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Hypoglycemia impact on psychiatric symptoms and brain changes in anorexia nervosa

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Abstract

This study examines the potential impact of hypoglycemia on mental comorbidity in anorexia, comparing it to similar changes in diabetes. Anorexia, characterized by low body weight, is linked to hypoglycemia, possibly affecting mental health. Recurrent hypoglycemia in diabetes leads to mood changes and cognitive impairment. Anorexic individuals may experience deficits in cognitive functioning and psychiatric comorbidities, including affective disorders and anxiety. Imaging studies show structural changes in the brains of both anorexia and diabetes patients, but the direct link between hypoglycemia and psychoorganic changes in anorexia remains inconclusive, warranting further investigation.

Aim of this study:

This study investigates the impact of hypoglycemia on psychiatric symptoms in anorexia nervosa, comparing it to similar symptoms observed in diabetes. Additionally, the study examines common imaging findings in anorexia and diabetes patients, aiming to determine if these changes are responsible for neuropsychiatric symptoms

Material and methods:

A systematic review of the scientific and medical literature from the PubMed and Google Scholar databases was carried out.

Key words: Hypoglycemia, Anorexia nervosa, Diabetes, Psychiatric symptoms

Introduction

Hypoglycemia is one of the complications of nutritional deficiency in individuals with anorexia, and complication that is also common in diabetics. In this study, we analyzed the potential impact of low blood sugar on the mental comorbidity in patients with anorexia, considering similar changes in those with diabetes.

Definition of anorexia nervosa

Anorexia nervosa is an eating disorder characterized by a reluctance to eat, as well as behaviors aimed at maintaining a low body weight, such as excessive physical activity or the use of laxatives. People suffering from this disorder perceive their low body weight as excessive, which may lead to further actions to reduce weight. This disorder is frequently observed in teenagers and young adults and is associated with high mortality rates. [1, 2] The criteria for diagnosing anorexia according to the International Statistical Classification of Diseases and Related Health Problems - (ICD-11) is a BMI (body mass index) below 18.5 kg/m2 in adults and BMI for age below the 5th percentile in children and adolescents. Another diagnostic criterion may be rapid weight loss, e.g. 20% within 6 months after meeting other diagnostic criteria. [1]

Definition of hypoglycemia

Hypoglycemia is a condition characterized by a low concentration of glucose in the blood. Hypoglycemia is diagnosed when the blood glucose level falls below 70 mg/dl, regardless of the presence of clinical symptoms.The acute symptoms of hypoglycemia depend on the rate of decline in blood glucose levels and the final value that the glycemia reaches. At glucose levels of 90–60 mg/dl, profuse sweating, muscle tremors, hunger, paleness of the skin, palpitations, anxiety, irritability, dizziness, and headaches may occur. Additional symptoms affecting the central nervous system (neuroglycopenic symptoms) appear at values of 60–30 mg/dl, including speech disturbances, visual disturbances, sensory and motor coordination

disturbances, excitement, and potential aggression. Glucose levels below 30 mg/dl can lead to loss of consciousness, coma, and even death of the patient. [3, 4]

It is noteworthy that recurrent episodes of hypoglycemia, in addition to clinical symptoms, can also induce permanent degenerative changes in the body of diabetic patients,especially in the central nervous system, and thus induce even psychiatric symptoms and losses of neurocognitive functions.

Hypoglycemia in anorexia nervosa

Hypoglycemia, which often occurs in the course of anorexia, can be asymptomatic. Prolonged starvation impairs hepatic gluconeogenesis. [5] Furthermore, individuals with anorexia respond to attempts at refeeding with excessive insulin secretion. [6] Intense physical activity can be a cause of low blood sugar levels. [7] A laboratory indicator heralding hypoglycemia may be prealbumin. It is a protein produced by the liver which has a short half-life. In malnutrition and diseases causing it, such as anorexia, prealbumin levels tend to decrease. [8] Another marker indicating an increased risk of hypoglycemia may be increased levels of hepatic transaminases. [9]

In addition, low body weight may correlate with a increased risk of hypoglycemia in anorexia. It has been suggested that severe hypoglycemia in patients with anorexia may herald a poor prognosis, as it may be one of the causes of sudden death in anorexia. [5, 8]

Psychiatric symptoms in diabetic patients

Long-term exposure to frequent hypoglycemic episodes in diabetes can lead to mood changes and impairment of cognitive functions such as verbal skills, attention, reaction time, learning [10], and short-term memory, verbal memory, alertness, and visuospatial memory. [11] Additionally, chronic diabetes and episodes of hypoglycemia in older patients may cause serious brain damage resulting in the development of dementia. [12, 13, 14, 15, 16, 17]

Recurrent hypoglycemic episodes in adults with type 1 diabetes lead to impairment of brain function, manifesting as reduced overall intelligence, information processing speed, psychomotor efficiency, attention, mental flexibility, and visual perception compared to a control group of healthy individuals without diabetes. [18, 19, 20] Being a patient with type 1 or type 2 diabetes was found to be a risk factor for somatisation, depression, phobic anxiety, excessive anger and hostility. In addition, a history of type 1 diabetes appeared to be a risk factor for symptoms of organic brain disease and psychotic symptoms. [22, 23, 24, 25]

Changes in the structure and functioning of the brain may be the cause of anhedonia, which is one of the main symptoms of depression. Anhedonia intensifies with the duration of diabetes. [26]

Adolescents with type 2 diabetes obtained lower scores than obese individuals in all cognitive tests - they had significantly lower overall intellectual functioning, lower scores in verbal memory, and lower psychomotor efficiency. [27]

The impact of hypoglycemia on the central nervous system has also been documented. Twelve years after the diagnosis of type 1 diabetes in adolescents, whose neurocognitive profile at the onset of the disease did not differ from the profile of individuals in the control group. The subjects were characterized by lower verbal IQ and full scale IQ than the control group. [28] It has been proven that hypoglycemia is most harmful in children because their brains are still developing. If the brain is not fully developed yet, even minor damage can have dramatic consequences compared to relatively minor consequences seen in the case of the same minor damage in a fully matured brain. The implications of the early onset of diabetes appear to encompass various areas of the brain, including motor functions and executive functions of the frontal cortex, parietal lobes, and temporal lobes. In children diagnosed with type 1 diabetes before 5 years of age, recurrent mild to moderate hypoglycemia can result in decreased attention, mental abilities; spatial memory, working memory; verbal abilities; non-verbal processing speed; and IQ during adolescence. Frequent and severe episodes of hypoglycemia resulted in poor psychomotor speed, selective attention behavior, lexical fluency, and word list learning. [20, 21, 29, 30, 31] The reasons for all these neurocognitive impairments can be found in the structural and degenerative changes of the CNS caused by recurrent episodes of hypoglycemia in the course of diabetes.

Psychiatric comorbidity in patients with anorexia

Patients with long-term anorexia who had poor eating disorder treatment outcomes were characterised by poorer psychosocial functioning and higher rates of psychiatric comorbidity. Affective disorders, such as depression or dysthymia, are most commonly comorbid with anorexia, followed by anxiety disorders (social phobia and obsessive-compulsive disorder). [32, 55] The course of these additional psychiatric disorders remains unclear. [32]

Acute starvation can trigger depression, anxiety and obsessive disorders in patients with anorexia. Furthermore, pre-existing anxiety disorders may exacerbate during the course of

prolonged anorexia. [33] An important symptom in the course of anorexia is also anhedonia. [34, 35] Other mental disorders that can occur in anorexia include psychoses. Anorexia may cause visual or auditory hallucinations or delusions of "self-healing through energy." With an increase in weight, auditory hallucinations tend to diminish. [36, 37, 38]

Acute clinical symptoms can pose a challenge in distinguishing anorexia from primary psychotic disorders, as both conditions are characterized by poor insight and overvalued ideas. [36] Autistic symptoms, which resemble the negative symptoms of schizophrenia, may also appear in the course of anorexia nervosa. Patients avoid both verbal and visual contact. Facial expressions and gestures remain unchanged and modest. They give the impression of being internally empty. [39]

Chronic starvation can lead to dysfunction of neurons in adults, most likely due to altered neurotransmitter metabolism and endocrinological changes. [40] Participants in a study with a medical history of anorexia showed deficits in cognitive functioning across a wide range of neuropsychological domains compared to a healthy control group. [41] Anorexic individuals exhibited poorer memory, reaction time, and motor speed than those in the control group, and the impairment in cognitive functioning in anorexics was interpreted as an attentional deficit. [42] Patients with anorexia, in comparison to a healthy control group, demonstrated a lower level of IQ. [43]

Imaging changes in patients with diabetes

Patients with type 1 diabetes, compared to control subjects, had reduced grey matter volume on MRI (magnetic resonance imaging) bilaterally in the thalamus and right parahippocampal gyrus and insular cortex; in addition, selective deficits in grey matter volume or density were observed in the frontal, parietal, posterior and temporal cortex. White matter volume was reduced bilaterally in the parahippocampal gyri, left temporal lobe and middle frontal area. [28, 44, 45, 46] Automated MRI-based structural analyses of the brain revealed both reduced white matter volume and enlarged CSF (Cerebrospinal fluid) space throughout the brain, particularly in the frontal lobe, and reduced total brain volume. [21, 27] In addition, diabetics have significantly larger lateral ventricles and dilated subarachnoid spaces in the cerebral vault and cerebellum due to atrophy, by up to 37% compared to healthy controls. [21] Increased rates of cortical atrophy have been described in numerous reports, including a study of young adults with a relatively short duration of the disease. Brain atrophic changes in adults with diabetes may be interpreted as a form of accelerated aging. [18, 21] Musen et al. found that a history of severe

hypoglycemia correlated with lower gray matter density in the left posterior cerebellar lobe, in the left hemisphere, including the posterior cingulate gyrus, hippocampus, and superior temporal gyrus, as well as the right parahippocampal gyrus. These specific cortical areas are responsible for language processing, memory, and attention. [47] Perantie et al. demonstrated that the occurrence of severe hypoglycemia was associated with lower gray matter density in the left superior temporal region. [48] It has been shown that children diagnosed with diabetes early (before the age of 6) more frequently exhibited structural abnormalities on MRI scans throughout the cerebral cortex. Specifically, mesial temporal sclerosis, or atrophy, was found in the dominant hemisphere of 15% of participants. Such atrophy can cause sensory problems, changes in behaviour or emotions, muscle spasms or seizures. [21]

Imaging changes in patients with anorexia

Severe cases of anorexia nervosa may appear similar to Alzheimer's disease in MRI, as the ventricles are enlarged, and cortical substance is reduced. [49] Another study using MRI revealed that individuals with anorexia have significantly reduced brain volume, as well as an increased amount of cerebrospinal fluid. [50] In a 2021 study, Mishima et al. demonstrated that individuals with anorexia have a smaller gray matter volume and a decreased amount of white matter. [51, 52] The atrophy of gray and white matter is more pronounced with a longer history of the disease and lower body weight upon admission to the hospital. [53] Underweight patients with anorexia were also characterised by enlargement of the ventricular system of the brain [54] In a 2017 study, Boto et al. showed reduced volume of the insula and cerebellum on MRI imaging in patients with anorexia. [56] Additionally, another study noted changes in several structures of the gray matter in the limbic system, most commonly in the vault and the cingulate gyrus. [57] In a different study, Frieling et al. (2012) identified bilateral reductions in fractional anisotropy maps in the posterior and the left medialdorsal thalamus. [58]

Discussion

Based on the examples cited of psychoorganic symptoms in patients with anorexia, we hypothesise that frequent episodes of hypoglycemia in the course of this disease lead to degenerative changes in the central nervous system and induce psychiatric disorders, primarily including affective disorders, anxiety disorders, dementia-like syndromes, and memory disorders. Nevertheless, affective and anxiety disorders often occur before the manifestation of eating disorders - Kaye et al. have proven that these disorders often precede the onset of

anorexia. [32] On the other hand, Pollice, in his work, presents evidence indicating an increase in symptoms of depression, anxiety, and obsessions during anorexia. [33] During the hospitalization of patients with anorexia, it is important to monitor blood sugar levels, as low levels can cause degenerative changes in the brain and even lead to the death of the patient. Common findings in imaging studies for both anorexia and diabetes patients include a reduction in gray and white matter, an increase in cerebrospinal fluid quantity, and enlargement of ventricles. Other changes in brain imaging in both diseases involve alterations in the cingulate gyrus, thalamus, and cerebellum. However, it is not known whether these changes are responsible for neuropsychiatric symptoms in diabetes and anorexia. In summary, based on available literature, it is not possible to conclusively confirm the hypothesis that hypoglycemia influences psychoorganic changes in anorexia. Nevertheless, the impact of hypoglycemia on mental health in individuals with diabetes has been proven, so it is necessary to document further cases of co-occurrence of anorexia and hypoglycemia. Although similar imaging changes occur in both diabetes and anorexia, it is not possible to conclude unequivocally whether hypoglycemia is the cause and therefore requires further investigation.

Disclosure:

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Data Availability Statement

As a review paper, our work does not present new data or analyses. Therefore, there are no specific datasets or data availability to report. The information and findings presented in this review are based on previously published studies, which can be accessed through their respective sources as cited in the reference section.

Conflict of Interest Statement

The authors declare that there are no significant conflicts of interest associated with this research work.

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