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Expression and Activity of Metalloproteinases in Depression

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Data Interpretation D
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Background: Depression is one of the most common mental disorders and often co-exists with somatic diseases. The most probable cause of comorbidity is a generalized inflammatory process that occurs in both depression and somatic diseases. Matrix metalloproteinases MMPs play a role in modulating inflammation and their impact in many inflammatory diseases has been investigated. The purpose of this study was to evaluate gene expression for selected polymorphisms of MMP-2 (C-735T), MMP-7 (A-181G), and MMP-9 (T-1702A, C1562T), which have been confirmed to participate in development of depression, and TIMP-2 (G-418C, tissue inhibitor of MMP). Activity variability of pro-MMP-2 and pro-MMP-9 was measured in a group of people with depression and a group of healthy individuals.

Material/Methods: The examined population comprised 142 individuals suffering from depression and 100 individuals who formed a control group (CG). Designations were carried out for MMP-2 (C-735T), MMP-7 (A-181G), MMP-9 (T-1702A, C1562T), and TIMP-2 (G-418C).

Results: For all examined and tested MMPs and for TIMP-2, gene expression at the mRNA level was higher in patients with depression than in the CG. Similar results were recorded for gene expression at the protein level, while expression on the protein level for TIMP-2 was higher in the CG. Change in activity of MMP-2 and pro-MMP-2 was statistically more significant in the group with depression. The opposite result was recorded for MMP-9 and pro-MMP-9, in which the change in activity was statistically more significant in the CG.

Conclusions: Changes in MMPs and TIMP expression may be a common element in, or perhaps even a marker for, recurrent depressive disorders and somatic diseases.

MeSH Keywords: Depression • Gene Expression • Inflammation • Tissue Inhibitor of Metalloproteinases

Abbreviations: **BBB** – blood-brain barrier; **CNS** – central nervous system; **MMP** – matrix metalloproteinases; **MP** – multiple sclerosis; **PCR** – polymerase chain reaction; **pro-MMP** – pro-enzyme of metalloproteinase; **TIMP** – tissue inhibitor of MMP; **TNF** – tumor necrosis factor

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Background

Depression is one of the most common mental disorders [1,2]. The lifetime risk of depression is estimated at up to 15% [2]. Presently, the burden of unipolar depression measured in the magnitude or value of the DALY (disability-adjusted life years) rate is third in the global ranking. It is estimated that with the risk of suicides (90% of people committing suicide suffer from depression) the disease will have moved up to second place by 2030 [3].

Depression often co-exists with somatic diseases [4]. People suffering from depression fall ill with somatic depressions more frequently and vice versa. It was proven that cardiovascular diseases, brain and heart strokes, multiple sclerosis, and cancers are dysfunctions associated with a higher risk of depression onset [5–7]. Somatic comorbidity accompanying depression is a possible factor affecting drug resistance, which occurs in more than 30% of people treated for depression [8].

The most probable cause of this more frequent comorbidity is a generalized inflammatory process that occurs in both depression and somatic diseases [9–12]. Significant participation of matrix metalloproteinases (MMPs) in the development and modulation of the inflammatory process has been reported in pathological processes, such as Alzheimer disease (AD), cancers, and cardiovascular diseases, brain and heart strokes, and multiple sclerosis [13–18]. Inflammatory diseases affect neurodegenerative processes of the central nervous system (CNS) [19,20] by influencing damage to the blood-brain barrier (BBB) [19]. Recent reports show that MMPs play an important role in pathological processes in the CNS [21]. Because depression is a systemic inflammatory disease [10,22–24] and MMPs are engaged in the modulation of inflammatory processes – described in detail in a review paper [25] – the role of MMPs in the development and course of depression is interesting. MMPs are synthesized in the form of pre-proenzyme, which is an inactive form of MMP (pro-MMP) [26,27]. Activation takes place by cutting the signal domain under the influence of numerous inflammatory factors or some MMPs, or by acting on the surface of transmembrane MMP cells (MT-MMP), in which a tissue inhibitor of MMP is required (TIMP-2) [28–31]. TIMPs (TIMP-1, -2, -3, and -4) are endogenous proteins that inhibit the activity of MMPs [32]. They also play a protective function in the modulation of the tissue inflammatory process [33].

The most thoroughly examined MMPs involved in CNS pathologies are MMP-2 and MMP-9 [15], which are responsible for developmental and regenerative processes such as neurogenesis, axonal growth and regeneration, and myelin formation [15,34,35].

Expression of both MMPs and TIMPs can be controlled by cytokines [36], and their role in the etiology and course of rDD has already been emphasized in many papers [37]. Yang et al. [38] failed to identify any evidence that depressive symptoms are consistently associated with modulation of MMP or TIMP expression. However, they did find that activation of the sympathetic-adrenal medullary (SAM) and the hypothalamic-pituitary-adrenal (HPA) axes could have an impact on MMPs level. A significant link between symptoms of depression and levels of MMP-9 in plasma has been recently found in a middle-aged healthy population in Sweden [39]. Moreover, MMP-9 in plasma was indicated to be one of the strongest markers of major depression after carrying out a large protein profiling investigation, the aim of which was to identify novel biomarkers of psychiatric disorders [40]. Lutgendorf et al. [41] reported that patients with ovarian cancer who also have increased depressive symptoms had increased levels of MMP-9 in tumor-associated macrophages in comparison to patients without any symptoms of depression.

The purpose of this study was to evaluate gene expression for selected polymorphisms of MMP-2 (C-735T), MMP-7 (A-181G), and MMP-9 (T-1702A and C1562T), which have been confirmed to participate in depression development [35], and TIMP-2 (G-418C). The expression was evaluated at the protein and mRNA levels. Moreover, activity variability of pro-MMP-2 and pro-MMP-9 was measured in comparison with the activity of MMP-2 and MMP-9 in a group of people with depression and a group of healthy individuals.

Material and Methods

The examination was carried out on a group of 142 patients with diagnosed depression and 100 non-depressed individuals forming a control group. People who were 18 to 67 years old were qualified to take part in the study. The patients with depression were classified on the basis of criteria described in the International Classification of Diseases and Related Health Problems (ICD – 10) [42].

All subjects taking part in the study underwent examinations during their hospitalization. Axis I and II disorders other than episodes of depression, as well as diagnosed somatic diseases and injuries of the CNS, were considered exclusion criteria. Other exclusion criteria included: autoimmune or inflammatory disorders and lack of willingness to provide informed consent. Examination of the patients was carried out on admission (i.e., during the symptomatic phase) before or shortly after modification of a previous antidepressant drug regimen.

Prior to the main study procedure, case history was obtained from all the subjects participating in the study, using the

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Table 1. Characteristics of the studied population.

Features	Control Number (freq.) (*N*=100)	Depression Number (freq.) (*N*=142)	*p*
Age (years)			
Mean ±SD	29.67±8.64	48.35±11.09	**<0.001**
Median (25%; 75%)	26 (25; 30)	51 (42; 56)	
Range	21–53	20–67	
Sex			
Females	64 (0.646)	82 (0.577)	0.345
Males	35 (0.354)	60 (0.423)	

p – level of statistical significance; p<0.05 in bold, as compared with the control group; control – control group; N – number of participants in particular groups; SD – standard deviation; range – between minimum and maximum value; age – at the time of the study;% – percentage.

standardized Composite International Diagnostic Interview (CIDI) [43].

The CG included 100 healthy subjects with negative family history for psychiatric disorders. The healthy controls were community volunteers who were qualified for the study based on the criteria of a psychiatric CIDI interview [43]. Individuals with other diagnosed psychiatric diseases, such as axis I and II disorders, neurological disorders, or, substance abuse or dependence, were excluded from the study.

None of the subjects had any medical illness, including infections and inflammatory or allergic reactions. No control subject or depressive patient was treated with the use of drugs known to have an influence on metabolism of lipids, endocrine function, or immune response. The control subjects had not taken any medications for at least 2 months prior to blood sampling. The individuals from the control group were neither drinkers nor heavy smokers, and had never taken psychotropic drugs.

In every case, examination of the subjects was conducted by the same person (the same physician-psychiatrist).

For the genotype study, peripheral blood was used in volumes of 5 ml. Detailed characteristics of the population are presented in Table 1.

The examined population comprised unrelated inhabitants of central Poland. During the experiment, we followed all confidentiality rules for data storage. The Bioethics Committee of the Medical University of Lodz (No. NN/469/11/KB) approved the study.

In both groups, gene expression on the mRNA and protein levels was evaluated for MMP-2, MMP-7, MMP-9, and TIMP-2. A change in activity was marked for MMP-2/pro-MMP-2 and MMP-9/pro-MMP-9.

Statistical analysis of expression and activity

SigmaPlot 11.0 and GraphPad Prism 5 (Statsoft, Tulsa, OK, USA and GraphPad Software, La Jolla, CA, USA, respectively) were used to perform data analyses and design graphs. The chi-square test and Mann-Whitney rank sum test, as appropriate, were used to compare demographic variables between cases and controls. The Shapiro-Wilk test was used to assess normality of the studied group. In case of failure, the Mann-Whitney rank sum test was used to compare variables between cases and controls; otherwise, the *t* test was used. Data in graphs are shown as medians with boundaries of the lower and upper quartiles. The correlation between expression on the RNA/protein level or activity of proteins and depression features was calculated using Spearman's rank-order correlation.

Extraction and reverse transcription of RNA

TRIZOL (*Invitrogen Life Technologies*) – a reagent used in RNA extraction – was used to extract total RNA from the blood samples, in accordance with the standard method of acid-guanidinium-phenol-chloroform. After extraction, RNA was analyzed by agarose gel electrophoresis. The study was conducted only on the basis of cases with preserved 28S, 18S, and 5S ribosomal RNA bands with good RNA quality. DnaseI (*GIBCO*) was used to digest total RNA at room temperature for 15 min. Five micrograms of digested RNA were subject to reverse transcription at 42°C for a period of 60 min (total reaction volume of 20 ml) using the ImProm-II™ Reverse Transcription System kit (*Promega, USA*). The resulting cDNA was used in a real-time PCR reaction.

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Gene expression detection based on the method of real-time RT-PCR

TaqMan™ technology-based real-time PCR was carried out using a master mix, which was prepared with the FastStart Universal Probe Master (*ROX*) from Roche Applied Science. Primers and probes were designed with the use of the on-line Universal Probe Library (*www.universalprobelibrary.com*). The following primer sequences and probe numbers were used: MMP-2 (forward, 5'-ACTGTTGGTGGGAACTCAGAAG-3', reverse, 5'-CAAGGTCAAT GTCAGGAGAGG-3', probe: #1), MMP-7 (forward, 5-CGGATGGTAAGCAGTCTAGGG-3', reverse, 5'-AGGTTGGATACATCACTGCA3TTAG-3', probe: #49), MMP-9 (forward, 5-TGGGTGTACGACGGTGAAAA-3', reverse, 5'-CATGGGTCTCTAGCCTGATA-3' probe: #31), TIMP-2 (forward 5'-TCTGGAAACGACATTTATGG-3', reverse 5'-GTTGGAGGCCTGCTTATGGG-3' and 18sRNA (forward 5'-CCGATAACGAACGAGACTCTGG-3', reverse 5'-TAGGGTAGGCACACGCTGAGCC-3' probe: #29), which served as internal control for real-time PCR.

A final volume of 50 µl was used for real-time PCR, with 0.05 µg of cDNA, 25 µl of FastStart Universal Probe Master (*ROX*) 2×, 250 nM of probe, and 1 µM of each primer. The process of amplification lasted 10 min at 95°C and its aim was to activate FastStart Taq DNA polymerase; amplification and signal analysis was the objective of forty 15-s rounds at 95°C and 1-min rounds at 60°C. ABI Prism 7000 Sequence Detection System (Applied Biosystems) was used to determine amplification values. Every sample was assayed in triplicate in the course of independent reactions. Real-time PCR data were automatically calculated using the data analysis module. Generated results were analyzed based on the $2^{-\Delta\Delta Ct}$ method. PCR efficiency validation was carried out with a standard curve. Standard curves were prepared for each gene by serial dilution.

Determination of serum MMP-2,-7,-9, TIMP-2 levels with the use of Enzyme-Linked Immunosorbent Assay (ELISA)

The RayBio® Human ELISA (*Enzyme-Linked Immunosorbent Assay*) from RayBiotech was used to perform quantitative determination of circulating serum human MMP-2, -7, -9, and TIMP-2. Each sample of serum was analyzed 3 times. We followed the manufacturer's instructions for definition and calculating results. Standards and samples were pipetted into wells with immobilized antibodies specific for human MMP-2, -7, -9, and TIMP-2, and then were incubated. After incubation and washing, biotinylated antihuman MMP-2,-7,-9, TIMP-2 antibody was added. Having washed away any unbound substances, biotinylated antibody and horseradish peroxidase-conjugated streptavidin was pipetted into the wells, which were washed once again. TMB (tetramethylbenzidine) substrate solution was added to the wells; color developed proportionally to the amount of MMP-2, -7, -9, and TIMP-2 bound. Color development was discontinued (Stop Solution) and its intensity was measured using the Thermo Labsystems Multiskan Ascent 354 (Lab Recyclers) at 450 nm.

Zymography

MMP-2/MMP zymography from the blood samples was conducted. Gelatinolytic activity appeared as a clear band over a blue background. Using an Image Master VDS (*Pharmacia Biotech*), images taken with the same magnification were quantified by densitometry based on their contour quantity after background subtraction. Arbitrary densitometry units were correlated with the standard curve prepared by serial dilution of human recombinant gelatinases across a linear range (0.030–1.25 ng/ml). Seventy-six BAL samples in total were selected for examination and analysis [44–50].

Results

Expression on the level of mRNA for MMP-2, MMP-7, MMP-9, and TIMP-2 in patients with depression and in the control group

For all examined and tested MMPs (MMP-2, MMP-7, and MMP-9), gene expression on the mRNA level was statistically more significant in patients with depression as compared to the control group. For TIMP-2, expression on the mRNA level was also statistically more significant for patients with depression. The results can be found in Table 2.

Expression on the protein level for MMP-2, MMP-7, MMP-9, and TIMP-2 in patients with depression and in the control group

Similar results were recorded for gene expression on the protein level. This expression was statistically more significant in the depression group for MMP-2,-7, and -9, while expression on the protein level for TIMP-2 was higher in the control group. The results are presented in Table 3.

Change of activity for MMP-2/pro-MMP-2 and MMP-9/pro-MMP-9

Activity of MMP-2 and MMP-9, as well as their inactive pro-enzymes, was measured in the present study. A change in activity of MMP-2 and pro-MMP-2 were statistically more significant in the group with depression. The opposite result was recorded for MMP-9 and pro-MMP-9, in which change in activity was statistically more significant in the control group. The results are presented in Tables 4 and 5, and in Figures 1 and 2.

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Table 2. Expression of level of mRNA for MMP-2, MMP-7, MMP-9, and TIMP-2 in patients with depression and in the control group.

	Control			Depression			Normality/equal variance test	*p*
	N	Median (25%; 75%)	Mean ±SD	N	Median (25%; 75%)	Mean ±SD		
mRNA								
MMP-2	100	0.262 (0.183; 0.318)	0.256 ±0.0775	142	0.320 (0.250; 0.390)	0.321 ±0.0886	<0.05/0.138	<0.001
MMP-7	100	0.128 (0.112; 0.142)	0.129 ±0.0233	142	0.230 (0.190; 0.290)	0.240 ±0.0708	<0.05/<0.05	<0.001
MMP-9	100	0.374 (0.314; 0.434)	0.371 ±0.0899	142	0.580 (0.510; 0.640)	0.563 ±0.106	<0.05/0.100	<0.001
TIMP-2	100	0.294 (0.215; 0.328)	0.289 ±0.0800	142	0.220 (0.180; 0.300)	0.236 ±0.0792	<0.05/0.871	<0.001

p – level of statistical significance; control – control group; depression – depression group; N – number of participants in particular groups; SD – standard deviation.

Table 3. Expression of protein level for MMP-2, MMP-7, MMP-9, and TIMP-2 in patients with depression and in the control group.

	Control			Depression			Normality/equal variance test	*p*
	N	Median (25%; 75%)	Mean ±SD	N	Median (25%; 75%)	Mean ±SD		
Protein								
MMP-2	100	365.5 (298.0; 414.0)	359.1 ±73.7	142	411.0 (332.0; 485.0)	411.2 ±86.9	<0.05/0.073	<0.001
MMP-7	100	135.0 (120.0; 165.0)	142.7 ±31.3	142	232.5 (193.0; 274.0)	236.8 ±53.7	<0.05/<0.05	<0.001
MMP-9	100	458.0 (384.0; 520.0)	448.0 ±93.7	142	598.0 (539.0; 669.0)	587.5 ±99.1	<0.05/0.617	<0.001
TIMP-2	100	356.0 (286.5-426.5)	355.8 ±79.2	142	308.0 (275.0; 385.0)	318.1 ±73.7	<0.05/0.777	0.004

p – level of statistical significance; control – control group; depression – depression group; N – number of participants in particular groups; SD – standard deviation.

Discussion

The assessed polymorphisms in the genes of MMPs have importance for the development of depression [35]. Depending on the distribution of genotypes and frequency of alleles for the examined polymorphisms, they may play a protective role or may increase the risk of depression development. It has been reported [35] that mRNA expression of MMP-9 was significantly higher in patients with depression than in a control group, which is consistent with our results in the present study. Jonsson et al. [35] also demonstrated no significant associations between depressive symptoms and measurements of MMP-9, TIMP-1, or TIMP-2 on any level (mRNA in PBMCs, protein release from PBMCs or plasma concentrations).

Additionally, there were no significant correlations between cynicism or mastery and measurements of MMP-9 or TIMPs. MMP-9 or TIMPs did not correlate with IL-6 levels in plasma, nor did psychological factors [35]. In the present study, in the group of patients with depression, expression on the protein level was statistically more significant for all the examined MMPs, except for TIMP-2, for which expression on the protein level was higher in the control group. Our search of the literature failed to find any study evaluating change in MMP activity in relation to the inactive form in a group of individuals diagnosed with depression. The results recorded in the present study indicate a significantly greater change in pro-MMP-2/MMP-2 activity in the group of patients with depression and a statistically significant change in pro-MMP-9/MMP-9 activity in the control group. The conversion of pro-MMP-2 into MMP-2 depends to a large extent on the activity of TIMP-2 [51].

MMP-9 has recently been considered a candidate marker of depression. A significant link between depressive symptoms and

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Table 4. Activity of MMP-2 and MMP-9, as well as pro-MMP-2 and pro-MMP-9, in the patients with depression and in the control group.

	Control			Depression			Normality/equal variance test	*p*
	N	Median (25%; 75%)	Mean ±SD	N	Median (25%; 75%)	Mean ±SD		
Activity								
MMP-2	100	0.340 (0.280; 0.400)	0.346 ±0.0980	76	0.470 (0.400; 0.520)	0.462 ±0.0860	<0.05/0.527	<0.001
MMP-7	100	0.585 (0.510; 0.645)	0.580 ±0.117	76	0.510 (0.470; 0.565)	0.513 ±0.0833	0.435/<0.05	<0.001
MMP-9	100	0.410 (0.340; 0.480)	0.411 ±0.0988	76	0.290 (0.215; 0.360)	0.286 ±0.0989	0.115/0.697	<0.001
TIMP-2	100	0.740 (0.610; 0.835)	0.711 ±0.163	76	0.825 (0.655; 1.175)	0.876 ±0.332	0.082/<0.05	<0.001

p – level of statistical significance; control – control group; depression – depression group; N – number of participants in particular groups; SD – standard deviation.

Table 5. Change in activity of MMP-2/pro-MMP-2 and MMP-9/pro-MMP-9 in the patients with depression and in the control group.

	Control			Depression			Normality/equal variance test	*p*
	N	Median (25%; 75%)	Mean ±SD	N	Median (25%; 75%)	Mean ±SD		
Activity ratio								
MMP-2/ pro-MMP-2	100	0.570 (0.499; 0.711)	0.607 ±0.161	76	0.906 (0.839; 0.955)	0.904 ±0.126	<0.05/<0.05	<0.001
MMP-9/ pro-MMP-9	100	0.578 (0.508; 0.647)	0.594 ±0.144	76	0.309 (0.250; 0.405)	0.375 ±0.210	<0.05/0.063	<0.001

p – level of statistical significance; control – control group; depression – depression group; N – number of participants in particular groups; SD – standard deviation

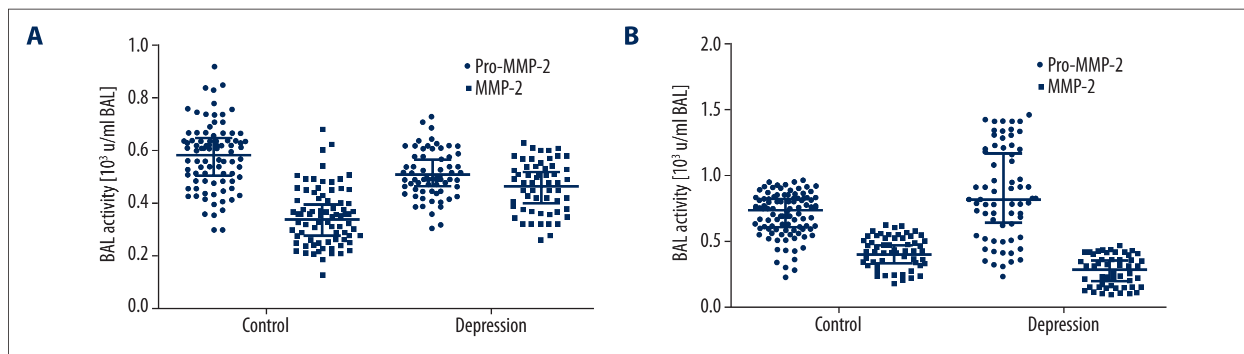

Figure 1. Activity of MMP-2 and MMP-9, as well as pro-MMP-2 and pro-MMP-9, in patients with depression and in the control group.

MMP-9 levels in plasma was recently confirmed in a Swedish population [39]. Moreover, it has been shown that MMP-9 in plasma is one of the strongest markers of major depression and may be considered a novel biomarker of psychiatric disorders [40]. Other papers indicate significant participation of MMP-9 as a risk factor for depression onset and as a disease that accompanies somatic diseases [35,41].

The results presented above may indicate that changes in MMPs and TIMP expression are common elements in, or perhaps even

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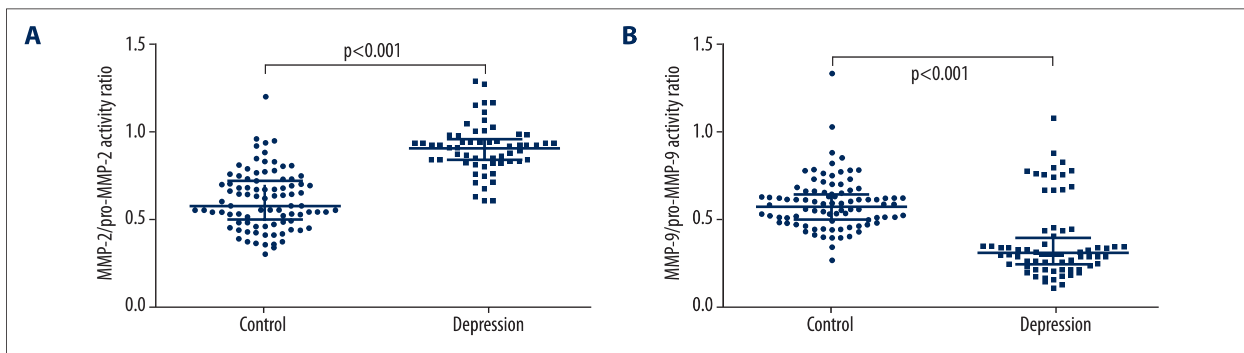

Figure 2. Change in activity of pro-MMP-2/MMP-2 and pro-MMP-9/MMP-9 in patients with depression and in the control group. Control – control group; depression – depression group; p – level of statistical significance.

a marker for, recurrent depressive disorders and somatic diseases. Expression of MMPs and their impact on CNS is a multifactorial process that can be subject to modulation on many levels. The results obtained in the present study, which indicate changes in expression on the mRNA and protein levels, as well as changes in activity, are significant for the evaluation of depression risks and protective factors, especially with co-existing somatic diseases [18,19,52].

Further studies on MMPs expression and activity in patients with depression are necessary to learn more about the role of these processes in the development of depression and in treatment. Expanding knowledge in this field may help to discover and implement therapeutic methods, especially in drug-resistant depression or with accompanying somatic diseases.

Conclusions

Changes in MMPs and TIMP expression may be a common element of, or perhaps even a marker for, recurrent depressive disorders and somatic diseases.

Study limitations

Study limitations include the small size of the patient group. There is a need to conduct similar studies in other populations to determine the effect of the stratification factor.

The obtained results may be affected by antidepressant therapy and age of the examined subjects.

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