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Pharmacological and dietary modulators of paraoxonase 1 (PON1) activity and expression: the hunt goes on*

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Abstract

Paraoxonase 1 (PON1) is a high density lipoprotein (HDL)-associated enzyme displaying esterase and lactonase activity. PON1 hydrolyzes several organophosphorus (OP) insecticides and nerve agents, a number of exogenous and endogenous lactones, and metabolizes toxic oxidized lipids of low density lipoproteins (LDL) and HDL. As such, PON1 plays a relevant role in determining susceptibility to OP toxicity, cardiovascular diseases and several other diseases. Serum PON1 activity in a given population can vary by at least 40-fold. Most of this variation can be accounted for by genetic polymorphisms in the coding region (Q192R, L55M) and in the promoter region (T-108C). However, exogenous factors may also modulate PON1 activity and/or level of expression. This paper examines various factors that have been found to positively modulate PON1. Certain drugs (e.g. hypolipemic and anti-diabetic compounds), dietary factors (antioxidants, polyphenols), and life-style factors (moderate alcohol consumption) appear to increase PON1 activity. Given the relevance of PON1 in protecting from certain environmental exposure and from cardiovascular and other diseases, there is a need for further mechanistic, animal, and clinical research in this area, and for consideration of possible alternative strategies for increasing the levels and activity of PON1.

Keywords

Paraoxonase 1; statins; hypolipemic drugs; anti-diabetic drugs; antioxidants; polyphenols; alcohol

1. Introduction

Paraoxonase 1 (PON1) is a member of a three-gene family which also comprises PON2 and PON3, all clustered in tandem on the long arm of human chromosome 7 (q21.22). PON1 is

*The title refers to an earlier article on this topic [1].

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synthesized primarily in the liver and a portion is secreted in the plasma, where it is associated with high density lipoproteins (HDL); low levels of PON1 may be expressed in a number of tissues, primarily in epithelia. PON1 received its name from its ability to hydrolyze paraoxon, the active metabolite of the organophosphorus (OP) insecticide parathion, which is its first and most studied substrate. However, PON1 also hydrolyzes the active metabolites of several other OP insecticides (e.g. chlorpyrifos oxon, diazoxon), as well as nerve agents such as sarin and soman. In addition to its esterase activity, PON1 also acts as a lactonase, and is capable of hydrolyzing a variety of lactones, including certain drugs (e.g. the antibacterial prodrug prulifloxacin), endogenous compounds (e.g. lactone metabolites of arachidonic acid, or homocysteine thiolactone), and N-acyl-homoserine lactones, which are quorum sensing signals of pathogenic bacteria [2,3]. PON1 also protects low density lipoproteins (LDL), as well as high density lipoproteins (HDL) from oxidation [4]. Because of all these activities, the role of PON1 in modulating susceptibility to OP insecticides, cardiovascular disease, and several other diseases, has been extensively investigated [4,5].

2. PON1 is a polymorphic enzyme

Earlier observations had indicated that the serum paraoxonase activity in human populations exhibited a polymorphic distribution [4]. Subsequent studies led to the purification, cloning and sequencing of human and rabbit PON1s, and in the molecular characterization of its polymorphisms [6]. Two polymorphisms were observed in the PON1 coding sequence: a Gln(Q)/Arg(R) substitution at position 192, and a Leu(L)/Met(M) substitution at position 55. The allele frequencies of the PON1 192 and 55 genotypes have been examined in several populations, and shown to vary significantly [7]. In addition to these two polymorphisms in the coding region of PON1, additional polymorphisms have been found in the non-coding region of the PON1 gene. One of the most significant is a polymorphism at position −108, with the −108C allele providing levels of PON1 about twice as high on average as those seen with the −108T allele [7]. Re-sequencing of PON1 from more than 40 individuals has led to the identification of nearly 200 new single nucleotide polymorphisms, some in the coding regions, and others in introns and regulatory regions of the gene. These polymorphisms have for the most part not been yet characterized, but may affect regulation by miRNAs, splicing efficiency, message stability or efficiency of polyadenylation.

The coding region polymorphisms of PON1 have been investigated for effects on the catalytic efficiencies of hydrolysis of specific substrates. The L/M polymorphism at position 55 does not appear to affect catalytic activity, but has been associated with plasma PON1 protein levels, with $PON1_{M55}$ being associated with low plasma PON1 activity. However, this appears to result primarily from linkage disequilibrium with the low efficiency of the −108T allele of the −108 promoter region polymorphism [7]. The Q/R polymorphism at position 192 significantly affects the catalytic efficiency of PON1 for some substrates. The $PON1_{R192}$ allozyme hydrolyzes paraoxon or chlorpyrifos oxon more readily than $PON1_{Q192}$, while the opposite is true in case of sarin or soman [4]. In the case of diazoxon, both PON1 alloforms hydrolyze this compound with the same efficiency [4].

Lactones are hydrolyzed preferentially by either $PON1_{R192}$ or $PON1_{Q192}$, depending on their structure [8]. For example, $PON1_{R192}$ is more efficient at hydrolyzing homocysteine thiolactone, while δ-valerolactone and 2-coumaranone are more rapidly hydrolyzed by $PON1_{Q192}$ [8]. $PON1_{Q192}$ has also a higher efficiency in protecting against LDL oxidation than the R192 allozyme [9].

3. PON1 levels and Q192R polymorphism define an individual's PON1 status

Most studies investigating the association of PON1 with various diseases have examined nucleotide polymorphisms (mainly Q192R, L55M, C-108T) with PCR-based assays. A functional genomic analysis, by measuring enzymatic activity of various variants, however, provides a much more informative approach, as measurement of an individual's PON1 function (serum activity) takes into account all polymorphisms and other factors that might affect PON1 activity or expression. This is accomplished through the use of high-throughput two-dimensional enzyme assays involving two PON1 substrates (usually diazoxon and paraoxon at high salt concentration) [10]. This approach, which provides a functional assessment of the plasma PON_{192} alloforms, including information on the plasma level of PON1 for each individual, has been referred to as the determination of PON1 "status" for an individual [10]. In a given population, plasma PON1 activity can vary up to 40 to 50-fold, and differences in PON1 protein levels up to 13–15-fold are also present within a single $PON1_{192}$ genotype in adults [4,10].

An issue that has hampered a wider use of PON1 status measurements is the need of using two highly toxic OPs, diazoxon and paraoxon. It has been recently reported that measuring the hydrolysis of phenylacetate at high (2 M) salt, and of 4-(chloromethyl) phenylacetate at low salt, provides an excellent resolution of functional PON1 phenotypes. Both the old assay with the two OPs and the new assay provide a clear separation of the three PON1 192 functional genotypes (QQ, QR, RR), as well as information on enzyme activity within each genotype [11].

Most studies examining PON1 activity have not utilized the two-dimensional assay, but have relied on the use of a single substrate. Given that PON1 activity is strongly determined by enzyme genotype, assays using paraoxon as a substrate would provide equivocal results, if each group is not matched for genotype. Use of PON1 substrates that are not affected by the R192Q polymorphisms (e.g. phenylacetate hydrolysis at low salt) is certainly indicated, as is analysis of PON1 concentration (e.g. by ELISA).

4. Implications of PON1 status in response to toxic exposures, in cardiovascular health and in other diseases

The importance of PON1 status in modulating susceptibility to the acute toxicity of a number of OP insecticides has been shown by several studies [4,12]. Studies with transgenic animal models have shown that PON1-deficient mice are highly susceptible to the toxicity of specific OPs [4]. Depending on the OP, PON1 levels alone (as in case of diazoxon) or PON1 192 alloform as well as level (as in case of chlorpyrifos oxon), may determine the degree of protection against a specific OP [12].

Alterations in circulating PON1 levels have been found in a variety of diseases involving oxidative stress, including cardiovascular disease, diabetes, Alzheimer's disease, chronic renal failure, chronic liver impairment [13,14]. Studies investigating the role of PON1 in cardiovascular disease have provided evidence that PON1 status (encompassing genotype and activity levels) is a much better predictor of disease than PON1 genotype alone [15].

5. Factors that may increase PON1 activity or expression

Given the role of PON1 in protecting against toxic pesticide exposures and cardiovascular disease [4], and its decrease in a number of pathological conditions [14], it is not surprising

that particular attention has been devoted to factors that may modulate PON1 activity or expression [1,13,16].

While a major determinant of PON1 activity is represented by genetic polymorphisms, additional factors, not discussed in this review, should also be mentioned. Age plays the most relevant role, as PON1 activity is very low before birth and gradually increases during the first year or two of life in humans [13]. PON1 activity may also decline with aging, possibly because of the development of oxidative stress conditions [13]. An influence of gender has also been suggested, with females displaying higher PON1 activity [13].

5.1. Drugs

Several studies investigating modulation of PON1 have involved pharmaceutical drugs, particularly lipid-lowering compounds such as statins and fibrates, as well as some other drugs. A few human studies are available, together with some animal and in vitro studies (Table 1).

5.1.1. Statins—Statins are a major class of hypolipidemic drugs, which block cholesterol synthesis by inhibiting the enzyme HMG-CoA reductase. In humans, treatments with simvastatin [17,18], or atorvastatin [18–20] have been shown to increase serum paraoxonase activity. Increases are small, ranging from 5 to 23%. Other studies, however, failed to find any changes in serum paraoxonase activity following simvastatin or atorvastatin [21]. Animal and in vitro studies provide similar contrasting results. Two earlier studies by Beltowski et al. (see [13]) showed that treatment of rats with fluvastatin, but not with pravastatin, decreased rather than increased, serum and liver paraoxonase activity. A similar decrease of PON1 mRNA and activity levels induced by pravastatin, simvastatin and fluvastatin in a human hepatoma cell line (HuH7) was reported by Gouedard et al. [22]. Statins significantly decreased PON1 promoter activity, and their effects were reversed by mevalonate. Further, the effects of statins were antagonized by 22(R)-hydroxycholesterol, which activates LXR receptors, implicating the latter in the modulation of PON1 expression (see below). In contrast to the findings of Gouedard et al. [22], and in agreement with most human studies, several other investigators reported that statins increase PON1 expression and activity in various in vitro systems. Aviram et al. [23] initially found that two metabolites of atorvastatin (p-hydroxy and o-hydroxy), but not the parent compound, increased paraoxonase activity in isolated HDL. In HepG2 cells (a human hepatoma cell line), simvastatin was found to upregulate the activity of the PON1 promoter by increasing a nuclear transcription factor, sterol regulatory element-binding protein-2 (SREBP-2); these effects were reversed by mevalonate [17]. Similar findings were reported by Ota et al. [24], who found that pitavastatin, atorvastatin, and simvastatin increased PON1 promoter activity in HepG2 cells and in HEK293 cells (human embryonic kidney cells). The effect of statins on PON1 expression appeared to be mediated by activation of Sp1, and was reversed by mevalonate. In a follow-up to their earlier study, Deakin et al. [25] confirmed the role of SREBP-2 and Sp1 in the increase of PON1 expression caused by simvastatin in HepG2 cells. They also found that simvastatin-induced binding of these transcription factors, and that the ensuing increased promoter activity was more pronounced with the −108C allele, than the −108T allele. Thus, patients with the −108C allele, which already have higher PON1 levels, may further benefit from a treatment with statins. Indeed, Deakin et al. [25] showed that serum PON1 expression was increased (by about 12%) by simvastatin in patients homozygous for −108C (CC), but not in TT individuals. At difference with these findings, Sardo et al. [26] found that treatment of hypercholesterolemic patients with atorvastatin increased serum PON1 activity independent of the T(−108)C, as well as the Q192R and L55M polymorphisms. A more recent study in HuH7 cells reported that pivastatin increased PON1 promoter activity and PON1 expression through Sp1 and

SREBP-2 [27]. Activation of the transcription factors was in turn mediated by activation by pivastatin of mitogen activated protein kinases p44/42, raising the possibility that other factors acting through this pathway may affect PON1 expression. Still, in HuH7 cells, simvastatin was recently shown to increase PON1 activity by two-fold with an EC50 of 6.8 uM [28].

5.1.2. Fibrates—A few studies have investigated the effects of these lipid-lowering agents on serum paraoxonase activity. Three studies by the same research group reported increases of PON1 activity (18–49%) in patients with type 2 diabetes treated with gemfibrozil, in patients with coronary heart disease treated with micronized fenofibrate, and in patients with metabolic syndrome treated with ciprofibrate [13,29]. In support of these findings, Aviram et al. [23] reported that a metabolite of gemfibrozil, but not the parent compound, increased paraoxonase activity in isolated HDL. Additionally, Gouedard et al. [22] found a 70% increase in PON1 activity and mRNA in HuH7 cells upon exposure to fenofibrate. In contrast to these results, two studies in patients with familial hyperlipoproteinemia treated with ciprofibrate [30], bezafibrate mono, or gemfibrozil [31] found no evidence of significant changes in serum paraoxonase activity.

5.1.3. Other cardiovascular drugs—The activity of serum PON1 was found to be increased (by ~13%) in coronary patients who took low-dose aspirin (acetylsalicylic acid), which prevents platelet aggregation [32]. However, administration of aspirin to healthy volunteers did not alter serum PON1 activity in another study [33]. An additional study investigating the effect of aspirin (2 mg/day for six days) in LDLr $^{-/-}$ or C57BL6 mice fed an atherogenic diet [34], reported a two-fold increase in serum PON1 activity, which was accompanied by a 7-fold induction of liver PON1 gene expression. Of interest is that aspirin did not cause the same increase in PON1 in mice lacking the Ah receptor. These authors also observed a significant induction of PON1 by aspirin in HepG2 cells, with evidence of an involvement of the Ah receptor [34]. The aspirin derivative nitro-aspirin, and its metabolite salicylic acid, also increased PON1 activity and expression. It should also be noted that PON1 had been reported to hydrolyze aspirin and nitro-aspirin [35]. Aspirin also increased PON1 activity (by 2-fold) in HuH7 cells with an EC50 of 19 uM [28]. The cholesterol lowering drug probucol (500 mg/kg/day for 14 weeks) was found to up-regulate serum paraoxonase activity and PON1 expression in hepatocytes of hypercholesterolemic rabbits [36]. Ezetimibe (a drug inhibiting cholesterol absorption) given to hyperlipidemic patients for twelwe weeks (10 mg/day) was recently reported to increase serum PON1 activity [37].

5.1.4. Rosiglitazone and other anti-diabetic drugs—The peroxisome proliferator-activated receptor (PPAR)-γ agonist rosiglitazone, used in the treatment of type-2 diabetes, has been investigated in a few studies for its effects on PON1. Administration of rosiglitazone to diabetic patients was found to cause a small (9–13%) increase in fasting and post-prandial serum PON1 activity [38]. A similar increase (21%) of serum PON1 activity was found in rabbits treated with rosiglitazone for six weeks (0.32 mg/kg/day; [39]). Treatment of rats with rosiglitazone was also shown to increase (by about 67%) hepatic PON1 activity, which had been decreased by feeding with a high fructose diet to mimic the human metabolic syndrome [40]. Eplerenone, a selective aldosterone blocker used in diabetics, was found to increase hepatic PON1 activity in control and in streptozotocin-treated diabetic mice [41]. Two sulphonylureas, glimepiride and glibenclamide, used as oral hypoglycemic agents in diabetes, were reported to increase PON1 activity in the liver of control and of streptozotocin-treated, diabetic rats [42]. However, plasma PON1 activity was either decreased (in control rats) or unchanged (in diabetic rats) [42].

5.1.5. Other drugs—Various other pharmaceutical drugs have been investigated in different experimental protocols for their effects on PON1 activity and/or expression. The cholinergic muscarinic antagonist atropine was reported to inhibit human plasma paraoxonase in vitro at high concentrations (Ki = 0.25 mM; [13]). Certain antibiotics, such as sodium ampicillin, ciprofloxacin and clindamycin sulfate, but not rifamycin, inhibited purified human PON1 with Ki values ranging from 65 nM to 30 uM [43]. When the same antibiotics were given in vivo to mice, however, increases or decreases of serum PON1 activity at different time-point were observed, with similar results observed in the liver [43].

Cyclophosphamide, an anti-tumor drug, was reported to cause a >2-fold increase in renal PON1 activity in rats [44], which was interpreted as a defense mechanism against drug-induced oxidative stress. Oral contraceptives (desogestrel or levonorgestrel in combination with ethinyl estradiol) were found to significantly decrease liver PON1 activity, but to increase serum PON1 activity in mice [45]. In postmenopausal women, intranasal administration of estradiol had no significant effect on serum PON1 activity [46], while a hormone-replacement therapy (estrogen and methoxyprogesterone acetate) in diabetic post-menopausal women caused a small increase (10%) of serum PON1 activity [47]. Erythropoietin beta, used in patients with anemia, increased serum PON1 activity by ~23% in a group of predialysis patients with chronic renal disease and anemia [48]. In contrast, the anabolic steroid nandrolone decanoate, which is suggested as an adjuvant therapy to erythropoietin in anemia, has been shown to cause a small, but significant decrease of serum PON1 activity [49]. Among drugs affecting the central nervous system, the antidepressant citalopram (a selective serototonin uptake inhibitor) was reported to not significantly affect serum PON1 activity, which was reduced in untreated depressed patients relative to controls [50].

As indicated earlier, an involvement of the LXR receptor in the modulation of PON1 had been suggested by results obtained with statins [22]. More recently the LXR agonist T0901317 restored serum PON1 activity in rats upon its decrease induced by leptin [51]. Activation of another nuclear hormone receptor, the farnesoid X receptor (FXR), identified as the target for bile acids, has been shown to induce a decrease in serum PON1 activity and liver PON1 expression in mice [52].

D-4F, an apoA-I mimetic peptide in development for use in patients with coronary heart disease, has been shown to slightly increase plasma PON1 activity in mice and non-human primates [16].

5.2. Dietary antioxidants

As PON1 is easily inactivated by exogenous or endogenous oxidants [53], several strategies to increase PON1 have focused on the administration of dietary antioxidants (Table 2).

5.2.1. Vitamin C and vitamin E—A handful of studies in animals and humans examined the effects of the antioxidant vitamin C (ascorbic acid) and vitamin E (α-tocopherol) on paraoxonase activity. An earlier study reported that dietary vitamin C and E intake (estimated from a food survey) was associated with increased paraoxonase activity in male Caucasian subjects [54]. An experimental study by Gursu et al. [55] in quail showed that administration of vitamin C reversed the decrease in serum paraoxonase activity induced by heat stress, particularly when given in association with folic acid. Hypochlorite-induced paraoxonase activity loss in human plasma in vitro was shown to be antagonized by vitamin C [56]. Two additional studies in rats and rabbits showed that vitamin E supplementation increased paraoxonase activity. In rats, vitamin E reversed the decrease in serum paraoxonase activity caused by experimental hypothyroidism induced by propylthiouracyl, and caused a small increase of serum PON1 activity in control animals [57]. In rabbits fed a

high cholesterol diet, vitamin E increased serum and liver paraoxonase activity, but did not affect hepatic PON1 mRNA levels [58]. A small study in humans (healthy male basketball players) recently showed that supplementation with vitamin E prevented the exercise-induced reduction in serum PON1 activity [59]. In contrast, a three month treatment of hemodialysis patients with vitamin E-coated dialysis membranes showed no effect of serum paraoxonase activity [60]. Furthermore, studies in Finland reported that high intake of vegetables, possibly rich in vitamins C and E, was associated with lower serum PON1 activity [61].

5.2.2. Quercetin, resveratrol, and other dietary polyphenols—Several dietary polyphenols, and in particularly quercetin, have been shown to up-regulate PON1. In an earlier study, Hayek et al. (see [13]) showed that consumption of red wine or its polyphenols quercetin or catechin by apolipoprotein E-deficient mice (whose plasma PON1 activity is lower than controls), was associated with an increase in serum paraoxonase activity. Quercetin (0.05 mg/day for two weeks) was the most effective molecule for increasing PON1 activity (by 113%). In transgenic ApoE3 mice (expressing the human ApoE3 allele) dietary quercetin (2 mg/g of diet) for six weeks increased PON1 mRNA levels (by 37%), while a lesser effect was found in transgenic ApoE4 mice [62]. Administration of a mixture of red wine polyphenols (3 mg/day, containing 25 ug catechin and several other compounds) increased hepatic PON1 activity in mice, while a higher dosage levels (12 mg/day with 100 ug catechin) had an opposite effect [63]. The low dose of polyphenols was also capable of reversing the decrease of plasma and hepatic PON1 activities and of liver mRNA levels present in hyperhomocysteinemic mice [63]. Quercetin (10 mg/L in a liquid diet for 4 weeks) was found to increase hepatic PON1 expression by 35%, liver PON1 activity by 57%, and serum PON1 activity by 29% [64]. In C57BL/6 mice, dietary administration of quercetin (0.05–2 mg/g of diet) increased hepatic PON1 mRNA and protein levels to a maximum of 200% and 150% of controls, respectively [65]. Administration of quercetin to mice lacking the LDL receptor ($LDL^{-/-}$) for four weeks was reported to increase liver PON1 mRNA and serum PON1 activity by 40–90%, depending on the dose [66]. In HuH7 hepatoma cells PON1 activity and mRNA levels were increased by quercetin (50 uM) and by other polyphenols (naringenin, flavone), but not by catechin [67]. Such effects appeared to be mediated by activation of the Ah receptor, and of a xenobiotic response element (XRE)-like sequence within the PON1 promoter, which was also activated by 3-methylcholanthrene (3-MC). Indeed, 3-MC caused a 2-fold increase in PON1 mRNA, and a 49% increase in PON1 activity. In contrast, 2,3,7,8 tetrachlorobenzodioxin (TCDD), a potent inducer of the CYP1A1 gene, was a poor inducer of PON1, causing a small, non significant increase in PON1 mRNA, and a small (18%) increase in PON1 activity [67]. The author suggested that the XRE-like sequence in the PON1 promoter differs from the consensus XREs from the CYP1A1 gene in the response to 3-MC, quercetin and TCDD [67]. However, this issue is not fully clear and needs to be further investigated. In a reporter gene assay in the same HuH7 cells, quercetin and its methylated metabolite isorhamnetin (both at 25 uM) increased PON1 promoter activity by 1.4- and 2.7-fold, respectively [65]. A two-fold increase in PON1 activity in HuH7 cells by quercetin (EC50 = 6.0 uM) was also recently reported [28]. In these same cells, quercetin (10 and 20 uM) was found to increase PON1 activity protein and mRNA levels, by up to two-fold [68]. Interestingly, quercetin was found to act through SREPB-2, as it caused translocation of this transcription factor from the endoplasmic reticulum to the nucleus, where is interacts with sterol responsive elements-like sequence on the PON1 promoter [68].

In contrast to all these animal and in vitro studies, a single human study in which quercetin was administered at doses of 50, 100 or 150 mg/day did not cause any alterations in serum paraoxonase activity [65]. However, a study in hemodialysis patients showed that dietary exposure to a catechin mixture (containing epicatechin, gallocatechin, epigallocatechin,

epicatechin gallate and epigallocatechin gallate, as found in green tea extracts), increased serum paraoxonase activity [69]. Green tea, given at 2% in water to streptozotocin-induced diabetic rats, was also found to increase serum PON1 activity [70]. Resveratrol, a polyphenolic phytoalexin found in grapes and wine, was shown to increase PON1 gene expression in human hepatocyte primary cultures and in HuH7 cells [65,71]. This effect appeared to be dependent upon activation of the Ah receptor and to involve an XRE-like element in PON1's promoter within the −126 and −106 region [71]. Grape seed extracts have also been reported to increase serum paraoxonase activity in control, and particularly in streptozotocin-induced diabetic rats [72]. Freeze-dried blueberries, known to contain high levels of polyphenols, were found to increase serum PON1 activity (by ~ 25%) in Apo E-deficient mice, when fed at 1% in the diet for 20 weeks [73]. The dietary supplement Protandim®, containing various herbs rich in polyphenols) was shown to increase plasma PON1 activity by 35% in muscular dystrophy *Mdx* mice fed this supplement before birth and up to six months of age at the huma recommended dose of 675 mg/day [74].

A series of studies have examined the effects of pomegranate juice and extract, containing several polyphenolic compounds such as punicalagin, gallic acid and ellagic acid, on PON1 activity and expression. Aviram et al. (see [13]) reported a 20% increase in plasma PON1 activity in humans given 20–80 mL/day of pomegranate juice. This was subsequently confirmed in patients with carotid artery stenosis (a 83% increase in serum PON1 activity after consumption of pomegranate juice for one year), in mice (a 26% increase in serum PON1 activity), and in diabetic patients (a 34–45% increase) [75,76]. An analysis of pomegranate fruit parts indicated that only pomegranate juice and arils increased serum paraoxonase activity, whereas seeds, peels and flowers were devoid of effects [77]. In vitro, pomegranate juice was reported to increase HDL-associated PON1, and recently, pomegranate juice polyphenols have been shown to increase the binding of a recombinant PON1 to HDL [78]. In HuH7 hepatoma cells pomegranate juice and its major polyphenols up-regulated PON1 expression and release by sequential activation of protein kinase A and PPAR-γ [79]. Consumption of dates of the Hallawi variety, containing various polyphenols including ferulic and sinapic acid, and coumaric acid derivatives, caused a small (~15%) increase in serum PON1 activity [80].

5.2.3. Other—Taurine, an antioxidant and hypolipidemic agent, was shown at high doses (2–3% of the diet) to reverse the decrease in serum paraoxonase activity found in propylthiouracil-treated hypothyroid rats [81]. Pulp from Acai (a palm variety found in the Brazilian Amazon, containing flavonoids, unsaturated fatty acids and phytosterols), fed to control rats was shown to significantly increase (by 75%) serum PON1 activity, while a 60% increase was observed in rats also fed a hypercholesterolemic diet [82]. Administration of soy isoflanones (e.g. genistein, daidzein, which have estrogenic activity) caused a small increase of serum PON1 activity in rats [83].

5.3. Dietary lipids

Consumption of olive oil increased postprandial serum PON1 activity in diabetic patients, particularly in females (+18%), while safflower oil had no effect [84]. This was confirmed in another study showing that consumption of olive oil (determined from a 12-h recall questionnaire) was associated with an increase in serum PON1 activity but only in individuals with the 192RR genotype [85]. Consumption of a Mediterranean meal rich in monounsatutared fats, was shown to increase postprandial serum PON1 activity by 16% [86], similar to the results obtained following administration of ω–3 polyunsaturated fatty acids (PUFA) in a group of individuals with familial combined hyperlipidemia [87]. However, ω–3 PUFA, in spite of their promising hypolipidemic effects, may increase generation of reactive oxygen species, which may inactivate PON1 [97]. In vitro studies

have shown that oleic acid protects PON1 from oxidative inactivation, while polyenoic fatty acids inhibited PON1 activity [88]. However, oleic acid itself has also been shown to inhibit PON1 activity, possibly binding to a different site [89].

5.4. Alcohol

As moderate doses of alcohol exert a protective role in cardiovascular disease, by modulating HDL levels, some studies have investigated the modulation of PON1 by ethanol. An early in vitro study had indicated that several aliphatic alcohols, including ethanol (IC50 = 100 mM), inhibited human serum PON1 activity [13]. In contrast, two subsequent studies in humans showed that moderate alcohol consumption (~40 g/day for three weeks) caused a small (5–10%) increase in serum PON1 activity [90,91]. However, a similar exposure (~26 g/day for three weeks) did not alter serum paraoxonase activity and slightly decreased arylesterase activity in another study [92]. A comparative study in rats and humans was carried out by Rao et al. [93]. In rats, moderate alcohol consumption for eight weeks [leading to blood alcohol levels of about 8. 3 mM (39 mg/dl)] caused a 20 and 25% increase of serum and liver PON1 activity, respectively, with a concomitant increase in hepatic PON1 mRNA levels [113]. $LDL^{-/-}$ mice fed 18% ethanol in the diet for four weeks, also presented with a 31% increase in liver PON1 mRNA levels and a 64% increase in plasma PON1 activity [66]. A higher ethanol dosage (25% in the diet) caused lesser increases [66]. Similarly, in humans, consumption of a moderate amount of alcohol (13–39 g/day for 6 months or longer) caused a >3-fold increase in serum PON1 activity. It has been suggested that an effect of alcohol on protein kinase C (PKC), which may phosphorylate Sp1 and regulate its binding to the Sp1 binding site in the promoter region of PON1 [94], may explain the effect of alcohol on PON1 levels [93]. An involvement of PKC and Sp1 in the transactivation of the human PON1 gene in HepG2 cells has also been reported with D-glucose, which may represent a compensatory mechanism against diabetes-induced, oxidative stress-mediated, decrease of PON1 [95]. However, it should be noted that while an overexpression of Sp1 enhances PON1 promoter activity, overexpression of PKC reduces PON1 promoter activity [94].

In contrast to moderate alcohol consumption, heavy alcohol drinking leads to opposite effects, i.e. a significant decrease of PON1 activity [93]. In rats, administration of alcohol for eight weeks [leading to blood concentrations of 30 mM (140 mg/dl)] decreased serum and liver PON1 activity (by 25%) along with liver PON1 mRNA levels. In humans, consumption of 80 g/day for six months or longer caused a 45% decrease of serum PON1 activity. Indeed, in chronic alcoholics, serum PON1 activity was found to be decreased by 53%, and even further (to 72%) in alcoholics with liver cirrhosis [96]. In rats, administration of a diet containing 36% alcohol was reported to decrease liver PON1 mRNA levels by ~25%, and plasma PON1 activity by 23–58%. These changes were antagonized by concomitant administration of betaine (trimethyl glycine) [97].

6. Conclusions and research needs

The ability of PON1 to protect against the acute toxicity of certain OP insecticides, but most importantly against oxidative stress involved in major diseases such atherosclerosis and diabetes, underlines the notion that strategies aimed at increasing PON1 activity and/or expression would have several benefits. There is at least a 40-fold variation in serum PON1 activity among individuals [10]; while a portion of this variation is explained by genetic polymorphisms, the potential influence of exogenous factors also needs to be taken into account. Though this commentary focuses on factors which may increase PON1 activity and/or expression, one should not ignore that additional factors (e.g. smoking, a fat-rich diet, environmental heavy metals) may decrease PON1 activity [13].

In order to increase serum PON1 activity, two general strategies may be considered. A first approach, which was the focus of this commentary, may rely on the administration of an exogenous factor(s), such as pharmaceutical drugs or dietary factors, that would increase endogenous PON1 activity. Among drugs, statins have been the most studied, but have not always provided consistent results; other drugs (e.g. certain antidiabetic compounds, other hypolipemic drugs) have mostly shown a positive modulation of PON1. However, because of potential adverse health effects of several of these drugs, chronic administration to healthy individuals with the purpose of increasing PON1 would not be recommended. In contrast, dietary components and/or supplements are an area of great promise. Extracts from various fruits containing polyphenols or similar compounds have indeed been consistently shown to increase PON1 activity. Various other antioxidants have provided similar positive results, which is not surprising given that PON1 is easily inactivated by endogenously generated oxidants [53]. In all cases, however, the effects on PON1 are relatively small, usually leading to increases of 50% or less. A limited number of in vitro studies have shown that up-regulation of gene expression would be possible by specifically targeting certain signal transduction pathways and transcription factors. PKC, p44/42 MAPK, Sp1, SREBP-2, and Ah receptors are among the targets that have been associated with increased PON1 expression, however, much more research is needed in this area. Some newly-developed assay systems that would allow rapid screening of chemicals, as well as provide the means for mechanistic studies, may be considered [28].

A second approach may rely on direct administration of exogenous PON1; this has been done in animal models, in which exogenous PON1 has been shown to confer protection toward the acute toxicity of OP insecticides by acting as a catalytic scavenger [4]. Recently, engineered PON1 with higher catalytic activity toward OPs has been shown to be very effective in this regard [98]. Whether this approach will be applicable to humans, given potential adverse immune responses, still needs to be ascertained. Administration of recombinant human PON1 without glycation should reduce this risk [98]. Recently, a protective effect of human PON1 adenovirus administration on atherosclerosis in apolipoprotein E-deficient mice has been reported [99,100]. PON1 mutants with high higher activity toward oxidized lipids and/or thiolactones may be engineered, and tested in various animal models of diseases. Direct administration of PON1 provides a severalfold increase in serum PON1 levels, something that may not be possible by attempting to increase endogenous PON1 levels with drugs or dietary supplements. These two strategies should nevertheless be pursued in parallel, as both may lead to ways for providing clinical benefits.

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Table 1

Pharmaceutical drugs found to increase PON1 activity/expression in animals or Humans

Drugs	PON1 increase	Reference
Cardiovascular drugs		
Statins (simvastatin, atorvastatin)*	5–23%	[17–20,25]
Fibrates (Gemfibrozil, fenofibrate)*	18–59%	[23,29]
Probucol	50%	[36]
Ezetimibe	32%	[37]
Aspirin*	13%	[32,34]
Antidiabetic drugs		
Rosiglitazone	10–67%	[38–40]
Eplerenone	60%	[41]
Sulphonylureas (glimepiride, glibenclamide)	28–64%**	[42]
Other drugs		
Erythropoietin beta	23%	[48]

* Studies with these drugs have provided contrasting results. See text for details.

** Increase only in liver, decrease in plasma [42].

Table 2

Dietary antioxidants found to increase PON1 activity/expression in animals or Humans

Antioxidant	PON1 increase	Reference
Vitamin C, Vitamin E	7–80%	[55–59]
Quercetin	30–200%	[62–66]
Green tea	17–40%	[70]
Grape seed extract	21–87%	[72]
Blueberries	25%	[73]
Pomegranate juice	20–80%	[75–77]
Dates (Hallawi variety)	15%	[80]
Protandim®	35%	[74]