



Review article

Pathophysiological mechanisms involved in the relationship between diabetes and major depressive disorder



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ABSTRACT

Diabetes mellitus (DM) and major depressive disorder (MDD) are diseases that are expanding globally. Separately, each presents with several comorbidities for patients. When the two diseases present simultaneously in the same subject, there is a drastic worsening in the quality of life of the patient. This study reviewed the literature relating to the relationship between MDD and DM, bringing forward studies showing that DM develops due to MDD, and others that report the opposite. According to the studies reviewed, DM and MDD are both debilitating conditions that are associated with significant morbidity, mortality, and healthcare costs. When these two diseases coexist, the association results in a decreased adherence to treatment, poor metabolic control, higher rates of complications, a decrease in the quality of life for the patient, increased healthcare use and cost, increased disability and lost productivity, and an increased risk of death. Therefore, it becomes essential that there are larger studies targeting the association of these two diseases, as for the patient, preventing even one of them will ensure improvements in their quality of life.

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1. Introduction

It is estimated that in 2020, chronic disease will be responsible for the majority of deaths and disabilities worldwide. However, one of the

main challenges for the scientific community is comorbidity, which is a clinical condition where two or more diseases occur simultaneously in the same person. For example, MDD and DM that are both highly prevalent conditions, with DM having already affected around 346 million people around the world [1], and MDD affecting over 350 million people worldwide, both of which have a significant impact on health outcomes [2]. Both MDD and DM are extremely disabling, since they are closely associated with other diseases such as; Diabetic retinopathy,

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atherosclerosis, which can lead to a heart attack or stroke, and diabetic neuropathy and diabetic nephropathy, all of which can increasingly worsen the health of each patient. A study conducted in collaboration with the World Health Organization [3], had the aim of showing the damage that is caused to the lives of people who suffer with MDD. The study involved 60 countries, with a total of 245,404 participants, and demonstrated that out of all of the diseases that have been associated with MDD, such as arthritis, asthma, and coronary heart disease; DM is the one which is associated with the greatest deterioration in the health of patients.

Other studies have shown that there is a high prevalence of MDD in diabetic patients [4–5]. Lustman et al. [6], demonstrated that MDD is usually recurrent over a patient's life when in association with DM. Furthermore, Santos et al. [7] showed a prevalence of between 7.8 and 12% for MDD and depressive symptoms in diabetic patients. In a meta-analysis that directly confirmed the association of DM and MDD, the authors came to the following conclusions: 1) Patients suffering with DM had almost double the risk of MDD; 2) One in every three diabetic patients have MDD; 3) The prevalence of MDD varies systematically according to the instrument and the sample used; 4) Diabetic women have a higher risk of MDD; and 5) There was no difference in the prevalence of MDD amongst either DM1 or DM2 [8]. A longitudinal study that accompanied diabetic patients who had MDD as a comorbidity to DM, showed that over 40% of these patients developed MDD after a period of two years, with the study attributing anxiety suffered by these patients as a predictor of the onset of MDD over the next 2 years [9]. Anxiety in patients with diabetes was also associated with a worsening quality of life [10].

The diagnosis and treatment of MDD in diabetic patients has become indispensable in improving their quality of life, since MDD is associated with increased hyperglycemia, and the treatment of this disorder may lead to an increase in the number of patients with good glycemic control [9]. However, there are a high number of patients with MDD and DM, and it is not known which of the two diseases leads to the other, or if the two diseases occur simultaneously. Therefore, the aim of this review is to understand the pathophysiological mechanism involved in the relationship of MDD and DM.

1.1. Major depressive disorder (MDD)

Currently, MDD is considered to be a disease that is caused by multiple factors, and results from the integration of biological, psychological and social risks, as well as being associated with stressful events. It is considered the second major cause of incapacitation amongst all medical conditions in individuals between the ages of 15 and 44 years, and is also associated with a wide range of changes within many biological systems and pathways, such as alterations to the patients emotional, cognitive, psychomotor, autonomic, neuroendocrine and neurochemical systems [11].

Neurobiological studies have shown various abnormalities in individuals with the pathophysiology of MDD, such as decreased monoaminergic neurotransmission [12], low levels of brain-derived neurotrophic factor (BDNF), increases in the levels of inflammatory cytokines [13–17], dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) [11,16,18,19], cortical and subcortical anatomical changes, cerebral functional disorders, and alterations to certain genes that increase the risk for the development of MDD [20]. Thus, it is understood that the integration of all these data shows that MDD is a systemic disorder that can progress towards neurodegeneration [11]. Numerous studies have shown that there is hyperactivity in the HPA axis [11,18,19] in up to 50% of depressed patients, and this can be caused by chronic stress, which in itself can be caused by DM2, thereby reducing the inhibition of the HPA axis and increasing the levels of glucocorticoids in the brain and periphery. These findings have been associated with functional abnormalities and apoptosis of hippocampal neurons, with the

chronic use of antidepressants having the tendency to reverse this phenomenon.

There are three main depressive states: Disruptive Mood Dysregulation Disorder, MDD and dysthymia. The common characteristic shared by these disorders is the presence of sad or irritable moods, which are accompanied by somatic and cognitive changes that significantly affect the operating capacity of the individual [3]. What differs between them are aspects of duration, time or presumed etiology [21].

Disruptive Mood Dysregulation Disorder is characterized by an explosive temper with severe and recurrent verbal or physical manifestations of disproportionate aggression, both in intensity or duration, to a situation or a provocation. The symptoms should manifest at least three times a week in two or more environments, and should persist for at least one year. The disorder must also be first identified between the ages of six and eighteen years [22]. However, individuals with MDD present with symptoms such as: depressed mood or anhedonia – that is, the lack of pleasure and interest in activities that usually give joy and satisfaction, and secondary symptoms such as: self-devaluation and excessive guilt, deficits in concentration and memory, marked indecision, thoughts of death or suicide (cognitive), isolation, slowness or agitation, attempted suicide (behavioral), a decrease or increase in appetite and weight, sleep disorders, fatigue or lack of energy (somatic), with these symptoms presenting for a period of at least two weeks, and having a significant impact on a person's life [18].

Dysthymia or persistent MDD is more chronic and less intense. The depressive mood extends for a period of at least two years, with changes in appetite and sleep, low self-esteem, fatigue or low energy, difficulty concentrating and indecision or pessimism [21]. MDD is undoubtedly the most serious type of depression, although there is a favorable therapeutic response in >50% of cases in the first episode. However, if the condition is not treated properly, it becomes applicant, and in most cases the evolution becomes chronic [20]. It is estimated that around 20% to 30% of patients with DM develop MDD in its various forms [8]. However, these numbers are not accurate because many diabetics are not diagnosed with the disorder [21], and this lack of diagnosis and treatment leads to a significant worsening of the symptoms of both DM and MDD, causing a greater level of damage to public health and also an increase in numbers of deaths due to DM.

1.2. Diabetes mellitus (DM)

Diabetes can be divided into two types: type 1 diabetes mellitus (DM1) and type 2 diabetes mellitus (DM2). DM1 is a process in which the immune system attacks the beta cells within the pancreas, and as a consequence, glucose stays in the blood rather than being used as energy. There is also gestational diabetes, which may arise from a temporary disturbance during pregnancy, and impacts around 2 to 4% of pregnant women, causing an increased risk of development for the mother and fetus [23]. DM1 is also subdivided into two types: autoimmune and idiopathic. About 5 to 10% of people have this type, which normally appears in childhood or adolescence, though in some cases it can also develop in adults. The treatment used for DM1 is a combination of insulin, medications, diet planning and physical activities [23].

DM2 has the highest prevalence amongst the four types, reaching 90% of patients worldwide, and is rare in children, manifesting mostly in adults. This disease is characterized by insulin resistance, abnormal insulin secretion and/or an eventual pancreatic beta-cell failure [24]. A patient with DM2 does not usually make use of exogenous insulin for survival, but some may require this treatment to achieve an adequate level of metabolic control. DM2 results from an interaction between genetic, environmental and behavioral risk factors [19]. In this way, bad lifestyles play an important factor in the development of DM2, examples of which are: physical inactivity, a sedentary lifestyle, cigarette smoking, over consumption of alcohol and obesity. A study has shown that obesity has been found to contribute to approximately 55% of cases of DM2 [25].

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