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INFLAMMATORY BIOMARKERS AND DEPRESSIVE DISORDERS: DIAGNOSTIC IMPLICATIONS AND THERAPEUTICS - INTEGRATIVE SYSTEMATIC REVIEW

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ABSTRACT

Objective: Critically analyze the scientific evidence regarding the association between inflammatory biomarkers and depressive disorders, with emphasis on their diagnostic, prognostic, and therapeutic implications.**Methods:**An integrative systematic review was conducted, guided by the PRISMA 2020 recommendations. Searches were carried out in the PubMed/MEDLINE, Scopus, Web of Science, Embase, PsycINFO, Cochrane Library, and SciELO databases, covering publications available up to July 2026. Original studies were included that were conducted with adults and investigated peripheral or central inflammatory biomarkers in association with depression, symptom profile, neurobiological alterations, therapeutic response, or treatment resistance. The final sample comprised 35 publications, organized into four axes: epidemiological and phenotypic association; neuroinflammation and neurobiological mechanisms; prognostic and predictive value; and anti-inflammatory or immunomodulatory interventions. Due to clinical and methodological heterogeneity, the data were synthesized narratively.**Results:**C-reactive protein and interleukin 6 were the most frequently investigated biomarkers and showed the most consistent associations with depression, neurovegetative symptoms, metabolic alterations, and treatment resistance. Inflammation was particularly related to fatigue, anhedonia, sleep and appetite disturbances, reduced energy, and psychomotor slowing. Neuroimaging studies identified changes consistent with neuroimmune activation, impaired cortico-striatal reward circuits, and modifications in glutamatergic metabolism. Inflammatory biomarkers also demonstrated potential to predict differential response to antidepressants, physical exercise, electroconvulsive therapy, and anti-inflammatory interventions. However, trials involving infliximab, celecoxib, minocycline, and omega-3 fatty acids showed heterogeneous results, with more evident benefits in subgroups with high baseline inflammation.**Conclusion:**Inflammation is a biologically relevant, though not universal, dimension of depressive disorders. No single biomarker showed sufficient performance for diagnostic independence. The main potential application lies in the identification of immunometabolic phenotypes, prognostic stratification, and treatment personalization. Clinical incorporation of these markers still depends on prospective validation, laboratory standardization, definition of cutoff points, and conducting profile-driven trials guided by the inflammatory profile.

Keywords: Major Depressive Disorder; Biomarkers; Inflammation; Precision Medicine.

INTRODUCTION

Depressive disorders are complex, heterogeneous, and multifactorial psychiatric conditions characterized by persistent changes in mood, motivation, cognition, sleep, appetite, and psychosocial functioning. Although classic neurobiological models have primarily emphasized alterations in monoaminergic systems, accumulating evidence from recent decades indicates that immunological and inflammatory mechanisms play a relevant role in a subgroup of patients. This perspective has broadened the pathophysiological understanding of depression by considering the interaction between the central nervous system, the immune system, metabolism, the hypothalamic–pituitary–adrenal axis, and environmental factors as components of an integrated network of vulnerability and disease maintenance.

Epidemiological and population-based studies have shown consistent associations between depressive symptoms, major depressive episodes, and elevated peripheral inflammatory markers, especially C-reactive protein, interleukin 6, and tumor necrosis factor alpha[1-5]. In different age groups and clinical settings, individuals with depression exhibited higher concentrations of these mediators than participants without depressive symptoms. However, the magnitude of these associations varied according to sex, age, adiposity, presence of chronic diseases, smoking, use of medications and specific characteristics of the psychiatric profile[1-4,7]. These findings indicate that inflammation is not a universal feature of depressive disorders, but rather a biologically relevant in certain clinical phenotypes.

The symptomatic heterogeneity of depression appears to directly influence the relationship between inflammation and disease. Population-based analyses indicated that elevations in inflammatory markers are more strongly associated with neurovegetative and energy-related symptoms, including fatigue, sleep disturbances, increased or decreased appetite, anhedonia, psychomotor retardation, and reduced motivation[6]. This distribution suggests the existence of an immunometabolic depressive phenotype in which low-grade inflammatory responses are associated with metabolic alterations, abdominal obesity, dyslipidemia, and insulin resistance. Therefore, the combinat-

ion of elevated C-reactive protein, atypical symptoms, and metabolic dysregulation may offer greater clinical stratification ability than the use of a single biomarker[8].

The biological plausibility of this association is supported by neuroimaging studies and investigations of central biomarkers. Studies using positron emission tomography demonstrated higher expression of the l8 kDa translocator protein in regions such as the anterior cingulate cortex, prefrontal cortex, and insula during major depressive episodes, a finding interpreted as indirect evidence of neuroimmune activation[9,10]. In a complementary manner, higher levels of peripheral inflammation were associated with reduced functional connectivity in cortico-striatal circuits related to reward, motivation, and motor control[11]. Relationships were also observed between elevated C-reactive protein, increased glutamate in the basal ganglia, anhedonia, and psychomotor retardation[12]. These results suggest that inflammation may interfere with neurotransmission, neuronal plasticity, and the function of brain circuits involved in mood regulation.

Communication between peripheral inflammation and the central nervous system may occur through different mechanisms, including vagal signaling, transport of cytokines across the barrier hematencephalic, activation of endothelial cells, recruitment of immune cells, and modulation of microglial activity. The correlation between Creativa plasma protein and inflammatory markers no cerebrospinal cerebrospinal fluid strengthens the hypothesis that systemic alterations may reflect, at least in part, a neuroinflammatory environment[13]. In this context, mediators such as IL-6, TNF-α, IL-lβ and their soluble receptors may modify the availability of neurotransmitters, activate the kynurenine pathway, increase oxidative stress, and impair processes related to neurogenesis and synaptic plasticity.

In addition to its association with the presence and clinical expression of depression, inflammatory biomarkers have been investigated as prognostic indicators and predictors of therapeutic response. Clinical studies have observed that elevated levels of IL-6, TNF-α, and other mediators may be associated with a lower response to conventional antidepressants and the persistence of symptoms

in patients with treatment-resistant depression[14- 17]. Inflammatory signatures at the level of gene expression have also been associated with less favorable therapeutic outcomes, suggesting that basal immune activity may influence the efficacy of pharmacological treatments[18].

C-reactive protein has received special attention due to its availability, low cost, and widespread use in clinical laboratories. Studies derived from the GENDEP and CO-MED projects showed that the baseline concentration of this marker may differentially modify the response to certain classes or combinations of antidepressants[19,20]. Lower values were associated with better relative outcomes with strategies predominantly serotonergic, whereas higher levels indicated potential benefit from treatments with greater noradrenergic or dopaminergic action. Similarly, IL-l7 and proteomic panels have been investigated as possible tools for medication selection, although the results remain exploratory and require prospective validation[21,22].

The therapeutic relevance of inflammation was also examined in non-pharmacological interventions and in treatments with immunomodulatory properties. Baseline inflammation showed potential capacity to predict response to physical exercise, suggesting that patients with higher immune activation may experience a differential benefit from certain interventions[23]. Trials involving infliximab, omega-3, celecoxib, and minocycline demonstrated heterogeneous results, with no overall efficacy in part of the samples, but signals of benefit in subgroups with higher inflammation[24-32]. These findings indicate that anti-inflammatory therapies should not be used indiscriminately, but may become relevant when associated with strategies for biological selection of patients.

Other antidepressant treatments, such as ketamine and electroconvulsive therapy, have also been associated with inflammatory changes. Ketamine administration produced rapid cytokine modulation in patients with treatment-resistant depression, although it is still unclear whether this effect represents the causal mechanism of the antidepressant response or a parallel consequence of other neuro-

biological changes[33]. During electroconvulsive therapy, acute inflammatory elevation was observed after sessions, accompanied, in responders, by a subsequent reduction in baseline levels of IL-6 [34]. In addition, higher initial concentrations of this marker were associated with better outcomes in some samples subjected to treatment[35]. These findings demonstrate that the prognostic significance of a biomarker may vary depending on the intervention used.

Despite advances, the clinical application of inflammatory biomarkers in depressive disorders remains limited. No isolated marker has sufficient validated sensitivity, specificity, predictive value, or cutoff point to replace diagnostic assessment based on clinical criteria. C-reactive protein, although promising, is nonspecific and may be influenced by infections, obesity, smoking, cardiovascular diseases, metabolic disorders, and medication use. Cytokines such as IL-6 and TNF-α show preanalytical and laboratory variability, while molecular neuroimaging methods have high cost and low applicability in routine care. Additionally, differences between populations, study designs, laboratory techniques, and definitions of therapeutic response make direct comparison between studies difficult.

Given this scenario, integrating the available evidence is necessary to clarify the role of biomarkers inflammatory in

identification of depressive subtypes, in clinical prognosis and therapeutic personalization. Joint investigation of peripheral markers, symptomatic characteristics, metabolic alterations, and therapeutic outcomes can contribute to the development of more accurate stratification models. This approach aligns with the principles of precision psychiatry, in which clinical decisions are guided not only by categorical diagnosis, but also by individualized biological and phenotypic characteristics.

Thus, this integrative systematic review aimed to critically analyze the scientific evidence on the association between inflammatory biomarkers and depressive disorders, with an emphasis on their diagnostic, prognostic, and therapeutic implications. The goal was to identify the most investigated markers, evaluate their relationship with symptoms and neurobiological mechanisms, examine their ability to predict treatment response,

and discuss the limitations that still prevent their routine incorporation into clinical practice.

METHODOLOGY

A systematic review of an integrative nature was conducted, developed with the purpose of identifying, critically appraising, and synthesizing the available evidence on the relationship between inflammatory biomarkers and depressive disorders, with emphasis on diagnostic, prognostic, and therapeutic implications. The conduct and reporting of the review followed the methodological principles of

PRISMA 2020 recommendations, adapted to the characteristics of an integrative synthesis composed of observational studies, investigations mechanistic studies, neuroimaging research, and clinical trials.

The guiding question was structured using the PICOS strategy. The population comprised adults with major depressive disorder, depressive episodes, or clinically relevant depressive symptoms; the exposure or intervention involved the presence, concentration, or modulation of peripheral or central inflammatory biomarkers; the comparators included individuals without depression, patients with different levels of inflammation, treatment responders and non-responders, or groups receiving placebo and alternative interventions; the outcomes encompassed the occurrence and severity of depression, symptom profiles, neurobiological changes, therapeutic resistance, response, remission, and changes in biomarker concentrations; and the eligible study designs included cross-sectional studies, case-control studies, cohorts, population-based analyses, neuroimaging studies, biomarker investigations, randomized clinical trials, and secondary analyses of clinical trials.

The established research question was: which inflammatory biomarkers have been associated with depressive disorders, and what are their possible applications in diagnosis, clinical stratification, prediction of therapeutic response, and treatment selection?

The searc- bibliographic were hes conducted in databases

PubMed/MEDLINE, Scopus, Web of Science, Embase, PsycINFO, Cochrane Library, and Scientific Electronic Library Online. A complementary search was also performed by analyzing the reference lists of potentially eligible articles, with the aim of identifying additional studies not initially retrieved by the electronic strategies. The search period comprised records available from the beginning of indexing of each database up to July 2026.

Controlled descriptors from the Medical Subject Headings and the Health Sciences Descriptors were used, combined with free-text terms related to depression and inflammation. The strategy included combinations of the terms “major depressive disorder”,“depression”, “depressive disorders”,“inflammation”, “inflammatory biomarkers”, “C-reactive protein”, “CRP”, “interleukin-6”, “IL-6”, “tumor necrosis factor-alpha”, “TNF-alpha”, “interleukin-l”, “IL-l”, “interleukin-l7”, “cytokines”, “neuroinflammation”, “translocator protein”, “TSPO”, “treatment response”, “antidepressants”, “treatment-resistant depression”, “antiinflammatory treatment”, “diagnosis”, “prognosis” and “personalized medicine”. Boolean operators AND and OR were used to combine the concepts, and the strategies were adapted to the specific syntax of each database.

In the PubMed/MEDLINE database, the main strategy was structured as follows: (“Depressive Disorder, Major” [Mesh] OR “Depressive Disorders” [Mesh] OR major depressive disorder OR depression OR depressive symptoms) AND (“Inflammation” [Mesh] OR “Biomarkers” [Mesh] OR “CReactive Protein” [Mesh] OR cytokines OR “interleukin-6” OR “tumor necrosis factor-alpha” OR “interleukin-1” OR “interleukin-17” OR neuroinflammation OR TSPO) AND (diagnosis OR prognosis OR phenotype OR “treatment response” OR antidepressant OR “treatment-resistant depression” OR therapy). Additional terms were used in specific searches for interventions with infliximab, celecoxib, minocycline, omega-3 fatty acids, ketamine, physical exercise, and electroconvulsive therapy.

Original articles published in peer-reviewed scientific journals were included. They were conducted with adult human participants and directly investigated the association between clinically relevant depressive disorders or depress-

ive symptoms and at least one peripheral or central inflammatory biomarker. Studies were also eligible if they examined the prognostic or predictive value of these markers, their relationship with treatment resistance, or their effects as response modifiers of pharmacological and non-pharmacological interventions.

C-reactive protein, interleukins 1, 6, 8, 10 and 17, the tumor necrosis factor alpha, soluble cytokine receptors, receptor antagonists, signatures proteomic and transcriptomic inflammatory markers, markers present in cerebrospinal fluid and indicators of neuroinflammation obtained by positron emission tomography, including the 18 kDa translocator protein.

Studies conducted exclusively with animals, cell models, or in vitro samples were excluded; case reports or series; editorials; letters; comments; protocols without results; congress abstracts without full publication; narrative, systematic reviews, or meta-analyses; unpublished dissertations and theses in journals; pediatric studies; investigations in which depression was not a central variable; and studies that assessed inflammation without objective measurement of biomarkers. Studies focused exclusively on bipolar disorder, schizophrenia, neurodegenerative diseases, or other psychiatric conditions were also excluded when results related to depression could not be analyzed separately.

No initial language restrictions were applied during the search. For final inclusion, articles published in English, Portuguese, or Spanish were considered, provided they had full text available and sufficient information to assess the methods and results. When different publications derived from the same population, each article was included only if it presented a distinct objective, biomarker, or outcome. In such cases, the common sample origin was recorded to avoid misinterpreting the publications as independent evidence.

The retrieved records were organized in a bibliographic database, and duplicates were removed before screening. Selection took place in two stages. Initially, titles and abstracts were assessed for compatibility with the research question. Subsequently, the full texts of

potentially eligible studies were reviewed according to the predefined criteria. Reasons for exclusion during the full-text screening phase were recorded for later presentation in the selection flowchart. At the end of the process, 35 articles were considered eligible and included in the synthesis.

Data extraction was performed using a standardized instrument developed for this review. Information was collected regarding authors, year of publication, country, study design, sample source, number of participants, age range, diagnostic criteria, clinical characteristics, presence of therapeutic resistance, biomarkers assessed, type of biological material, laboratory or neuroimaging method, intervention, comparator group, duration of follow-up, clinical outcomes, main results, adjustments for confounding factors, limitations, and contribution to the research question.

In observational studies, measures of association adjusted for potential confounding factors were prioritized, including age, sex, body mass index, smoking, cardiovascular diseases, metabolic disorders, medication use, and the presence of inflammatory conditions. In clinical trials, information was extracted on randomization, blinding, intervention, comparator, losses to follow-up, intention-to-treat analysis, response, remission, adverse events, and the interaction between baseline biomarkers and therapeutic effects.

Methodological quality was analyzed according to the design of each publication. For clinical trials randomized, were considered the domains of sequence generation, allocation concealment, blinding, deviations from the proposed interventions, loss to follow-up, outcome measurement, and selection of the reported results. For observational studies, representativeness of the sample, definition of the exposure, validity of biomarker measurement, diagnosis or assessment of depression, identification and control of confounders, appropriateness of the statistical analyses, and completeness of the data were evaluated. For neuroimaging studies, additional factors were examined, including sample size, the radioligand used, correction for genetic characteristics related to TSPO binding, motion control,

definition of regions of interest, and the risk of analytical multiplicity.

Methodological appraisal was not used as an automatic exclusion criterion, since the integrative proposal sought to encompass different levels of evidence and stages of translational development of the biomarkers. However, the limitations and risk of bias of each study were considered when interpreting the consistency, applicability, and strength of the results.

Publications derived from the same cohort or clinical trial were identified and grouped during the synthesis. Studies from NHANES III, GENDEP, CO-MED, PREDDICT, and MINDEP were considered related analyses, rather than completely independent replications. This distinction was applied to prevent overestimation of the amount of available evidence.

Due to the clinical and methodological heterogeneity of the studies, no meta-analysis was performed. Differences in populations, diagnostic criteria, biomarkers, laboratory methods, cut-off points, interventions, assessment scales, and response definitions prevented an appropriate quantitative pooling of results. A structured narrative synthesis was conducted, comparing the direction, magnitude, consistency, and clinical relevance of the identified associations.

The findings were organized into four thematic axes: epidemiological, diagnostic, and phenotypic associations between inflammation and depression; neuroinflammation biomarkers and neurobiological mechanisms; the prognostic and predictive value of inflammatory markers for treatment response or resistance; and the effects of anti-inflammatory or immunomodulatory interventions on depressive symptoms. The final interpretation considered consistency across studies, independence of the samples, methodological quality, biological plausibility, and the possibility of clinical application.

Because this review used exclusively secondary data from published studies with scientific access, it did not involve direct contact with participants, collection of identifiable information, or clinical intervention. Accordingly, submission to a research ethics committee was not necessary. The principles of scientific integrity, source traceability, faithful reproduction of the original results, and transparency in presenting the limitations

were respected.

RESULTS

General Characteristics of the Included Studies

The integrative synthesis consisted of 35 original publications, published between 2000 and 2025, that investigated the association between inflammatory biomarkers and depressive disorders in different epidemiological, clinical, and therapeutic settings. The studies showed high diversity in terms of study design, sample size, participant characteristics, methods of psychiatric assessment, biomarkers measured, and interventions analyzed.

The publications were grouped into four main themes. The first included eight epidemiological, population-based, and phenotypic studies that assessed the association between peripheral inflammation, the occurrence of depression, and specific symptomatic manifestations[1-8]. The second gathered five investigations on central inflammation, neuroimaging and mechanisms neurobiological[9- 13]. The third included ten studies that examined biomarkers as prognostic factors or predictors of therapeutic response[14-23]. The fourth theme consisted of 12 studies on anti-inflammatory interventions or treatments

Antidepressants with possible immunomodulatory effects[24-35].

The Sample Sizes Ranged From 24 participants in exploratory clinical studies to 73,131 individuals in population analyses. Epidemiological studies used large databases and community cohorts, whereas research in neuroimaging and central biomarkers involved smaller samples due to the complexity and cost of the procedures. Clinical trials, for the most part, included patients with major depressive disorder or treatment-resistant depression.

C-reactive protein was the most frequently investigated marker, followed by interleukin 6, tumor necrosis factor alpha, interleukin 1, interleukin 17, and soluble cytokine receptors. Other studies assessed proteomic and transcriptomic signatures, markers in cerebrospinal fluid, and the 18 kDa translocator protein by positron emission tomography.

Although 35 publications were included, not all represented independent

populations. Studies 1 and 3 used NHANES III data; studies 18 and 19 derived from the GENDEP project; studies 20, 21, and 22 used samples from the CO-MED trial; studies 28 and 29 derived from the PREDDICT trial; and studies 30 and 31 corresponded to MINDEP trial analyses. These publications were retained because they addressed distinct biomarkers or outcomes, but they were interpreted as related analyses.

Association between peripheral inflammation and depression

Population studies have shown a recurring association between depression, depressive symptoms, and increased peripheral inflammatory markers. Elevated C-reactive protein was associated with the presence of a major depressive episode, psychological distress, antidepressant use, and depression-related hospitalization[1,3,5]. However, this association did not occur uniformly across all participants.

In studies derived from NHANES III, the relationship between major depression and C-reactive protein was more evident among men, particularly in the presence of recent or recurrent episodes [1,3]. Among women, the associations were attenuated after controlling for variables such as body mass index, smoking, and clinical conditions. These results suggested a possible influence of biological sex and metabolic factors on the relationship between inflammation and depression.

In older adults, elevated levels of IL-6, TNF-α, and C-reactive protein were associated with a higher frequency of depressive symptoms[2]. However, in another geriatric cohort, only IL-6 maintained an independent association with major depression after adjustment for chronic diseases, cognitive capacity, and medication use[4]. The discrepancy among the biomarkers showed that the presence of inflammation was not represented equivalently by all proteins evaluated.

The analysis of 73, 131 participants showed a graded relationship between increasing concentrations of C-reactive protein and different indicators of psychological distress and depression[5]. Individuals with higher levels had a greater likelihood of depressive symptoms, use of antidepressants, and subsequent hospitalization. Despite this dose–response association, diagnostic specificity for C-reactive protein was not established.

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The pooled analysis of 15 population-based studies indicated that inflammation was more strongly associated with specific symptoms than with the overall diagnosis of depression[6]. C-reactive protein and IL-6 showed more consistent associations with fatigue, sleep disturbances, loss of interest, reduced energy, appetite changes, and increased effort to carry out activities. Associations with predominantly emotional or cognitive symptoms were smaller.

The results of Elgellaie et al.[7]also showed differences between biomarkers and between sexes. Unmedicated patients with major depression had elevated IL-1α and IL-6, whereas TNF-α did not consistently differentiate the clinical group from controls. The increase in IL-6 was particularly evident among women.

The combination of inflammation, metabolic alterations, and clinical manifestations was investigated by Zwiep et al.[8]. Patients with C-reactive protein greater than 1 mg/L and a higher burden of energy-related symptoms showed more pronounced changes in IL-6, TNF-α, GlycA, leptin, glucose, triglycerides, HDL, body mass index, and abdominal circumference. The combination of biomarker and symptomatic profile showed a better ability to identify immunometabolic dysregulation than C-reactive protein alone.

Table 1. Synthesis of the Main Findings from the Included Studies

Evidence axis	Studies	Biomarkers or methods	Main results
Population-level association between depression and inflammation	[1-5]	CRP, IL-6, and TNF-α	Depression and depressive symptoms were associated with elevated inflammatory markers, with variations by sex, age, obesity, and comorbidities.
Inflammatory symptomatic profile	[6-8]	CRP, IL-6, TNF-α, GlycA, and metabolic markers	Inflammation showed a stronger association with fatigue, anhedonia, sleep disturbances, appetite, energy, and psychomotor slowing.
Neuroinflammation by PET	[9,10]	TSPO	Depressed patients showed stronger TSPO binding in the anterior cingulate cortex, prefrontal cortex, and insula; greater signal was also observed in participants with suicidal ideation.
Brain circuits and neurotransmission	[11,12]	CRP, cytokines, Functional magnetic resonance imaging and	Inflammation was associated with reduced connectivity of reward circuits and with

		Spectroscopy	Increased glutamate in the basal nuclei.
Association between peripheral and central inflammation	[13]	CRP and cytokines in plasma and cerebrospinal fluid	Plasma CRP was correlated with CSF CRP and with clusters of central inflammatory mediators.
Resistance to antidepressants	[14-18]	IL-6, TNF-α, CRP, and gene expression	Greater baseline or persistent inflammatory activity was associated with a reduced response to antidepressants and with treatment-resistant depression.
Selection of antidepressants	[19-22]	CRP, IL-17, and proteomic panels	Baseline inflammation differentially modified the response to antidepressant classes and combinations, although the findings derived from secondary analyses.
Physical exercise	[23]	TNF-α and other cytokines	Elevated TNF-α was associated with a greater reduction in symptoms during an exercise intervention.
Infliximab and omega-3	[24,25]	CRP, IL-6, and other markers	No uniform benefit was observed, but participants with high baseline inflammation showed signs of differential response.
Celecoxib	[26-29]	IL-6 and CRP	Small trials indicated a benefit; however, a subsequent larger study did not confirm overall efficacy or consistent selection by CRP.
Minocycline	[30-32]	CRP and IL-6	A small trial suggested benefit in participants with higher CRP, but a multicenter trial did not demonstrate efficacy in the overall sample.
Ketamine and electroconvulsotherapy	[33-35]	CRP, IL-6, TNF-α, and IL-1RA	There was rapid or longitudinal modulation of cytokines, with possible associations between baseline inflammation and therapeutic response.

Biomarkers of Neuroinflammation and neurobiological mechanisms

Neuroimaging research has shown changes consistent with neuroimmune activation during depressive episodes. Setiawan et al.[9]observed higher density of the l8 kDa translocator protein in the prefrontal cortex, anterior cingulate cortex, and insula of unmedicated patients with major depression. Signal intensity in the anterior cingulate cortex was also associated with symptom severity.

Holmes et al.[l0]identified greater TSPO binding in the cortex

anterior cingulate of depressed patients. Participants with suicidal thoughts showed a more pronounced increase in the anterior cingulate cortex and the insula.

Although the studies used different radioligands, both pointed to inflammatory changes in regions involved in emotional regulation, interoceptive integration, and cognitive control.

Peripheral inflammation was also associated with functional alterations in brain circuits. Felger et al.[11]showed that higher concentrations of C-reactive protein were related to decreased connectivity between the ventral striatum and the ventromedial prefrontal cortex. This change was associated with anhedonia. Reduced connectivity in dorsal striatal circuits was linked to motor slowing.

Haroon et al.[12]observed that elevated C-reactive protein was associated with increased glutamate in the basal ganglia. Higher glutamate concentrations were related to anhedonia and reduced psychomotor speed. No equivalent relationship was identified in the anterior cingulate cortex, suggesting regional specificity.

The correspondence between peripheral and central markers was examined by Felger et al.[13]. Plasma C-reactive protein showed a correlation with its concentration in cerebrospinal fluid. Patients with plasma C-reactive protein higher than 3 mg/L showed greater activation of central inflammatory clusters. TNF in cerebrospinal fluid was associated with reduced motivation, whereas components of IL-6 signaling were associated with anhedonia.

Biomarkers Associated With Response and therapeutic resistance

The prognostic studies demonstrated that basal or persistent inflammation was associated with a lower response to antidepressants in part of the samples. Lanquillon et al.[14]observed differences in the production of IL-6 between patients who subsequently responded or did not respond to amitriptyline. However, C-reactive protein was elevated in both groups and did not adequately differentiate outcomes.

Patients who did not respond to selective serotonin reuptake inhibitors had higher concentrations of IL-6 and TNF-α than healthy controls and patients who achieved remission[15]. Similarly, elevated TNF-α was associated with a lower likelihood of response to escitalopram [16], while increased concentrations of IL-6 were observed in patients resistant to selective

serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors[17].

The analysis of the expression of inflammatory genes in the GENDEP project showed that higher basal expression of TNF-α, IL-1β, and macrophage migration inhibitory factor was associated with less favorable therapeutic outcomes [18]. Some of these changes decreased with treatment, but the correspondence between gene expression, protein concentration, and immunological activity was not uniform.

C-reactive protein showed relevant results as a possible modifier of the choice of the antidepressant. In the GENDEP study, low levels of C-reactive protein were associated with a better relative response to escitalopram, whereas higher levels favored nortriptyline[19]. In CO-MED, participants with C-reactive protein levels below 1 mg/L had a better relative outcome with serotoninergic monotherapy, while those with levels equal to or above 1 mg/L showed better progress with the combination of bupropion and a selective serotonin reuptake inhibitor[20].

Elevated IL-17 was also associated with a better relative response to the combination of bupropion and a selective serotonin reuptake inhibitor[21]. The proteomic analysis of the same trial identified distinct patterns of inflammatory proteins related to the outcomes of antidepressant strategies[22]. However, the findings derived from CO-MED represented secondary analyses of the same population and did not constitute independent validations.

The relationship between biomarkers and response showed no uniform direction across all interventions. In the exercise trial, higher baseline concentrations of TNF-α were associated with a greater reduction in depressive symptoms[23]. This result differed from the associations between elevated TNF-α and a poorer response to conventional antidepressants, demonstrating that the meaning of the biomarker varied according to the treatment analyzed.

Results of Anti-Inflammatory Interventions

Infliximab showed no superiority over placebo in the overall sample of patients with treatment-resistant depression[24]. However, participants with hig-

her baseline levels of C-reactive protein demonstrated a signal of differential benefit. The effect was most evident among those with Creativa protein higher than approximately 5 mg/L. In patients with low inflammation, no benefit from TNF-α blockade was observed.

Omega-3 fatty acid supplementation also showed heterogeneous response[25]. The formulation enriched in eicosapentaenoic acid produced better relative results among participants with higher baseline inflammatory activity. This pattern was not reproduced with equal intensity in individuals with low concentrations of inflammatory markers.

The first trials of celecoxib combined with antidepressants demonstrated a greater reduction in symptoms compared with antidepressant treatment alone[26, 27]. In one of these studies, the clinical improvement was accompanied by a reduction in IL-6[27]. However, both studies had small samples and a duration of six weeks.

The PREDDICT trial, with a larger number of participants, did not confirm the superiority of the combination of celecoxib and vortioxetine for depression, cognition, and functioning outcomes[28]. Stratified analysis by C-reactive protein also did not consistently demonstrate that participants with concentrations higher than 3 mg/L showed differential benefit [29].

Minocycline showed similarly divergent results. In the MINDEP trial, there was no significant difference in the primary outcome for the total sample[30]. However, participants with C-reactive protein levels equal to or greater than 3 mg/L showed greater symptomatic reduction with minocycline. Baseline IL-6 was also higher among responders. Sex-stratified analysis indicated possible differences in the predictive capacity of C-reactive protein and IL-6, especially among women[31].

In contrast, the multicenter trial by Hellmann-Regen et al.[32], with l68 participants, did not demonstrate superiority of minocycline over placebo. This study did not select patients according to the presence of high-grade inflammation, making it impossible to determine whether a specific inflammatory subgroup could derive benefit.

Antidepressant Treatments With immunomodulatory effects

Ketamine produced rapid changes in the concentrations of inflammatory med-

iators in patients with treatment-resistant depression[33]. Early reduction in TNF-α in the group receiving 0.5 mg/kg was associated with a subsequent decrease in depressive symptoms. Inflammatory changes occurred in the first hours after infusion, following the temporal pattern of the rapid antidepressant response.

Studies on electroconvulsotherapy, in studies on electroconvulsotherapy, each session was followed by an acute increase in IL-6[34]. However, patients who achieved remission showed reduced baseline levels of this marker at the end of treatment. This result demonstrated the coexistence of an acute inflammatory response induced by the procedure and a possible longitudinal reduction in inflammation in patients who improved.

Kruse et al.[35]observed that higher baseline levels of IL-6 were associated with lower depression scores at the end of electroconvulsotherapy. Creative protein, IL-8, and TNF-α did not show equally consistent predictive capability. The findings suggested that elevated IL-6, although related to resistance to conventional antidepressants in other studies, could identify patients more likely to respond to electroconvulsotherapy.

Summary of Findings

C-reactive protein and IL-6 were the biomarkers that showed the highest recurrence and consistency across studies. C-reactive protein stood out for its association with depression in large populations, its link to immunometabolic symptoms, and its potential to modify therapeutic choice. IL-6 was associated with depression in older adults, with specific symptoms, with pharmacological resistance, and with response to certain interventions.

Despite these associations, none of the studies demonstrated sufficient diagnostic performance for an isolated biomarker to be used as a confirmatory test for depressive disorder. The greatest observed utility was focused on identifying subgroups with increased inflammation, neurovegetative symptoms, metabolic alterations, or treatment resistance.

The therapeutic results were heterogeneous. Infliximab, celecoxib, minocycline, and omega-3 showed no uniform benefit in the studied populations. The

most favorable signals occurred predominantly in subgroup analyses with high baseline inflammation. In contrast, larger trials without prior biomarker-based selection produced negative results.

The synthesis of the 35 studies therefore demonstrated an association between inflammation and depression at the epidemiological, symptomatic, neurobiological, and therapeutic levels. However, the clinical usefulness of the biomarkers depended on the patient's phenotype, the treatment evaluated, the marker used, and the control of metabolic and clinical factors.

DISCUSSION

The findings of this integrative systematic review showed that the relationship between inflammation and depressive disorders is biologically plausible, epidemiologically consistent, and potentially relevant for therapeutic stratification. However, this relationship was not uniform across all patients, biomarkers, or treatment modalities. The main interpretation arising from the 35 analyzed studies is that inflammation does not constitute a universal mechanism of depression, but rather seems to characterize a clinical subgroup with particular symptomatic, metabolic, and therapeutic features.

C-reactive protein and interleukin 6 were the most frequently associated markers with depressive disorders. Large population-based studies identified a higher frequency of elevated C-reactive protein in individuals with depressive episodes, psychological distress, antidepressant use, and depression-related hospitalizations[1,3,5]. In older adults, high concentrations of IL-6, TNF-α, and Creative protein were also related to depressive symptoms, although IL-6 showed a more consistent association after adjustment for clinical factors in some populations[2,4]. These findings support the presence of low-grade systemic inflammation in some patients, but they do not allow such markers to be considered specific to depression.

Nonspecificity is one of the main limitations for diagnostic application. C-reactive protein can be elevated by obesity, smoking, infections, cardiovascular diseases, metabolic disorders, medication use, and chronic inflammatory conditions. IL-6 and other cytokines also show

variations related to the time of blood collection, physical activity, diet, acute stress, and laboratory procedures. Thus, identifying an elevated marker does not, by itself, determine whether inflammation directly participates in the depressive pathophysiology or instead reflects associated comorbidities.

Heterogeneity in depressive disorders helps explain some of the divergences among studies. Analysis of individual symptoms showed that inflammation was more strongly associated a manifestations with neurovegetative and motivational features, including fatigue, sleep disturbances, changes in appetite, anhedonia, reduced energy, and psychomotor slowing[6]. This pattern suggests that the categorical diagnosis of major depression may group biologically distinct patients. While some show greater involvement of mechanisms inflammatory and metabolic, others may present clinical presentations predominantly related to psychosocial factors, neuroendocrine alterations, vulnerability genetic factors or dysfunctions of neurotransmitter systems without detectable inflammation.

The identification of an immunometabolic phenotype represents one of the most relevant contributions in recent literature. The combination of elevated C-reactive protein, energy-related symptoms, abdominal obesity, dyslipidemia, and glycemic alterations showed a greater capacity for biological characterization than the isolated measurement of a single marker[8]. This finding suggests that the clinical usefulness of inflammation may depend on integrating laboratory data with phenotypic characteristics rather than adopting a single test.

Sex-related differences have also been observed. Some population-based studies identified a more evident association between C-reactive protein and depression in men[1,3], whereas clinical investigations observed greater elevation of IL-6 or higher predictive capacity of certain markers in women[7,31]. These seemingly contradictory findings may result from differences between populations, diagnostic criteria, body composition, sex hormones, prevalence of metabolic diseases, and use of medications. It is also possible that men and women present distinct inflammatory pathways associated with depressive symptoms. How-

ever, many sex-specific analyses were conducted in small subgroups and should be interpreted with caution.

Neuroimaging and central biomarker studies provided mechanistic support for peripheral associations. The strongest binding ofthe l8 kDa translocator protein in the anterior cingulate cortex, prefrontal cortex, and insula indicated alterations compatible with neuroimmune activation during depressive episodes[9, 10]. The association between higher TSPO signal and suicidal thoughts suggested a possible role for central inflammation in more severe presentations[10]. However, TSPO is not a specific marker of microglial activation and can be expressed in astrocytes, endothelial cells, and other cell types. In addition, the studies used small samples and different radioligands, limiting direct comparison.

The functional and neurochemical changes observed were also consistent with an inflammatory symptom profile. Reduced connectivity between the striatum and prefrontal regions was associated with anhedonia and psychomotor slowing [11], whereas increased glutamate in the basal ganglia nuclei was related to elevated C-reactive protein and motivational changes[12]. These findings support the hypothesis that inflammatory mediators may affect reward circuits, neurotransmitter availability, glutamatergic metabolism, and synaptic plasticity.

The correspondence between peripheral and central markers reinforced this interpretation. The correlation between plasma and cerebrospinal fluid C-reactive protein, as well as the association between elevated peripheral levels and clusters of cytokines in the cerebrospinal fluid, indicated that systemic inflammation may partially reflect changes in the central nervous system[13]. However, this relationship does not imply complete equivalence. Peripheral C-reactive protein does not identify which brain region is affected, which cell is activated, or which immunological pathway participates in the depressive process.

In the prognostic field, higher inflammatory activation was frequently associated with therapeutic resistance. Elevated concentrations of IL-6 and TNF-α were identified in patients who did not respond to serotonergic antidepressants [15-17]. Increased expression of genes related to TNF-α, IL-lβ, and other inflammatory pathways was also associated

with a lower response[18]. These findings suggest that inflammation may interfere with the action of antidepressants through changes in neurotransmission, the hypothalamic–pituitary–adrenal axis, neuroplasticity, and tryptophan metabolism.

Despite this trend, inflammation should not be interpreted only as a marker of poor prognosis. Its meaning varied according to the treatment evaluated. Elevated TNF-α was associated with a lower response to conventional antidepressants, but also with a greater relative benefit from an intervention with physical exercise[23]. Elevated IL-6 was related to pharmacological resistance in some studies[17], but to better outcomes after electroconvulsive therapy in others[35]. Thus, a biomarker may act simultaneously as an indicator of severity, a marker of resistance to one strategy, and a favorable predictor for another.

This distinction between prognostic and predictive biomarkers is fundamental. A prognostic marker provides information about the likely course regardless of treatment, whereas a predictive marker identifies the possibility of differential response to a specific intervention. The GENDEP and CO-MED studies provided evidence that C-reactive protein could play a predictive role in selecting antidepressants[19,20]. Lower levels were associated with a better relative response to predominantly serotoninergic strategies, while higher levels favored treatments with noradrenergic or dopaminergic components.

These findings are promising for precision psychiatry, especially because C-reactive protein is widely available and low cost. However, the cutoffs used were derived from secondary analyses rather than prospective clinical trials in which patients were randomized according to the biomarker. In addition, studies 18 and 19 were derived from GENDEP, whereas studies 20, 21, and 22 used data from CO-MED. Therefore, different publications do not necessarily represent independent replications.

IL-17 and proteomic panels expanded the possibility of using more complex immunological signatures[21,22]. Combining multiple biomarkers may overcome the limitations of a single marker and better capture the diversity of infl-

ammatory pathways. However, studies with numerous analytes present a high risk of spurious associations, statistical overfitting, and low reproducibility. Multimarker models will need to be validated in external populations and translated into laboratory-standardized tests before clinical application.

Trials with anti-inflammatory therapies produced heterogeneous results. Infliximab was not superior to placebo in the overall sample, but showed a signal of benefit among patients with higher C-reactive protein[24]. Supplementation with omega-3 enriched in eicosapentaenoic acid also demonstrated a relatively better outcome in participants with higher baseline inflammation[25]. These findings support the hypothesis that anti-inflammatory treatment may be effective only when the corresponding biological pathway is sufficiently activated.

Studies with celecoxib illustrated the challenges of replication. Small initial trials indicated clinical improvement and reduced IL-6 when

the medication was combined with anti-

depressants[26,27]. However, the PREDDICT trial, with a larger sample, did not demonstrate overall efficacy for the combination with vortioxetine[28]. Stratification by C-reactive protein also did not identify a consistent benefit[29]. The discrepancies may be related to sample size, the antidepressant used, duration of the intervention, degree of therapeutic resistance, and the absence of rigorous biological selection.

Similar results were observed with minocycline. The MINDEP trial suggested a possible benefit among participants with higher C-reactive protein, although the primary outcome in the total sample was negative[30]. Sex-stratified analysis indicated possible predictive differences for C-reactive protein and IL-6[31], but this was limited by the small number of participants. In contrast, a larger multicenter trial showed no superiority of minocycline[32]. Because this study did not select patients with high-grade inflammation, it remained uncertain whether the intervention could benefit a specific subgroup.

The negative results from larger trials are particularly important because they prevent the interpretation that anti-inflammatory agents are broadly used antidepressants. Medications such as inf-

liximab, celecoxib, and minocycline have their own risks, including infections, cardiovascular effects, changes gastrointestinal and adverse events related to prolonged use. Prescribing without evidence of relevant inflammation could expose patients to risks without likely benefit.

Ketamine and electroconvulsotherapy showed distinct immunological effects. Ketamine induced rapid modulation of cytokines, including an early reduction in TNF-α associated with clinical improvement[33]. However, it was not possible to establish whether this change constituted a causal mechanism of the response or a consequence of other neurobiological effects. Electroconvulsotherapy produced an acute increase in IL-6 after the sessions, followed by a return to baseline between patients who achieved remission [34]. This pattern demonstrated that transient inflammatory increases may coexist with favorable therapeutic effects and a longitudinal reduction in inflammation.

The interpretation of the results must also consider the variable methodological quality. Population-based studies had large samples, but were often cross-sectional or relied on self-reported symptoms. Neuroimaging studies provided detailed mechanistic data; however, they involved few participants. Several prognostic and therapeutic studies used secondary analyses, multiple biomarkers, and subgroups that had not been predefined. The small positive trials had a higher risk of overestimating the effect, whereas larger studies frequently did not confirm overall efficacy.

Another relevant factor was the lack of standardization of laboratory methods. Different studies used serum, plasma, whole blood, or cerebrospinal fluid, in addition to assays with different sensitivities. The collection times, fasting conditions, sample storage, presence of subclinical infections, and criteria for excluding extreme values were not uniform. The cutoff points adopted for C-reactive protein also varied, including values above 1, 3, or 5 mg/L. This diversity made direct comparison difficult and prevented the definition of a universal clinical threshold.

This review's main strength was the integration of different levels of evidence, encompassing population-based studies, mechanistic investigations, analyses of

therapeutic response, and clinical trials. This approach made it possible to examine inflammation from its epidemiological association to its potential application in therapeutic decision-making. The inclusion of studies with negative results also reduced the risk of an overly favorable interpretation of anti-inflammatory interventions.

Among the limitations of the review, heterogeneity of study designs stood out, populations,
biomarkers, and outcomes, which prevented the conduct of a meta-analysis. In addition, part of the publications derived from the same cohorts or trials, reducing the apparent independence of the base. Including observational studies and exploratory analyses expanded integrative understanding, but produced different levels of certainty. Limiting the review to published articles may also have favored publication bias, especially in small clinical trials.

From a clinical standpoint, the findings do not support the use of inflammatory biomarkers as diagnostic tests for depression. Diagnosis should remain grounded in clinical assessment, psychiatric criteria, and the exclusion of other medical conditions. Measuring C-reactive protein may be considered a complementary resource in research settings or in patients with neurovegetative symptoms, metabolic changes, and therapeutic resistance; however, its interpretation must be integrated with the clinical picture and comorbidities.

The most promising application of biomarkers is in stratification of patients and the selection of treatments. For this approach to be incorporated into practice, prospective trials will be needed in which participants are selected or randomized based on previously defined markers. These studies should use validated cutoffs, standardized laboratory protocols, sufficiently large samples, and systematic assessment of adverse events.

Also relevant will be models that integrate C-reactive protein, cytokines, symptoms, metabolic measures, sex, age, body composition, and clinical data. The isolated use of a single biomarker is likely to be insufficient to capture the immunological complexity of depression. Multimodal panels may offer greater predictive capability, provided they are reproducible, economically feasible, and clinically int-

erpretable.

In summary, inflammation represents a relevant, though not universal, dimension of depressive disorders. The evidence was more consistent for C-reactive protein and IL-6, especially in patients with neurovegetative symptoms, metabolic alterations, and treatment resistance. The results of interventions anti-inflammatory showed that biological selection is likely essential to obtain benefit. Despite the potential for precision psychiatry, the routine use of these biomarkers still depends on prospective validation, methodological standardization, and demonstration of clinical utility.

CONCLUSION

The evidence analyzed showed that inflammatory biomarkers present relevant association with depressive disorders, especially in subgroups characterized by symptoms neurovegetative symptoms, metabolic alterations, anhedonia, fatigue, psychomotor slowing, and therapeutic resistance

Among the investigated markers, C-reactive protein and interleukin-6 showed the highest recurrence and consistency in both population studies and clinical, mechanistic, and therapeutic research.

However, no isolated biomarker demonstrated sufficient sensitivity, specificity, or predictive value to be used as an independent diagnostic tool. Inflammation proved to be a biological dimension present only in a portion of patients, reinforcing the pathophysiological heterogeneity of depressive disorders. Therefore, the interpretation of markers must consider factors such as obesity, metabolic diseases, smoking, infections, medication use, sex, age, and the clinical characteristics ofthe depressive episode.

Neuroimaging and central biomarker studies provided support for the existence of mechanisms neuroinflammatory associated with depression. Changes in the expression of the l8 kDa translocator protein, in the connectivity of cortico-striatal circuits, and in glutamatergic metabolism suggested that inflammation may interfere with brain systems related to reward, motivation, motor control, and

emotional regulation. However, these methods still have low clinical applicability due to cost, complexity, and the lack of standardization.

In the prognostic context, elevated levels of C-reactive protein, IL-6, TNF-α, and other inflammatory signatures were associated with a lower response to conventional antidepressants across different studies. At the same time, these markers showed potential for identifying patients with a higher likelihood of response to specific strategies, including pharmacological combinations, physical exercise, electroconvulsive therapy, and interventions with anti-inflammatory properties.

Clinical trials with infliximab, celecoxib, minocycline, and omega-3 fatty acids produced heterogeneous results. Overall, there was no uniform efficacy in the total samples, whereas more favorable signals were observed in subgroups with elevated baseline inflammation. These findings indicated that anti-inflammatory therapies should not be used indiscriminately in the treatment of depression and that their potential effectiveness depends on appropriate patient selection.

The most promising clinical application of inflammatory biomarkers lies, therefore, in biological stratification and therapeutic personalization. The combination of laboratory markers, symptomatic profile, metabolic status, and individual characteristics may help identify immunometabolic phenotypes and guide more precise therapeutic decisions. C-reactive protein has practical advantages because it is accessible, low cost, and widely available; however, it still does not have sufficiently validated cut-off points to routinely guide the choice of antidepressant treatment.

It was concluded that inflammation is a relevant, though not universal, component of the pathophysiology of depressive disorders. Inflammatory biomarkers have potential as tools for complementary stratification, prognosis, and treatment selection, but their incorporation into clinical practice requires prospective validation, standardization of laboratory methods, definition of cut-off points, and demonstration of clinical benefit in biomarker-guided trials.

Future studies should prioritize larger, independent samples, uniform labo-

ratory protocols, longitudinal assessment, and stratified randomization by inflammatory profile. It will also be necessary to develop multimodal models that integrate biomarkers, symptoms, metabolic variables, clinical data, and sociodemographic characteristics. Advancing these strategies could bring psychiatry closer to a precision medicine model, in which the therapeutic choice is guided not only by categorical diagnosis, but also by the biological heterogeneity of each patient.

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