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Biomarkers in Mood Disorders Among the Elderly: Can They Contribute to Diagnosis and Prognosis?

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Abstract Late-life depression is one of the most common neuropsychiatric disorders in the elderly population. Its clinical presentation is heterogeneous and has some distinctive features from depression in adults. In recent years, it has been demonstrated that patients with late-life depression present significant abnormalities in several neurobiological cascades. Among them, inflammatory, neuroendocrine, and neurotrophic cascades are of paramount importance. In this review, we revise the evidence of involvement of these cascades in the pathophysiology of late-life depression and the potential of the associated molecules (such as cytokines, neurotrophic factors, and hormones) as diagnostic and prognostic biomarkers. Despite the unequivocal advance in the understanding of its neurobiological basis, to date there is no sufficient evidence to support any biomarker of late-life depression. The search for valid biomarkers of late-life depression is warranted because they may contribute to correct diagnostic classification and to predict clinical outcome.

Keywords Aging · Major depression · Late-onset depression · Immunosenescence · Inflammaging · Cytokines · Adhesion molecules · Lymphocytes · Cortisol · Estrogen · Brain-derived neurotrophic factor · GSK-3beta

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Introduction

Late-life depression (LLD) is one of the most common neuropsychiatric disorders in the elderly population [1]. LLD is a debilitating disorder and has a major impact on the patients' life. It is associated with worsened quality of life, loss of productivity, increased medical comorbidity, health service use, and higher risk of death [2]. The prevalence of LLD is variable and depends on several factors such as study setting, definition of depressive episode, measurement scales, and assessment of psychiatric and medical comorbidities. In community-dwelling elderly patients, prevalence of major depressive episode ranges from 4 % to 22 % [1, 3]. The prevalence of subsyndromal or minor depression and clinically relevant depressive symptoms are much more frequent than major depressive episode, ranging from 20 % to 40 % [4–6]. The most consistent risk factors for LLD episodes are older age, low educational attainment, presence of multiple medical and neurological comorbidities, living alone, and lack of social support [7].

In this article, we review recent advances in the understanding of biomarker changes in LLD and how they can inform about diagnosis, prognosis, and the neurobiological substrates for LLD.

Clinical Presentation of Late-Life Depression: Does Age of Onset Matter?

The clinical presentation of LLD is heterogeneous and has some distinctive features from depressive episodes in adults. Complaints about sadness or downcast mood are less common in elderly persons. On the other hand, lack of energy and apathy along with somatic complaints and psychomotor retardation are prominent features of LLD. Psychotic phenomena, in particular nihilistic and guilty delusions, are also common in LLD [8, 9]. Patients with LLD show significant global cognitive impairment [10, 11]. Specific cognitive domains, such as executive function, short-term episodic memory, and processing of information speed, are particularly affected [11, 12].

Age of onset of LLD is an important feature of this condition and has a significant impact on clinical presentation. Patients are classified in early-onset LLD (EOD) if their first episode of major depression occurs at younger age or in late-onset LLD (LOD) if the first major depression episode occurs after age 65 years. Patients with LOD tend to have worse long-term prognosis and with increased comorbid cardiovascular disease as compared to EOD [13, 14]. Patients with LOD depict more severe and generalized cognitive deficits compromising most cognitive domains [11]. Executive functioning is particularly affected in LOD and may mediate the significant disability and functional impairment observed in these patients [15, 16, 17•]. Patients with EOD also may present significant cognitive impairment, notably of short-term episodic memory and information processing speed [11].

The heterogeneity of clinical manifestations and cognitive impairment patterns according to age of onset in LLD raised the question of whether this may reflect distinct underlying neurobiological substrates. Structural and functional neuroimaging studies have been shedding light on cerebral changes related to LLD. A large body of evidence suggests that patients with LLD show a significant higher frequency of cerebrovascular lesions (mainly periventricular and deep white matter hyperintensities and lacunar infarcts) and cerebral atrophy as compared to normal elderly control patients [18–21]. However, the pattern of cerebral structural changes is dependent on the age of onset of LLD. LOD patients usually show more significant cerebrovascular lesions as compared to patients with EOD [22–25]. These changes are most commonly located in the basal ganglia and in the fronto-subcortical white matter and seem to be associated with cognitive impairment, in particular executive dysfunction [25]. Given this close association between cerebral and cognitive changes, the term "vascular depression" has been coined to describe a subgroup of patients who presents LOD with history of cardio- and cerebrovascular diseases, accompanied by cerebrovascular lesions on the MRI and significant executive dysfunction [26–28, 29•].

Conversely, patients with EOD frequently show a significant regional cerebral atrophy, mostly in the hippocampal formation [30, 31]. Hippocampal atrophy correlates with the duration of the index depressive episode and the number of recurrent episodes [32, 33], and might be a harbinger of future dementia in some patients [34]. Such structural changes are in parallel with progressive short-term episodic memory decline in EOD patients. The exact neurobiological mechanisms that lead to hippocampal atrophy in these patients are unknown, but is possibly related to the sum of multiple mechanisms including hypothalamic-pituitary-adrenal (HPA) axis dysfunction, high cortisolemia, and reduced neurotrophic support [32, 35].

Inflammaging as a Pathogenic Mechanism in Late-Life Depression

In the past two decades a growing body of evidence emerged suggesting that a deregulation of inflammatory control, with increased proinflammatory status, plays a significant role in the pathophysiology of depression across the lifespan.

Chronic low-grade inflammation (called "inflammaging") has been observed during human aging (particularly in unhealthy populations), and it has been associated with frailty, morbidity, and mortality in elderly patients [36]. Indeed, chronic inflammation is considered to be involved in the pathogenesis of major age-related diseases, including Alzheimer's disease (AD), atherosclerosis, diabetes, sarcopenia, cancer, and major depression [37]. Cytokines are well known to mediate central effects of peripheral inflammation, including sickness behavior and fever.

There are multiple mechanisms through which cytokines may lead to depression. One mechanism involves the metabolism of certain neurotransmitters, such as serotonin, dopamine, and glutamate [38••]. Tryptophan is the main component of serotonin synthesis. Once inflammatory cytokines reach the brain, the activation of various transcription factors (eg, mitogen-activated protein kinase and nuclear factor-κB) takes place, leading to the activation of the enzyme indoleamine 2,3 dioxygenase (IDO). IDO is capable of metabolizing tryptophan into kynurenine, resulting in decreased synthesis of serotonin. Interestingly, patients undergoing interferon-alpha therapy for Hepatitis C virus infection or melanoma had decreased peripheral tryptophan levels and increased kynurenine levels concomitant with depressive symptoms development. Otherwise, kynurenine is preferentially converted into kynurenic acid in the brain, which interferes with the release of glutamate and dopamine. Dopamine also can be affected by inflammatory cytokines in a second way: cytokines reduce the levels of tetrahydro-biopterin (BH_4), which is an important co-factor

for tyrosine hydroxylase, a rate-limiting enzyme for dopamine synthesis, resulting in decreased dopamine levels. Another mechanism involves the metabolism of neurotrophic factors like brain-derived neurotrophic factor (BDNF). Cytokines induce glutamate release by astrocytes and reduce the expression of glutamate transporters, reducing glutamatergic reuptake. The glutamate released by astrocytes has preferential access to extra-synaptic N-methyl-D-aspartate receptors, which will reduce BDNF expression and decrease neurotrophic support. This reduced neurotrophic support will lead to increased neuronal susceptibility to oxidative stress.

Therefore, by modulating brain metabolism, "inflammaging" may be a relevant factor for the development of LLD. In addition, low-grade increases in levels of circulating tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, soluble IL-2 receptor, and C-reactive protein (CRP) are strong predictors of all-cause mortality risk in several longitudinal studies of elderly cohorts. It is worth mentioning, however, that low-grade inflammation was not observed in strictly healthy elderly persons or centenarians, suggesting that "inflammaging" is more likely a feature of unsuccessful aging [39].

Proinflammatory Profile in Late-Life Depression

Cytokines and Acute-Phase Proteins

Cytokines and acute-phase proteins are important mediators of inflammatory response. These proteins can be readily assessed in different biological matrices and, thus, can be reliable biomarkers of inflammatory activity in an individual patient. Cytokines can be produced in the periphery and by central nervous system cells, such as activated microglia, exerting active biological effects in glial and neuronal functions [40]. Some of these effects are directly related to the physiopathology of depression, as previously mentioned, presenting also long-term consequences such as the emergence of neurodegenerative changes in the brain [41, 42].

Several studies have examined peripheral levels of cytokines and acute-phase proteins in patients with LLD. IL-1β, a potent proinflammatory cytokine, was found significantly elevated in patients with LLD [43]. In a study carried out in our group, IL-1β was also significantly elevated in patients with LLD. Nonetheless, patients with EOD showed the highest plasma levels of IL-1β [44]. It is noteworthy that recurrent depressive episodes in adults was also associated with increased circulating levels of inflammatory markers like CRP [45], suggesting that recurrent depression is associated with cumulative proinflammatory burden.

TNF-α is the prototype proinflammatory cytokine and has been involved in the physiopathology of several chronic inflammatory disorders [46]. Despite studies in adult patients showing that TNF-α levels are significantly increased in patients with major depression [47••], the only study in LLD did not find significant differences between depressed patients and elderly control patients [48•]. Nonetheless, patients with LLD presented significant higher levels of soluble TNF-α receptor 2 (sTNF-R2, or p75), with no significant change in the levels of soluble TNF-α receptor 1 (sTNF-R1, or p55). These findings suggest that, despite patients with LLD not having significant changes in TNF-α levels, they present with an abnormal regulation of the TNF-α signaling system during depression [48•]. In line with this, a recent study found that elevated serum levels of sTNF-R1 were associated with higher depressive symptoms, as measured by the Geriatric Depression Scale, in elderly patients 1 year after hip fracture [49]. Other proinflammatory cytokines and acute-phase proteins, such as IL-6, CRP, and α1-antichymotrypsin, are also increased in patients with LLD [49–51].

Overall, current research findings suggest that LLD is characterized by a deregulation of inflammatory control with increased proinflammatory status. Such changes tend to correlate with the severity of depressive symptoms in most studies and recurrent depressive episodes may have a cumulative proinflammatory effect. These proinflammatory changes are in excess of those expected during the senescence process, suggesting that abnormalities in the inflammatory control may play a significant role in the physiopathology of LLD.

Despite that these findings are relevant for the understanding of LLD neurobiological basis, they are nonspecific and do not help the diagnostic process for this disorder. Elevated inflammatory markers also have been reported in other major psychiatric disorders, such as bipolar disorder, schizophrenia, and obsessive-compulsive disorder [52–56]. Neurodegenerative disorders common in older patients, such as AD and Parkinson's disease, also show increased levels of proinflammatory cytokines [57, 58]. It is worth highlighting the overlap of the profile of circulating biomarkers in LLD and AD, preventing any differentiation between these two conditions based on them (see Table 1). In this context, CSF biomarkers may be of great value. Patients with other neurological diseases, such as multiple sclerosis, in which depressive symptoms are very common, also present with high levels of proinflammatory cytokines [59]. Nonetheless, a recent study combining nine serum biomarkers related to inflammatory, neurotrophic, and endocrine-metabolic cascades (α1-antitrypsin, apolipoprotein CIII, BDNF, cortisol, epidermal growth factor, myeloperoxidase, prolactin, resistin, and sTNF-R2) showed a high accuracy for the diagnosis of major depression in younger adults [60••]. This promising result needs to be confirmed by independent studies and it is uncertain whether it is valid

Table 1 Peripheral biomarkers during aging, late-life depression, and Alzheimer's disease

Biomarkers	Aging	Late-life depression	Alzheimer's disease
IL1-α	↑	↑	—
IL1-β	↑	↑	↑
IL6	↑	↑	↑
TNF-α	↑	↑	↑
NK cells	↑	↑	—
CD45RA+ (naive T cell)	↓	↓	↓
CD45RO+ (memory T cell)	↑	↑	—
CD8+CD28- (senescent cells)	↑	↑	↓
CD4/CD8 ratio	↓	↑	—
Adhesion molecules	↑	↑	↑
Sexual hormones	↓	↓	↓
BDNF	↓	↓	↓
Cortisol	↑	↓↑	↑

↑ increased; ↓ decreased; *IL* interleukin; *TNF-α* tumor necrosis factor alpha; *NK* natural killer; *BDNF* brain-derived neurotrophic factor

for LLD. The prognostic value of inflammation-related molecules in LLD has not been investigated yet.

Adhesion Molecules

Adhesion molecules play an important role in the inflammatory process. Once inflammation is triggered, upregulation of adhesion molecule genes takes places in endothelial and immune cells to facilitate leukocyte adhesion and migration to sites of inflammation. Data regarding levels of soluble adhesion molecules such as soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) are scarce and contradictory. Levels of sICAM-1 and sVCAM-1 were found elevated in the periphery of depressed elderly patients [61]. Postmortem studies also found increased expression of ICAM-1 and VCAM-1 in dorsolateral prefrontal cortex of depressed elderly patients [62]. Conversely, Thomas and colleagues [63] did not find any association between peripheral levels of sICAM-1 or sVCAM-1 and depression in elderly patients.

As observed for cytokines, sICAM-1 levels were also found increased in patients undergoing interferon-α treatment who developed major depression [64]. However, given the high frequency of ischemic changes during the aging process, it is difficult to define whether elevated levels of adhesion molecules are due to depression or not. Vascular depression theory postulates that LOD is associated with vascular and ischemic diseases to which adhesion molecules are considered good markers [61]. Accordingly, sICAM-1 levels were found elevated in individuals who developed major depression after an episode of acute coronary syndrome [65]. Interestingly, these levels were significantly higher in patients with no past history of depressive disorder than those who had [65]. Adhesion molecules are widely expressed on blood–brain barrier endothelial cells and can be related to its increased permeability during inflammatory processes, allowing cytokines to cross this barrier and exert its effects in the brain [61]. Together, these data point to a possible mechanism of action through which low-grade inflammation is involved in the development of LOD. The absence of studies assessing adhesion molecules levels in elderly patients diagnosed only with major depression (with no comorbidity) makes difficult to establish the precise role of these molecules as biomarkers and in the development of depressive states.

Leukocyte Subsets

Data regarding immune cell subsets in LLD are scarce. Changes in number and function of these cells would not be surprisingly, as they are responsible for the production of many cytokines observed altered in this context. However, cellular alterations are also common to the aging process itself, being hard to address the precise role of these putative biomarkers in LLD. Quantitative changes in leukocytes such as decreased in naïve T cells ($CD45RA^+$), increased number of memory T cells ($CD45RO^+$), expansion of $CD8^+CD28^-$ T cells (known as "senescent cells"), and increased natural killer (NK) cells have been observed during aging, particularly in elderly patients with increased depressive symptoms [66, 67]. Increased T cell counts have been found in elderly depressed patients with no antidepressant treatment. NK-T cells, $CD8^+$ cytotoxic T cells, and CD4/CD8 ratio also have been found increased in this population [68]. Interestingly, when analyzing cell subsets from elderly depressed patients undergoing antidepressant treatment, the numbers of $CD8^+$ and NK-T cells did not differ from healthy individuals, while the CD8/CD4 ratio is unaltered by antidepressant treatment [12, 13, 68, 69]. More studies are needed to better understand the role of lymphoid subsets during aging and their possible role in LLD.

Neuroendocrine Changes in Late-Life Depression

Hypothalamic-Pituitary-Adrenal Axis

Current literature suggests that both major depression and aging are associated with significant activation of the HPA axis. LLD seems to follow the same scenario. Adults with major depression have shown increased plasma cortisol levels and enlarged anterior pituitary and adrenal glands, as well as failure to suppress cortisol levels following dexamethasone administration [70, 71]. The increased HPA axis

activity is thought to be related, at least in part, to diminished feedback regulation by endogenous glucocorticoids. Remarkably, successful antidepressant treatment is associated with normalization of feedback regulation of the HPA axis induced by glucocorticoids. Increased circulating cortisol might contribute to depression pathogenesis, as correction of hypercortisolemia with cortisol synthesis inhibitors also has been reported to ameliorate depression [72].

The HPA axis activation is regarded to be fundamental for the body to deal with changing environmental demands by increasing circulating energy substrates such as glucose and fatty acids. However, long-term increase in cortisol levels will negatively impact key brain areas involved with HPA axis feedback regulation (hippocampus and hypothalamus), impairing cognitive functions as well as leading to poorer cell-mediated immune responses. We have previously observed that lymphocytes of depressed patients are resistant to glucocorticoid treatment in vitro or in vivo [73, 74]. Ineffective action of glucocorticoids on target tissues could lead to immune activation as shown by chronic low-grade inflammation. Conversely, inflammation can stimulate the HPA axis via both a direct action of cytokines on the brain and by inducing glucocorticoid resistance [75]. Hypercortisolemia may have important long-term consequences for health, including higher allostatic load and accelerated aging. Indeed, depression has been associated with features of premature aging, and depressed individuals have a higher incidence of various age-related diseases, including cardiovascular and cerebrovascular diseases, metabolic syndrome, and dementia [76].

Aging is also associated with significant activation of the HPA axis. We have observed that strictly healthy elderly persons had remarkably higher salivary cortisol but low dehydroepiandrosterone (DHEA) levels throughout the day compared to young adults [4]. These hormonal changes were found in parallel to age-related psychological distress, including increased depressive symptoms. DHEA is produced by the adrenal glands and is under the regulation of the HPA axis. It has been suggested that DHEA may antagonize many physiologic changes of cortisol, including enhancing immune functions [77]. The lack of appropriate DHEA levels could be a detrimental factor during aging. Interestingly, it has been shown that low DHEA levels were associated with depressed mood in older women [78] and DHEA supplementation significantly improved memory performance and depression ratings in elderly patients with depression [79].

The presence of depression seems to amplify the changes of the adrenal secretory pattern, already present in the physiological aging. Elderly patients with major depression or patients reporting increased self-reported ratings of depressive symptoms had increased nocturnal cortisol levels compared to healthy control patients [80, 81]. In a recent large population-based study, it was observed that LLD is associated with both hypo- and hypercortisolemia [82]. Nevertheless, only hypercortisolemic depression was associated with older age, cardiovascular diseases, and cognitive impairment [82].

Taken together, these studies suggest that changes in HPA axis molecules are not reliable biomarkers of LLD, but rather common phenomena observed during aging and depressive disorder.

Sexual Hormones

The role of sexual hormones in depression has long been addressed in an attempt to explain the higher susceptibility carried by women to develop mood disorders. Because depressive symptoms are common to women experiencing the low-estrogen phase of menstrual cycle, after childbirth, and during climacteric and menopause, it is believed that these hormones are related to physiopathology of depression in women [83–85].

During the climacteric phase (ie, the transition to menopause) the gradual decline in ovarian function leads to a reduction in sexual hormones production, including estrogen, testosterone, and progesterone. Estrogen reduction or deprivation can lead to many physiological changes, such as alterations in neuronal plasticity and neurotransmission [83]. More precisely, estrogen can modulate the serotonergic system, which is greatly involved in mood control. There is a high risk of depression during this phase, but several studies failed to establish any association between the levels of sexual hormones and development of depressive symptoms [83–88, 89•]. Therefore, sexual hormones do not seem useful as biomarkers in this context. Interestingly the longer climacteric phase, the higher risk of developing major depression [87, 89–91]. Moreover, studies described reduction in depressive symptoms after hysterectomy and oophorectomy in climacteric women, supporting the idea of hormonal fluctuations having worse effect on mood than low estrogen levels itself [28, 29•].

Hormonal replacement has been reported as increasing well-being in climacteric women, but its effects in ameliorating depressive symptoms remain controversial [84]. While women in estrogen therapy show a better response to fluoxetine treatment [84], postmenopausal women demonstrated increased risk to develop depressive disorders during hormonal replacement [85]. The development of major depression in menopausal state seems to be more common in women with a previous history of depressive disorder and to be related with psychosocial stress instead of sexual hormones [84–86].

Neurotrophic Factors in Late-Life Depression

Neurotrophic factors are a broad family of proteins that play several roles in the central nervous system, mainly

maintenance of neuronal homeostasis, neuroprotection against insults, neuronal repair and regeneration, and synaptic formation and strengthening [92]. BDNF is the most abundant neurotrophic factor in the brain. Several studies found significant lower circulating levels of BDNF in patients with LLD as compared to nondepressed controls [93, 94]. When studies stratified LLD according to the age of onset, patients with LOD had lower BDNF levels than those with EOD [95]. In addition, a recent study reported that older patients with subsyndromal depression showed levels of BDNF that were intermediate between patients with major depression and nondepressed control patients, suggesting a gradient effect [94]. In contrast, a community-based study failed to find significant changes in BDNF levels in LLD [96]. Differences in samples, assessment of depressive symptoms, and severity of depressive symptoms may help to explain such conflicting results.

The dynamics of other neurotrophic factors have not been extensively explored in LLD. The glial cell line–derived neurotrophic factor (GDNF) plays a major role in the protection of catecholaminergic, dopaminergic, and cholinergic neurons [97] and axonal regeneration after injury [98]. Studies in LLD have reported contradictory results showing either elevated [99] or reduced GDNF levels [100] in LLD when compared to age- and sex-matched control patients. Likewise, studies with the nerve growth factor (NGF) also have reported contradictory findings in LLD, with one study reporting nonsignificant differences [96] and another reporting a significant reduction in LLD [101]. In the latter study, we found that older patients with previous history of depression, but who were euthymic and under antidepressant treatment at the time of laboratory assessment, also showed a significant reduction in NGF levels, comparable to those observed in patients with current depressive episode [101]. In light of these results, we hypothesized that lower NGF levels may represent a state marker of depressive disorder in elderly patients and also may indicate a significant disruption in the neurotrophic regulatory mechanism that takes place during the depressive episode and does not completely recover despite clinical improvement after treatment.

Other Peripheral Biomarkers in Late-Life Depression

Changes in other neurobiological cascades that may have physiopathologic and clinical relevance in LLD have been recently reported. Increased oxidative stress markers have been consistently reported in adult patients with major depression and bipolar disorder [102, 103]. In LLD, one study so far reported a significant increase in the peripheral levels of plasma 8-iso-prostaglandin F2-α (8-iso-PGF2-α), a marker of oxidative damage, in patients with LLD [50]. Such changes were correlated to increased proinflammatory status in these patients, suggesting a significant crosstalk between oxidative damage and inflammatory status in LLD patients.

The glycogen synthase kinase-3β (GSK-3β) is an intracellular enzyme that is involved in many cellular functions such as energy metabolism, structural plasticity, neurogenesis, and resilience to cellular injury [104]. Its activity is regulated by the phosphorylation of serine 9 epitope, rendering the enzyme inactive. As GSK-3β is involved in diverse cellular functions, it is plausible to hypothesize that this enzyme may be related to the physiopathology of mood and neurodegenerative disorders [105]. A recent study showed patients with LLD had lower levels of phosphorylated GSK-3β with no changes in total GSK-3β in platelets, suggesting that GSK-3β is possibly overactive in patients with LLD [106]. Moreover, these changes were markedly pronounced in patients with more severe cognitive impairment and depressive symptoms, indicating that GSK-3β overactivation is a state marker of more severe depressive episodes in older patients. Further studies are warranted to confirm this finding.

Cerebrospinal Fluid Biomarkers in Late-Life Depression

Few studies addressed changes in cerebrospinal fluid (CSF) biomarkers in LLD. Most studies focused on the accuracy of AD-related biomarkers (amyloid-β_{42}, total Tau, and phosphorylated Tau proteins) to differentiate between LLD and AD disease. In general, patients with LLD showed a pattern similar to those observed in elderly control patients when compared to AD profile that is characterized by low levels of total and phosphorylated Tau proteins and high levels of amyloid-β_{42} [107–109]. Schneider and colleagues [110•] recently proposed that the only feasible tools to discriminate LLD and early AD (which is commonly associated with depressive symptoms) are the CSF biomarkers for AD. Their high negative predictive value could be regarded as inverse evidence ("negative depression biomarker") that LLD is the sole cause of cognitive symptoms in depressed elderly patients as opposed to prodromal or early Alzheimer's disease.

In a small study that included LLD patients and nondepressed elderly control patients, the former group showed higher levels of amyloid-β_{42} and no difference in total and phosphorylated Tau proteins as compared to the latter group [111]. Nonetheless, LLD patients showed a higher CSF/serum albumin ratio, suggesting dysfunction of the blood–brain barrier possibly due to vascular processes. Another study showed increased CSF levels of a nonspecific marker of neurodegeneration, the neurofilament light protein, in LLD as compared to healthy control patients [112]. These results suggest that patients with LLD may develop nonspecific neurodegenerative and vascular changes during mood episodes that may render these patients more vulnerable to the development of dementia [113, 114].

Conclusions and Perspectives

A growing body of evidence suggests that LLD patients present significant abnormalities in several neurobiological cascades, determining changes in peripheral and central nervous system biomarkers. These studies contributed to the understanding of the physiopathological features of LLD and its relationship with medical comorbidities and neurodegenerative and cerebrovascular disorders. However, they are much less informative regarding diagnosis, prognosis, and treatment selection for individual patients. To date, there are no sufficient data to support any biomarker as diagnostic or prognostic of LLD.

Advances in this field will be possible by integrating distinct approaches and taking into consideration diverse biomarkers derived from several neurobiological cascades involved in LLD. New strategies for biomarkers discovery and development, including the "-omics" (genomics, proteomics, metabolomics), new structural neuroimaging (iron imaging, microbleeds, tractography), and functional and molecular imaging techniques should be incorporated to long-term clinical and epidemiological studies to determine the diagnostic and prognostic values of different biomarkers. Moreover, these strategies should be systematically included in clinical trials to provide more specific (neurobiological-based) selection criteria for patients, and to predict responsiveness or refractoriness to treatment.

The identification of LLD biomarkers may contribute to the development of more specific and personalized interventions aiming not only at the treatment of current depressive episodes but also the prevention of adverse outcomes, mainly functional and cognitive decline that ultimately lead to clinical diagnosis of dementia.

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- • Of importance
- •• Of major importance

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