The bidirectional relationship between depression and diabetes

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Abstract

Introduction and objective: In recent years, depression and diabetes have become more and more serious medical issues. The number of patients suffering from one or both of these disorders increases year by year, which significantly worsens their quality of life. The aim of the study is to present the current state of knowledge on the basic mechanisms and risk factors influencing the development of depression in patients with diabetes, as well as the bidirectional relationship between these illnesses. The study was based on a literature review and an analysis of publications available on PubMed and Google Scholar platforms. The search has been conducted with the use of a combination of keywords like: "diabetes type 1", "diabetes type 2", "depression", "mental health".

An abbreviated description of the state of knowledge: Every third patient with diabetes shows depressive symptoms. These psychological disorders are more common in people with type 1 diabetes. The most vulnerable group of patients are single women with low socioeconomic status and comorbidities. Numerous biochemical and psychosocial changes in the life of diabetic patients, significantly increase the risk of developing depression. The latest scientific

reports also draw attention to the two-way relationship between diabetes and depression. The inclusion of cognitive-behavioral therapy brings positive results in managing diabetes with comorbid depression.

Summary: The available scientific data clearly shows the existence of psychological and biological links between these two disease entities. Appropriate diagnosis and treatment of depressive disorders can improve the course of diabetes.

Key words: diabetes type 1, diabetes type 2, depression, mental health

INTRODUCTION AND PURPOSE

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels resulting from insulin resistance, insufficient insulin secretion, or excess glucagon secretion. Chronic hyperglycemia in diabetes leads to retinopathy, kidney, cardiovascular and nervous system dysfunctions [1]. There are two main types of diabetes. Type 1 diabetes mellitus (T1DM) is an autoimmune disease that causes impairment of the beta cells of the pancreas. Type 2 diabetes (T2DM), which is much more common, results from insulin resistance and hence ineffective use of glucose by cells [2].

This disease affects over 420 million people worldwide, causing 1.5 million deaths annually [3]. For several decades, there has been a steady increase in the number of new cases of diabetes. Moreover, it has been found to correlate with the increase in obesity, sedentary lifestyle and the aging of the world's population over the past 30 years [4,5].

Depression, as a common disease, severely limits psychosocial functioning and reduces the quality of life of patients. According to the WHO, severe depression is the third most common cause of the burden of disease worldwide. However, it is expected to take first place by 2030 [6]. Apart from social and cultural factors that determine the occurrence of this condition, it is largely genetic and other basic biological factors that determine the occurrence of depression [7,8].

Depression as a clinical condition is characterized by low mood, decreased energy level and reduced motor and physical activity, with disturbed motivation, agitation and reward system [9]. Other symptoms may also include significant weight loss or gain, insomnia or excessive sleepiness, a sense of worthlessness or guilt, and difficulty concentrating [10].
The greatest probability of the first episode of depression is in the period from mid-puberty to the mid-40s. However, in almost 40% of patients, the first episode occurs before the age of 20 [11, 12]. Moreover, depression affects women twice as often as men, with the peak incidence occurring in the second and third decades of life [12, 13]. This difference may result from the biological and psychological susceptibility of sex and the influence of environmental factors [14].

The course of depression may vary throughout life, but is episodic in most patients. The duration of episodes, the number and pattern of their occurrence are variable due to the unpredictable course of the disease [15]. The likelihood of relapse increases with each episode. Additionally, the older age of onset may increase this probability, and almost 80% of patients experience at least one consecutive episode in their life [16].

It is also worth mentioning that depression increases the risk of T2DM development, as well as hyperglycemia, insulin resistance, and micro- and macrovascular complications. On the other hand, the diagnosis of diabetes carries the risk of depression or may contribute to its more severe course, which indicates a two-way relationship between these diseases [17].

The aim of our work is to present the current state of knowledge on the basic mechanisms and risk factors influencing the development of depression in patients with diabetes, as well as the bidirectional relationship between these diseases. In order to find the proper publications, the search has been conducted with the use of a combination of keywords like: "diabetes type 1", "diabetes type 2", "depression", "mental health".

RESULTS

Epidemiology of depression in diabetes

Recent studies have shown that the comorbidity of depression and diabetes is very common. On the one hand, patients with diabetes have an increased risk of developing depressive symptoms, and on the other hand, patients with depression have an increased risk of developing diabetes [18]. The incidence of depression is moderately increased in patients with pre-diabetes and significantly increased in patients with T2DM compared to those without any chronic disease [19]. Epidemiological data suggest that at least one-third of people with diabetes suffer from clinically significant depressive disorders [18]. It is believed that the phenomenon of depression is up to three times more common in patients with type 1 diabetes and twice as frequent in people with type 2 diabetes compared to the general population worldwide [20]. One in four patients with type 1 or type 2 diabetes struggles with the feeling of anxiety [21]. Children and adolescents that suffer from diabetes have a 2-3 times higher incidence of depression than adolescents without diabetes [22]. Women with diabetes, as well as women without diabetes, suffer from depression more often than men [20].

Researchers agree that several factors may be associated with the risk of developing depression. This risk increases with the presence of the above characteristics: female gender, people living alone, people with poor social support and people with low socio-economic status. It has been found that all these factors affecting the general population increase the risk of depression also in the group of patients with diabetes [23, 24]. Moreover, it has been found that diabetes-specific risk factors for depression include the coexistence of diabetes-related complications, especially vascular complications, persistent poor glycemic control, and insulin therapy in T2DM [25,26].

Pathophysiology of depression in diabetes

The biochemical and physiological changes associated with diabetes, as well as the psychosocial burden of chronic disease may lead to depression. One of its causes is the reaction to lifestyle modifications and dietary restrictions [27]. Moreover, changes such as the stimulation of the nervous system may be responsible for an increased risk of depression in people with diabetes [28].

Limitations and additional activities requiring a high level of self-care among diabetic patients include frequent blood glucose monitoring, special management of pharmacological treatment, and the aforementioned strict dietary guidelines. Due to its chronic nature, the disease can result in medical complications and reduced mobility. This forces patients to develop new skills necessary to adapt to the current life situation [20, 28].

The difficulty of coping with difficult social situations can cause significant emotional stress that can mimic symptoms of depression. Emotional disorders related to diabetes or

stress related to it affect from 12 to 25% of patients [29]. It is also worth mentioning that patients prescribed a multifaceted treatment plan showed a greater level of distress in the first year after diagnosis. On the other hand, patients undergoing less intensive treatment may not experience it for several years after diagnosis [30]. Reducing the diabetic distress index is associated with an increased chance of reducing depressive symptoms and remission [31].

Recent findings indicate that insulin and its signaling pathways are involved in the neuromodulation, neuroprotection and neurotransmission of various key neurotransmitters. Moreover, it has been shown that brain insulin resistance, which may be secondary to peripheral insulin resistance, may cause depressive symptoms through changes in neuronal functions [32].

Additionally, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may be a critical link in the high incidence of depression and diabetes mellitus. It is considered a frequent mechanism for depression and insulin resistence [33]. Regulating the functioning of the HPA axis is one of the body's response mechanisms to acute and chronic stress [34]. Chronic stress, on the other hand, can weaken the feedback mechanisms that restore the normal function of the hormone systems responsible for the release of corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the anterior pituitary, and cortisol from the adrenal glands. The consequence may be chronic elevation of cortisol, catecholamines and inflammatory markers [33, 35].

Genetic studies have confirmed that depression may be causally related to diabetes. Thirty-four single nucleotide polymorphisms (SNPs) that were present on different chromosomes are associated with diabetes mellitus. On the other hand, a higher score of these SNPs has been linked to the presence of depression [36].

It was also noted that the circadian rhythm is related to glucose homeostasis and mood regulation, and its disturbance is associated with insulin resistance and diabetes, as well as depression [37]. However, it is likely that the mechanisms underlying this co-morbidity are not as simple as for a unidirectional relationship. Factors determining the pathophysiology of depression in diabetes are presented in Fig. 1.
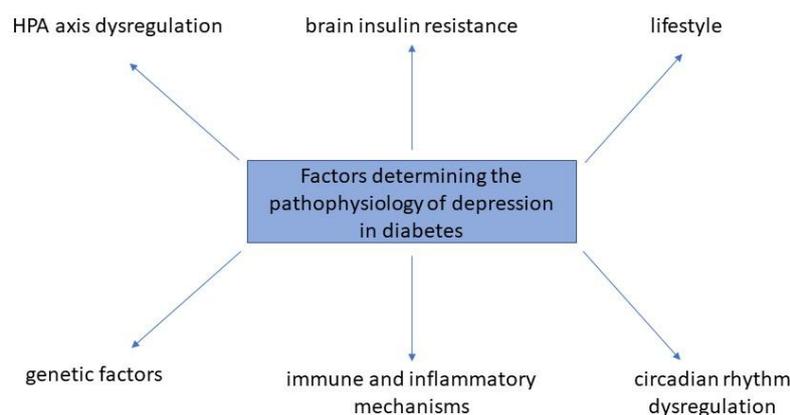

Fig. 1. Factors determining the pathophysiology of depression in diabetes.

Bidirectional relationship between type 2 diabetes and depression

Depression and type 2 diabetes can interfere with each other and complicate each other's course when they interact [20]. One study showed that the risk of developing depression in patients with diabetes compared to patients without diabetes is similar to the risk of developing diabetes in patients with depression compared to patients without depression [38]. Moreover, other studies also confirmed this bidirectional relationship. It has been shown that people with T2DM have a 15% higher risk of depression compared to people without diabetes, and people with depression have a 60% higher risk of developing T2DM [39]. In a 20-year study of the team of Pan et al. It has been shown that the relative risk of type 2 diabetes in people with depressed mood was higher compared to non-depressed subjects after adjusting for all covariates. In the same study, people with diabetes had an increased relative risk of developing clinical depression compared with those without diabetes [40].

The bidirectional relationship between depression and diabetes can be explained by the common pathogenesis of both disorders. Inflammation, dysregulation of the HPA axis, leptin, and common genetic factors such as the MC4R, NR3C1, and NR3C2 genes are among the factors associated with the cause of these diseases [41]. Another factor involved in the pathogenesis of both diabetes and depression is disturbed $Ca2+$ signaling [42].

Impact of depression on the course of type 2 diabetes

Numerous studies show that patients with depression show an increased risk of developing type 2 diabetes [39,43,44]. The coexistence of both of these pathologies significantly worsens the response to treatment, lowers the quality of life and increases mortality [45]. Affective disorders intensify metabolic disorders as well as cardiovascular complications by activating inflammatory factors and overactivity of the pituitary-adrenal and sympathoadrenergic systems [46]. Depression and its symptoms are associated with worse management of the course of diabetes, ie lack of regular physical activity, bad eating habits, which ultimately lead to higher blood glucose levels [30]. Diabetic patients suffering from depression are less likely to follow pharmacotherapy and diet regimens, which in turn reduces their quality of life and increases health care expenses [47].
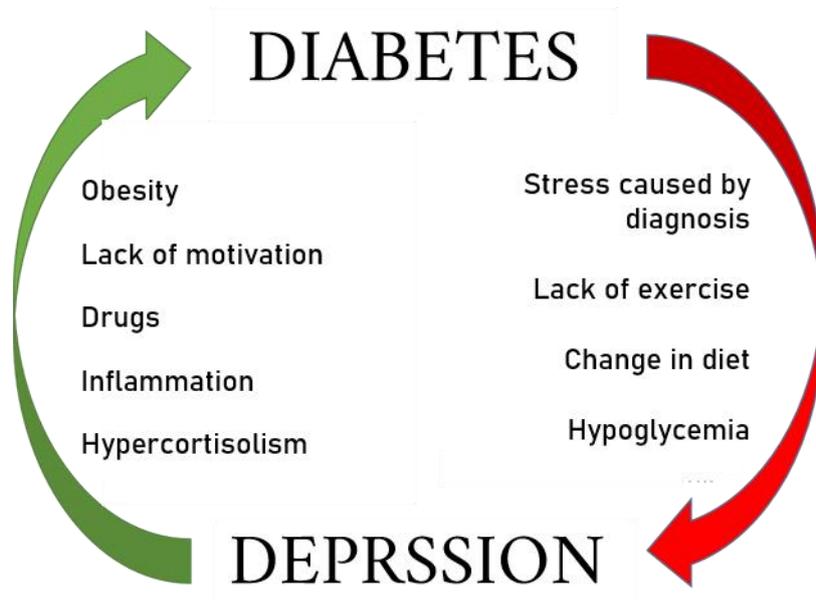
Fig. 2. The bidirectional relationship between depression and diabetes.

Kammer in his 2016 study documented that diabetic patients using many types of antidepressants struggled with increased levels of glycated hemoglobin (Hb1Ac). This suggests that antidepressant treatment may be a risk factor for suboptimal glycemic control [48]. Other studies have shown that short-term use of antidepressants improves insulin sensitivity, with the exception of noradrenergic drugs. However, in the case of long-term treatment, the negative influence of these drugs on glycemic control and an increased risk of developing diabetes is indicated [46]. Additionally, it has been reported that serotonin reuptake inhibitors (SSRIs) are the only class of antidepressants that can improve glucose control in patients with both short and long-term use [46]. Depression enhances the psychological impact of diabetes diagnosis, increasing stress related to diabetes [49]. In a study on the Japanese population, episodes of severe hypoglycemia related to the intensification of depressive symptoms in patients with T2DM were observed, regardless of glycemic control, insulin treatment, lifestyle factors and diabetic complications [50].

A better understanding of the two-way relationship between diabetes and depression may provide a more efficient diagnosis and more accurate treatment, which may lead to an improvement in the quality of life of patients [51, 52].

Treatment of depression and type 2 diabetes

Studies report that reducing depression symptoms is associated with improved glycemic control. A greater reduction of depressive symptoms leads to a better result of glycated hemoglobin (HbA1c). It also allows achieving the HbA1c target level of <7.5%. The above mentioned arguments justify the necessity to treat depression in diabetes patients due to better diabetes control and quality of life [53].

Regarding pharmacological interventions, treatment targeting insulin resistance may play an important role in reducing cognitive impairment and anhedonia in patients with depression in diabetes [32]. There was also a moderate beneficial effect of antidepressants on

the assessment of depression severity and clinical outcomes compared to placebo in the treatment of short-term depression [54,55]. If possible, it is better to choose a selective serotonin reuptake inhibitor (SSRI) for its treatment in patients with diabetes mellitus. However, attention should be paid to the existing risk of hypoglycaemia while using SSRIs. In the case of treatment with tricyclic antidepressants, more careful glycemic monitoring is recommended [56].

Problem-solving therapy has been reported to improve metabolic parameters such as HbA1c and cholesterol in patients with diabetes mellitus and comorbid depression or anxiety [57]. Cognitive-behavioral therapy (CBT) is an effective treatment for depression in patients who are characterized by distorted negative thinking about themselves, their future and everyday experiences. This therapy teaches depressed patients how to systematically characterize these thinking patterns [58].
Its effectiveness was confirmed in the Lustaman syndrome study, where after 10 weeks of treatment and again after 6 months, the percentage of patients in remission was significantly higher in the group that received CBT compared to the control group [59].

Compared to standard diabetes-specific CBT and CBT, both groups experienced reductions in depression and anxiety levels, with better glycemic and dietary control in the diabetic group. This indicates that the modified intervention is better compared to the standard psychological intervention in the treatment of depression in diabetes [60]. Moreover, it has been shown that CBT is responsible for the reduction of insulin resistance [32].

SUMMARY

The comorbidity of depression and diabetes is a very common phenomenon. By interacting, each of these diseases can affect and complicate the other. This bidirectional relationship between depression and diabetes can be explained by the common pathogenesis of both disorders. Factors related to their cause include inflammation, dysregulation of the HPA axis, effects of leptin, and common genetic factors. Moreover, the coexistence of these pathologies significantly worsens the response to treatment, lowers the quality of life and increases mortality. For this reason, understanding the relationship between depression and diabetes, and consequently improving the diagnostic process and improving therapeutic options, is so important.

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