Original Article

Does Depression Change the Levels of Inflammatory Markers in Patients With Acute Myocardial Infarction in the Hospitalization Period?

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ABSTRACT

Background: Myocardial infarction (MI) is a major cause of death worldwide. Several acute-phase inflammatory proteins such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been examined as the potential indicators of atherosclerosis and the risk of coronary artery disease (CAD). This study aimed to examine whether inflammation could explain the relationship between depression and CAD.

Methods: In this repeated-measure cross-sectional study, we measured CRP and IL-6 in 162 patients with acute MI at the time of admission and on the fifth day. The patients were categorized into depressed and non-depressed groups based on the Beck Depression Inventory questionnaire. Additionally, on the fifth day of hospitalization, a checklist of acute MI complications was completed for each patient.

Results: The depressed patients had a significantly higher mean value of IL-6 and CRP than the non-depressed group (for IL-6, F=17.06 and *P*<0.001; for CRP, F=8.92 and *P*=0.002). Moreover, the depressed patients experienced more post-MI brady- and tachyarrhythmias.

Conclusions: The depressed patients with acute MI had a higher level of inflammatory factors and more complications such as arrhythmias in their hospitalization period, which might have affected their prognosis. Therefore, it is imperative that more attention be paid to CAD patients with depressed mood in terms of the management and assessment of their prognosis. ***(Iranian heart Journal 2018; 19(3): 20- 29)***

KEYWORDS: Myocardial infarction, Inflammatory factors, Depression, Interleukin-6, C-reactive protein

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Coronary artery disease (CAD) is responsible for approximately one-third of deaths worldwide, and that figure will surely increase in both developing and developed countries as risk factors for the disease—primarily dyslipidemia, hypertension, obesity, diabetes, physical inactivity, poor diet, and smoking—continue to increase. [1, 2] Despite the increasing rate of deaths and CAD risk factors, clinical treatment regimens are effective and reducing the incidence. However, there is still a need for a better understanding of the underlying mechanisms. Atherosclerosis, once thought to be the bland accumulation of lipid in the arterial wall, is now recognized to have a prominent inflammatory component. [3] The substrate for the development and progression of the atherosclerotic lesion is complex and poorly understood. The inadequacy of the current knowledge was recently illustrated in the JUPITER trial, [4] which showed that even in the patients without traditional risk factors—but with elevated high sensitivity C-reactive protein (CRP) levels—statin therapy significantly reduced the incidence of major cardiovascular events. [5]

A better understanding of the inflammatory cascade involved in the atherosclerotic disease process could lead to a better risk stratification and more targeted therapy for CAD and atherosclerosis. Several acute-phase inflammatory proteins such as interleukin-6 (IL-6), CRP, cytokines, and intracellular adhesion molecules have been examined as the potential risk factors for underlying atherosclerosis and the risk of future cardiovascular events such as myocardial infarction (MI). [6] Those who have higher levels of inflammatory factors have more MI complications during days 1 to 5. [7] In addition, a curved time course with elevated levels already on admission is seen with IL-6. [6, 7]

The acute coronary syndrome (ACS) is associated with a massive acute inflammatory response. [5] The magnitude of the acute inflammatory response during the ACS is predictive of a poor cardiac outcome. Biasucci et al [8] showed that patients suffering from unstable angina with elevated levels of IL-1Ra and IL-6 measured 48 hours after admission had a greater risk of in-hospital cardiac events. Elevated CRP predicts 14-day mortality in unstable angina and non–Q-wave MI independently of troponin responses. [9, 10]

Depression is a common disorder in patients suffering from CAD, with a prevalence rate nearly 3 times that in the general population. [11] Depression is also associated with worse cardiac prognoses and greater mortality rates. [10] However, there is still considerable debate regarding how depression contributes to a worse cardiac outcome or a higher mortality rate. [12] Inflammation is seen in both cardiac disease and depression and is a plausible physiological link between depression and CAD. Several cross-sectional studies have demonstrated an association between depression and inflammation in otherwise healthy subjects [13, 14] and also in cardiac patients. [12, 15] Still, relatively little is known about the nature of the association between all the 3 variables of inflammation, outcomes following the ACS, and depression.

Accordingly, in the present study, we sought to describe the association between changes in inflammatory biomarkers during hospitalization in patients with acute MI with and without depression.

METHODS

This repeated-measure cross-sectional study recruited 172 patients with acute MI who were under medical follow-up and admitted to 2 university-based hospitals of Noor and Chamran (academic hospitals affiliated to Isfahan University of Medical Sciences, Isfahan, Iran) with first acute MI between February and August 2013. Consecutive sampling was used for selecting samples from the patients referred to these hospitals.

All the patients were evaluated by a cardiologist and were diagnosed with acute MI based on the World Health Organization's definition. [16] The inclusion criteria for the participants were: 1) age younger than 65 years; 2) hemodynamic stability; 3) the ability to read and write; 4) no previous history of the ACS; 5) willingness to participate in the study; 6) no history of major psychiatric disorders such as depression, anxiety, and major depressive disorder; and 7) no current treatment with statins. The exclusion criteria comprised the presence of any organic disease such as adrenal, hepatic, thyroid, autoimmune, and rheumatologic disease, as well as any history of malignancies, allergies, and medications with an impact on the inflammatory process such as corticosteroids and statins. Ten patients were excluded because of unwillingness to participate in the study or meeting some of the exclusion criteria. After the patients were given full explanations about the study, informed consent was obtained from all the participants. The study protocol was approved by the Ethics Committee of the Cardiovascular Research Institute of Isfahan University of Medical Sciences.

Measurements

At the time of admission, a trained nurse took venous blood samples from all the participants. After the confirmation of the hemodynamic stability of the study subjects, they were asked to complete a questionnaire to determine demographic characteristics such as age, gender, education level, smoking status, and past history of hypertension, diabetes, and dyslipidemia.

The Beck Depression Inventory (I) (BDI [I]), which is a 21-item self-report questionnaire was used to determine whether the subjects presented clinical symptoms of depression. This 4-point scale ranges from 0 to 63, with a cutoff value of 17. Scores of 17 and above are considered to denote depression. [17] The patients with acute MI were then categorized into depressed and non-depressed groups.

The anthropometric characteristics of height, weight, and the waist circumference were measured with the participants wearing hospital clothing and light slippers. The waist circumference was measured in the standing position, midway between the lowest rib and the iliac crest with a flexible anthropometric tape. The body mass index (BMI) was computed as weight (kg) divided by height (m) squared. Blood pressure was measured in the right arm in the sitting position with a standard mercury sphygmomanometer.

On the fifth day of hospitalization, venous blood samples were taken again and a checklist of acute MI complications was completed by a cardiologist based on the patients' hospital documents—including recurrent MI, mechanical complications (septal and free wall rupture), respiratory arrest, cardiogenic shock, bradyarrhythmia, tachyarrhythmia, and extrasystole.

The venous blood samples that were obtained from all the patients at the time of admission were used for laboratory tests—including blood glucose, white blood cells, lipid profiles, CRP, and IL-6. The measurement of CRP and IL-6 was repeated on the fifth day of hospitalization as well. The lipid profile— consisting of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs)—was measured via the enzymatic method with an ELAN 2000 autoanalyzer. The Friedewald formula was applied to calculate the LDL-C level, while in the individuals with a minimum TG level of 400 mg/dL, the level of LDL-C was measured directly. The blood glucose measurement was done with the same machine and Biosystem (France) kits. The level of CRP was measured with a Hitachi 902 autoanalyzer (Japan) using Pars Azmoon (Iran) analytical kits. The level of IL-6 was measured via the standard enzyme-linked immunosorbent assay (ELISA) with Boster Biological Technology Ltd (Wuhan, China) kits.

Statistical Analysis

The demographic characteristics and the cardiovascular risk factors were compared between the groups using the 2-sample independent *t*-test and the χ^2 test. The Fisher exact test was utilized to compare the hospital complications between the 2 groups. The patients with acute MI were categorized into a depressed group and a non-depressed group. A general linear model (GLM) analysis was employed for repeated measures to evaluate both between-groups and within-groups differences in the levels of IL-6 and CRP for all the time points. The IL-6 and CRP levels were assessed on 2 occasions: day 0 (first day of hospitalization) and day 5. The levels of IL-6 and CRP which were distributed normally were recorded as a separate variable for each assessment; thus, a within-subjects factor was defined in 2 levels for the 2 assessments. A separate GLM analysis was performed using age, smoking, TC, and HDL as covariates to check their interactive effect on the IL6 and CRP differences between the 2 groups. A pairwise analysis with the Student *t*-test was used for comparisons in each time point. The Statistical Package for Social Sciences software (SPSS Inc, Chicago, Illinois, USA), version 15.0, was used for the analyses. A *P* value of 0.05 or less was considered statistically significant for all the analyses.

RESULTS

A total of 162 patients with acute MI, comprised of 127 men and 35 women at a mean age of 61.07±13.71 years, were categorized into depressed and non-depressed groups. In the depressed group, 62 (74.7%) patients were male and 6 (7.2%) were graduated. Apropos of the demographic characteristics, there was a significant difference in age between the non-depressed group (64.73±11.91) and the depressed group (59.58±14.07) (*P*=0.03). Regarding the cardiovascular risk factors, there were significant differences in smoking status (*P*=0.01), CT (*P*=0.02), and HDL (*P*=0.01) between the 2 groups at the baseline of assessment. Albeit not significantly different, the BMI, systolic blood pressure, fasting blood glucose, and LDL were higher in the depressed patients.

On the fifth day of hospitalization, significant differences were observed in the incidence of bradyarrhythmia (*P*=0.009) and tachy-arrhythmia (*P*=0.001) in the hospital complications between the 2 groups. In addition, 2 cases of septal and free wall rupture and 2 cases of respiratory arrest were observed on the fifth day of hospitalization (Table 1). Table 2 shows the bivariate analysis of the levels of IL-6 and CRP in the 2 study groups at baseline and on day 5 of hospitalization.

The GLM analysis was used to compare IL-6 and CRP at baseline and on day 5 of hospitalization between the depressed and non-depressed patients. Significant values for repeated assessments (the within-subjects factor; F=16.23 and *P*<0.001) and their interaction with the groups (the between-groups factor; F=11.15 and *P*=0.003) were found using the GLM multivariate test, indicating that both of them contributed to the model.

In the between-groups analysis, the depressed patients had a significantly higher mean of IL-6 and CRP levels than the non-depressed group. The CRP values on day 5 did not differ significantly between the 2 groups. The GLM analysis showed major between-groups effects (non-depressed vs depressed) for the levels of IL-6 (F=17.06 and *P*<0.001) and CRP (F=8.92 and *P*=0.02).

In the within-groups analysis, the mean value of the IL-6 and CRP levels had significant differences regarding the time course of the trial. The GLM analysis showed major within-groups effects for the levels of IL-6 (F=19.25 and *P*<0.001) and CRP (F=12.04 and *P*<0.001).

The GLM analysis revealed significant interactions between the changes in the levels of IL-6 (F=16.25 and *P*<0.001) and CRP (F=7.35 and *P*=0.037) and the non-depressed

group versus the depressed group at baseline and 5 days later. Hence, the GLM analysis illustrated that the change in the levels of IL-6 and CRP over the course of the trial was greater in the depressed group than in the non-depressed group. After sex, age, smoking, CT, and HDL were entered in the analysis as covariates, no significant changes were found.

Table 1. Comparisons of the demographic characteristics, risk factors, and in-hospital complications between the depressed and non-depressed groups

Variable	No Depression n=79 (48.8%)	Depression n=83 (51.2%)	*P*
Demographic Characteristic			
Age (y)	64.73±11.91	59.58±14.07	**0.03**
Sex (male), %	65 (82.3%)	62 (74.7%)	0.29
Education (graduate), %	10 (12.7%)	6 (7.2%)	0.63
Risk Factor on the First Day			
Current smoker, %	23 (29.1%)	34 (41.0%)	**0.01**
Past history of hypertension, %	23 (29.1%)	35 (42.1%)	0.15
Past history of diabetes, %	17 (21.5%)	18 (21.7%)	0.98
Past history of dyslipidemia, %	16 (20.2%)	22 (26.5%)	0.54
Body mass index	25.78±3.70	26.52±4.05	0.28
Waist circumference (cm)	95.51±10.66	94.56±10.47	0.62
Systolic blood pressure (mm Hg)	131.98±26.95	138.79±26.10	0.15
Diastolic blood pressure (mm Hg)	85.37±19.16	84.00±17.96	0.67
White blood cells	11566.66±13029.17	15738.80±21350.45	0.18
Fasting blood glucose (mg/dL)	127.31±53.09	143.22±55.75	0.09
Triglyceride (mg/dL)	134.29±67.14	133.07±52.17	0.90
Cholesterol (mg/dL)	162.35±32.26	176.72±39.22	**0.02**
Low-density lipoprotein (mg/dL)	94.96±32.72	104.21±38.61	0.13
High-density lipoprotein (mg/dL)	48.90±13.86	43.32±9.74	**0.01**
In-hospital Complication on the Fifth Day			
Recurrent myocardial infarction, %	1 (1.3%)	1 (1.2%)	0.97
Mechanical complication (septal and free wall rupture),%	0 (0.0%)	2 (2.4%)	0.14
Respiratory arrest, %	1 (1.3%)	2 (2.4%)	0.53
Cardiogenic shock, %	1 (1.3%)	0 (0.0%)	0.48
Bradyarrhythmia	2 (3.0%)	11 (13.2%)	0.009
Tachyarrhythmia	8 (10.1%)	23 (27.7%)	0.001
Extrasystole	4 (5.1%)	12 (14.5%)	0.15

Table 2. Analysis of the changes in the levels of interleukin-6 and C-reactive protein at the time of admission and on the fifth day in the depressed and non-depressed groups (mean±SD)

Variable		No Depression	Depression	*P*
Interleukin-6 (mg/dL)	First day	35.34±10.96	46.87±11.96	<0.001
	Fifth day	34.81±9.69	37.39±10.79	0.02
	P	0.81	<0.001	
C-reactive protein (mg/dL)	First day	23.31±7.18	28.94±8.21	0.01
	Fifth day	33.77±11.39	33.15±10.67	0.45
	P	<0.001	0.01	

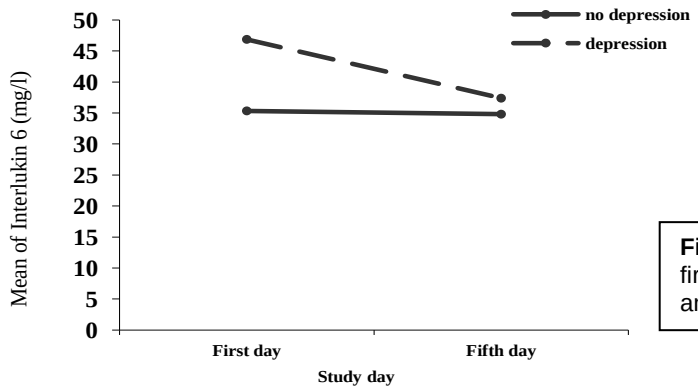

Figure 1. Mean of the level of interleukin-6 on the first and fifth days in the groups with depression and no depression

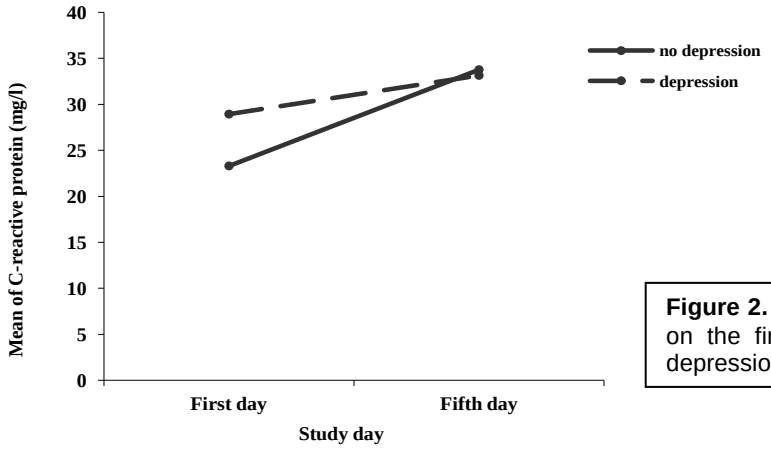

Figure 2. Mean of the level of C-reactive protein on the first and fifth days in the groups with depression and no depression

DISCUSSION

In the present study, we investigated the role of inflammation in the relationship between depression and CAD. We found that in the hospitalization period of patients with acute MI, the changes in the levels of CRP and IL-6—as the established biomarkers of inflammation—were more pronounced in those with depression than in their non-depressed counterparts. In addition, complications such as arrhythmias were more commonly seen in the former group during hospitalization.

Concerning cardiovascular risk factors, we found a higher frequency of some of these risk factors in the depressed patients with acute MI than in their non-depressed counterparts, which is in line with previous studies. [18, 19] For instance, in our study, the HDL level in the depressed patients was found to be significantly lower than that in the others. Some potential mechanisms that are propounded for dyslipoproteinemia in patients with depression include adverse behaviors, unhealthy lifestyle, and reduced exercise capacity. [19] Conversely, declining physical activity predicts more depression symptoms. [20]

We found a higher prevalence of smoking in the depressed group than in the non-depressed one. This finding is concordant with that reported by previous studies insofar as cigarette smoking is frequently co-morbid with depression and it is harder for patients with depression to quit smoking. [21, 22] Two sets of

explanations have been presented for this co-morbidity. Several studies have demonstrated common genetic and environmental influences as the reason for the co-morbidity of smoking and depression. [23, 24] On the other hand, the relationship could be in a causal manner. Depression increases the risk of smoking, or smoking increases the risk of depression. Cigarette smoking could be a result of self-medication for depressive symptoms or smoking may increase the risk of depression. [25, 26] If smoking and hyperlipidemia are more prevalent or more severe in depressed than in non-depressed patients, then depressed patients might be at increased risk for cardiac events not because of their depression, but instead due to these other risk factors.

However, there are several reasons to doubt this possibility. First, some studies which have shown depression to predict cardiac events have failed to find any association between depression and these risk factors. [27, 28] Second, depression has remained an independent predictor of cardiac morbidity and mortality after controlling these risk factors. [29, 30] Third, as we found in the current study, the mean age at the time of the MI occurrence in the depressed patients was less than that in non-depressed ones, which is consistent with some prior studies. The lower age of CAD in depressed patients makes atherosclerotic events or its risk factors a less possibility; therefore, some intrinsic factors other than atherosclerosis risk factors might be responsible as the cause of MI in these patients. [28] With an improved understanding of the pathogenesis of CAD, the most possible factors are certain markers of inflammation as indicated in a variety of recent investigations which have shown that inflammation has a great role in the progression of atherosclerosis. Among the vast array of serologic markers of systemic inflammation, CRP and IL-6 have been the most thoroughly investigated. Possible mechanisms exist for a bidirectional relationship between inflammation and depression. Each one could be the cause or the result of the other one. Another scenario having been previously presented is the contribution of common genetic variants to depressive symptoms and inflammatory markers. [14] We suggest that the relationship between depression and CAD could be mediated by inflammation. Stewart et al, [13] in a cross-sectional study in 2009 among 263 healthy elderly men and women enrolled in the Pittsburg Healthy Project (a 6-year prospective cohort study), found that inflammation might be one of the mechanisms through which depression contributed to cardiovascular risk. A study in 2013 showed that the potential pathway to explain the relationship between depression, inflammation, and increased cardiovascular thrombosis might be found when both platelet activation and inflammation were measured. [31]

The inter-relationships between depression, inflammation, and CAD or its outcome have been previously evaluated and some possibilities have been presented. Depression might induce inflammation, which in turn can mediate the relationship between depression and CAD. Inflammation by itself might also lead to depression. Either depression or inflammation might cause CAD through separate mechanisms; as a result, depression and inflammation might have a common precursor which is linked to CAD. Depression is probably the proximal mediator through which inflammation increases the risk for CAD events. Of course, the relationship between depression, inflammation, and CAD could be more complex and there are other possible scenarios. [32] Nonetheless, only a few studies have examined these possibilities. Vaccarino et al [29] measured CRP and IL-6 in women with suspected coronary ischemia who completed the BDI. They reported that the women with depression had a 70% higher CRP level and a 25% higher IL-6 level than those without depression, and they considered depression to be a significant predictor of CAD. It means that inflammatory biomarkers might explain the

association between depression and CAD. Similarly, Empana et al [33] and Davidson et al [15] suggested that depressive mood was related to CAD due to these inflammatory markers.

With respect to hospital complications, we found that the depressed patients with a higher range of inflammatory factors experienced significantly more brady- and tachyarrhythmias in their hospitalization period than the other patients. This finding is consistent with the data from previous studies which have indicated that the prognostic impact of post-MI depression is related to arrhythmia. [12, 31] Such findings confirm the independent risk associated with elevated BDI scores and demonstrate that the impact of depression is highlighted in patients with arrhythmias. Most studies have shown that patients with atrial fibrillation have an increased incidence of depression and anxiety due to an impaired quality of life. [12, 34, 35] On the other hand, prospective trials have shown that the elevated levels of CRP and other inflammatory factors measured at baseline are associated with adverse cardiovascular prognoses among healthy individuals as well as among those at high risk. The level of IL-6 has been linked to increased morbidities in unstable angina and acute MI. [7]

The present study has a few limitations. We evaluated the complications only in the hospitalization period. A better understanding of this association requires longitudinal studies with longer durations.

Because we measured the depression score once at baseline and in the paper-pencil method, we were unable to assess the possible impact of its changes on CAD events. Another weakness of note is that we did not examine other psychiatric or personality disorders in our patients, which may have negatively impacted our results.

In conclusion, we observed that the depressed patients with acute MI in our study had a higher level of inflammatory factors in their hospitalization period than their non-depressed counterparts and they experienced more complications such as arrhythmias at this time, which might have affected their prognosis. Therefore, it is imperative that we pay more attention to CAD patients with depressed mood in respect of the management and assessment of their prognosis.

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Conflict of Interest: The Authors declare that there is no conflict of interest.

REFERENCES

1. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.

2. Deaton C, Froelicher ES, Wu LH, Ho C, Shishani K, Jaarsma T. The global burden of cardiovascular disease. Eur J Cardiovasc Nurs. 2011;10 Suppl 2:S5-S13.

3. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32(9):2045-2051.

4. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-2207.

5. Kushner I, Broder ML, Karp D. Control of the acute phase response. Serum C-reactive protein kinetics after acute myocardial infarction. J Clin Invest. 1978;61(2):235-242.

6. Gregersen I, Holm S, Dahl TB, Halvorsen B, Aukrust P. A focus on inflammation as a major risk factor for atherosclerotic cardiovascular diseases. Expert Rev Cardiovasc Ther. 2016;14(3):391-403.

7. Gabriel AS, Martinsson A, Wretlind B, Ahnve S. IL-6 levels in acute and post myocardial

infarction: their relation to CRP levels, infarction size, left ventricular systolic function, and heart failure. Eur J Intern Med. 2004;15(8):523-528.

8. Biasucci LM, Liuzzo G, Fantuzzi G, Caligiuri G, Rebuzzi AG, Ginnetti F, et al. Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. Circulation. 1999;99(16):2079-2084.

9. Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol. 1998;31(7):1460-1465.

10. Poole L, Dickens C, Steptoe A. The puzzle of depression and acute coronary syndrome: reviewing the role of acute inflammation. J Psychosom Res. 2011;71(2):61-68.

11. Zuidersma M, Conradi HJ, van Melle JP, Ormel J, de Jonge P. Depression treatment after myocardial infarction and long-term risk of subsequent cardiovascular events and mortality: a randomized controlled trial. J Psychosom Res. 2013;74(1):25-30.

12. De Jonge P, Rosmalen JGM, Kema IP, Doornbos B, van Melle JP, Pouwer F, et al. Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: a critical review of the literature. Neurosci Biobehav Rev. 2010;35(1):84-90.

13. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain Behav Immun. 2009;23(7):936-944.

14. Su S, Miller AH, Snieder H, Bremner JD, Ritchie J, Maisano C, et al. Common genetic contributions to depressive symptoms and inflammatory markers in middle-aged men: the Twins Heart Study. Psychosom Med. 2009;71(2):152-158.

15. Davidson KW, Schwartz JE, Kirkland SA, Mostofsky E, Fink D, Guernsey D, et al. Relation of inflammation to depression and incident coronary heart disease (from the Canadian Nova Scotia Health Survey [NSHS95] Prospective Population Study). Am J Cardiol. 2009;103(6):755-761.

16. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mähönen M, Ngu Blackett K, et al. World Health Organization definition of myocardial infarction: 2008-09 revision. Int J Epidemiol. 2011;40(1):139-146.

17. Beck A, Ward TC, Mendelson M. Beck depression inventory (BDI). Arch Gen Psychiatry. 1961;4(6):561-571.

18. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. Diabetes Care. 2012;35(5):1171-1180.

19. Van Reedt Dortland AKB, Vreeburg SA, Giltay EJ, Licht CMM, Vogelzangs N, van Veen T, et al. The impact of stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression. Psychoneuroendocrinology. 2013;38(2):209-218.

20. Harris AHS, Cronkite R, Moos R. Physical activity, exercise coping, and depression in a 10-year cohort study of depressed patients. J Affect Disord. 2006;93(1-3):79-85.

21. Rohde P, Kahler CW, Lewinsohn PM, Brown RA. Psychiatric disorders, familial factors, and cigarette smoking: II. Associations with progression to daily smoking. Nicotine Tob Res. 2004;6(1):119-132.

22. Roohafza H, Omidi R, Alinia T, Heidari K, Farshad M, Davari H, et al. Psychological and Familial Factors of Depression in Relation to Adolescent Smoking Behavior. Adv Biomed Res. 2017;6(1):3.

23. Audrain-McGovern J, Lerman C, Wileyto EP, Rodriguez D, Shields PG. Interacting effects of genetic predisposition and depression on adolescent smoking progression. Am J Psychiatry. 2004;161(7):1224-1230.

24. Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: Tests of causal linkages using a longitudinal birth cohort. Br J Psychiatry. 2010;196(6):440-446.

25. Kang E, Lee J. A longitudinal study on the causal association between smoking and depression. J Prev Med Public Heal. 2010;43(3):193-204.

26. Steuber TL, Danner F. Adolescent smoking and depression: which comes first? Addict Behav. 2006;31(1):133-136.

27. Mykletun A, Overland S, Aarø LE, Liabø H-M, Stewart R. Smoking in relation to anxiety and depression: evidence from a large population survey: the HUNT study. Eur Psychiatry. 2008;23(2):77-84.

28. Munafò MR, Hitsman B, Rende R, Metcalfe C, Niaura R. Effects of progression to cigarette smoking on depressed mood in adolescents: evidence from the National Longitudinal Study of Adolescent Health. Addiction. 2008;103(1):162-171.

29. Vaccarino V, Johnson BD, Sheps DS, Reis SE, Kelsey SF, Bittner V, et al. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. J Am Coll Cardiol. 2007;50(21):2044-2050.

30. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry. 2010;68(8):748-754.

31. Patel D, Mc Conkey ND, Sohaney R, Mc Neil A, Jedrzejczyk A, Armaganijan L. A systematic review of depression and anxiety in patients with atrial fibrillation: the mind-heart link. Cardiovasc Psychiatry Neurol. 2013;2013:159850.

32. Williams MS, Rogers HL, Wang N-Y, Ziegelstein RC. Do platelet-derived microparticles play a role in depression, inflammation, and acute coronary syndrome? Psychosomatics. 2014;55(3):252-260.

33. Empana JP, Sykes DH, Luc G, Juhan-Vague I, Arveiler D, Ferrieres J, et al. Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Circulation. 2005;111(18):2299-2305.

34. Francis JL, Weinstein AA, Krantz DS, Haigney MC, Stein PK, Stone PH, et al. Association between symptoms of depression and anxiety with heart rate variability in patients with implantable cardioverter defibrillators. Psychosom Med. 2009;71(8):821-827.

35. Thomas SA, Friedmann E, Lee H-J, Son H, Morton PG. Changes in anxiety and depression over 2 years in medically stable patients after myocardial infarction and their spouses in the Home Automatic External Defibrillator Trial (HAT): a longitudinal observational study. Heart. 2011;97(5):371-381.