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Review

BIOMARKERS OF DEPRESSION ASSOCIATED WITH COMORBID SOMATIC DISEASES

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SUMMARY

Depression is heterogeneous clinical entity with different clinical symptoms, that imply diverse biological underpinning, different molecular substrates and pathways. Besides different psychiatric comorbidities, depression is frequently interrelated with somatic diseases. Multi-morbidities, i.e. somatic diseases associated with depression, reduce quality of life, worsen clinical picture and increase mortality. The most frequent somatic diseases co-occurring with depression are cardiovascular and metabolic diseases. Vulnerable individuals will develop depression, and the goal in modern research and in precision/personalized medicine is to determine vulnerability factors associated with development of depression and to find easy available biomarkers of depression, especially comorbid with somatic diseases. This mini-review aimed to describe the latest published data (from 2015-20120) considering biomarkers of depression related to somatic diseases. Biomarkers related to inflammatory processes, atherosclerosis, imbalance of the hypothalamic-pituitary-adrenal axis, autonomic nerve system, sympathetic and parasympathetic nervous system, heart rate variability and endothelial dysfunction could improve the understanding of the underlying biological mechanisms of the common pathways of depression comorbid with somatic diseases. These targeted biomarkers might be used to reduce the symptoms, improve the treatment of these interrelated diseases, and decrease the morbidity and mortality.

Key words: *biomarkers - depression - comorbid somatic disorders - HPA axis - inflammatory response - endothelial dysfunction*

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INTRODUCTION

Major depressive disorder (referred as depression in this article) is a prevalent, chronic and recurrent mental disorder (APA 2013). Characteristic symptoms include a diminished interest or loss of pleasure in activities and a presence of a depressed mood. Besides these, further symptoms are changes in weight or appetite, disturbed sleep, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, reduced ability to think or concentrate, inability to make decisions and suicidal behavior (APA 2013), and all these symptoms cause important functional or social difficulties. The greater severity of depressive symptoms limits psychosocial functioning and quality of life. There are a lot of neurobiological hypotheses of depression, but the clear underlying ethiopathogenesis is still not fully understood. Depression develops in vulnerable subjects, resulting from complex interactions between various biological, genetic, social and environmental factors, including exposure to a childhood traumatic experience (Nikkheslat et al. 2015). Different symptoms related to mood, sleep, energy, memory, cognition, weight, and appetite reveal that biological background of depression is associated with disturbances in many different biological systems, pathways and circuits (Wang et al. 2017, Nedic Erjavec et al. 2017, Nikolac Perkovic et al. 2018). Depression is frequently associated with a poor treatment response, or with treatment resistant depression (TRD) (Ionescu et al. 2015), since only 30% of patients achieve remission, and around 30% patients do not achieve good response or remission, although they have been treated with multiple treatments (Culpepper et al. 2015). This lack of response or a poor response induce non-adherence to treatment, frequent disability, impairment in social and personal relationship, professional functioning and major health costs and disease burden (Ionescu et al. 2015, Halaris 2016).

Besides stress, which is a major risk for depression (Fogaça et al. 2019), other stressful life events such as work stress and tensions in the job (Madsen et al. 2017), traumatic events in the family such as interpersonal loss, separation from parents or death of parent(s) during adolescence (Simbi et al. 2020), loss of spouse (Kristiansen et al. 2019), are all major risk factors for development of depression with long lasting consequences.

Depression is heterogeneous clinical entity with different clinical symptoms, that imply diverse biological underpinning, different molecular substrates and pathways (Belujon et al. 2017). Vulnerable, and not resilient individuals will develop depression, and the goal in modern research and in precision/personalized medicine is to determine vulnerability factors associated with development of depression and to find easy available biomarkers of depression (Kennis et al. 2020). Unfortunately, at present, validated, specific and sensitive, non-invasive and non-expensive biomarkers still do not exist. These biomarkers could be used to distinguish

between subtypes of depression, and to improve the diagnosis of depression, predict development of suicidal behavior, or metabolic syndrome, but also advance the treatment (Hacımusalar & Eşel 2018, Strawbridge et al. 2017). Biomarkers are helpful as they can increase our understanding of the biological background of depression and they can dissect particular pathways involved in different facets of depression.

This mini-review aimed to describe the latest published data (collected from the public data-bases from 2015-2020, written in English language) considering biomarkers of depression related to somatic diseases.

DEPRESSION AND SOMATIC DISORDERS

Depression is a common mental disorder characterized by a collection of cognitive, affective, and somatic symptoms, frequently associated with different comorbidities. These comorbid disorders include substance use disorders (alcohol abuse), metabolic disorders, cardiovascular disorders, but also a lack of exercise and complete physical inactivity, high BMI and resulting obesity, problems in sleep and insomnia, heavy smoking, and unhealthy diet. All these factors might be associated with development of different chronic comorbid somatic diseases (Vermeulen-Smit et al. 2015).

Multi-morbidity, defined as a presence of two or more chronic medical conditions, becomes common problem with overall prevalence 33% (Nguyen at al. 2019). In a complex network of multi-morbidity, depression appears to be important connector and great burden considering a number of included diseases (Birk et al. 2019, Steffen et al. 2020). Risk of depression is two to three times higher in patients with multi-morbidity compared to those without multi-morbidity or with those without any chronic somatic disease at all (Read et al. 2017). Since depression is rarely isolated and frequently co-occurring with different chronic diseases, depression is frequently seen as a systemic illness. High rate of mortality accompanying depression is due to completed suicide, but also to higher risk for development of heart diseases, diabetes, and stroke (Otte et al. 2016). Depression co-occurring with other chronic somatic diseases exerts more profound health deterioration then combination of any other chronic diseases without depression (Steffen et al. 2020). In the case of multi-morbidity, it is very important to distinguish diseases whose co-occurrence is accidental (simple multi-morbidity) and those with possible interrelations (associative multi-morbidity).

There is a strong interconnection of depression and somatic disease(s) (Birk and al. 2019, Steffen et al. 2020). Namely, somatic illnesses are related to development of depression, and vice versa, depression is independent risk factor and negative prognostic factor for development of somatic disease(s), but also reduced quality of life, more severe course of somatic illness, increased functional impairment, greater disability, and increased mortality (Steffen et al. 2020). This interrelation is seen in depression comorbid with coronary heart disease and type 2 diabetes mellitus (T2DM). Namely, patients with type 2 diabetes mellitus (Eker et al. 2018, Khaledi et al. 2019), myocardial infarction (Feng et al. 2019), coronary heart disease (Birk et al. 2019), heart failure (Gagin et al. 2018), breast cancer (Park et al. 2018, Pilevarzadeh et al. 2019), stroke (Arwert et al. 2018) and metabolic diseases (Sartorius 2018, Speed et al. 2019) have an increased risk for depression.

It is estimated that patients with stable coronary heart disease in 15% cases develop major depressive disorder (Baghai et al. 2018). In patients with myocardial infarction, depression is associated with extension of infarction size (Sun et al. 2020) and adverse clinical outcome after acute coronary syndrome (Lichtman et al. 2014), percutaneous coronary intervention (Zhang et al. 2019), or coronary artery bypass graft surgery (Poole et al. 2017). Generally, coronary heart disease comorbid with depression is associated with two-fold risk of death (May et al. 2017). Depression increases a risk of type 2 diabetes mellitus development by 60% (Birk et al. 2019). The risk of depression co-occurrence in patients with type 2 diabetes mellitus is 28% (Bąk et al. 2020).

Besides somatic disorders, multiple sclerosis (Solaro et al. 2018, Boeschoten et al. 2017, Steffen et al. 2020), sleep disorders and migraine (Steffen et al. 2020), Parkinson's disease (Camargo et al. 2018) and epilepsy (Kim et al. 2019, Steffen et al. 2020), are also strongly connected with development of depression.

BEHAVIORAL AND LIFESTYLE FACTORS

Many chronic somatic diseases, same as coronary heart disease and type 2 diabetes mellitus are frequently associated with pain, fear, disability, decreased quality of life, and all these factors may worsen course of depression. With increasing somatic disease burden, cumulative negative impact on depression course is demonstrated (Hegeman et al. 2017). On the other hand, depression is associated with unhealthy living (alcohol abuse, physical inactivity, obesity, smoking, sleep deprivation, poor nutrition habits) and psychological stress, which are risk factors for coronary heart disease and type 2 diabetes mellitus, but also for other somatic diseases (Dhar & Burton 2016, Vermeulen-Smit et al. 2015).

Some studies suggest that unhealthy food (Nicolaou et al. 2019) and reduced intake of zinc and iron (Li et al. 2017) might induce depression, while, on the other hand, exercise (Kvam et al. 2016, Roeh et al. 2020) and increased physical activity (Schuch et al. 2018) are repeatedly shown to protect against depression. In addition, the intake of n-3 PUFA (Grosso et al. 2016) is believed to protect against development of depression.

Besides behavioral factors, most prominent biological mechanisms involved in the development of depression are: inflammatory response, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, sympathetic and the parasympathetic nerve systems imbalance and endothelial dysfunction with platelet activation. It seems that exposure to chronic stressors with prolonged inflammatory responses plays the central role in the development of depression comorbid with many somatic diseases.

BIOLOGICAL BACKGROUND

In addition to being a serious and complex mental disorder, depression is usually comorbid with different somatic diseases (Nguyen et al. 2019), and is associated with a great burden considering a number of included diseases (Birk et al. 2019).

Many risk factors such as genetic factors, autonomic nerve system dysfunction, neurohormone imbalance, disturbed immune system, oxidative stress, chronic stress, environment, behavior, socioeconomic status etc. could contribute to the etiopathogenesis of the co-occurred diseases (Suls et al. 2016). Biological systems underlying neurobiology of depression are the HPA axis and the inflammatory response system (Malhi 2018). Namely, stress induces the activation of the HPA axis (van Bodegom et al. 2017) and also neuroinflammation (Calcia et al. 2016).

Inflammation

Inflammatory response is one of the proposed biological mechanisms involved in etiopathogenesis of depression and coronary heart disease, and a possible link between these two diseases. Studies found that depression is associated with a low-grade inflammatory state with C-reactive protein (CRP) elevation (Baghai et al. 2018). Recent meta-analysis (Kohler at al. 2017) reported higher levels of interleukins IL-6, IL-10, IL-13, IL-18, IL-12 and tumor necrosis factor α (TNFα) in patients with depression compared to healthy controls. In contrast, peripheral levels of IL-1ß, IL-2, IL-4, IL-8, IL-5, IL-17 and transforming growth factor ß1 (TGF-ß1) did not differ significantly (Kohler at al. 2017). Among this broad spectrum of altered cytokines, some of them overlap with inflammatory profile connected with coronary heart disease. Coronary heart disease is considered as an inflammatory disease with elevated levels of inflammatory mediators such as CRP and IL-6, and in coronary heart disease comorbid with depression this elevation is even higher (Nikkheslat et al. 2015). Link between inflammatory response and coronary heart disease is presumably atherosclerosis. Inflammation plays an important role in the process of atherosclerotic plaque formation, progression, rupture and thrombosis. Many adhesion molecules, pro-inflammatory mediators (CRP, IL-6, IL-1ß), signaling pathways, and bioactive lipids are included (Moriya 2019). Well-established risk factors for coronary heart disease such as hyperlipidemia (Westerterp et al. 2018), hypertension (Loperena et al. 2018), central obesity (Saltiel & Olefsky 2017), and diabetes mellitus (Liu et al. 2016) are related to inflammatory pathways. Therefore, many studies target inflammatory mediators and pathways involved in the process of atherogenesis with aim to improve the course of the coronary heart disease and comorbid depression (Ridker et al. 2019, Ridker et al. 2017).

Atherosclerosis

Considering atherosclerosis and coronary heart disease as chronic inflammatory diseases, various pro-inflammatory mediators are proposed as biomarkers for the prediction of adverse cardiovascular events. IL-6 and CRP are the most frequently evaluated and proposed as such biomarkers (Zhu et al. 2018). Elevated plasma level of IL-6 above 1 pg/ml is predictive for coronary artery disease in the intermediate risk patients, and reflects severity of disease (Wainstein et al. 2017). Additionally, levels of IL-6 and CRP are elevated in acute coronary syndrome (Pang et al. 2017), and might independently predict adverse cardiovascular events (cardiovascular death, myocardial infarction or stroke) and heart failure (Fanola et al. 2017). Similarly, with cardiovascular diseases, elevated plasma level of IL-6 and CRP increases risk of type 2 diabetes mellitus development (Phosat et al. 2017). Persistent inflammation and CRP elevation in coronary heart disease patients could predict development of depression in patients without previous diagnosis of depression (Sforzini et al. 2019). Therefore, CRP could be used as a predictive biomarker in a case of co-occurrence of depression and chronic somatic diseases connected with inflammation (Sforzini et al. 2019). Centrally or peripherally produced cytokines could interfere with other biological pathways and cause further damages. One of the altered pathways is serotonin (5-HT) metabolism through cytokine induced kynurenine pathway, by activating enzyme indoleamine 2,3 dioxygenase (IDO). This process leads to reduced levels of tryptophan, a precursor of 5-HT, and elevated level of kynurenine. Higher ratio of kynurenine/tryptophan (indicator of activated IDO) is observed in patients with CHD and coexisted depression compared with patients with coronary heart disease without depression (Nikkheslat et al. 2015). Inflammatory response could alter downstream kynurenine pathway favoring neurotoxic metabolites in depressed persons (Savitz et al. 2015). Kynurenine and associated metabolites are involved in the development of insulin resistance (Oxenkrug 2015) and heart failure (Konishi et al. 2016). In patients with suspected stable cardiovascular diseases, kynurenine and some metabolites predict myocardial infarction (Pedersen et al. 2015) and overall mortality associated with cardiovascular diseases (Zuo et al. 2016).

Hypothalamic-pituitary-adrenal (HPA) axis dysregulation

The HPA axis has important role in stress response and cortisol secreted from the adrenal gland is involved in practically all biological processes such as stress response, cardiovascular function, immune and metabolic system regulation. The HPA axis is also involved in development of depression comorbid with somatic diseases. Two thirds of depressed patients show HPA axis dysregulation (Adam et al. 2017, Doolin et al. 2017, Jia et al. 2019). Important factor in this dysregulation is glucocorticoid receptor resistance (GR) owing to decreased receptor expression and sensitivity (Nandam et al. 2020). The HPA axis is a major regulator of the physiological balance, especially in stress conditions. Activation of the HPA axis results in coordinated changes in the endocrine, nervous and immune system, with the aim to prepare the organism to cope with stress and to recover from it. However, in stress-free and illness-free conditions, control of the HPA axis is regulated by the negative feedback mechanism exerted by increased cortisol levels. In conditions of stress or depression, disturbances of these systems result in dysregulated HPA axis, and consequent hypercortisolism, hypertension and vascular damage that might lead to cardiac arrest (Burford et al. 2017). Through cortisol secretion it plays important role in stress response and mediates many biological processes such as metabolism, immunity, cognition, and cardiovascular function. Disturbed HPA activity, associated with depression (Adam et al. 2017, Doolin et al. 2017, Jia et al. 2019) is associated with glucocorticoid receptor (GR) resistance in depression (Perrin et al. 2019), reduced GR expression and sensitivity, and altered negative feedback, as cortisol is not able to inhibit the activated HPA axis (Kim et al. 2016) and to suppress the immune system (Nikkheslat et al. 2015). Cortisol binds to its GR and affects and modulates the regulation of metabolic processes, energy distribution (e.g. glycogenesis, fat and protein metabolism), immune system, reproduction, behavior and cognitive functions (Gjerstad et al. 2018). Chronic stress alters HPA axis and creates pro-inflammatory state, that in turn supports inflammation. Alterations in normal cortisol signaling pathways and inflammation have profound effect on cardio-metabolic homeostasis, leading to insulin resistance, hyperlipidemia, and central type of obesity (Burford et al. 2017). All these disturbances may play a role in initiation or progression of atherosclerosis, type 2 diabetes mellitus or coronary heart disease. Even in a young population, without co-morbidities, plasma cortisol is positively associated with many risk factors related to coronary heart disease (Le-Ha et al. 2016). Disturbed diurnal cortisol slope predicts alterations in glucose metabolism (Hackett et al. 2016) and increases risk of mortality, especially for coronary heart disease (Burford et al. 2017).

Sympathetic and parasympathetic nervous system

Fine balance between two branches of autonomic nerve system, parasympathetic nervous system and sympathetic nervous system, is essential for the maintenance of body homeostasis. Activation of the sympathetic nervous system produces deleterious effect on heart, leading to a decreased blood flow, ventricular arrhythmias, ventricular hypertrophy, increased oxygen consumption, myocardial infarction and sudden cardiac death (Dhar & Barton 2016). In individuals with carotid plaque, autonomic dysfunction, inflammation and atherosclerosis are interrelated (Ulleryd et al. 2017). Since depression and cardiovascular disease frequently co-occur (Baghai et al. 2018, Birk et al. 2019), many studies associate activated autonomic nerve system with development of depression.

Heart rate variability

Heart rate variability is a useful method for assessment of the cardiac autonomic function. It represents normal variation of heart rate around the mean value and reflects the balance between sympathetic and parasympathetic nerve system activity. Sympathovagal imbalance, represented as reduced heart rate variability, is present in depression (Alvares et al. 2016, Brown et al. 2018, Koch et al. 2019) and it may also predict appearance of the future depressive symptoms (Jandackova et al. 2016). Impaired heart rate variability is also observed in coronary heart disease patients with (Luo et al. 2018) or without (Simula et al. 2014) depression. Simpathovagal imbalance, created by reduction in parasypmathetic tone or by sympathetic predominance, promotes inflammation and metabolic disturbance. Increased heart rate, impaired glucose and lipid metabolism create substantiation risk for coronary heart disease development (Hu et al. 2018).

Endothelial dysfunction

Endothelial dysfunction is another pathophysiological process involved in the development of depression as well as atherosclerosis, hypertension, coronary heart disease, heart failure and type 2 diabetes mellitus. This process is characterized by the endothelial cell activation and damage, and by the impairment of the endothelium dependent vasodilatation. Chronic inflammation and oxidative stress with overproduction of reactive oxygen species (ROS) can cause reduction in nitric oxide (NO) bioavailability. In such circumstances, pro-inflammatory cytokines induce expression of adhesion molecules along the endothelium, providing a base for recruitment and attachment of leucocytes and thrombocytes. Balance on endothelial layer is shifted towards vasoconstriction, inflammation, platelet and leukocyte activation, pro-coagulation and cell proliferation state creating the endothelial dysfunction. Additionally, ROS

overproduction can impair cell structure causing DNA, protein and lipid oxidative damage. Many metabolic disorders such as hyperglycemia, excessive free fatty acids and insulin resistance may interfere with NO metabolism leading to endothelial dysfunction and atherogenesis (Incalza et al. 2018, Kaur et al. 2018). Endothelial dysfunction, leading to depression comorbid with somatic diseases, can be estimated by using non-invasive methods such as flow mediated dilatation, finger plethysmography, peripheral-artery tonometry and positron emission tomography. Another approach is measurement of blood biomarkers of endothelial activetion and damage. There are many proposed biomarkers such as von Willebrand factor, plasminogen activator inhibitor 1, soluble P-selectin, soluble E-selectin, soluble fraction of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, endothelin-1 (Kaur et al. 2018), as well as plasma level of circulating endothelial cells and endothelial progenitor cells (Lopez-Vilchez et al. 2016). Depression is connected with oxidative stress and excessive production of the ROS with subsequent reduction in NO-dependent vasodilatation, and dysfunction of the vascular smooth muscles (Greaney et al. 2019). In vitro examination confirms increased ROS production and decreased expression of endothelial nitric oxide synthetase in cultivated endothelial cells exposed to sera of depressed patients (Lopez-Vilchez et al. 2016). The serum markers of inflammation and endothelial dysfunction are also elevated in depressed patients (Lopez-Vilchez et al. 2016, van Dooren et al. 2016). Endothelial dysfunction along with autonomic nerve system imbalance and impaired action of cortisol make depressed patients more susceptible to cardiovascular and metabolic disorders.

CONCLUSION

Overall, biomarkers related to inflammatory processes, atherosclerosis, imbalance of the HPA axis, autonomic nerve system, parasympathetic nervous system and sympathetic nervous system, heart rate variability and endothelial dysfunction could improve the understanding of the underlying biological mechanisms of the common pathways of depression comorbid with somatic diseases. These targeted biomarkers might be used to reduce the symptoms, improve the treatment of these interrelated diseases, and decrease the morbidity and mortality (Dhar & Barton 2016).

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Contribution of individual authors:

Nela Pivac developed the original idea.

Sandra Uzun, Marina Sagud & Nela Pivac wrote the first draft of the article, and performed literature search.

Nela Pivac wrote the final draft of the article.

All authors have read and approved the final version and have contributed substantially to the design, performance, analysis, and reporting of this study.

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