



## Diabetes and Depression: A Bidirectional Phenomenon

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### ABSTRACT

Diabetes mellitus is a strong molecular etiological upstream event that leads to different pathological problems like Cardio-vascular disease, nephropathy, neuropathy, retinopathy, hearing loss, and immunological disturbances, the most common of which is depression. Diabetes and depression relationship is thought to be bidirectional, meaning that depression can lead to diabetes and diabetes can assist the onset of depression. Depression is one of the most overlooked symptoms in diabetes patients, and it is strongly related to a decline in quality of life. Several pathological links are discussed in this review, including dysregulation of the hypothalamic pituitary-adrenal (HPA) axis and neurotransmitter systems, particularly the monoaminergic system, the role of oxidative stress, neuroinflammation, and cell death, impaired neurogenesis and BDNF synthesis, particularly in the hippocampus and prefrontal cortex, brain areas that regulate emotional behaviour, and finally, epigenetic factors.

**Keywords:** Diabetes mellitus, Depression, Bidirectional, Hypothalamic pituitary-adrenal axis.

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### INTRODUCTION

Diabetes is a chronic metabolic condition that requires medical treatment, self-management, support for families and education for preventing or delaying end-organ harm.<sup>1,2</sup> Diabetes has become a national burden because of the societal cost of pain and suffering, high medical expenditures owing to undiagnosed diabetes, and other diabetes-related health care expenditures.<sup>2</sup> According to a World Health Organization report (November 2014), by 2030, there will be approximately 347 million diabetics worldwide, and diabetes will be the seventh leading cause of death.<sup>3</sup> During diabetes, our body cannot metabolize sugar properly on target tissues either because of insensitivity towards target receptor or low amount of insulin production from beta cells of pancreas. This will stimulate the break down mechanism body's own fat, protein, and glycogen to produce glucose, which will cause for high blood sugar levels with excess ketones production in liver as a by-product.<sup>61</sup> Patients with type I and type II diabetes are more likely to suffer from depression. Diabetes and depression have a bidirectional connection, which implies that diabetes may cause depression and depression can induce diabetes. Almost 26% of diabetes patients worldwide are said to suffer from different neurological

diseases, including depression.<sup>4</sup> Many ideas exist to explain the aetiology of depression, including monoamine deficiency, oxidative stress, socioeconomic burden, inadequate sleep/excess sleep, lack of exercise, obesity, inflammation, immunological dysfunction, and stress hormone overproduction.<sup>5</sup> The primary goal of this review is to describe the many pathophysiological factors associated with diabetes-induced depression. An interview with an expert in that field of mental care should confirm the screening for depression, and short questions should be answered to detect depression. The Beck Depression Inventory, the Centre for Epidemiologic Studies Depression Scale (CES-D), the Hospital Anxiety and Depression Scale, and several versions of the Patient Health Questionnaire (PHQ) were the most often used screening tools for depression.<sup>6</sup>

It is quite challenging for medical experts to manage individuals who have depression as well as diabetes mellitus. According to research, glucocorticoid hypersecretion and dysregulation, in addition to low monoamine levels, have a role in the pathophysiology of depression.

The hypothalamic-pituitary-adrenal (HPA) axis is responsible for regulation of the hypothalamus pituitary adrenal axis. Depression is attributed to reduction of glucocorticoid receptors in the brain regions that cause for feedback inhibition mechanism in the hippocampus region. Treatment with antidepressants might control the neurochemical and neuroendocrine changes in depression. Therefore, controlled regulation of glucocorticoid and monoamine level plays an important role for the development of antidepressant agents.<sup>7</sup> There are currently existing antidepressants that can treat



depression comorbidly with diabetes. The effectiveness of these drugs depends upon controlling the altered monoaminergic functions in the brain which regulate behaviour and emotional activities in the brain. Existing antidepressant therapy for depression co-morbid with diabetes has a number of disadvantages. It has been observed that fluoxetine causes hyperglycaemia, imipramine causes increased body mass index and decreases insulin secretion in depressed individuals, mirtazapine causes weight gain and increases leptin concentration, and so on.<sup>8</sup> In an experimental study on chronic administration of 4i (N-(3-chloro-2-methylphenyl) quinoxalin-2-carboxamide), a novel 5HT<sub>3R</sub> antagonist reversed diabetes-induced depression in mice by modulating serotonergic system.<sup>9</sup>



**Figure 1:** Different pathophysiological mechanisms of diabetes induced depression

#### Depression with comorbid diabetes:

According to the World Health Organization, depression is a serious mental illness causing prevalent health problem worldwide. There are number of theories which can explain the pathogenesis of depression, including monoamine deficiency, oxidative stress, overactivity of the hypothalamic-pituitary-adrenal (HPA) axis, neurodegeneration and others.<sup>7</sup> Depressive patients often will have features like anxiety disorders, and those with anxiety disorders in future will have depression. It becomes very important to detect the specific depressive disorder and the specific anxiety disorder like post-traumatic stress disorder, social phobia (social anxiety disorder), agoraphobia, generalized anxiety disorder, panic disorder and obsessive-compulsive disorder, as each may require different interventions.<sup>26</sup> Major depressive disorder illustrate change of mood, characterized by sadness or irritability and cause for several psychophysiological changes, such as lack of sleep, appetite, or sexual desire; constipation; inability to experience pleasure in normal day to day work; negative

thoughts; and slowing down of speech and action loss of energy, feelings of worthlessness or guilt, difficulty with concentration or thinking. Depression patients soon or later will have manic episodes which comprise with hyperactivity, euphoria, and an increase in pleasure seeking.<sup>27</sup> Globally female gender, middle aged people, unmarried people, people with low income, family history of depression, history of childhood abuse, other psychiatric disorders, and chronic medical conditions like diabetes will more likely to have depression in near future.<sup>28</sup>

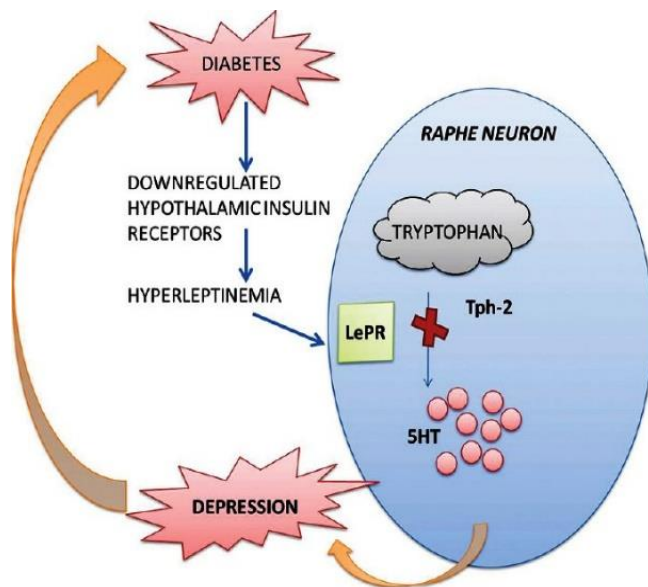
Elevations in depressive symptoms or the prevalence of major depressive disorder (MDD) have been seen mostly among diabetics as compared to non-diabetic individuals. Multiple community-based, large-scale prospective studies have recently established that patients with type 2 diabetes had a significantly higher risk of depression than control participants (17.6 percent vs. 9.8 percent, OR = 1.6 [95 percent confidence interval (CI) of 1.2–2.0]).<sup>2</sup> Depression was shown to be more frequent among persons with diabetes, whether diagnosed or undiagnosed, according to a recent epidemiological research involving 90686 participants.<sup>6</sup>

#### Diabetes induced depression: pathophysiological mechanisms:

##### *5-Hydroxytryptamine System related to diabetes and depression*

Monoamines such as 5-hydroxytryptamine, dopamine, epinephrine, and nor-epinephrine play a significant part in the neurological process of depression, and any of these monoamines that are depleted can contribute to depression.<sup>1</sup> A clear link has been found between 5-HT transporter (5-HTT) polymorphisms and depression in diabetics, lending credence to 5-HT's potential role in diabetic-related depression.<sup>10</sup> Polymorphisms in the lower expressing allele of the 5-HTT gene 5' promoter region may lead to an increased vulnerability to depression in response to a complete environmental stress stimuli. The lower expressed allele also had a larger contribution to severe depression as a result of stress events like diabetes compared with the higher expression allele.<sup>10</sup>

Decreased 5-HTT gene expression in victims of depressed suicides shows the significance of carriers in depression.<sup>11</sup> Diabetes has been demonstrated to alter the balance of FFT (free fraction of L-tryptophan) with other neutral amino acids which are necessary to determine the quantity of FFT to be converted into 5-HT, eventually leading to 5-HT suppression.<sup>12,13</sup> Though the specific mechanism is unknown, it has been proposed that brain corticosterone regulates postsynaptic 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub>, resulting in 5-HT mediated behavioural, neuroendocrine, and temperature regulating effects.<sup>14,15</sup> 5-HT<sub>1A</sub> receptors are potential targets for novel antidepressant medicines with efficacy in diabetes-induced depression because they may alter Glucocorticoid levels, which influence glycaemic control.<sup>14</sup>



**Figure 2:** The levels of brain leptin regulates synthesis of serotonin. Increase in excess brain leptin levels decreases tryptophan hydroxylase-2 resulted in decreased circulating neuronal levels of serotonin

#### **Inflammation related to diabetes and depression**

The interplay of immune system and central nervous system (CNS) components in the development of MDD has been widely investigated and addressed in numerous studies.<sup>16,17,18</sup> On one hand, a systemic inflammatory reaction can be transmitted to the CNS via inflammatory cytokines and immune cells, inducing illness behaviour, which refers to behavioural abnormalities associated with infection, such as tiredness, anhedonia, and anorexia.<sup>19,20</sup> Acute and chronic psychosocial stresses, on the other hand, can be mediated by immune signalling inside the brain parenchyma and have a huge impact on systemic immune activity as well as on intra- and inter-regional communication within the brain, affecting mental processes and behaviours.<sup>16</sup> Pro-inflammatory metabolic malfunction may occur which raises the glutamatergic burden in the synapse and more general inflammatory MDD procedures imply immune-mediated malfunctions, especially in the glutamate neurotransmission and glutamate turnover, in MDD pathogenesis.<sup>21,22</sup> Similar problems have been found in T2DM animal models, suggesting similar glutamatergic immune-mediated disruption across the course of both conditions. In diabetic patients with depressive illness, pro-inflammatory cytokines have a key function and studies have shown that the interleukin 6 (IL-6) and tumour necrosis alpha (TNF- $\alpha$ ) levels in depressed patients are greater than in those without depression. Dutheil and colleagues observed high fat diet (HFD) induced anxiety and depression-like behaviour, and increase in the expression of IL-1, IL-6, TNF-, and TLR-4 in the hippocampus, coupled with glucose intolerance, and by inhibiting inflammatory activation HFD-induced anxiety and depression-like behaviour were avoided, indicating that inflammatory mediators connect the metabolic and behavioural effects of HFD.<sup>23</sup>

#### **Oxidative stress related to diabetes and depression**

Oxidative stress results from the imbalance between reactive oxygen (ROS) generation, hydrogen peroxide, radical hydroxylic and superoxide anion production as well as endogenous antioxidant levels.<sup>60</sup>

Cells differ in their ability to use nitrogen or dioxygen to produce energy, generating both reactive oxygen species (ROS) such as hydrogen peroxide, hydroxyl radicals, and superoxide anion, and reactive nitrosative species (RNS) such as nitric oxide, peroxyxynitrite, and nitrogen dioxide under basal metabolic conditions.<sup>24</sup>

Endogenous antioxidants levels will be decreased and the generation of these free radicals will be enhanced during oxidative stress. Due to the high metabolic activity and presence of low amount of endogenous antioxidants inside the brain, the brain is especially vulnerable to reactive oxygen (ROS) and reactive nitrogen species (RNS).<sup>25</sup>

This results in major alterations in cell function and biomolecular damage, such as carbonyl deformation, breaking of DNA with purine and pyrimidine basis damage and increasing lipid peroxidation involving the destruction of the electron transmission system and interrupting mitochondrial activity.<sup>24,30</sup>

Therefore, laboratory investigations have revealed that diabetes animals have more significant depressant-like attitudes than normal glycaemic animals, which can lead, in the hippocampus and pre-frontal brain, to decreased SOD, CAT & GSH activities.<sup>31,33,34</sup>

#### **Hypothalamic–pituitary–adrenal (HPA) axis dysregulation related to diabetes and depression**

The activation of the HPA axis modulates and maintains homeostasis, primarily in circumstances such as emotional stress, physical or metabolic stress.<sup>35</sup>

The activation signalling is initiated by the neurosecretory neurons in the hypothalamic paraventricular nucleus, which release corticotropin-releasing hormone and arginine vasopressin into the portable pituitary circulation, both of which will harmoniously stimulate and release the pro-opiomelanocortin peptide fragment, the adrenocorticotropin cell, into a pituitary corticotrophin cell.<sup>36</sup>

This circulatory glucocorticoid regulation directly on the hypothalamus and in pituitary or hippocampus and pre frontal cortex modulates the activity of the HPA axis via negative feedback.<sup>37</sup>

The baseline plasma hormone (ACTH) and the increasing level of corticosteron hormone in diabetic animals have been reported during diabetic studies in laboratory animals.<sup>29</sup>

In contrast, the prolonged activation of the stress system or the hyperactivity of this HPA-axis may change brain areas such as the hippocampus and prefrontal cortex brain



areas associated with HPA axis ownership controls, and also the autonomic stress responses.<sup>38,39</sup>

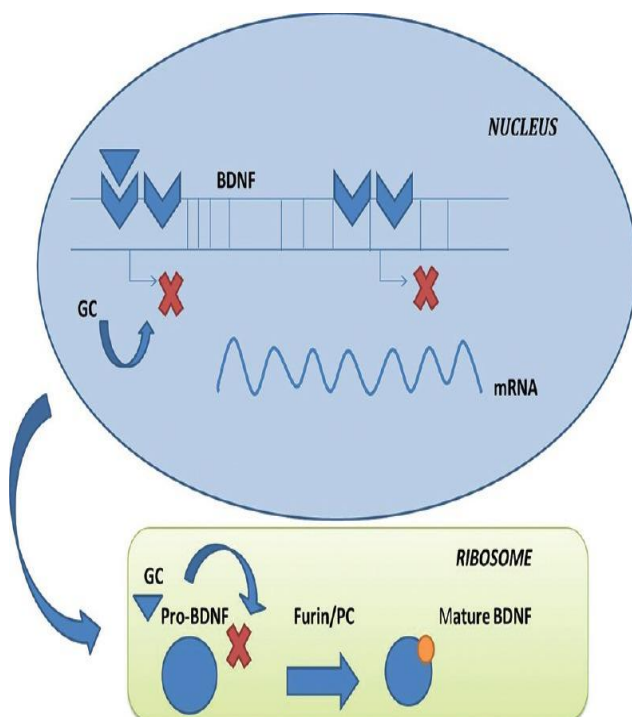
The alterations in diabetes and depressed patients, which indicate that an enhanced glucocorticoid response to stress might result in reduced hippocampus cell proliferation and correlate diabetes with depression, are particularly relevant for the module of the HPA system response via feedback loops.<sup>37</sup>

### **Impaired Neurogenesis and BDNF synthesis related to diabetes and depression**

Neurogenesis is a process in which new cells proliferate from progenitor cells, differentiate into astrocytes, oligodendrocytes, or neurons, and are incorporated into specific brain regions.<sup>40,41</sup>

Neuroplasticity is recognized as an important tool for brain adaptability, memory development, and cognitive and emotional processes in the hippocampus and subventricular zone, which are more vulnerable to environmental stress, hyperactivity of the HPA axis, and inflammation.<sup>29</sup>

One of the primary neurotrophins involved in neurogenesis, the neural network BDNF, is crucial for differentiation and the survival of the neuronal network in the way it modulates the synaptic topology.<sup>42</sup> In addition, research show that antidepressants promote hippocampus neurogenesis through the BDNF and TrkB receptors.<sup>43,44</sup> Therefore by increasing BDNF levels in specific area of the brain could be the novel therapeutic target for treating diabetes induced depression.



**Figure 3:** The transcription of neurotrophic factors (BDNF) regulated by Glucocorticoids (GCs). GCs increase the synthesis of BDNF by alteration of transcription in nucleus and translation in ribosomes

### **Neurotransmitter dysregulation related to diabetes and depression**

Apart from the monoamine theory some studies also focuses on the involvement of other neurotransmitters, like the gamma-aminobutyric acid (GABA) and/or glutamate, in which reduced levels of GABA and increased concentrations of glutamate in plasma or cerebrospinal fluid is seen in the patients with depression.<sup>45,46</sup> Other studies have investigated the involvement of other molecular mechanisms in depression, including the participation of neuropeptidergic systems (such as substance P, corticotrophin releasing factor, neuropeptide Y, vasopressin, oxytocin, galanin, and melanin-concentrating hormone), glucocorticoids, opioid and cannabinoid receptors.<sup>47,48</sup>

Some experimental studies have shown that both depressed individuals and diabetics have considerably reduced plasma tryptophan levels.<sup>49,50</sup> It was also discovered that diabetic animals had changes in serotonin levels in the examined brain regions such as the thalamus/hypothalamus, cerebellum, and brainstem, while these levels were increased in the cerebral cortex and midbrain.<sup>51</sup>

Thus, it is critical to emphasise the link between depression and diabetes, and it has been established that neurotransmitter dysregulation can contribute to both depression and diabetes.

### **Epigenetic factors related to diabetes and depression**

Genetic factors have also been implicated in the pathophysiology of several diseases including depression associated with diabetes.<sup>52</sup>

Diabetically and depressively affecting cellular transcription in target bodies leads to enhanced gene expression that supports cell growth and activation of pro-inflammatory, pro apoptotic and pro-fibrotic substances.<sup>52,53,54</sup> Epigenetic changes like DNA cytosine methylation, histone post-translational modifications in chromatin, and in non-coding RNAs, will affect gene expression individually and can modulate disease states.<sup>54</sup> Furthermore, the significance of epigenetic processes in the aetiology and pathophysiology of depression and diabetes has been widely studied, and epigenetic drugs may specifically alter the culprit gene responsible for causing the disease and produce an immediate effect on both conditions - diabetes and depression - with less or no adverse effects.<sup>54,55,56,57,58,59</sup>

### **CONCLUSION**

Often, depression coexists with diabetes, affecting the prognosis of patients and causing an increase in the overall cost of therapy. It is very difficult to treat depression and with comorbid DM it becomes even bigger challenge. In conclusion many theories have been suggested as mentioned in this review, but additional research and more work should be done on an accurate and timely diagnosis; and an understanding of the relationship

between diabetes and depression. Considering the metabolic side effects of different antidepressants and the therapy choices available, this complex disease profile suggests new integration potential between clinical characteristics in clinical decision-making bodies.

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