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The Bidirectional Link Between Diabetes and Depression: Mechanisms and Management

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Abstract

The bidirectional relationship between diabetes and depression represents a significant public health challenge, necessitating a deeper understanding of their interconnected mechanisms and integrated management strategies. This review highlights the urgent need to address the high prevalence of comorbid depression in diabetic patients, the shared biological pathways exacerbating both conditions, and the gaps in current therapeutic approaches. By synthesizing existing evidence, this paper aims to inform clinicians and researchers about effective interventions to improve patient outcomes. The review explores key insights, including the roles of neuroendocrine dysregulation, chronic inflammation, oxidative stress, and gut-brain axis dysfunction in linking diabetes and depression. It also examines psychosocial and behavioral factors, such as lifestyle choices and treatment adherence, that contribute to this bidirectional relationship. Additionally, the paper discusses pharmacological treatments, such as selective serotonin reuptake inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors, alongside non-pharmacological interventions like cognitive-behavioral therapy (CBT) and integrated care models. Case studies and genetic research further elucidate the complex interplay between these conditions, offering evidence-based strategies for management. Future research should focus on longitudinal studies to clarify causal pathways, personalized medicine approaches to tailor treatments, and the development of novel therapies targeting shared mechanisms like inflammation and metabolic dysregulation. Expanding access to integrated care models and addressing socioeconomic disparities will be critical in mitigating the burden of comorbid diabetes and depression. Ultimately, advancing interdisciplinary collaboration and public health policies will pave the way for more effective, holistic patient care.

Keywords: Bidirectional relationship, Depression, Diabetes, Gut-brain axis, Inflammation, Integrated care, Neuroendocrine dysregulation, Oxidative stress

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Introduction

The bidirectional relationship between diabetes and depression has garnered increasing scientific attention, emphasizing the complex interplay of biological, psychological, and environmental mechanisms [1-6]. The literature underscores that these conditions do not exist in isolation but influence each other through multifaceted pathways, necessitating integrated management strategies [7-11]. One of the central mechanisms linking diabetes and depression involves neuroendocrine dysregulation, particularly within the hypothalamic–pituitary–adrenal axis. Gianotti et al. [12] highlight that stress-induced dysregulation of the hypothalamic–pituitary–adrenal axis plays a pivotal role in both conditions. Stress-related activation of this axis can lead to increased cortisol levels, which contribute to insulin resistance and inflammation, thereby exacerbating diabetes. Conversely, the metabolic disturbances in diabetes can further dysregulate the hypothalamic–pituitary–adrenal axis, creating a vicious cycle that sustains or worsens depressive symptoms. This bidirectional influence underscores the importance of stress management and neuroendocrine regulation in therapeutic approaches [13-16].

Inflammation emerges as another critical shared pathway. The literature indicates that systemic inflammation is a common denominator in both depression and diabetes. Liu et al. [17] elaborate that inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are elevated in both conditions, promoting insulin resistance and neuroinflammation. This inflammatory milieu not only impairs glucose metabolism but also affects neurotransmitter function and neuroplasticity, contributing to depressive symptoms. Similarly, Zhao and Shen [18] discuss how systemic inflammation, driven by periodontal disease and diabetic retinopathy, can influence mood disorders, further illustrating the interconnectedness of inflammatory pathways across different diabetic complications and depression.

Oxidative stress is another shared mechanism. The accumulation of reactive oxygen species damages cellular structures and impairs insulin signaling, as noted by Liu et al. [17]. Oxidative stress also affects neuronal health, leading to neurodegeneration and mood disturbances. The role of natural products and traditional Chinese medicine in mitigating oxidative stress and inflammation has been explored by Lu et al. [19], suggesting potential adjunct therapies that target these shared

pathogenic processes. The gut-brain axis has gained prominence as a novel mechanistic pathway linking diabetes and depression. Makris et al. [20] and Nanthakumaran et al. [21] emphasize that the bidirectional communication between the gut microbiota and the brain influences mood and metabolic health. Alterations in gut microbiota composition can lead to increased intestinal permeability, systemic inflammation, and neurochemical changes that predispose individuals to depression and metabolic dysregulation. Tsai et al. [22] further support this by demonstrating correlations between gut microbiota diversity, depressive symptoms, and brain structure in late-life depression, suggesting that microbiota modulation could be a therapeutic target.

Neuroimmune interactions also play a significant role. The immune system's activation in response to metabolic disturbances can influence brain function [23-26]. For instance, the immune response to periodontal disease, as discussed by Barutta et al. [27], can exacerbate systemic inflammation, impacting both glycemic control and mood regulation. Similarly, stress and immune dysregulation can influence the progression of inflammatory bowel disease, which shares bidirectional links with depression, as highlighted by Ge et al. [28].

Management strategies for this bidirectional relationship are evolving. Sridhar [29] discusses the potential of democratized care models, where non-specialist health workers are trained to manage depression in diabetic patients, demonstrating the importance of accessible, multidisciplinary approaches. Pharmacological interventions targeting shared pathways, such as anti-inflammatory agents and SGLT2 inhibitors, are also under investigation [30-33]. Kale et al. [34] explore the role of SGLT2 inhibitors and their potential to modulate aging-related proteins like Klotho, which may confer protective effects against diabetic complications and associated mood disorders. Complementary and alternative therapies, including traditional Chinese medicine and natural products, have shown promise in addressing the shared mechanisms of insulin resistance, oxidative stress, and inflammation. Lu et al. [19] suggest that these therapies could expand treatment options for patients with comorbid depression and diabetes, especially by targeting underlying pathophysiological processes.

The importance of interprofessional education and collaborative care is emphasized by Siddiqi et al. [35], who advocate for increased awareness among healthcare providers regarding the bidirectional nature of these conditions. Recognizing the interconnected pathways can facilitate early intervention, improve treatment adherence, and ultimately enhance patient outcomes. Furthermore, the literature indicates that comorbid conditions such as periodontal disease, diabetic retinopathy, and even tuberculosis can influence the diabetes-depression nexus through inflammatory and immune pathways [18, 27, 36]. These findings highlight the necessity of comprehensive care that addresses systemic inflammation and infection control as part of managing the bidirectional relationship.

In conclusion, the bidirectional link between diabetes and depression involves complex mechanisms including neuroendocrine dysregulation, systemic inflammation, oxidative stress, gut microbiota alterations, and immune responses. These interconnected pathways not only contribute to the pathogenesis of each condition but also offer potential targets for integrated therapeutic strategies. Recognizing and addressing these shared mechanisms through multidisciplinary care, novel pharmacological agents, and lifestyle interventions can improve outcomes for patients suffering from both diabetes and depression [37-40]. Continued research into these pathways will be essential for developing personalized and effective management approaches that can break the cycle of comorbidity. Diabetes and depression are two prevalent chronic conditions that often coexist, creating a complex interplay that significantly impacts patient health and quality of life. This article explores the bidirectional relationship between diabetes and depression, examining the underlying mechanisms and potential management strategies.

Prevalence of Depression in Diabetic Patients

The prevalence of diabetes and depression is a significant public health concern, with both conditions showing a complex bidirectional relationship [41-45]. This relationship is characterized by a higher prevalence of depression among individuals with diabetes and an increased risk of developing diabetes in those with depression [46-50]. Diabetes affects 422 million people globally, with projections indicating a rise to 439 million by 2030 if current trends continue. Depression is more common in women, with a lifetime risk of 20% for women and 12% for men [51, 52]. Depression is twice as frequent in individuals with diabetes compared to those without. Approximately 10% of individuals with diabetes have major depression, and 30% have both major and minor depression [53, 54]. The prevalence of depression among individuals with type 2 diabetes varies by region, with higher rates in Asia (32%) and Australia (29%) compared to Europe (24%) and Africa (27%) [55]. In middle-income countries like Brazil, Chile, China, Indonesia, and Mexico, the prevalence of diabetes among individuals with depressive symptoms was found to be slightly higher (28.9%) compared to those without depressive symptoms (23.8%) [56]. In Ireland, England, and the USA, the prevalence of undiagnosed depression was higher among people with diabetes, with significant variations across countries. For instance, in England, the prevalence was 19.3% among those with diabetes compared to 11.8% in those without [57]. The international prevalence and treatment of diabetes and depression (INTERPRET-DD) study, conducted across 14 countries, found that 10.6% of people with type 2 diabetes were diagnosed with major depressive disorder, and 17.0% reported moderate to severe depressive symptoms [58]. In Ethiopia, a study reported a high prevalence of depression (37.2%) among diabetes patients, with factors such as social support and educational level being significantly associated with depression [59].

A meta-analysis study by Khaledi et al. [55], which included 248 observational studies and 273 reported prevalence rates, found that out of 83,020,812 participants, 23,245,827 (28%; 95% confidence interval (CI): 27, 29) suffered from varying severity levels of depressive disorders. This indicates that nearly one in four adults with type 2 diabetes experienced depression. Depression prevalence was separately reported for males and females, involving 137,372 males and 134,332 females. Of these, 31,396 males (23%, 95% CI: 20, 26) and 45,673 females (34%, 95% CI: 31, 38) were found to be depressed. Compared to the global estimated prevalence of 28%, depression prevalence varied by region: lower in Europe (24%) and Africa (27%), higher in Australia (29%) and Asia (32%), equal to the global estimate in America (28%). Depression was more common in subjects younger than 65 years (31%) compared to older individuals (21%). Given the high prevalence of depressive disorders among diabetic patients, the study highly recommends screening these patients for co-morbid depression and its associated risk factors. In summary, the study revealed a significant prevalence of depression among individuals with type 2 diabetes, with variations observed across gender, geographical regions, and age groups, underscoring the importance of routine screening.

Understanding the Bidirectional Relationship

The relationship between diabetes and depression is multifaceted, with each condition influencing the other. Studies have shown that individuals with diabetes are at a higher risk of developing depression, while those with depression are more likely to develop diabetes [60-65]. This bidirectional link is supported by various epidemiological studies, which indicate that depression can lead to poorer glycemic control and increased complications in diabetic patients [17, 66]. Conversely, the stress associated with managing diabetes can exacerbate depressive symptoms, creating a vicious cycle that complicates treatment [1, 29].

A study by Maina et al. [67] on depression and type 2 diabetes reported causal relationship between depression and type 2 diabetes. Mendelian randomization analysis indicated a significant causal effect of depression on type 2 diabetes. The odds ratio was 1.26 (95% CI: 1.11 to 1.44), with a p value of 5.46×10^{-4}. Conversely, the study found no causal effect in the reverse direction, meaning type 2 diabetes did not causally affect depression. Mediation analysis revealed that body mass index accounted for a significant portion of the effect of depression on type 2 diabetes. Specifically, 36.5% (12.4 to 57.6%, p = 0.0499) of this effect was mediated by body mass index. Standard genome-wide association studies (GWAS) for type 2 diabetes and depressive symptoms did not identify any shared genetic loci. However, multiphenotype GWAS (MP-GWAS) successfully identified seven shared loci. These loci were mapped to genes including transcription factor 7-like 2 (TCF7L2), cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1 (CDKAL1), insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2), sprouty RTK signalling antagonist 2 (SPRY2), CCND2-AS1, insulin receptor substrate 1 (IRS1), and cyclin-dependent kinase inhibitor 2B (CDKN2B)-AS1. Major depressive disorder did not show any significant associations in either the standard GWAS or the MP-GWAS. Most of the loci identified by MP-GWAS were associated with expression quantitative trait loci. Notably, single nucleotide polymorphisms implicated the cell cycle gene CCND2 in pancreatic islets and the brain, and the insulin signaling gene IRS1 in adipose tissue. These findings suggest a complex, multitissue, and pleiotropic underlying mechanism connecting depression and type 2 diabetes. In summary, the study demonstrates a significant causal link from depression to type 2 diabetes, partially mediated by body mass index. While traditional GWAS did not find shared genetic links, MP-GWAS revealed several common genetic loci with implications for cell cycle and insulin signaling across multiple tissues, highlighting the importance of managing depressive symptoms and maintaining a healthy weight to prevent type 2 diabetes.

Mechanisms Linking Diabetes and Depression

Several physiological and psychosocial mechanisms contribute to the bidirectional relationship between diabetes and depression (Table 1). Inflammation, oxidative stress, and neuroendocrine dysregulation are key biological pathways that link these conditions [68-72]. For instance, chronic inflammation associated with diabetes can affect brain function and mood regulation, leading to depressive symptoms [17]. Additionally, psychosocial factors such as social support, lifestyle choices, and stress management play significant roles in this relationship [17]. Research has also highlighted the impact of the gut-brain axis in the development of depression among diabetic patients. Dysbiosis, or an imbalance in gut microbiota, can influence both metabolic and mood disorders, suggesting that interventions targeting gut health may offer new therapeutic avenues for managing comorbid diabetes and depression [20, 21].

Biological mechanisms

- Inflammation and oxidative stress: Both diabetes and depression are associated with increased inflammation and oxidative stress. These processes can lead to neuronal damage and impaired neurotransmission, contributing to the development and progression of both conditions [17, 47].

- Neuroendocrine dysregulation: Dysregulation of the hypothalamic-pituitary-adrenal axis is a common feature in both diabetes and depression. Elevated cortisol levels, a result of hypothalamic-pituitary-adrenal axis dysregulation, can lead to insulin resistance and hyperglycemia, which are risk factors for diabetes [47, 73].

- Insulin resistance and neurotransmitter dysfunction: Insulin resistance, a hallmark of type 2 diabetes, can impair serotonin signaling in the brain, potentially leading to depression. Conversely, depression can exacerbate insulin resistance through lifestyle factors and stress [47, 73].

Psychological and behavioral mechanisms

- Lifestyle factors: Depression often leads to poor lifestyle choices, such as unhealthy eating and physical inactivity, which can worsen glycemic control and increase the risk of diabetes. Similarly, the stress of managing diabetes can contribute to the onset of depression [73, 74].

- Adherence to treatment: Depression can impair self-management in diabetic patients, leading to poor adherence to treatment regimens and worse health outcomes. This can create a vicious cycle where poor diabetes management exacerbates depression [75, 76].

Psychosocial factors

- Socioeconomic status and social support: Lower

Table 1: Mechanisms linking diabetes and depression.

Mechanism	Description	Impact on diabetes	Impact on depression
Neuroendocrine dysregulation	Dysregulation of the hypothalamic-pituitary-adrenal axis, leading to elevated cortisol levels	Promotes insulin resistance and hyperglycemia	Triggers mood disturbances and reduces neurogenesis
Chronic inflammation	Elevated pro-inflammatory cytokines (e.g., IL-6, TNF-α) in both conditions	Worsens insulin resistance and β-cell dysfunction	Disrupts neurotransmitter balance (e.g., serotonin) and neuroplasticity
Oxidative stress	Accumulation of reactive oxygen species damaging cells	Impairs insulin signaling and pancreatic function	Causes neuronal damage and exacerbates depressive symptoms
Gut-brain axis dysbiosis	Altered gut microbiota composition and increased intestinal permeability	Linked to metabolic endotoxemia and insulin resistance	Affects serotonin production and neuroinflammation
Insulin resistance and neurotransmitter dysfunction	Impaired insulin signaling in the brain affects neurotransmitter systems (e.g., serotonin, dopamine)	Exacerbates hyperglycemia and metabolic dysfunction	Reduces mood regulation and cognitive function
Psychosocial and behavioral factors	Poor self-care, physical inactivity, and chronic stress	Poor glycemic control and higher complication rates	Worsens depressive symptoms and treatment adherence

socioeconomic status and lack of social support are significant risk factors for both diabetes and depression. These factors can influence access to healthcare and the ability to manage both conditions effectively [74, 77].

- Demographic variables: Age, gender, and race can modulate the relationship between diabetes and depression, with certain groups being more vulnerable to the comorbidity [75, 78].

While the bidirectional relationship between diabetes and depression is well-documented, the exact mechanisms remain partially understood. The interplay of biological, psychological, and social factors suggests that a multifaceted approach is necessary for effective management. Future research should focus on longitudinal studies and precision medicine approaches to better understand and address the shared mechanisms of these conditions. This will help in developing personalized interventions that can improve outcomes for individuals suffering from both diabetes and depression.

Clinical Implications and Management Strategies

Depression is more prevalent in individuals with diabetes, occurring two to three times more frequently than in the general population, and vice versa, diabetes increases the risk of developing depression [79]. The co-occurrence of these conditions is associated with poor self-management, higher glycated haemoglobin (HbA1C) levels, and increased diabetes-related complications, which can further exacerbate depressive symptoms, creating a vicious cycle [80]. Shared physiological mechanisms, such as inflammation, oxidative stress, and neuroendocrine dysregulation, contribute to the bidirectional relationship between diabetes and depression [17, 81]. Given the bidirectional relationship between diabetes and depression, integrated management strategies are essential. Screening for depressive symptoms in diabetic patients should be a routine part of diabetes care, as early identification can lead to more effective interventions [66, 79].

Pharmacological approaches

Pharmacological treatments for depression in diabetic patients must be approached with caution, as some antidepressants may adversely affect glycemic control [82]. However, certain medications, such as selective serotonin reuptake inhibitors, have shown promise in improving both mood and metabolic parameters [21, 82]. Additionally, newer classes of antidiabetic medications, such as SGLT2, may have beneficial effects on mood and cognitive function [34].

Psychosocial interventions

Psychosocial interventions, including CBT and lifestyle modifications, can also play a crucial role in managing comorbid diabetes and depression. These interventions can help improve self-management behaviors, enhance coping strategies, and ultimately lead to better glycemic control and mood stabilization [17, 29]. Furthermore, community-based programs that integrate mental health support into diabetes care can enhance treatment accessibility and effectiveness, particularly in underserved populations [1, 29].

Integrated management strategies

- Integrated care models that combine psychological support with medical management are recommended to address the intertwined nature of diabetes and depression. These models require collaboration across multiple healthcare disciplines, including endocrinology, psychiatry, and primary care [83].

- Routine screening for depressive symptoms in diabetic patients and vice versa is crucial for early detection and intervention [81, 84].

- Primary care providers play a critical role in the management of these conditions by using person-centered, non-judgmental language to foster trust and patient engagement [84].

- Access to behavioral health professionals and collaboration with diabetes care and education specialists are essential to support problem-solving in diabetes self-management [84].

- Selective serotonin reuptake inhibitors are effective in treating depression in diabetic patients and can positively influence glycemic control [81].

While integrated management strategies are essential for addressing the comorbidity of diabetes and depression, there are significant barriers to effective management, such as stigma, psychological resistance, and health literacy. These barriers need to be addressed through patient-centered education and support systems to improve treatment adherence and outcomes [83]. Additionally, future research should focus on longitudinal studies and novel therapeutic targets to further elucidate the causal relationships and improve healthcare models aimed at preventing the onset of one condition in individuals diagnosed with the other [83].

Case Studies

The relationship between diabetes and depression is complex and bidirectional, with each condition potentially exacerbating the other. Studies have been conducted to explore interventions that address both conditions simultaneously, focusing on improving both glycemic control and depressive symptoms. These studies have employed various strategies, including CBT, psychoeducational interventions, and integrated care models, to assess their efficacy in managing comorbid diabetes and depression.

A study by Su et al. [85] investigated the effects of the antidiabetic drug glyburide (Glb) on depressive-like behavior and insulin resistance comorbid with chronic unpredictable mild stress (CUMS) in mice. Twelve weeks of CUMS led to depressive-like behavior, characterized by reduced sucrose preference and increased immobility in the tail suspension test, alongside insulin resistance. This comorbidity was attributed to long-term mild inflammation. Inflammatory markers, CUMS significantly increased serum corticosterone and IL-1β levels. In the hippocampus, CUMS upregulated protein levels of IL-1β, caspase-1 p10, and NOD-like receptor family pyrin domain-containing protein 3 (NLRP3). Similarly, in the pancreas, NLRP3 and caspase-1 p10 protein levels were promoted, and IL-1β levels were elevated. Insulin signaling disturbance, CUMS resulted in a larger area under the curve in the insulin tolerance test compared to the control group, indicating insulin resistance. Fasting plasma insulin concentrations were higher in CUMS mice. In the hippocampus, CUMS enhanced phosphorylation of IRS1 serine 307 (IRS1Ser307) and downregulated p-AktSer473, indicating impaired insulin signaling. Pancreatic changes, CUMS led to a significant decrease in insulin-positive areas in pancreatic islets and an increase in F4/80-positive cells (macrophages), suggesting inflammation and potential β-cell dysfunction. Glb effectively prevented the experimental comorbidity, improving behavioral performance such as sucrose preference and reducing immobility time in the tail suspension test. Its effects were comparable to fluoxetine (Flx), a known antidepressant. Glb ameliorated insulin intolerance, as evidenced by a smaller area under curve in the insulin tolerance test compared to the

CUMS + vehicle group. It also prevented the CUMS-induced changes in hippocampal IRS1 and Akt phosphorylation. Inhibition of NLRP3 inflammasome activation, Glb hindered the upregulation of IL-1β, caspase-1 p10, and NLRP3 in both the hippocampus and pancreas. Suppression of thioredoxin-interacting protein (TXNIP) expression, Glb suppressed the expression of TXNIP, an upstream molecule that activates the NLRP3 inflammasome, in both the hippocampus and pancreas. This suggests that Glb beneficial effects are mainly due to its inhibition of the NLRP3 inflammasome via TXNIP suppression. Glb normalized the elevated serum corticosterone and IL-1β levels caused by CUMS. In summary, this paper provides evidence that chronic stress leads to a comorbidity of depressive-like behavior and insulin resistance, mediated by the activation of the NLRP3 inflammasome. The antidiabetic drug Glb effectively prevents this comorbidity by inhibiting NLRP3 inflammasome activation, primarily through suppressing TXNIP expression, suggesting a potential therapeutic target for clinical comorbidity of diabetes and depression (Figure 1).

A pragmatic cluster-randomized trial by Wang et al. [86] evaluating the community-based integrated care for patients with diabetes and depression (CIC-PDD) model in China yielded significant positive results, particularly in the intervention group compared to the enhanced usual care group (Figure 2). The study enrolled 630 participants, with 275 in the intervention group and 355 in the control group. At 12 months, a significantly higher percentage of patients in the intervention group achieved the primary outcome, which involved at least a 50% reduction in depressive symptoms and a reduction of at least 0.5 percentage points in HbA1c. Depressive symptoms reduction, the intervention group showed a risk difference of 31.03% (62.06% vs 31.02% in the control group; 95% CI: 21.85 to 40.21). HbA1c reduction, the intervention group exhibited a risk difference of 19.16% (32.41% vs 13.25% in the control group; 95% CI: 11.35 to 26.97). The intervention group also demonstrated significant improvements in several secondary outcomes at 12 months. Mental quality of life, patients in the intervention group experienced a mean difference of 6.74 (46.57 vs 39.83 in the control group; 95% CI: 3.75 to 9.74). Diabetes self-care activities, a mean difference of 0.69 was observed (3.46 vs 2.78 in the control group; 95% CI: 0.52 to 0.86). Medication adherence, there was a mean difference of 0.72 (6.49 vs 5.78 in the control group; 95% CI: 0.37 to 1.07). Experience of care, patients showed a mean difference of 0.89 (3.84 vs 2.95 in the control group; 95% CI: 0.65 to 1.12). Rural participants specifically benefited more from the intervention. In conclusion, the CIC-PDD model proved effective in improving both clinical and patient-reported outcomes for individuals with diabetes

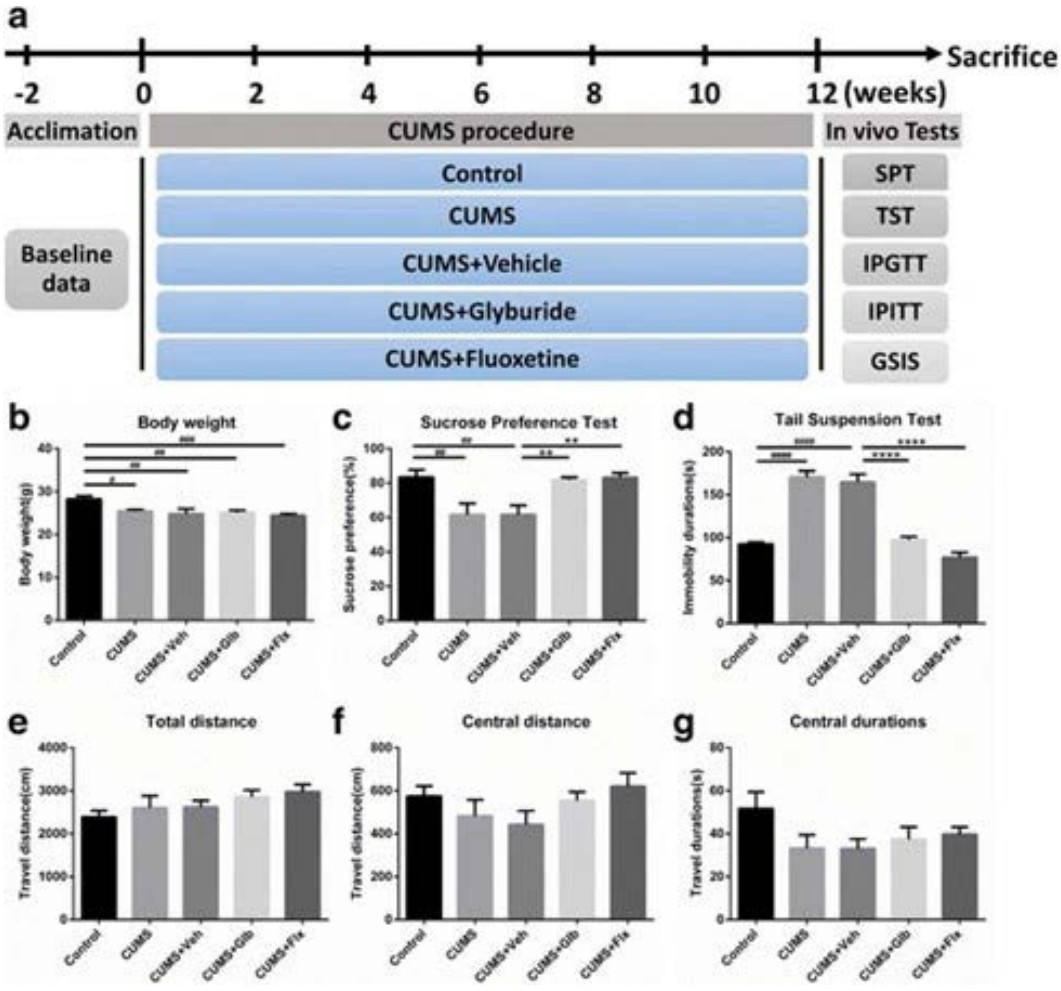

Figure 1: (a) The CUMS protocol was conducted over 12 weeks, with drug treatment administered once daily throughout the entire duration. **(b)** Stressed mice exhibited significantly lower body weight gain compared to controls. **(c)** Mice subjected to CUMS (both the CUMS-only and CUMS + vehicle groups) showed reduced sucrose preference and **(d)** longer immobility durations in the tail suspension test. However, no notable differences were observed in open field test measures **(e–g)**. Notably, mice treated with Glb (CUMS + Glb) or Flx (CUMS + Flx) displayed improved sucrose preference **(c)** and reduced immobility time and **(d)** compared to the CUMS + vehicle group [85].

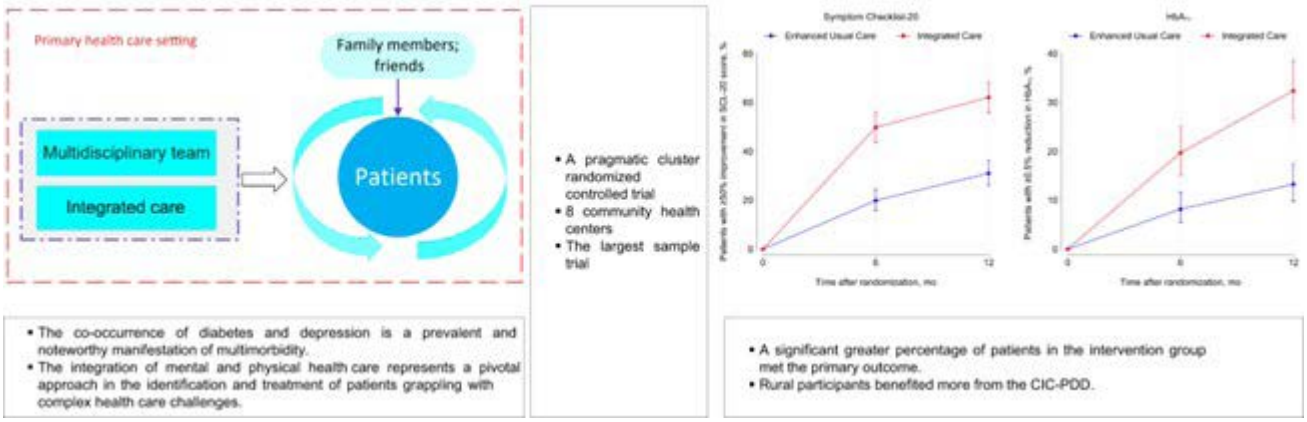

Figure 2: Effect of CIC-PDD in China, a pragmatic cluster-randomized trial [86].

and depression, suggesting its potential as a blueprint for integrated care in primary health settings.

A study by Mansour et al. [87] investigated the efficacy of brief CBT in patients with comorbid type 2 diabetes and depression. Both the CBT intervention group and the control group were matched at baseline, showing no significant statistical differences in sociodemographic characteristics or initial Beck depression index (BDI) scores ($p = 0.129$). Baseline anthropometric measures (weight, height, body mass index, and waist circumference) and laboratory tests (Fasting plasma glucose, two-hour post-load glucose, and HbA1c) also showed no significant differences between groups ($p > 0.05$). The majority of participants (41%) had one comorbid condition, with hypertension being the most common (58% in the control group and 48% in the CBT group). The CBT group demonstrated a significant reduction in depressive symptoms post-intervention. After adjusting for baseline BDI scores, there was a significant difference in BDI scores between the groups ($F [1, 74] = 7.074$, $p = 0.010$), with the CBT group showing significantly lower BDI scores. HbA1c levels were significantly improved in the CBT group compared to the control group, even after controlling for pre-intervention BDI scores and body mass index ($F [1, 73] = 4.27$, $p = 0.042$). The results suggest that CBT intervention is effective in improving both diabetes control and depression in patients with type 2 diabetes. Out of 394 screened patients, 100 met the inclusion criteria and completed baseline assessment, with 50 randomized to each group. In the CBT group, 38% attended four sessions, 38% attended three, and 40% attended two or fewer sessions. At post-intervention assessment, 82% of the CBT group and 72% of the control group provided complete data. No study-related adverse events were reported. In summary, the study provides compelling evidence that brief CBT is an effective intervention for improving both glycemic control and depressive symptoms in patients with comorbid type 2 diabetes and depression. These findings underscore the potential of integrating psychological interventions like CBT into primary healthcare settings for managing chronic conditions.

A program adult coming together to increase vital exercise (ACTIVE) II (NCT03371940) study by De Groot et al. [88] investigated the comparative effectiveness of CBT and/or community-based exercise (EXER) on depression and diabetes outcomes in adults with type 2 diabetes mellitus and major depressive disorder. The results demonstrated significant improvements in depression outcomes across all intervention groups, with some notable effects on glycemic control and psychosocial well-being. All intervention groups (CBT, EXER, and CBT + EXER) showed significantly higher rates of full major depressive disorder remission compared to usual care. Specifically, the odds of achieving full major depressive disorder remission in the intervention groups were 5.0 to 6.8 times greater than in the usual care group. Participants in the CBT, EXER, and CBT + EXER groups reported greater improvements in depressive symptoms and negative automatic thoughts compared to the usual care group. The mean values for depressive symptoms moved from moderate/severe to mild/none ranges. When considering the entire sample, there was no significant main effect of EXER or CBT on the change in glycemic control (HbA1c). The combined CBT + EXER group demonstrated improved HbA1c compared with usual care. For participants with a baseline HbA1c of 7.0% or higher, an exploratory post-hoc subgroup analysis revealed that the CBT + EXER group had a significant 1.1% improvement in HbA1c after controlling for covariates. This suggests an additive effect on glycemic control when CBT and EXER are delivered concurrently. Participants in the EXER and CBT + EXER groups showed improvements in physical quality of life and diabetes-specific quality of life compared to usual care. All three active intervention groups (CBT, EXER, and CBT + EXER) showed improvements in diabetes-related distress compared to usual care. Mean values for diabetes distress moved from clinically high to moderate ranges. Modest improvements in total cholesterol were observed in the CBT and EXER arms compared with usual care. In summary, the program ACTIVE II study successfully demonstrated that community-based behavioral interventions, including CBT, exercise, and their combination, are effective in improving depression outcomes, psychosocial well-being, and, in the case of the combined intervention, glycemic control in adults with type 2 diabetes mellitus and major depressive disorder. These findings highlight the potential for community-based approaches to complement medical care and expand access to treatment in both rural and urban areas.

A study by Kumar et al. [89] compared the effects of Escitalopram and Agomelatine on glycemic control and depression symptoms in patients with type 2 diabetes mellitus and depression. The Escitalopram group demonstrated a significant reduction in both fasting blood glucose and HbA1c values when compared to the Agomelatine group. This significant difference was observed at both the 1-month and 2-month marks of the study. Hamilton depression rating scale (HDRS) scores, patients treated with Escitalopram showed significantly lower HDRS scores compared to those receiving Agomelatine. Specifically, at 1 and 2 months, the Escitalopram group's HDRS scores were 8.85 ± 5.86 and 15.6 ± 2.5 respectively, indicating better improvement in depression symptoms. Montgomery Asberg depression rating

scale (MADRS) scores, similarly, the escitalopram group exhibited significantly lower MADRS scores than the Agomelatine group at both 1 and 2 months. The scores for the escitalopram group were 13.6 ± 1.85 and 21.15 ± 2.34, respectively, further supporting its superior efficacy in reducing depression symptoms. Based on these results, escitalopram appears to be more effective than agomelatine in improving glycemic control and alleviating symptoms of depression in patients diagnosed with both type 2 diabetes mellitus and depression.

A study by Yasui-Furukori et al. [90] investigated the relationship between personality traits and depressive symptoms in individuals with type 2 diabetes mellitus. Among the 435 type 2 diabetes mellitus patients studied, a significant portion exhibited depressive symptoms. 130 patients (29.9%) showed possible depression based on a center for epidemiologic studies depression (CES-D) score of 15.5 or higher. 68 patients (15.6%) had probable depression, defined by a CES-D score of 21 or higher. The observed prevalence of depression (29.9% for possible and 15.6% for probable) falls within the range of previous research findings (15 to 43%). All five personality traits (extraversion, agreeableness, conscientiousness, neuroticism, and openness) showed significant differences between patients with and without possible depression. Similar differences were found for probable depression, except for openness. Logistic regression analysis identified extraversion, agreeableness, and neuroticism as factors associated with possible depression. For probable depression, smoking habits, alcohol consumption habits, extraversion, agreeableness, and neuroticism were found to be associated factors. Neuroticism trait was significantly associated with depression in both logistic regression and linear regression analyses, indicating it as a risk factor for depression in type 2 diabetes mellitus patient. Agreeableness trait was inversely associated with depression in both logistic regression and linear regression analyses, suggesting it acts as a protective factor. While extraversion was associated with depression in logistic regression analyses for both possible and probable depression, it was not correlated with the severity of depression in multiple regression analysis. Scores for conscientiousness differed between depressed and non-depressed patients, but it was not significantly associated with depression in the adjusted logistic regression analysis. The study found no significant relationship between depression and HbA1c levels. The findings suggest that extraversion and agreeableness are protective factors, while neuroticism is a risk factor for depression in type 2 diabetes mellitus patients. Psychological therapy that focuses on personality traits may be beneficial in reducing depressive symptoms in type 2 diabetes mellitus patients. This includes interventions like supportive psychotherapy or CBT designed to help patients manage personality aspects related to their illness. In summary, the paper highlights that depression is common among type 2 diabetes mellitus patients and that specific personality traits, particularly neuroticism (risk factor) and agreeableness/extraversion (protective factors), play a significant role in an individual's depressive status. These results underscore the potential for personality-focused psychological interventions to improve mental health outcomes in this population.

While these studies highlight the potential of various interventions to improve outcomes for patients with comorbid diabetes and depression, challenges remain. Access to psychological care is often limited, and the effectiveness of interventions can vary based on patient characteristics and baseline conditions. Future research should focus on understanding the mechanisms linking diabetes and depression and developing interventions that are both effective and accessible. Additionally, exploring the long-term impact of these interventions on diabetes complications and mortality rates could provide further insights into their benefits.

Theoretical and Practical Implications

The intricate bidirectional relationship between diabetes and depression extends beyond clinical comorbidity, carrying profound implications for both scientific understanding and real-world patient care. Emerging research has elucidated shared pathophysiological mechanisms—including chronic inflammation, neuroendocrine dysregulation, and metabolic dysfunction—that challenge traditional disease silos and demand integrated theoretical frameworks. These insights not only refine etiological models but also translate into actionable strategies, from personalized treatment plans to systemic healthcare reforms. This section synthesizes the theoretical advances that reshape our conceptualization of the diabetes-depression nexus, while mapping their practical applications in clinical, community, and policy settings to bridge the gap between mechanistic knowledge and patient outcomes (Table 2).

Theoretical implications

- The bidirectional relationship between diabetes and depression is supported by converging evidence highlighting shared biological pathways such as inflammation, neuroendocrine dysregulation, and insulin resistance. These mechanisms underscore a complex interplay rather than a simple cause-effect relationship, advancing theoretical models that integrate metabolic, neurological, and psychological factors [17, 47, 91].
- Genetic studies employing Mendelian randomization and

Table 2: Theoretical and practical implications.

Aspect	Theoretical implications	Practical implications
Shared biological pathways	Supports integrated models combining metabolic, neurological, and psychological mechanisms (e.g., inflammation, hypothalamic-pituitary-adrenal axis dysregulation)	Encourages development of dual-target therapies (e.g., anti-inflammatory drugs)
Genetic and epigenetic links	Mendelian randomization reveals depression as a causal risk factor for type 2 diabetes mellitus (mediated by body mass index)	Highlights need for early depression screening in diabetes management
Psychosocial factors	Biopsychosocial models emphasize role of stress, socioeconomic status, and lifestyle	Calls for patient-centered care addressing social determinants (e.g., access to mental health services)
Integrated care models	Demonstrates superiority of combined medical-psychological interventions over siloed approaches	Advocates for collaborative care (e.g., endocrinologists + psychiatrists) and routine depression screening in diabetes clinics
Lifestyle interventions	Confirms bidirectional benefits of diet/exercise on mood and metabolism	Promotes community programs (e.g., CBT + diabetes education, exercise therapy)
Pharmacological targets	Identifies novel targets (e.g., NLRP3 inflammasome, gut microbiota)	Repurposing antidiabetic drugs (e.g., SGLT2 inhibitors) for mood benefits
Policy and education	Stresses need for systemic changes to reduce stigma and improve access	Recommends policy reforms (e.g., insurance coverage for integrated care, provider training)

MP-GWAS have provided causal evidence that depression increases the risk of type 2 diabetes, mediated partly by body mass index, while the reverse causality is less supported. This refines theoretical understanding by emphasizing depression as a potential upstream factor in diabetes pathogenesis [67, 92].

- The role of chronic low-grade inflammation as a shared pathophysiological substrate for both conditions is increasingly recognized, linking immune system activation with neuroendocrine and metabolic disturbances. This supports inflammation-centered models of comorbidity and suggests new avenues for mechanistic research [85, 91, 93].

- Behavioral and psychosocial factors, including lifestyle behaviors, stress, and socioeconomic determinants, are integral to the theoretical framework explaining the bidirectional link, highlighting the necessity of biopsychosocial models that encompass environmental and individual-level influences [17, 94, 95].

- The heterogeneity in treatment response and disease progression observed in clinical studies suggests that individual differences in genetic predisposition, inflammation profiles, and psychosocial context must be incorporated into theoretical models to better predict outcomes and tailor interventions [95-97].

Practical implications

- Integrated care models that combine medical, psychological, and behavioral interventions demonstrate significant improvements in both glycemic control and depressive symptoms, supporting their adoption in clinical practice to address the intertwined nature of diabetes and depression effectively [86, 98].

- Routine screening for depression in diabetic patients and vice versa is essential for early identification and intervention, as untreated comorbidity exacerbates disease burden and complicates management. This calls for policy initiatives to mandate and standardize screening protocols in healthcare settings [64].

- Pharmacological treatments targeting shared biological pathways, such as inflammation and insulin resistance, hold promise for dual therapeutic effects but require further research to optimize efficacy and minimize adverse effects. Repurposing antidiabetic drugs with anti-inflammatory properties may offer novel treatment strategies [85, 97, 99].

- Lifestyle interventions focusing on diet, physical activity, and stress management are effective adjuncts that improve both metabolic and mental health outcomes, underscoring the importance of multidisciplinary approaches that incorporate behavioral health and patient education [73, 100].

- Public health policies should prioritize integrated mental and physical health services, reduce stigma associated with depression in diabetic populations, and address social determinants of health to improve access and adherence to comprehensive care [86, 101, 102].

- Future clinical guidelines should emphasize personalized treatment plans that consider genetic, biological, and psychosocial factors to enhance patient-centered care and improve long-term outcomes for individuals with comorbid diabetes and depression [67, 94, 95].

Conclusion

The literature elucidates the complex bidirectional relationship between diabetes and depression, underscored by interconnected biological, behavioral, genetic, and psychosocial mechanisms. Central to this interplay are shared pathophysiological pathways involving chronic low-grade inflammation, neuroendocrine dysregulation—particularly of the hypothalamic-pituitary-adrenal axis—insulin resistance, oxidative stress, and disturbances in neurotransmitter signaling. These biological processes not only foster the onset and progression of both conditions but also contribute to their mutual exacerbation. Genetic studies employing Mendelian randomization and multi-phenotype GWAS approaches reveal pleiotropic loci implicating insulin signaling and cell cycle regulation, with body mass index serving as a partial mediator. Such findings underscore the multifaceted genetic and metabolic underpinnings linking depression and type 2 diabetes, highlighting the necessity for early preventive measures targeting depressive symptoms and weight management.

Behavioral and psychosocial factors emerge as critical modulators of this relationship. Lifestyle behaviors, including diet, physical activity, sleep patterns, and medication adherence, significantly influence disease trajectories, while psychosocial stressors such as stigma, emotional distress, and social support shape vulnerability and treatment responsiveness. The reciprocal negative impact of depression on diabetes self-management and glycemic control accentuates the importance of addressing these factors within comprehensive care frameworks. Demographic variables such as age, gender, ethnicity, and socioeconomic status further modulate prevalence, risk, and treatment outcomes, calling for culturally sensitive and population-specific interventions.

Intervention research converges on the efficacy of integrated care models that synergistically combine pharmacological treatments, lifestyle modifications, and psychological therapies. These multidisciplinary approaches demonstrate superior outcomes in reducing depressive symptoms and improving glycemic control compared to isolated treatments. CBT, mindfulness, and behavioral activation are consistently effective psychological strategies, while lifestyle interventions focusing on nutrition and physical activity ameliorate both metabolic and mood symptoms. Pharmacological agents, particularly selective serotonin reuptake inhibitors, effectively alleviate depression, though their effects on glycemic control are variable, underscoring the need for personalized treatment plans. Emerging pharmacological targets addressing inflammation and metabolic pathways hold promise but require further validation.

Despite significant advances, limitations persist, including heterogeneity in study designs, short follow-up durations, and underrepresentation of diverse populations. The nuanced causal pathways remain incompletely defined, particularly regarding type 1 diabetes and specific depression subtypes. Future research should prioritize longitudinal, multi-omics, and precision medicine approaches to clarify mechanisms, optimize interventions, and translate biological insights into clinical practice. Overall, the literature advocates for holistic, patient-centered care that integrates biological, behavioral, and psychosocial dimensions to improve outcomes for individuals grappling with the intertwined burdens of diabetes and depression.

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Conflict of Interest

None.

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