UDC 616-089-053:610.08

Clinical and dynamic features of depressive disorders in patients with type II diabetes mellitus and their impact on the development of diabetic polyneuropathy

Istamov M.B.

Bukhara State Medical Institute

https://orcid.org/0009-0006-6331-2396

Istamov Mirmuhsinjon Bahodirovich-Abu Ali Ibn Sino Bukhara State Medical Institute. Assistant of the Department of Psychiatry, Narcology and Medical Psychology Bukhara, Uzbekistan

Abstract. This article examines the clinical and dynamic characteristics of depressive disorders in patients with type 2 diabetes mellitus and their impact on the development of diabetic polyneuropathy. Pathogenesis mechanisms of comorbidity are analyzed , including chronic inflammation, hypothalamic-pituitary-adrenal axis dysfunction, insulin resistance, and deficiency of neurotrophic factors. Diagnostic methods, clinical manifestations, and current approaches to the treatment of depressive disorders in diabetes are discussed.

Key words: type II diabetes mellitus, depressive disorders, diabetic polyneuropathy, pathogenesis, comorbidity , cytokines, BDNF, antidepressants, cognitive behavioral therapy.

Клинические и динамические особенности депрессивных расстройств у пациентов с сахарным диабетом 2 типа и их влияние на развитие диабетической полинейропатии

Истамов М.Б.

Бухарский государственный медицинский институт

https://orcid.org/0009-0006-6331-2396

Истамов Мирмухсинжон Баходирович-Абу Али Ибн Сино, Бухарский государственный медицинский институт. Ассистент кафедры психиатрии, наркологии и медицинской психологии, Бухара, Узбекистан

Аннотация. В данной статье рассматриваются клинические и динамические характеристики депрессивных расстройств у пациентов с

сахарным диабетом 2 типа и их влияние на развитие диабетической полинейропатии. Анализируются механизмы патогенеза сопутствующих заболеваний, включая хроническое воспаление, дисфункцию гипоталамо-гипофизарно-надпочечниковой оси, инсулинорезистентность и дефицит нейротрофических факторов. В статье обсуждаются методы диагностики, клинические проявления и современные подходы к лечению депрессивных расстройств при сахарном диабете.

Ключевые слова: сахарный диабет II типа, депрессивные расстройства, диабетическая полинейропатия, патогенез, сопутствующие заболевания, цитокины, BDNF, антидепрессанты, когнитивно-поведенческая терапия.

Background. Type 2 diabetes mellitus (T2DM) remains one of the most common chronic diseases worldwide. According to the International Diabetes Federation, the number of patients with diabetes continues to grow steadily, creating a significant burden on healthcare systems (1). Diabetic polyneuropathy (DPN) develops in 50–60% of patients with a long-term history of diabetes and is a significant cause of disability (2). Concomitantly, depressive disorders are detected in 11–31% of patients with T2DM, which is 2–3 times higher than in the general population (3). Comorbidity of depression and diabetes is accompanied by worsening glycemic control, decreased treatment adherence, accelerated progression of complications, and an increased risk of mortality (4,5).

Research shows that painful polyneuropathy is a more significant predictor of depression than other diabetes complications (6). In a study of 170 patients with diabetes, painful polyneuropathy was associated with an odds ratio of 4.6 ($p = 0.038$) for the development of depression (6). This indicates a close relationship between pain, mental status, and metabolic disorders (7).

The pathogenesis of comorbidity is based on a complex interaction of biological factors. Chronic hyperglycemia leads to the formation of advanced glycation end products (AGEs), which activate RAGE receptors on immune and glial cells (8). This initiates a cascade of inflammatory processes with an increase in proinflammatory cytokines TNF-α, IL-1β, and IL-6 (9). A meta-analysis showed

that IL-6 and TNF-α levels are significantly higher in patients with depression compared to healthy individuals (10). IL-6 is involved in systemic inflammatory processes and activates the release of glucocorticoids, increases immunoglobulin production, and enhances monocyte recruitment (9,10). TNF-α, produced by macrophages and T cells, is a key proinflammatory cytokine (11).

Elevated cytokine levels disrupt the integrity of the blood-brain barrier and cause neuroinflammation , microglial activation , and neuronal damage (8,12). This supports the so-called " cytokine hypothesis" of depression, which explains the development of depressive symptoms in somatic diseases (12). Functional MRI studies have shown that peripheral inflammatory markers IL-6 and TNF-α correlate with the functional connectivity of brain networks at rest, differing between patients with depression and healthy individuals (13).

Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is a key pathogenetic link (14). Chronic stress and depression lead to hyperactivation of this axis with an increase in cortisol, ACTH, and CRF (14,15). Dysregulation of the HPA axis is associated with depression and anxiety in type 2 diabetes and involves a disruption of negative feedback mediated by the prolonged action of TNF-α (15). Hypercortisolemia aggravates hyperglycemia through stimulation of gluconeogenesis and increased insulin resistance. At the same time, chronically elevated cortisol is associated with a decrease in neurotrophic support, hippocampal atrophy, impaired synaptic plasticity, and cognitive impairment (14). Up to 50% of patients with depression have hypercortisolemia , which is also typical for patients with diabetes with poor metabolic control (15).

Insulin resistance and impaired central insulin signaling play a significant role in the development of both metabolic and psychiatric complications (16). Insulin not only regulates peripheral glucose metabolism but also modulates brain neurotransmitter systems, including the serotonergic and dopaminergic systems, which are critical for mood regulation (16, 17). Insulin resistance disrupts insulin signaling in the central nervous system, leading to decreased serotonin transporter function, decreased

dopaminergic activity, and cognitive deficits (17). Central insulin resistance is also associated with impaired reward processing and increased anxiety (16).

Decreased levels of brain-derived neurotrophic factor (BDNF) are observed in the comorbidity of depression and diabetes (18). BDNF mediates neurogenesis, synaptic plasticity, and neuronal survival. Low BDNF levels are detected in both depressed and diabetic patients and correlate with the severity of depressive symptoms, poor glycemic control, and the development of complications (18,19). BDNF is essential for peripheral nerve function, myelination , and pain regulation; its deficiency contributes to the progression of DPN (19). BDNF interacts with TrkB receptors in the hippocampus and limbic structures, maintaining their volume and function, which are critical for mood and memory (18).

Neuroimaging studies reveal structural changes in the comorbidity of depression and type II diabetes, including atrophy of the hippocampus, basal ganglia, orbitofrontal cortex (20). Patients with depression and diabetes have decreased gray matter thickness in the prefrontal regions and anterior cingulate cortex , which are involved in mood regulation (20). High HbA1c levels correlate with smaller hippocampal volume, suggesting a direct neuroanatomical influence of metabolic dysregulation on the development of depression and cognitive impairment (20). Structural changes in the thalamus and white matter have been identified in patients with DPN, including a decreased N- acetylaspartate to creatine ratio, indicating neuronal dysfunction (21). Functional reorganization of the primary somatosensory cortex in painful DPN promotes central sensitization, where non-painful stimuli are perceived as painful (allodynia) and pain responses are enhanced (hyperalgesia) (21).

Clinical manifestations of depression in patients with type 2 diabetes are characterized by polymorphic symptoms (22). Affective symptoms include persistent depression, anhedonia, apathy, hopelessness, and pessimism regarding disease control (22,23). Cognitive impairments include decreased attention, memory, slowed psychomotor reactions, and difficulty making decisions (22). Somatic symptoms—fatigue, changes in appetite and weight, sleep disturbances, and vague pain—often mask depression and are perceived as manifestations of

diabetes, complicating diagnosis (23). Patients with depression and diabetes are 2–5 times more likely to report diabetic symptoms with the same objective metabolic control compared to non-depressed patients (6). Depression is observed in 60% of patients with chronic pain, and 29.7% meet the criteria for major depressive disorder and generalized anxiety disorder (24).

Diabetic polyneuropathy in the presence of depression is characterized by a more pronounced clinical picture (25). Painful DPN occurs in 13-35% of patients with diabetes and is manifested by burning, stabbing, shooting pain, paresthesia, allodynia , mainly in the distal parts of the lower extremities (21). In a cross-sectional study of 61 patients with neuropathic pain, the prevalence of depression was 65.6%, and anxiety - 73.7% (24). Depression increases the subjective perception of pain through impaired central modulation of pain signals, a decrease in the pain threshold and neuroplastic changes in pain-processing structures (25,26). Painful DPN is the most disabling form, affecting role limitations, pain, physical function and energy level (7). Depressive symptoms sn reduce adherence to diabetes therapy, leading to worsening glycemic control and accelerated progression of polyneuropathy (27).

Diagnosis of depressive disorders requires a comprehensive approach (28). Standardized instruments include the Beck Depression Inventory (BDI-II), the Hospital Anxiety and Depression Scale (HADS), the Patient Health Questionnaire-9 (PHQ-9) for screening, and the Hamilton Anxiety Scale (HAM-D) for severity assessment (28,29). Diagnosis of DPN is based on a clinical neurological examination with assessment of various types of sensation, reflex testing, and quantitative scales— Michigan Diabetic Neuropathy Score (MDNS), Neuropathy Disability Score (NDS) (30). Objectification includes electroneuromyography (ENMG), which measures nerve conduction velocity, quantitative sensory testing (QST), and corneal confocal microscopy to assess intraepidermal nerve fiber density (31). Pain assessment is performed using the Neuropathic Pain Questionnaire (DN4), Visual Analogue Scale (VAS), and Brief Pain Inventory (BPI) (32).

Treatment of depression in patients with type 2 diabetes should be comprehensive (33). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine

reuptake inhibitors (SNRIs) are first-line drugs due to their tolerability and safety (33,34). A meta-analysis of 16 randomized controlled trials showed that fluoxetine, citalopram , and escitalopram significantly reduced blood glucose levels compared with placebo in patients with type 2 diabetes (35). Paroxetine did not increase blood sugar but did not demonstrate significant improvement (35). In an animal model, sertraline counteracted the increase in glycemia after an oral glucose load in diabetic and nondiabetic rats, while fluoxetine induced glycemic peaks (36). The mechanism of the beneficial effect of SSRIs involves increased insulin secretion, a direct effect on beta cells, and improved treatment behavior (37). Serotonin and paroxetine act on pancreatic beta cells to increase glucose-stimulated insulin secretion (38). However, in a study of 40 patients with comorbid depression and diabetes, neither sertraline nor fluoxetine had a statistically significant effect on fasting glucose, postprandial glucose, HbA1c, and body mass index, although the reduction in triglycerides was significant (39).

Duloxetine (an SNRI) has a dual action—an antidepressant effect and an effect on painful diabetic neuropathy through modulation of descending serotonergic and noradrenergic pathways involved in pain control (40). Multimodal therapeutic approaches combining pharmacotherapy, cognitive-behavioral therapy (CBT), and neuromodulation are being studied for the relief of neuropathic pain (41). Cognitive-behavioral therapy demonstrates efficacy in the treatment of depression in diabetes through the correction of dysfunctional beliefs and the development of adaptive coping strategies (42). A systematic review of 66 studies found that psychological interventions demonstrate large positive effects on pain severity in the short term, small effects on pain interference, and a moderate effect on depression (7). In the medium term, large effects on pain severity and interference, as well as a moderate effect on depression, were confirmed. Long-term results have reported significant improvements in pain interference, mood, and self-care behavior (7). Acceptance and Limit Therapy (ACT) is a new approach aimed at increasing psychological flexibility and achieving improvements in functioning (24). ACT focuses on

accepting unchangeable issues such as pain, acting on values, and connecting with the present moment (24).

An integrated multidisciplinary model that brings together endocrinologists, psychiatrists, and psychologists is recognized as the most effective for managing comorbid patients (43). Collaborative care includes regular depression screening, treatment coordination, psychoeducation , and adherence monitoring (44). Physical activity, a balanced diet, weight loss, and smoking cessation have been proven effective in improving metabolic control and reducing depressive symptoms (45). New strategies include GLP-1 receptor agonists and SGLT-2 inhibitors, which can improve glycemia and mental health through their effects on neuroinflammation (46).

A review of the literature confirms a bidirectional association between depression and type 2 diabetes, mediated by biological and behavioral factors (47). Painful DPN is a stronger predictor of depression, requiring a comprehensive approach to pain treatment that includes antidepressants and psychotherapy (48). The choice of antidepressants should take into account the impact on the metabolic profile; SSRIs and duloxetine remain the drugs of choice (49). Early diagnosis and adequate treatment of depression improve glycemic control, reduce hospitalizations, and slow the progression of complications (50).

Depressive disorders in patients with type 2 diabetes mellitus represent a significant clinical challenge, significantly impacting the development of DPN, quality of life, treatment adherence, and prognosis. The pathogenesis is driven by chronic inflammation with elevated IL-6 and TNF-α, HPA axis dysfunction, insulin resistance, impaired neurotrophic support, and structural brain changes. Comprehensive therapy, including pharmacological and non-pharmacological methods and a multidisciplinary approach, are key to improving outcomes. This topic requires further study of the mechanisms of comorbidity and optimization of therapeutic strategies.

List of abbreviations

Type II diabetes mellitus Type 2 diabetes mellitus

DPN Diabetic polyneuropathy

HPA axis Hypothalamic-pituitary-adrenal axis

AGEs End products glycation (Advanced Glycation End Products)

RAGE Receptors To final products glycation (Receptor for Advanced Glycation End Products)

IL-6 Interleukin -6

IL-1 β Interleukin - 1 beta

TNF- α Factor necrosis tumors alpha (Tumor Necrosis Factor alpha)

BDNF Neurotrophic factor head brain (Brain-Derived Neurotrophic Factor)

TrkB Tropomyosin - binding receptor kinase B (Tropomyosin receptor kinase B)

HbA1c Glycated hemoglobin (Hemoglobin A1c)

ACTH Adrenocorticotropic hormone

CRF Corticotropin- releasing factor

CNS Central nervous system

SSRIs Selective serotonin reuptake inhibitors

SNRIs Serotonin-norepinephrine reuptake inhibitors

CBT Cognitive Behavioral Therapy

ACT Acceptance and Commitment Therapy (Acceptance and Commitment Therapy)

QST Quantitative Sensory Testing (Quantitative Sensory Testing)

ENMG Electroneuromyography

DN4 Neuropathic Pain Questionnaire (Douleur Neuropathique en 4 Questions)

YOUR Visual Analogue Scale

BPI Brief Pain Inventory (Brief Pain Inventory)

MDNS Michigan Diabetic Neuropathy Scale (Michigan Diabetic Neuropathy Score)

NDS Neuropathy Disability Scale (Neuropathy Disability Score)

PHQ-9 Patient Health Questionnaire, 9 items (Patient Health Questionnaire-9)

HADS Hospital Anxiety and Depression Scale (Hospital Anxiety and Depression Scale)

BDI-II Beck Depression Inventory, 2nd edition (Beck Depression Inventory (II)

HAM-D Scale depression Hamilton Depression Rating Scale
GLP-1 Glucagon-like peptide -1 (Glucagon-Like Peptide-1)
- 2 Sodium Glucose Sodium-Glucose Co - Transporter 2
CCC Cardiovascular system
CNS Central nervous system
MRI Magnetic resonance imaging
NM Neuromodulation
PB Mental Well-Being
QL Quality of life
HAC Higher Attestation Commission of the Republic of Uzbekistan
WHO World Health Organization

Bibliography

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care . 2001;24(6):1069–1078.
2. Antidepressant Therapy and Glycemic Control in Canadian Patients. Front Nutr . 2018;5:47 .
3. Antidepressants for depressed patients with type 2 diabetes mellitus. Neurosci Biobehav Rev . 2022;139:104782 .
4. Antidepressants and type 2 diabetes: highways to knowns and unknowns. Biomedicines . 2023;11(9):2496.
5. The acute effect of different antidepressants on glycemia in diabetic and non-diabetic rats. Braz J Med Biol Res . 2001;34(1):57–64.
6. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful diabetic neuropathy. JAMA. 1998;280(21):1831-1836.
7. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
8. Brain-derived neurotrophic factor in depression and diabetes. Psychoneuroendocrinology . 2024;161:106922 .
9. Breaking the diabetes-depression cycle: pathophysiology and mechanisms. World J Diabetes . 2025;16(7).

10. BDNF as a biomarker in depression and type 2 diabetes. Neurosci Biobehav Rev . 2023;146:105069 .
11. de Groot M, Golden SH, Wagner J. Psychological conditions in adults with diabetes. Am Psychol . 2016;71(7):552–562.
12. Depression and type 2 diabetes: causal relationship and mechanisms. Diabetes Obes Metab . 2023;25(12):3456-3468.
13. Depression and diabetes mellitus: the role of adiposity. J Affect Disord .