

Effect of Stress, Depression and Type D Personality on Immune System in the Incidence of Coronary Artery Disease

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Abstract

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BACKGROUND: Psychoneuroimmunology (PNI) is the study of the interaction between psychological processes and the nervous and immune systems of the human body. The impact of psychological factors on the immune system and the role of this system in Coronary Artery Disease (CAD) are confirmed. Coronary Heart Disease (CHD) is arisen due to the failure of blood and oxygen to the heart tissues.

AIM: The present study aimed to describe psychoneuroimmunological processes which contribute to CAD and CHD progression.

METHOD: Such psychological risk factors like stress, depression and type D personality were investigated here. Psychoneuroimmunological pathways of all three mentioned risk factors were described for CAD.

RESULTS: The studies review indicated that stress could be accompanied with myocardial ischemia and help to rupture. The depression involves in the transfer of stable atherosclerotic plaque to unstable, and type D personality is effective in the initial stages of a CAD.

CONCLUSION: As more information on cardiovascular immunity becomes available, this will provide a better understanding and thus act as the foundation for the potential development of new treatment strategies for treatment of cardiovascular disorders.

Introduction

About 3 decades ago, some evidence was obtained that showed immune system interacts with the central nervous system and endocrine system, and such evidences indicated the impact of psychological factors on these systems. This awareness led to scientific findings and quick growth of a field called “psychoneuroimmunology” [1] [2]. The life of this field crystallised by the publication of brain, behaviour and immunity magazine in 1987 [1]. The psychoneuroimmunology studies the mutual relations between psychological factors, immunity and Neuroendocrine mechanisms as well as the application of the findings related to such relations in health and disease [2]. Also, it tries to present a

picture of mutual relations between behaviour and immunity to explain mechanisms of the autonomic nervous system and Hypothalamic-Pituitary-Adrenal axis (HPA or HTPA axis) to relate central nervous system and immunity responses [2]. The relation between psychological factors and immunity system performance indices were seen from the common cold to the immune response to vaccination [3].

The impact of psychological interventions on immunity indicators was also seen in previous studies [4]. Therefore, psychological factors are related to some factors of immunity system that play a considerable role in the aetiology of coronary heart syndrome [5]. The brain influences immune responses through the HPA axis. This axis enhances/suppresses inflammatory responses through secretion of Corticotropin-releasing hormone (CRH) and

Adrenocorticotrophic-releasing hormone, respectively from the hypothalamus and pituitary glands, and the secretion of cortisol from the adrenal. However, the paths between the brain and the immune system have not well been known [1].

The pathophysiological mechanisms effective among psychological factors and CAD progress can be related to immunological processes [6]. Recent research findings indicate that CAD is an important clinical appearance of psychoneuroimmunological mechanisms in heart disease progression and acute coronary syndromes. Kop classifies psychological risk-factors into three groups based on the duration, that is, their persistent or temporary presence [7]: Acute triggers such as psychological stress and anger [8], episodic factors with duration of few weeks to 2 years such as depression and exhaustion [1], and Chronic Factors such as negative personality characteristics (enmity in Personality Type A and Personality Type D) and low socioeconomic level.

The review studies which relate psychoneuroimmunological factors to coronary heart disease will provide helpful information to understand the psychoneuroimmunology of heart diseases. In the present paper, we will study the works which take advantage of the role of stress, depression and Personality Type D on the immune system while these factors lead to CAD progression. The results here allow physicians and specialists to realise the importance of the immune system as a relation between mind and cardiovascular system and pay more attention to mental health maintenance to prevent coronary artery disease.

Therefore, the present paper will study the following items:

- Stress effect process in the immune system and the incidence of coronary artery disease
- Depression effect process in the immune system and the incidence of coronary artery disease
- Personality Type D effect process in the immune system and the incidence of coronary artery disease

And finally, to find a response to the below question:

Do Stress, Depression and Type D Personality have different impacts on the immune system and incidence of coronary artery disease?

Materials and Methods

The present study was carried out as a review work. The search was conducted on the platforms

associated with medical and psychiatric journals based on such keywords as stress, depression, type D personality, immune system and Coronary Artery Disease (CAD). This process took three months during which total of 38 papers and 108 authoritative abstracts were collected through Pubmed and Google Scholar. They ultimately were used to write and prepare for this review.

Results

Emotional stress is harmful to the heart. Statistical and clinical studies show that stress can increase the mortality associated with acute myocardial infarction. Of every seven adult Americans who suffer heart attacks, one person is experiencing stress. Tobacco and caffeine can increase heart rate up to 14 beats per minute, and if they are along with stress, the increase will reach to 38 beats per minute. Immune system responses to stress can potentially help to form Atherosclerotic plaque and avulsion or detachment of plaque. Most of the studies on psychoneuroimmunology show increased CD8+ cells, decreased CD4+ cells, increased blood viscosity and stimulated the immune system versus acute psychological challenges [7] [9].

Psychological stress activates the SNS, which regulates heart rate and release of catecholamines, and the HPA axis, which regulates the release of corticosteroids from the adrenal glands [10]. In acute psychological stress, catecholamines predominantly affect natural killer (NK) cell circulation. The relationship between acute stress, SNS and leucocytes are illustrated in Figure 1. In chronic stress, the activity of the HPA axis may decrease, leading to fatigue and increased activation of immune-mediated inflammation [11] [12].

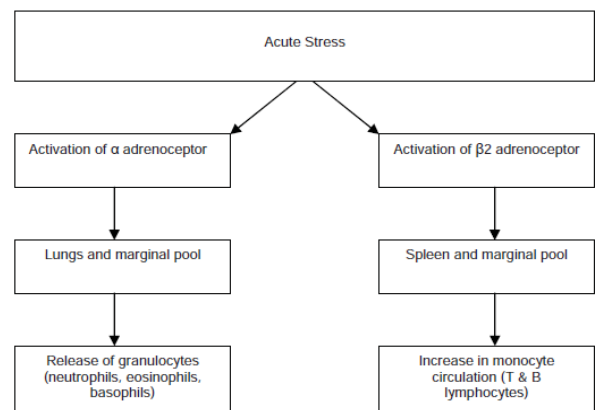


Figure 1: The relationship between acute stress, the sympathetic nervous system and the white blood cells

Owen and Steptoe studied the associations

between NK cells, proinflammatory cytokine stress responsiveness and heart rate in humans. Increases in NK cell counts the following stress were positively associated with heart rate responses and individual differences in sympathetically-driven cardiac stress responses were associated with NK and proinflammatory cytokine responses to psychological stress [13].

An acute psychological stressor increases proinflammatory cytokines including mononuclear cell IL-1 β gene expression and plasma interleukin-6 (IL-6). The increased IL-1 β gene expression was positively correlated with heart rate and systolic blood pressure reactivity [14]. The cytokines also affect the brain and evoke feelings of malaise, sickness and tiredness [15] [16]. These cytokines can induce the proliferation and migration of smooth muscle cells by stimulating other growth factors that lead to coronary lesions [5] [17]. Mann suggested that the short-term expression of stress-activated cytokines within the heart may be an adaptive response to stress, whereas long-term expression of these molecules may be frankly maladaptive by producing cardiac decompensation [18].

Chronic psychosocial stressors increase both haemostatic factors (e.g. Factor VII) and acute phase proteins (e.g. Fibrinogen) [19]. Lonely individuals also displayed greater fibrinogen response to stress [20]. Fibrinogen is thought to promote atherosclerosis by promoting platelet aggregation, enhancing the release of endothelial-derived growth factors, stimulating smooth muscle cell proliferation and increasing plasma and whole blood viscosity [14] [21]. Acute and chronic stress may activate the coagulation cascade and lead to thrombus formation and myocardial infarction (MI). There is robust evidence from epidemiological studies and meta-analyses that higher levels of acute phase proteins such as CRP and fibrinogen predict future cardiovascular death and are associated with low socioeconomic status. Psychological stress is associated with increased platelet activation and increases the risk of cardiovascular disease [20].

The relationship between depressive symptoms and coronary artery disease (CAD) is mediated in part by immune system parameters. This review describes research on the psychoneuroimmunological pathways accounting for the association between depression and CAD and addresses conceptual and methodological issues [21].

The Immune-Cytokine Model of Depression (ICMD) is an entirely new concept for understanding the riddle of depression. This is the only model of depression to bridge the conceptual and diagnostic gap between physical and mental disorders [22]. ICMD views depression to be any number of chronic physical-biological disorders that have mental-emotional symptoms. From the perspective of ICMD, depression isn't a disease, but rather a multifaceted

sign of chronic immune system activation. During chronic immune system activation, greater than normal amounts of various cytokines are secreted. The cytokines produce the multifaceted signs and symptoms of depression [23].

Cytokines are at the heart of the immunological basis of depression since they provoke a wide spectrum of neuropsychiatric symptoms when given to human volunteers. The profound effects of cytokines on mood though, and behaviour was first discovered in the early 1980's. For the first time in history, physicians had found molecules made by the human body which, when given to humans, produced all the symptoms necessary for the diagnosis of depression [24].

Depressed patients, compared to healthy controls, have an elevated white blood cell count. A high white count is called leukocytosis. The white blood cells (leukocytes) include all of the immune cells found in the blood; consequently, leukocytosis is a reliable sign of an activated immune system [24].

Increased numbers of monocytes in the blood (called monocytosis) of depressed patients were first reported by Maes et al. and recently confirmed by Seidel et al. Monocytes are found in the blood, which makes them easy to sample and measure. They are the chief source of IL1, IL6, TNF and INF α in the blood [25] [26].

Monocytes migrate from the blood into solid tissues where they are transformed into macrophages. Macrophages never return to the blood. This means they are rarely evaluated in humans because almost all immune system analyses are done on blood. Nevertheless, in animal experiments, whenever there is monocytosis, there is macrophage activation someplace in the body. Thus, the monocytosis exhibited by depressed patients indicates that macrophages are activated someplace in their bodies [24].

Maes two papers on monocytes cited above also found high levels of neutrophils (a condition called neutrophilia) in the blood of depressed patients. The most severely depressed individuals had the highest numbers of neutrophils. Neutrophils, the most plentiful of the white blood cells, are members of the inflammatory arm of the immune system. Neutrophilia is a well-established sign of immune system activation. Thus the discovery of neutrophilia in depression is another persuasive piece of evidence showing that depressed individuals have activated immune systems [24].

The total number of lymphocytes does not appear to be increased in depressed patients. Nevertheless, within the various types of lymphocytes, there are very important changes. In a recent study by Maes et al., of 106 subjects, there was a significantly increased number and percentage of B-lymphocytes in depressed subjects compared to controls [27]. This

was confirmed in another study of depressed patients [28]. B-lymphocytes are the antibody-producing cells. (They are called B-lymphocytes because they are matured in bone.) Increased numbers and percentages of B-lymphocytes are clear signs of immune system activation [24].

The T stands for the fact that these lymphocytes mature in the thymus. By secreting regulatory cytokines like IL-2 and INF γ , T-lymphocytes exert remarkable control over immune system activity. Immunologists have identified many different types of T-lymphocytes. Two of the most important is the T-helper lymphocytes (these are identified by the so-called CD4 antigen on their cell surface) and the T-suppressor lymphocytes (these are identified by the so-called CD8 antigen on their cell surface) [24].

Maes et al., in one of his many landmark papers on depression, reported extraordinarily consistent evidence of T lymphocyte activation in depressed patients. Healthy controls were compared to 101 depressed inpatients consecutively admitted to the Psychiatric Ward of the University Hospital of Antwerp. Depressed patients had significantly higher percentages of T-helper lymphocytes and lower percentages of T-suppressor lymphocytes than healthy controls. The T-helper/T-suppressor ratio was significantly elevated in depressed patients. The patients with the most severe depression had the highest percentage of T-helper lymphocytes and the highest T-helper/T-suppressor ratio [28].

A high percentage of T-helper lymphocytes combined with the finding of monocytosis in depression means that both the lymphocyte and the macrophage arms of the immune system are activated. The reduced percentage of T-suppressor lymphocytes is another clear sign of the immune system is energised. The high T-helper/T-suppressor ratio is a reliable indicator of immune system activation. In the same paper, Maes et al. provided additional evidence of lymphocyte activation [28].

Recently Müller et al. investigated the lymphocyte subsets of severely depressed patients. Their results were very similar to Maes et al.'s findings. Müller et al.'s paper provided independent confirmation of over-active immune systems in severely depressed patients. Several earlier papers by other scientists have also reported a high T-helper/T suppressor ratio in depressed patients [29].

Another reliable sign of lymphocyte activation in the presence of interleukin2 receptors on the outer surfaces of lymphocytes. Maes et al. reported that increased interleukin2 receptors on lymphocytes are a hallmark for major depression. This is further independent evidence of immune activation with depression [30].

The usual antibodies made by activated B-lymphocytes will clump and identify foreign proteins. As soon as a foreign protein is tagged with an

antibody, it will be devoured by macrophages and killer lymphocytes. In this way, the immune system can quickly identify and destroy foreign invaders. In sharp contrast, autoantibodies, clump and identify self-proteins (that is, proteins which are an integral part of your own body). Self-proteins, after they are tagged with autoantibodies, will be attacked and devoured by macrophages and killer lymphocytes. In other words, when autoantibodies are produced, the immune system begins attacking the very body it is supposed to defend. Diseases which are caused by the immune system attacking the body are called autoimmune diseases. Another profound similarity between depression and autoimmune disease is the very high incidence of depression with autoimmune diseases.

Typically, biomedical scientists either have no explanation for the high rates of depression occurring with autoimmune diseases or very convoluted explanations. In sharp contrast, the immune-cytokine model of depression has a clear and direct explanation, i.e., the activated immune systems in persons with autoimmune disease secrete excessive amounts of cytokines. Excessive cytokines provoke the symptoms and signs of depression [31].

Evidence suggests that these associations can be affected by a) the clinical characteristics of depression (e.g., typical depression versus atypical depression and exhaustion), b) the duration and severity of depressive symptoms, and c) the stage of an underlying CAD. Depressive symptoms are hypothesised to affect the transition primarily from stable CAD to acute coronary syndromes via plaque activation and prothrombotic processes and may play an additional role in response to injury at early stages of coronary atherosclerosis [24].

Type D personality is a behavioural model in which people experience negative emotions such as depression, anger, hostility and anxiety while they refuse to express it. Denolt (2000) identifies type D personality in the long-term by an increased risk of the first myocardial infarction [32]. Type D personality can lead to increased fatigue or depression among the people with such a personality type. Therefore, these factors will be correlated with increase reactivity to acute stresses [33].

Type D personality is specified by a combination of two fixed personality structure: negative affectivity and social inhibition [34][35]. Negative affectivity is the tendency to experience negative emotions constantly such as restlessness, boredom, fear and irritability in all times and situations. Social inhibition is the tendency to inhibit expressing the emotions, high levels of insecurity experience in social situations and extreme control of self-revelation for fear of others' displeasures [32]. Type D personality is relatively common. The estimations show a range of 21-28% of cardiovascular patients and 53% of the people with high blood

pressure among the public population [35] [36]. Type D personality theorists believe that the synergistic effect of high negative affectivity and high social inhibition predict less health and especially poor prognosis in the heart [34].

Previous studies indicate that type D personality predicts severe heart disease and it may be associated with psychological and physiological indicators of poor prognosis in patients with heart disease [37] [38]. Type D personality is parallel to psychological distress in patients with CHD including signs of social alienation, depression, anger, anxiety, paranoia and vital exhaustion [39]. The patients with type D are more likely to commit maladaptive health behaviours such as smoking and a poor diet. The people with type D personality use the solutions for dysfunctional coping strategies in response to disease [40]. Therefore, type D personality can lead to a poorer prognosis by affecting the selection of lifestyles among the patients with CVD [41]. Also, the studies show the relationship between anger (as one of the negative affectivity components in type D personality) and the increased cardiovascular diseases [42] [43].

Type D individuals tend to experience negative emotions such as depressed mood, anxiety, anger, hostile feelings, and to inhibit these emotions while avoiding social contacts [44] [45] [46]. Situations involving fear, anxiety, helplessness, and loss of control result in the release of cortisol [47] [48]. The relationship between negative affect and cortisol activity has been documented in several studies using structured laboratory stressors, such as public speaking and mental arithmetic [49] and aversive stimulation [48], and in the scientific literature related to changes in the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients [50] [51]. A recent study has documented relationships between negative affect, positive affect and cortisol in response to naturalistic stressors [52]. Both the experience of a current stressor and anticipating a stressor were associated with increased salivary cortisol levels. Negative affect was associated with higher cortisol levels, and positive affect was associated with lower cortisol levels. Another study also found that stressful daily events were associated with increased cortisol secretion in healthy volunteers [53]. Distress, as reflected by the mood states 'negative affect' and 'agitation', was associated with higher cortisol levels. Mood plays a mediating role in the relationship between stressful events and cortisol secretion [52] [53]. Negative affectivity is not just a confounder but is related to elevated cortisol secretion during normal daily activities. In a recent study, both type D dimensions (negative affectivity and social inhibition) were associated with greater cortisol reactivity to stress [46], although the results were not significant in more stringent regression analyses. However, it is reasonable to suggest that there is a difference in HPA regulation in type D individuals and people with other personality types.

Depression appears to be an independent risk factor for the development of coronary heart disease and osteoporosis and affects the prognosis of these and other medical disorders [54] [55]. Considerable evidence suggests an association between depression and hypertension, peptic ulcers, and diabetes [54] [55]. Elevated cortisol may be a mediating factor in these relationships. Cortisol has many effects that promote coronary heart disease. For example, cortisol inhibits the growth hormone and gonadal axes. Growth hormone deficiency is associated with a higher relative risk for premature cardiovascular disease in adults [56] [57]. Cortisol is a potent stimulus to visceral fat. Inhibition of the growth hormone and gonadal axes exacerbates visceral fat accumulation. Excess visceral fat leads to dyslipidaemia and, along with hypercortisolism, to insulin resistance, hyperinsulinism, and their sequelae [58]. Similar mechanisms may increase the vulnerability of type D individuals to cardiac and other medical illnesses. Elevated cortisol may be a mediating factor in the association between type D personality and the increased risk for coronary heart disease and, possibly, other medical disorders. It is important to note that cortisol is not the only mediating factor in this association. A recent study suggests that type D personality is associated with increased circulating levels of cytokine tumour necrosis factor α and its soluble receptors 1 and 2, which are predictors of mortality in chronic heart failure [59].

Depression is associated with impairment in feedback control of the HPA axis, contributing to higher cortisol levels during episodes of depression [50] [60]. Prolonged exposure to elevated cortisol levels may be neurotoxic, especially for brain regions rich in corticosteroid receptors, and may mediate neuronal vulnerability to stressors. Recurrent depression is associated with atrophy of the hippocampus and amygdala [61] [62] as well as the prefrontal cortex [63]. A gradual deterioration of hippocampal feedback inhibition of the HPA axis due to down-regulation of glucocorticoid receptors from repeated stress has been demonstrated [64] [65]. Evidence suggests that age and/or length of depression and/or the number of depressive episodes affect HPA regulation in depressed patients [51] [61] [62]. The potentiating or additive effect of age in conjunction with depression on pituitary-adrenocortical activity was suggested by some studies [51] [62] [67]. Mean 24-h cortisol level increases with age in depression [68]. Elderly depressives who are cortisol non-suppressors after dexamethasone need more time for pituitary adrenocortical normalisation to occur than do younger subjects [69]. An increase in post-dexamethasone cortisol levels with age has been reported in major depressive disorder [70]. A significant effect of age on cortisol release in depressed patients has been observed during the combined dexamethasone-corticotropin-releasing hormone test: older patients had higher post-dexamethasone cortisol levels [71]. In patients with

endogenous depression, advancing age leads to higher baseline cortisol and a greater likelihood of being a dexamethasone non-suppressor [72]. Cortisol responses to fenfluramine administration in depressed patients increased with the number of major depressive episodes [51]. Other authors have reported similar observations [66] [68] [73]. However, some authors suggest that age does affect HPA regulation in healthy humans [74] [75]. Differences in the results of studies have been explained by differences in a sample size, screening criteria, and some other factors, such as differences in sleeping patterns [51] [76].

Equivocal results of these studies may be, in part, related to a different prevalence of type D individuals in study samples: i.e. some type D individuals may have alterations within the HPA axis that are similar to HPA axis changes in depressed patients [77]. Future studies of HPA function should control for the presence of type D individuals. Type D individuals should perhaps not participate in psychobiological studies as healthy controls. Studies of HPA function should also control for other personality traits that may affect the HPA axis. For example, individuals with borderline or antisocial personality features may have HPA axis abnormalities [78] [79] [80].

Results

To clarify the discussion, it is necessary to have a glance at some studies associated with psychological risk factors including depression, stress and type D personality on CAD. The stress is also addressed by plenty of researchers. Lots of studies report changes in quantity and ratio of T and B cell as well as changes in Natural Killer (NK) Cells and cytokines and failure in functional responses due to acute psychological stresses. Nevertheless, recent studies often focus on the relationship between stress with other psychological factors and inflammatory markers [34].

Bosch et al. (2003) show a considerable amount of Chemokine receptor incidence by T cells caused by induced stress [81]. Mills et al., (1995) show that immune responses caused by stress are strengthened among the people with high blood pressure [82]. Besides, Fuligni et al., (2009) show an increased CRP level due to increased experience of daily stresses, considering CRP as one of the inflammatory indices for cardiovascular diseases [83]. Benson et al., indicate that acute stress leads to a significant increase of CRP and IL-6 in fat women [84]. Steptoe et al. (2007) conclude, in a review study on interface mechanisms between psychological factors and cardiovascular diseases risk that IL-1 and IL-6 increase after acute stress [9].

Also, Mommersteeg et al., (2008) indicate the relationship between hostility and Cytokine/Chemokine clusters [85]. They also confirm the relationship between hostility and increased proinflammatory and anti-inflammatory cytokines [85]. Bacon et al., (2006) address that mental stress leads to heart pain and myocardial ischemia among the patients with cardiovascular patients [86]. Decreased plasma volume may be a mechanism by which potential mental stress is increased for acute cardiovascular events [87]. Bosch et al., (2003) also show that acute stress causes to move T cells which were initially induced for response to inflamed endothelium [81]. Acute stressors can help to absorb circulation of immune cells under endothelium and hence to accelerate plaque formation and lead to the effects caused by acute stressors. This mechanism can help to express the relationship between stress and cardiovascular diseases [88].

Also, the depression risk factor is addressed by plenty of researchers. Masselman and Freedland (2002) show biological processes associated with the role of depression on CHD risk in women [89]. They conclude that the depression causes to increase blood pressure and also elevate the risk of coronary arteries occlusion by platelet aggregation and accumulation of steroid hormones [89]. Ladwig et al., (2003) and Miller et al., (2003) show both the relationship between depressive disorders and inflammation markers as well as significant relations among the people with overweight [90] [91]. Miller et al., (2003) use Structural Equation Modeling to determine the role of leptin regarding depression, obesity and CRP and IL-6 markers. Von Kanel et al., (2008) indicate that depression signs-as one of the cardiovascular diseases risk factors-predict increases TNF- α level and decreased IL-4 as well as the elevated ratio of IL-4 to TNF- α [92]. Ranjit et al., (2007) show, in a study on psychosocial risk factors for cardiovascular disease, the positive relationship between severity of depression and an increase of IL-6 level [93]. Personality type risk factor is also studied in several papers. Denollet et al., (2003) address type D personality for chronic negative affectivities and present some evidence on increased TNF- α among the patients with congenital heart failure having type D compared to those without type D [94]. Gridon et al., (2003) investigate the conventional chemical indices among the admitted patients without acute coronary syndromes and observe that chronic psychological risk factors are associated with increased white blood cell count and lymphocyte percentage [95]. Pedersen and Middel (2001) recognised type D personality independent of such factors as disease severity and argue it causes to increase the risk of bad prognosis up to 2-5 times, decrease life quality and arise factors of stress and depression [96].

Although there exists low information about harmful impacts of type D personality in clinical results, these can be some possible causes: immune

system, the behaviours associated with health including smoking and refusal of medical commands. Pederson et al., (2004) the study impact of type D personality on the occurrence of side effects among the patients with Ischaemic Heart Disease (IHD) after Percutaneous Coronary Intervention (PCI) by Sirolimus-Eluting Stent (SESs) or Bare Metal Stent (BMSs) for nine months [97]. Regardless of the stent type, the patients with type D personality are more likely to be on the subject of death and MI compared to those without type D personality for nine months [97]. The patients with depression or type D personality are in the subject of the risk of improper response to treatment by the stent. The patients with type D personality often expect unsuitable clinical consequences in IHD along with Left ventricular dysfunction [97].

Also, some studies focus on stem cells. Recent studies in this regard have expanded our knowledge on Haematopoietic Stem Cell (HSC) niches which are important to maintain and conduct renewal and differentiation the HSC. Osteoblasts, Mesenchymal Stem Cells (MSCs) and CXCL12-Abundant Reticular (CAR) cells are components of the bone marrow microenvironment and are associated with HSCs which are specified in the performance of body immune system and Homeostasis. It is noteworthy to say that cell populations of the bone marrow microenvironment send a message for different and proper functions of the immune system through G Protein-Coupled Receptors (GPCRs) [98].

MI is the main mortality cause in industrial countries. Therefore, stem cells-based therapeutical approaches are an important necessity for MI in Regenerative Medicine and coronary arteries. The experimental studies show that stem cells derived from Bone marrow endothelial progenitor cells can improve the coronary performance after Myocardial Infarction. Phases I and II studies started quickly to transfer these concepts to the clinical stage. However, impacts of stem/ progenitor cells on MI in a clinical stage have not met the expectations so far. Therefore, a better understanding of the common limitation causes is necessary for cell therapy approaches. It is again noteworthy to mention that quantity and performance of endothelial progenitor cells is decreased among the patients with cardiovascular risk factors or CAD. These observations may provide the opportunities to optimise and amend cell therapy approaches. In present review study, a summary of current evidence on the role of stem/progenitor cells in pathophysiology and treatment of ischemic diseases is presented including properties of the cells, regeneration capacity in the colony of stem/progenitor cells. Also, stem/progenitor cells delivery methods, their implantation adjustment as well as potential approaches to start employment of stem/ progenitor cells in cell therapy methods are explained for cardiovascular diseases [99].

While the requests are increasing

considerably for effective therapeutic choices for chronic coronary failure, the recent identification of physiologic and pathologic changes of myocytes in the adult human's heart has presented the fundamental base of regeneration therapy. Different methods have been represented experimentally in this regard among which some selected cases were used. This history starts with skeletal myoblasts and bone marrow-derived cells and then proceeds already with stem/Mesenchymal stromal cells inside the heart. Among them, C-KIT (positive) cardiac stem cell transplantation caused leading results with long-term impacts without side effects in the patients with chronic ventricular dysfunction. For more optimisation of present methods, we should identify different factors including the target disease, cellular population and quantity of injected cells as well as cell transfer method. Identification of former clinical tests results allows us to predict an ideal cell therapy for different cardiovascular disorders [100].

Discussion

The connection between heart and mind is a deep and prolonged bond. Advances in modern behavioural medicine have shifted psychology specialists towards the key role of abiotic factors in CHD. The researches on this disease have paid psychological factors into attention for a while, and the relationship between immune system parameters and psychological factors is an important topic of today studies on the progression of a CAD. In this regard, the present study aimed to investigate the effect of three psychological factors including depression, stress, and Type D personality on the immune system in coronary artery disease. Generally, the research findings discussed in this review confirm the validity of the hypothesis that psychoneuroimmunologic processes involved cardiovascular diseases. A set of these findings which have been published earlier are based on hypotheses about the potential role of psychoneuroimmunologic pathways in the pathogenesis of cardiovascular diseases.

Figure 2 which is derived from Kop's theory shows three categories of psychological factors (acute, episodic and chronic), immune system parameters related to CAD progression and progression stages of heart diseases and pathologic changes/lesions in coronary arteries, respectively from left to right [7]. As it can be seen at the right edge of the figure, the initial stages of coronary arteriosclerosis are specified by monocytes deposition in arteries wall that in this process, adhesion molecules play an important role. In the next stages of CAD, cytokines involved in the activation of T cells and the formation of macrophage foam cells. In this stage, the performance of Endothelial will diminish

and thereby its dilation, and contractile properties will be lowered to respond to blood flow and other arteries vasodilatation stimuli.

After initial vascular lesions, Smooth muscle cells will proliferate and migrate to plaque surface and finally contribute to form a fibrous coating with a stable riation on atherosclerotic lesions. In severe CAD mode, several factors may cause to stimulate the plaque and result in lesion instability and thinning of the fibrous coating. The plaque rupture leads to partial or complete occlusion of coronary arteries. This lesion often is caused by thrombus formation resulting from blood contact with collagen. Sudden occlusion of coronary arteries can cause cardiac ischemia and chest pain while complete and continuous clotting results in myocardial infarction [101] [102]. More precise studies on this complex process can be followed up in several types of research. Psychological risk factors are effective through differentiated immunologic processes in the pathophysiological trend of heart.

Pathophysiologic mechanisms involved in stress include Catecholamines increase due to the sympathetic nervous system, increased heart rate and blood pressure, decreased plasma volume and coronary vasoconstriction [86]. Immune system responses to stress can potentially help Atherosclerotic plaque rupture. Most of the studies on psycho-immunology show increased CD8+ cells and decreased CD4+ cells, as well as increased blood viscosity and stimulating the immune system in response to acute psychological challenges [7] [9]. These responses are the same as acute phase reactivity and relate to Hemodynamic responses to acute stresses [1].

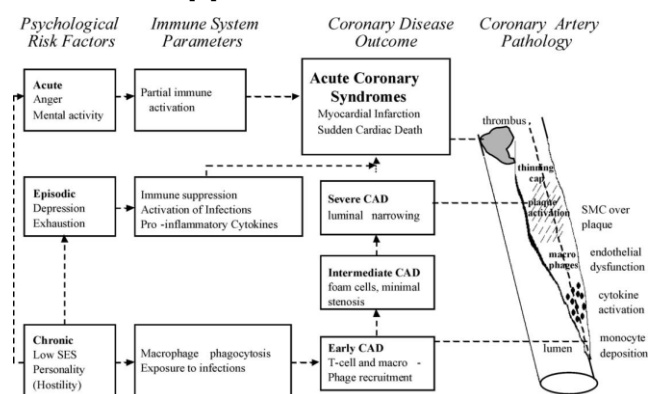


Figure 2: Acute, episodic and chronic psychological risk factors model by the immune system parameters involved in Coronary Arteries Disease

The value of depression- as the predictor variable for unsuitable long-term cardiac consequences- relates to its relapsing nature [1] [103]. In major depression, secretion of Corticotropin-Releasing Hormone (CRH) and repeated activation of HPA axis and thereby irregularity in this axis are seen [103] [104] [105]. Since psychological risk factors of

depression have temporary nature. In most of the studies, no significant correlation is found between these factors and CAD severity [103]. Therefore, the processes involved in atherosclerotic plaques transition from stable to unstable mode are the probable factors which contribute on the formation of predictor role for depression and other episodic factors in acute coronary syndromes [1] [6] [106]. Immunologic correlates of depression include increased leukocytes of peripheral blood (mainly neutrophils and monocytes), decreased lymphocyte count, elevated serum cytokines (IL-6 and TNF- α), reduced indices of cell function and increased viral antibodies (e.g. cytomegalovirus) [7] [106].

Stable conditions such as type D personality are related to increased risk of first myocardial infarction in a long-term period [107]. Pro-atherogenic processes-which cause to increase lipid deposition and inflammatory processes due to the sympathetic nervous system-are of the well-known pathophysiologic pathways among chronic risk factors and initial stages of CAD [7]. Also, chronic psychological factors involved in the appearance of episodic risk factors. For instance, these factors can be associated with an increased incidence of depression or exhaustion [104]. Therefore, the prediction power of chronic psychological factors is somewhat influenced by their relation with episodic and acute [sychological risk factors for CAD. Kop refers to Jeron et al., in which neurohormones are proved as the potential factors for cytokine myocardial (IL-6) adjustment using an experimental model [7].

Regarding the mechanism of type D personality components effectiveness on coronary arteries narrow, the effects they make on the coronary system can be referred. Negative affectivity causes to increase Cortisol levels. Therefore, the people who experience negative affectivities are more prone to increased blood pressure and heart failure. In other words, stress hormones like Cortisol may be adjusted unsuitably among the patients with type D personality [43] [108]. This leads to increase blood pressure and blood vessel blockages. The arteries occlusion does not allow the blood full of oxygen to reach sufficiently the heart. On the other hand, the patients with type D personality may have a more active immune system with more inflammation which may damage blood vessels.

Briefly, the present study aimed to describe psychoneuroimmunological processes which contribute to CAD and CHD progression. Such psychological risk factors as stress, depression and type D personality were investigated here. Psychoneuroimmunological pathways of all three mentioned risk factors were described for CAD. The studies review indicated that stress could be accompanied with myocardial ischemia and help to rupture. The depression involves in the transfer of stable atherosclerotic plaque to unstable, and type D personality is effective on initial stages of a CAD.

However, most of the statistical indices in this regard have a small effect size which is likely to be due to the role of different risk factors role in cardiovascular disease progression. Therefore, more researches are required on psycho-immunological mechanisms along with other cardiovascular risk factors including blood pressure, obesity, insulin resistance and age. Several studies in this regard show that other risk factors play as contributors in the relationship between psychological factors and immune system parameters associated with CAD [7]. As a result, some studies should be carried out by advanced methodologies including structural equations modelling. Also, to show clinical application of the reported relations, longitudinal studies are proposed to be conducted. Future clinical measures and researches on the integration of cardiovascular behavioural medicine and psycho-immunology can lead to increase classification accuracy of vulnerable patients as well as potentially improve intervention strategies.

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