International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
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ARTICLE TITLE	THE BIDIRECTIONAL RELATIONSHIP BETWEEN DIABETES MELLITUS AND DEPRESSION: A SYSTEMATIC REVIEW OF BIOLOGICAL AND PSYCHOLOGICAL MECHANISMS
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6519
RECEIVED	27 May 2026
ACCEPTED	17 August 2026
PUBLISHED	28 August 2026
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THE BIDIRECTIONAL RELATIONSHIP BETWEEN DIABETES MELLITUS AND DEPRESSION: A SYSTEMATIC REVIEW OF BIOLOGICAL AND PSYCHOLOGICAL MECHANISMS

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ABSTRACT

Diabetes mellitus and depression are two major global health challenges that frequently co-occur, with depression being two to three times more prevalent in individuals with diabetes than in the general population. Current evidence confirms a bidirectional relationship, where depression increases the risk of developing type 2 diabetes by 34%, and diabetes elevates the risk of incident depression by 28%. This systematic review explores the complex biological and psychological mechanisms underlying this interplay. Biological pathways include chronic low-grade inflammation characterized by elevated cytokines (IL-6, TNF-α, CRP), dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis resulting in hypercortisolemia, and impaired neuroplasticity linked to reduced levels of brain-derived neurotrophic factor (BDNF). Additionally, central insulin resistance and neurotransmitter alterations in serotonin and dopamine systems further exacerbate both conditions. Psychological and behavioral mediators include the specific emotional burden of diabetes distress, the significant self-management burden associated with insulin therapy and glucose monitoring, and lifestyle factors such as sedentary behavior, poor diet, and sleep disturbances. The presence of comorbid depression is a critical predictor of poor glycemic control (higher HbA1c), increased microvascular complications (retinopathy, nephropathy), and higher mortality rates. Consequently, clinical management must transition toward integrated, multidisciplinary care models that prioritize universal screening and collaborative treatment strategies. Future research should focus on longitudinal studies and the validation of biomarkers to enable precision medicine and improve the long-term prognosis for these patients.

KEYWORDS

Diabetes Mellitus, Depression, Bidirectional Relationship, Comorbidity, Inflammation, HPA Axis, Insulin Resistance, Diabetes Distress, Glycemic Control

CITATION

Vladyslav Romaniuk, Agnieszka Benecka, Zuzanna Wieczorek, Alicja Benecka, Urszula Szuleta, Wiktoria Zawada, Natalia Prankiewicz, Jakub Pietrończyk, Krystian Kaczmarek, Zofia Jadwiga Leszczyńska, Iga Tartas. (2026) The Bidirectional Relationship Between Diabetes Mellitus and Depression: a Systematic Review of Biological and Psychological Mechanisms. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6519

Materials and Methods

The PubMed, Scopus, EMBASE, Cochrane Library, and Web of Science databases were searched for publications concerning the co-occurrence of diabetes and depression. The search was focused on articles published between 2017 and 2024 to capture both foundational research on the bidirectional link and the most recent advancements in molecular diagnostics and multidisciplinary care. The search was limited to publications in English. Inclusion criteria consisted of randomized controlled trials (RCTs), systematic reviews, meta-analyses, and human observational studies (prospective cohort, cross-sectional, and case-control) providing quantitative data such as Odds Ratios (OR) and glycated hemoglobin (HbA1c) levels. Studies were required to investigate either the biological pathways (e.g., cytokines, cortisol, BDNF) or the psychological and behavioral mediators (e.g., self-management burden, lifestyle factors) linking the two conditions. Additionally, the reference lists of retrieved articles and clinical practice guidelines from the American Diabetes Association (ADA) and the World Health Organization (WHO) were used as sources of clinical and diagnostic standards. The review process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and scientific rigor.

1. Introduction.

1.1. Epidemiology of Diabetes.

Diabetes mellitus (DM) is a chronic metabolic disease whose prevalence is increasing globally, primarily due to lifestyle modifications and increasing life expectancy (Zhuang et al., 2017). Estimates provided by the International Diabetes Federation (IDF) indicate that the number of adults living with diabetes reached 415 million in 2015 and is projected to rise to 642 million by 2040 (Zhuang et al., 2017; Ahola et al., 2020). Other recent data suggests that approximately 463 million people worldwide are currently afflicted, with projections reaching 108 million in the Middle East and North Africa region alone by 2045 (Aljohani et al., 2021; Dahal et al., 2022). In the United States, about 30 million people, or 12.2% of the adult population, have the disease (Owens-Gary et al., 2019). This rapid growth reflects a significant core health challenge of the 21st century, as the condition leads to serious long-term complications affecting the eyes, kidneys, nerves, and cardiovascular system (Zhuang et al., 2017; Nübel et al., 2022; Abbas et al., 2024).

1.2. Epidemiology of Depression.

Depression is a serious psychiatric mood disorder and one of the largest single causes of disability globally (Zhuang et al., 2017; Mei et al., 2023). The World Health Organization (WHO) ranks it among the top causes of morbidity and mortality worldwide, affecting more than 300 to 340 million people (Subba et al., 2021; Albasheer et al., 2018; Shirali et al., 2023). Over the past 30 years, the number of incident cases has increased by nearly 50% (Monroe et al., 2022). It is characterized by symptoms such as persistent low mood, loss of interest, sleep disturbances, and cognitive impairment (Aljohani et al., 2021; Subba et al., 2021). Depression carries a heavy burden on public health and health budgets, and its prevalence is expected to continue rising during the next two decades (Zhuang et al., 2017; Subba et al., 2021).

1.3. Comorbidity Prevalence.

The co-occurrence of diabetes and depression is remarkably high, with studies indicating that depression is two to three times more prevalent in individuals with diabetes compared to those without the condition (Subba et al., 2021; Zhang et al., 2023). Among patients with type 2 diabetes mellitus (T2DM), approximately one in four (25–28%) is diagnosed with comorbid depression (Grigolon et al., 2019). A meta-analysis of 42 studies found that the prevalence of major depression in diabetic populations was 11%, while clinically relevant depressive symptoms affected 31% of patients (Prabu et al., 2020). In specialized clinical settings, these rates can be even higher, with some reports showing that up to 41% of diabetic patients suffer from depression (Prabu et al., 2020; Sharif et al., 2019). While less extensively studied, patients with type 1 diabetes (T1DM) also show high rates of depressive symptomatology, ranging from 8% for clinical disorders to 30% for general depressive affect (Grigolon et al., 2019; Ahola et al., 2021).

1.4. Significance of Bidirectional Relationship.

Evidence strongly supports a bidirectional relationship between diabetes and depression, where each condition increases the risk of developing the other (Zhuang et al., 2017; Al-Jabi, 2024). Quantitative assessments show that patients with depression have a 34% increased risk of developing diabetes (OR = 1.34), while patients with diabetes have a 28% increased risk of developing depression (OR = 1.28) (Zhuang et al., 2017). This interplay is significant because comorbid depression is a major risk factor for poor glycemic control, reduced adherence to medical treatment, and a higher incidence of macro- and microvascular complications, such as retinopathy and nephropathy (Albasheer et al., 2018; Prabu et al., 2020; Al-Jabi, 2024). Furthermore, the combination of both disorders results in a significantly increased risk of mortality and a substantial increase in healthcare costs (Zhuang et al., 2017; Owens-Gary et al., 2019; Al-Jabi, 2024).

Understanding this link is crucial because depression often remains unrecognized and untreated in diabetic clinical practice, yet its management is essential for improving the overall quality of life and prognosis for these patients (Zhuang et al., 2017; Shirali et al., 2023; Khan et al., 2019).

2. Epidemiological Evidence of Bidirectional Relationship

2.1. Depression in patients with diabetes

2.1.1. Prevalence

The co-occurrence of depression and diabetes is a significant global health issue, with research indicating that depression is twice as common in individuals with diabetes compared to the general population (Al-Jabi, 2024; Khan et al., 2019). Prevalence rates vary depending on the diabetes type, geographical region, and diagnostic tools used. In patients with type 2 diabetes (T2DM), one in four is diagnosed with depression (Grigolon et al., 2019; Prabu et al., 2020). International estimates for depression in diabetes generally range between 25% and 35% (Zhang et al., 2023; Sharif et al., 2019). Specifically, a meta-analysis showed a 28% prevalence in T2DM participants (Grigolon et al., 2019). Higher rates have been reported in clinical studies from specific regions, such as Pakistan (40% to 49.2%), Saudi Arabia (37.9% to 73%), and India (approximately 22%) (Aljohani et al., 2021; Albasheer et al., 2018; Shirali et al., 2023; Sharif et al., 2019; Khan et al., 2019). In type 1 diabetes (T1DM), clinically diagnosed depressive disorders affect approximately 8% to 10% of patients, while general depressive affect is reported by 25% to 30% (Ahola et al., 2021).

2.1.2. Impact on glycemic control

Depression has a demonstrably negative effect on the management of blood glucose levels. Patients with comorbid depression and diabetes often exhibit higher levels of glycated hemoglobin (HbA1c) compared to those without a mood disorder (Ahola et al., 2020; Albasheer et al., 2018; Khan et al., 2019). Research indicates a linear relationship where higher HbA1c levels are associated with an increased frequency of depression (Sharif et al., 2019). This impact is largely mediated by behavioral factors; symptoms of depression—such as loss of energy and feelings of worthlessness—compromise appropriate self-management, leading to missed insulin doses, poorer adherence to dietary regimens, and reduced physical activity (Ahola et al., 2020; Shirali et al., 2023; Ahola et al., 2021).

2.1.3. Complications and mortality

The presence of depression is a strong predictor of advanced diabetic complications and increased mortality. Depressive symptomatology is positively associated with the presence of microvascular complications, including diabetic nephropathy, retinopathy, and neuropathy (Ahola et al., 2020; Aljohani et al., 2021; Sharif et al., 2019; Sun et al., 2022). For instance, patients with retinopathy or nephropathy are significantly more likely to have clinical depression than those without these conditions (Sharif et al., 2019). Furthermore, depression is associated with a higher incidence of major adverse cardiovascular events (MACE) (Ahola et al., 2020; Aljohani et al., 2021). Long-term longitudinal data shows that diagnosed depression increases the risk of diabetic nephropathy progression by up to 53% (Ahola et al., 2021). Ultimately, the combination of these disorders results in a significantly increased risk of premature mortality (Subba et al., 2021; Prabu et al., 2020; Ahola et al., 2021; Al-Jabi, 2024).

2.2 Risk of diabetes in depressed patients

2.2.1. Lifestyle factors

Depression acts as an independent risk factor for the development of incident T2DM. Individuals with depression have a 34% to 60% increased risk of developing diabetes compared to non-depressive subjects (Zhuang et al., 2017, Mei et al., 2023). This risk is partially driven by unhealthy lifestyle choices common in depressed populations, such as lack of physical exercise and non-compliance with healthy weight recommendations (Zhuang et al., 2017; Ahola et al., 2020). Additionally, patients with major depressive disorder often adopt maladaptive coping mechanisms, such as binge eating or "comfort food" consumption, which contribute to obesity and insulin resistance (Subba et al., 2021). Poor sleep quality has also been identified as a mediator that increases the risk of depressive symptoms and metabolic dysfunction in this group (Wang et al., 2021).

2.2.2. Neuroendocrine pathways

The biological link between depression and the onset of diabetes involves complex molecular changes. A primary pathway is the hyper-activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased cortisol secretion (Subba et al., 2021; Prabu et al., 2020; Al-Jabi, 2024). Excess cortisol directly contributes to hyperglycemia, insulin resistance, and visceral obesity (Ahola et al., 2020) (Subba et al., 2021; Prabu et al., 2020). Furthermore, shared biological processes such as chronic low-grade inflammation, oxidative stress, and mitochondrial dysfunction are linked to both disorders (Ahola et al., 2020) (Subba et al., 2021; Zhang et al., 2023). Dysregulation of adipokines (e.g., lower adiponectin levels) and central neurotransmitter alterations (serotonin and dopamine) also play key roles in this bidirectional relationship (Subba et al., 2021).

2.2.3. Antidepressant effects

The relationship is further complicated by the use of psychotropic medications. Some drugs used to treat depression may lead to weight gain and obesity, potentially predisposing individuals to diabetes (Zhuang et al., 2017; Salinero-Fort et al., 2018). However, the data is nuanced; for example, the use of certain antidepressants has been associated with an increased risk of disease progression in some studies, while others suggest that specific agents like Sertraline might improve both depressive symptoms and weight/BMI over time (Subba et al., 2021; Ahola et al., 2021). Interestingly, in younger T1DM cohorts, the total number of antidepressant purchases has shown a modest association with a reduced risk of renal progression, suggesting potential protective effects in some clinical contexts (Ahola et al., 2021).

3. Biological Mechanisms

3.1. Inflammation

Chronic low-grade inflammation is recognized as a fundamental characteristic of type 2 diabetes mellitus (T2DM) and a key mediator in its relationship with depression (Zhang et al., 2023; Al-Jabi, 2024; Amanat et al., 2020). This state is characterized by increased systemic levels of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) (Grigolon et al., 2019; Amanat et al., 2020; Kuang et al., 2024; Guo et al., 2023). Persistently high glucose levels lead to the increased production of advanced glycation products (AGEs), which activate the expression of inflammatory genes (Grigolon et al., 2019). This inflammatory cascade is not limited to peripheral tissues; it also involves central activation, where microglial cells in brain regions such as the hippocampus and amygdala produce inflammatory mediators that disrupt neural stability and synaptic function (Subba et al., 2021; Guo et al., 2023; Ni et al., 2024).

3.2. HPA axis dysregulation

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis represents a critical neuroendocrine link between chronic stress, depression, and diabetes (Zhuang et al., 2017; Ahola et al., 2020; Subba et al., 2021). Chronic stress triggers the persistent activation of this axis, leading to the hypersecretion of cortisol (Subba et al., 2021; Prabu et al., 2020). Elevated cortisol levels directly contribute to the pathogenesis of T2DM by promoting hyperglycemia, increasing insulin resistance, and fostering visceral obesity (Ahola et al., 2020; Subba et al., 2021; Prabu et al., 2020). Furthermore, the negative feedback loop of the HPA axis often becomes dysfunctional in both depressed and diabetic patients, resulting in a state of chronic physiological stress that exacerbates both conditions (Subba et al., 2021). Early life stress (ELS) has also been identified as a factor that can permanently alter HPA axis reactivity, increasing the risk of developing this comorbidity in adulthood (Subba et al., 2021).

3.3. Insulin resistance and metabolic dysfunction

Metabolic dysfunction in diabetes involves profound changes that extend to the central nervous system. Insulin resistance in the brain often parallels peripheral resistance and is a significant driver of cognitive decline and executive dysfunction (Subba et al., 2021; Grigolon et al., 2019). Insulin is crucial for maintaining neuronal health, and its signaling is necessary for proper synapse formation and dendritic development (Subba et al., 2021). Impaired glucose metabolism, resulting from either hyperglycemia or repeated episodes of hypoglycemia, leads to modifications in brain structure, such as cortical atrophy and a reduction in grey matter density. Furthermore, these metabolic disturbances alter functional brain connectivity, particularly in areas responsible for mood regulation and memory (Grigolon et al., 2019).

3.4. Neurotransmitter alterations.

The bidirectional link is further reinforced by alterations in key neurotransmitter systems and markers of neuroplasticity.

3.4.1. Serotonin.

Diabetes is frequently associated with reduced brain serotonin activity and turnover (Ahola et al., 2020; Subba et al., 2021). This dysfunction is often linked to reduced levels of tryptophan (its precursor) and altered sensitivity of serotonin receptors (e.g., 5-HT1A and 5-HT2A) in the hippocampus and prefrontal cortex (Subba et al., 2021).

3.4.2. Dopamine.

Central insulin resistance can dysregulate dopamine transmission in the brain's reward circuits, such as the nucleus accumbens and striatum (Subba et al., 2021; Grigolon et al., 2019). This impairment is a biological basis for anhedonia, a core symptom of depression that reduces a patient's motivation for diabetes self-care (Subba et al., 2021).

3.4.3. Neuroplasticity.

A key marker of impaired neuroplasticity in both conditions is the decreased level of brain-derived neurotrophic factor (BDNF). BDNF is essential for the survival, differentiation, and maintenance of neurons (Zhang et al., 2023; Prabu et al., 2020). Reduced BDNF levels contribute to synaptic loss and impaired hippocampal neurogenesis, creating a structural vulnerability to mood disorders and cognitive impairment (Subba et al., 2021; Zhang et al., 2023; Prabu et al., 2020).

4. Psychological and Behavioral Mechanisms.

4.1 Diabetes distress.

Diabetes distress is an emotional state distinct from clinical depression, resulting from the cumulative emotional burden, worry, and burnout associated with managing a chronic condition. While depression is a general psychiatric disorder, diabetes distress is specifically tied to the frustrations of life with diabetes, such as the fear of complications or the daily demands of self-care. Research indicates that approximately one-third of adults with type 2 diabetes (T2DM) experience diabetes distress, and while it can overlap with clinical depression, it often requires different clinical interventions. Persistently high levels of distress are independently associated with poor glycemic control (higher HbA1c) and a reduced motivation for self-management, effectively fueling a cycle of deteriorating health (Owens-Gary et al., 2019, Al-Jabi, 2024).

4.2. Self-management burden.

The complex and demanding nature of diabetes management represents a significant psychological weight that can trigger or exacerbate depressive symptoms.

4.2.1. Glucose monitoring.

Maintaining blood glucose within a target range requires constant vigilance and frequent testing. Comorbid depression often leads to irregular glucose monitoring, which prevents patients from reaching metabolic targets and increases the risk of long-term microvascular complications (Ahola et al., 2021). Studies show that depressed individuals are twice as likely to be non-adherent to monitoring protocols compared to those without mood disorders (Owens-Gary et al., 2019).

4.2.2. Insulin therapy.

The initiation and maintenance of insulin therapy are major contributors to the self-management burden. Patients often perceive insulin treatment as a sign of disease progression, which can cause significant psychological distress (Khan et al., 2019; Salinero-Fort et al., 2018). Furthermore, the requirement for painful injections and the constant need for dose adjustments based on food intake and activity levels can lead to a sense of loss of control and stigma, further predisposing patients to major depressive episodes (Ahola et al., 2020; Mei et al., 2023; Salinero-Fort et al., 2018).

4.3 Lifestyle factors.

Shared behavioral pathways, including physical activity, diet, and sleep, serve as critical mediators in the bidirectional link between diabetes and depression.

4.3.1. Physical inactivity.

Depression is strongly associated with a lack of physical exercise and a sedentary lifestyle (Al-Jabi, 2024; Sun et al., 2022). This inactivity contributes to the worsening of obesity and insulin resistance, thereby accelerating the progression of diabetes (Zhuang et al., 2017; Subba et al., 2021). Conversely, regular physical activity has been shown to lower the risk of developing psychiatric conditions and can alleviate existing depressive symptoms in diabetic patients (Aljohani et al., 2021; Salinero-Fort et al., 2018).

4.3.2. Diet.

Negative emotions frequently lead to a neglect of dietary regimens designed to control blood sugar (Shirali et al., 2023). Patients suffering from depression may use unhealthy eating—such as "comfort foods" high in fat and sugar—as a maladaptive coping mechanism to manage stress. This behavior disrupts glucose homeostasis and contributes to metabolic syndrome, creating a direct biological link between emotional state and physical health (Subba et al., 2021).

4.3.2. Sleep disorders.

Poor sleep quality and short sleep duration are significant risk factors for both disorders. Sleep restriction has been shown to reduce insulin sensitivity and elevate free fatty acid levels, contributing to pancreatic beta-cell dysfunction. Furthermore, sleep quality acts as a mediator between perceived stress and the onset of depressive symptoms in diabetic populations, where chronic sleep deprivation further impairs neurogenesis and drives abnormal neurotransmission (Subba et al., 2021; Wang et al., 2021).

5. Clinical Implications.

5.1. Screening for Depression in Diabetes.

The significant prevalence of unrecognized mood disorders in diabetic populations highlights the necessity of implementing systematic diagnostic protocols within routine medical evaluations (Albasheer et al., 2018; Shirali et al., 2023). Major clinical guidelines, including those from the American Diabetes Association (ADA) and the U.S. Preventive Services Task Force, advocate for universal and periodic screening for depression and diabetes-related distress (Owens-Gary et al., 2019). Early identification is particularly critical for emerging adults, as early-stage risk assessments may prevent the development of more severe psychiatric conditions later in life (Yadav et al., 2023). Validated instruments such as the Patient Health Questionnaire-9 (PHQ-9) are highly effective for initial assessment, with a cutoff score of 10 or higher demonstrating strong sensitivity for detecting major depressive episodes (Owens-Gary et al., 2019; Sharif et al., 2019). However, because self-report tools can be limited by social desirability or recall bias, positive screens should be followed by formal clinical interviews with mental health professionals to confirm the diagnosis (Ahola et al., 2021; Salinero-Fort et al., 2018). Despite these clear recommendations, barriers such as patient-related stigma, provider time constraints, and a lack of access to specialists continue to hinder effective screening in primary care settings (Owens-Gary et al., 2019).

5.2. Integrated Care.

A transition from traditional, siloed treatment models to integrated care is essential for addressing the multifaceted needs of patients with comorbid diabetes and depression (Al-Jabi, 2024; Khan et al., 2019). Collaborative care models—which utilize coordinated services between primary providers, nurses, and psychologists—have demonstrated superior outcomes in managing both glycemic levels and psychiatric symptoms compared to standard care (Owens-Gary et al., 2019; Albasheer et al., 2018). These integrated programs often prioritize problem-solving therapies and meticulous medication management to improve treatment adherence (Owens-Gary et al., 2019, Ahola et al., 2021). Beyond clinical efficacy, integrated care offers significant economic benefits; research indicates that collaborative management can result in medical cost savings of approximately $896 per patient over a two-year period by reducing hospitalizations and outpatient service utilization (Owens-Gary et al., 2019). Furthermore, a more holistic approach that includes discussions of stressful life events and the enhancement of social support networks can identify vulnerable individuals before they reach clinical thresholds for depression (Salinero-Fort et al., 2018; Lloyd et al., 2020).

5.3. Multidisciplinary Treatment.

Effective management of the diabetes-depression comorbidity requires a multidisciplinary team approach involving diabetologists, psychiatrists, and general physicians working in tandem (Khan et al., 2019; Yadav et al., 2023). Interdisciplinary collaboration is vital because psychological health directly influences metabolic outcomes; for instance, treating depression can be a prerequisite for achieving glucose control, as improved mood enhances a patient's capacity to follow complex self-care regimens (Salinero-Fort et al., 2018). Treatment plans should ideally incorporate evidence-based psychological support, such as Cognitive Behavioral Therapy (CBT), which has been proven to alleviate depressive symptoms while simultaneously improving HbA1c levels (Subba et al., 2021; Al-Jabi, 2024). Additionally, the team should explore integrative and non-pharmacological strategies, including regular physical exercise to improve insulin sensitivity and emerging therapies like acupuncture, which may modulate neurotrophic factors like BDNF (Subba et al., 2021; Zhang et al., 2023). Ultimately, the integration of mental health professionals into the core diabetes care team ensures that both physical and psychological stressors are addressed, thereby changing the long-term prognosis and preventing further morbidity (Shirali et al., 2023; Zhang et al., 2023; Yadav et al., 2023).

6. Future Research Directions.

6.1. Longitudinal Studies.

To establish definitive causality between diabetes and depression, future research must shift from cross-sectional designs to rigorous longitudinal studies (Ahola et al., 2020; Prabu et al., 2020; Wang et al., 2021). Current evidence suggests that while these conditions frequently co-occur, cross-sectional data cannot determine if the mood disorder precedes metabolic decline or vice versa (Sharif et al., 2019; Ahola et al., 2021). Prospective tracking of patients from the initial onset of depression is of the highest priority to identify which individuals will follow a highly recurrent clinical trajectory versus those with a single lifetime episode (Monroe et al., 2022). Furthermore, long-term assessments are needed to monitor the progression of microvascular complications, such as retinopathy and nephropathy, over follow-up periods exceeding six years to accurately map the deleterious influence of mood on physical outcomes (Ahola et al., 2020; Shirali et al., 2023; Ahola et al., 2021). Future designs should also incorporate larger, more diverse samples, including participants from both urban and rural backgrounds, to account for socioeconomic and cultural mediators (Mei et al., 2023; Sharif et al., 2019).

6.2. Biomarkers.

The identification and validation of unique "neuroendocrine signatures" represent a critical frontier for clinical diagnostics. Emerging research highlights miR-128, brain-derived neurotrophic factor (BDNF), cortisol levels, and telomere length as inter-linked molecular signatures that could serve as robust biomarkers for both conditions (Prabu et al., 2020). Specifically, long non-coding RNAs (lncRNAs) like DANCR have shown significant diagnostic potential for identifying diabetic nephropathy in patients with type 2 diabetes (Kuang et al., 2024). Advances in multi-omics factor analysis now allow for the integration of transcriptomic, lipidomic, and metabolomic data to identify latent factors that predict rapid beta-cell decline (Armenteros et al., 2024). Additionally, the use of TSPO-PET imaging as a clinical biomarker for microglial activation offers a promising method for monitoring neuroinflammation and predicting treatment responses in patients with comorbid mood disorders (Guo et al., 2023).

6.3. Precision Medicine.

The future of diabetes and depression management lies in precision medicine, which aims to tailor interventions based on an individual’s unique genetic and biological profile (Zhang et al., 2023; Prabu et al., 2020). Personalized therapeutic strategies could involve predicting a patient's specific response to antidepressant medications based on baseline biomarkers like adiponectin levels or BDNF Val66Met polymorphisms (Subba et al., 2021; Zhang et al., 2023). Integrating artificial intelligence (AI) and machine learning into electronic health records can further refine risk prediction by processing complex multi-parametric datasets to identify vulnerable individuals before they reach clinical thresholds for both disorders (Owens-Gary et al., 2019; Armenteros et al., 2024; Guan et al., 2023). This stratification of patients into "slow" vs. "rapid" disease progressors will enable smarter, shorter clinical trial designs and more targeted prevention programs (Armenteros et al., 2024).

6.4. Multidisciplinary Treatment.

Refining multidisciplinary care models is essential for addressing the bidirectional burden of these disorders. Effective management requires the seamless integration of diabetologists, psychiatrists, and primary care physicians into a cohesive team that addresses both somatic and psychological stressors (Khan et al., 2019; Yadav et al., 2023). Current standards of care, such as those advocated by the American Diabetes Association (ADA), emphasize that including mental health professionals in core diabetes care teams is critical for improving patient adherence and long-term prognosis (Yadav et al., 2023). Future treatment frameworks should also explore non-pharmacological interdisciplinary approaches, such as regular physical exercise and acupuncture, which have shown potential in modulating neurotrophic factors like BDNF while simultaneously improving glycemic control (Subba et al., 2021; Zhang et al., 2023). Expanding this collaborative effort to include expertise from neuroscience and psychology will ensure a more holistic and effective approach to patient care (Zhang et al., 2023; Limenih et al., 2024).

Conclusions

This systematic review confirms that the relationship between diabetes mellitus and depression is profoundly bidirectional, with each condition significantly increasing the risk of developing the other and worsening its overall prognosis. The co-occurrence of these disorders is remarkably high, affecting approximately one in four patients with type 2 diabetes. This comorbidity is a critical driver of poor glycemic control (higher HbA1c levels), an increased incidence of microvascular complications such as nephropathy and retinopathy, and a significantly higher risk of premature mortality.

The complex interplay between these conditions is supported by shared biological mechanisms, including chronic low-grade inflammation (elevated IL-6, TNF-α, and CRP), dysregulation of the HPA axis leading to hypercortisolemia, and impaired neuroplasticity associated with reduced BDNF levels. These are complemented by psychological and behavioral pathways, where diabetes distress, the heavy burden of self-management (including insulin therapy and glucose monitoring), and maladaptive lifestyle factors like physical inactivity and sleep disturbances create a self-perpetuating cycle of health decline.

In clinical practice, it is essential to move away from isolated treatment silos toward integrated and multidisciplinary care models. Implementing universal and periodic screening using validated tools like the PHQ-9 is vital for identifying at-risk patients early. Collaborative efforts between diabetologists, psychiatrists, and primary care providers ensure that both metabolic and mental health needs are addressed, which is a prerequisite for improving patient adherence and long-term outcomes.

Future research should prioritize longitudinal studies to establish clearer causal pathways and focus on the validation of unique biomarkers—such as miR-128, BDNF, and specific lncRNAs—to facilitate the transition toward precision medicine. Leveraging artificial intelligence and machine learning to analyze complex patient data will further enable personalized interventions, ultimately reducing the global burden of this dual diagnosis.

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All authors have read and agreed with the published version of the manuscript.
Founding Statement: The study did not receive funding.
Conflict of Interest Statement: The authors declare no conflicts of interest.
Declaration of the use of generative AI and AI-assisted technologies in the writing process: During the preparation of this manuscript, the authors utilized ChatGPT to enhance linguistic quality, improve readability, and assist with formatting and basic data processing. All AI-generated output was thoroughly reviewed and edited by the authors, who maintain full accountability for the integrity and accuracy of the final work.

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