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DEPRESSION ASSOCIATED CO-MORBID CARDIOVASCULAR AND METABOLIC COMPLICATIONS

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ABSTRACT

Depression currently observed as the second largest killer disease across the globe commonly noticed because of negative feeling such as sadness and despair which also often involves physical and behavioural symptoms. Epidemiologic studies have confirmed that depression is an extremely common condition, but as also the one that is associated with an unexpectedly broad spectrum of morbidity. Depression is a major problem that can increase the chances of co-morbid cardiovascular and other metabolic complications, where the under-recognition and improper treatment is especially common. A large number of studies assessing the relationship between depression and medical burden have focused on patients with cardiac diseases and metabolic disorders. The present review is focused on the presence of the various cardiovascular complications and metabolic disorders associated with depression. Many previous studies have suggested depression as a risk factor for mortality, in patients with cardiovascular and metabolic complications.

KEY WORDS: Co-morbid disorders, depression, metabolic complications, diabetes, leptin

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INTRODUCTION

When a person has depression, it interferes with his/her daily life, such as going to work or school, taking care of children, and relationships with family and friends. It is a common but serious illness[1]. Depression is more common in women than in men[2] and associated with events like loss of a loved one, stress and hormonal changes, or traumatic injury may trigger depression at any age, which may be short lived or persist for longer periods[2, 3].

DSM-IV (Diagnostic and Statistical Manual For Mental Disorder) Criteria For Depression[4]

The depression criteria given by DSM–IV are as shown (**Table-1).** The signs and symptoms may be different in men, women, younger children and older adults[4].

Neurobiology of Depression

Various psychological, psycho-social, evolutionary and biological causes of depression have been proposed[5] and most of the hypotheses are based on the imbalance in endogenous amines such as serotonin, nor-epinephrine and dopamine. These amines are naturally present in the brain which also assists communication between nerve cells.[6] This was consistent with the observation that reserpine, a anti-hypertensive drug which act by depleting the level of endogenous amines in vescicles, which leads to depression and increase the tendency of suicide among patients. The second approach to understanding the pathophysiology of depression came about through the observation that stress appears to play a role in depression and that depressed patients often exhibit increased activity in the hypothalamic-pituitary-adrenal (HPA) axis.[7, 8] Third approach to test amine hypothesis is by looking for biochemical abnormalities in cerebrospinal fluid (CSF), by measuring the concentration of biogenic amines in normal as well as depressed subjects[9, 10].

Co-Morbid Illnesses with Depression [10, 11]

Some illnesses or disorders that may occur along with depression are diabetes, obesity, heart disease, anxiety disorders[10], post-traumatic stress disorder (PTSD), [11, 12] alcohol abuse, [13] and stroke[10]. This review mainly focused on various cardiovascular and metabolic complications associated with depression.

DEPRESSION AND ITS ASSOCIATION WITH CARDIOVASCULAR DISORDERS AND METABOLIC DISORDERS LIKE DIABETES AND OBESITY

The association of depression with cardiovascular and metabolic diseases such as diabetes and obesity can have serious consequences. Patients with depression have both increased cardiovascular morbidity and mortality. Presence of depression increases the chances of various myocardial infarction (MI) and ischemic heart disease (IHD) [14].

Depression and Heart Disease

Patients with major depression are four times as likely to die in the first 6 months after an acute MI as compare to those without depression15. Depression is implicated in both the development and undesirable outcomes of cardiac disease. Biologic pathways involved in pathophysiology are the sympathetic nervous system, the hypothalamic-pituitary axis, the coagulation pathway. A quantitative review also concluded that depressive symptoms contribute a clinically significant independent risk factor for the onset of coronary disease[16].

Pathophysiology of Co-Morbid Cardiovascular Complication

Depression has been associated with a number of physiological derangements such as; 1) increased cortisol level 2) dysregulation of sympatho-medullary and autonomic nervous system function 3) dyslipidemia and 4) altered platelet activity, which leads to adverse cardiac outcomes[17].

Hypothalamic-Pituitary-Adrenal Axis Hyperactivity

Many studies have evidenced a hyperactive hypothalamic- pituitary (HPA) axis as one of the important factor for depression[18]. This is evidenced by attenuation of the adrenocorticotropic hormone response to exogenous corticotropin-releasing hormone (CRH), non-suppression of endogenous cortisol after dexamethasone, and elevated CRH concentrations in the cerebrospinal fluid of depressed patients[19]. Long term exposure to high amount of endogenous or exogenous cortisol can cause depression, sympathomedullary hyperactivity, and mobilization of free fatty acids that trigger endothelial inflammation, excessive clotting and hyper-lipidemia with various cardiovascular complications such as high blood pressure and myocardial infarction[20] as shown in (**Fig. 1).**

Increased Activity of Sympathetic System

Higher cerebrospinal fluid levels of CRH in depressed patients is associated with both central[21,22] and peripheral noradrenergic hyperactivity[23]. Norepinephrine stimulates the release of CRH from forebrain areas (*eg,* paraventricular nucleus of the hypothalamus, bed nucleus of the stria terminalis and the central nucleus of the amygdala) resulting in a reinforcing positive feedback loop. Excessive sympathomedullary activity presumably enhances risk of IHD through its impact on the heart, blood vessels, inflammatory response, and platelets[24]. Norepinephrine and epinephrine also causes hypercortisolemia by enhancing the release of cytokines. This long term activation of cortisol increases the risk of various cardiovascular diseases[25-27].

Parasympathetic Abnormality

Major depressive disorder (MDD) has significantly been linked with diminished high-frequency heart rate variation, suggesting an association between depression and diminished vagal tone[28]. Successful treatment of depression has been related with normalization of high frequency heart rate variability[29].

Altered Platelet Activity

The relationship between major depression and increased platelet activity has been previously indicated by several studies[30]. Platelets, the smallest corpuscular component of human blood, are central to various crucial biologic pathways in the human body. Altered platelet function is thought to contribute to the increased risk of ischemic heart disease in patients with major depressive disorder, which increased the morbidity and diminished survival of depressed patients after an index myocardial infarction[31]. Several studies have been done assessing the state of platelet activation in depressed patients with or without concomitant cardiovascular disease. The results shows depression was associated with increased platelet reactivity as assessed by increased plasma levels of platelet factor 4 (PF4) and thromboglobulin (TG) and increased expression of procoagulant platelet surface receptors[32,33]. Enhanced platelet activation was also found in patients with depression and IHD as compared to non-depressed patients with IHD[34-36].

Dyslipidemia

Hypothalamic-pituitary axis hyperactivity is associated with a number of endocrine changes, in addition to causing depression, can also contribute to increases level of visceral fat mass and free fatty acids[37]. This is associated with hypercortisolemia, glucocorticoid-associated deficiencies of gonadal steroids and growth hormone, and glucocorticoid induced insulin-resistance, each contribute to increased visceral fat mass with consequent release of peripheral and portal fatty acids. An increase of peripheral fatty acids can trigger excessive clotting and decreased fibrinolysis by elevating hepatic production of fibrinogen and plasminogen activator inhibitor-1 (PAI-1)[38] and other anti-fibrinolytic mediators[39].

ASSOCIATION OF DEPRESSION WITH DIABETES AND OBESITY[40, 41]

Diabetes and obesity are two important modifiable risk factors for depression. Patients with diabetes have a higher incidence of MDD and a poorer prognosis after stroke[42]. Risk-factor modification is the most important aspect of prevention of stroke in diabetes and obesity. This includes lifestyle modifications and different therapeutic modalities to control conditions, such as diabetes, hypertension, dyslipidemia and arrhythmia. Recent landmark studies have shown the beneficial effects of statins in diabetic patients even with close to normal or normal low-density lipoprotein cholesterol[43]. Obesity, which is a risk factor for diabetes, hypertension and hyperlipidemia has been shown to be an independent risk factor for MDD. Increased leptin, dysregulation of adipocyte proteins, increased insulin resistance and C-reactive protein may be factors involved in the increased incidence of cardiovascular morbidity and mortality directly related to obesity. The level of inflammatory mediators like TNF-α is significantly increased in depression with increase in the incidence of diabetes and obesity[44-46].

Co-Morbid Diabetic Complications with Depression Hypothesis

A novel hypothesis in which depression precedes and predisposes individuals to diabetes mellitus may enlighten the development of type 2 diabetes among patients diagnosed with depression several years earlier.[47] This theory proposes that diabetes may develop via the psychosocial effects of depression, including adiposity and negative health behaviors like poor diet, physical activity, smoking, and medication adherence as a result of biological mechanisms such as activation of the HPA axis[48] and inflammatory responses[49] that contribute to insulin resistance and decreased glucose uptake[50,51] as shown in (**Fig 2).** While research supports a trend in which depression precedes type-2 diabetes, causal mechanisms for this association remains speculative.[52] Variations in the extent to which depression increased the risk of type 2 diabetes after accounting for known risk factors suggest that additional factors affect this relationship.[47] Inflammatory markers interleukin-6 and C-reactive protein were elevated in depressed individuals and have been identified as risk factors for developing type 2 diabetes, yet models accounting for these variables were still unable to explain the association between depression and the incidence of type 2 diabetes where it was observed that insulin resistance was not related to depressive symptoms, further challenging the proposed mechanisms underlying this relationship[53].

CO-MORBID OBESE COMPLICATION WITH DEPRESSION

It has been long known that the frequency of overweight and obese people is higher among depressed and bipolar patients than in the general population.[54] The marked alteration of body weight (and appetite) is one of the most frequent of the 9 symptoms listed in introduction of major depressive episode, and these symptoms occur during recurrent episodes of depression with a remarkably high consequence.[54, 55] According to studies with representative adult population samples, in case of obesity (BMI over 30) unipolar or bipolar depression is significantly more frequently (20-45%) observable.[55] Eating and physical activity, the important determinants of obesity and both play an important part in linking obesity and depression.[56] Although the DSM-IV finds both overeating, with weight gain and under eating with weight loss among the diagnostic criteria for major depression[57]. The study of eating and physical activity as potential mediators of depression has been limited. The physical inactivity not only characterized many depressed person but also predict weight gain and physical activity has been used with some success in the treatment of depression[58]. Since in case of depressed patients appetite and body weight reduction is observable during the acute phase, the more frequent obesity in case of depressed patients is related (primarily) not only to depressive episodes, but rather to lifestyle factors, to diabetes mellitus also more frequently occurring in depressed patients, to comorbid bulimia, and probably to genetic-biological factors (as well as to pharmacotherapy in case of medicated patients). Certain lifestyle factors relevant to healthy metabolism (calorie reduction in food intake, regular exercise) may be protective factors related to depression as well[59, 60].

CONCLUSION

Depression may directly worsen glycemic control and accelerate the development of diabetic complications that are at the root of the morbidity and mortality associated with diabetes. In addition, depression significantly decreases adherence to medication and dietary regimens prescribed for glycemic control. Depression has been shown to redirect the development of coronary heart disease independently of other risk factors in patients with type 1 diabetes mellitus. In addition to the exacerbation of physical symptoms, the depressed patients in this study were also more likely to incur greater medical costs in primary care and speciality offices, emergency departments, hospitals, and mental health facilities. Total health care costs were 86% higher in diabetic patients who were depressed than in non-depressed diabetic patients. Major depressive disorder and depressive symptoms have been identified as independent risk factors for cardiac morbidity and mortality in patients with ischemic heart disease. Increased susceptibility to platelet activation has been proposed as one of the mechanisms by which depression acts as a significant risk factor for thrombotic events. Mortality rate is much higher in patient suffering with cardiovascular disease and co-morbid depression than the cardiovascular complications alone. Co-morbid obese complications are also a big challenge in patients suffering from major depressive disorders and commonly associated with overeating. It is proved that life style modification; exercise, proper diet regimen, yoga and proper counseling can reduce the risk of depression as well as associated cardiovascular and metabolic complications. The drugs used for these co-morbid complications generally used in combination to reduce the risk of treatment resistance.

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Table 1: DSM-IV Criteria for Depression[4]

If a person have an episode of depression lasting at least two weeks with at least five of the following symptoms: (1) You are depressed, sad, blue, tearful. (2) You have lost interest or pleasure in things you previously liked to do. (3) Your appetite is much less or much greater than usual and you have lost or gained weight. (4) You have a lot of trouble sleeping or sleep too much. (5) You are so agitated, restless, or slowed down that others have begun to notice. (6) You are tired and have no energy. (7) You feel worthless or excessively guilty about things you have done or not done. (8) You have trouble concentrating, thinking clearly, or making decisions. (9) You feel you would be better off dead or have thoughts about killing yourself.

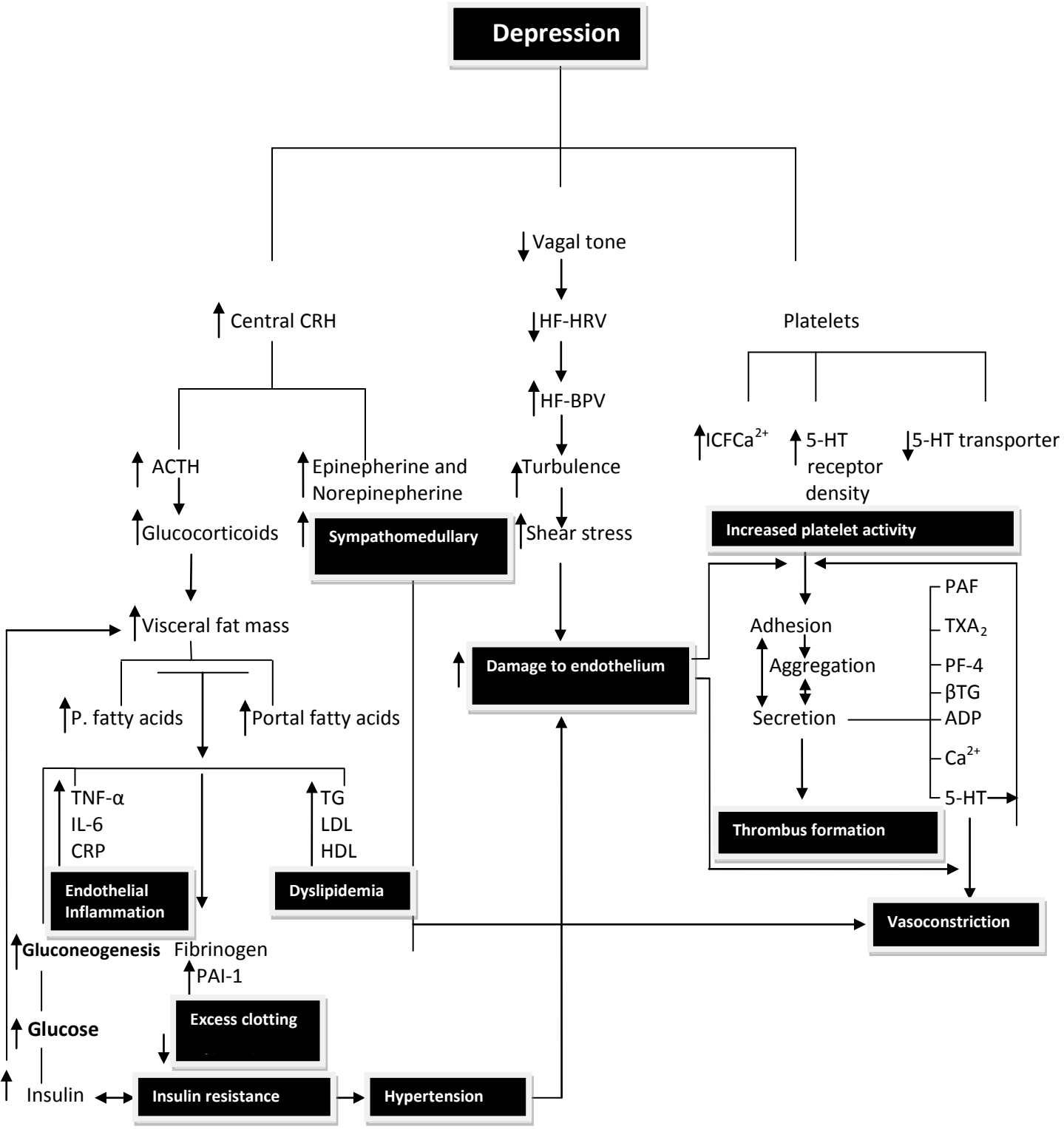

Figure 1. Hypothetical mechanisms by which depression and other psychosocial factors increase risk of ischemic heart disease and insulin resistance.ACTH—adrenocorticotropic hormone; CRH—corticotropin-releasing hormone; CRP—C-reactive protein; HDL—high-density lipoprotein; HF-BPV—high-frequency blood pressure variability; HF-HRV—high-frequency heart rate variability; IL-6—interleukin-6; LDL—low-density lipoprotein; PAF—platelet-activating factor; PAI-1—plasminogen activator inhibitor-1; TG—triglyceride; TNF- α —tumor necrosis factor-alpha; TXA_2—thromboxane A_2 P.fatty acid—peripheral fatty acid.[20]

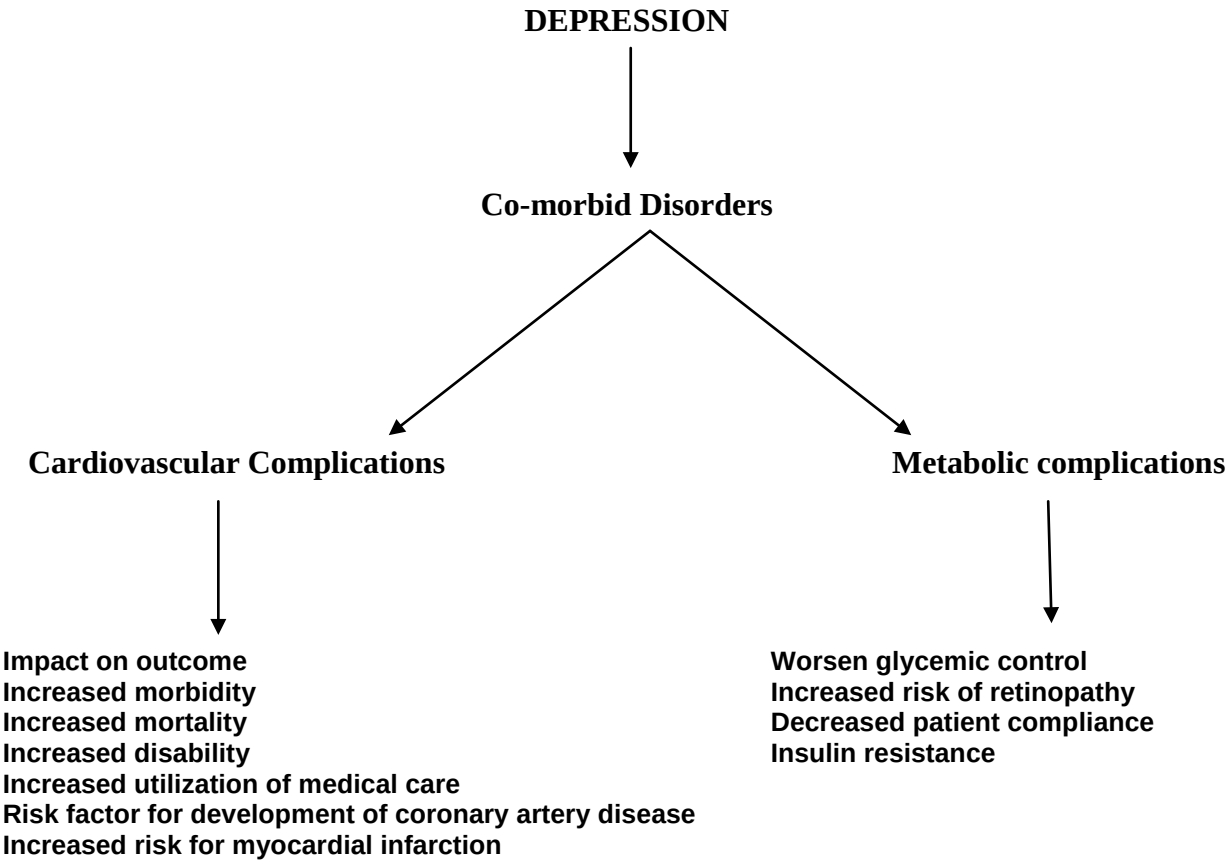

Figure. 2
Consequences of depression with concomitant cardiovascular disorders and metabolic complications

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