Shokri, Y., Fallahpour, S., Zargari, M., Bagheri, B., Abediankenari, S., Alizadeh, A., Mahrooz, A., 2019. The combined utility of myeloperoxidase (MPO) and paraoxonase 1 (PON1) as two important HDL-associated enzymes in coronary artery disease: Which has a stronger predictive role?. Atherosclerosis 280, 7-13. doi:10.1016/j.atherosclerosis.2018.11.004.

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com

doi: *Review paper*

Резиме

Параоксоназа ензими – параоксоназа 1 и неговата улога во функционалноста на HDL и предвидување на развој на кардиоваскуларна болест

Катерина Крстева Јакимовска*, Соња Топузовска

Медицински Факултет, Универзитет „Св. Кирил и Методиј“, ул. 50 Дивизија бр.6, 1000 Скопје, Република Северна Македонија

Клучни зборови: PON1, HDL, кардиоваскуларни, PON1 полиморфизми

Серумските параоксонази (PON) се фамилија на ензими чие присуство е докажано кај цицачите. Првично е откриен ензимот PON1, кој е одговорен за хидролиза на органофосфатните соединенија во ткивата. Според структурата, ензимот PON1 претставува гликопротеин. Откако PON1 ќе се синтетизира во црниот дроб, се локализира на клеточната мембрана пред да се излачи во крвотокот каде што станува специфично поврзан со HDL. Функционалноста на HDL во спречувањето на оксидацијата на липопротеините, особено LDL, се должи на PON1 и протеините поврзани со HDL. Многу студии покажуваат дека проценката на протеомот на HDL липопротеинот, особено ензимските компоненти - вклучително и PON1, може да имаат важно клиничко значење во предвидувањето на несакани кардиоваскуларни настани.

Активноста на PON1 е регулирана од генетски и надворешни фактори. Идентификувани се неколку еднонуклеотидни полиморфизми на генот што го кодира PON1. Неколку од нив имаат влијание врз активноста и концентрацијата на PON1 и покажуваат врска со намалување на поназа активноста во плазмата.

Кај македонската популација сèуште не е проучена преваленцата на евентуално присутни еднонуклеотидни полиморфизми поврзани со генот за PON1. Спроведувањето на студија од овој карактер би помогнало да се разјасни поврзаноста на полиморфизмите со варијациите на активноста и концентрацијата на PON1 и поврзаноста со функционалноста на HDL. Тоа би можело да има потенцијал да помогне во предвидувањето на ризикот од несакани кардиоваскуларни настани кај македонската популација.

*Corresponding author e-mail: katekr@yahoo.com

UNEDITED PROOF

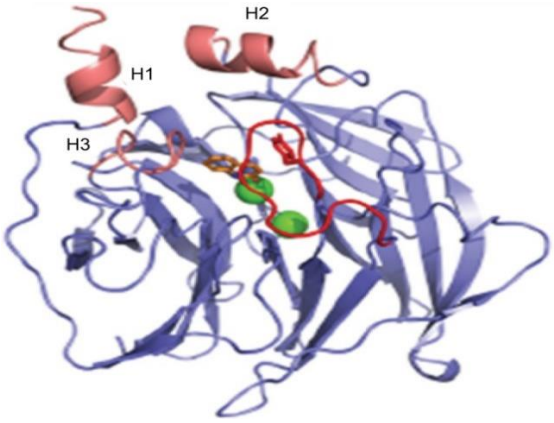


Fig. 1. Structure of recombinant PON1 illustrating the position of Ca2+ ions (marked in green) and the three helices (marked in pink).

UNEDITED PROOF

*Corresponding author e-mail: katekr@yahoo.com