NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

REVIEW

Arch Neuropsychiatry 2018;55:280–290
https://doi.org/10.5152/npa.2017.19482

Suggested Biomarkers for Major Depressive Disorder

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ABSTRACT

Currently, the diagnosis of major depressive disorder (MDD) mainly relies on clinical examination and subjective evaluation of depressive symptoms. There is no non-invasive, quantitative test available today for the diagnosis of MDD. In MDD, exploration of biomarkers will be helpful in diagnosing the disorder as well as in choosing a treatment, and predicting the treatment response. In this article, it is aimed to review the findings of suggested biomarkers such as growth factors, cytokines and other inflammatory markers, oxidative stress markers, endocrine markers, energy balance hormones, genetic and epigenetic features, and neuroimaging in MDD and to evaluate how these findings contribute to the pathophysiology of MDD, the prediction of treatment response, severity of the disorder, and identification of subtypes. Among these, the findings related to the brain-derived neurotrophic factor, the hypothalamo-pituitary-adrenal axis, cytokines, and neuroimaging may be strong candidates for being biomarkers MDD, and may provide critical information in understanding biological etiology of depression. Although the findings are not sufficient yet, we think that the results of epigenetic studies will also provide very important contributions to the biomarker research in MDD.

The availability of biomarkers in MDD will be an advancement that will facilitate the diagnosis of the disorder, treatment choices in the early stages, and prediction of the course of the disorder.

Keywords: Depression, biomarkers, brain-derived neurotrophic factor, cytokines, genetics, neuroimaging

Cite this article as: Hacımusalar Y, Eşel E. Suggested Biomarkers for Major Depressive Disorder. Arch Neuropsychiatry 2018;55:280-290. https://doi.org/10.5152/npa.2017.19482

INTRODUCTION

Currently, the diagnosis of major depressive disorder (MDD) mainly relies on clinical examination and subjective evaluation of depressive symptoms. At present there is no approved biomarker as part of the diagnostic criteria for any psychiatric disorder (1-3). However, biomarkers can be helpful in the treatment choice and in predicting the course of the disorder during the early stages. In this paper, articles were scanned by using PubMed, National Academic Network and Information Center (ULAKBIM) and Psychiatry Index databases. For this purpose, in addition to MDD keyword, biomarkers, proteomic markers, growth factors, brain-derived neurotrophic factor (BDNF), cytokines, oxidative stress markers, hypothalamo-pituitary-adrenal (HPA) axis, genetic, brain imaging, hippocampus keywords and their English equivalents were scanned and the appropriate articles were used as a reference. The results of monoaminergic system were not sufficient and consistent therefore except BDNF other growth factors and plasma metabolics data were not included.

In the medical literature, a biomarker is defined as "a property that can be objectively measured and considered as an indicator of a normal biological process, a pathological process, or a response of an individual to a therapeutic intervention" (4). Biomarkers are categorized into two groups, i.e., the diagnostic biomarker which is useful in distinguishing the presence or absence of a disorder and the treatment biomarker which is useful in predicting treatment response. It has been reported to be clinically useful that a biomarker should have high sensitivity and specificity (>80%) in the diagnosis and classification of a disorder (5). Moreover, for a biomarker to be used in everyday clinical practice, it needs to be reproducible, reliable, inexpensive and non-invasive.

Apart from the distinction between diagnostic and treatment biomarkers, biomarkers are also categorized into three groups as trait, state, and endophenotype markers. Trait biomarkers are persistent and show pathologies that exist before the onset of the disorder, during the disorder, and after remission. These can be used for determining which individuals are at risk for the disorder. On the other hand, state biomarkers are transient, related to the clinical condition, present at the onset of and during the disorder, but normalized with remission. Endophenotypic biomarkers are in fact a subgroup of trait biomarkers, based on the association between genes and specific depressive phenotypes; they are persistent, and found to be higher in family members than in the normal population (2).

Despite great effort having been expended for decades, a noninvasive and quantitative test that can be used for the diagnosis and treatment of MDD has not yet been found (Table 1) (3). The reason for this is the existence of many problems related to the investigation of the biological mechanisms underlying MDD. The main obstacles in this area may consist of the lack of a suitable animal model of depression, the inclusion

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Received: 14.12.2016, **Accepted:** 08.06.2017, **Available Online Date:** 28.05.2018

Table 1. Biomarkers for Major Depressive Disorder

Biomarkers	Major Depressive Disorder			Change after treatment	Conclusion
Serum and plasma BDNF		Decrease[16,22,23]		Normalization [16,22,23,27,28]	Candidate
Serum IL-1, IL-6, TNF and peripheral mRNA expressions	Increase[54,55]			Normalization [56,57]	Candidate
MDA	Increase [65,66]			Normalization [65,66]	Candidate
SOD	Increase in erythrocytes [65,66]	Decreased in serum [67,68]			Not consistent
HPA activity	Increase [70,71]			Normalization [78,79]	Candidate
Cortisol response to DEX/CRH	Increase [87]			Normalization	Candidate
Leptin	Increase [103,104]	Decrease [101,102]	Unchanged [105,106]		Not consistent
Ghrelin	Increase [106]	Decrease [107]		Increase [108] -Decrease[106,109]	Not consistent
5-HT transporter mRNA in blood	Increase [111]	Decrease [112]			Not consistent
Hippocampus volume		Decrease [154]		Normalization [155,156]	Candidate

BDNF: Brain-derived neurotrophic factor, **IL:** Interleukin, **TNF:** Tumor necrosis factor, **mRNA:** Messenger ribonucleic acid **MDA:** Malondialdehyde, **SOD:** Superoxide dismutase, **HPA:** Hypothalamo-pituitary-adrenal **DEX/CRH:** Dexamethasone/corticotropin releasing hormone **HT:** Hydroxy tryptamine

of a set of biologically and clinically heterogeneous disorders in MDD, the presence of different subtypes and the continual change of this subgrouping, the high incidence of comorbidities of MDD with many other physical or psychiatric disorders, and the lack of specificity and sensitivity rates of a single biomarker.

The wide variety and nonspecificity of the manifestations of depression may lead to the inclusion of biologically heterogeneous subgroups into MDD as an umbrella term. In this sense, many different disorders are diagnosed as being the same disorder, so the search for a single biomarker in a cluster essentially consisting of different disorders becomes meaningless (6, 7). Based on this argument, it seems reasonable to suggest the formation of more homogeneous samples (subtyping) sharing the same symptom groups and to investigate the biological changes in these subtypes. In this article, while we go through individual biomarkers, we will discuss the biologic features that are found in depression subtypes and that are promising for the differentiation of these subtypes from each other if indicated.

In addition, there is also an attempt to find treatment markers that may be useful in treatment selection and in estimating treatment response in MDD. Finding the optimal treatment for depressed patients is still done by the trial and error method, which is also quite time consuming. Therefore, as soon as possible, the discovery of biomarkers that are likely to predict the treatment response appears to be an urgent need for the regulation of individualized treatment (8).

Baron and Kenny (1986) suggested that treatment markers should be treated as two types consisting of moderators and mediators (9). Treatment moderators are the factors which show for whom the treatment will be successful and under what conditions, that is, which patient will benefit more from the treatment (10). In general, treatment moderators are variables that are initially present and predict the treatment response. Therefore, a positive moderator indicates that a particular treatment should be selected, and a negative moderator indicates another one. A treatment mediator is often described as a changing factor in response to a specific intervention (10). Ideally, an early change in the mediator with treatment should inform us of the rate of future recovery from the disorder, and the absence of this change should indicate that the treatment response will be inadequate (11).

Growth factors, cytokines and inflammatory markers, oxidative stress markers, endocrine markers, energy balance hormones, genetic findings, epigenetic studies, structural and functional imaging findings will be discussed in order to be used as biomarkers in MDD.

PROTEOMIC MARKERS

Proteins are the main actors in the cell. The total protein content of a cell is called the proteome. In depression, growth factors, inflammatory proteins, and oxidative stress-related enzymes have been investigated as proteome.

Growth factors

In some clinical trials, it has been shown that in patients with MDD, some growth factors (BDNF, vascular growth factor, insulin-like growth factor-1) change both gene expression and peripheral levels, while antidepressants have a normalizing effect (2, 12–14).

The most investigated growth factor in MDD is BDNF. BDNF regulates neural plasticity, migration, and survival in the central and peripheral nervous system (15). Apart from neurons, it is also released from peripheral cells such as leukocytes, endothelial cells, and platelets and may pass through the blood-brain barrier (16).

There are sufficient data showing that BDNF is important in the stress response and that it exhibits protective effects against the changes due to stress in the brain. BDNF may reverse the structural and synaptic plasticity changes due to stress in the adult brain, and this effect increases cognitive flexibility, thus adapting to the environment (17, 18). It has also been shown in animal studies that physical or psychological stress causes a rapid decrease in hippocampal BDNF expression (19, 20). Based on animal studies, it has been suggested that chronic stress exposure reduces neurogenesis and resilience by causing a down-regulation in the BDNF transmission pathways (21). Taken together, it is thought that a reduction in the hippocampal BDNF activity might be directly related to the pathophysiology of MDD, a stress-related disease, and this activity has been extensively studied.

Many studies and meta-analyses have shown that serum and plasma BDNF levels are decreased in depressed patients (16, 22, 23). It is suggested that the reduction in BDNF levels in depression is probably

due to increased corticosteroids, because activation of the glucocorticoid receptors (GRs) negatively affects the BDNF gene (24). In this regard, there is no difference between bipolar disorder and MDD (16), although serum BDNF levels are reported to be lower in bipolar depression compared to MDD (25). Also, a finding associated with the subtypes of depression is that BDNF levels in geriatric depression are even lower (26).

In studies and meta-analyses, a consistently reported finding is that the reduction in BDNF levels existing in depression is reversed by antidepressant drugs or electroconvulsive therapy (ECT) (16, 22, 23, 27, 28). ECT and long-term use of antidepressants increase hippocampal BDNF expression (29, 30). It is suggested that the final common pathway for various antidepressant treatments may be their effect on BDNF levels (31). In addition, initial BDNF levels in patients with MDD responding to treatment have been found to be higher (32). A meta-analysis concluded that BDNF levels could be used as a predictor of successful antidepressant therapy (treatment mediator) because serum BDNF levels remained unchanged in patients who did not respond to antidepressant medications but increased in treatment respondents and those who achieved remission (16).

Despite these findings indicating that BDNF levels in MDD may be regarded as a marker of diagnosis and treatment, there are still significant issues that remain unresolved in this regard. Although the main source of central BDNF is the hippocampus, it is suggested that peripheral BDNF measurements are less likely to reflect central activity because almost all peripheral tissues produce this growth factor. It is also not clear whether peripheral BDNF can cross the blood-brain barrier to produce behavioral effects (33). Moreover, the fact that BDNF changes are not specific to depression and found in many other psychiatric disorders suggests that this may be a neurobiological susceptibility factor for any psychiatric disorder (5).

In addition to these problems, the question of whether peripheral BDNF findings are state or susceptibility markers still appears to be unresolved (2). Although some studies have reported that BDNF levels are lower during full remission from depression compared to healthy controls (34, 35), a recent meta-analysis has concluded that BDNF is not lower in remission (16). Moreover, the relationship between depression and BDNF becomes even more complicated by the yet unanswered question of whether the reduction in BDNF expression is the cause or the result of depression (2, 34).

Thus, it can be said that findings support the idea that BDNF may be a biomarker for depression. In addition, there seems to be increasing functional importance of BDNF in the understanding of the pathophysiology of depression and in treatment.

Cytokines and inflammatory markers

Interacting with each other, the neuroendocrine and immune systems play an important role in stress response. For this reason, inflammatory markers have been extensively investigated in stress-related disorders and depression. Evidence supports the view that inflammation may play an important role in the pathophysiology of MDD (36). Inflammatory mediators have been found to affect many factors (monoamine and glutamate neurotransmission, GR resistance, and hippocampal neurogenesis) that are thought to be important in the etiopathogenesis of MDD. This suggests that inflammatory markers may be used as a marker for the diagnosis and treatment response of depression (37).

Cytokines are members of the interleukin (IL) family. They are produced by macrophages, natural killer cells, and T lymphocytes. Cytokines are classified as pro-inflammatory or anti-inflammatory. IL-1, IL-6, and tumor necrosis factor α (TNFα) are known as pro-inflammatory cytokines, and IL-4, IL-10, and IL-13 are known as anti-inflammatory cytokines (38).

As well as being important in brain development, cytokines play a role in the maintenance of normal brain function by supporting neuronal integrity, neurogenesis, and synaptic remodeling (39). They also create behavioral responses by influencing neurotransmitter systems (40). It has been reported that the cytokines released by peripheral immune cells and adipose tissue enter the central nervous system (CNS) through some regions of the blood-brain barrier or by the active reuptake mechanism and thereby affect behaviors. In the brain, they are mainly produced by microglia and some by astrocytes (41).

It is suggested that inflammatory variables may lead to depression by i) affecting neurotransmitters, ii) decreasing serotonin and inducing glutamate toxicity by stimulating indolamine 2,3 dioxygenase (IDO) in glial cells, iii) suppressing neurogenesis by decreasing BDNF activity, or iv) increasing HPA axis activity (38, 41, 42). Pro-inflammatory cytokines stimulate IDO in glial cells. IDO converts the tryptophan to kynurenine, which is then converted to neurotoxic quinolinic acid in the brain. Quinolinic acid binds to N-methyl D-aspartate (NMDA) receptors. Thus, because of the pro-inflammatory cytokines inducing IDO, depression may develop as a result of the decrease in serotonin levels due to reduced tryptophan on the one hand and glutamatergic neurotoxicity on the other (42). In a meta-analysis, confirmation of low plasma tryptophan levels in MDD supports the importance of IDO in linking cytokines to depression (43).

Both stress and subsequent inflammatory cytokine activation have been reported to adversely affect neurogenesis and neuroplasticity (44, 45). It has been reported that IL-1 suppresses hippocampal proliferation (46) and that cytokines such as TNFα and IL-6 exert a direct suppressive effect on hippocampal neurogenesis (47, 48).

Furthermore, it is also known that increased levels of cytokines stimulate the HPA axis (80). The effect of cytokines on the HPA axis may be directly through stimulation of the corticotropin releasing hormone (CRH) (50) or through altering the GR expression to induce GR resistance (51).

Of the inflammatory markers, those which most confirm the changes in depression are proinflammatory cytokines (52) such as IL-1, IL-6 and TNFα, and C reactive protein (CRP) (53). It has been reported that serum levels of IL-1, IL-6, and TNFα and the messenger ribonucleic acid (mRNA) expressions of these in peripheral cells are increased in patients with MDD (52, 54, 55). In several studies, this increase has been reported to return to normal with antidepressants (56, 57). A meta-analysis showed that selective serotonin reuptake inhibitors (SSRIs), in particular, reduce IL-6 and TNFα levels (58). ECT has also been shown to reduce plasma TNFα levels (59).

In some studies, elevated levels of IL-1, IL-6, and TNFα prior to treatment have been reported to be associated with non-response to antidepressant treatment (55, 60). These findings suggest that increased inflammatory parameters prior to treatment may be used as biomarkers of poor response to treatment (37, 57).

There has started to be research into whether or not cytokine levels differ for some subtypes of depression. It has been reported that there is a more evident increase in proinflammatory cytokines in those attempting suicide, in depression with suicidal ideas, and in geriatric depression (42, 61), whereas atypical and melancholic depressions show increased levels of CRP and IL-6 compared to typical depressions (62).

When all the findings are considered, it can be concluded that depression is accompanied by an imbalance between pro- and anti-inflammatory cytokines and that antidepressant treatment improves this imbalance. At the same time, the results in this area also suggest that cytokines can

be used as a biomarker for the diagnosis and treatment response of depression. However, based on these results, it is not possible to currently suggest that depression is a primary inflammatory disease (37).

Oxidative stress markers

Oxidative stress means that the balance between anti-oxidant and pro-oxidant processes in the cell is permanently degraded in favor of pro-oxidants. The result is overproduction of reactive oxygen species called free radicals. Free radicals cause damage to structures such as proteins, lipids, and DNA in the cell, and thus trigger apoptosis and cell death (63).

It has been suggested that increased oxidative stress and reduced anti-oxidant defenses exist in MDD, and that specific components of oxidative stress play a role in the pathophysiology of depression (63, 64). Therefore, the biomarkers of oxidative stress are currently being investigated in patients with MDD.

Levels of lipid peroxidation products such as malondialdehyde (MDA) have been reported to be generally elevated in depressed patients (65, 66). There are also studies reporting that MDA levels are higher in patients with recurrent depression than in those with a single episode (67). MDA levels have mostly been reported to decrease and return to normal with antidepressant therapy (65, 66).

Another parameter investigated as an oxidative stress marker in patients with MDD is superoxide dismutase (SOD) activity. The results of SOD studies are not as consistent as those in MDA studies. In depressed patients, several studies have reported that serum SOD is decreased (67, 68) or that erythrocyte SOD is increased (65, 66).

A meta-analysis of 17 trials evaluating the majority of lipid peroxidation markers in MDD found that these markers were elevated in patients with depression and found an association between the levels of these and the severity of depression (69).

In summary, although changes in the parameters relation to oxidative stress may be seen in MDD, it can be said that the findings are not strong or consistent enough to suggest that they can be used as a biomarker.

ENDOCRINE MARKERS

The biological field that was the first to be studied in depression and has collected a large amount of data is the field of endocrine changes. The most studied in this respect is the HPA axis.

In depression, the regulation of the HPA axis seems to be changed. It has been reported that depressed patients have a steady increase in cortisol and CRH release in a certain proportion of patients, and such findings have been suggested to signal increased HPA activity in MDD (70, 71). In accordance with this, CRH mRNA expression has been found to be elevated in different brain structures in patients with MDD who committed suicide or in animal models of depression (72, 73). In contrast, there are also recent postmortem studies reporting reduced hippocampal CRH mRNA expression in patients with MDD (74).

In depressed patients, HPA axis findings including abnormal cortisol levels during awakening, abnormalities in the diurnal rhythm of cortisol release, and abnormal cortisol response to pharmacological suppression tests such as the dexamethasone suppression test (DST) or experimental stress have been reported (75–77). HPA axis changes in depression are accepted as mostly state-dependent, that is, they improve with treatment (78, 79). It is suggested that the increased activity of the HPA axis in MDD is largely due to the reduced negative feedback of endogenous glucocorticoids (80). This is also partly related to the reduced GR expression in patients with depression (71). It has been suggested that elevated cortisol in some patients with depression develops to compensate for reduced GR expression and function (81). Indeed, postmortem human studies have shown a reduction in GR mRNA expression in the frontal and temporal regions of patients with MDD (82). Preclinical studies have shown that the use of antidepressants upregulates GR expression and function in the brain, thereby increasing the negative feedback of the HPA axis (71).

To demonstrate HPA axis alterations in MDD, the CRH stimulation test, which has been shown to be more sensitive in this regard, is frequently used in studies (83, 84). In this test, depressive patients respond to intravenous (IV) CRH administration with blunted adrenocorticotropic hormone (ACTH) and normal cortisol release. This finding is considered to be indicative of decreased sensitivity of the hypophyseal CRH receptor secondary to CRH hypersecretion (85).

After these initial studies investigating the HPA axis in MDD, the combined dexamethasone-CRH stimulation test (DEX/CRH) was proposed to further increase the sensitivity of HPA axis findings (86). For this test, samples are taken 15 hours after oral administration of dexamethasone (at 23.00), and then repeated samples are taken after IV CRH is applied. In the DEX/CRH test, depressive patients show increased cortisol response (87). Treatment with antidepressants or ECT has been reported to normalize this abnormal response (88, 89). It is reported that relapse risk and treatment resistance rates are high in patients with continued abnormalities in this test (90, 91).

Another important finding in this regard is that an increase in cortisol is more prominent in melancholic, psychotic, severe, and elderly depressed patients (7, 79). In patients with melancholic depression, plasma cortisol and nonsuppression rates in the DST are significantly higher than in other depressive conditions (7, 92). The finding that severity of depression and cortisol responses in the DEX/CRH test are positively correlated confirms that this neurobiological change is more related to severe and melancholic depression (7, 93).

In some depression subgroups, the inverse of the aforementioned findings related to the HPA axis is interesting, i.e., excessive suppression with dexamethasone and hypocortisolemia. Over-suppression of cortisol has been reported particularly in atypical depressions (94, 95) and in depressed patients with stories of early-life trauma exposure (96).

Energy balance hormones

Increasingly in recent years, studies have been carried out on the levels of hormones such as leptin and ghrelin that regulate the balance of body energy in MDD. Circulating hormones such as leptin and ghrelin transmit information related to the homeostatic levels of peripheral energy to the brain (97). Chronic stress has been reported to reduce serum leptin levels (98). In addition, it has also been shown that the administration of acute leptin in animals can produce an antidepressant effect, which is accompanied by increased hippocampal BDNF expression (99, 100). The leptin level results in patients with MDD are not consistent. Serum or plasma leptin levels were found to be decreased (101, 102), increased (103, 104), or unchanged (105, 106).

The data related to ghrelin in depression are also inconsistent. There are studies that found decreased (107) or increased ghrelin levels (106) and others which reported that it increases (108) or decreases (106, 109) with antidepressant treatment.

As a result, we can conclude that the findings related to leptin and ghrelin levels are still inadequate to allow them to serve as biomarkers in depressed patients.

Genetic findings

It is known that depression is a disorder that develops as a result of the complex interaction between a large number of genetic and environmental factors. Numerous studies are underway to address both gene expression levels and polymorphisms in genes related to substances in protein structure, such as neurotransmitters, hormones, growth factors, and secondary messengers, which are suggested to play a role in the pathophysiology of MDD, as biomarkers.

Postmortem studies have reported a decrease in 5-hydroxy tryptamine (5-HT)1A mRNA levels in the hippocampus and prefrontal cortex of patients with MDD (110). There are also studies reporting that the levels of 5-HT transporter mRNA in peripheral blood circulation increased (111) or decreased (112) in MDD. A meta-analysis combining postmortem and in vivo imaging studies revealed a decrease in 5-HT transporter expression in many brain regions (113). There are other studies reporting increased platelet 5-HT1A receptor expression in patients with MDD (114).

Polymorphisms in genes associated with serotonin transporter, serotonin 2A receptor, monoamine oxidase (MAO)A, BDNF, tryptophan hydroxylase, and GRs have been investigated as potential biomarkers in depression (115–117). When the results of these investigations are taken together, we can conclude that gene studies did not find a single common gene variant that significantly increases the MDD risk.

Furthermore, studies investigating the relationship between gene polymorphisms and response to depression treatment are increasing. Pharmacogenetic research assumes that treatment response or tolerability will be affected by inherited factors. Indeed, some observational studies confirm the hereditary basis of antidepressant treatment outcomes. For this purpose, several gene studies have been carried out including the genes of the serotonin transporter, serotonin receptor-2A, catechol o-methyltransferase (COMT), MAO-A, BDNF, cytochrome P450 enzyme, and ABCB1 (2, 117, 118). However, the results of these studies are not consistent.

For example; In the study of Mrazek et al. (2009), there was no correlation between genetic variations of serotonin transporter and response to citalopram (119). A more recent meta-analysis has concluded that the long allele of the serotonin transporter gene promoter may be a predictor of better antidepressant response in some races (120). In another study, it was found that single gene polymorphisms of the 5-HT2A receptor may be associated with citalopram response (121).

In addition, associations between the Met allele of BDNF gene Val/Met polymorphism and response to SSRI and between COMT gene polymorphism and response to some antidepressants have been reported (122, 123).

In conclusion, we can state that the data revealing the connection between pharmacodynamic candidate genes and treatment response are not sufficient to be beneficial in clinical use (33, 124).

Epigenetic studies

Today, it is believed that the predisposition to depression is caused by the collective influence of genes and the environment, and that the contribution of heredity is about 30-40%, the latter being complemented by the adverse effects of negative life events (8). Thus, as a result of the combination of genetic predisposition and certain environmental and life events, epigenetic irregularities in the CNS transcriptional program lead to the phenotypic manifestation of MDD (125).

The expression of genes can also be altered by epigenetic factors other than genetic variations. Recognizing epigenetic effects has led to the understanding that the long-term effects of environmental factors on behavioral responses occur by altering gene expression. Because these epigenetic modifications alter gene expression without altering the genetic code and regulate long-term neurobiological adaptations with this mechanism, the discovery of such a mechanism has opened up another dimension in depression studies (126). For example, epigenetic modifications due to stressors in early life may increase or decrease the risk of future depression by affecting the expression of certain receptors (e.g., GR in the hippocampus) (117).

Epigenetic factors include changes such as DNA methylation, histone modification, and microRNA (miRNA) dysregulation (127). Stress has been shown to induce epigenetic mechanisms such as histone modification and DNA methylation, which lead to maladaptive behavior (128). The most consistent findings in this area came from studies investigating the relationship among stress, depression, and epigenetic effects on the BDNF gene (129). It has been reported in animals that stressors such as chronic social stress or maternal separation in the postnatal period lead to decreased BDNF levels in different structures of the brain through histone demethylation and DNA methylation in the BDNF gene promoter region (128, 130). Sustained use of antidepressants also reverses stress-induced suppression of BDNF expression through epigenetic mechanisms such as histone-3 acetylation and histone-3 lysine-4 methylation (128). In human studies, changes in DNA methylation in the BDNF gene promoter region were also detected in MDD patients (131).

Epigenetic modifications may also alter the susceptibility to depression via the serotonergic system. For example, it has been reported that there is a positive correlation between childhood adverse life events and hypermethylation of the promoter region of the SLC6A4 gene, the serotonin transporter gene (132). Indeed, in a monozygotic twin study, an association between hypermethylation of the SLC6A4 promoter region in leukocytes and increased score of depression has been reported (133). There are also studies that could not find this relationship (134).

It is also known that epigenetic modifications due to prenatal or early life events may predispose to depression, especially by altering the stress response of the HPA axis for a lifetime. By disrupting the programming of the HPA system through epigenetic pathways, such stressful life events lead to a persistent stress sensitivity in neuroendocrine, autonomic, oxidative, and immune responses (135). The evidence shows that different stress types cause multiple epigenetic changes in both the limbic regions and the HPA axis (136). For example, it has been found that the children of mothers who did not show enough maternal behavior exhibited reduced GR17 expression in adulthood through increased methylation of the GR variant GR17 promoter (137).

miRNAs are small RNA molecules that consist of about 22 nucleotides, which regulate the translation of mRNA but do not carry genetic information themselves, i.e., do not encode proteins (138). miRNAs can alter the expression of 30-50% of genes encoding neuron specific proteins (139). Until now, over 1,500 different miRNA chains have been reported in humans. The level of miRNA expression in the mammalian brain changes constantly according to environmental stimuli. These molecules affect neuronal development and differentiation, synapse formation, and synaptic plasticity by affecting many cellular processes in the brain (140).

There are findings suggesting that stress exerts its effects on the brain through altering miRNA expressions (141, 142). For instance, acute restriction stress in animals causes down-regulation of miR-124 and miR-135a in the amygdala (143). Similarly, it has been reported that conditions such as maternal separation or chronic social stress in animals have led to an increase in the expression of some miRNAs in the medial prefrontal cortex (144) or a decrease in miR-451 levels in the hippocampus (145),

and that these changes were reversed with fluoxetine treatment given during adolescence (145).

It has been reported that miRNA levels in serum or peripheral blood cells are altered in depressed patients (146, 147), and that global miRNA expression in the prefrontal cortex is reduced in patients who committed suicide (148). It has been proposed that the relationship between depression and miRNA alterations may be mediated by GRs, and that the GR expression in the brain is strongly affected by miRNA, and consequently the changes in GR expression due to early life events may be mediated by miRNA dysfunction, which may also predispose to depression (138, 149). It has been further proposed that the miRNA effect may also be brought about by disrupting synaptic plasticity via BDNF or altering the expression of serotonin transporter (138, 150).

In summary, it can be suggested that long-term epigenetic modifications play an important role in stress-triggered behavioral responses, susceptibility to depression, and antidepressant response. However, for epigenetic findings to be used as biomarkers in MDD, further research in this field is required.

Structural and functional imaging findings

Structural and functional imaging studies in MDD are increasingly being conducted and are helping to clarify the neurobiological mechanisms underlying the disorder. Structural and functional changes in MDD have been reported especially in the brain structures related to emotion processing and mood regulation (151).

Unlike bipolar disorder, in patients with MDD there is no global brain volume reduction (208, 151). In MDD patients, morphological abnormalities have been reported including volume reduction in several brain structures such as the hippocampus, basal ganglia, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (DLPC), decreased cortical thickness, decrease in gray matter volume, and deterioration in white matter integrity (152, 153). These regional volumetric changes are thought to be part of the wider neural network and pathways present in depression.

Meta-analyses show that the volumes of both the left and right hippocampus decrease (on average, 4% on the left and 4.5% on the right) even in the first episode of depression (154). There are also reports that treatment with antidepressants or ECT reverses the decreased hippocampal volume in patients with depression (155, 156). It is, therefore, suggested that volume changes in the hippocampus may be a potential diagnostic marker in depression.

Based on the finding that patients with MDD generally exhibit lower hippocampal volumes during depressive episodes compared to those during remission, there are some who suggest that structural changes in the brain are situational features (5, 155), but this is still a controversial issue (152). There are also writers who claim that low hippocampus volume is a genetic predisposition. In relation to this, it has been suggested that Met-BDNF allele carriers have smaller hippocampal volume and may consequently be susceptible to depression (157). Gonul et al. (2011) showed a decrease in the left hippocampal volumes of drug-free depressed patients and that this was associated with Val66Met BDNF gene polymorphism (158).

In addition, it is suggested that the decreased volume of the hippocampus found in depressed patients may be regarded as a marker for the treatment. Two separate studies have shown that larger pre-treatment hippocampal volumes can predict better response to 8-week treatment (159, 160). In some meta-analyses, it has been shown that decreased volume of the right hippocampus may be a predictor of insufficient response to treatment in depression (161). There are also studies reporting the same for the left hippocampus (162). These findings provide strong evidence that measurements of hippocampal volume before treatment can be used as moderators of treatment. However, a 2-year follow-up study reported that the presence of a larger hippocampus in males is associated with lower relapse rates (163), implying that hippocampal volume may also be considered as a prognostic marker. A more recent meta-analysis confirmed a positive relationship between increased hippocampal volume and the likelihood of treatment response and increased remission (164).

Functional imaging studies in patients with MDD also reveal important findings. Patients with depression exhibit activity changes in areas such as the OFC, DLPC, ventromedial prefrontal cortex (VMPC), insula, amygdala, and ACC, which are particularly associated with cognitive functions such as the regulation of emotions, cognitive control, and reward processing (165, 166). In a meta-analysis, frontal region activity changes in depression were found to be more situational, while striatal changes were trait characteristics of susceptibility (167).

Patients with MDD generally show hypoactive responses to emotional stimuli in the frontal regions and hyperactive responses in the limbic regions (153). For example, when looking at frightened or sad face images, depressed patients show an increased activity in the amygdala, ventral striatum, and medial prefrontal cortex and decreased activity in the dorsal prefrontal cortex (168–170). They respond to a favorable emotional stimulus or a reward expectation with decreased ventral striatal activity (171, 172). These functional imaging findings seem to indicate the selective attention of depressed patients to negative stimuli rather than positive emotional and reward related stimuli. Increased activity in the amygdala and striatum is normalized by successful treatment with antidepressants or by cognitive-behavioral therapy (168, 170, 173); that is, it seems to be a situational feature.

In an earlier meta-analysis, frontal hypometabolism before treatment and the reversal of this with treatment were reported to be the best predictor of treatment response to both antidepressants and cognitive-behavioral therapy (174). In addition, the increase in subgenual ACC activity before treatment and the reduction of this activity with different antidepressant treatments, including cognitive therapy, suggest that this finding can also be used as a marker of treatment response (175). It has been demonstrated in recent studies that increased ACC activity before treatment may predict good response to treatment, and it has been suggested that this increased activity may also include the OFC (161).

CONCLUSION

Biomarkers can help predict the course of the disorder and the choice of treatment. Although studies investigating biomarkers for MDD have been carried out to facilitate the diagnosis and identification of subgroups, no test is as yet available for this purpose (Table 1). MDD is a clinically and biologically heterogenous disease, with different clinical appearance and courses of sub-groups, and problems such as the low sensitivity and specificity of the recommended markers reduces the benefit of biomarkers in this disease.

As a solution to the problem of low sensitivity and specificity of a single biomarker, some authors have recommended the examination of a biomarker panel of several biological factors rather than a single biomarker in the diagnosis of depression and the evaluation of the response to treatment (11). Thus, it has been suggested that a wider and multivariable approach could be more useful, including a combination of neuro-imaging, genetic, epigenetic, proteomic and metabolomic approaches to include the majority of multiple biological abnormalities,

which contribute to the differences in the clinical appearance and response to treatment of MDD. Therefore, research of multiple factors would enable the diagnosis and treatment of depression to be personalized and would contribute to the better understanding of the neurobiology of depression sub-types.

Within the parameters examined as potential biomarkers of MDD, some have been studied in more detail and it is noticeable that more consistent results have been obtained. Data related to BDNF seems to be extremely consistent, and it has been shown with great consistency that BDNF is reduced in some areas of the brain in patients with depression and this has been corrected with anti-depressant treatment. Despite the problem of specificity, several authors have accepted from these findings that BDNF is related to the pathophysiology of depression. Similarly, there is great consistency in HPA axis findings in depression and a strong relationship has been established with the pathophysiology of the disease. The DEX/CRH test has been found to be related particularly to the severity of depression and subtypes and promising results have been presented in this area. It can also be said that cytokines, of the potential biochemical markers, and imaging findings are strong candidates both in terms of being markers of depression and in providing important information about the biological etiology of MDD. In addition, although studies have only started in recent years and there are not yet sufficient findings, the results of epigenetic studies can be considered to make an important contribution to the subject of MDD markers.

Although research into biomarkers of MDD has been shown to be useful at a level that could reflect clinical use, better understanding of the biological etiology of MDD and re-organization of the sub-groups of the disease on a biological basis would be of great use.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - YH, EE; Design - YH, EE; Supervision - YH, EE; Resource - YH; Materials - YH, EE; Data Collection and/ or Processing - YH, EE; Analysis and/or Interpretation - YH, EE; Literature Search - YH, EE; Writing - YH, EE; Critical Reviews - YH, EE.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

KAYNAKLAR

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