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Mini Review

TYPE 2 DIABETES MELLITUS, RECURRENT DEPRESSIVE DISORDER AND ANXIETY DISORDERS

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ABSTRACT

There are gender differences in the comorbidity of major depressive disorder, anxiety disorders, and type 2 diabetes, according to several studies. New research reveals that insulin and insulin signalling are connected to neurotransmission of several significant neurotransmitters, as well as neuro-modulation and neuroprotection, refuting the notion that the brain is insulin insensitive. Brain insulin resistance, which may result from peripheral insulin resistance, has been linked to depressive symptoms through changes in neuronal functions. Antidepressant effects may be enhanced by IGF-I's direct stimulation of neurogenesis. Other widely accepted pathophysiological mechanisms that have been proposed by several authors include GR, MR, HPA, adipokine hormones such as ghrelin and the orexigenic hormone, as well as pro-inflammatory factors and adiponectin, leptin, and resistin.

Key words: Diabetes, mellitus, depression, anxiety

GENDER, AGE AND PREVALENCE IN COMORBIDITY

One of the top five reasons for the number of years spent disabled is major depressive disorder (MDD). (1). When compared to the general population, individuals with MDD have a significantly higher prevalence of T2DM. (2). Of those with type 2 diabetes mellitus (T2DM), one in four have clinically significant depression. Diabetes patients may experience depression at higher rates in low- and middle-income nations than in high-income nations. (3). A T2DM diagnosis may be linked to a more severe course of depression and raises the chance of incidental depression. (4). T2DM patients have a 1.5 times increased risk of depression (5). Patients with type 2 diabetes have depression nearly twice as frequently as the general population (6). Perrin NE et al. (7) conducted a thorough meta-analysis of 55 studies, finding that 36% of individuals with type 2 diabetes had an overall prevalence of diabetic distress based on established cut-off outcomes. Secondary analyses have revealed that gender and the presence of co-occurring depressive symptoms were significant factors influencing prevalence. It has been demonstrated to be greater in predominately female groups that have a higher frequency of co-occurring depression symptoms. A different meta-analysis conducted by Anderson RJ et al. (8) reveals that individuals with type 2 diabetes have much higher chances of developing depression than those without the disease, and that women with diabetes have much higher odds of depression than men. Another review by Roy T et al. (9) supports this, demonstrating that women are more likely than men to experience depression, both in those with and without diabetes. One of the factors that contributes to the incidence of depression among T2DM patients under 65 is female gender (10). According to Yang et al.'s research (11), there is a positive correlation between the number of diabetes complications and depressive symptoms, and diabetic distress acts as a mediator in this relationship. Hessler et al. (12) demonstrate in a randomized controlled trial that the alleviation of depression symptoms and the decrease in diabetic distress can happen at the same time. Findings from a different study on T2DM comorbidity, depression, and post-stroke states indicated that the odds of developing severe cognitive impairment were

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doubled for one comorbidity and tripled for two (13).

Adolescents with T2D have increased symptoms of depression at a rate similar to the overall adolescent population (14). Regardless of other comorbidities, persons with type 2 diabetes have a higher risk of depression in the US and the UK, especially if they were diagnosed at an early age (15). Diabetes has been strongly associated with higher depression scores. A plausible explanation could be that an extended illness heightens the likelihood of the disease developing complications. Costs related to the disease are also more likely to be incurred when a chronic illness persists. When all of these factors are present, the patient is more likely to experience mental stress, which raises the risk of depression (16). Depression and the complications of diabetes are closely related. The length of diabetes is a risk factor that is substantially linked to higher anxiety scores in patients with type 2 diabetes. (17).

In individuals with type 2 diabetes, anxiety symptoms ranging from mild to moderate to severe are a relevant clinical comorbidity, and men may be a particularly vulnerable subgroup. Individuals who reported being inactive were found to be 1.4 times and 1.7 times more likely to have mild anxiety symptoms, respectively, than those who reported moderate to severe anxiety symptoms (18). Anxiety following CR is more common in patients with diabetes, particularly in younger patients who smoke or have recently stopped (19). Diabetic anxiety screening has not received enough attention in the past. Specifically, during the first two years of illness, anxiety appears to be more common than depression (20).

Depression is linked to a 1.5–2.6 fold increase in mortality among people with type 2 diabetes mellitus, according to multiple meta-analyses (21). When depressed symptoms worsen, patients with type 2 diabetes who do not take insulin are more likely to die (22).

AFFECTING FACTORS

Anxiety and depression can affect behaviour, which in turn can influence how quickly diabetes develops. Depression is linked to increased likelihood of inactivity and decreased propensity to avoid saturated fats. Anxiety is linked to a higher chance of eating veggies and a feeling of difficulty managing diabetes that is more than twice as high (23). Insulin initiation later in life is linked to anxiety but not to symptoms of depression. Initiation of insulin therapy is also less common in those with high levels of anxiety and depression. (24).

Adults with type 2 diabetes have an increased risk of developing depression; the likelihood of depression in people with type 2 diabetes is also influenced by age, gender, and socioeconomic status. (25). People with type 2 diabetes have a higher risk of depression and a lower quality of life, per a study by Athar M. et al. (26). Furthermore, antidiabetic medications—both old and new—can impair these patients' quality of life and result in neurobehavioral issues. Type 2 diabetes mellitus (T2DM), a risk factor for cardiovascular disease and early mortality, may be more common in patients with depression. According to Tao H et al. (27), there is a causal relationship between major depressive disorder and Attention Deficit Hyperactivity Disorder (ADHD) and an increased risk of type 2 diabetes. This relationship may be mediated by phenotypes associated with obesity and smoking. A meta-analysis by Yu M et al. (28) found that persons with depression had a 41% higher chance of getting diabetes mellitus and a 32% higher risk of type 2 diabetes, with the exact mechanisms underlying the associations as of yet unknown. Another study found a positive correlation between depression symptoms and a direct measure of insulin resistance in individuals who were overweight or obese but did not have diabetes or clinical depression. The family history of T2DM attenuates this association (29).

Numerous studies have demonstrated that depression raises the risk of developing progressive insulin resistance and incidental type 2 diabetes mellitus; however, the relationship between stress and diabetes is less clear because of variations in study design and the types and levels of stress that are experienced. The hypothalamic-pituitary-adrenal (HPA) axis, the immune system, and the autonomic nervous system are among the biological systems involved in adaptation that mediate the relationship between stress and physiological functions. One of the body's mechanisms for responding to both acute and chronic stress is the highly regulated HPA axis. (30) A combined total of all depression measures showed that depression was linked to

an 18% (95% CI 1,12–1,24) higher risk of type 2 diabetes. One study using a standardized diagnostic interview showed the strongest association, while another using a doctor-diagnosed depression showed the weakest link. (31)

Furthermore, Xuan, L. et al. (32) discovered a correlation between depression and genetically determined T2D. A major depressive disorder's estimated hereditary component is 0.35. (33) Depression patients' cognitive function may be impacted by genetic variation. Keller, J. et al. (34) found that while variations in the NR3C2 gene (mineralocorticoid receptors) are more likely to predict the encoding and retrieval of longer-term memories, which functions more dependent on the hippocampus and the medial temporal area, variations in the NR3C1 gene (glucocorticoid receptors) appear to be more likely to predict attention and executive function tasks, suggesting involvement of the prefrontal cortex or cingulate.

Diabetes mellitus type 2 (T2DM) is a complex illness. One risk factor for type 2 diabetes in college students is psychological stress (35). As a common mechanism for both insulin resistance and depression, dysregulation of the hypothalamic-pituitary-adrenal axis may play a major role in the high prevalence of comorbid diabetes and depression (30). Type 2 diabetes mellitus and depression may be causally related, according to MR analysis (32). It was previously believed that the brain was insensitive to insulin, but new research indicates that neuromodulation, neurodefence, and neurotransmission of several important neurotransmitters are all correlated with insulin and insulin signalling. Through changes in neuronal functions, brain insulin resistance—which may be a byproduct of peripheral insulin resistance—is linked to depressive symptoms. The direct stimulation of neurogenesis by IGF-I can amplify the effects of antidepressants. (36). Although variations in metabolic parameters (METv) have been linked to poor health outcomes in people with type 2 diabetes, there is currently no research on the connection between METv variability and depression. Higher METv are a separate risk factor for depression in people with type 2 diabetes. Individuals under 65 years old and men are at a notably higher risk. (37).

It is vital to assess this relationship because vascular damage is a known side effect of type 2 diabetes. According to the vascular depression hypothesis, depression may develop later in life as a result of vascular injury in the frontal and subcortical regions of the brain, which are involved in mood regulation (38). According to Van Agtmaal, M.J.M. et al. (39), there is a correlation between an increased risk of depression towards the end of life and cerebral and peripheral forms of microvascular dysfunction.

Serotonin is a neurotransmitter that regulates mood, satiety, insulin and leptin action, carbohydrate metabolism, and inflammatory cytokines, among other processes that combine depression, type 2 diabetes, and obesity (40). Depression and metabolic disorders are both associated with reduced serotonergic tone. There is an inverse relationship between serotonin and food intake. (41). Type 2 diabetes (T2DM) prospective patients had higher serum tryptophan levels and lower IDO activity (42). In addition to the well-known inflammatory and antioxidant characteristics of metformin, experimental research indicates enhanced serotonin activity and improved synaptic function (43).

Serotonin, dopamine, and norepinephrine neurotransmission are inhibited due to impaired insulin signalling. Additionally, ghrelin, the orexigenic hormone, and adipokine hormones like resistin, adiponectin, and leptin are linked to T2DM and depression (44). Diabetic retinopathy remains associated with a higher risk of impaired cognitive function even after controlling age, low education, the presence of arterial hypertension, and symptoms of depression (45).

According to Wang J et al. (46), patients with diabetes mellitus may be at risk for depression if their systemic immune inflammatory factor (SII) index is high. SII may be a practical and affordable method for diagnosing depression in DM patients.

GENERAL PATHOPHYSIOLOGICAL MECHANISMS

A plausible explanation for the co-occurrence of depression and type 2 diabetes is the impact of psychological stress on the HPA axis. In studies on depression and cognitive abilities, higher levels of psychosis and depression could be used in place of higher cortisol levels (34). An increasing amount of research indicates that hyperglycaemia raises cortisol levels, which are linked to the onset of depression (47). The HPA

axis' feedback is regulated by two different types of receptors: glucocorticoid (GR) and mineralocorticoid (MR) receptors. Even at basal cortisol concentrations, MRs bind to both cortisol and aldosterone with greater occupancy than GR, but they are not as specific as GR. On the other hand, GRs respond to higher levels of cortisol and bind to it more precisely than MRs. When under acute or ongoing stress, MRs seem to regulate the cortisol feedback loop. However, GRs are triggered during periods of severe or protracted stress (48). Sayadi AR et al. (49) reported that mindfulness-based stress reduction (MBSR) training had an impact on stress, anxiety, depression, and serum cortisol levels in T2DM patients during the COVID-19 outbreak. According to their research, middle-aged T2DM patients had higher levels of cortisol at midnight and lower fasting levels of two-hour C-peptide when they had more severe depression. Leptin and ghrelin are two other hormones that share a pathophysiological role in depression and type 2 diabetes. Sang YM et al. (50) found that in middle-aged T2DM patients, there was a correlation between higher midnight cortisol levels and lower fasting levels of two-hour C-peptide and higher depression severity. When comparing the T2DM depression group to the non-T2DM depression group, blood sugar variations were significantly higher in the former. Furthermore, compared to the non-depressed T2DM and non-diabetic groups, the depression group with T2DM exhibited significantly higher evening cortisol and significantly lower levels of two-hour post-meal C-peptide.

People with type 2 diabetes and depression have shorter telomeres, lower BDNF levels, and higher blood levels of serum cortisol and miR-128 in a study by Prabu P et al. (51). These neuroendocrine markers changed more markedly in those with diabetes and depression. Patients with type 2 diabetes who are obese may be more vulnerable to stress and depression, per a different study by Tyagi K et al. (52). Moreover, biomarkers for type 2 diabetes may include physiological indicators like cortisol and adiponectin, which can aid in the early identification of these comorbidities.

It has been demonstrated that pro-inflammatory cytokines in the central nervous system (CNS) impair the synthesis of monoaminergic neurotransmitters, obstruct serotonergic transmission, and enhance glutamatergic activity via a number of well-established pathways, including kynurein pathway activation or tetrahydrobiopterin pathway interference. (53, 54). TNF levels are correlated with depression and type 2 diabetes. Patients with type 2 diabetes mellitus and major depression had significantly higher serum TNF-α levels than those without the condition. (55). All patients with diabetes had decreased cortical grey matter thickness in the left anterior part of the singula, according to a study by Ajilore O et al. (56). Moreover, individuals with diabetes and depression exhibited notable bilateral losses of prefrontal cortical grey matter in comparison to healthy controls. Cortical grey matter thickness and clinical features exhibited a significant negative correlation with cerebrovascular risk factors in all three groups, with the strongest negative association observed in the left dorsomedial prefrontal cortex. Tian J. et al. (57) discovered that the bilateral posterior cingulate cortex (PCC), hippocampus, and right putamen displayed aberrant neural activity in T2DM patients with depression and those without it. Subcortical central grade of the right hippocampus and putamen is higher in patients with T2DM and depression than in those without depression. Furthermore, cortical amplitude of low-frequency fluctuation (ALFF) in PCC, subcortical DC in the putamen of depressed T2DM, and hippocampus of undepressed T2DM are correlated with cognitive outcomes. T2DM is the cause of metabolic disorder, decreased salivary alpha-amylase activity, and cognitive decline, according to Thummasorn S et al. (58). Moreover, T2DM patients with depression have higher rates of hyperglycaemia and cognitive decline than do T2DM patients without depression.

COMPLICATIONS AND EFFECT ON SYMPTOMS

Brain anatomical abnormalities and decreased performance in several domains of cognitive function are strongly correlated with type 2 diabetes mellitus (T2DM). It is anticipated that as the population ages and the diabetes epidemic spreads, the neurological effects of the disease will worsen and pose a threat to future health. The primary mechanism underlying this condition is undoubtedly the dysfunction of the insulin signal, which results in the inability of neurons to take up glucose for energy (59). A higher prevalence of depression was

consistently linked to a lower proportion of somatic symptoms and a higher proportion of anhedonia, cognitive, cognitive, negative affect, and symptoms of disturbed sleep (60). Depression in diabetics who have refused antidepressants has been linked to cognitive declines (61). In hypertensive patients, type 2 diabetes was found to be significantly correlated with the anhedonic subtype of major depression in another study (62). Silva N et al. (63) discovered conflicting data regarding the connection between insulin resistance and depression. The majority of observational studies' findings, which are typically cross-sectional and have a tendency to find positive associations, are not supported by cohort studies. People with type 2 diabetes experience higher levels of anxiety and depression in response to blood sugar fluctuations and poor sleep, according to a retrospective analysis by Yang W. et al. (64). One main risk factor for depression and anxiety is neuropathic pain, its intensity, and cognitive processing (pain catastrophizing) (65).

Those with type 2 diabetes who also have depression have an increased risk of both fatal and non-fatal CVDs (66). Patients with depression also experience cognitive decline and vascular damage as a result of T2DM. According to a study by Qiu, C. et al. (67), people with diabetes perform worse on tests of processing speed and executive function than people without the condition, and this difference is primarily mediated by neurodegeneration and cerebrovascular disease. Alghafri RM et al. (68) note a significant increase in depressive symptoms in patients with neuropathy, compared to those without neurological complications, confirming the link between depression and diabetic peripheral neuropathy (DPN).

Preclinical and clinical studies have demonstrated that endogenous glucose production (EGP) can be disrupted by critical illness through a variety of mechanisms. Glucocorticoids and vasopressors, which are given as part of clinical care, are two examples of iatrogenic stroke mechanisms. Other mechanisms include increased systemic inflammation, the release of catecholamines and counterregulatory hormones, modifications in the hypothalamic-pituitary axis, insulin resistance, lactic acidosis, and insulin resistance. Both abnormally elevated and abnormally suppressed EGP during critical illness contribute to hyperglycaemia and hypoglycaemia, which are independently linked to increased mortality rates. Furthermore, elevated EGP may stimulate protein catabolism, exacerbating myopathy in critical illness and potentially complicating treatment. (69) In the typical clinical scenario, peripheral tissues use glucose less efficiently due to increased counterregulatory hormones, which also speed up the processes of glycogenolysis and gluconeogenesis and ultimately result in diabetic ketoacidosis. (70)

In conclusion, additional research is necessary to confirm these findings and establish the association between depression, anxiety, and type 2 diabetes, even though there is a wealth of data supporting the mechanisms behind this association.

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