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The correlation between diabetes mellitus and depression

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Abstract

Depression is the most prevalent mental health condition. It's estimated that nearly 5% of adults suffer from this disorder globally. Depression is marked by ongoing sadness and a loss of interest or pleasure in activities that were once enjoyable or fulfilling. It can also lead to disruptions in sleep and eating patterns. Common symptoms include fatigue and difficulty concentrating.

According to WHO diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose which leads to the damage of the heart, blood vessels, eyes, kidneys and nerves. Nowadays the occurrence of diabetes mellitus, obesity and depression is getting higher and higher. Both conditions stand as prominent health issues in today's society. Recent pandemic, wars, problems of the current world can cause depression and anxiety disorders. The fast-paced nature of our lives, work-life balance issues, sedentary habits, and time constraints can lead to opting for fast food and neglecting a healthy diet. People with diabetes are more prone to experiencing depression. Moreover, a significant portion of cases remains underdiagnosed.

Key words: diabetes mellitus and depression, dm and depression, treatment of depression in patients with dm, treatment of diabetes in patients with depression, physical activity in people with depression and diabetes

Purpose

The purpose of this review was to show the links between depression and diabetes mellitus. The objective was also to underscore the importance of detecting depression within the diabetic population, emphasizing the need for increased screening in individuals at risk. The other goal of this project is to improve the treatment of diabetes in individuals with depression, raising awareness of potential issues with compliance and effectiveness that may occur in those patients during treatment. The other aim of this article was to increase awareness of these diseases, improve the outcomes of diseases, and to help patients and doctors to treat them.

Materials and methods

The review was based on the analysis of materials collected in the „Pubmed", Google Scholar, ResearchGate databases, books and other scientific articles. The search was performed using the keywords: „diabetes mellitus and depression", „dm and depression" „treatment of depression in patients with dm" „treatment of diabetes in patients with depression" „physical activity in people with depression and diabetes"

Pathophysiology

There are three possible hypotheses for the correlation between diabetes and depression. First assumes that both diseases have common etiology, second supposes that diabetes increases the prevalence or risk for developing depression in the future and third presumes that depression increases the prevalence or risk for future diabetes. In recent research, any common genetic factors associating depression and diabetes were found. However, there are some epigenetic factors that may activate pathways promoting diabetes mellitus type 2 and depression. [1]. One of them is a low socioeconomic status. [2,3] It increases the odds for diabetes t.2 and it also appears to be a cause of depression. Poor sleep, diet and lack of physical activities are also

common causes for DM2 and depression. These factors may indicate that a common pathway of these two diseases involves the activation and disturbance of the stress system. Chronic stress causes activation of the hypothalamus-pituitary-adrenal axis and increases the production of cortisol, adrenaline and noradrenaline by sympathetic nervous system [4]. Prolonged sympathetic nervous system's activation and chronic hypercortisolemia cause insulin resistance, visceral obesity, and can lead to metabolic syndrome and diabetes mellitus t.2.

On the other hand, „stress hormones" such as adrenaline, noradrenaline and cortisol have an impact on human behaviour. They determine anxiety, anorexia or hyperphagia.

Hypercortisolemia disturbs neurogenesis in the hippocampus, a region involved in DM2 as well as in depression. [5,6]

Chronic stress also increases the production of inflammatory cytokines. High levels of inflammatory cytokines interact with the β-cells produced by pancreas and induce insulin resistance, so that it promotes occurrence of diabetes t.2 It is known that proinflammatory cytokines interact with neurotransmitter metabolism, synaptic plasticity, metabolic and endocrine functions, playing a significant role in developing depression. [7].

Interestingly, children and youth with diabetes have 2-3 times bigger prevalence of depression that adolescents without diabetes. [8]

When it comes to diabetes mellitus t.1, it seems that DM1 and depression have common pathophysiological pathways [9]. There is not much research on the link between DM1 and depression, but some important reviews show a biological connection between them, among others the lack of insulin, increased level of cytokines affect neurogenesis and neurotransmitter metabolism, hyperactivity of the hipothalamus-pituitary-adrenal axis. Curiously enough, poor glycemic control in children with DM1 is related to depression and lower socioeconomic status. Risk of depression in these patients increases as glycemic control worsens. [10]

Risk of depression in patients with DM

Patients with diabetes have twice the prevalence of depression than those who do not have diabetes [11].

Apart from mechanisms explained earlier, a recent study showed that using antidepressants increased the level of HbA1C. It is suggested that antidepressants agents may cause suboptimal glycemic control [12]. Long-term anti-depressive treatment may have a negative impact on insulin sensitivity [13]. On the contrary, the data from prior studies showed that short-term anti-depressive therapy of nondiabetic patients can improve insulin sensitivity and lessen symptoms of depression [14].

Noradrenergic antidepressants may cause impaired insulin sensitivity even in nondiabetic individuals [15].

Serotonin selective reuptake inhibitors are the only class of antidepressants with confirmed positive effect on glycemic control (both on short and long term use).

The use of antidepressants is more strongly associated with a higher risk of diabetes than depression alone.

It's crucial for both doctors and patients to be aware of the potential negative effects of antidepressant therapy on glycemic control and to make efforts to minimize them.

Moreover, comorbidity of DM and depression increases risk of complications of depression such as suicide and hospitalization. [16]

Risk of DM in patients with depression

It has been demonstrated that depression was more prevalent in individuals with diabetes, regardless of whether they have been diagnosed or have undiagnosed DM. This effect may be provoked by „psychological burden" of being sick and this may play a significant role in triggering anxiety and depression. [17].

Depression has also a higher prevalence in patients with previously undiagnosed diabetes and it can be a result of stressful life, lack of physical activity, unhealthy diet and bad lifestyle habits.

In theory, the use of anti-diabetic treatment may potentially exacerbate depression. A significant correlation was observed between depression in individuals in their forties who were receiving oral diabetes treatment, as opposed to those in their seventies [18]. Conversely, insulin therapy in elderly individuals with type 2 diabetes resulted in the alleviation of depressive symptoms without impacting the health-related quality of life for these patients [19].

Diabetes induces structural alterations in the brain, including cerebral atrophy, lacunar infarcts, and changes in blood flow involving both hypo- and hyperperfusion [20]. Patients with diabetes exhibited reductions in brain volumes, particularly in the hippocampus, with a documented inverse relationship between glycemic control and hippocampal volume. HbA1C was identified as the sole significant predictor of hippocampal volume [21]. Similarly, depression is linked to neurodegenerative processes, particularly in the prefrontal cortex and hippocampus.

Treatments for Depression among Individuals with Diabetes

The presence of depression in individuals with diabetes is linked to lower adherence and unfavorable health results.[22]

Depressed patients with DM have elevated rates of mortality, cardiac events, hospitalizations, diabetes-related complications, functional impairment, healthcare costs, medical symptom burden, and reduced quality of life compared to diabetic patients without depression. Meta-analyses indicate a consistent association between depression and heightened hyperglycemia, as well as an increased risk of diabetes-related complications such as diabetic retinopathy, nephropathy, neuropathy. [23] They are also less adherent to the treatment of DM than non-depressed people. [24]

Remarkably, it has been established that some psychological interventions, e.x. cognitive-behavior therapy, psychotherapy, counseling were effective in reducing glycosolated hemoglobin A1c (HbA1c) levels and improving quality of life in both types of diabetes.[25].

We can divide types of intervention into three groups psychosocial, pharmacological, and collaborative care.

As for pharmacological intervention, SSRIs are the most commonly prescribed antidepressants due to their favorable safety profile and effectiveness, making them a recommended choice for depressed patients with diabetes. [26,27].

E.x. fluoxetine, not only possess antidepressant properties but may also contribute to hypoglycemia and weight loss, and it shows potential for improving glycemic control [28]. Another effective medicine is bupropion, it also has positive effects on weight and glycemic control, particularly in patients with obesity and diabetes [29].

Nevertheless, certain other antidepressant medications can pose undesirable side effects, which may be particularly problematic for patients with diabetes. Monoamine oxidase inhibitors may lead to weight gain, while tricyclic antidepressants can induce hyperglycemia [30].
Atypical antipsychotics, though effective in treating depression and approved for such use, can cause weight gain and worsen glycemic control in diabetic patients, potentially leading to glycemic abnormalities, including the development of diabetes in those without a pre-existing diagnosis [31].

A possible role of glucagon-like peptide-1 receptor agonists in the treatment of depression

Glucagon-like peptide-1 receptor antagonists appear to be usable in conjunction with classic antidepressants to enhance the effectiveness of the treatment. They possess pro-cognitive and neuroprotective properties, exerting an impact on the immune system, as well as endocrine and metabolic processes. In patients with depression, brain regions that regulate emotions and stress response, such as hippocampus and the prefrontal cortex, undergo changes compared to individuals without depression. It was proven that intracerebroverticular administration of GLP-1 enhances associative and spatial learning. It was also shown that associative contextual learning can be improved by hippocampal Glp1r somatic cell gene transfer. It’s noteworthy that liraglutide administration weakened depressive and anxiety-like behaviors in a depression mouse model. What’s more chronic administration of this substance protects synaptic plasticity. Studies show that GLP-1R agonists may be useful to treat cognitive impairment observed in people affected by depression, especially women.

Depressive symptoms are often associated with a deficit of brain-derived neurotrophic factor in the brain and studies show that GLP-1R agonists in animal models increased the expression of BDNF in the brain.

It is said that the inflammatory process in the brain and increased number of pro-inflammatory cytokines may be one of the key factors leading to depression. GLP-1 and its therapeutic analogs seem to decrease the level of inflammatory markers but further studies are needed to better explain their actions.

The data shows that GLP-1 have a role in regulation of the stress axis. According to studies, GLP-1 brain administration elevated concentration of ACTH and corticosterone and enhanced anxiety behaviors. Recent studies showed that GLP-1R agonists may also modulate the stress response via hypothalamic-pituitary-adrenal axis.

Moreover, the usage of GLP-1 in depressed patients may prevent some metabolic diseases such as diabetes and obesity, which are often associated with depression and adverse reactions to some antidepressants agents.

To sum up, it has been established that treatment with GLP1 agonists resulted in the reduction of depression symptoms, as measured by the Hamilton Depression Rating and Beck's Depression Inventory, However, further research is needed to fully understand their phenomenon. [32].

The role of physical activity on depression in adults with diabetes

Physical exercise is good for everyone - World Health Organization recommends engaging in regular moderate-intensity exercise for at least 5 days a week, for at least 30 minutes a day [33]. We know that physical activity has also an effect on both depression and diabetes mellitus.[34] The results of the study suggest that the risk of diabetes may be influenced by lifestyle. It has been shown that the risk of diabetes is higher among office workers because of sedentary lifestyle. Moderate-intensity physical activity improves blood sugar metabolism. As we know regular physical activity helps to regulate normal glucose uptake into peripheral tissues, and increases insulin receptors and insulin sensitivity, thus contributing to blood glucose control [35].

By contrast, excessive high intensity exercise can lead to fatigue and it can increase depression. [36]. Moreover, it is believed that engaging in physical activity of moderate intensity, conducive to enhancing health, can potentially alleviate stress and depression. It would be advantageous for healthcare practitioners, including occupational therapists and exercise instructors, to design age-appropriate exercise regimens with suitable intensity, duration, and frequency specifically tailored for individuals with diabetes. Implementing such programmes in community health centers and welfare centers could prove beneficial for the well-being of patients.

People should look for an activity suitable for them - for example, dancing can be both a popular social activity and an exercise that facilitates joint movement. [37] Even small changes in lifestyle can have positive effects - walking regularly for 30 minutes every day improves muscular endurance, and also enhances concentration.[38] Muscular endurance exercises can also help maintain people's health. Endurance exercises reduce age-related problems by increasing muscle mass and allowing increased bone density, reducing the effects of osteoporosis.[27]

To sum up, a structured program for recreational activities and formal educational opportunities are essential to assist individuals in coping with the challenges of stress and depression in their everyday lives. Furthermore, fostering community and familial backing is crucial in motivating individuals to engage in regular, moderately intense exercise and adopt lifestyle changes that encourage physical activity [35]. We should also remember that mental health disorders enhance appetite and cravings and decrease motivation for physical activity.[40]

Nutritional aspects [41]

Evidence suggests that elevated sugar consumption has been correlated with depression and anxiety in various cross-sectional and observational studies. Similarly, research investigations have established a connection between the consumption of refined carbohydrates, inflammatory markers in circulation, and their influence on mental well-being. Studies have indicated that individuals with mental disorders tend to have a diminished intake of vegetables, fruits, whole grains, and fiber in their dietary habits. [42,43]. Consequently, a low-quality diet consumed

during episodes of depressive symptoms may increase the risk of developing diabetes. High glycemic index diet turn out to be a risk factor for depression.

Bad diet and unhealthy lifestyle are known as risk factors contributing to the pathogenesis of diabetes. It was also established that ingestion of sugar-sweetened beverages and processed foods is linked with increased risk of DM2. Processed foods are also associated with an increased risk of subsequent depression. [44]
Diet is crucial in the management of DM and complications.
On the contrary a healthy diet with high intake of vegetables, fruits, whole grains was correlated with decreased risk of DM2. Studies show that a low-carbohydrate diet improves glycemic control and reduces the need for medications in patients with diabetes.
People should also pay attention to protein intake – a higher intake of plant protein is linked with a lower risk of DM. On the contrary, studies show that women with higher animal protein intake have higher risk of developing symptoms of depression. No significant association between mental disorders and plant protein was found. [45]

Likewise, healthy, balanced diet is related with better mental health.[46]
Mediterranean diet turns out to be correlated with a lower risk of some psychological disorders like anxiety and depression, psychological distress [47], [48]. Data shows that mediterranean diet is appropriate for people with diabetes - it improves glycemic control and also reduces cardiovascular risk.
It was also established that such a diet decreases the risk of diabetes.
All things considered - the mediterranean diet is effective in mitigating symptoms of DM and depression when studied separatorly - however we lack knowledge about this diet in individuals suffering from both DM and depression simultaneously.

Evidence suggests that supplementing omega-3 fatty acid reduces depressive symptoms in individuals with diabetes experiencing mild or moderate symptoms of depression [48].
Studies show that deficiencies in some nutrients like omega-3 fatty acids, vitamin B and D, macroelements, microelements such as zinc, chromium, magnesium, and selenium are associated with developing both DM and mental health disorders.
All these findings show the importance of a healthy diet in people’s lives. They also present a potential area for interesting research.

Certainly, healthy, appropriate diet is helpful in treating individuals with DM and in maintaining overall health and well-being, also considering mental health.
There is evidence showing a link between diabetes, depression and nutrition, but further research is needed to better understand these connections.

Clinical practice

In diabetic patients, depression may be underdiagnosed. Raising awareness of depression in diabetes could lead to improved outcomes, with a starting point being the incorporation of a straightforward depression screening method into regular diabetic follow-ups. Depression has a combined impact on individuals with both DM1 and DM2, escalating the risk of complications in both microvascular and macrovascular realms, intensifying hyperglycemia, and predicting higher mortality rates. In the elderly, this comorbidity also forecasts an earlier onset of complications [49]. Although both diabetes and depression individually diminish an individual's quality of life, their coexistence has an even more detrimental effect. It’s very important for doctors to be aware of this quite common co-morbidity. Specialists should have multidisciplinary approach towards the patients. It would improve outcomes of diseases, help treatment of those illnesses and improve the quality of life of the patients.

While depression screening questionnaires might overestimate the prevalence of depression [50], they offer a simple and rapid assessment. Therefore, positive screening results should be validated through an interview with a mental health specialist. Among the various short questionnaires employed to identify depression, the Beck Depression Inventory (BDI) and the Center for Epidemiologic Studies Depression Scale (CES-D) are the most widely used, followed by the Hospital Anxiety and Depression Scale (HADS) and different versions of the Patient Health Questionnaire (PHQ) [52]. The PHQ–9, with high sensitivity and specificity, is the most utilized and validated screening test for depression in people with diabetes [52]. A study proposing an increased cut-off for major depression at ≥ 12 points (instead of 10 points) in diabetic patients using the PHQ-9 may enhance discrimination between diabetes-related and depressive symptoms [51].

Upon diagnosing depression in a diabetic patient, it is advisable to address both conditions simultaneously. Some authors prioritize the treatment of depression, as antidepressant responses are typically observed within 2-4 weeks, while improvements in glycemic control and HbA1C levels take several months. Patients with better moods are also more likely to adhere to their diabetic treatment. They propose a stepped model for treating depression and diabetes based on the severity of depression [52].

Lifestyle modifications, such as increased physical activity, dietary adjustments, sufficient relaxation and sleep, social interaction, mindfulness-based meditation techniques, and reducing recreational substances like nicotine, drugs, and alcohol, have demonstrated benefits in improving both depression and diabetes.

Conclusion

It is crucial for society to prevent, identify and treat diseases. Diabetes and depression represent a prevalent, bidirectional, and impactful comorbidity that affects the quality of life for the patients and their families, glycemic self-management, long-term diabetes complications, usage of medical services, medical costs, and early mortality.

However, the World Health Organization highlights a significant gap between the burden caused by mental disorders and the available resources for prevention and treatment. It is estimated that four out of five people with serious mental disorders in low and middle-income countries do not receive the necessary mental health service. Depression remains underdiagnosed in diabetic patients, emphasizing the need for awareness among diabetic specialists. A multidisciplinary approach to diabetic patients could enhance disease outcomes, reduce disability-adjusted life years (DALYs), and even decrease mortality.

It’s important also from an economical point of view - Approximately 20% of the overall medical expenses covered by the national health insurance scheme in Korea are attributed to the treatment of diabetes patients. The average healthcare expenditure per diabetic patient is roughly three times higher than that of individuals without diabetes [53]. Consequently, the national expenditure on health insurance is on the rise. Therefore, it is imperative to focus on initiatives that enhance and sustain the health of diabetic patients, aiming to mitigate medical costs and lower the mortality rate associated with diabetes.

A further research is needed to identify common triggers for depression and diabetes and to know more about co-morbidity of these two diseases.

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