

Mental disorders after myocardial infarction: potential mediator role for chemokines in heart-brain interaction?

Parth Patel¹, Feiyan Yang², Dumitru A. Iacobas³, Lei Xi^{4,✉}

1. Department of Biology, College of Humanities and Sciences, Virginia Commonwealth University, Richmond, VA, USA; 2. Department of Cardiology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; 3. The Texas Undergraduate Medical Academy, Prairie View A & M University, Prairie View, TX, USA; 4. Pauley Heart Center, Division of Cardiology, Department of Internal Medicine, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA

✉ Correspondence to: lexi@vcu.edu or lei.xi@vcuhealth.org

<https://doi.org/10.26599/1671-5411.2024.09.004>

ABSTRACT

Acute myocardial infarction (MI) remains one of the leading causes of mortality and morbidity in the global communities. A prevailing topic that has attracted increasing attentions over the past few decades is the so-called heart-brain interaction, in particular following a major traumatic event such as MI. Increased prevalence of depression and other mental disorders has been recognized in cardiac patients after MI, coronary catheterization, or cardiothoracic surgeries. In this review, we focus on the potential pathogenic mechanisms and pre-clinical transcriptomic evidence for identifying potential mediators of post-MI depression. We first summarize the conventional mechanistic understanding that leads to the current clinical management of post-MI depression with the use of selective serotonin reuptake inhibitors (SSRIs) and cognitive behavior and exercise therapies. We further envisage a possible role played by certain chemokines, e.g., Chemokine (C-X-C motif) ligand 12 (CXCL12) and Chemokine (C-C motif) ligand 2 (CCL22), in serving as signaling molecules to connect the MI-induced heart damage to the pro-depressive changes in brain during the post-MI period. Future in-depth investigations into this chemokine hypothesis will be instrumental in developing new chemokine-targeted therapies for better management of the cardiac patients suffering from post-MI depression.

Acute myocardial infarction (MI) remains to be one of the most lethal cardiovascular events with an estimated over 800,000 patients suffering from acute MI each year in the United States alone and many of them have high comorbidity burden (e.g., hypertension, vascular disease, dyslipidemia, and diabetes), which can negatively affect the post-MI clinical outcomes.^[1] Among these comorbidity-driven factors, a so-called heart-brain connection has drawn increasing attention in recent decades. As early as mid-1970s, 34 out of 101 Canadian patients were found to have depression issues 16-18 months after MI.^[2] Another study in 1989 reported that 27% of 283 American patients hospitalized for MI had minor depression and 18% met the criteria for major depression, and 33% of the patients still had depression 3-4 months after the MI event.^[3] Another Canadian study in 1999 showed that 32% of 896 post-MI patients had a Beck's Depression Inventory (BDI) score of 10 or

higher, which signified at least a mild depression.^[4] A seminal review by Ziegelstein, based on clinical reports published from 1989 to 2001, suggested that about 20% of the patients with MI experienced major depression and at least 33% of them had significant symptoms after the MI event.^[5] It is notable that most patients who had depression during their initial hospitalization due to MI often showed depressive symptoms for additional 1-4 months.^[6] The cumulative incidence of anxiety and depression was also higher for Chinese patients after acute MI with adjusted hazard ratio (HR) of 7.23^[7] and 35% of Canadian patients with AMI had at least mild depression.^[8] Other forms of mental issues include post-traumatic stress disorder (PTSD) from trauma induced by heart attack can lead to depressive symptoms.^[9,10] Interestingly, among the about 39% of cardiac patients who claimed to have insomnia for at least two weeks before their MI, 50% of them met the criteria for major depressive disorder (MDD).^[11]

Table 1 Chronological list of the representative clinical observations of mental depression in patients after survival from myocardial infarction or other major cardiac events/procedures.

Author/Journal Information	Number of Cardiac Patients with Mental Health Conditions Studied	Key Clinical Findings
Kavanagh, <i>et al.</i> , <i>Can Med Assoc J</i> 1975 [2]	101 patients	34% of patients were depressed 16-18 months after MI.
Schleifer, <i>et al.</i> , <i>JAMA Internal Medicine</i> 1989 [3]	283 patients	27% met criteria for minor depression and 18% met criteria for MDD. 33% of the patients still had depression 3-4 months later.
Hance, <i>et al.</i> , <i>Gen Hosp Psychiatry</i> 1996 [18]	200 patients	The 200 patients were undergoing cardiac catheterization and coronary angiography and received a psychiatric interview. 17% were diagnosed with a current major depressive episode and 17% were diagnosed with a current minor depressive episode. Of the 90% of patients that consented to a 12-month follow up, half of the patients with MDD remained depressed or relapsed. Half of those with minor depression remitted and 42% developed MDD.
Frasure-Smith, <i>et al.</i> , <i>Psychosom Med</i> 1999 [4]	896 patients	290 of the patients (about 32%) had a BDI score of 10 or higher which signifies mild depression.
Ziegelstein, <i>JAMA</i> 2001 [5]		Approximately 17% of patients experience MDD.
Lauzon, <i>et al.</i> , <i>Can Med Assoc J</i> 2003 [8]	550 patients	35% of patients who had acute MI after hospitalization had mild depression.
Bush, <i>et al.</i> , <i>Agency for Healthcare Research and Quality Evidence Report</i> 2005	3 clinical studies in depressed vs. nondepressed patients.	Most patients that have depression in the initial MI hospitalization still have depression 1 to 4 months later.
Horne, <i>et al.</i> , <i>J Thorac Cardiovasc Surg</i> 2013 [16]	436 patients	Patients completed the patient health questionnaire while waiting for cardiac surgery and on the day of their discharge from the hospital. It was found that there was an increase in depression from 23.6% to 37.7%. New depression at discharge was 29.2%.
Okamoto <i>et al.</i> , <i>Asian Cardiovasc Thorac Ann</i> 2013 [17]	128 patients (49 who had aortic surgery and 79 who had coronary artery bypass)	Of the 49 patients that underwent thoracic aortic surgery, 28% had depression and of the 79 patients that underwent CABG, 20% had depression.
Faria, <i>et al.</i> , <i>Rev Port Cir Cardiorac Vasc</i> 2014 [14]	52 patients	The patients had no previous history of depression, and it was found that 21 had mild depression and 6 had severe depression following elective open-heart valve surgery.
Feng, <i>et al.</i> , <i>Medicine</i> 2016 [7]	1396 patients with MI and 13960 patients without MI	Patients with acute MI had a higher risk of depressive disorders (adjusted Hazard Ratio = 7.23).
Açikel, <i>Braz J Cardiovasc Surg</i> 2019 [12]	65 patients	Depression levels on BDI jumped from 8.1 ± 5.4 before CABG surgery to 12.4 ± 6.4 three days after the surgery.
Wegermann, <i>et al.</i> , <i>J Am Heart Assoc</i> 2022 [15]	990 patients	Patients that underwent surgical aortic valve replacement had a higher chance of anxiety and/or depression at 3 months (12.4% versus 8.8%), 6 months (15.6% versus 13%), and 1 year (20.1% versus 19.3%) after the surgery than those who did not undergo the surgery.

BDI: Beck's depression inventory; CABG: coronary artery bypass graft; MI: myocardial infarction; MDD: major depressive disorder.

Furthermore, as summarized in Table 1 with a chronological list of the representative clinical observations in the patients after survival from MI or other major cardiac events/procedures, their mental issues may be linked to not only acute MI but also other cardiac injurious events. For example, depression levels were higher in 65 Turkish patients after coronary artery bypass graft (CABG) surgery, in which the average BDI scores jumped from 8.12 ± 5.44 preoperatively to 12.43 ± 6.36 on the third day after

CABG surgery.^[12] The findings are in agreement with the previous study by Connerney, *et al.*^[13] in 309 patients undergone CABG that showed 20% of the post-CABG patients had MDD. Similarly, out of 52 Portuguese patients with no previous history of depression, 21 patients had mild depression and 6 patients had MDD following their elective open-heart valve replacement surgery.^[14] A recent study also showed that U.S. patients who underwent surgical aortic valve replacement had a higher preval-



ence of anxiety and/or depression than non-surgery controls at 3 months (12.4% vs. 8.8%), 6 months (15.6% vs. 13%), and 1 year (20.1% vs. 19.3%) after the surgery.^[15] There was an increase in depression prevalence from 23.6% to 37.7% in the patients before and after their cardiac surgery.^[16] The incidence of mild or significant anxiety was 14% in the Japanese patients after thoracic aortic surgery and 16% after CABG.^[17] Interestingly, among 200 American patients received relatively less invasive cardiac catheterization and coronary angiography, 17% were diagnosed with minor depression and 17% with major depression. 50% of major depressive patients remained depressed or relapsed at the 12-month follow-up, whereas half of patients with minor depression remitted and 42% developed major depression.^[18] Intriguingly, there are contradictory results concerning the effect of age on prevalence of post-MI depression. For example, a recent study in 911 patients with a variety of cardiovascular complications (acute MI, acute coronary syndrome, unstable angina, and CABG surgery) evaluated these patients with Hospital Anxiety and Depression scale and found that the risk of depression after the cardiac conditions was significantly higher in younger individuals (< 55 years old).^[19] To the contrary, a meta-analysis of 7 studies reported that older age (> 65 years) had higher risk of depression after acute MI,^[20] which is conceptually in agreement with the earlier observation by Kavanagh, *et al.*^[2] who found that the severely depressed patients were older, with a greater tendency to hypertension and angina.

IMPACT OF MENTAL DISORDERS ON POST-MI PROGNOSIS AND REHABILITATION

Due to the potential heart-brain interaction involving multiple pathogenic factors and pathways at brain, heart, and whole body levels (Figure 1), the prevalence and severity of depression after MI can substantially affect the patients' rehabilitation process. For example, patients with post-MI depression are more likely to exhibit noncompliance with medical advice after MI, lower heart rate variability, increased platelet activation, and a lower rate to undergo percutaneous coronary intervention (PCI) or CABG.^[6] These adverse factors not only make the

patients more susceptible to recurrent MI, but also increase the overall mortality rate.

Frasure-Smith, *et al.*^[4] studied 222 patients who had suffered MI and were discharged and found that 12 of them had died at 6 months post-MI follow-up. Depression proved to be a significant predictor (HR = 5.74, $P < 0.001$). Subsequently, the same group reported 21 patients had died in the 18-month time frame, among them 7 met the criteria for depression and 12 had increased BDI scores, which suggested a link between the increased depression and elevated mortality post-MI.^[21,22] This early conclusion was confirmed in 2007 in a study on 666 patients (316 depressed, 350 non-depressed) with a recent acute MI. The researchers found that the survival rate of those with depression was lower than non-depressed controls, with odds ratio (OR) of 2.4 ($P = 0.02$).^[23] Another 3-week study of 560 male survivors of acute MI found 12 cardiac deaths and 17 arrhythmic events occurred, both of which linked to severe post-MI depression.^[24]

New cardiovascular events are also more common in those with depression (OR = 1.95; $P < 0.001$), as shown in a meta-analysis of 22 papers on post-MI depression and negative health outcomes.^[25] For example, the depressed patients had increased abnormal heart rate turbulence (risk factor adjusted OR = 1.8; $P = 0.03$).^[23] Depression was also related to reduced heart rate variability, which indicates a reduced vagal tone and a sympathovagal imbalance.^[26] Angina pectoris is another common post-MI depression-related symptom. For instance, in 377 male survivors of acute MI with depression, the unadjusted HR for angina pectoris among the patients with severe depression was 3.12.^[27]

Depressive disorder in the post-MI patients also raises many concerns about their quality of life. For instance, the self-reported life quality themes in a 1-year post-MI follow-up of 468 cardiac patients indicated that the increased health complaints, cardiac problems, and disability as well as decreased overall quality of life occurred more frequently in those with depressive disorders post-MI.^[28] Similarly, depression predicts poor outcomes at 1 year on all aspects of the 36-item short-form of quality-of-life measures and on the specific measures of everyday activity and reports of chest pain, use of primary care resources, and secondary prevention life-



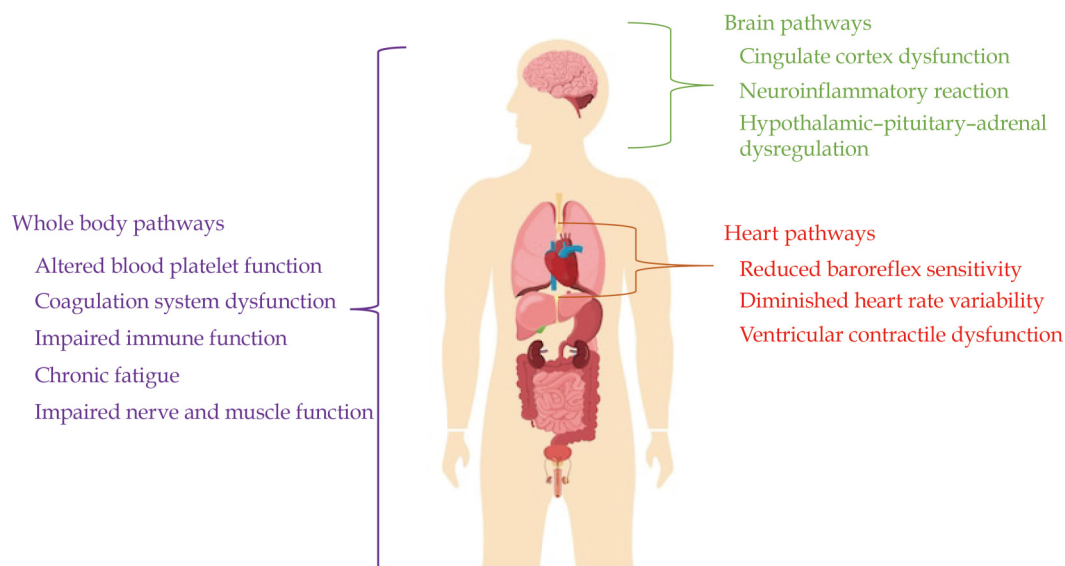


Figure 1 Potential pathogenic mechanisms underlying mental depression after survival from myocardial infarction and other major cardiac events or procedures.

style changes in post-MI patients.^[29] Moreover, most of the patients with major depression syndrome did not return to work.^[3]

CLINICAL MANAGEMENT FOR MENTAL DISORDERS IN POST-MI PATIENTS

Antidepressant Drug Therapies

Drug therapies including the use of antidepressants to treat depression after cardiac events remain the mainstay in the current clinical management of the mental problems occurred post-MI. The most commonly used class of antidepressants is the selective serotonin reuptake inhibitors (SSRI), such as sertraline which was used in depressive patients after acute MI. This drug caused no significant changes in heart rate, blood pressure, cardiac conduction, or left ventricular ejection fraction, whereas there was a trend for reduced ventricular ectopic activity. No consistent change in coagulation measures such as the time of bleeding was evident.^[30] Another study in 369 patients, who received either a placebo or sertraline to treat their post-acute coronary syndrome (ACS) depression, revealed a reduced number of cases of severe cardiovascular adverse events in the sertraline-treated group as compared to the placebo group.^[31] Fluoxetine is another SSRI that was studied in 54 patients with MDD after MI. This drug decreased the post-MI pa-

tients' hostility scores without affecting cardiac function.^[32] Lespérance, *et al.*^[33] studied the effects of citalopram, a commonly used SSRI, in 284 patients with coronary artery disease and found that citalopram was effective in decreasing depression scores and readmission rates. Escitalopram, an active S-enantiomer of citalopram, also improved long-term cardiac outcomes in 142 patients with recent ACS, including a decreased rate of major adverse cardiac outcomes (i.e., 40.9% vs. 53.6% in placebo group).^[34] In patients with chronic heart failure (HF) and depression, paroxetine significantly decreased their depression scores and increased general psychological health levels.^[35]

Several non-SSRI drugs have also been administered in managing post-MI depression. For example, mirtazapine was given to 91 patients with depression after MI and demonstrated effectiveness on the BDI, dSCL-90 (depression subscale of the symptom checklist 90), and CGI (clinical global impression) scale.^[36] Magnesium oxide tablet is another non-SSRI that has the potential to improve cardiac and depressive outcomes. In 60 patients following open-heart surgery, those received two 250 mg magnesium oxide tablets for five days had significantly decreased anxiety and depression.^[37] The use of nefazodone in patients with depression and congestive HF led to a decreased heart rate (69.7 to 64.8 beats/min) and increased QT intervals (425 to



444 ms), whereas 3/4 of the 19 participants who completed the entire 12-week trial had at least 50% decline in their Hamilton rating scale for depression (HRSD) scores.^[38] In addition, a pre-clinical study by Wang, *et al.*^[39] investigated the effects of minocycline, a tetracycline antibiotic, on the depressive behaviors seen in rats after MI. The depression-like symptoms, measured with a sucrose intake test, were significantly mitigated in minocycline-treated rats.

Cognitive Behavior and Exercise Therapies

Cognitive behavior therapy is a non-pharmaceutical approach in treating cardiac patients with depression. A multi-center study in 2481 patients with post-MI depression found that cognitive behavior therapy (individual or grouped) given around 17 days after MI and continued with 11 sessions over the next 6 months led to favorable psychosocial outcomes, in terms of HRSD score.^[40] Cognitive behavior therapy and stress management were also effective in treating depression after CABG surgery, indicated by the mean HRSD score 5.5 for cognitive behavior therapy, 7.8 for stress management, and 10.7 for usual care.^[41]

Therapeutic exercise was demonstrated to improve depressive outcomes in 101 patients with coronary heart disease (CHD) and elevated depressive symptoms, aerobic exercise led to better HRSD as compared with the placebo group (mean: -7.5 vs. -4.5) and a reduction in depressive symptoms.^[42] Blumenthal, *et al.*^[43] further studied 2322 stable patients with depression following HF, who underwent either aerobic exercise or education and usual guideline-based HF care. The exercise therapy resulted in lower BDI-II at 3 months (8.95 in exercise group vs. 9.70 in usual care group) and 12 months (8.86 vs. 9.54) of the treatment period.

Combinatorial Management

The combination of exercise and medication has demonstrated better effectiveness in treating post-MI depression. The collaborative care of antidepressants and psychotherapy given before cardiovascular disease (CVD) lowered the risk of depressive events by 48%.^[44] Davidson, *et al.*^[45] investigated 150 patients with depression after ACS who received 6 months of centralized depression care or

locally determined depression care. They observed a significantly larger decrease in depressive symptoms in the active treatment group than the usual care group. In 302 patients with depression after CABG and a non-depressed group of 151 patients, who received telephone-delivered collaborative care for 8 months, the intervention increased health-related quality of life, physical function, and mood.^[46] Similarly, 183 patients hospitalized for ACS, arrhythmia, or HF, who also had clinical depression, generalized anxiety disorder, or panic disorder, received low-intensity telephone-based multicomponent collaborative care for depression and anxiety for 24 weeks, which led to a better physical and mental health and general function, measured by the Short Form-12 Mental Component Score (i.e., 11.21 in the collaborative care group versus 5.53 points in the enhanced usual care group).^[47] Another study proposed four main aspects related to CHD and depression/anxiety, i.e., (1) treating depression in CHD patients with multimorbidity; (2) psychometric properties of instruments for assessing depression and anxiety in CHD patients, (3) depression or anxiety in post-PCI patients; and (4) other mental diseases in CHD patients.^[48]

Other Confounding Factors

Inflammation is also thought to play a key role in the development of depression after MI, since MI-induced peripheral cytokines release may cause cerebral endothelial leakage and hence induces a neuroinflammatory reaction. Since the current standard cardiovascular therapy does not help the symptoms of depression much,^[49] other pathogenic factors have been proposed, including hypothalamic-pituitary-adrenal dysregulation, diminished heart rate variability, altered blood platelet function, noncompliance with medical treatments, reduced baroreflex sensitivity, impaired immune function, chronic fatigue, and the co-morbidity of depression and anxiety that may be related to major cardiac events and depression.^[50] While SSRIs and other medications can reduce post-MI depression, some negative consequences may be present, for example, fluoxetine was associated with higher mortality rates (HR, 1.66).^[51] In patients with major depression and left ventricular impairment, ventricular arrhythmias, and/or conduction dis-



ease, the use of bupropion for 3 weeks caused a rise in supine blood pressure and 14% of patients ended the treatment due to adverse effects of exacerbation of baseline hypertension.^[52]

Two major neurotransmitters for mood control, serotonin (5-HT) and dopamine, have also been studied post-cardiac events for a better understanding of the pathogenic process of depression post-MI. For example, Liu *et al.* investigated whether 5-HT, 5-HT_{2A} receptor (5-HT_{2AR}), and 5-HT transporter are related to the disease states of depression, MI, and MI with depression. The blood concentration of serotonin significantly decreased in the rats with depression (303.25 ± 9.99 vs. 352.98 ± 13.73 in controls), and significantly increased in rats with MI alone (381.78 ± 14.17), but declined to the control level in the rats with MI + depression (360.62 ± 11.40), whereas the platelet lysate concentration of 5-HT_{2AR} and serotonin transporters significantly increased in the depression, MI, and MI + depression groups as compared with the control group.^[53] 5-HT levels were also reported by Han, *et al.*^[54] in 63 patients with ACS and 60 patients with chronic stable angina (CSA) who were treated with PCI. Whereas the similar baseline (ACS: 8.6 ± 14.6 and CSA: 10.3 ± 15.9 ng/mL) and pre-PCI (ACS: 18.3 ± 30.7 ng/mL and CSA: 19.7 ± 47.8 ng/mL) 5-HT levels were observed, the post-PCI 5-HT levels were significantly increased in the ACS group (55.2 ± 120.0 ng/mL) as compared with the CSA group (20.1 ± 24.0 ng/mL), and there was a drop in 5-HT levels 48 h after PCI.^[54] In addition, plasma 5-HT levels were found significantly higher in 14 patients with Tako-Tsubo cardiomyopathy and 14 patients with ST-elevation myocardial infarction (STEMI) at admission (5.7 ± 5.6 ng/mL) than the healthy control subjects (3.9 ± 4.6 ng/mL).^[55]

There is abundant evidence that salt added in foods increases the risk of CVD^[56] by affecting the metabolic pathways^[57] with indirect consequences on mental health.^[3,4] One of these consequences is the decreased behavioral inhibition. In a mouse study by Gilman, *et al.*^[58], utilizing mice and their normal behaviors, it was found that a high-salt diet led to lower behavioral inhibition which is common in many neuropsychiatric diseases including depression. Furthermore, a 2019 study using a urine sample analysis on 84 adolescents in conjunc-

tion with the Center for Epidemiological Studies Depression 10 scale, found interesting results. It was concluded that those who secreted higher levels of sodium (meaning they consumed a diet higher in salt) developed depressive symptoms at a higher rate.^[59] The benefits of reducing the salt intake for lowering the blood pressure^[60] stimulated the World Health Organization to issue the "Guideline: Sodium Intake for Adults and Children".^[61] A recent genomic study^[62] proved that the low-salt diet up-regulate the pathways of: cardiac muscle contraction, adrenergic signaling in cardiomyocytes and oxidative phosphorylation, while weakening the synchronization of the pathways responsible for several chronic heart diseases.

POTENTIAL ROLE OF CHEMOKINES FOR POST-MI HEART-BRAIN INTERACTION

Gene expression profiling has emerged as a useful tool in investigating the molecular mechanisms underlying the connections between cardiac and mental diseases. Studies on mouse models of post-ischemic HF^[63] have shown that acute MI results in activation of the immune/inflammatory response, ventricular remodeling, and HF. Lachtermacher, *et al.*^[64] demonstrated that the ischemia effects caused by acute MI were fairly reversed through bone-marrow cell therapy. Accordingly, we reanalyzed the raw expression data deposited in the NCBI/GEO publicly accessible gene datasets (GSE18703, GSE-29769) to identify the MI-triggered transcriptomic alterations of several functional pathways related to "Chemokine signaling"^[65] and their recovery following stem cell treatment. Figure 2 presents the affected genes within the KEGG-constructed functional pathway of Chemokine Signaling in the left ventricles collected from the mice with MI alone (IN, Figure 2A) or those treated with stem cell therapy post-MI (IT, Figure 2B), as compared to the control mice (NN, i.e. animals had no MI, nor stem cell therapy).^[66]

Therefore, future studies using the Gene Expression Recovery score^[66] in analyzing the available clinical human specimens and pre-clinical animal samples of heart, brain and blood, simultaneously would reveal some useful genomic and transcriptomic information linking the heart-brain interac-



tions that are discussed in the review. Looking at the relationship between Table 2 and Figure 2, three different chemokines are present in both. These include CXCL12 and CCL22, which are two chemokines that are not regulated as seen by the color code.

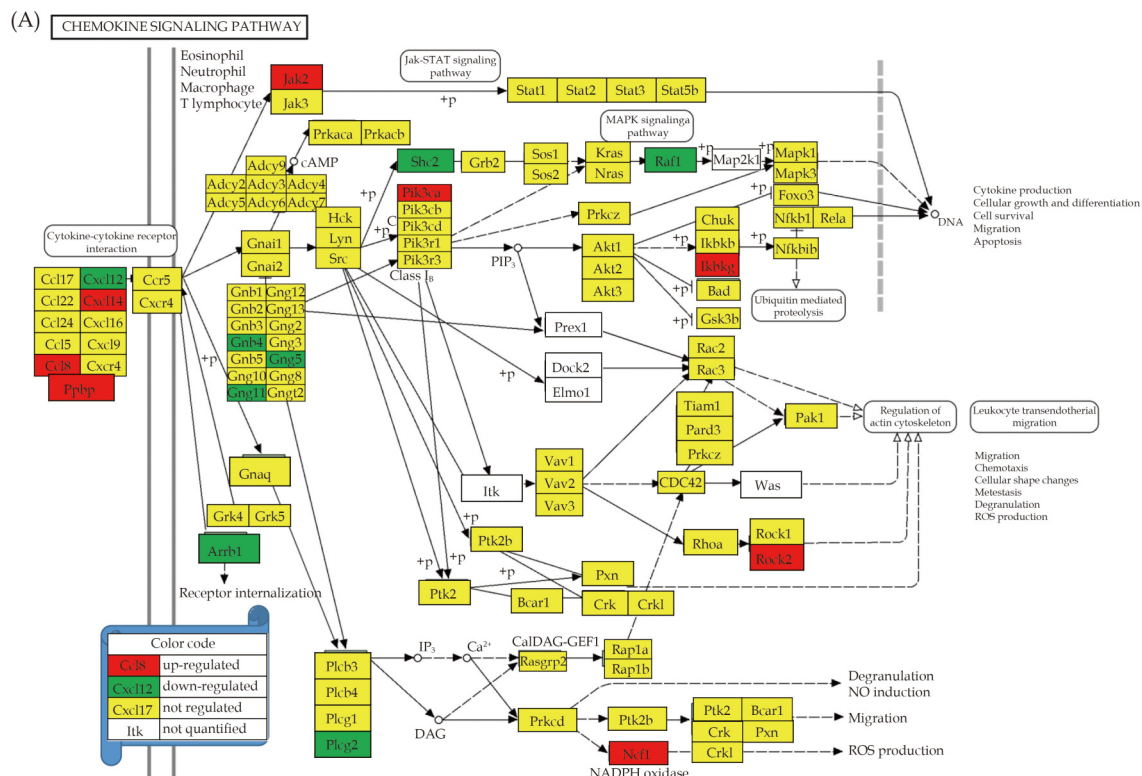
CXCL12 was shown to increase under stress, which is an important factor in depression.^[67] Since it is not regulated, when it is increased it causes more and stronger effects which could cause the depression seen in these patients.^[68] CXCL12 is a prominent component of the transmigration of lymphocytes across the blood-brain barrier (BBB).^[69] Further it is shown that can be CXCL12 expressed at the BBB and even attract protective natural killer cells in times of need such as an ischemic stroke.^[70]

CCL22^[71] is also not regulated and its pathway is better described. It was seen that CCL22 is a macrophage-derived chemokine that is highly active in patients of MDD who respond to anti-depressive therapy. This suggests that chemotaxis and infiltration of monocytes, and the recruitment of T-helper 2 cells (Th2) and T-regulatory cells through the blood brain barrier is a potential pathway for the role of chemokines in MDD. Furthermore, CCL22 expres-

sion is highly active at the lymph nodes. Also, using the CCR4 receptor, cell to cell contact points and interactions are created between regulatory T cells and dendritic cells.^[72]

Another chemokine that seems to play an important role in myocardial infarction is CCL2/MCP-1. It is constantly upregulated in canine,^[73] rat,^[74,75] and mouse^[76] models that exhibit MI. In mice with a loss of MCP-1 showed attenuated dilative remodeling which was further related to delayed macrophage infiltration in the healing infarct. Furthermore, this model had a reduced pro-inflammatory gene expression. However, the process to replace or remove damaged and dead cardiomyocytes, respectively, was inefficient.^[77] These findings could be explained by the fact that MCP-1 loss leads to a worsened recruitment of pro-inflammatory monocytes.^[78] CCR2 is the receptor for MCP-1 and a loss of CCR2 has been shown to protect mice from post-MI chamber dilation.^[79]

A study conducted by Misiak, *et al.*,^[80] viewed the difference in chemokine levels of multiple chemokines including MCP-1 in peripheral blood of those with bipolar disorder. The patients included 1221 with bipolar disorder and 663 controls. MCP-1 was



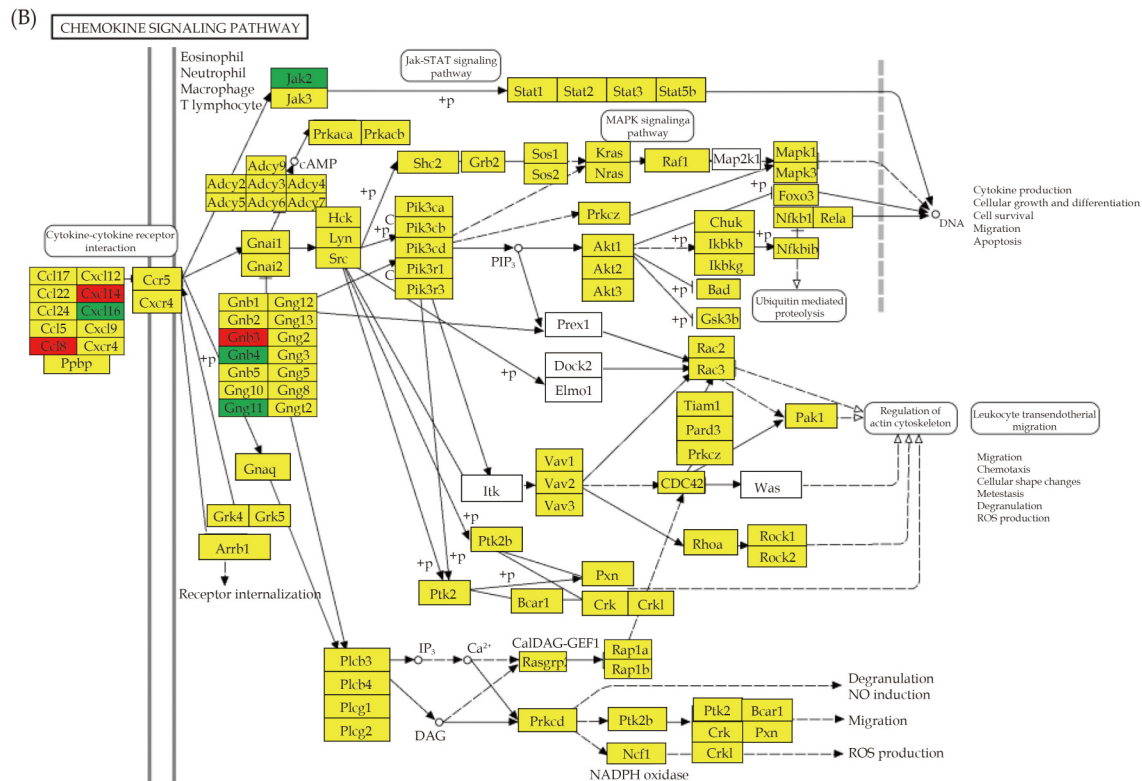


Figure 2 Regulated chemokine signaling pathway in the left ventricle of the mice with acute myocardial infarction (MI; Graph A) and the mice with acute MI and treated with stem cells (Graph B), in respect to the control mice received sham treatment. Arrb1: Arrestin beta 1; Ccl8: Chemokine: C-C motif ligand 8; Cxcl12/14/16: Chemokine: C-X-C motif ligand 12/14/16; Gnb3/4: Guanine nucleotide binding protein: G protein, beta 3/4; Gng11/5: Guanine nucleotide binding protein: G protein, gamma 11/5; Ikbkg: Inhibitor of kappaB kinase gamma; Jak2: Janus kinase 2; Ncf1: Neutrophil cytosolic factor 1; Pard3: Par-3: partitioning defective 3 homolog; Pik3ca: Phosphatidylinositol 3-kinase; catalytic; alpha polypeptide; Plcg2: Phospholipase C, gamma 2; Ppbp: Pro-platelet basic protein; Raf1: V-raf-leukemia viral oncogene 1; Rock2: Rho-associated coiled-coil containing protein kinase 2; Shc2: SHC: Src homology 2 domain containing transforming protein 2.

found increased in patients with bipolar disorder, specifically elevated during the depressive phase. Through the evidence, we can clearly see a potential pathogenic role played by MCP-1 in both depression and MI.

SUMMARY AND PERSPECTIVES

Acute MI remains a primary cause of mortality and morbidity in the modern societies. There has been an increasing recognition on an apparent link between MI and depression, which is the focus of this review. While the exact percentage of prevalence reported in different studies and/or patient groups may vary, there is an apparent positive correlation between MI and depression. Post-MI mental impairment poses extra difficulties for the cardiac patient as the mental struggles affect both medical and daily-life aspects of their lives. Besides the

medical challenges, the post-MI patients often have an overall poor quality of life, difficulty returning to work, increased health complaints and disabilities, decreased use of primary care resources, and low preventative lifestyle change. The vicious cycle also contributes to noncompliance with medical advice thus furthering medical concerns.

Hereby we focused on the potential pathogenic mechanisms underlying post-MI depression, which affect brain, heart, and total body as shown in Figure 1. For the brain, cingulate cortex dysfunction, neuroinflammatory reaction, and hypothalamic-pituitary-adrenal dysregulation are potential pathogenic pathways post-MI. These changes may be associated with or caused by the post-MI cardiac abnormalities such as reduced baroreflex sensitivity and diminished heart rate variability. Lastly, altered blood platelet function, coagulation system dysfunction, impaired immune function, chronic fa-



Table 2 List of representative chemokines that have been linked to mental disorders.

Chemokines	Key cellular characters and pathophysiological function	Mental disorders	Evidence supporting the potential link between chemokines and mental disorder
CXC superfamily			
CXCL1	Chemokine (C-X-C motif) ligand 1 (CXCL1) is a small peptide that acts as a chemoattractant for immune cells, especially neutrophils to the site of injury or infection and plays an important role in regulation of immune and inflammatory responses. CXCL1 is also involved in the processes of wound healing and tumorigenesis. CXCL1 contributes to the release of prostaglandins and thus causes increased sensitivity to pain and drives nociceptive sensitization.	Depressive symptoms Depression	Rats treated with CXCL1 showed a decrease in burrowing behavior and open-field activity. ^[81] Repeated social defeat in mice caused an increase in the CXCL1 levels in the brain. This suggests higher leukocyte recruitment in the brain vasculature. ^[82]
CXCL2	Chemokine (C-X-C motif) ligand 2 (CXCL2) is also called macrophage inflammatory protein 2- α (MIP2- α) and serves as a neutrophil chemoattractant. CXCL2 is involved in immune responses including wound healing, cancer metastasis, and angiogenesis.	Depression	Repeated social defeat in mice also caused an increase in the CXCL2 levels in the brain. ^[83]
CXCL4	Chemokine (C-X-C motif) ligand 4 (CXCL4) is also known as Platelet factor 4 (PF4), and plays a major role in neutralization of heparin-like molecules on the endothelial surface of blood vessels, thereby inhibiting local antithrombin activity and promoting coagulation. CXCL4 is a chemoattractant for neutrophils and fibroblasts and is involved with inflammation and wound repair.	Depression	Increased levels of CXCL4 were seen in depressed patients. ^[83]
CXCL7	Chemokine (C-X-C motif) ligand 7 (CXCL7) is released in large amounts from platelets following their activation. CXCL7 may function as an immediate-early mediator of neutrophil recruitment released from platelets at sites of inflammation.	Depression	Increased levels of CXCL7 were also seen in depressed patients. ^[83]
CXCL8	Chemokine (C-X-C motif) ligand 8 (CXCL8) is the most potent human neutrophil-attracting chemokine and plays crucial roles in the response to infection and tissue injury. CXCL8 is also known as Interleukin 8 (IL-8), which is produced by macrophages and other cell types such as epithelial cells, airway smooth muscle cells, and endothelial cells. CXCL8 plays a key role in neutrophil recruitment and degranulation and its secretion serves as a key parameter in localized inflammation.	Depression	Levels of CXCL8 in blood samples for depressed patients were higher than the average for control subjects but this was after controlling for only healthy patients. This suggests that inflammatory changes of underlying physical disease could mask the changes in chemokine levels in depressed patients. ^[83]
CXCL10	Chemokine (C-X-C motif) ligand 10 (CXCL10), also known as Interferon gamma-induced protein 10 (IP-10), is a circulating inflammatory marker. CXCL10 is a biomarker for the development of heart failure and left ventricular dysfunction.	MDD with suicidal ideation	Significantly higher blood levels of CXCL10 were seen in patients with MDD with suicidal ideation as compared to MDD alone. ^[84]
CXCL12	Chemokine (C-X-C motif) ligand 12 (CXCL12) is also known as stromal cell-derived factor 1 (SDF-1). CXCL12 is strongly chemotactic for lymphocytes and is involved with cell migration that contributes to inflammation, including neuroinflammation by attracting leukocytes across the blood brain barrier. Excessive production and accumulation of CXCL12 are cytotoxic.	Stress	Increased level of CXCL12 in the hippocampus and prefrontal cortex suggests the excessive activation of microglial cells. ^[85]

Continued

Chemokines	Key cellular characters and pathophysiological function	Mental disorders	Evidence supporting the potential link between chemokines and mental disorder
CC superfamily			
CCL2	Chemokine (C-C motif) ligand 2 (CCL2) is also called as monocyte chemoattractant protein-1 (MCP-1), which attracts monocytes in the circulatory system helping them to enter the encompassing injured and inflamed tissues where they transform into tissue macrophages. CCL2 is involved in the neuro-inflammatory processes in various neurodegenerative diseases.	MDD Stress Bipolar disorder	This specific chemokine is a type of inflammatory chemokine which is implicated in chemotactic migration of peripheral monocytes to the brain. ^[86] Increased levels of CCL2 are seen in patients with bipolar disorder. ^[87]
CCL3	Chemokine (C-C motif) ligand 3 (CCL3) is also known as macrophage inflammatory protein 1 α (MIP-1 α). CCL3 is involved in acute inflammatory state in recruitment and activation of polymorphonuclear leukocytes.	Depression	Depressed patients had a higher level of CCL3 which also acts as a macrophage inflammatory protein-1 α when compared to healthy control. ^[83,88,89]
CCL4	Chemokine (C-C motif) ligands 4 (CCL4) is also known as macrophage inflammatory protein 1 β (MIP-1 β) and is produced during inflammation and tissue damage to attract immune cells such as leukocytes to migrate into peripheral tissues.	Depression	Plasma levels of CCL4 were shown to be decreased in depressed patients. ^[83,90,91]
CCL11	Chemokine (C-C motif) ligand 11 (CCL11) is also known as eosinophil chemotactic protein and eotaxin-1. CCL11 selectively recruits eosinophils by inducing their chemotaxis, and is implicated in allergic responses as well as neurogenesis and mental disorders.	Depression	Increased levels of CCL11 are seen in patients with bipolar disorder as well as depression. ^[83]
CCL22	Chemokine (C-C motif) ligand 22 (CCL22) plays a role in trafficking of the activated T lymphocytes to inflammatory sites.	MDD	MDD patients who responded to anti-depressive therapy had increased levels of CCL22. This is a macrophage-derived chemokine which suggests that chemotaxis and infiltration of monocytes, and the recruitment of T-helper 2 cells (Th2) and T-regulatory cells through the blood brain barrier is a potential pathway for the role of chemokines in MDD. ^[68]

CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; MDD: major depressive disorder.

tigue, and impaired nerve and muscle function all could be the contributing factors leading to the higher prevalence of depression after MI.

A salient point we have postulated in this review is that chemokines could serve as major components in the pathogenic signaling network that connects heart and brain during the post-MI period and contributes to post-MI depression. In particular, three chemokines attracted our interests are CXCL12, CCL22, and MCP-1. Among them, CXCL12 is an integral component of the transmigration of lymphocytes across the BBB, which is important in the development of depression. CXCL12 is vital in the body's response to MI, and it also aids in the re-

cruitment of T-helper 2 cells (Th2) and T-regulatory cells through the BBB. MCP-1 is constantly upregulated in canine, rat, and mouse models that exhibit myocardial infarction. Also, when studying bipolar patients, it was found that MCP-1 was specifically increased during the depressive phase of bipolar disorder making the link between MI and depression clear. Taken together, we envisage that a chemokine-targeted new therapeutic approach may potentially improve the efficacy of current treatment of depression in post-MI settings, which currently rely on SSRIs and cognitive behavior and exercise therapies. Apparently, combinatorial management has been shown to provide better outcomes in post-MI



depression and overall rehabilitation. Future research needs to test and validate this chemokine-related hypothesis on post-MI depression and to identify new therapies to treat mental disorders that could severely hamper the patient's ability to return to normal life following acute MI.

REFERENCES

- [1] Zghebi SS, Rutter MK, Sun LY, *et al.* Comorbidity clusters and in-hospital outcomes in patients admitted with acute myocardial infarction in the USA: A national population-based study. *PLoS One* 2023; 18: e0293314.
- [2] Kavanagh T, Shephard RJ, Tuck, JA. Depression after myocardial infarction. *Can Med Assoc J* 1975; 113: 23–27.
- [3] Schleifer SJ, Macari-Hinson MM, Coyle DA, *et al.* The nature and course of depression following myocardial infarction. *Arch Intern Med* 1989; 149: 1785–1789.
- [4] Frasure-Smith N, Lespérance F, Juneau M, *et al.* Gender, depression, and one-year prognosis after myocardial infarction. *Psychosom Med* 1999; 61: 26–37.
- [5] Ziegelstein RC. Depression in patients recovering from a myocardial infarction. *JAMA* 2001; 286: 1621–1627.
- [6] Bush DE, Ziegelstein RC, Patel UV, *et al.* *Post-Myocardial Infarction Depression: Summary*; Agency for Healthcare Research and Quality: Maryland, USA, 2005.
- [7] Feng HP, Chien WC, Cheng WT, *et al.* Risk of anxiety and depressive disorders in patients with myocardial infarction: A nationwide population-based cohort study. *Medicine* 2016; 95: e4464.
- [8] Lauzon C, Beck CA, Huynh T, *et al.* Depression and prognosis following hospital admission because of acute myocardial infarction. *Can Med Assoc J* 2003; 168: 547–552.
- [9] von Känel R, Schmid JP, Abbas CC, *et al.* Stress hormones in patients with posttraumatic stress disorder caused by myocardial infarction and role of comorbid depression. *J Affect Disord* 2010; 121: 73–79.
- [10] Gander ML, von Känel R. Myocardial infarction and post-traumatic stress disorder: frequency, outcome, and atherosclerotic mechanisms. *Eur J Cardiovasc Prev Rehabil* 2006; 13: 165–172.
- [11] Carney RM, Freedland KE, Jaffe AS. Insomnia and depression prior to myocardial infarction. *Psychosom Med* 1990; 52: 603–609.
- [12] Açikel MET. Evaluation of Depression and Anxiety in Coronary Artery Bypass Surgery Patients: A Prospective Clinical Study. *Braz J Cardiovasc Surg* 2019; 34: 389–395.
- [13] Connerney I, Shapiro PA, McLaughlin JS, *et al.* Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet* 2001; 358: 1766–1771.
- [14] Faria J, Gomes M, Costa G, *et al.* Prevalence and risk analysis for depression after open-heart valve replacement surgery. *Rev Port Cir Cardiorac Vasc* 2014; 21: 31–35.
- [15] Wegermann ZK, Mack MJ, Arnold SV, *et al.* Anxiety and Depression Following Aortic Valve Replacement. *J Am Heart Assoc* 2022; 11: e024377.
- [16] Horne D, Kehler S, Kaoukis G, *et al.* Depression before and after cardiac surgery: do all patients respond the same? *J Thorac Cardiovasc Surg* 2013; 145: 1400–1406.
- [17] Okamoto Y, Motomura N, Murashima S, *et al.* Anxiety and depression after thoracic aortic surgery or coronary artery bypass. *Asian Cardiovasc Thorac Ann* 2013; 21: 22–30.
- [18] Hance M, Carney RM, Freedland KE, *et al.* Depression in patients with coronary heart disease. A 12-month follow-up. *Gen Hosp Psychiatry* 1996; 18: 61–65.
- [19] Murphy B, Le Grande M, Alvarenga M, *et al.* Anxiety and Depression after a Cardiac Event: Prevalence and Predictors. *Front Psychol* 2020; 10: 3010.
- [20] Khan Z, Musa K, Abumedian M, *et al.* Prevalence of Depression in Patients With Post-Acute Coronary Syndrome and the Role of Cardiac Rehabilitation in Reducing the Risk of Depression: A Systematic Review. *Cureus* 2021; 13: e20851.
- [21] Frasure-Smith N, Lespérance F, Talajic M. Depression Following Myocardial Infarction: Impact on 6-Month Survival. *JAMA* 1993; 270: 1819–1825.
- [22] Frasure-Smith N, Lespérance F, Talajic, M. Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995; 91: 999–1005.
- [23] Carney RM, Howells WB, Blumenthal JA, *et al.* Heart rate turbulence, depression, and survival after acute myocardial infarction. *Psychosom Med* 2007; 69: 4–9.
- [24] Ladwig KH, Kieser M, König J, *et al.* Affective disorders and survival after acute myocardial infarction. Results from the post-infarction late potential study.. *Eur Heart J* 1991; 12: 959–964.
- [25] van Melle JP, de Jonge P, Spijkerman TA, *et al.* Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004; 66: 814–822.
- [26] Patron E, Messerotti Benvenuti S, Favretto G, *et al.* Depression and reduced heart rate variability after cardiac surgery: the mediating role of emotion regulation. *Auton Neurosci* 2014; 180: 53–58.
- [27] Ladwig KH, Röhl G, Breithardt G, *et al.* Post-infarction depression and incomplete recovery 6 months after acute myocardial infarction. *Lancet* 1994; 343: 20–23.
- [28] de Jonge P, Spijkerman TA, van den Brink RH, *et al.* Depression after myocardial infarction is a risk factor for declining health related quality of life and increased disability and cardiac complaints at 12 months. *Heart* 2006; 92: 32–39.
- [29] Mayou RA, Gill D, Thompson DR, *et al.* Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med* 2000; 62: 212–219.
- [30] Shapiro PA, Lespérance F, Frasure-Smith N, *et al.* An open-label preliminary trial of sertraline for treatment



- of major depression after acute myocardial infarction (the SADHAT Trial). Sertraline Anti-Depressant Heart Attack Trial. *Am Heart J* 1999; 137: 1100–1106.
- [31] Glassman AH, O'Connor CM, Califf RM, *et al.* Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; 288: 701–709.
 - [32] Strik JJ, Honig A, Lousberg R, *et al.* Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. *Psychosom Med* 2000; 62: 783–789.
 - [33] Lespérance F, Frasere-Smith N, Koszycki D, *et al.* Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA* 2007; 297: 367–379.
 - [34] Kim JM, Stewart R, Lee YS, *et al.* Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial. *JAMA* 2018; 320: 350–358.
 - [35] Gottlieb SS, Kop WJ, Thomas SA, *et al.* A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. *Am Heart J* 2007; 153: 868–873.
 - [36] Honig A, Kuyper AM, Schene AH, *et al.* Treatment of post-myocardial infarction depressive disorder: a randomized, placebo-controlled trial with mirtazapine. *Psychosom Med* 2007; 69: 606–613.
 - [37] Saba S, Faizi F, Sepandi M, *et al.* Effect of short-term magnesium supplementation on anxiety, depression and sleep quality in patients after open-heart surgery. Effect of short-term magnesium supplementation on anxiety, depression and sleep quality in patients after open-heart surgery. *Magnes Res* 2022; 35: 62–70.
 - [38] Lespérance F, Frasere-Smith N, Laliberté MA, *et al.* An open-label study of nefazodone treatment of major depression in patients with congestive heart failure. *Can J Psychiatry* 2003; 48: 695–701.
 - [39] Wang HW, Ahmad M, Jadayel R, *et al.* Inhibition of inflammation by minocycline improves heart failure and depression-like behaviour in rats after myocardial infarction. *PLoS One* 2019; 14: e0217437.
 - [40] Berkman LF, Blumenthal J, Burg M, *et al.* Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* 2003; 289: 3106–3116.
 - [41] Freedland KE, Skala JA, Carney RM, *et al.* Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Arch Gen Psychiatry* 2009; 66: 387–396.
 - [42] Blumenthal JA, Sherwood A, Babyak MA, *et al.* Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: results from the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study. *J Am Coll Cardiol* 2012; 60: 1053–1063.
 - [43] Blumenthal JA, Babyak MA, O'Connor C, *et al.* Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. *JAMA* 2012; 308: 465–474.
 - [44] Stewart JC, Perkins AJ, Callahan CM. Effect of collaborative care for depression on risk of cardiovascular events: data from the IMPACT randomized controlled trial. *Psychosom Med* 2014; 76: 29–37.
 - [45] Davidson KW, Bigger JT, Burg MM, *et al.* Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: CODIACS vanguard randomized controlled trial. *JAMA Intern Med* 2013; 173: 997–1004.
 - [46] Rollman BL, Belnap BH, LeMenager MS, *et al.* Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. *JAMA* 2009; 302: 2095–2103.
 - [47] Huffman JC, Mastromauro CA, Beach SR, *et al.* Collaborative care for depression and anxiety disorders in patients with recent cardiac events: the Management of Sadness and Anxiety in Cardiology (MOSAIC) randomized clinical trial. *JAMA Intern Med* 2014; 174: 927–935.
 - [48] Zhou Y, Zhu XP, Shi JJ, *et al.* Coronary Heart Disease and Depression or Anxiety: A Bibliometric Analysis. *Front Psychol* 2021; 12: 669000.
 - [49] Liu H, Luiten PG, Eisel UL, *et al.* Depression after myocardial infarction: TNF- α -induced alterations of the blood-brain barrier and its putative therapeutic implications. *Neurosci Biobehav Rev* 2013; 37: 561–572.
 - [50] Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev* 2002; 26: 941–962.
 - [51] Diez-Quevedo C, Lupón J, González B, *et al.* Depression, antidepressants, and long-term mortality in heart failure. *Int J Cardiol* 2013; 167: 1217–1225.
 - [52] Roose SP, Dalack GW, Glassman AH, *et al.* Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry* 1991; 148: 512–516.
 - [53] Liu MY, Ren YP, Wei WL, *et al.* Changes of Serotonin (5-HT), 5-HT_{2A} Receptor, and 5-HT Transporter in the Sprague-Dawley Rats of Depression, Myocardial Infarction and Myocardial Infarction Co-exist with Depression. *Chin Med J* 2015; 128: 1905–1909.
 - [54] Han D, Choi JH, Kim S, *et al.* Changes in serum serotonin levels in patients with acute coronary syndrome and stable angina undergoing percutaneous coronary intervention. *J Int Med Res* 2020; 48: 300060520970104.
 - [55] Rouzaud Laborde C, Delmas C, Mialet-Perez J, *et al.* First evidence of increased plasma serotonin levels in Tako-Tsubo cardiomyopathy. *Biomed Res Int* 2013; 847069.



- [56] Ma H, Wang X, Li X, *et al.* Adding Salt to Foods and Risk of Cardiovascular Disease. *J Am Coll Cardiol* 2022; 80: 2157–2167.
- [57] Aksentijević D, Shattock MJ. With a grain of salt: Sodium elevation and metabolic remodeling in heart failure. *J Mol Cell Cardiol* 2021; 161: 106–115.
- [58] Gilman TL, George CM, Andrade MA, *et al.* High Salt Intake Lowers Behavioral Inhibition. *Front Behav Neurosci* 2019; 13: 271.
- [59] Mrug S, Orihuela C, Mrug M, *et al.* Sodium and potassium excretion predict increased depression in urban adolescents. *Physiol Rep* 2019; 16: e14213.
- [60] Aliasgharzadeh S, Tabrizi JS, Nikniaz L, *et al.* Effect of salt reduction interventions in lowering blood pressure: A comprehensive systematic review and meta-analysis of controlled clinical trials. *PLoS One* 2022; 17: e0277929.
- [61] Guideline: Sodium Intake for Adults and Children. <https://www.who.int/publications/i/item/9789241504836> (accessed Apr 16, 2024).
- [62] Iacobas DA, Allen H, Iacobas S. Low-salt Diet Regulates the Metabolic and Signal Transduction Genomic Fabrics, and Remodels the Cardiac Normal and Chronic Pathological Pathways. *Curr Issues Mol Biol* 2024; 46: 2355–2385.
- [63] Lachtermacher S, Esporcatte BL, Montalvão F, *et al.* Cardiac gene expression and systemic cytokine profile are complementary in a murine model of post-ischemic heart failure. *Braz J Med Biol Res* 2010; 43: 377–89.
- [64] Lachtermacher S, Esporcatte BL, Fortes Fda S, *et al.* Functional and transcriptomic recovery of infarcted mouse myocardium treated with bone marrow mononuclear cells. *Stem Cell Rev Rep* 2012; 8: 251–61.
- [65] Kyoto Encyclopedia of Genes and Genomes Chemokine signaling pathway. https://www.kegg.jp/kegg-bin/show_pathway?mmu04062 (accessed Dec 7, 2023).
- [66] Iacobas DA, Xi L. Theory and Applications of the (Cardio) Genomic Fabric Approach to Post-Ischemic and Hypoxia-Induced Heart Failure. *J Pers Med* 2022; 12: 1246.
- [67] CXCL12/SDF-1(PBSF). <https://www.rndsystems.com/research-area> (accessed Apr 16, 2024).
- [68] Milenkovic V M, Stanton E H, Nothdurfter C, *et al.* The Role of Chemokines in the Pathophysiology of Major Depressive Disorder. *Int J Mol Sci* 2019; 20: 2283.
- [69] Man S, Tucky B, Cotleur A, *et al.* CXCL12-induced monocyte-endothelial interactions promote lymphocyte transmigration across an in vitro blood-brain barrier. *Sci Transl Med* 2012; 4: 119ra14.
- [70] Wang S, de Fabritus L, Kumar PA, *et al.* Brain endothelial CXCL12 attracts protective natural killer cells during ischemic stroke. *J Neuroinflammation* 2023; 20: 8.
- [71] Williams A. Chemokines: CC Family. In *Encyclopedia of Respiratory Medicine*, 2nd Edition; Academic Press: 2022; 332-356.
- [72] Rapp M, Wintergerst MWM, Kunz WG, *et al.* CCL22 controls immunity by promoting regulatory T cell communication with dendritic cells in lymph nodes. *J Exp Med* 2019; 216: 1170–1181.
- [73] Kumar AG, Ballantyne CM, Michael LH, *et al.* Induction of monocyte chemoattractant protein-1 in the small veins of the ischemic and reperfused canine myocardium. *Circulation* 1997; 95: 693–700.
- [74] Ono K, Matsumori A, Furukawa Y, *et al.* Prevention of myocardial reperfusion injury in rats by an antibody against monocyte chemotactic and activating factor/monocyte chemoattractant protein-1. *Lab Invest* 1999; 79: 195–203.
- [75] Kakio T, Matsumori A, Ono K, *et al.* Roles and relationship of macrophages and monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 in the ischemic and reperfused rat heart. *Lab Invest* 2000; 80: 1127–1136.
- [76] Tarzami ST, Cheng R, Miao W, *et al.* Chemokine expression in myocardial ischemia: MIP-2 dependent MCP-1 expression protects cardiomyocytes from cell death. *J Mol Cell Cardiol* 2002; 34: 209–221.
- [77] Dewald O, Zymek P, Winkelmann K, *et al.* CCL2/Monocyte Chemoattractant Protein-1 regulates inflammatory responses critical to healing myocardial infarcts. *Circ Res* 2005; 96: 881–889.
- [78] Nahrendorf M, Swirski FK, Aikawa E, *et al.* The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. *J Exp Med* 2007; 204: 3037–3047.
- [79] Liehn EA, Piccinini AM, Koenen RR, *et al.* A new monocyte chemotactic protein-1/chemokine CC motif ligand-2 competitor limiting neointima formation and myocardial ischemia/reperfusion injury in mice. *J Am Coll Cardiol* 2010; 56: 1847–1857.
- [80] Misiak B, Bartoli F, Carrà G, *et al.* Chemokine alterations in bipolar disorder: A systematic review and meta-analysis. *Brain Behavior Immun* 2020; 88: 870–877.
- [81] Campbell SJ, Meier U, Mardiguan S, *et al.* Sickness behaviour is induced by a peripheral CXC-chemokine also expressed in multiple sclerosis and EAE. *Brain Behav Immun* 2010; 24: 738–746.
- [82] Sawicki CM, McKim DB, Wohleb ES, *et al.* Social defeat promotes a reactive endothelium in a brain region-dependent manner with increased expression of key adhesion molecules, selectins and chemokines associated with the recruitment of myeloid cells to the brain. *Neuroscience* 2015; 302: 151–164.
- [83] Leighton SP, Nerurkar L, Krishnadas R, *et al.* Chemokines in depression in health and in inflammatory illness: a systematic review and meta-analysis. *Mol Psychiatry* 2018; 23: 48–58.
- [84] Xu Y, Liang J, Gao W, *et al.* Peripheral blood cytokines as potential diagnostic biomarkers of suicidal ideation in patients with first-episode drug-naïve major depressive disorder. *Front Public Health* 2022; 10: 1021309.
- [85] Ślusarczyk J, Trojan E, Glombik K, *et al.* Prenatal stress is a vulnerability factor for altered morphology and



- biological activity of microglia cells. *Front Cell Neurosci* 2015; 9: 82.
- [86] Ge S, Song L, Serwanski DR, *et al.* Transcellular transport of CCL2 across brain microvascular endothelial cells. *J Neurochem* 2008; 104: 1219–1232.
- [87] Drexhage RC, Hoogenboezem TH, Versnel MA, *et al.* The activation of monocyte and T cell networks in patients with bipolar disorder. *Brain Behav Immun* 2011; 25: 1206–1213.
- [88] Simon NM, McNamara K, Chow CW, *et al.* A detailed examination of cytokine abnormalities in Major Depressive Disorder. *Eur Neuropsychopharmacol* 2008; 18: 230–233.
- [89] Dahl J, Ormstad H, Aass HCD, *et al.* The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. *Psychoneuroendocrinology* 2014; 45: 77–86.
- [90] Lehto SM, Niskanen L, Herzig K-H, *et al.* Serum chemokine levels in major depressive disorder. *Psychoneuroendocrinology* 2010; 35: 226–232.
- [91] Einvik G, Vistnes M, Hrubos-Strøm H, *et al.* Circulating cytokine concentrations are not associated with major depressive disorder in a community-based cohort. *Gen Hosp Psychiatry* 2012; 34: 262–267.

Please cite this article as: Patel P, Yang F, Iacobas DA, Xi L. Mental disorders after myocardial infarction: potential mediator role for chemokines in heart-brain interaction? *J Geriatr Cardiol* 2024; 21(9): 913–926. DOI: 10.26599/1671-5411.2024.09.004

