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# BIDIRECTIONAL INTERACTION OF BLOOD GLUCOSE AND MENTAL STATUS AND ITS ROLE IN DEVELOPING DIABETES MELLITUS AND PSYCHIATRIC DISORDERS – SYSTEMATIC REVIEW

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## ABSTRACT

Blood glucose concentration in certain situations affects current mental status. Anxiety occurring during hunger or lack of concentration associated with hypoglycemia are well-known phenomenon. Variations of glucose levels may also present a long-term impact on mental status and mental health. Moreover, impaired mental status leads to neglecting health-promoting life choices in some individuals, while psychiatric disorders may contribute much more to the development of metabolic diseases.

**Aims:** The aim of this review is to assess the current state of knowledge about the bidirectional interaction of blood glucose levels, including its fluctuations and management, and mental status.

Methods: In our publication we used scientific sources such as publications and textbooks.

**Results:** Studies show the most significant correlation between diabetes and psychiatric disorders, mostly depression, but also indicate that healthy individuals may present a correlation of metabolic and mental disorders. Diabetic patients are more prone to develop psychiatric disorders, but also psychiatric patients are more commonly affected by diabetes mellitus. Moreover, those suffering from both diseases show the highest risk of overall mortality. Inflammatory pathology of both diabetes and depression, which is the most common psychiatric disorder in diabetic patients, suggests that chronic inflammation may play the main role in this relationship.

**Conclusion:** Analyzing different risk factors of comorbidity, the significance of reversible ones is indisputable. Taking that into account, some lifestyle changes may be beneficial for metabolic and mental disorders prevention. Further studies could indicate certain pathological relationships and help understand the correlation between blood glucose and mental state in healthy individuals.

**Keywords:** glycemic variability, glycemic fluctuations, diabetes, hyperglycemia, hypoglycemia, mood disorders, depression, mental status, psychiatric disorders, mood.

## INTRODUCTION

As many as 1 in every 4 people experiences an episode of mental disorder during their lifetime [29]. Every year almost 40% of the European population gets affected [48]. The incidence of psychological disorders such as depression or bipolar disorder is increasing worldwide and has become one of the main healthcare challenges. Depression and anxiety are the most common and probably most harmful psychological disorders for one's life quality [13].

Metabolic disorders, being a major health problem, are also highly increasing in the global population. Prevalence of metabolic syndrome characterized by abdominal obesity, low level of serum HDL-lipoproteins, elevated serum triglycerides, elevated fasting blood glucose and high blood pressure, varies in different regions and can be as high as 40% [41]. It is estimated that in 2019 9.3% of the world population suffered from diabetes and this is going to rise to over 10% by 2030, due to the fact, that about 20% of the population is affected by prediabetes. This health condition is described as impaired fasting glucose and impaired glucose tolerance, which will progress to type 2 diabetes within 3-5 years in approximately 25% of patients [49,21,40].

Both types of diabetes, type one diabetes mellitus (T1DM) and type two diabetes mellitus (T2DM), are becoming more common not only because of the increasing duration of life, but probably also because of modern–day lifestyles characterized by a high dose of stress, poor diet, and lack of physical activity. Comorbidity of mental and metabolic disorders decreases the quality of life and the overall mortality [20].

The correlation between blood glucose levels and the function of the central nervous system is undisputed. The brain receives 20% of circulating glucose, which is its main energy substrate [23]. Early symptoms of hypoglycemia appear when the blood glucose level is below 70 mg/dL and include lack of concentration, dizziness, headache, blurred vision, or confusion. All of those are neuroglycopenia symptoms [33]. This seems to be much more complicated and probably works bilaterally.

## MATERIALS AND METHODS

The available articles were reviewed for their clinical relevance to the bilateral association between glycemic fluctuations and mental status. The eligible English-language publications retrieved from the PubMed database were reviewed by using keywords in different combinations: "glycemic variability", "glycemic fluctuation", "hypoglycemia", "hyperglycemia", "mood", "mental disorder" "depression" and "mental status".

## RESULTS AND DISCUSSION

### IMPACT OF BLOOD GLUCOSE CONCENTRATION ON MENTAL STATUS IN DIABETES

Disturbances in carbohydrate metabolism and thus glycemia are most observed in diabetes. The majority of the publications include patients affected by both T1DM and T2DM of the disease. T1DM individuals are more likely than T2DM to experience hypoglycemia because they use insulin treatment and therefore may also present greater glycemic variability [33,42]. However, this is not synonymous with overall glycemic control. Type 1 patients are often not only more aware of the disease but also more willingly follow recommendations [42,9,32]. The indicator of long–term glycemic control is undoubtedly glycated hemoglobin (HbA1c). Another factor related to glucose fluctuations is time-in-range. It refers to the amount of time that a person's glucose level remains within the proposed target range (70–180 mg/dL) per day and it is expressed as a percentage. It is recommended that patients of both types of diabetes stay in range for at least 70% of the day (50% for older high-risk type 2 individuals) [39,7]. All of these variables remain under the consideration of scientists.

Banariu et al. (2021) analyzed the relationship between glycemic variability and depression including its two common patterns: anxiety and low self-esteem in patients with T1DM (n=490) and T2DM (n=500) diabetes. Evaluation of fasting glucose level was performed for every person for 10 days. Additionally, the Hamilton anxiety scale (HRSA), Rosenberg self-esteem test, and Beck depression inventory were used to assess the severity of depressive symptoms. The authors observed a statistically significant positive correlation between higher glycemic oscillation and depression occurrence for both anxiety and low self-esteem [5].

In another study, Polonsky and Fortmann (2020) observed a cohort of 219 (T1DM) adults for two weeks. A

real-time continuous glucose monitoring system (RT-CGM) was used to assess daily changes in continuous glucose monitoring (CGM) metrics and their association with nightly reports of positive and negative moods. Even though the authors did not state a correlation of glucose level variability with mood disturbances, they found that a greater daily percentage of time-in-range and less time in "severe" hyperglycemia were related to higher ratings on all positive mood elements and lower ratings on most negative mood elements. Moreover, daily changes in time spent in hypoglycemia (< 70 mg/dL) did not have any significant impact on mood [34].

The impact of long-term glucose variability on depressive symptoms was assessed by Ravona-Springer, Heymann, Schmeidler, et al. (2017). Eight hundred thirty-seven T2DM patients' HbA1c levels were tested repeatedly for an average of 18 measurements. Variability of glycemic control was defined as the HbA1c-standard deviation (SD) for each subject. The authors observed a 31% increase in the occurrence of depressive symptoms for each additional 1% increase in HbA1c-SD. Moreover, to eliminate the possibility of reverse causality depression symptoms severity was also assessed at the entry to the study and it did not show any significant correlation [37].

Impact of blood glucose concentration on mental status in the non-diabetic population

Glycemic fluctuations, however, do not only occur in diabetes. Many factors such as meals, physical activity, stress level, or infections affect carbohydrate metabolism throughout the day. It was observed that also in the non-diabetic population variability in blood glucose concentration may contribute to the development of serious psychiatric conditions. In a large study, 151,814 subjects who had at least three health screenings were analyzed for depression and anxiety occurrence. Visit to visit fasting plasma glucose variability was positively correlated with the incidence of depression and anxiety disorders during follow-up [28].

Another study that included 264,480 Korean non-diabetic patients also suggests that glycemic variability may be a predictor of depression incidence independently of diabetes occurrence. The glycemic variability of individuals who did not have depression at baseline was calculated based on their visit-to-visit fasting glucose levels. A number of 198,267 participants, who met the inclusion criteria of the study, were observed during 2008–2013 for depression incidence. Analyzed data indicates a significantly higher risk of depressive disorder in those who showed higher glycemic variability [27]. There are though some limitations resulting from the retrospective nature of this study. Factors such as smoking, alcohol consumption, or stress level may impact not only fasting serum glucose, but also depression incidence independently.

Mechanisms that could cause the observed correlation are not fully known yet. It is suggested that factors like oxidative stress or increased proinflammatory cytokine concentration, causing neuroinflammation and consequently telomere shortening, may be significant in depression development. It is also enhanced by the fact that all of these occur in depression disorders [44,35,22]. Another important aspect is that dysregulation in central and peripheral serotoninergic systems contributes to diabetes development. The most common depression-development monoaminergic theory suggests that serotonin is the main factor for this disease [11]. This correlation shows another possible factor of comorbidity. Increased intestinal serotonin production may cause hyperglycemia and, in long-term effect, the development of diabetes and obesity. Moreover, decreased hypothalamic serotonin level also presents an impact on blood glucose dysregulation [8].

## GLYCEMIC VARIABILITY OCCURRENCE IN MENTAL DISORDERS

There is no doubt that depression promotes chronic stress and, in that way, leads to hormonal and metabolic changes. Stress is associated with the secretion of hormones including cortisol, catecholamines, growth hormone or prolactin [36]. Consequently, there are increased requirements for insulin and blood sugar levels which in the long term lead to the development of carbohydrate metabolism disorders, diabetes mellitus and also hormonal regulation abnormalities [43]. Moreover, mental disorders may lead to diabetes-promoting behaviors as a result of inappropriate stress management or lack of interest in health self-control. It was observed that individuals suffering from depression are neglecting healthy eating habits and exercise and consequently their risk of diabetes development is increased by 60% [38,26,30,6].

Results achieved by Mishra, Singh, Rajotiya, Singh, Raj et al. (2023) are consistent with the above. The authors observed non-diabetic depressive individuals for glycemic variability using flash glucose monitoring for 2 weeks and assessed the severity of depressive symptoms for each of them. Patients with severe depressive symptoms (those who scored at least 33 in The Center for Epidemiologic Studies Depression Scale) showed higher glycemic variability not only in flash glucose monitoring but also in HbA1c. The authors also highlight that hormonal and above all glucocorticoid imbalances may play a huge role in serum glucose fluctuations and diabetes development. What is more, they suggest that comorbidity of depression and diabetes mellitus, both related to endothelial dysfunction, may increase cardiovascular risk [31].

Another study examined type I diabetic adolescents for the occurrence of anxiety and its impact on HbA1c, diabetic distress, and automatic negative thinking. The severity of anxiety did not correlate with HbA1c directly, but the authors observed that anxiety may have an indirect impact by enhancing automatic

negative thinking and diabetic distress [47].

Type 1 diabetic patients were also assessed for incidence of sleep disorders. Collected data indicates that a higher level of fear of hypoglycemia promoted sleep disturbances and, consequently, led to the development of anxiety and worsened psychological well-being. However, glycemic variability did not differ significantly between those who slept well and those suffering from sleep disturbances [45].

## OTHER POSSIBLE LINKAGES

Inflammation is significant, but not the only possible factor, that leads to diabetes and mental disorders comorbidity. Some authors suggest that genetic predisposition may also play a role.

Amin et al. (2022) examined variants of corticotropin–releasing hormone receptor type 2 (CRHR2) gene in 212 Italian families. Despite some limitations of the study, including homogeneity of the group and indirect relationship of gene variant and comorbidity, authors suppose that CRHR2 pleiotropism may increase the risk of developing the both types of diabetes and depression [2]. Although, inherited risk factors may play a significant role, what is crucial is the impact of the reversible factors.

Godos et al. (2023) assessed 683 young Italian adults (aged 18-35) for ultra-processed foods (UPF) consumption and the occurrence of depressive symptoms. A food frequency questionnaire (FFQ) was used to establish the average consumption of 110 foods and beverages. Every of these was classified into 1 of 4 NOVA classification groups: unprocessed or minimally processed foods, processed culinary, processed foods or ultra–processed foods. CES-D-10 was used for depressive symptoms screening. Authors observed that higher consumption of UPFs was associated with an increased likelihood of depressive symptoms occurrence. The association was even stronger after adjustment for adherence to the Mediterranean diet [14]. Another study performed on the French population showed similar results. During an over 5 year follow-up of 26730 individuals, 2221 incident cases of depressive symptoms were reported. Authors established an increasing risk of depressive symptoms for 21% for every 10% increase in UPFs consumption [1]. These studies suggest that lifestyle changes may play a huge role in reducing the incidence of depressive disorders.

## CONSEQUENCES OF COMORBIDITY

Coincidence of mental illness such as depression and diabetes seems to be a much larger problem than only multi-morbidity. Both affect each other, contributing to their exacerbation. A decrease in brain pH level, which is induced by hyperglycemia, can change gene expression causing the development of psychiatric disorders such as bipolar disease, schizophrenia, autism spectrum disorders or depression [46,19]. As a result burdened people may experience chronic stress, which, as mentioned above, plays an important role in hormonal changes, that further increase blood glucose levels [36,43]. Comorbidity though imitates a self-propelling mechanism. Depressive patients more commonly develop complications of diabetes such as diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction [10]. Similarly, diabetic patients are affected by more severe depression symptoms and more often present anxiety [5,37,28].

Moreover, the cardiovascular risk of those suffering from both diabetes and depression, which is the most common comorbid mental illness, [25] is significantly higher, than for those with only one of these illnesses [12,4].

Another important aspect is difficult treatment. Adverse effects of antipsychotics, mainly clozapine and olanzapine, include weight gain and impaired glucose tolerance [16]. Also, mood stabilizers such as lithium and sodium valproate may induce these effects. Long-term use of antidepressants, even in moderate doses, may be a risk factor for diabetes [3]. Therefore, selecting an appropriate treatment may be problematic and undesirable results should always be taken into consideration.

## MANAGING REVERSIBLE RISK FACTORS

Given that environmental factors contribute to both mental and somatic disease development, applying lifestyle changes may be highly supportive in the prevention of both diabetes and depression. While the importance of physical activity and healthy eating habits is commonly known for the management of metabolic disorders such as diabetes, the consciousness of their role in psychiatric diseases is not generally recognized in the population.

Major depressive disorder (MDD) and bipolar disorder (BD) are both strongly associated with metabolic dysregulation such as dyslipidemia or glucose intolerance and the association seems to be bidirectional [24,15]. Pharmacotherapy with lipid-lowering agents above all statins and polyunsaturated fatty acids (PUFA) and antidiabetics such as metformin or Glucagon-like Peptide 1 (GLP-1) Agonists was observed to reduce the incidence and severity of depressive symptoms in MDD and BD patients [24].

Prevention of metabolic disorders development may be even more valuable as it allows to avoid

complications as well as side effects of pharmacotherapy. One of the most effective lifestyle changes is diet improvement. The Mediterranean Diet (MD), which is not only thought to be the most beneficial for most of the world's population, but also the most studied one, is effective also in this aspect. MD is characterized by whole food consumption, including cereals, vegetables, legumes, fruits, fish and olive oil and avoidance of animal fats, sweets and processed foods. It is also rich in fiber, PUFAs, vitamins and micronutrients. Compared to Western Diet (WD), which is rich in ultra-processed foods, red meat, and refined grains and poor in vegetables, fruits or legumes, MD is associated with significantly lower depressive symptoms incidence in adolescents [50]. Moreover maintaining a low-glycemic index diet showed better cognitive functions, glycemic response, mood, and satiety during the day relative to a high-glycemic-index diet [17]. Physical activity does not remain negligible. Higher physical activity level, above all performed in low or mild severity, is associated with a lower incidence of depressive symptoms [18].

## CONCLUSION

Blood glucose level, its variability and metabolism undoubtedly impact mental status and may lead to the development of psychiatric disorders. Moreover, depression and other mental illnesses show a significant influence on the risk of metabolic disorders including diabetes mellitus. Comorbidity not only increases the risk of overall mortality but also makes therapy more difficult.

Studies show mainly a joint relationship between metabolic and mental impairments in disease-burdened patients, but some of them indicate that it may also occur in healthy individuals, which should be considered in the prevention of both of these types of disorders.

The mechanism of this interaction may result from joint inflammatory pathology of psychiatric and metabolic disorders, but further studies need to be conducted to establish certain correlations in non-diabetic and non-psychiatric patients.

As metabolic dysregulation and mental condition remain in strong association, some lifestyle changes, such as the implementation of a Mediterranean Diet or some low-severity physical activity may be highly beneficial in the prevention of psychiatric diseases as well as metabolic ones.

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