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Review

# Non-genetic factors influencing serum PON1 levels

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**Abstract.** Paraoxonases (PON) are probably ancestral enzymes which, unlike other more modern enzymes from an evolutionary point of view, have a wide range of specificities and their catalytic versatility makes it possible to achieve a variety of functions. The PON enzyme family comprises three members: PON1, PON2, PON3, whose genes are located adjacent to each other on chromosome 7 (7q21-7q22). So far, more PON1 activities have been identified, namely: phosphotriesterase, arylesterase, lipo-lactonase activity. Lipid lowering compounds have been the focus of most studies on PON1 modulation by pharmacological agents. Aspirin may increases the activity and plasma concentration of serum PON1, probably due to the anti-inflammatory effect. Antibiotics (chloramphenicol and clarithromycin) reduced both serum and hepatic PON1 activity. Cigarette smoke irreversibly inhibits plasma PON1 activity, this effect being due to reactive aldehydes (acetaldehyde, formaldehyde, acrolein and crotonaldehyde) and aromatic hydrocarbons. Low levels of alcohol increased PON1 concentrations and activity. Antioxidants protect the enzyme from inactivation under oxidative stress control, which indirectly increases its activity. Pomegranate juice has increased PON1 activity in apolipoprotein E-deficient mice, as well as in people suffering from diabetes or in healthy male volunteers and healthy subjects. Human studies have shown that serum paraoxonase activity is reduced at birth and increases to 6-15 months, later remaining more or less stable. In elderly people, there is a progressive decline in paraoxonase and HDL activity, probably related to the development of oxidative stress, possibly as a consequence of the alteration of free sulfhydryl groups. Pregnancy was associated with reduced enzyme activity, and moderate physical exercise increased PON1 activity, even in smokers. Further research has to clarify the molecular mechanisms by which different substances in the environment modulate PON1 activity and expression, so that, by various nutritional or pharmacological interventions, we would be able to achieve therapeutic efficiency.

**Key Words:** paraoxonase, activities, drugs, food, age



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## Introduction

Even though the complexity of living organisms throughout their evolution has recorded a tremendous growth, there have been minor changes in terms of their molecular features. Paraoxonases (PON) are probably ancestral enzymes which, unlike other more modern enzymes from an evolutionary point of view, have a wide range of specificities and their catalytic versatility makes it possible to achieve a variety of functions. Gene duplication and divergence has led to the appearance of more specialized proteins with a high metabolic efficiency. This property was called "enzyme promiscuity", an enzyme with multiple "partners" or more substrates (Camps et al 2009).

The PON enzyme family comprises three members: PON1, PON2, PON3, whose genes are located adjacent to each other on chromosome 7 (7q21-7q22) (Aldirmaz et al 2011; Camps et al 2009).

Adkins et al (Adkins et al 1993) were the first ones who studied PON1 genetic polymorphisms, decoding the sequences in the coding region of PON1 from the human cDNA library (Camps et al 2009).

From a functional perspective, PON1 was initially described as an organophosphorus (OP) compound hydrolase (She et al 2012; Samy et al 2011; Aldirmaz et al 2011; Camps et al 2009), its name being due to the paraoxon substrate (Deakin et al 2004). So far, more PON1 activities have been identified, namely: phosphotriesterase activity associated with the hydrolysing activity on nerve agents, such as tabun, sarin, soman and organophosphorus insecticide and pesticide O-analogs like paraoxon, chlorpyrifos oxon, diazinon (She et al 2012, Aldirmaz et al 2011; Camps et al 2009).

Another activity is arylesterase activity, by which the enzyme hydrolyzes phenylacetate and other aromatic arylesterases. Due to this function, PON1 plays an important role in the metabolism of certain drugs (She et al 2012; Aldirmaz et al 2011; Camps et al 2009).

It took a long time until PON1 native function has been specified. Numerous studies have established that the primary role of PON1 is that of lipo-lactonase (Khersonsky et al 2005; Camps et al 2009), which has acquired new types of substrate specificity, some of the most preferred being the aliphatic cyclic lactone (Khersonsky et al 2006; Camps et al 2009, She et al 2012). This ancestral property enables PON1 to decompose exogenous lactones (glucocorticoid gamma-lactones, various bacterial agents) and endogenous lactones (homocystein thiolactone, derivatives of delta-Valerolactone resulting from the

hydrolysis of oxidized phospholipids) (Aldirmaz et al 2011; She et al 2012; Camps et al 2009).
The enzyme can facilitate the hydrolysis of biologically active oxidized phospholipids, as well as that of the platelet-activating factor (Aldirmaz et al 2011; Camps et al 2009) due to its similar activity to phospholipase A2.
Another activity, controversial to some extent, is the "peroxidase-like" activity, which involves PON1 in the breakdown of lipid peroxides and H2O2 (Aldirmaz et al 2011). PON1 facilitates the hydrolysis of 25% of the H2O2 resulted from atherogenic oxidative stress (Aldirmaz et al 2011).
The physiological role of PON1 was first approximated by Mackness et al (Mackness et al 1991), who have observed that this enzyme prevents the generation of lipoperoxides in the oxidation of LDL (Camps et al World J Gastroenterol 2009; Camps et al 2009). In turn, PON1 is inactivated by oxidized lipids, as demonstrated by Aviram et al (Aviram et al 1999; Camps et al 2009). Further studies have shown that PON1 alters certain oxidized esters of cholesterol and some oxidized phospholipids contained in lipoproteins, thus protecting HDL and LDL from lipid peroxidation (Mackness et al 1993; Navab et al 1996, Aviram et al 1998). On the other hand, PON1 prevents the modification of proteins by homocysteinthiolactone (She et al 2012).
So far, more than 180 PON1 gene polymorphisms have been identified, some located in the coding region, others in the introns or in the regulatory region of the gene (Costa et al 2005). The amount and/or catalytic efficiency of PON1 are the result of point mutations (single nucleotide polymorphisms, SNPs) (She et al 2012). In the human population, there is a polymorphic distribution of plasma paraoxonase activity and there may be three different phenotypes showing low, intermediate or high paraoxonase activity. The frequency of SNPs that determines high or low activities is variable among ethnic groups or in relation to the geographical region (Costa et al 2005; Camps et al 2009).
In our previous study, we analyzed PON1 activity in patients with hepatic steatosis and the possible association of lifestyle factors with all three enzyme activities of PON1 for the first time in Romania (Ciumarnean et al 2013).

## Modulation of PON1 by exogenous compounds

### Chemicals in the environment

Calcium is essential for PON1 activity and EDTA irreversibly inhibited enzyme activity (Costa et al 2005). Barium, copper, zinc and mercury decreased hepatic PON1 activity (Gonzalo et al 1997, Costa et al 2005). The study on human serum of individuals with PON1 192Q has revealed similar results in terms of the inhibitory effect of magnesium, cobalt, cadmium and nickel (Costa et al 2005), which are the most potent in vitro enzyme inhibitors in PON1 192R carriers (Costa et al 2005).
A marked decrease of over 80% in hepatic PON1 activity was recorded after the administration of carbon tetrachloride in mice (Costa et al 2005).

### Drugs

Lipid lowering compounds have been the focus of most studies on PON1 modulation by pharmacological agents. (Deakin et al 2004) Human studies have had contrasting results. There was an increase in serum PON1 activity in patients treated with simvastatin or other statins, fibrates (gemfibrozil and fenofibrate), while other studies have found no change in serum PON1 activity in patients treated with these drugs (Costa et al 2005; She et al 2012). Through their effect, statins (atorvastatin) improved lipid profile of individuals and even if they did not change PON1 activity towards paraoxon, they improved PON1 activity towards LDL cholesterol (Tsimihodimos et al 2002; She et al 2012). We have also obtained similar results when comparing subjects with and without hepatic steatosis. There was no difference between the groups related to PON1 enzyme activities (Ciumarnean et al 2013).
We have also obtained significant differences between the two groups of participants for total cholesterol and HDL levels, which could be explained by the statistically significant differences observed between the 2 groups compared in terms of lipid-lowering medication use by the participants in the study. This could be the explanation of these discordant results (Ciumarnean et al 2013).
In a group of subjects using aspirin, a significant increase has been reported in the activity and plasma concentration of serum PON1, probably due to the anti-inflammatory effect (Costa et al 2005). Other studies have noted increases in serum PON1 activity by about 13%, but only in patients with coronary heart disease (Blatter-Garin et al 2003; She et al 2012), whereas there has been no improvement in enzyme activity in healthy individuals (Kurban et al 2010, She et al 2012).
Dexamethasone increased PON1 mRNA level in hepatocytes in mice, whereas other studies using a muscarinic cholinergic antagonist – atropine have revealed a decreased human PON1 in both plasma and hepatic activities (Costa et al 2005).
Oral antidiabetics (rosiglitazone, eplerenone or sulfonylurea) caused an increase in PON1 activity (She et al 2012).
Estrogen replacement therapy improved PON1 activity in postmenopausal diabetic women (Sutherland et al 2001; She et al 2012), but intranasal administration of estradiol did not have significant effects (Fenkci et al 2006; She et al 2012).
Antibiotics (chloramphenicol and clarithromycin) reduced both serum and hepatic PON1 activity (She et al 2012).
Administered to anemic patients with chronic renal failure, erythropoietin β increased plasma PON1 activity by approximately 20% (Marsillach et al 2007; She et al 2012).
The impact of food supplements on paraoxonase 1 activity has also been shown. A recently published study has shown that the nutritional supplement ALAnerv® (containing, among others, alpha-lipoic acid, linoleic acid and gamma-linolenic acid, vitamins E, B1, B2, B5, B6, and selenium) can improve serum PON1 activity in patients with post-stroke syndrome (Manolescu et al 2013).

### Classical inducers

Despite the generally inconsistent current data, findings have suggested that PON1 is not susceptible to modulation by classical enzyme inducers. Although the mechanism has not yet been identified, it appears that phenobarbital reduces the release of PON1 by the liver in the circulation (Vitarius et al 1995; Costa et al 2005). This, though effective with preference to certain cytochrome P450 isoenzymes, caused a modest increase in PON1

activity (20-150%) together with the increase in hepatic mRNA levels (Costa et al 2005). Serum PON1 activity decreased during therapy with phenobarbital (Kaliste-Korhonen et al 1998; Vitarius et al 1995, Costa et al 2005).

## Modulation of PON1 by lifestyle factors

Cigarette smoke irreversibly inhibits plasma PON1 activity, this effect being due to reactive aldehydes (acetaldehyde, formaldehyde, acrolein and crotonaldehyde) and aromatic hydrocarbons (Nishio et al 1997, She et al 2012). In our research, smoking had a significant influence on arylesterase activity (Ciumarnean et al 2013).

Low levels of alcohol increased PON1 concentrations and activity (Sierksma et al 2002; She et al 2012). PON1 activity may increase by 395% in subjects drinking small amounts of alcohol, whereas in subjects drinking big amounts of alcohol, serum activity was lower by 45% compared to people who are abstinent (Rao et al 2003, Costa et al 2005; She et al 2012). Data regarding alcohol consumption are controversial because some studies have failed to demonstrate increases in PON1 activity (Sarandol et al 2003; She et al 2012), although they used alcohol doses similar to other studies, which have reported significant changes in enzyme activity (She et al 2012). In the research carried out in our study, only paraoxonase activity was influenced by alcohol (Ciumarnean et al 2013), probably as a consequence of the action of alcohol on protein kinase C. This is important in the phosphorylation of an Sp1 active site in the promoter region of the PON1 gene (Costa et al 2005).

In mice, there has been a significant increase in PON1 activity (46%) after a diet rich in triolein (Costa et al 2005). Current data regarding the consumption of fish oil were surprising: it caused a decrease of approximately 39% in PON1 activity (Kudchodkar et al 2000, Costa et al 2005). In women, olive oil caused an even larger increase in PON1 activity than in men, and of these, only in those with the PON1 192RR genotype (Thomas et al 2001, Costa et al 2005). On the other hand, linoleic acid inhibited its activity, whereas oleic acid was effective in stabilizing PON1 and in antioxidant protection (Nguyen et al 2003). In other studies, myristic acid and gadoleic acid were positively associated with PON1 activity, while oleic acid, alpha-linolenic, arachidonic and eicosapentaenoic acid have been negatively associated with PON1 activity (Kim et al 2013).

Fasting, but only short-term fasting, managed to increase PON1 activity, but this increase in enzyme activity was actually an adaptive response to the decrease in lipid peroxidation (Thomas-Moya 2007).

Kim et al have shown that five components of the human diet (cholesterol, alcohol, vitamin C, iron, and folic acid) influenced PON1 activity (Kim et al 2012). Probiotics increased the PON1 activity in animals (

Antioxidants protect the enzyme from inactivation under oxidative stress control, which indirectly increases its activity. Pomegranate juice has increased PON1 activity in apolipoprotein E-deficient mice (Kaplan et al 2001), as well as in people suffering from diabetes (Rock et al 2008) or in healthy male volunteers (Aviram et al 2000) and healthy subjects (Aviram et al 2013). Various studies have reported discrepancies regarding the influence of the consumption of vitamins C and E on PON1: some studies have found a positive correlation (Jarvik et al 2002; She et al 2012), whereas others have found no correlation (Ferre et al 2003), or negative correlations (Rantala et al 2002; Kleemola et al 2002). The treatment with phytoalexin resveratrol caused an increase in hepatic PON1 expression (Altenhofer et al 2010), as well as in plasma enzyme activity (She et al 2012).

## Effects of age, gender and various physiological conditions on PON1 activity

Human studies have shown that serum paraoxonase activity is reduced at birth and increases to 6-15 months, later remaining more or less stable (Mueller et al 1983; Ecobichon et al 1973). In premature infants, PON1 activity is up to 24% lower than in full-term babies (Ecobichon et al 1973), which is relevant for the increased susceptibility to certain OPs (Costa et al 2005).

In elderly people, there is a progressive decline in paraoxonase and HDL activity, probably related to the development of oxidative stress, possibly as a consequence of the alteration of free sulfhydryl groups (Seres et al 2004; Jaouad et al 2006). PON1 arylesterase activity and concentration are the only one that did not appear to suffer significant changes related to aging (Jaouad et al 2006).

In our study, age did not influence any of the PON1 enzyme activities (Ciumarnean et al 2013).

Gender did not influence PON1 activity, due to genetic heterogeneity (Ali et al 2003), even though there have been slightly higher mean values of serum PON1 activity in women (Costa et al 2005; She et al 2012). Similar to other studies (Costa et al 2005), we did not observe any effect of gender on enzyme activities when comparing subjects with and without hepatic steatosis (Ciumarnean et al 2013).

Pregnancy was associated with reduced enzyme activity (Weitman et al 1983), and moderate physical exercise increased PON1 activity, even in smokers (Costa et al 2005). In our research, values were close to the threshold of statistical significance when analyzing the relationship between physical exercise, cold cut and sausage consumption and paraoxonase levels (Ciumarnean et al 2013), similar to other studies (She et al 2012; Costa et al 2005).

## Conclusions

Further research has to clarify the molecular mechanisms by which different substances in the environment modulate PON1 activity and expression, so that, by various nutritional or pharmacological interventions, we would be able to achieve therapeutic efficiency.

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