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The impact of the ketogenic diet on the course of schizophrenia and bipolar disorder

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Abstract

Introduction and purpose

Schizophrenia (SZ) and bipolar disorder (BPD) are serious mental disorders that significantly affect the functioning and efficiency of a person. The ketogenic diet (KD) reduces inflammation in the body and improves the efficiency of the nervous system. The aim of this article is to present the impact of the ketogenic diet on the course of these diseases.

Material and methods

The review was conducted based on the analysis of materials collected in the "PubMed" databases. The following keywords were entered when searching for scientific articles: ketogenic diet; bipolar affective disorder; schizophrenia; pathophysiology of schizophrenia; ketogenic diet shizophrenia; ketogenic diet bipolar disease. A total of 32 articles published in 2020-2025 were taken into account for the study and their relevance in the context of the topic of the effect of the ketogenic diet on the course of schizophrenia and bipolar disorder was verified.

Description

The way of eating significantly affects the human body. It provides it with fuel for functioning and soothes the symptoms of many diseases. It is worth focusing on the KD, which has been proven to have a wide range of effects: from anti-inflammatory, through mood stabilization and

reduction of productive symptoms, to weight loss and improvement of laboratory test parameters.

Summary

Bipolar disorder and schizophrenia are psychiatric conditions that significantly impair a person's life and functioning. Their treatment most often involves pharmacotherapy, which may be ineffective in controlling symptoms. In such cases, a ketogenic diet can be used to help stabilize mood and alleviate symptoms of a psychological nature. Therefore, expanding research in this direction may be crucial in developing new strategies to support the treatment of BPD and SZ with KD.

Keywords:

ketogenic diet, bipolar affective disorder, schizophrenia, ketogenic diet schizophrenia, ketogenic diet bipolar affective disorder

Introduction and purpose

There is no doubt that diet has a significant impact on human function and body condition. Its nutritional content influences the development and metabolism of the gut microbiota, which plays a role in modulating inflammation. In addition, it influences the levels of neurotransmitters, such as dopamine and serotonin. The microbiota regulates the gut-brain axis via metabolites, so it may play an important role in the pathogenesis of psychiatric diseases. Therefore, an unhealthy lifestyle, including an inadequate diet, increases the risk of central nervous system diseases [1].

Research shows that in mental illnesses, such as schizopherania (SZ), there are adverse changes in carbohydrate metabolism and insulin signalling in the body. In addition, signalling between neurons and astrocytes, abnormal glutamate neurotransmission, decreased GABA, dysfunction

of circulating lactate and impaired glycolysis are all impaired in this disease [2, 3]. These changes lead to impaired production of ATP necessary for central nervous system (CNS) function, a likely factor also involved in the pathogenesis of bipolar affective disorder (BPD) [2].

The primary treatment for these mental illnesses is pharmacotherapy, which is sometimes associated with a number of side effects and failure to achieve the expected therapeutic goal, which can translate into patient frustration and lack of motivation to continue treatment [3].

The ketogenic diet (KD) not only has an effect on nervous system function, but also results in an overall reduction of inflammation in the body, oxidative stress and supports mitochondrial function, which is responsible for ATP synthesis [2]. In a group of people with obesity and type II diabetes, KD has been shown to be compelling in its stabilising effects and there have been improvements in mood, sleep, mental clarity and cognitive abilities [2, 4, 5]. Furthermore, increased craving for carbohydrates may be associated with atypical depression. Animal studies have shown the potential of this diet to have antidepressant and anxiety-reducing effects. It has also been observed to attenuate psychotic symptoms in patients, who started using KD [4]. It also has a positive effect on inflammatory cytokine levels by, among other things, lowering IL-17, which has a pro-inflammatory effect, and raising the anti-inflammatory IL-10. This results in the anti-inflammatory effect mentioned earlier, as well as an additional neuroprotective effect [2, 6].

This piece aims to review the available knowledge on the impact of a non-pharmacological intervention, i.e. the use of a KD by people with SZ and BPD on the course of these illnesses.

Material and methods

The review was conducted based on the analysis of materials collected in the "PubMed" databases. The following keywords were entered when searching for scientific articles: ketogenic diet; bipolar affective disorder; schizophrenia; pathophysiology of schizophrenia; ketogenic diet shizophrenia; ketogenic diet bipolar disease. A total of 32 articles published in 2020-2025 were taken into account for the study and their relevance in the context of the topic of the effect of the ketogenic diet on the course of schizophrenia and bipolar disorder was verified.

Bipolar affective disorder

Bipolar affective disorder (BPD) is a severe, chronic mental disorder associated with severe mood changes [7, 8]. During its course, there are symptoms of mania/hypomania alternating with depression, or mixed episodes with euthymia inbetween [9]. BPD is divided into two subtypes. The first is characterised by at least one lifetime episode of mania with subsequent depressive symptoms, while in type II the patient experiences symptoms of hypomania with a subsequent depressive episode diagnosed on the basis of DSM-5 criteria [7, 10].

A manic or hypomanic episode is associated with, among other things, elevated mood, euphoria, feelings of grandiosity, hyperactivity and increased sexual activity, despite a decreased need for sleep. In addition, the patient may present with irritability or aggression [8, 9].

In contrast, during depression, there is anhedonia, sadness or reduced motor drive. Up to 60% of patients present suicidal thoughts, while almost half may attempt to take their own lives. ⅕ of those affected by BPD die by suicide [8]. In addition to BPD-related complaints, patients often suffer from other conditions, such as diabetes, cardiovascular disease or respiratory disease. Furthermore, their life expectancy is nine years shorter than the population life expectancy [8].

Scientific articles on BPD estimate the total number of people diagnosed to be approximately 50 million worldwide (1-4% of the population), where the average age of sufferers is approximately 20 years [8, 10]. Such an early age of onset may be associated with serious consequences, e.g. worse prognosis, more comorbidities, the first symptom in the form of depression and its more severe course and also delays in treatment or misdiagnosis [10]. This results in young adults with a diagnosis of BPD being significantly more likely to use psychoactive substances and commit suicide compared to the older patient population [11].

Despite continuous medical advances, the definitive etiopathology of the disease is not known. It has been noted that the development of the disease is influenced by a number of factors interacting with each other, including genetic, environmental or neurochemical component [7, 8].

BPD has been shown to be a heritable and polygenic condition, with heritability rates as high as 80% [8, 10]. In addition, it shows a possible, albeit incomplete, genetic overlap with many

other psychiatric conditions, e.g. SZ, as has been demonstrated, e.g. by studies on twins [10, 12]. Children whose parents have disclosed abnormalities in mental functioning are more likely to develop similar symptoms [12]. To date, as many as 64 unrelated loci have been identified that may increase the risk of BPD [9]. Furthermore, genetic overlap between conditions means that traditional pharmacological treatments may not be effective [12].

Neurochemical factors also play a significant role in the pathophysiology of the disease. Oxidative stress (OS), which disrupts mitochondrial function and the dopamine system, is important in BPD. The increased amounts of dopamine present during mania, in a sequence of chemical reactions, lead to the formation of reactive oxygen species (ROS), resulting in protein oxidation [7]. The combination of the above factors, along with chronic inflammation in the body and sleep disturbances, can lead to cognitive dysfunction and intellectual disability, as well as the occurrence of worsening episodes of the illness or treatment failure [8, 12].

Environmental factors that increase the risk of BPD are also worth mentioning. These include perinatal respiratory failure, abnormal growth and development during the perinatal period. In addition, childhood abuse is also a major influence, which can result in more severe episodes of mood changes, earlier illness or increased risk of suicide. Exposure to air pollutants or the recently popular COVID-19, which has resulted in increased hospitalisations and mortality in people with BPD and SZ, is also an important environmental factor [9].

In the treatment of BPD, lithium, anticonvulsants, as well as some typical and atypical neuroleptics have documented effects. Attention should be paid to difficulties in treating depression symptoms associated with BPD, due to the possibility of inducing mania or hypomania during use, for example SSRIs [8].

Schizophrenia

SZ is a severe mental illness ranked among the 15 leading causes of disability worldwide. It is associated with the presence of productive symptoms or so-called positive symptoms, such as delusions, visual, auditory, olfactory or tactile hallucinations. These describe phenomena which are not occurring at the time. In addition, the disorder also distinguishes negative symptoms, which in turn can be explained by the absence of some usual behaviour, such as social

withdrawal, anhedonia, avolition, allogia, loss of affect, including monotone tone of voice and immobile facial expressions, impairment in attention, learning, problem solving and working memory [13, 14].

The disease usually has its onset in young people in early adulthood and the number of sufferers is approximately 0.7% of people worldwide [14, 15]. It shortens life expectancy by about 20 years, mainly due to the presence of comorbidities, such as type II diabetes [16].

Due to the high heritability of the illness (80%), the incidence is higher among relatives. Children whose one parent has the illness have a 17% risk of developing SZ, while the risk is as high as 35% for both parents with the illness [14, 15]. In addition, large GWAS studies of SZ have identified as many as 140 loci associated with the development of the disease, as well as the discovery of rare variants, making the disease characterised by high complexity and high heterogeneity [14].

In addition to genetics, the development of SZ is also favoured by environmental aspects, including activation of the maternal immune system, hypoxia, nutritional deficiency and various toxins. As a result of animal experiments, environmental factors have been shown to cause epigenetic modifications permanently altering the genome of the organism, which is identical to the neurodevelopmental hypothesis of SZ [14].

Disorders of dopamine, serotonin, glutamate and γ-aminobutyric acid (GABA) neurotransmission play a significant role in the pathophysiology of the disease [13, 17]. These cause symptoms characteristic of SZ, including cognitive deficits [13].

To date, four pathways of dopamine action have been described. Too high quantity of this catecholamine in the mesolimbic pathway and hyperactivation of the D2 receptors cause positive symptoms of the disease [17]. The mesolimbic pathway connects the ventral tegmental area to the limbic areas. As another, we distinguish a mesocortical pathway that also starts from the ventral region of the nutritive field, but its termination takes place in the prefrontal cortex. In this case, symptoms are triggered by insufficient transmitter and reduced D1 receptor activation in the prefrontal cortex, causing cognitive impairment and the onset of negative symptoms of schizophrenia [13, 17]. In addition, it has been noted that the use of N-methyl-D-

aspartate (NMDA) receptor antagonists, such as phencyclidine, causes the onset of schizophrenic symptoms. The researchers also noted post-mortem changes in glutamate levels in the cerebral and subcortical cortex in areas of the brain responsible for reward processing. Furthermore, the actions of glutamate and dopamine are linked, due to the fact that NMDA receptor insufficiency leads to impaired connections between glutamatergic neurons from the prefrontal cortex and dopaminergic neurons of the midbrain causing SZ symptoms by affecting the mesolimbic and mesocortical pathways [13].

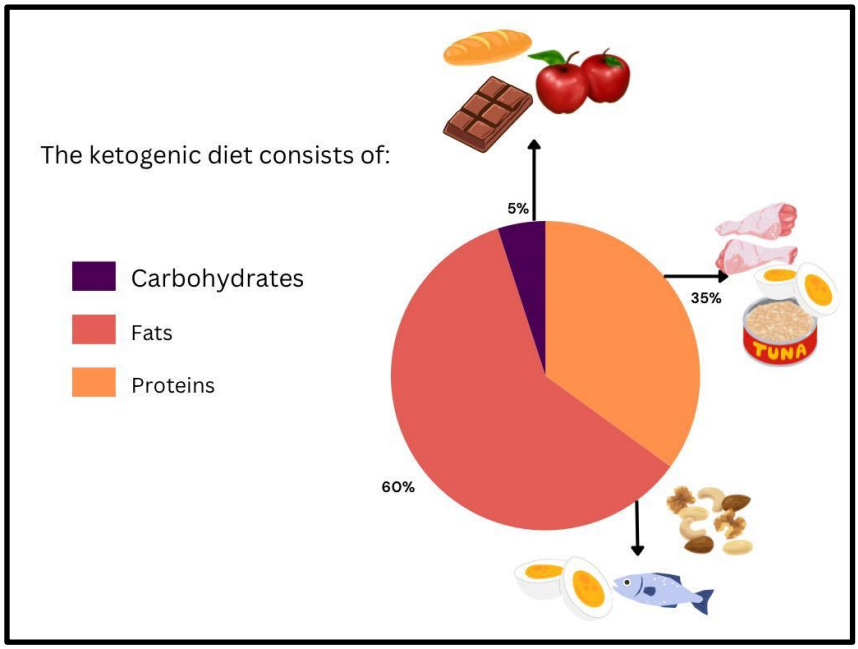
Antipsychotics used in the treatment of SZ that inhibit the D2 receptor allow positive symptoms to be controlled, while they do not show the expected efficacy in controlling negative symptoms, which unfortunately can make treatment difficult [13, 17].

Ketogenic diet

KD was first introduced by Dr Russell Wilder in 1921. He was the first to formulate the theory of ketosis and discovered that a low-carbohydrate diet could be used as a treatment for childhood epilepsy. It was he, who coined the term 'ketogenic diet' [18].

The basis of KD is to drastically reduce carbohydrate intake and replace it with fats, making it mainly based on fats and proteins. This action causes the body to enter a state of ketosis - a metabolic process in which the body burns fat to produce ketones instead of glucose, i.e.: acetoacetic acid, β-hydroxybutyric acid, and acetone [5, 19]. The state of ketosis is defined when blood levels of ketone bodies are maintained at 1.5 to 3 mmol/L [3].

Figure 1. Diagram showing the proportions of fats, proteins and carbohydrates in the ketogenic diet. Reference: [20].



KD has not only been used for weight loss, but has also been implicated in many diseases, ranging from metabolic to neurodegenerative. The brain can function perfectly well using ketone bodies as an energy source. In many cases, ketones become the main source of energy when glucose is in short supply. Brain cells contain monocarboxylate transporters (MCTs) that allow ketone bodies to be transported for energy, similar to other cells in the body [21].

The positive effects of KD have been used in the treatment of drug-resistant epilepsy in children, as evidenced by the 'Ketogenic diets for drug-resistant epilepsy' study conducted by the Cochrane Epilepsy Group. Children following a KD were up to three times more likely to be completely seizure-free and up to six times more likely to have a reduction in seizure frequency of 50% or more. In one study, more than half of the children following the classical KD became seizure free, while only 15% of children achieved this effect with the less restrictive Atkins diet [22].

The benefits of KD were highlighted in a meta-analysis published in 2021, which analysed 49 animal studies conducted between 1979 and 2020. The results showed strong neuroprotective effects, including a reduction in neuronal death, damage and dysfunction in cases of acute central nervous system injury [21].

Additionally, the combination of KD with a caloric deficit enhances neuroprotective effects by increasing levels of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial cell lineage-derived neurotrophic factor (GDNF) and neurotrophin-3 (NT-3), as well as chaperone proteins. This approach improves mitochondrial function, increasing energy efficiency [21].

Furthermore, KD exhibits anti-inflammatory properties by inhibiting cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) activity and blocking the synthesis of pro-inflammatory interleukins (IL-1β, IL-2, IL-4, IL-6) and tumour necrosis factor alpha (TNFα). It also reduces levels of nuclear factor kappaB (NFκB), a key component of the inflammatory response [21].

The KD has also been studied in terms of its effects on improving metabolic and psychiatric health. Studies have shown that it can provide significant benefits in the treatment of comorbidities, such as type 2 diabetes mellitus (T2DM), insulin resistance and obesity. In a comparative study on T2DM, the KD led to significantly greater reductions in HbA1c levels, ranging from -0.5% to -1.5%, compared to reference diets, which showed smaller changes (from +0.2% to -0.5%) [23]. Additionally, a study by Jing T et al. showed that KD was superior to other diets in terms of glycaemic control in patients with type 2 diabetes [24].

Recent studies also indicate that KD has therapeutic potential in the treatment of mental illnesses, including SZ and BPD, which have their basis in metabolic disturbances, such as oxidative stress, glucose hypometabolism in the brain and mitochondrial and neurotransmitter dysfunctions. These changes have a significant impact on neuronal excitability and synaptic connections. Furthermore, people with mental illness often have an increased risk of comorbidities, such as type 2 diabetes, insulin resistance and obesity. Therefore, KD, by providing an alternative energy source for the brain and body, has a beneficial effect on both, supporting the treatment of comorbidities and mental illness [25].

Ketogenic diet and bipolar affective disorder

The KD acts on sodium channels, calcium channels, blocks AMPA receptors, increases GABA levels and affects the receptors for this neurotransmitter. This action combines the individual mechanisms of action of the antiepileptic drugs used in the treatment of BPD [3]. In addition, it is able to influence GABA and glutamate levels via the brain-gut axis [26]. Moreover, β-

hydroxybutyrate formed in the process of ketogenesis, reduced glucose and insulin levels and a reduced LDL to HDL ratio during the use of KD have a positive effect on the symptoms of depressive episodes [5].

Chmiel I. in his case report presents a patient, who, thanks to the use of KD, achieved an improvement in cognitive function and concentration, mood stabilisation, a reduction in the duration of depressive episodes, an increase in energy and a cessation of the occurrence of hypomania, which also made it possible to reduce the patient's medication dose. Interestingly, the patient's condition had already improved when ketogenesis began, but when he was not yet in ketosis. As the diet was adjusted and the patient progressed into ketosis, the results were more and more promising, with noted resolution of anxiety, improvement in sleep quality and even complete remission of the disease [3]. The results of a pilot study of KD therapy in people with a diagnosis of SZ (five participants) and BPD (sixteen participants) confirm increasingly better results, the longer the KD was used, as the proportion of participants classified as recovering, according to Clinical Mood Monitoring (CMF) assessments, increased from 38% at the start of the study to 81% at the end of the study. Of the sixteen participants with BPD, six were already in recovery at the start of the study and seven had achieved this by the end of the study. Only three participants with BPD did not achieve recovery according to CMF assessments - of which one patient was non-compliant and two were half-compliant [25]. Similarly, other research findings indicate a reduction in the severity of depressive symptoms, the occurrence of anxiety, impulsivity and psychosis in patients using KD, and it has allowed an overall reduction in the number of drugs used, as well as their doses [2, 4, 5, 27, 28].

Other positive aspects of KD include weight loss and improvements in parameters, such as glycated haemoglobin, lipidogram, glucose levels and tissue sensitivity to insulin, which may be particularly important in patients with diabetes [5]. In the aforementioned study by Sethi S et al. several metabolic changes were observed in these patients over a four-month period. Mean body weight decreased by 10%, waist circumference by 11% and systolic blood pressure by 6.4%. In addition, body fat mass index showed a 17% decrease, while BMI - 10% [25]. Changes in metabolic biomarkers included a 27% reduction in visceral fat and a 20% decrease in triglyceride levels. LDL levels increased by 21%, while HDL - only by 2.7%. HbA1c levels fell by 3.6%. In contrast, in this study, there was no significant change in atherosclerotic cardiovascular disease (ASCVD) risk score at 10 years in the entire cohort [25]. However, the

study by Campbell IH et al. reported a decrease in systolic blood pressure of 7.4 mmHg on average [28].

The mitochondrial impairment that occurs in BPD and the consequent inefficient production of ATP leads to dysfunction of the sodium-potassium pump, for which ATP is essential for function. ATP deficiency may contribute to manic and depressive episodes due to the malfunction of the Na/K pump in neurons. KD supports mitochondrial function, ATP synthesis and thus has a role in electrolyte changes within cells giving a neuroprotective effect seen in mood stabilisation. Thus, the disease can be slowed down or even stopped. It has also been suggested that KD has similar effects to mood-stabilising drugs, but without the side effects [25].

Changes in the patients' condition can be visualised numerically, using disease severity scales such as CGI-S, MADRS, HAM-D. All of these scales showed statistically significant decreases in values after the patient's use of KD: the CGI-S scale decreased from 4.8 to 2.0, the MADRS decreased from 29.9 to 11.8 and the HAM-D decreased from 24.9 to 9.2, where in all scales a higher value indicates a more severe case of disease [27]. The results of Nicole Laurent's case study on the Depression Anxiety Stress Scales (DASS) are also promising, as there was a significant reduction in all symptoms measured by this scale, i.e. stress, anxiety and depression levels, after a 21-week dietary period [29].

BPD, like SZ, is associated with an increased risk of type II diabetes, obesity, cardiovascular disease and premature death; therefore, the KD, by providing an alternative source of energy for the brain and body, has a beneficial effect on both, supporting the treatment of comorbidities [25, 28]. All this translates into better control of the aforementioned conditions and a statistically significant increase in patients' life satisfaction (17% increase in the Manchester Short Assessment of Quality of Life and Global Assessment of Functioning scales) [25].

Diet and Schizophrenia

The previously mentioned oxidative stress, inflammation and mitochondrial dysfunction are involved in the pathogenesis of SZ [2, 30]. The resulting free radicals can lead to damage in the cell membrane, which in turn impairs neurotransmission and the appearance of disease symptoms [30]. The ketogenic diet has a positive regulating effect on the processes mentioned above and, in addition, raises levels of GABA, which has an inhibitory effect in the CNS, has

a modulating effect on GABA receptors and lowers levels of glutamate, which in turn is a major excitatory neurotransmitter [2, 3].

Studies show that in patients with SZ/schizoaffective disorder, the use of KD has a positive effect on the course of the illness. In these patients, a reduction in the severity of positive symptoms was noted after the use of KD and also no relapse of symptoms was observed. However, these symptoms recurred after coming down from a state of ketosis [5]. Mood stabilisation was also observed and there were positive changes both in behaviour and improvements in cognitive abilities [5, 25].

A case was described of a patient with SZ of 50 years' duration who, after taking KD, noticed a cessation of hallucinations after just one week of starting the diet [25]. The longer the diet is followed, the less severe the positive and negative symptoms become [31]. It is worth mentioning that antipsychotics are designed to negate the occurrence of positive symptoms in the patient, while they often have a small, insufficient effect on negative symptoms, which significantly affects patients' comfort and daily functioning [25, 32]. KD, on the other hand, has a positive effect on both the productive and negative symptoms of SZ. In addition to psychotic symptoms, there were improvements in sleep quality, overall life satisfaction and a 34% improvement in Clinical Global Impression [25]. The association of carbohydrates with SZ is evidenced by clinical studies reporting that patients had a craving for carbohydrates shortly before their exacerbation. Furthermore, it has been noted that populations that did not intentionally consume low-carbohydrate diets had fewer cases of SZ (e.g. countries in the South Pacific or after World War II, when wheat supplies were reduced). A link has also been made between SZ and coeliac disease - when gluten consumption was discontinued, there was a significant improvement in the symptoms of the psychiatric illness [32].

Returning to the previously mentioned scales, statistically significant decreases in the severity of schizoaffective disorder could be observed, respectively: in HAM-D from 28.2 to 7.0, MADRS 32.7 to 9.3, CGI-S from 5.4 to 2.6 and also a decrease in the PANSS value from 91.4 to 49.3 was noted [27]. The Sethi S et al. study also achieved a statistically significant 32% reduction in disease symptoms measured on the Brief Psychiatric Rating Scale [25].

As in the case of BPD, patients with schizoaffective disease according to a retrospective analysis of Danan et al. in more than half of cases after the use of KD, doses and/or number of

drugs were reduced in more than 60% of the analyzed patients. This also happened in a 70-year-old patient suffering from SZ after following the nutrition according to KD principles, her doses of drugs were reduced and her daily functioning improved so much that she stopped needing a caregiver [5]. In addition, thanks to the beneficial effect of this diet on glucose and fat metabolism, it was possible to discontinue or reduce the use of drugs used in diabetes and hypercholesterolemia [27]. It is worth remembering that people with SZ tend to have abnormal glucose tolerance, reduced insulin sensitivity, type II diabetes, visceral fat deposition, increased triglycerides and a decrease in HDL. In addition, the pharmacotherapy of this disease often leads to weight gain, impaired glucose and fat metabolism. This diet not only positively affects these aspects, but also allows you to reduce drugs. All this allows not only better control of the symptoms of the disease and associated diseases, but also to a reduction in cardiovascular risk and mortality associated with them [30].

Summary

The KD is an important tool to help not only maintain a healthy body weight or fight insulin resistance and diabetes, but also to treat conditions such as BPD and SZ. Its use translates into a statistically significant increase in the quality of life of patients, improvement of their biochemical parameters and reduction in the incidence of relapses of these diseases. In addition, KD is a neuroprotective factor preventing the progressive loss of cognitive functions as a result of mental diseases and allows to reduce the doses of drugs used in their treatment, which translates into a reduction in the number of side effects. Therefore, expanding research on the KD and its use could be crucial in developing new recommendations for the treatment of BPD and SZ with KD, which would significantly improve the quality of life of patients with these conditions.

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References:

1. Kurowska A, Ziemichód W, Herbet M, Piątkowska-Chmiel I. The Role of Diet as a Modulator of the Inflammatory Process in the Neurological Diseases. Nutrients. 2023 Mar 16;15(6):1436. PMID: 36986165; PMCID: PMC10057655. https://doi.org/10.3390/nu15061436

2. Choi J, Kang J, Kim T, Nehs CJ. Sleep, mood disorders, and the ketogenic diet: potential therapeutic targets for bipolar disorder and schizophrenia. Front Psychiatry. 2024 Feb 14;15:1358578. PMID: 38419903; PMCID: PMC10899493. https://doi.org/10.3389/fpsyt.2024.1358578

3. Chmiel I. Ketogenic diet in therapy of bipolar affective disorder - case report and literature review. Psychiatr Pol. 2022 Dec 31;56(6):1345-1363. English, Polish. Epub 2022 Dec 31. PMID: 37098202. https://doi.org/10.12740/PP/OnlineFirst/136356

4. Dietch DM, Kerr-Gaffney J, Hockey M, Marx W, Ruusunen A, Young AH, Berk M, Mondelli V. Efficacy of low carbohydrate and ketogenic diets in treating mood and anxiety disorders: systematic review and implications for clinical practice. BJPsych Open. 2023 Apr 17;9(3):e70. PMID: 37066662; PMCID: PMC10134254. https://doi.org/10.1192/bjo.2023.36

5. Chrysafi M, Jacovides C, Papadopoulou SK, Psara E, Vorvolakos T, Antonopoulou M, Dakanalis A, Martin M, Voulgaridou G, Pritsa A, Mentzelou M, Giaginis C. The Potential Effects of the Ketogenic Diet in the Prevention and Co-Treatment of Stress, Anxiety, Depression, Schizophrenia, and Bipolar Disorder: From the Basic Research to the Clinical Practice. Nutrients. 2024 May 21;16(11):1546. PMID: 38892480; PMCID: PMC11174630. https://doi.org/10.3390/nu16111546

6. Zambrano AK, Cadena-Ullauri S, Guevara-Ramírez P, Frias-Toral E, Ruiz-Pozo VA, Paz-Cruz E, Tamayo-Trujillo R, Chapela S, Montalván M, Sarno G, Guerra CV, Simancas-Racines D. The Impact of a Very-Low-Calorie Ketogenic Diet in the Gut Microbiota Composition in Obesity. Nutrients. 2023 Jun 13;15(12):2728. PMID: 37375632; PMCID: PMC10305724. https://doi.org/10.3390/nu15122728

7. Madireddy S, Madireddy S. Therapeutic Interventions to Mitigate Mitochondrial Dysfunction and Oxidative Stress-Induced Damage in Patients with Bipolar Disorder. Int J Mol Sci. 2022 Feb 6;23(3):1844. PMID: 35163764; PMCID: PMC8836876. https://doi.org/10.3390/ijms23031844

8. Scaini G, Valvassori SS, Diaz AP, Lima CN, Benevenuto D, Fries GR, Quevedo J. Neurobiology of bipolar disorders: a review of genetic components, signaling pathways,

biochemical changes, and neuroimaging findings. Braz J Psychiatry. 2020 Sep-Oct;42(5):536-551. PMID: 32267339; PMCID: PMC7524405. https://doi.org/10.1590/1516-4446-2019-0732

9. Scott MR, McClung CA. Bipolar Disorder. Curr Opin Neurobiol. 2023 Dec;83:102801. Epub 2023 Oct 27. PMID: 38223491; PMCID: PMC10786345. https://doi.org/10.1016/j.conb.2023.102801

10. O'Connell KS, Coombes BJ. Genetic contributions to bipolar disorder: current status and future directions. Psychol Med. 2021 Oct;51(13):2156-2167. Epub 2021 Apr 21. PMID: 33879273; PMCID: PMC8477227. https://doi.org/10.1017/S0033291721001252

11. Post RM, Grunze H. The Challenges of Children with Bipolar Disorder. Medicina (Kaunas). 2021 Jun 11;57(6):601. PMID: 34207966; PMCID: PMC8230664. https://doi.org/10.3390/medicina57060601

12. Haggarty SJ, Karmacharya R, Perlis RH. Advances toward precision medicine for bipolar disorder: mechanisms & molecules. Mol Psychiatry. 2021 Jan;26(1):168-185. Epub 2020 Jul 7. PMID: 32636474; PMCID: PMC10290523. https://doi.org/10.1038/s41380-020-0831-4

13. Velligan DI, Rao S. Schizophrenia: Salient Symptoms and Pathophysiology. J Clin Psychiatry. 2023 Jan 18;84(1):MS21078COM7. PMID: 36652679. https://doi.org/10.4088/JCP.MS21078COM7

14. Khavari B, Cairns MJ. Epigenomic Dysregulation in Schizophrenia: In Search of Disease Etiology and Biomarkers. Cells. 2020 Aug 5;9(8):1837. PMID: 32764320; PMCID: PMC7463953. https://doi.org/10.3390/cells9081837

15. Hogenaar JTT, van Bokhoven H. Schizophrenia: Complement Cleaning or Killing. Genes (Basel). 2021 Feb 11;12(2):259. PMID: 33670154; PMCID: PMC7916832. https://doi.org/10.3390/genes12020259

16. Prestwood TR, Asgariroozbehani R, Wu S, Agarwal SM, Logan RW, Ballon JS, Hahn MK, Freyberg Z. Roles of inflammation in intrinsic pathophysiology and antipsychotic drug-induced metabolic disturbances of schizophrenia. Behav Brain Res. 2021 Mar 26;402:113101. Epub 2021 Jan 14. PMID: 33453341; PMCID: PMC7882027. https://doi.org/10.1016/j.bbr.2020.113101

17. Park HJ, Choi I, Leem KH. Decreased Brain pH and Pathophysiology in Schizophrenia. Int J Mol Sci. 2021 Aug 4;22(16):8358. PMID: 34445065; PMCID: PMC8395078. https://doi.org/10.3390/ijms22168358

18. McGaugh E, Barthel B. A Review of Ketogenic Diet and Lifestyle. Mo Med. 2022 Jan-Feb;119(1):84-88. PMID: 36033148; PMCID: PMC9312449.

19. Masood W, Annamaraju P, Khan Suheb MZ, Uppaluri KR. Ketogenic Diet. StatPearls https://www.ncbi.nlm.nih.gov/books/NBK499830/ (access: 2025.03.28)

20. Baylie T, Ayelgn T, Tiruneh M, Tesfa KH. Effect of Ketogenic Diet on Obesity and Other Metabolic Disorders: Narrative Review. Diabetes Metab Syndr Obes. 2024 Mar 21;17:1391-1401. PMID: 38529169; PMCID: PMC10962461. https://doi.org/10.2147/DMSO.S447659

21. Dyńka D, Kowalcze K, Paziewska A. The Role of Ketogenic Diet in the Treatment of Neurological Diseases. Nutrients. 2022 Nov 24;14(23):5003. PMID: 36501033; PMCID: PMC9739023. https://doi.org/10.3390/nu14235003

22. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020 Jun 24;6(6):CD001903. PMID: 32588435; PMCID: PMC7387249 https://doi.org/10.1002/14651858.CD001903.pub5

23. Stocker RK, Reber Aubry E, Bally L, Nuoffer JM, Stanga Z. Ketogene Diät: evidenzbasierte therapeutische Anwendung bei endokrinologischen Erkrankungen [Ketogenic Diet and its Evidence-Based Therapeutic Implementation in Endocrine Diseases]. Praxis (Bern 1994). 2019 Jun;108(8):541-553. German. PMID: 31185843. https://doi.org/10.1024/1661-8157/a003246

24. Jing T, Zhang S, Bai M, Chen Z, Gao S, Li S, Zhang J. Effect of Dietary Approaches on Glycemic Control in Patients with Type 2 Diabetes: A Systematic Review with Network Meta-Analysis of Randomized Trials. Nutrients. 2023 Jul 15;15(14):3156. PMID: 37513574; PMCID: PMC10384204. https://doi.org/10.3390/nu15143156

25. Sethi S, Wakeham D, Ketter T, Hooshmand F, Bjornstad J, Richards B, Westman E, Krauss RM, Saslow L. Ketogenic Diet Intervention on Metabolic and Psychiatric Health in Bipolar and Schizophrenia: A Pilot Trial. Psychiatry Res. 2024 May;335:115866. Epub 2024 Mar 20. PMID: 38547601. https://doi.org/10.1016/j.psychres.2024.115866

26. Bohnen JLB, Wigstrom TP, Griggs AM, Roytman S, Paalanen N, Andrews HA, Bohnen NI, Franklin JJH, McInnis MG. Ketogenic-Mimicking Diet as a Therapeutic Modality for Bipolar Disorder: Biomechanistic Rationale and Protocol for a Pilot Clinical Trial. Nutrients. 2023 Jul 7;15(13):3068. PMID: 37447394; PMCID: PMC10346691. https://doi.org/10.3390/nu15133068

27. Danan A, Westman EC, Saslow LR, Ede G. The Ketogenic Diet for Refractory Mental Illness: A Retrospective Analysis of 31 Inpatients. Front Psychiatry. 2022 Jul 6;13:951376. PMID: 35873236; PMCID: PMC9299263. https://doi.org/10.3389/fpsyt.2022.951376

28. Campbell IH, Needham N, Grossi H, Kamenska I, Luz S, Sheehan S, Thompson G, Thrippleton MJ, Gibbs MC, Leitao J, Moses T, Burgess K, Rigby BP, Simpson SA, McIntosh E, Brown R, Meadowcroft B, Creasy F, Mitchell-Grigorjeva M, Norrie J, McLellan A, Fisher C, Zieliński T, Gaggioni G, Campbell H, Smith DJ. A pilot study of a ketogenic diet in bipolar disorder: clinical, metabolic and magnetic resonance spectroscopy findings. BJPsych Open. 2025 Feb 25;11(2):e34. PMID: 39995103. https://doi.org/10.1192/bjo.2024.841

29. Laurent N. Retrospective case study: ketogenic metabolic therapy in the effective management of treatment-resistant depressive symptoms in bipolar disorder. Front Nutr. 2024 Aug 12;11:1394679. PMID: 39188977; PMCID: PMC11346312. https://doi.org/10.3389/fnut.2024.1394679

30. Rarinca V, Vasile A, Visternicu M, Burlui V, Halitchi G, Ciobica A, Singeap AM, Dobrin R, Burlui E, Maftei L, Trifan A. Relevance of diet in schizophrenia: a review focusing on prenatal nutritional deficiency, obesity, oxidative stress and inflammation. Front Nutr. 2024 Dec 13;11:1497569. PMID: 39734678; PMCID: PMC11673491. https://doi.org/10.3389/fnut.2024.1497569

31. Garner S, Barkus E, Kraeuter AK. Positive and negative schizotypy personality traits are lower in individuals on ketogenic diet in a non-clinical sample. Schizophr Res. 2024 Aug;270:423-432. Epub 2024 Jul 10. PMID: 38991418. https://doi.org/10.1016/j.schres.2024.07.010

32. Omori NE, Malys MK, Woo G, Mansor L. Exploring the role of ketone bodies in the diagnosis and treatment of psychiatric disorders. Front Psychiatry. 2023 Apr 17;14:1142682. PMID: 37139329; PMCID: PMC10149735. https://doi.org/10.3389/fpsyt.2023.1142682