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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.

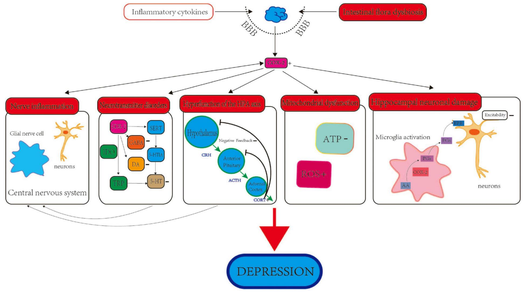
The World Health Organization estimates that, by 2030, depression will have become the leading cause of disability worldwide. An important issue in depression is that of low remission rates. Only approximately half of the patients achieve complete remission and with each subsequent treatment remission 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.



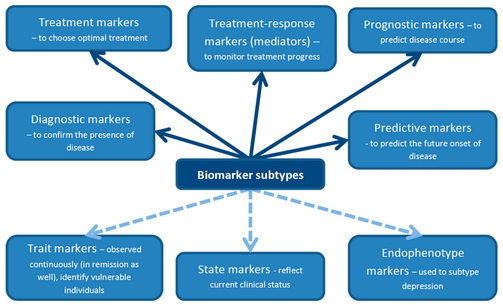
Results and discussion

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.

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.