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Review Article

Decreased PON1 activity as a biological marker for depressive disorders: a narrative review

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ABSTRACT

Background: This study conducts a narrative review to summarize evidence regarding changes in serum/plasma paraoxonase 1 (PON1) activity in patients with major depressive disorder (MDD) or other depressive disorders and assess their possible marker value.

Methods: We searched the PubMed database for articles published from inception to December 2024 on the relationship between depression and PON1 activities/concentrations.

Results: Seventeen articles from 2006 to 2022 were included in the final analysis. 70 % of the studies demonstrated a decline in PON1 (predominantly arylesterase activity) during MDD episodes and depressive disorders induced by methamphetamine and Parkinson`s disease. Lower PON1 paraoxonase activity was associated with the number of previous depressive episodes (DE), worse outcomes, and higher DE severity. Two studies showed an increase in PON1 activity after antidepressant treatment. The decline of PON1 has a genetic predisposition. QQ and QR genotypes of PON1 increased the odds of depression. MDD patients with QQ genotype (in contrast to QR and RR) showed lowered PON1 activity.

Conclusion: There is a decline in arylesterase/paraoxonase activity and PON1 concentrations in MDD and secondary depressive disorders. The decline is also associated with the severity and number of DE. Antidepressant treatment might increase PON1 activity. Genetic predisposition and epigenetic mechanisms that decrease PON1 activity might disrupt antioxidative mechanisms and lipid metabolism, which could be a part of complex pathogenesis and/or lead to comorbid somatic MDD pathology related to accelerated aging. PON1 activity and concentrations decline might be a marker for MDD and other DE, whereas PON1 increase – for treatment efficacy.

1. Introduction

Major depressive disorder and the search for biomarkers

Major Depressive Disorder (MDD) is a leading source of disability worldwide, causing a high medical and socioeconomic burden (Smith, 2014b). There is a growing interest in the biological underpinnings of major depression, which are reflected by altered levels of biological markers (Nobis et al., 2020). Among the many biological prerequisites for MDD, oxidative stress and immune activation have been particularly extensively investigated (Mosiołek et al., 2021).

Various literature sources have demonstrated the overproduction of reactive oxygen species and nitric oxide with a simultaneous decrease in total antioxidant capacity in MDD (Carvalho et al., 2020; Nobis et al., 2020). It has been shown that MDD is associated with elevated levels of pro-inflammatory cytokines, e.g., IL-1β, IL-6, IFN-γ, TNF-α, and C-reactive protein (Wohleb et al., 2016). Cytokines belong to a group of diverse biochemical molecules produced by immunocompetent cells: lymphocytes, macrophages, and natural killers (Maes, 2011). As neuromodulators, cytokines disrupt the regulation of affective, cognitive, and autonomic brain networks through various mediators, neurohumoral, neuroplastic, and other mechanisms (Mosiołek et al., 2021). This leads to specific phenotypic manifestations that make up the clinical structure of a depressive episode (Woelfer et al., 2019).

Some known biological markers can be considered as molecules through which different pathological pathways are interfaced. For example, S100B protein, which connects cerebral ischemia and inflammatory reactions of neuroglia (Levada and Trailin, 2012), or IGF-1, which combines growth signaling pathways and aging mechanisms can be mentioned (Levada and Troyan, 2020).

Given the above facts, the study of pathogenetic links that combine

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the processes of hyperoxidation and immune inflammation is of interest from both theoretical and practical points of view. From an application perspective, this could provide targets for pathogenetic therapy and possible biomarkers for validating MDD diagnosis and therapy effectiveness. In this regard, it may be of interest to study paraoxonase 1 (PON1), an enzyme that has various roles in different biochemical pathways, including defense from oxidative lesions and lipid peroxidation, involvement in innate immunity, detoxification of reactive molecules, and controlling of proliferation or apoptosis of cells (Cerón et al., 2014).

PON1: general characteristics and functions

According to the Enzyme Commission of the International Union of Biochemistry and Molecular Biology, PON1 is currently classified as an aryldialkylphosphatase (EC 3.1.8.1) (Mackness et al., 1998). Aryldialkylphosphatase is an important hydrolytic enzyme that degrades a range of organophosphate compounds, particularly those containing aryl and dialkyl phosphate structures (Costa et al., 2005).

PON1 is a high-density lipoprotein (HDL) associated enzyme that contributes to HDL`s antioxidant and anti-atherogenic properties (Mackness M. and Mackness B., 2015; Marsillach et al., 2021). PON1 hydrolyzes oxidized phospholipids and lipid peroxides in both HDL and low-density lipoprotein (LDL), thus preventing the formation of pro-inflammatory oxidized LDL, a key step in the pathogenesis of atherosclerosis (Mackness et al., 1998; Marsillach et al., 2008). HDL not only serves as a carrier for PON1 but also stabilizes and modulates its activity. The lipid and protein composition of HDL, particularly apolipoprotein A-I (ApoA-I, the major protein in HDL), influences PON1 binding and function. Conversely, PON1 enhances the protective functions of HDL by preserving its ability to promote cholesterol efflux and inhibit oxidation (Efrat and Aviram, 2010; Ferretti and Bacchetti, 2012). Therefore, PON1 and HDL are functionally interdependent: PON1 enhances HDL's antioxidative potential, while HDL provides a necessary platform for PON1′s enzymatic activity.

PON1 is synthesized generally in the liver and secreted into the blood, where it is associated with HDL (Deakin et al., 2002). Together with ApoA-I and clusterin, PON1 is mainly associated with a specific HDL sub-species (HDL_3) (Mackness M. and Mackness B., 2015). After ultracentrifugation, most PON1 resides on the small dense HDL_3 subfraction (Davidson et al., 2009).

Measurement of the enzymatic activity of PON1 in various medical conditions was proposed as a biological marker (Cerón et al., 2014). Notwithstanding, numerous studies suggest that PON1 is a highly versatile enzyme displaying diverse functions such as arylesterase, lactonase, and paraoxonase, among others (Petrič et al., 2021). Therefore, measurement of its activity can be determined using different substrates (Cerón et al., 2014); for example, its paraoxonase activity (paraoxon is a substrate), arylesterase activity (non-phosphorous arylester, e.g., phenyl acetate or 4 (p)-nitrophenyl acetate is a substrate) or by lactonase activity (5-thiobutil butyrolactone –TBBL- or other lactones, e.g., dihydrocoumarin are substrates) (Cerón et al., 2014). Some authors use 4-(chloromethyl)phenyl acetate (CMPA) as an alternative to the use of toxic paraoxon, i.e., for investigating paraoxonase activity (Richter et al., 2008).

Enzymatic activity of PON1 is influenced by a range of factors, which can be grouped as genetic, epigenetic, proteomic, lipidomic, age, and gender-related, linked to lifestyle (exercises, nutrition), and caused by medical conditions and treatment (Petrič et al., 2021). A comprehensive presentation of these factors was beyond the scope of this publication. They are discussed in detail in special reviews (Dardiotis et al., 2019; A. Mahrooz et al., 2019; Petrič et al., 2021; Shunmoogam et al., 2018; Wishart et al., 2018) and original articles (Ferretti et al., 2009; Quillen et al., 2012; Rainwater et al., 2009; Rosenblat et al., 2006, 2012). We will only briefly consider those that may be important for our topic.

Factors influencing PON1 activity

The PON1 gene is located on chromosome 7 (Rainwater et al., 2009). It has nearly 200 SNPs (single nucleotide polymorphisms) (Richter et al., 2010). The two most frequently reported SNPs in the coding region of the human PON1 gene are A > G transition in the 192nd position (192 Q/R, rs662) and A > T at codon 55 (55 M/L, rs854560) that were found to affect the PON1 activity and concentration (Dardiotis et al., 2019; Shunmoogam et al., 2018).

The PON1 R192 isoform hydrolyses paraoxon much more rapidly as compared to the PON1 Q192 isoform, whereas Q192 isoform hydrolyses diazoxon much more rapidly as compared to R192 isoform (Richter and Furlong, 1999). Conversely, phenylacetate hydrolysis, i.e., arylesterase activity, is not affected by Q192R polymorphism and has been shown to correspond with PON1 levels (Richter et al., 2010). It was also revealed that $M/M + L/M$ vs. L/L genotypes of PON1 L55M polymorphism had lower serum arylesterase activity (Asefi et al., 2012). There is also evidence that 192 Q/R, rs662 and 55 M/L, rs854560 cause 8.3 and 4.1 % of interindividual variation in PON1 lactonase activity, respectively (Quillen et al., 2012). Consequently, both mentioned SNPs, given their relationship to PON1 activity, may be connected to a decrease in antioxidant protection and an increase in immune inflammation (Shahmohamadnejad et al., 2015) and their associated medical conditions.

Epigenetic mechanisms of PON1 activity through non-coding RNA (ncRNA) were studied. Low levels of long ncRNA Linc-OIP5 corresponded to lower levels of PON1 expression and activity, whereas high expression of the microRNA miR-616 gene decreased PON1 expression and its enzymatic activity (Chen et al., 2020). The conclusion was made that Linc-OIP5 positively regulates the expression of the PON1 gene and its protein level, while miR-616 has the opposite effect (Chen H et al., 2020).

Serum PON1 lactonase activity can be reduced under the influence of homocysteine thiolactone (HCTL) (Ferretti et al., 2010), the so-called homocysteinylation process (Bełtowski J, 2005). Among seven investigated metals, zinc, by binding to several histidines, inhibits arylesterase, paraoxonase, and lactonase PON1 activities, but lactonase was the only activity significantly affected by the addition of zinc (Josse et al., 2002).

Regarding the lipidomic aspect, arylesterase, paraoxonase, and lactonase PON1 activities exert selectively and predominantly in the environment of HDL (Rosenblat et al., 2006). It was suggested that HDL stabilizes PON1's structure, while displacement from HDL causes protein conformational changes that decrease its activity (Rosenblat et al., 2006). Similarly, an increase in the concentration of very low-density lipoproteins (VLDL) causes a decrease in HDL-linked PON1 enzymatic activity (Rosenblat et al., 2012).

To date, there are no systematic studies of PON1 activity in various age groups (Petrič et al., 2021). It has only been demonstrated that the lactonase activity of the enzyme in newborns is significantly lower than in adults (Gugliucci et al., 2014), and neonatal PON1 arylesterase activity is much lower than that of toddlers (Cole et al., 2003).

Data on the effect of gender on the enzymatic activity of PON1 is controversial. Petrič B. et al. (2021) suggested that gender does not substantially explain the interindividual variation of lactonase activity (Petrič et al., 2021). At the same time, higher PON1 lactonase activity in women than in men was detected, even after accounting for influencing factors such as HDL and cholesterol levels, age, body mass index, and smoking (Trentini et al., 2019). Quillen et al. (2012) reveal that only 0.4 % of the interindividual differences in paraoxonase and arylesterase activities can be explained by gender (Quillen et al., 2012).

The influence of diet on enzymatic PON1 activity is considered to be a potential confounder (Petrič et al., 2021). In most controlled studies, different foods, namely a diet high in polyunsaturated fatty acids (Kopál et al., 2014), a protein and vegetable diet (Kameyama et al., 2016), grape juice, and wine (Aviram and Rosenblat, 2012), did not significantly impact PON1 activity. At the same time, the use of pomegranate and currant juice significantly increased lactonase, paraoxonase, and arylesterase activities of the enzyme (Aviram and Rosenblat, 2012; Rock et al., 2008).

Evidence has been obtained that risperidone (Risperdal) and

clozapine medications reduce the lactonase activity of PON1 (Gîlcă et al., 2014). On the contrary, paraoxonase and arylesterase activities were increased in the group treated with antipsychotics (Gîlcă et al., 2014). It was shown that the use of oral contraceptives increases the lactonase activity of PON1 (Kowalska et al., 2018). There is also an indication that exercise enhances the lactonase and paraoxonase activities of the enzyme (Russo et al., 2018).

Lactonase PON1 activity is significantly lower in patients with cardiovascular disease (Murillo-González et al., 2020). Moreover, decreased lactonase and arylesterase activities are considered risk factors for coronary artery disease in some ethnic populations (Gugliucci et al., 2015).

The lactonase activity of the enzyme is significantly decreased in obese subjects compared with nonobese controls (Alaminos-Castillo et al., 2019; Bacchetti et al., 2019; Ferré et al., 2013), although not all studies have confirmed this fact (Cervellati et al., 2017; Rupérez et al., 2013). Cervellati et al. (2017) revealed a substantial reduction in arylesterase PON1 activity in very obese patients; however, they did not show any difference in paraoxonase activity of the enzyme (Cervellati et al., 2018).

A significant decrease in lactonase PON1 activity was revealed in diabetes 1 type patients (Craciun et al., 2016), whereas no difference was found between cases and controls for paraoxonase or arylesterase activities. Data from type 2 diabetes is also not so clear-cut. Passaro et al. registered no correlation between lactonase PON1 activity and the presence of this diabetes type, whereas diabetic patients, on average, had significantly lower arylesterase activity than healthy controls (Passaro et al., 2018).

Different PON1 activities are considered to be lower in idiopathic inflammatory myopathies (Bae et al., 2022), Alzheimer's disease (Bacchetti et al., 2015), and several other medical conditions, such as cancer (Bains et al., 2019), chronic kidney disease (Gugliucci et al., 2010), and pancreatitis (Marek et al., 2018).

Most of the medical conditions mentioned occur predominantly in the advanced age group. It is reasonable to assume that decreasing PON1 activities in these conditions may reflect the basic pathological processes underlying accelerated aging. It is considered proven that the processes of accelerated aging play a key role in the pathogenesis of MDD (Levada and Troyan, 2020). Consequently, changes in PON1 activities may reflect the presence and severity of these processes in depressed patients and, therefore, be used as a biological marker.

This study conducts a narrative review to summarize evidence regarding changes in serum/plasma PON1 activities (lactonase, arylesterase, or paraoxonase) in MDD patients and assess their possible marker value.

2. Methods

Two independent researchers (OAL and OST) screened PubMed databases with the keywords: paraoxonase 1 or PON1 or lactonase or arylesterase or paraoxonase or PON1 activity and major depressive disorder or depression or MDD. We selected full-text articles written in English and published in peer-reviewed journals from inception to December 2024. We included articles that compared serum PON1 activities in patients with MDD and healthy controls. The exclusion criteria were studies without a control population, to be comments, review articles, meta-analyses, or articles with only an abstract.

3. Results and discussion

3.1. Studies selected

The initial database search yielded 317 articles. We removed duplicate articles ($n = 100$) and screened the titles/abstracts of the remaining records ($n = 207$). The titles and abstracts of these studies were screened by both authors independently. The lead reviewer found 80 articles suitable for reviewing the full text. Fig. 1 illustrates the study selection process.

In the final analysis, we included seventeen articles (Table 1), fourteen of which had case-control design comparing peripheral (plasma/serum) PON1 activity or concentrations in depressive patients and healthy controls (HC), and three belonged to longitudinal/population studies that investigated different aspects of PON1 activities as a prognostic factor for further occurrence and progression of depressive symptoms.

It should be mentioned that most of the case-control studies ($n = 8$) investigated both paraoxonase and arylesterase PON1 activity (Atagün et al., 2018; Barim et al., 2009; Bortolasci et al., 2014; Kotan et al., 2011; Moreira et al., 2019b; Ogłodek, 2017; Roomruangwong et al., 2017; Sarandöl et al., 2006), whereas three studies assessed only arylesterase (Kodydková et al., 2009; Maes et al., 2018) or paraoxonase (Kamath et al., 2019;) PON1 activity. The rest three studies assessed PON1 concentrations (Bliźniewska-Kowalska et al., 2022; Ghavidel et al., 2020; Zhou et al., 2020). Lactonase PON1 activity has not been investigated in the studies of depressive patients yet; moreover, it has not been studied in patients with psychiatric disorders at all (Morris et al., 2021).

3.2. PON1 activity and depression

Eight case-control studies revealed that a decline in PON1 was associated with depression. Six of them obtained significantly low PON1 activities or concentrations in patients with MDD (Barim et al., 2009; Bortolasci et al., 2014; Kotan et al., 2011; ; Moreira et al., 2019b; Ogłodek, 2017; Zhou et al., 2020), and two at the level of trend (Atagün et al., 2018; Kodydková et al., 2009). It should be mentioned that five studies showed a decline in arylesterase activity. One of the articles reported a decrease of PON1 concentration in methamphetamine-induced depressive disorder (Ghavidel et al., 2020), and one in MDD comorbid with generalized anxiety disorder (arylesterase activity) (Maes et al., 2018). Meanwhile, two studies reported no significant differences in either arylesterase or paraoxonase activity (Sarandöl et al., 2006) or PON1 concentrations (Bliźniewska-Kowalska et al., 2022) in MDD patients compared to healthy controls. Similar to this study, Roomruangwong et al. (2017) demonstrated that PON1 total activity was not associated with depressive symptoms in women during the perinatal period. Only one source found an elevation of plasma PON1 concentrations in patients with moderate depression than in controls (Kamath et al., 2019).

70 % of the studies (10 out 14) demonstrate a decline in PON1 during MDD episodes. Therefore, decreased PON1 levels might be associated with the etiopathology of MDD. Barim et al. (2009) previously suggested a relationship between decreased PON1 and psychiatric disorders, similar to other antioxidant mechanisms, since antioxidant capacity declines in psychiatric disorders (Barim et al., 2009). It was also concluded that serum levels of PON1 and other antioxidants are lower in patients with depression compared to control groups (Liu et al., 2015).

3.3. Declined PON1 activity and depressive episodes` characteristics

Moreover, the mentioned case-control studies showed some other clinical associations with PON1 decrease in depressive patients. Moreira et al., 2019b discovered that significantly lower PON1 paraoxonase activity was partly related to the number of previous depressive episodes, and lowered paraoxonase activity was linked to a worse outcome of depression, such as quality of life and increased disability (Moreira et al., 2019b). The severity of depressive episodes was inversely correlated with PON1 paraoxonase activity (Ogłodek, 2017). Generalized anxiety contributed to an additional decline of paraoxonase and arylesterase PON1 activity in MDD patients (Maes et al., 2018). In methamphetamine-induced depressive disorder a reduction of PON1 concentrations was associated with frontocingulate dysfunction on functional magnetic resonance imaging (fMRI) (Ghavidel et al., 2020).

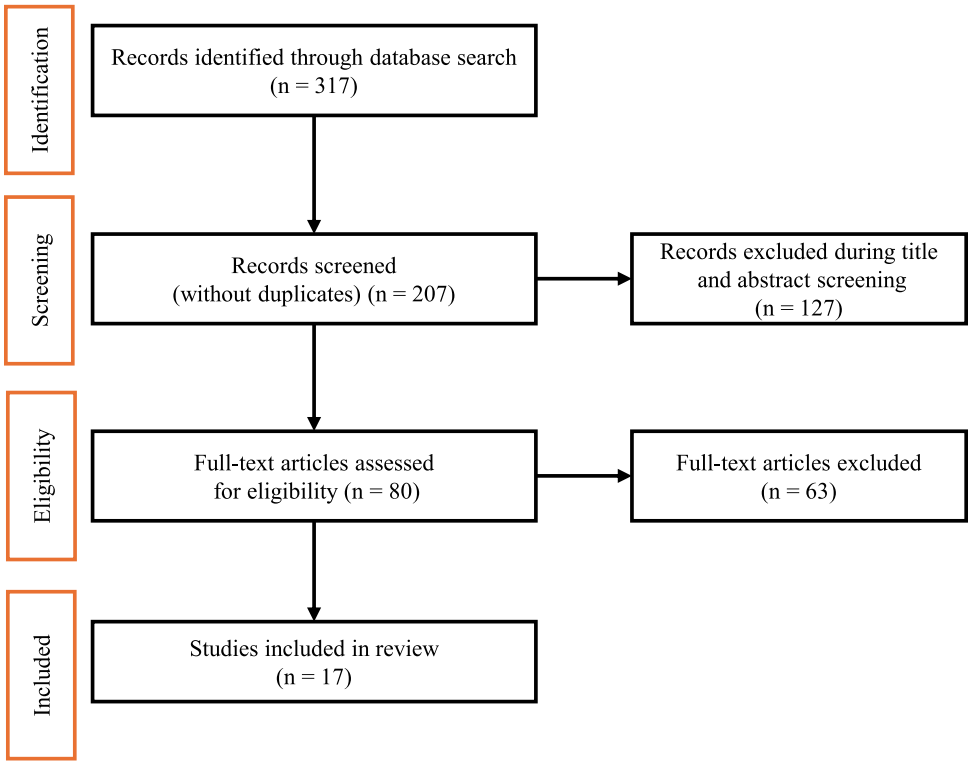

Fig. 1. Flowchart for study selection.

3.4. PON1 Q192R genotype and depression

The most studied polymorphisms in the coding region of PON1 gene are Q192R and L55M (E.G. Moreira et al., 2019). The Q192R polymorphism influences the PON1 catalytic activity, however, in the substrate-dependent direction. In contrast, the L55M polymorphism does not affect PON1 catalytic activity but has been associated with low plasma PON1 protein levels (E.G. Moreira et al., 2019).

Given previously proven data that PON1 activity varies prominently according to the PON1 Q192R genotype and obtained evidence that the arginine (R) genotype hydrolyzes peroxided lipids more rapidly and capably than the glutamine (Q) genotype (Ginsberg et al., 2009), some authors hypothesized that Q genotype might have greater liability to depressive disorders than the R genotype. Four case-control articles investigated those genetical predispositions of PON1 activity and their relationships with regard to predicting depressive disorders (Atagün et al., 2018; Bortolasci et al., 2014; Moreira et al., 2019b; Roomruangwong et al., 2017).

In pregnant women with MDD 192RR genotype had a positive association with PON1 total activity (Roomruangwong et al., 2017). In line with this data, Atagün et al. found that the PON1 QQ variant had a higher prevalence in depressive patients as compared to bipolar or healthy controls (Atagün et al., 2018). Another study demonstrated that in nonsmokers both QQ and QR genotypes increased the odds of depression (Bortolasci et al., 2014). Moreover, subjects with MDD with a QQ genotype (in contrast to QR and RR) showed lowered PON1 activity (Bortolasci et al., 2014). On the contrary, Moreira et al., 2019b obtained significantly lower PON1 total activity in RR genotype than in QQ and QR genotypes, while CMPAase activity was significantly different between the three genotypes and increased from QQ to QR to RR (Moreira et al., 2019b).

In one study, no association was found between L55M and Q192R polymorphisms of the PON1 gene in patients with depression (Yildiz et al., 2017).

Three population studies also explored relationships between PON1 Q192R polymorphism and depressive symptoms. In a study on British women aged 60–79 years, it was found that the R allele of PON1 Q192R was associated with increased odds of depression (Lawlor et al., 2007). However, these results are not in line with those of Rice et al. (2009), who demonstrated no relationship between PON1 Q192R polymorphism with depressive symptoms or a history of diagnosed depressive episodes in two population-based studies that covered a cohort of the same age as the previous research by Lawlor et al. (2007).

For PON1 L55M polymorphism, in a longitudinal cohort study, the MM genotype, which is related to "slower" PON1 metabolizing, was associated with a faster progression of depressive symptoms after Parkinson's diagnosis (Paul et al., 2017).

Previously, Zhao et al., 2019 conducted a meta-analysis of four case-control studies (Atagün et al., 2018; Yildiz et al., 2017; Nunes et al., 2015; Bortolasci et al., 2014a) to establish a relationship between PON1 Q192R and depression (Zhao et al., 2019). Obtained results demonstrated a trend that the R allele was less frequent in cases of MDD in the different models (RR vs. RQ + QQ, OR 0.78 (0.49, 1.24); RR vs QQ, OR 0.74 (0.45, 1.20); R vs Q, OR 0.81 (0.65, 1.02)) (Zhao et al., 2019). However, it should be mentioned that one of the meta-analysis studies did not distinguish between depressed and bipolar patients (Nunes et al., 2015).

3.5. Epigenetic mechanisms of PON1 activity

Although much of the existing research has focused on genetic polymorphisms of PON1 gene, emerging evidence highlights the role of epigenetic mechanisms – including DNA methylation, histone modifications, and microRNAs – in regulating PON1 expression and activity (A. Mahrooz et al., 2019; Chen et al., 2020). These epigenetic alterations can be influenced by environmental factors such as oxidative stress and inflammation, both of which are central to the pathophysiology of MDD. For instance, methylation of the PON1 promoter region has been shown to modulate its enzymatic expression and antioxidant function (A. Mahrooz et al., 2019), and altered methylation patterns in oxidative

Table 1
Characteristics and key results of studies examining PON1 activity in patients with MDD or secondary depressive syndromes.

	Source	Type of the study	Subjects	Genotype of PON1	Measure	Enzymatic activity	Results	Medication and its effects on PON1 activity
1	Sarandöl et al. (2006)	Case-control	86 MDD patients vs. 36 HC	n/a	Serum	Paraoxonase, Arylesterase	No significant differences in paraoxonase or arylesterase activities between MDD and HC	Patients had various antidepressant treatments in standard doses for 6 weeks. Pharmacotherapy reduced paraoxonase and arylesterase activities
2	Barim et al. (2009)	Case-control	24 MDD patients vs. 22 HC	n/a	Serum	Paraoxonase, Arylesterase	Arylesterase activity was significantly lower in MDD patients than in HC, while paraoxonase activity was lower at the level of trend	After three months of citalopram treatment arylesterase level was significantly higher relative to the pre-treatment level, while paraoxonase level slightly decreased
3	Kodydková et al. (2009)	Case-control	35 drug-naive women with MDD vs. 35 age-matched healthy women	n/a	Serum	Arylesterase	A trend to decrease of arylesterase PON1 activity in MDD patients	–
4	Kotan et al. (2011)	Case-control	50 MDD patients vs. 54 HC	n/a	Plasma	Paraoxonase, Arylesterase	Arylesterase PON1 activity was significantly lower in MDD patients compared to HC	Both arylesterase and paraoxonase activities were increased after 24 weeks of antidepressant treatment
5	Bortolasci et al. (2014)	Case-control	91 MDD patients vs. 199 HC	192QQ, 192QR and 192RR	Plasma	PON1	Significantly lower PON1 activity in MDD than in HC. Lower PON1 in MDD patients with the QQ genotype	-
6	Ogłodek, 2017	Case-control	360 MMD patients with or without PTSD, 60 PTSD patients, vs. 40 HC	n/a	Serum	PON1	Significantly lower PON1 activity in MDD patients than in HC. PON-1 concentrations decreased with the severity of depression in subjects both with and without comorbid PTSD	–
7	Roomruangwong et al. (2017)	Case-control	Pregnant women with and without prenatal depression and non-pregnant HC	192QQ, 192QR and 192RR	Plasma	PON1 total, CMPAase	PON1 activity was not associated with perinatal depressive symptoms 192RR genotype had a positive association with PON1 total activity. CMPAase activity was not associated with Q192R genotypes	–
8	Atagün et al. (2018)	Case-control	43 MDD patients vs. 43 HC	192QQ, 192QR and 192RR	Serum	PON1, stimulated paraoxonase, arylesterase	Lower PON1 levels and stimulated paraoxonase in MDD patients. PON1 QQ variant was more prevalent in MDD patients	–
9	Maes et al. (2018)	Case-control	23 MDD patients vs. 14 MDD + GAD patients	n/a	Serum	Arylesterase	Significantly lower PON1 in MDD + GAD patients than in MDD	–
10	Moreira et al., 2019b	Case-control	32 MDD patients vs. 59 HC	192QQ, 192QR and 192RR	Serum	Arylesterase/ CMPAase (paraoxonase)	Significantly lower PON1 total and CMPAase activity in MDD patients. Lowered CMPAase activity was associated with a worse outcome of MDD. PON1 total	–

(*continued on next page*)

Table 1 (*continued*)

	Source	Type of the study	Subjects	Genotype of PON1	Measure	Enzymatic activity	Results	Medication and its effects on PON1 activity
							activity was significantly lower in RR genotype than in QQ and QR genotypes. CMPAase activity significantly differed between the three genotypes, increasing from QQ to QR to RR.	
11	Kamath et al. (2019)	Case-control	24 MDD patients vs. 20 HC	n/a	Plasma	Paraoxonase	Significantly higher PON1 levels were in MDD patients than in HC	–
12	Zhou et al. (2020)	Case-control	Depressed patients vs. HC	n/a	Serum	PON1 concentration	PON1 was downregulated in depressed patients	–
13	Ghavidel et al. (2020)	Case-control	18 Methamphetamine-induced depressive disorder vs. 18 HC	n/a	Serum	PON1 concentration	Decreased PON1 levels in MDD patients compared to HC, which was also associated with frontocingulate dysfunction on fMRI	–
14	Bliźniewska-Kowalska et al. (2022)	Case-control	190 depressed patients vs. 100 HC		Serum	PON1 concentration	The expression of the PON1 genes was higher in depressive patients than in HC. mRNA expression of the PON1 genes was slightly higher in depressed patients than in HC	–
15	Lawlor et al. (2007)	Population study (British Women's Heart and Health Study)	3266 British women aged 60–79 years	PON1 Q192R polymorphism	Blood samples were taken for DNA analysis	n/a	R allele of PON1 Q192R was associated with depression: per-allele OR 1.22 (CI 1.05–1.41) in this population	–
16	Rice et al. (2009)	ELSA and InCHIANTI population study	$n = 3158$ from ELSA; $n = 761$ from InCHIANTI 60–79 years	PON1 Q192R polymorphism (rs662)	Blood samples were taken for DNA analysis	n/a	PON1 Q192R polymorphism was not associated with depressive symptoms in either study or meta-analyses OR 1.01 (CI 0.87–1.17)	–
17	Paul et al. (2017)	Longitudinal cohort	246 patients with Parkinson`s disease	PON1 L55M genotype	Blood or saliva samples were taken for DNA analysis	n/a	PON1 55 MM was associated with faster progression of depressive symptoms (GDS β=0.07; 95 % CI 0.01–0.13)	-

Abbreviations: Confidence Interval (CI), Generalized Anxiety Disorder (GAD), Healthy Controls (HC), Major Depressive Disorder (MDD), Not applicable (n/a), Paraoxonase 1 (PON1), Posttraumatic Stress Disorder (PTSD).

stress–related genes have been reported in individuals with depression (Park et al., 2019).

Beyond its established antioxidant role, PON1 also exhibits homocysteine thiolactonase activity, which is critical for detoxifying homocysteine thiolactone, a reactive and neurotoxic metabolite of homocysteine (Jakubowski, 2008; Perła-Kaján and Jakubowski, 2012). This dual enzymatic function positions PON1 as a key factor in protecting against both oxidative damage and homocysteine-related toxicity. Hyperhomocysteinemia has been consistently associated with MDD, contributing to neuronal damage through mechanisms such as oxidative stress, neuroinflammation, and impaired neurotransmitter synthesis (Bottiglieri et al., 2000; Folstein et al., 2007; Almeida et al., 2008). Elevated homocysteine levels are also recognized risk factors for cardiovascular and neurodegenerative diseases due to their pro-oxidant and pro-inflammatory properties (Morris, 2003; Wald et al., 2002). Notably, homocysteine metabolism itself is epigenetically regulated. Deficiencies in B vitamins – such as folate, B6, and B12, which serve as cofactors in homocysteine metabolism – can lead to DNA hypomethylation and subsequent genomic instability and neurotoxicity (Reynolds, 2002; Smith and Refsum, 2016; Perła-Kaján and Jakubowski, 2012; Perła-Kaján and Jakubowski, 2019). Moreover, microRNAs such as miR-616 have been shown to directly downregulate PON1 expression, potentially amplifying oxidative stress in MDD (Chen et al., 2020). Together, these findings underscore a complex interplay between epigenetic regulation of PON1, disrupted homocysteine metabolism, and oxidative burden – all of which may converge to exacerbate MDD pathology. This area warrants further investigation to elucidate novel biomarkers and therapeutic targets for depression and its somatic

comorbidities.

3.6. Changes in PON1 activity in depressive patients after antidepressant treatment

The effect of antidepressant treatment on PON1 was assessed in three studies, with two reporting increased activity and one showing no significant change. These findings are inconsistent and may be influenced by treatment duration or the type of antidepressant used. Sarandöl et al. (2006) reported decrements in the paraoxonase and arylesterase activities in the MDD group after 6 weeks of antidepressant treatment. Arylesterase activity is suggested to reflect the mass of the enzyme (Cao et al., 1999); therefore, the authors suggested that the decrements in enzyme activity may be explained by decreased enzyme synthesis, which may be due to the effects of medication on the liver. It should be mentioned that in this study (Sarandöl et al., 2006), there were no significant differences in PON1 activity between MDD patients and healthy controls. On the other hand, Barim et al. (2009) examined patients with depression before and after 12 weeks of therapy with citalopram at a dose of 40 mg/day. After treatment, they found significantly increased arylesterase and decreased paraoxonase activity (approximately the same as pretreatment). Similarly, Kotan et al. (2011) found that both arylesterase and paraoxonase activities were increased after 24 weeks of antidepressant treatment (venlafaxine, paroxetine, escitalopram, sertraline, citalopram, milnacipran, fluoxetine, tianeptine, moclobemide).

The duration of antidepressant treatment appears to be a potentially important factor influencing PON1 activity. Two studies suggests that prolonged antidepressant use (12 or 24 weeks) may be necessary to observe elevations in PON1 activity, while one other indicates a decrease over a shorter treatment period (6 weeks). While some evidence suggests that prolonged treatment may restore PON1 activity, data remain limited and inconclusive. Future studies should systematically assess how treatment length, class of medication, and baseline PON1 status interact to affect enzymatic activity.

We may suggest that low PON1 activity, due to its antioxidative and anti-inflammatory properties, may represent a promising biomarker for MDD. Its association with oxidative stress and homocysteine metabolism highlights its potential utility in identifying patients with an inflammatory or oxidative subtype of depression. This could guide the selection of adjunctive treatments targeting oxidative imbalance. However, the current evidence base is limited, and prospective studies are needed to establish causality, assess treatment predictive value, and evaluate PON1's specificity compared to broader inflammatory markers such as CRP or IL-6.

Events to be explored: Prospective studies tracking PON1 activity in individuals at risk for MDD, as well as studies examining its correlation with treatment response and symptom severity over time.

Advantages over current tests: Unlike standard diagnostic tools (e.g., clinical scales or general inflammatory markers), PON1 activity reflects a specific aspect of oxidative stress and lipid metabolism, providing a biochemically grounded and potentially modifiable marker.

Clinical benefit: If validated, PON1 activity testing could help stratify patients based on pathophysiological profiles (e.g., inflammation-dominant vs. monoamine-dominant depression), guiding more personalized treatment strategies such as antioxidant therapy or anti-inflammatory interventions.

4. Conclusions

Overall, summarizing the results of 17 studies, we can conclude that mainly paraoxonase or arylesterase activity or PON1 concentrations were assessed in relation to depressive patients.

Most studies show a decline in arylesterase activity and PON1 concentrations during MDD episodes and depressive disorders induced by psychoactive substances (methamphetamine) and neurodegenerative diseases (e.g., Parkinson`s disease). Decreased PON1 activity and concentrations are also associated with the severity and number of depressive episodes. Prolonged antidepressant treatment (>12 weeks) might increase arylesterase activity.

We can suggest that genetic predisposition and epigenetic mechanisms that decrease PON1 activity might disrupt antioxidative mechanisms and lipid metabolism, which could be a part of complex pathogenesis and/or lead to comorbid somatic MDD pathology related to accelerated aging.

It might be assumed that the decline of PON1 (presumably arylesterase) activity and concentrations might be a marker for MDD and other depressive disorders and antidepressant treatment efficacy.

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Oleg A. Levada: Writing – original draft, Project administration, Investigation, Data curation, Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Oleksandra S. Troian:** Writing – review & editing, Investigation, Data curation, Writing – original draft, Formal analysis.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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