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Review

DEPRESSION AND OXIDATIVE STRESS INTERACTION IN STABLE CORONARY HEART DISEASE

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It was concluded that depression (D) is an independent risk factor for cardiovascular diseases (CVD), and is not related to other previously determined cardiac risk factors. Compared with non-depressed patients, the risk of cardiac arrest increased in less severely depressed patients. D worsens the CVD prognosis by significantly increasing the risk of recurrent coronary heart disease (CHD). Some studies suggest that OS directly increases the risk of D in patients with CVD. Oxidative stress (OS) is considered an emergency mechanism that relates to both CVD and D pathophysiology. The common risk factors increase the production of OS and reduce antioxidant defences, thereby promoting the occurrence and development of interacted ischaemic CVD and D. At present, there is insufficient evidence that routine screening of D in patients with CHD will ultimately help improve the patient's condition. This review reiterates the need for a multidisciplinary approach, which is necessary to understand, diagnose and then treat this frequent co-morbid condition of CHD and D. Assessment of OS markers could modify risk stratification, diagnosis and prevention and treatment of patients with both CHD and D, in patients with and without previous cardiac history.

Key words: *stable coronary heart disease, mental health disorders, reactive oxygen species, malondialdehyde, glutatione peroxidase.*

INTRODUCTION

Epidemiological data indicate that cardiovascular disease (CVD) and depression (D) pose a huge global disease burden. The Global Burden of Disease 2016 study showed that CVD was the number one reason of years of life lost globally (Moraga, 2017). Also, it was reported that major depressive disorder was the third cause of years lived with disability after low back pain and headache disorders (GBD, 2017; 2018). Both coronary heart disease (CHD) and D are the leading causes of disability in high-income countries, and are expected to become so globally by 2030 (Murray and Lopez, 2013). Over the past 20 years, research has found that not only is D more common in cardiac patients than in the general population, but D is also a risk factor for cardiac morbidity and mortality, independent of traditional risk factors (Huffman *et al*., 2013). Besides impairing patients' quality of life, D has profound negative effects on the long-term prognosis of individuals with any type of cardiovascular disorder. These facts further underscore the importance for proper treatment of D in patients with CVD (Yekehtaz *et al*., 2013). The role of oxidative stress (OS) in CVD processes, such as atherogenesis, ischaemic-reperfusion injury and cardiac remodelling, has been increasingly

recognised in the past few decades. Much of the recent research in these areas has focused on the role of the immune system and inflammation in both depression and CVD. Currently, an increasing number of studies suggest that levels of OS markers in body fluids are raised (Vichova and Motovska, 2013). The common risk factors increase the production of reactive oxygen species (ROS) and reduce antioxidant (AO) defences, thereby promoting the occurrence and development of interacted ischaemic CVD and D (Lin *et al*., 2019).

The aim of this paper was to provide a narrative review of OS states associated with the risk of CVD in depressed patients. There is a need to find effective screening tools and therapies to control CVD and D. At present, there is insufficient evidence showing that routine screening of D in patients with CHD will ultimately help improve the patient's condition (Hasnain *et al*., 2011), which is why the study of the relationship between CHD, D, and OS is very important.

CARDIOVASCULAR DISEASE

According to the World Health Organization data, CVD is the leading cause of death globally, taking an estimated 17.9 million lives each year, an estimated 31% of all deaths worldwide (World Health Organization, 2017). Prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths steadily increased from 12.1 million in 1990, reaching 18.6 million in 2019 around the globe (Roth *et al*., 2020). In Latvia, CVD was the most common cause of death — 54.6% of all deaths, according to 2019 data (Ērglis *et al*., 2020). CVD is a group of diseases that include both the heart and blood vessels (World Health Organization, 2011), thereby including CHD and coronary artery disease (CAD), and several other conditions. CAD usually use to refer to the pathologic process affecting the coronary arteries (usually atherosclerosis), whilst CHD includes the diagnoses of angina pectoris, myocardial infarction, and silent myocardial ischaemia. CHD mortality results from CAD (Sanchis-Gomar *et al*., 2016). CAD continues to be a major focus of clinical and epidemiological research. Non-modifiable cardiovascular risk factors, such as age, gender, family history, and race, as well as modifiable risk factors, such as hypertension, weight, smoking, sedentary lifestyle, abnormal lipid profiles, inflammatory markers, diabetes, metabolic syndrome, and subclinical CAD, are associated with increased cardiovascular risk (Kuller *et al*., 2006; Khawaja *et al*., 2009). There is a lack of a definitive correlation between high-risk profiles, biological profiles, and the occurrence of CAD. A number of psychological states and traits, such as D, anxiety, anger, and stress, have also been implicated as potential risk factors for CAD (Khawaja *et al*., 2009).

DEPRESSION AND CARDIOVASCULAR DISEASE

A multitude of studies over the past 15 years have confirmed that depression is associated with adverse cardiovascular outcomes, independent of traditional risk factors. D in cardiac disease is common, persistent, under-recognised, and deadly. The prevalence of D is, compared with the general population, significantly higher in patients with CHD (Whooley and Wong, 2013).

There are three extensively replicated epidemiological observations regarding CHD and depression: 1) these conditions are highly comorbid, 2) depression is associated with increased risk of incident CHD and vice versa, and 3) depression is a strong predictor of poor prognosis in people with CHD (Khandaker *et al*., 2020). Depression, a frequently occurring disease, has a bidirectional relationship with ischaemic CVD and partially shares common risk factors (such as obesity and diabetes) and mechanisms (such as inflammation and OS) with CVD, which are correlated with atherosclerotic disease activity (Lin *et al*., 2019). More than one-fifth of all patients with CHD are depressed (with the risk of D highest in the most severe CHD cases), and up to one-third of them report elevated depressive symptoms. These are prevalence figures that are at least four times greater than in the general population (De Hert *et al*., 2018). A meta-analysis demonstrated that the overall risk of depressed but otherwise healthy individuals developing heart disease is 64% higher than for those without D (Van der Kooy *et al*., 2007). Five meta analyses reported a 60–80% increased risk of CHD in patients with D (Lin *et al*., 2019). If we look at figures from the community through to those who are hospitalised, we see rates of depression of 10% in general practice clinics (Cassano and Fava, 2002; Brown *et al*., 2009), which then increases to up to 30% in those with CHD in outpatient clinics (Dhar and Barton, 2016). In several studies, 17 to 44 per cent of patients with CAD also have a diagnosis of major D (Yekehtaz *et al*., 2013). Depressive symptoms are diagnosed in less than 15% of cases (Guck *et al*., 2011) and only 25% of patients with CHD and severe D are diagnosed with psycho-emotional disorder and approximately only half of them receive adequate antidepressant (AD) therapy (Moryś *et al*., 2016). Another 30–45% of patients with CHD suffer from clinically significant symptoms consistent with a minor D (Celano and Huffman, 2011), and this is a risk factor for the future of a major D episode in patients with CHD, associated with an increased risk of secondary acute ischaemic events, lower interventions and increased mortality, regardless of traditional cardiac risk factors (Januzzi *et al*., 2000; Barth *et al*., 2004; van Melle *et al*., 2004). Among patients with CVD hospitalised for acute cardiac events and found to meet criteria for depression during or shortly after admission, approximately 50–70% had ongoing depressive symptoms that preceded their cardiac event (Glassman *et al*., 2006; Lesperance *et al*., 2007) this finding is consistent with literature that describes persistent depression in patients with stable CAD. Furthermore, rather than being a transient reaction to a cardiac event, depression for many patients exists for months or years before and persists long after the event (Glassman *et al*., 2006; Lesperance *et al*., 2007; Huffman *et al*., 2011; 2013). Basing on the literature in patients with CVD, D is often chronic and recurrent. Among patients with CVD hospitalised for acute cardiac events and found to meet criteria for D during or shortly after admission, ap-

proximately 50–70% had ongoing depressive symptoms that preceded their cardiac event. This finding is consistent with literature that describes persistent D in patients with stable CAD. Depressed patients with unstable CAD appear to be at even greater risk for poor cardiac outcomes (Yekehtaz *et al*., 2013). D also has a significant effect on the outcome of cardiovascular diseases in patients with stable CHD (Frasure-Smith and Lespérance, 2010). Several previous papers suggest that depression can influence cardiovascular function, and vice versa cardiovascular diseases also influence affective states (Trebatická *et al*., 2017). Compared with non-D patients, the risk of cardiac arrest increased in less severely depressed patients. The authors concluded that D is an independent risk factor for CHD and is not related to other previously determined cardiac risk factors. This association persisted across all demographic groups in this well designed, case-control study (Khawaja *et al*., 2009). In addition, major D worsens the cardiovascular prognosis, particularly for CHD, by significantly increasing the risk of recurrent CHD. The relative risk of death in depressed patients during the 18 months following the cardiac event is twice that in non-depressed patients (Chauvet-Géliniera *et al*., 2013). Recent studies have also shown the harmful nature of D after myocardial infarction in terms of rehospitalisation or getting access to cardiac rehabilitation, which is particularly beneficial in this context (Myers *et al*., 2012). In fact, non-completion rates in cardiac rehabilitation have been shown to be in the order of 44% compared to 29% in the non-depressed group (Swardfager *et al*., 2011). Although CVD and D are very different pathologies, accumulating evidence reveals that CVD and D both are correlated and share common risk factors, particularly obesity, diabetes, and hypertension (Khawaja *et al*., 2009). Researchers suggest a hybrid model like the hybrid dependence of D and CHD, in which there is a bi-directional relationship between D and inflammation (Matthews, 2010). It is worth noting that chronic inflammation of low degree is an inalienable component of D (Adifbair *et al*., 2016). The inflammatory hypothesis as a common physio-pathological pathway in mood disorders and CVD is being put forward more and more frequently. CHD and D share some common patho-physiological characteristics and risk factors, such as increased production of pro-inflammatory cytokines, endothelial dysfunction, blood flow abnormalities, decreased glucose metabolism, elevated plasma homocysteine levels and disorder in vitamin D metabolism (Frasure-Smith and Lespérance, 2010), cell death signalling pathway, microbiome-gut-brain axis (Lin *et al*., 2019), increased susceptibility to blood coagulation due to changes in several stages of the coagulation cascade, including activation and aggregation of platelets, OS, subclinical hypothyroidism, decrease in the number of circulating endothelial progenitor cells and associated processes of arterial reconstruction, increased variability of heart rate, and the presence of genetic factors (Nemeroff and Goldschmidt-Clermont, 2012). Individuals with comorbid depression and CVD may also have imbalances in homeostatic regulation of different biological systems, with alterations observed in the hypothalamus–pituitary–adrenal axis, renin–angiotensin–aldosterone system, and serotonin/kynurenine pathways that are accompanied by inflammation and endothelial dysfunction (Halaris, 2017; Mattina *et al*., 2019). Sympathetic outflow is increased in depressed patients as compared to non-depressed patients through negative stress effects of catecholamines on the heart, blood vessels, and platelets. Further support of the catecholamine association with D is that increased urinary catecholamine levels are associated with negative emotions and decreased social support, and high norepinephrine and low platelet serotonin levels are associated with MI and D. D-induced altered autonomic tone associated with low heart rate variability leading to dysrhythmias (Khawaja *et al*., 2009). The diagnosis of D can be difficult in people with CVD, as D symptoms such as fatigue and low energy are common in people with CVD and may also be a side effect of some drugs such as beta blockers used to treat CVD. The diagnosis may be further complicated in such patients by their responses to their disease, which may include denial, avoidance, withdrawal, and anxiety (Carney and Freedland, 2008; Goodman *et al*., 2008). Given the sometimes sudden onset of a cardiovascular event, the normal psychological reaction to disease requires the patient to adapt, which leads to a certain physiological D in mood, the time to come to terms with the possible loss related to the disease and the sometimes very much changed future prospects for life (Chauvet-Géliniera *et al*., 2013). In a study of hospitalised patients with a variety of cardiac conditions, those who met criteria for clinical D during admission had improvement of adherence (to diet, exercise, and medication) if their D improved following hospitalisation. This suggests that reduced adherence to key secondary prevention behaviours in D cardiac patients may be modifiable with treatment of the D symptoms (Bauer *et al*., 2012). Considering the negative cardiac and cognitive effects of persistent D in patients with CHD, adequate treatment with AD is a clinically important need in the case of CHD. Patients who respond to AD therapy within the first year of treatment have been shown to experience significantly lower rates of morbidity and mortality (Jiang *et al*., 2011). Several studies have shown that the new generation of AD, in particular selective serotonin reuptake inhibitors, are well tolerated, have a satisfactory efficacy-tolerance profile and are easy to use in patients with cardiovascular disease (Chauvet-Géliniera *et al*., 2013). In addition, these molecules show clinical efficacy, acting on physio-pathological elements by improving endothelial function while reducing the concentration of inflammation markers (C-reactive protein, interleukin-6) (Pizzi *et al*., 2009). In the same way, a meta-analysis showed that selective serotonin re-uptake inhibitors used in the wake of an acute coronary syndrome led to fewer re-hospitalisations (Mazza et al., 2010; Chauvet-Géliniera *et al*., 2013).

CARDIOVASCULAR DISEASE, DEPRESSION AND OXIDATIVE STRESS

Oxidative stress. OS is defined by the imbalance between the production of reactive oxygen species (ROS) and the endogenous AO mechanisms to counteract the effects of ROS or to repair the resulting damages (Antoniades *et al*., 2009). Any oxidative imbalance resulting in the accumulation of oxidants will inflict oxidative damage on cells, such as al-

teration of cellular macromolecules, lethal changes in genetic materials, such as DNA and RNA, an increase in the rate of cell death by programmed- and non-programmed-cell death (apoptosis / pyroptosis / necroptosis / ferroptosis or necrosis), and structural damage to tissues and organs (Dhama *et al*., 2019). Accumulation of oxidants induces lipid peroxidation and disturbances in physiological adaptation and cellular signalling pathways, which together inflict OS (Puppel *et al*., 2015). Lipid peroxidation products, such as malondialdehyde (MDA), cause changes in the metabolism of dopamine, induce the synthesis of protein reactive dopaminergic toxins (Rees, 2007) and have an inhibitory effect on the reduction of nucleotide excision by direct interaction with cellular repair proteins (Feng, 2006). One of the most important and extensively studied oxidants is MDA. In the field of modern biology to assess OS, MDA is an extensively utilised biomarker. MDA is one of the most commonly used indicators of lipid peroxidation (Rio *et al*., 2005) and can be more resistant than other markers of the late stage (4-Hydroxynonenal, 8-isoprotane) of lipid peroxidation (Mazereeuw *et al*., 2017). The MDA molecule is stable and relatively inactive, compared with free radicals; however, it can not only significantly affect the stability and function of cells, but can also be indirectly involved in the OS reaction (Voicehovskis, 2013). The most potent AO actions are mediated by enzymes, especially superoxide glutathione peroxidase (GPx) (Dhama *et al*., 2019). The main biological role of GPx in the body is protection against damage caused by free radicals and active forms of oxygen (Vaváková *et al*., 2015). The level of serum GPx is an excellent measure of the oxidative status of an individual and is most often employed in diagnostics (Dhama *et al*., 2019). OS is an emerging mechanism relevant to both CVD and D pathophysiology (Adifbair *et al*., 2016).

Oxidative stress and depression. Studies have suggested that depression was accompanied by OS dysregulation, including abnormal total AO capacity, AO, free radicals, oxidative damage and autoimmune response products (Liu et al., 2015; Adifbair *et al*., 2016). The oxidative products include products of oxidative damage of lipoproteins, proteins and DNA in D. Abnormal MDA levels in D have been reported (Bal *et al*., 2012; Liu *et al*., 2015). Increased lipid peroxidation has been associated with the presence and severity of D symptoms (Mazereeuw *et al*., 2017). D is associated not only with inflammatory reactions taking place in the body, but also with an increased amount of pro-inflammatory cytokines and increased lipid peroxidation leading to OS (Vaváková *et al*., 2015). Thus, many clinical studies have accordingly associated D with an increase in the level of OS markers and lower overall AO activity (Sarandol *et al*., 2007; Cumurcu *et al*., 2009; Adifbair *et al*., 2016; Black *et al*., 2015). OS can also contribute to depressive disorder by acting on established aetiopathological components of D, including lipid signalling, monoamine regulation and inflammation (Maes *et al*., 2011; Moylan *et al*., 2014). The higher GPx activity might be a compensatory mechanism for the excess production of free radicals in D patients (Liu *et al*., 2015).

Oxidative stress and cardiovascular disease. OS activates the immune inflammatory pathways (Moylan *et al*., 2014; Liu *et al*., 2015). It was found that serum GPx and MDA were significantly greater in CHD patients than in healthy controls (Cheraghi *et al*., 2019). Moreover, OS is considered an important mechanism for the development of CVD (Kander *et al*., 2017). In the past two decades, numerous studies have demonstrated the importance of OS in the development of atherosclerosis and ischaemia-reperfusion injury (Vichova and Motovska, 2013). Inflammation, OS and activation of the hypothalamus–pituitary–adrenal axis are D and cardiac co-morbidities (Chauvet-Géliniera *et al*., 2013). OS may be an early causative factor in CVD pathology rather than a late consequence (Trebatická *et al*., 2017). Results of studies (Pezeshkian *et al*., 2001) showed that MDA levels increased significantly in heart diseases. Some other studies also reported increase of MDA and GPx levels in patients with CAD (Pezeshkian *et al*., 2001).

Studies have also reported increase of MDA and GPx levels in patients with coronary artery disease. GPx activation was significantly higher in patients with coronary artery disease than in healthy controls (Kaya *et al*., 2012). It has been demonstrated that AO enzyme activities are reduced in CHD, and this is linked to the increased disease risk. Many studies have indicated that free radical generation increases and AO defences decrease in response to increased OS in CHD patients. Activity levels of the AO enzymes GPx, and non-enzymatic AOs, are considered as predictors of CHD (Vichova and Motovska, 2013; Cheraghi *et al.*, 2019). Heart failure under both acute and chronic conditions is associated with increased levels of OS markers (eg, MDA, GPx). These findings suggest that CHD status may be determined by OS activity rather than the degree of coronary stenosis. Elevated concentrations of a variety of OS markers were linked with a more frequent occurrence of cardiac events (Vichova and Motovska, 2013).

Oxidative stress as a mediating factor between depression and coronary heart disease. The hypothesis that inflammation and OS are factors in both mood disorders and CHD seems to be growing stronger (Chauvet-Géliniera *et al*., 2013). Increased lipid peroxidation may be particularly relevant to D symptoms among patients with CAD, given the involvement of OS in that condition (Mazereeuw *et al*., 2017). Moreover, other research confirmed that the OS directly increases the risk of D in patients with CVD, whereas it increases the risk of CVD in depressed people. In summary, the common risk factors increase the production of OS and reduce AO defences, thereby promoting the occurrence and development of interacted ischaemic CVD and D (Lin *et al*., 2019). It has been shown that depressed patients have elevated levels of platelet adhesion and aggregation leading increased risk for cardiovascular events (Nezafati *et al*., 2015). OS can independently and directly affect stroke, CHD and D (Lin *et al*., 2019). Several pieces of evidence have pointed to the involvement of altered tryptophan metabolism in inflammation and the development of mood disorders (Mattina *et al*., 2019). Higher levels of serum kyn-

urenine compared with tryptophan, have been demonstrated in CVD patients and provide evidence for altered kynurenine synthesis (Wirleitner *et al*., 2003). The kynurenine/tryptophan ratio, as well as other kynurenine metabolites, are strongly associated with increased risk of poor outcomes following stroke (Brouns *et al*., 2010) and cardiovascular related mortality in the general population (Zuo *et al*., 2016). Furthermore, CHD patients with D show greater serum kynurenine/tryptophan ratio compared with those without D (Nikkheslat *et al*., 2015), suggesting that D coupled with CHD leads to increased activation of the kynurenine pathway (Mattina *et al*., 2019). Activation of the kynurenine pathway following chronic inflammation is modified to increase the production of neurotoxic metabolites and release ROS, resulting in lipid peroxidation and neurodegenerative brain changes (Wang *et al*., 2015; Jeon and Kim, 2017).

Oxidative stress and antidepressant therapy. There is an increasing body of evidence supporting that D may be associated with changes in OS markers and that AD agents (especially long-term treatment) may increase AO defences. It is possible that augmentation of AO defences may be one of the mechanisms underlying the neuroprotective effects of ADs observed in the treatment of D (Celano and Huffman, 2011). Meta-analysis supports the facts that the serum total AO capacity, paraoxonase and AO levels are lower, and the serum free radical and oxidative damage product levels are higher, in D patients than in controls. Also, the AO levels are increased and the oxidative damage product levels are decreased after AD medication (Liu *et al*., 2015). In fact, the use of selective serotonin reuptake inhibitors may prevent developing atherosclerotic plaques and also arterial thrombosis (Nezafati *et al*., 2015). Normalisation of the levels of ROS and AO activity after successful AD therapy (Cumurcu *et al*., 2009) suggests that OS mechanisms can be especially important in the study of pathophysiology and prognosis of D (Adifbair *et al*., 2016). Among patients with heart failure**,** those who respond to AD therapy within the first year of treatment have been shown to experience significantly lower rates of morbidity and mortality (Jiang *et al*., 2011). Several lines of evidence indicate that different cardiovascular considerations should be evaluated in patients who need to take AD medication (Yekehtaz *et al*., 2013).

CONCLUSION

Despite the potentially important role of the OS in pathogenesis of CHD and D, there are only a few studies on the role of OS in the development of D in patients with CHD. Furthermore, the role of OS in stable CHD recurrence in patients with stable CHD and D has not been studied previously. Assessment of OS markers could modify risk stratification, diagnosis and prevention and treatment of patients with both CVD and D, in patients with and without previous cardiac history. Appropriate, individualised AD therapy by reducing the level of OS may help reduce the risk of CVD (both primary event and recurrence) in patients with D. This requires further longitudinal, large-sample size, cohort studies to provide more conclusive outcomes. Summarising all of the above, a retrospective case-control study is necessary to identify and examine the relationship between the severity of D symptoms and indicators of OS in primary stable CDH patients and in patients with recurrent stable CHD.

REFERENCES

Adifbair, A., Saleem, M., Lanctôt, K., Herrmann, N. (2016). Potential biomarkers for depression associated with coronary artery disease: A critical review. *Curr. Mol. Med.,* **16**, 137–164.

Antoniades, C., Antonopoulos, A. S., Bendall, J. K., Channon, K. M. (2009). Targeting redox signaling in the vascular wall: from basic science to clinical practice. *Curr. Pharm. Des.,* **15** (3), 329–342.

Bal, N., Acar, S. T., Yazıcı, A., Yazıcı, K., Tamer, L. (2012). Altered levels of malondialdehyde and vitamin E in major depressive disorder and generalized anxiety disorder. *J. Psychiatry Neurol. Sci.,* **25** (3), 206–211.

Barth, J., Schumacher, M., Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosom. Med.,* **66** (6), 802–813.

Bauer, L. K., Caro, M. A., Beach, S. R., Mastromauro, C. A., Lenihan, E., Januzzi, J. L., Huffman, J. C. (2012). Effects of depression and anxiety improvement on adherence to medication and health behaviors in recently hospitalized cardiac patients. *Amer. J. Cardiol.,* **109** (9), 1266–1271.

Black, C. N., Bot, M., Scheffer, P. G., Cuijpers, P., Penninx, B. W. (2015). Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology,* **51**, 164–175.

Brouns, R., Verkerk, R., Aerts, T., Surgeloose D., Wauters, A., Scharpé, S., De Deyn, P. P. (2010). The role of tryptophan catabolism along the kynurenine pathway in acute ischemic stroke. *Neurochem. Res.,* **35** (9), 1315–1322.

Brown, A. D., Barton, D. A., Lambert, G. W. (2009). Cardiovascular abnormalities in patients with major depressive disorder: autonomic mechanisms and implications for treatment. *CNS Drugs*, **23** (7), 583–602.

Huffman, J. C., Mastromauro, C. A., Sowden, G. L., Wittmann, C., Rodman, R., Januzzi, J. L. (2011). A collaborative care depression management program for cardiac inpatients: Depression characteristics and in-hospital outcomes. *Psychosomatics,* **52** (1), 26–33.

Carney, R. M., Freedland, K. E. (2008). Depression in patients with coronary heart disease. *Amer. J. Med.,* **121** (11, Suppl 2), S20–S27.

Cassano, P., Fava, M. (2002). Depression and public health: An overview. *J. Psychosom. Res.,* **53** (4), 849–857.

Celano, C. M., Huffman, J. C. (2011). Depression and cardiac disease: A review. *Cardiol. Rev.,* **19** (3), 130–142.

Chauvet-Géliniera, J. C., Trojak B., Vergès-Patois B., Cottin Y., Bonin B. (2013). Review on depression and coronary heart disease. *Arch. Cardiovasc. Dis.,* **106** (2), 103–110.

Cheraghi, M., Ahmadvand, H., Maleki, A., Babaeenezhad, E., Shakiba, S., Hassanzadeh, F., (2019). Oxidative stress status and liver markers in coronary heart disease. *Rep. Biochem. Mol. Biol.,* **8** (1), 49–55.

Cumurcu, B. E., Ozyurt, H., Etikan I., Demir S., Karlidag R. (2009). Total antioxidant capacity and total oxidant status in patients with major depression: Impact of antidepressant treatment. *Psychiatry Clin. Neurosci.,* **63** (5), 639–645.

De Hert, M., Detraux, J., Vancampfort, D. (2018). The intriguing relationship between coronary heart disease and mental disorders. *Dialogues Clin. Neurosci.,* **20** (1), 31–40.

Dhama, K., Latheef, S. K., Dadar, M., Samad, H. A., Munjal, A., Khandia, R., Karthik, K., Tiwari, R., Yatoo, M. I., Bhatt, P., Chakraborty, S., Singh, K. P., Iqbal, H., Chaicumpa, W., Joshi, S. K. (2019). Biomarkers in stress

related diseases/disorders: Diagnostic, prognostic, and therapeutic values. *Front Mol. Biosci.,* **6**, p. 91.

Dhar, A. K., Barton, D. A. (2016). Depression and the link with cardiovascular disease. *Front Psychiatry,* **7**, 33.

Ērglis, A., Dzērve-Tāluts, V., Bajāre, I. (2020). *Latvijas iedzīvotāju kardiovaskulāro un citu neinfekcijas slimību riska faktoru šķērsgriezuma pētījums* [Cross-sectional study of cardiovascular and noninfectious diseases risk factors among Latvia's inhabitants]. Latvijas Universitātes Kardioloģijas un reģeneratīvās medicīnas zinātniskais institūts, Rīga. 13 pp. (in Latvian). https://esparveselibu.lv/sites/default/files/2020-10/LATVIJAS%20IEDZĪVOTĀJU%20KARDIOVASKULĀRO%20%20UN%20CITU%20NEINFEKCIJAS%20SLIMĪBU%20RISKA%20FAKTORU%20ŠĶĒRSGRIEZUMA%20PĒTĪJUMS%20.pdf (accessed 12.03.2022).

Feng, Z., Hu, W., Marnett, L. J., Tang, M. S. (2006). Malondialdehyde, a major endogenous lipid peroxidation product, sensitizes human cells to UV and BPDE-induced killing and mutagenesis through inhibition of nucleotide excision repair. *Mutat. Res.,* **601** (1–2), 125–136.

Frasure-Smith, N., Lespérance, F. (2010). Depression and cardiac risk: Present status and future directions. *Heart,* **96** (3), 173–176.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet,* **392** (10159), 1789–1858.

Glassman, A. H., Bigger, J. T., Gaffney, M., Shapiro, A. P., Swenson, J. R. (2006). Onset of major depression associated with acute coronary syndromes: Relationship of onset, major depressive disorder history, and episode severity to sertraline benefit. *Arch. Gen. Psychiatry,* **63** (3), 283–288.

Goodman, J., Shimbo D., Haas, D. C., Davidson, K. W., Rieckmann, N. (2008). Incident and recurrent major depressive disorder and coronary artery disease severity in acute coronary syndrome patients. *J. Psychiatr. Res.,* **42** (8), 670–675.

Guck, T. P., Kavan, M. G., Elsasser, G. N., Barone, E. J. (2011). Assessment and treatment of depression following myocardial infarction. *Amer. Fam. Physician,* **64** (4), 641–648.

Halaris, A. (2017). Inflammation-associated co-morbidity between depression and cardiovascular disease. *Curr. Top Behav. Neurosci.,* **31**, 45–70.

Hasnain, M., Vieweg, W. V., Lesnefsky, E. J., Pandurangi, A. K. (2011). Depression screening in patients with coronary heart disease: A critical evaluation of the AHA guidelines. *J. Psychosom. Res.,* **71** (1), 6–12.

Huffman, J. C., Celano, C. M., Beach, S. R., Motiwala, S. R., Januzzi, J. L. (2013). Depression and cardiac disease: Epidemiology, mechanisms, and diagnosis. *Cardiovasc. Psychiatry Neurol.,* **2013**, 695925.

Januzzi, J. L., Jr, Stern, T. A., Pasternak, R. C., DeSanctis, R. W. (2000). The influence of anxiety and depression on outcomes of patients with coronary artery disease. *Arch. Intern. Med.,* **160** (13), 1913–1921.

Jeon, S. W., Kim, Y. K. (2017). Inflammation-induced depression: Its pathophysiology and therapeutic implications. *J. Neuroimmunol.,* **313**, 92–98.

Jiang, W., Krishnan, R., Kuchibhatla, M., Cuffe, M. S., Martsberger, C., Arias, R. M., O'Connor, C. M., SADHART-CHF Investigators (2011). Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF Study). *Amer. J. Cardiol.,* **107** (4), 545–551.

Kander, M. C., Cui, Y., Liu, Z. (2017). Gender difference in oxidative stress: A new look at the mechanisms for cardiovascular diseases. *J. Cell Mol. Med.,* **21** (5), 1024–1032.

Kaya, Y., Çebı, A., Söylemez, N., Demır, H., Alp, H. H., Bakan, E. (2012). Correlations between oxidative DNA damage, oxidative stress and coen-zyme Q10 in patients with coronary artery disease. *Int. J. Med. Sci.,* **9** (8), 621–626.

Khandaker, G. M., Zuber, V., Rees, J., Carvalho, L., Mason, A. M., Foley, C. N., Gkatzionis, A., Jones, P. B., Burgess, S. (2020). Shared mechanisms between coronary heart disease and depression: Findings from a large UK general population-based cohort. *Mol. Psychiatry,* **25** (7), 1477–1486.

Khawaja, I. S., Westermeyer, J. J.., Gajwani, P., Feinstein, R. E. (2009). Depression and coronary artery disease: The association, mechanisms, and therapeutic implications. *Psychiatry (Edgmont)*, **6** (1), 38–51.

Kuller, L. H., Arnold, A. M., Psaty, B. M., Robbins, J. A., O'Leary, D. H., Tracy, R. P., Burke, G. L., Manolio, T. A., Chaves, P. H. M. (2006). 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Arch. Intern. Med.,* **166** (1), 71–78.

Lespérance, F., Frasure-Smith, N., Koszycki, D., Laliberté, M. A., van Zyl, L. T., Baker, B., Swenson, J. R., Ghatavi, K., Abramson, B. L., Dorian, P., Guertin, M. C., CREATE Investigators (2007). 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,* **297** (4), 367–379.

Lin, D., Wang, L., Yan, S., Zhang, Q., Zhang, J. H., Shao, A. (2019). The role of oxidative stress in common risk factors and mechanisms of cardiocerebrovascular ischemia and depression. *Oxid. Med. Cell Longev.,* **2019**, 2491927.

Liu, T., Zhong S., Liao, X., Chen J., He, T., Lai, S., Jia Y. (2015). A meta-analysis of oxidative stress markers in depression. *PLoS One,* **10** (10), e0138904.

Maes, M., Galecki, P., Chang, Y. S., Berk, M. (2011). A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **35** (3), 676–692.

Matthews, K. A., Schott, L. L., Bromberger, J. T., Cyranowski, J. M., Everson-Rose, S. A., Sowers, M. (2010). Are there bidirectional associations between depressive symptoms and C-reactive protein in mid-life women? *Brain Behav. Immun.,* **24** (1), 96–101.

Mattina, G. F., Van Lieshout, R. J., Steiner, M. (2019). Inflammation, depression and cardiovascular disease in women: The role of the immune system across critical reproductive events. *Ther. Adv. Cardiovasc. Dis.,* **13**, doi: 10.1177/1753944719851950.

Mazereeuw, G., Herrmann, N., Andreazza, A. C., Scola, G., Ma, D., Oh, P. I., Lanctôt, K. L. (2017). Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. *Brain Behav. Immun.,* **60**, 136–141.

Mazza, M., Lotrionte, M., Biondi-Zoccai, G., Abbate, A., Sheiban, I., Romagnoli, E. (2010). Selective serotonin reuptake inhibitors provide significant lower re-hospitalization rates in patients recovering from acute coronary syndromes: Evidence from a meta-analysis. *J. Psychopharmacol.,* **24** (12), 1785–1792.

Moryś, J. M., Bellwon, J., Adamczyk, K., Gruchała, M. (2016). Depression and anxiety in patients with coronary artery disease, measured by means of self-report measures and clinician-rated instrument. *Kardiol. Pol.,* **74** (1), 53–60.

Moylan, S., Berk, M., Dean O. M., Samuni Y., Williams, L. J., O'Neil, A., Hayley, A. C., Pasco, J. A., Anderson, G., Jacka, F. N., Maes, M. (2014). Oxidative & nitrosative stress in depression: why so much stress? *Neurosci. Biobehav. Rev.,* **45**, 46–62.

Murray, C. J., Lopez, A. D. (2013). Measuring the global burden of disease. *New Engl. J. Med.,* **369** (5), 448–57.

Myers, V., Gerber, Y., Benyamini, Y., Goldbourt, U., Drory, Y. (2012). Post-myocardial infarction depression: Increased hospital admissions and reduced adoption of secondary prevention measures — a longitudinal study. *J. Psychosom. Res.,* **72** (1), 5–10.

Nemeroff, C. B., Goldschmidt-Clermont, P. J. (2012). Heartache and heartbreak — the link between depression and cardiovascular disease. *Nat. Rev. Cardiol.,* **9** (9), 526–539.

Nezafati, M. H, Vojdanparast, M., Nezafati, P. (2015). Antidepressants and cardiovascular adverse events: A narrative review. *ARYA Atheroscl,* **11** (5), 295–304.

Nikkheslat, N., Zunszain, P. A, Horowitz, M. A, Barbosa, I. G., Parker, J. A., Myint, A. M., Schwarz, M. J., Tylee, A. T., Carvalho, L. A., Pariante, C. M. (2015). Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behav. Immun.,* **48**, 8–18.

GBD 2016 Causes of Death Collaborators (2017). Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet,* **390** (10100), 1151–1210.

Pezeshkian, M., Nouri, M., Zahraei, M., Afrasiabi, A., Abadi, N. A. (2001). Study of MDA, antioxidant vitamins, lipoproteins serum levels and anthropometry parameters in coronary artery disease patients. *Med. J. Islam. Acad. Sci.,* **14**, 5–8.

Pizzi, C., Mancini, S., Angeloni, L., Fontana, F., Manzoli, L., Costa, G. M. (2009). Effects of selective serotonin reuptake inhibitor therapy on endothelial function and inflammatory markers in patients with coronary heart disease. *Clin. Pharmacol. Ther.,* **86** (5), 527–532.

Puppel, K., Kapusta, A., Kuczyńska, B. (2015). The etiology of oxidative stress in the various species of animals, a review. *J. Sci. Food Agric.,* **95** (11), 2179–2184.

Rees, J. N., Florang, V. R., Anderson, D. G., Doorn, J. A. (2007). Lipid peroxidation products inhibit dopamine catabolism yielding aberrant levels of a reactive intermediate. *Chem. Res. Toxicol.,* **20** (10), 1536–1542.

Del Rio, D., Stewart, A. J., Pellegrini, N. (2005). A review of recent studies on malonaldehyde as toxic molecule and biological marker of oxidative stress. *Nutr. Metab. Cardiovasc. Dis.,* **15** (4), 316–328.

Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G., Ammirati, E., Baddour, L. M., Barengo, N. C., Beaton, A. Z., Benjamin, E. J., Benziger, C. P., *et al.* (2020). Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J. Amer. Coll. Cardiol*., **76** (25), 2982–3021.

Sanchis-Gomar, F., Perez-Quilis, C., Leischik, R., Lucia, A. (2016). Epidemiology of coronary heart disease and acute coronary syndrome. *Ann. Transl. Med.,* **4** (13), 256.

Sarandol, A., Sarandol, E., Eker, S. S., Erdinc, S., Vatansever, E., Kirli, S. (2007). Major depressive disorder is accompanied with oxidative stress: Short-term antidepressant treatment does not alter oxidative antioxidative systems. *Hum. Psychopharmacol.,* **22** (2), 67–73.

Swardfager, W., Herrmann, N., Marzolini, S., Saleem, M., Farber, S. B., Kiss, A., Oh, P. I., Lanctôt, K. L. (2011). Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease. *J. Clin. Psychiatry,* **72** (9), 1181–1188.

Trebatická, J., Dukát, A., Ďuračková, Z., Muchová, J. (2017). Cardiovascular diseases, depression disorders and potential effects of Omega-3 fatty acids. *Physiol. Res.,* **66** (3), 363–382.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., Beekman, A. (2007). Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. *Int. J. Geriatr. Psychiatry,* **22** (7), 613–626.

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J., van den Brink, R. H., van den Berg, M. P. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosom. Med.,* **66** (6), 814–822.

Vaváková, M., Ďuračková, Z., Trebatická, J. (2015). Markers of oxidative stress and neuroprogression in depression disorder. *Oxid. Med. Cell. Longev.*, **2015***,* 898393.

Vichova, T., Motovska, Z. (2013). Oxidative stress: Predictive marker for coronary artery disease. *Exp. Clin. Cardiol.,* **18** (2), e88–e91.

Voicehovskis, V. V., Margolina, J., Voicehovska, J. G, Miksons, A. (2013). Validation of the Latvian version of the Geriatric depression scale (GDS). *Psychother. Psychosom.,* **82** (S1), 122–123.

Wang, Q., Liu, D., Song, P., Zou, M. H. (2015). Tryptophan- kynurenine pathway is dysregulated in inflammation, and immune activation. *Front Biosci. (Landmark Ed),* **20**, 1116–1143.

Whooley, M. A., Wong, J. M. (2013). Depression and cardiovascular disorders. *Annu. Rev. Clin. Psychol.,* **9**, 327–354.

Wirleitner, B., Rudzite, V., Neurauter, G., Murr, C., Kalnins, U., Erglis, A., Trusinskis, K., Fuchs, D. (2003). Immune activation and degradation of tryptophan in coronary heart disease. *Eur. J. Clin. Invest.,* **33** (7), 550–554.

World Health Organization, Mendis, S., Puska, P., Norrving, B. (eds.) (2011). *Global Atlas on Cardiovascular Disease Prevention and Control*. World Health Organization. 155 pp.

Yekehtaz, H., Farokhnia, M., Akhondzadeh, S. (2013). Cardiovascular considerations in antidepressant therapy: An evidence-based review. *J. Tehran Heart Cent.,* **8** (4), 169–176.

Zuo, H., Ueland, P. M., Ulvik, A., Eussen, S. J., Vollset, S. E., Nygård, O., Midttun, Ø., Theofylaktopoulou, D., Meyer, K., Tell, G. S. (2016). Plasma biomarkers of inflammation, the kynurenine pathway, and risks of all-cause, cancer, and cardiovascular disease mortality. *Amer. J. Epidemiol.,* **183** (4), 249–258.

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DEPRESIJAS UN OKSIDATĪVĀ STRESA MIJIEDARBĪBA STABILĀ KORONĀRĀ SIRDS SLIMĪBĀ

Depresija (D) ir neatkarīgs kardiovaskulāro slimību (KVS) riska faktors, nesaistīts ar citiem iepriekš noteiktiem sirds slimību riska faktoriem. Pacientiem ar mazāk smagu depresiju tika konstatēts lielāks sirdsdarbības apstāšanās risks nekā pacientiem, kuriem depresijas nebija. D pasliktina KVS prognozi, ievērojami palielinot atkārtotas koronārās sirds slimības (KSS) risku. Daži pētījumi liecina, ka oksidatīvais stress (OS) tieši palielina D risku pacientiem ar KVS. OS tiek uzskatīts par mehānismu, kas saistīts gan ar KVS, gan ar D patofizioloģiju. Kopējie riska faktori palielina OS izstrādi un samazina antioksidantu aizsargspējas, tādējādi veicinot mijiedarbotu išēmisku KVS un D rašanos un attīstību. Pašlaik nav pietiekamu pierādījumu tam, ka profilaktisks D skrīnings pacientiem ar KSS palīdzēs uzlabot pacientu stāvokli. Šajā apskatā atkārtoti uzsvērta nepieciešamība pēc daudzdisciplināras pieejas, lai izprastu, diagnosticētu un pēc tam ārstētu šos bieži vien vienlaicīgi sastopamos saslimšanas gadījumus ar KSS un D. OS marķieru novērtējums varētu mainīt riska stratifikāciju, diagnostiku, profilaksi un ārstēšanu pacientiem, kuriem ir KSS un D, gadījumos ar un bez iepriekšējām sirds slimībām anamnēzē.