BIOCHEMICAL MARKERS OF DEPRESSION

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Introduction. Depression, or Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder worldwide and a leading cause of disease burden. It is mainly characterized by depressed mood, anhedonia, sleep and appetite disturbances, loss of interest or pleasure in activities once enjoyed and feelings of guilt or worthlessness. A high suicide rate among individuals suffering from the disorder is the darkest side of depression. Currently affecting around 300 million people worldwide and with 5-17% of the population suffering from the disorder at least once in their lifetime, depression is a major clinical, emotional and socioeconomic burden for society. The World Health Organization estimates that, by 2030, depression will have become the leading cause of disability worldwide. An important issue in depression is that of low remission rates. Only approximately half of the patients achieve complete remission and with each subsequent treatment remission rates decrease.

Aim of the study. The aim of the study was to provide a comprehensive review of potential depression markers. For some, currently available evidence is insufficient to allow for regarding of them as biomarkers *sensu stricto*. However, alterations in their concentrations may provide relevant information concerning the pathophysiology of depression and be a starting point for future, larger biomarker studies.

Materials and methods. A literature search was conducted in PubMed, Scopus and Web of Science databases using keywords: "depression", "biomarker", "proteomic", "metabolomic", "oxidative stress", "biosignature" as well as combinations of these terms. Relevant articles were then included with the intention to cover the widest possible spectrum of different markers for depression.

Results and discussion. In depression, as evidence to date suggests, five biological systems are mainly affected. Therefore, they constitute natural sources of potential biomarkers. These are the inflammatory, neurotransmitter, neuroendocrine, neurotrophic and metabolic systems. Each system can be assessed at different biological levels – from genomic and epigenomic, through transcriptomic and proteomic to metabolomic. It is worth emphasizing that not every technique is equally efficient in the evaluation of a particular system.

Metabolomic profiles are different in depressed individuals in comparison to healthy controls. It has been demonstrated that a combination of plasma TRP, glutamate and cysteine can differentiate depressive patients from healthy controls. Elevated plasma amino acid concentrations differentiated patients with melancholic depression from healthy controls. In patients with MDD and heart failure, higher concentrations of amino-acids glutamate, aspartate and cysteine have been observed along with the dysfunction of fatty acids. Downregulated N-methyl-nicotinamide and hippuric acid, and upregulated azelaic acid have been found in the urine of patients

suffering from depression alone. Paige found higher levels of lipid metabolites and neurotransmitter metabolites in the blood of elderly patients with MDD (dicarboxylic fatty acids, glutamate, and aspartate). GABA, citrate, glycerate, 9,12-octadecadienoate and glycerol concentrations were reduced in currently depressed patients. A urinary biomarker panel for diagnosing patients with depression and anxiety was proposed by Chen The simplified panel consisted of four metabolomic biomarkers: N-methyl-nicotinamide, amino-malonic acid, azelaic acid and hippuric acid. Significant differences in metabolic phenotypes between non-medicated depressed patients and healthy controls were revealed, whereas differences between non-medicated and medicated patients were found to be insignificant This may indicate that treatment of depression has a limited impact on metabolites in urine in the patient population.

A recently published systematic review performed by MacDonald analyzed metabolomic biomarkers for depression and BPD. The pathway that was most significantly affected both in MDD and BPD was the alanine, aspartate and glutamate pathway. For MDD and BPD, 10 out of 22 metabolic pathways were common. Those specific to MDD were valine, leucine, isoleucine biosynthesis and cyanoamino-acid metabolism. Valine, leucine and isoleucine are involved in the formation of glutamate, which is a major excitatory neurotransmitter responsible for excitotoxicity. In chromatography/nuclear magnetic resonance/mass spectrometry studies, the concentrations of eight metabolites appear to follow a specific trend in urine, CSF and blood of depressed patients. These are increased glutamate, alanine, citrate, formate and decreased phenylalanine, valine, aminoethanol, and hippurate. Glutamate, glycine and cysteine are required for the formation of glutathione. Decreased GABA and increased lactate have been reported to be specific for MDD. The majority of key metabolites are involved in processes such as mitochondrial energy metabolism, signalling /neurotransmission and neuronal integrity. In most studies using in vivo brain imaging techniques, a decrease in brain N-acetylaspartate (NAA), glutamate, creatine, GABA, GSH and phosphocreatine and an increase in brain choline and lactate have been observed. Increased choline levels are in line with cholinergic hyperactivity and adrenergic hypoactivity, described in depression. Mitochondrial dysfunction could cause anaerobic glycolysis which may explain elevated lactate levels in the brain. Aspartate is involved in the synthesis of glutamate and NAA. NAA is ubiquitous in neurons and is considered to be a marker of mitochondrial dysfunction and neuronal integrity. NAA increases after antidepressant treatment, which further supports the neurotrophic effects of antidepressants. Most robust biomarkers identified do not follow a specific up-or downregulation trend. This inconsistency is probably due to several variables which have not been taken into consideration in the review such as depressive subtypes, the patient's age, sex, BMI, hormonal and smoking status. Nevertheless, a diagnostic panel for MDD and BPD consisting of lactate, alanine, glycine, phenylalanine, tyrosine, sorbitol, pyroglutamate, aminoethanol and hippurate, and a panel for MDD alone comprising glutamate, citrate, valine and formate have been proposed. It is worth noting that metabolomic research requires strict observance of the patient's inclusion criteria and methodological procedures since the metabolome is highly variable and significant

differences in results may appear.

Conclusions. To sum up, it is very unlikely that a single marker for MDD is established. However, even if the diagnosis of depression continues to be based on clinical signs, biomarkers may be a valuable tool for stratifying particular patients with the disorder, defining subtypes, improving treatment matching, avoiding specific treatment modalities, predicting response, etc.