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Emotional Impact; the magic bullet in influencing chronic diseases

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ABSTRACT

Emotional stress is considered a potential contributor to chronic disease although its exact role is not clear. The involvement of psychological factors in the etiology of chronic diseases is of interest to the scientific community. It leads to the increased investigation on the neuropsychological correlates of a number of chronic diseases. The most common chronic somatic diseases (namely, cardiovascular disease, diabetes, oncological diseases and skin diseases) are often complicated by psychological symptoms or personal emotional/psychological grief, which underscores the close association that exists between these conditions. Whereas acute stressors (lasting minutes) were associated with potential adaptive up-regulation and down-regulation of some specific innate immune parameters, chronic stressors were also associated with suppression of both cellular and humeral measures. A number of studies have shown that personality traits and implicit emotion regulation are associated with the development, progression, frequency, and severity of chronic disease. This review provides a brief overview to investigate the impact of stress on some chronic diseases for instance; cardiovascular disease, diabetes, cancer and skin diseases.

Keywords: *Emotions; Stress; Chronic disease; Psoriasis*

1. Introduction

Stress, generally defined as any stimulus that disrupts the body's, internal balance . Heart diseases appear to be related directly to stress and emotions (Fan et al., 2008). Heart disease describes a range of conditions that affect heartbeat, blood vessels such as coronary artery disease; heart rhythm problems (arrhythmias); and heart defects (Coccaro et al., 2021). Evidence from both experimental and clinical trials indicate that inflammatory mediators are of importance in the pathogenesis of chronic heart failure (HF) contributing to cardiac remodeling and peripheral vascular disturbances (Vella et al., 2021). Several studies have shown raised levels of plasma inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) in HF patients, as well as in the failing myocardium especially in patient with risk factors for heart disease as age, sex, family history, smoking and stress (Segerstrom and Miller, 2004). Gender may moderate the effects of stress on immunity by virtue of the effects of sex hormones on immunity; generally, men are considered to be more biologically and psychosocially vulnerable than women (Maes, 1999).

Salaycik et al., (Salaycik et al., 2007) mentioned that depressive mood or subclinical depression precedes heart attacks or stroke. Furthermore, anger can trigger physiological changes that affect blood, temporarily elevating risk of a heart attack or related problem. Several studies showed that in the two hours after an angry outburst, a person has a slightly higher risk of angina, heart attack, stroke, or risky heart rhythm (Alonso et al., 2011). The increased coagulation tendency could be the "missing link" that explains why anxiety patients have a significantly higher risk of death by heart disease with a factor of 3 or 4. On the other side, not all patients with a marked anxiety disorders go through heart attack, a real health threat arises only when other risk factors, like smoking and obesity come into the equation (Kessler and Bromet, 2013) as both are directly related to coronary artery disease (Van der Kooy et al., 2007). Surprisingly, even stress related to enjoyable events may raise risk of a heart emergency for instance during a World Cup soccer event at (Munich) the German city; the incidence of myocardial infarction was recorded with elevation by a factor of 2.49, and of cardiac arrhythmia causing major symptoms by a factor of 3.07 during days when the nation's team was playing (Wilbert-Lampen et al., 2008).

The common pathways between stress exposure and pathophysiological processes underlying disease are still debatable. 75%–90% of human diseases are related to the activation of stress system. Poor sleep quality under stress, discrimination emotion stress, such as anger, hostility and aggressiveness were also involved in coronary artery disease (Salaycik et al., 2007). Chronic low-grade inflammatory load with elevated IL-6 and CRP, the two important biomarkers of systematic inflammation, are considered indicative and potentially predictive for atherosclerosis and may emerge as a possible link between chronic stress and contributed to early process, and thrombotic complications of atherosclerosis (Conversano, 2019). A study by Wassertheil-Smoller et al., (Wassertheil-Smoller et al., 2004) reported that life stressors as noisy communities induces significant increase in epinephrine and nor epinephrine (NE) leading to hypertension. NE promoted the production of inflammatory factors by facilitating the phosphorylation of mitogen activated protein kinase (MAPKs) through activation of NE α receptor. Neuropeptide Y (NPY) could elicit transforming growth factor B1 (TGF-β1) and tumor necrosis factor alpha (TNFα) production via Y1 receptor. NPY could also directly activate the high mobility group box protein (HMGB1) release and cytoplasmic translocation from the macrophage. Carney et al., (Carney et al., 2003) explained that the psychoneuro-endocrine immunology is a scientific field of study that investigates the link between bidirectional communications among the nervous system, the endocrine system, and the immune system besides the correlations of this cross-talk with physical health. Furthermore, the heart is able to process neurological signals independent from the brain and to the crosstalk with the endocrine and immune systems. In order to maintain the homeostasis of the whole body, the heart communicates with the psyche through the neuroendocrine-immune system in a highly integrated way. Lespérance et al., (Lespérance et al., 2002) showed that cute psychological stressors lead to leukocytosis, increased natural killer cell cytotoxicity and reduced proliferative response to mitogens while chronic psychological stressors may lead to adverse health effects. This will result in changes in cardiovascular function and development of coronary artery disease (CAD). Acute and chronic psychological stressors will increase haemostatic factors and acute phase proteins, possibly leading to thrombus development and myocardial infarction. An important hormonal response system to stress—the hypothalamic–pituitary–adrenal (HPA) axis—may be involved in this process, particularly stress hormones known as glucocorticoids and primarily cortisol (Wassertheil-Smoller et al., 2004). Neurons in the paraventricular nucleus (PVN) of the hypothalamus release two neurohormones: corticotropin releasing factor (CRF) and arginine vasopressin (AVP) into the blood vessels connecting the hypothalamus and the pituitary gland. Both hormones stimulate the anterior pituitary gland for production of adrenocorticotropic hormone (ACTH) into the general circulation. The ACTH, in turn, induces glucocorticoid synthesis and release from the adrenal glands. To protect against prolonged activity, the HPA system is carefully modulated through negative-feedback loops designed to maintain predetermined hormone levels and homeostasis. To this end, secretion of CRF, AVP, and ACTH in part are controlled by sensitive negative feedback exerted by cortisol at the level of the anterior pituitary gland, PVN, and hippocampus (Wassertheil-Smoller et al., 2004). There are two types of receptors for cortisol mineralocorticoid (type-I) and glucocorticoid (type-II) receptors; both of which participate in the negative feedback mechanisms. Cortisol binds more strongly for the mineralocorticoid receptors (MRs)1 than the glucocorticoid receptors (GRs). Due to the difference in the binding affinity, the MRs help maintain the relatively low cortisol levels circulating in the blood during the normal daily rhythm. Only when the cortisol concentration is high (e.g., during a stressful situation) it binds to the GRs with lower affinity; the resulting activation of the GRs terminates the stress response. This delicate negative feedback control mechanism maintains the secretion of ACTH and cortisol within a relatively narrow bandwidth. This is an extremely important homeostatic mechanism because too much or too little exposure to cortisol can have adverse

consequences to health and well-being FK506 binding protein 5 (FKBP5) that regulates GR sensitivity (Seifert et al., 2012). Binding of this protein to the GR reduces the receptor's affinity for cortisol and its movement to the nucleus. A genetic variation in prolyl isomerase 5 (FKBP5) is associated with enhanced expression of the protein following GR activation. This leads to more GR resistance, diminished negative feedback, and prolonged stress hormone activation following a stressor (Wassertheil-Smoller et al., 2004).

Stress and diabetes

Stress is a potential contributor to chronic hyperglycemia in diabetes. Stress has long been shown to have major effects on metabolic activity; energy mobilization in fight or flight response and it also stimulates the release of various hormones, which can result in elevated blood glucose levels. The literature on the effects of stress in both experimental models and in human type I diabetes is complicated and often contradictory, it does not allow to reach a clear conclusion about how stress impacts on the disease (Coccaro et al., 2021). In animal models, the effects of stress appear to depend on the type of stress and the particular model studied. Human studies are confusing, with some studies showing hyperglycemic effects, some showing no effects, and some showing idiosyncratic effects, with patients demonstrating either hyper- or hypoglycemia in response to the same stressor. These inconsistencies may reflect true individual differences in metabolic response to stress that could be related to other behavioral variables (Marcovecchio and Chiarelli, 2012). On the other hand, confounding conditions, such as autonomic neuropathy, which develops over time and would compromise any sympathetic nervous system response to stress, also may contribute to these apparent idiosyncratic responses to stress on the part of different patients. So limited conclusions about the effects of stress on type I diabetes control or how these effects would best be treated (Fisher et al., 2010). Further studies should carefully exclude patients with symptoms of autonomic neuropathy and should test patients on multiple occasions to detect idiosyncratic patterns. A theoretical rationale for the importance of stress effects on glycemic control in type II diabetes advocate that stress can affect glycemic control adversely. Evidence from different studies suggests that individuals with type II diabetes have altered adrenergic sensitivity in the pancreas, and perhaps other sites as well, which could make them particularly sensitive to stressful environmental stimulation (de Groot et al., 2001). Other stimuli of sympathetic activity, such as dietary fat and simple carbohydrates, also may contribute more to the development of diabetes through this adrenergic mechanism. But, although substantial data exists to show the theoretical importance of stress in type II diabetes, no direct evidence demonstrates that stress plays a clinically significant role in the expression or control of the human disease (Marcovecchio and Chiarelli, 2012). As in type I diabetes, clinical studies rarely have attempted to assess the role of individual behavioral differences in identifying those patients who show stress hyperglycemia or who may be particularly responsive to stress management. Some evidence suggest that stress may precipitate the onset of the disease or compromise glycemic control once the disease is established. Moreover, glucose toxicity that results from chronic, intermittent, stress-induced elevations in blood glucose further may compromise pancreatic secretory ability, leading to the progression of the disease (Fisher et al., 2018). More clinical research is needed to determine the degree to which stress affects the onset and course of diabetes and also stress-reducing maneuvers are recommended as treatment for this form of the disease.

Stress and skin conditions

Skin is the largest organ of the human body and one of the most complicated. The skin is unique in many ways, no other organ demands so much attention and concern in both states of disease and health (Jafferany and Pastolero, 2018). Skin disorders vary in symptoms and severity but it is often not life threatening. There is evidence in the literature showing that psychological stress may have a role in the onset or exacerbation of a variety of skin diseases (Al'Abadie et al., 1994). The anger can be a cause of skin problem like Eczema. The main causes trigger eczema could be overactive immune system that responds aggressively when exposed to irritants (Jafferany and Pastolero, 2018). A study by (Ciuluvica et al., 2019) suggests that stressful incidents occur before the onset of psoriasis flares in approximately 68% of adult patients. People with skin problems are at high risk of developing psychological problems. Chronic skin disease has an effect on a person's physical and psychological well-being (Jafferany and Pastolero, 2018). Besides psychopharmacology, multiple psychotherapeutic techniques have proved to be helpful in addressing the psychological sequelae of skin disease. The physical, psychological, and social consequences affect not only the patients, but also caregivers and family members as well. Common psychological problems associated with skin disease include feelings of stress, anxiety, anger, depression, shame, social isolation and low self-confident. Major depression is one of the main results of chronic skin disorders and in the other side stress and anxiety are known to be common triggers that can cause skin problems (Jafferany and Pastolero, 2018). Not only depression, a lot of intense emotions such as

stress, anger, fear, or pressure, can trigger acne and rosacea or cause psoriasis (Augustin et al., 2018). Skin patients reported more problems with their emotions and in controlling their impulses when experiencing negative emotions than healthy controls. Patients with more severe diseases are more likely to show a dysregulated emotional mechanism (Chren et al., 1996).

Indeed, the quality of life in psoriatic patients is significantly correlated with negative affectivity. However, the decisive role of emotion regulation in the etiology of psoriasis suggests the existence of an emotional vulnerability in patients with psoriasis. Negative emotions that last too long, excessive suppression of emotions, especially when paired with lack of behavioral expression can, through the vegetative nervous system, deregulate the hormonal and immunological systems, cause somatic dysfunction, and finally lead to disease or aggravate the disease course (Ciuluvica et al., 2019). Increasing production of stress hormones, suppress the immune system and cause an inflammatory response in the skin and disturb epidermal barrier. A disturbed epidermal barrier leads to dry skin which causes a non-specific hypersensitivity of the skin such as null mutations in the filaggrin and hornerin gene (Augustin et al., 2018). Filaggrin is expressed in the upper layers of the stratum corneum and is encoded within the epidermal differentiation complex (EDC). It also depends on the immune system because Th2 cytokines and IL -4 inhibit the expression of filaggrin and S100 proteins. In lymphoid tissue, Th2 cells induce the production of IgE antibodies by plasma cells. The cell-mediated dysfunction as patients with Eczema are prone to develop a variety of infectious diseases of fungal, viral or bacterial origin (Ciuluvica et al., 2019).

Stress and cancer

Chronic stress can cause corresponding changes in the body's immune function and inflammatory response, which is significant because a long-term inflammatory response with the decline of the body's immune surveillance capabilities is implicated in tumorigenesis (Dai et al., 2020). The effect of feelings or emotions on cancerous cells is being constantly studied. Cancerous cells are affected negatively or positively with the patient's feelings or emotions. Scientists are trying to use the positive effects as a new approach in the treatment of cancer or at least in aiding and promoting the chemotherapy. During anger or depression, lymphocytes were found to be negatively affected by cortisol release (mediated by depression or sadness) because Ig positive cells were dramatically down regulated. Also, the process of reproduction of new lymphocytes was adversely affected (Jackson, 2014). As a result, the body's immunity weakens and the patient's case is significantly affected. Anger causes the release of the stress hormone, cortisol which gives the body bursts of energy. However, Ample cortisol can cause assembly of negative effects in the body leading to an imbalance in blood glucose level that can suppress thyroid function, and decrease bone density. This hormonal imbalance also impacts the body's immune system (Niraula et al., 2018). Individuals under constant stress often have outbreaks of shingles and/or cold sores (Reiche et al., 2004). (Garfinkel et al., 2016) stated that in addition to the fuel glucose and arachidonic acid, insulin, growth factors and 16-hydroxyestrone, the stress hormones, play a major role in all steps of the development and progression of cancer. A study by (Reiche et al., 2004) reported that elevated cortisol suppresses the function of the Natural Killer cells, thus allowing cancer cells to survive in the body. Additionally, release of stress hormones can compromise DNA repair mechanisms, leading to the development of cancer. (Carney et al., 2003) demonstrated that epinephrine is not only up pressed the immune system when cancer cells were on the move, but also it allows the process of metastasis to happen. The stress reaction is also fueled by a secondary source; cytokines and inflammation. The proinflammatory cytokines IL-1, IL-6 and TNF (tumor necrosis factor) all contribute to the development of tumors. The role of IL-6 in cancer-cell proliferation and survival is well documented. IL-6 plays a pivotal role in the development of Kaposi's sarcoma and multiple myeloma. IL-6 has also been found to contribute to other cancers, such as colon cancer, lymphoma, breast cancer, and others. IL-1 was found to increase tumor invasiveness and metastasis (Dai et al., 2020). At the site of tumor development, IL-1 caused the tumor to adhere to healthy tissue, and it assisted malignant cells metastasis. TNF, involved in inflammation, was shown to enhance tumor progression, stimulate angiogenesis and metastasis, and impair the immune system by suppressing the white blood cells (Jackson, 2014). On the other hand, pleasant and positive emotions have been proofed to have a main role in improving cancer therapy. The specific physiological responses induced by pleasant stimuli were recently investigated with the immune and endocrine systems being monitored when pleasant stimuli such as odors and emotional pictures were presented to subjects which is due to an increase in secretory immunoglobulin A and a decrease in cortisol owed to pleasant emotions (van der Meer et al., 2020). IgA antibodies may have the additional advantages of forming natural dimers with improved signaling capacity on tumor cells, and being actively transported into mucosal secretions with the potential for improved targeting of certain carcinomas from the luminal surface (Dai et al., 2020). Human IgA1 antibodies efficiently

recruit immune effector cells that express the fragment crystallization (Fc) receptor for IgA. IgA1-mediated killing of tumor cells by isolated polymorphonuclear cells (PMNs) and in whole blood was found to proceed without the necessity to pre-activate effector cells with cytokines. In addition, the IgA1 anti epithelial cell adhesion molecule (anti-Ep-CAM) human monoclonal antibody triggered phagocytosis of tumor cells by monocyte-derived macrophages (Jackson, 2014). These results show that IgA1 antitumor human monoclonal antibodies are capable of recruiting the large population of peripheral blood PMNs for tumor cell killing (Dai et al., 2020). In a study subjected by (Ben-Shaanan et al., 2018), they experimented manipulating the brain's reward system in mouse models of melanoma (skin cancer) and lung cancer. Specifically, they targeted the dopamine-releasing neurons found in the ventral tegmental area (VTA) of the brain, a key region of the reward system. The VTA communicates with the limbic system, a brain structure tasked with processing emotions, and this interacts with the sympathetic and peripheral nervous systems. The interaction appeared to extend to the immune system. Consequently, by activating the ventral tegmental area, the nervous system was affected which considered as a therapeutic method. Consequently, once the reward system has been activated (by positive expectations), the ability to fight foreign bodies increases. By applying these effects in mouse models of melanoma and lung cancer, the results revealed that by stimulating the VTA, the immune system appeared to respond more effectively to the tumors. The results revealed that "after 14 days of repeated VTA activation," tumor size and tumor weight were reduced by 46.5% and 52.4% respectively.

Conclusions

It is well established that emotional stress is significantly associated with a wide variety of chronic physical disorders, comprising cardiovascular disease, diabetes mellitus, hypertension, cancer, arthritis, asthma, chronic respiratory disorders, and a variety of chronic pain conditions (Conversano, 2019). These associations have considerable individual and public health significance representing costs of depression as a causal risk factor leads to an increased prevalence of physical disorders associated with financial costs, impairments, and increased mortality risk. Also, a variety of poor health behaviors known to be linked to major depressive disorders, such as elevated rates of smoking and drinking, obesity, low compliance with treatment regimens, and a variety of biological dysregulations (Dai et al., 2020).

Resolving chronic disease should always include helping individuals to manage their stressors in addition to implementing changes in lifestyle via diet, exercising, and elimination of toxins. This won't only prevent the development of the chronic disease, but also will improve treatment outcomes and reduce the rate of recurrence.

Based on these considerations, our study revealed that psycho-educational intervention for acceptance and managing social impact is needed, which is also the first step to informing the development of a patient centered psychological intervention.

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Disclosure

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