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Ketogenic diet in therapy of bipolar affective disorder – case report and literature review

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Summary

Bipolar affective disorder is a chronic mental disorder, characterized by mood swings alternating between depression and manic or hypomanic episodes. Unfortunately, in some patients pharmacological treatment is not effective, and a certain group of patients shows treatment resistance. Therefore, other treatment methods are sought after, including a change in diet. The most promising is the ketogenic diet. In the presented case study of a male patient, thanks to the introduction of the ketogenic diet, full remission of the disease was achieved, doses of lamotrigine were reduced and quetiapine was completely discontinued. Previously, neither lamotrigine monotherapy nor combined treatment with quetiapine achieved euthymia. The effects of the diet may be related to, among others, the influence on ionic channels and increase in blood acidity (similar to the use of mood stabilizers), increase in gamma-aminobutyric acid (GABA) concentration, modulation of GABAA receptors, effects on the concentration of catecholamines, blocking of AMPA receptors by medium-chain fatty acids, with significant share of omega-3 fatty acids, reduction in insulin levels, and changes in the gut microbiota. The ketogenic diet influences glutamate metabolism and nerve cell metabolism, which uses ketone bodies as energy sources. Ketosis can also stimulate biogenesis of mitochondria, improve brain metabolism, act as a neuroprotective factor, as well as increase glutathione synthesis and reduce oxidative stress. Due to the limited size of the present study, literature review includes selected papers published in the last two decades in the PubMed and Google Scholar scientific literature databases, in English and Polish, with the following key words: ketogenic diet, bipolar affective disorder, depression, schizophrenia.

Key words: ketogenic diet, bipolar affective disorder, rapid cycling

Introduction

Bipolar affective disorder (BPAD) is a mental disorder characterized by periodic occurrence of manic or hypomanic and depressive episodes [1]. The prevalence of BPAD in the population is estimated at 1.5–2.4% [2] and due to the chronic nature

of the illness there is a high risk of recurrence [3]. Depending on many factors, such as the stage of the illness, pharmacotherapy does not always lead to euthymia and some patients are resistant to pharmacological treatment [4]. In view of the above, the subject of lifestyle changes, including mainly diet, physical activity and sleep, is increasingly being addressed. One of the most promising nutrition models with a strong influence on the nervous system is the ketogenic diet. It is a low-carbohydrate, high-fat and normal-protein nutrition system that causes increased synthesis of ketone bodies (acetone, acetoacetate, β-hydroxybutyrate) leading to ketosis. The ketogenic diet has a well-documented anti-epileptic effect [5, 6], and because of its effects on the CNS (central nervous system) it is also used in other neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and multiple sclerosis [7, 8]. Due to its pleiotropic properties, an increasing number of scientific papers also suggest potential use of the ketogenic diet in psychiatry. There is some indication of its antidepressant [9, 10] and antipsychotic effects [11, 12]. In bipolar disorder it may stabilize mood, among others, through its effect on glutamate and gamma-aminobutyric acid (GABA) transmission, monoamine concentrations, function and biogenesis of mitochondria, neurotrophins, reduction of oxidative stress and inflammation [13].

The aim of this paper is to present the benefits of a well-planned nutritional intervention in bipolar disorder and to review literature related to ketogenic diet therapy in affective disorders, mainly bipolar affective disorder.

Case study presentation

Male, born 1992, higher education degree, professionally active (office work), happily married. No comorbidities or addictions. Patient interview indicates a family history of mental illness (including BPAD and depression): uncle, father, grandfather. The first symptoms of the illness appeared in high school, at the age of 18. First came fear of space and crowds (agoraphobia), followed by hypomanic symptoms: elevated mood, talkativeness, cheerfulness. The moment that revealed the illness was a trip abroad for work. In the changed environment, mild depressive states began to appear, occurring every few days and lasting from 2 to 4 days. In retrospect, the patient mentions that there were also short periods (1–2 days) of significantly increased mood. The man did not experience manic episodes. The abovementioned symptoms appeared more frequently and lasted longer – depression from several to several dozen days. The patient, due to his prevalent depression, began to seek help. Between 2010 and 2012 he attended several specialists: two psychologists, two psychiatrists and a neurologist, however, a diagnosis of bipolar disorder was not made. During the last consultation with a psychiatrist, he received a drug from the SSRI (selective serotonin reuptake inhibitor) – Citalopram (Citabax), at a dose of 20 mg/day, but after which he reported that he felt worse. The drug did not improve mood stabilization and caused side effects, mainly concentration disorders, apathy, sleepiness, and anxiety. The treatment lasted for 3 months, after which the patient decided to discontinue pharmacotherapy.

Diagnosis and treatment

The diagnosis of bipolar affective disorder with ultra-rapid cycling was made in December 2012. The psychiatrist conducted a detailed interview, asked about history of diseases in the family and used a mood disorder questionnaire. The following treatment was introduced:

1. Lamotrigine (Lamitrin), January 2013–March 2013: dose 100 mg/day. No improvement after three months.
2. Lamotrigine (Lamitrin), April 2013–June 2013: dose increase to 200 mg/day. After a further three months of increasing the dose the patient continued to experience chronic depression.
3. Combination treatment: lamotrigine (Lamitrin) and quetiapine (Bonogren), July 2013–December 2013: doses of both drugs 200 mg/day. Improvement in mood, but patient continued to report depressive states.
4. Combination treatment (dose escalation): lamotrigine (Lamitrin) and quetiapine (Bonogren), January 2014–December 2016: doses 300 mg/day respectively. Significant improvement in mood, but no full remission. Patient still complained of depressive states, but of a lesser severity.

After the introduction of combination therapy there was an improvement, but never a complete remission. The patient continued to experience depressive episodes lasting from a few to around a dozen days, but they were much milder. Pharmacological treatment continued for 4 years (2013–2016), bringing significant benefits in stabilizing his mood. Unfortunately, the drugs did not cause a complete improvement and showed a number of side effects, in particular permanent sleepiness, fatigue and lack of energy, as well as problems with concentration, which in turn further reduced the patient's quality of life. The lack of a definite improvement and the side effects of the drugs drove the patient to seek ways and possible changes to achieve a state of full remission.

Diet therapy

While looking for information about his illness on the Internet, the patient came across an article on the ketogenic diet. Interested in this solution, he started to eliminate high-carbohydrate products himself. He then consulted a nutritionist in order to introduce the rules of the diet correctly. Dietary intervention can generally be divided into three stages.

In November 2016, the man started a low-carbohydrate and high-fat diet, lasting one year. The initial BMI was 22.6, the results of laboratory tests were normal (CBC, lipid profile, glucose, liver tests, creatinine, uric acid). Introduction of physical activity (impact of exercise on mood) was recommended, but the patient did not comply with these recommendations, explaining that he did not have time. The nutrition system involved eliminating products with high carbohydrate content, mainly cereal, sources

of starch (potatoes, legumes), as well as fruit rich in simple sugars (bananas, grapes, apples, pears, etc.), processed foods, sweets, salty snacks. The dominant products in the diet were eggs, fatty fish (herring, sardine, mackerel, salmon), fatty dairy products (blue cheese, hard cheese, cottage cheese) and meat, as well as vegetables (mainly green and red), added vegetable oils (olive oil, linseed oil, avocado oil, MCT oil, coconut oil), animal oils (butter, lard), olives, nuts, seeds, and a small amount of low-carbohydrate fruit (strawberries, raspberries, berries, currants, peaches). The dominant energy substrate was fat, while the diet was Mediterranean in nature (significant share of mono – and polyunsaturated fatty acids). During this process, the concentration of β-hydroxybutyrate oscillated between 0.3 and 0.5 mmol/l. The mood improved and stabilized, energy was increased during the day, better night-time regeneration (sleep) was achieved, with improved cognitive functions and concentration, and elimination of anxiety. Depressive states were shorter (1–4 days) and much milder. Periods of total remission of symptoms increased from a week to around a dozen days. No hypomania occurred. The doses of drugs were reduced to 200 mg of lamotrigine and 200 mg of quetiapine per day. The clinical presentation showed no significant weight change (BMI within 22.6–23.4), the patient's follow-up laboratory test results were within normal limits (CBC, lipid profile, glucose, liver tests, creatinine, uric acid).

In December 2017, it was decided to introduce a strict ketogenic diet (<30 g carbohydrates), based on the same products, with an accurate calculation of macro nutrients and energy by a qualified nutritionist. The energy value of the diet was 2500 kcal, with 15% protein, 80% fat and 5% carbohydrates. The patient's diet was characterized by a high content of omega-3 polyunsaturated fatty acids (EPA – eicosapentaenoic acid; DHA – docosahexaenoic acid; ALA – alpha-linolenic acid), MCT (medium chain triglycerides), omega-6 fatty acid (GLA gamma-linolenic acid). The diet was not changed in qualitative terms, but systematic proportions were introduced with regard to energy and building substrates. The concentration of β-hydroxybutyrate in blood ranged from 1.5 to 3 mmol/litre, which indicates the state of ketosis. This dietary intervention was followed by a spectacular improvement in the patient's mood, increased energy during the day, progression of cognitive functions, improved sleep quality, improved concentration, and lack of anxiety. Periods of remission were even longer: 2–4 weeks, interrupted by a mild, short depression lasting 1–2 days, without hypomania. Again it was decided to reduce the doses of the drugs to 100 mg of lamotrigine and 100 mg of quetiapine per day. There was no significant change in body weight (BMI 22.6–23.4) during this intervention, monitored laboratory results remained within normal ranges. Paradoxically, there was an improvement in lipid parameters (mainly an increase in HDL and a decrease in triglycerides).

In early November 2018, the last modification in the nutritional plan was made: the use of the ketogenic diet with a cyclic one-day fast introduced every 7–10 days to increase the intensity (i.e., depth) of ketosis. The energy value of the diet was increased due to the deficit caused by one-day fast, while the percentage share of macro nutrients remained unchanged. On the day of fasting the patient consumed only liquids (water,

green tea, black tea). The concentration of β-hydroxybutyrate invariably indicated ketosis, with elevation on fasting days to a maximum of 5 mmol/litre. All previous effects related to cognitive functions, mood stabilization, energy levels remained unchanged. The breakthrough was a complete absence of depression, which had accompanied the patient for 8 years, entry into a state of complete remission and discontinuation of quetiapine from the pharmacological treatment. The patient currently remains at a dose of 100 mg of lamotrigine, without any symptoms of illness – depression and hypomania. It is worth mentioning that lamotrigine in monotherapy did not bring the expected results, even in higher doses (300 mg/day). During follow-up appointments, no significant change in body weight was observed (BMI 22.6–23.4) and follow-up results of recommended laboratory tests remained within reference ranges (CBC, lipid profile, glucose, liver tests, creatinine, uric acid). An abdominal ultrasound was also performed in 2019 and showed no pathology.

On the basis of the described process, it can be assumed that not only the state of ketosis, but also its intensity (so-called depth) can determine the mood-stabilizing effect. In this regard, an interesting tool to monitor the effectiveness of the ketogenic diet therapy may be the GKI coefficient (Glucose Ketone Index), indicating the relation between the concentration of glucose and β-hydroxybutyrate [14].

Diet therapy played an important role in the patient's remission. After the introduction of the ketogenic diet, the man's mood changed drastically and an improvement occurred at every level of his functioning. The nutritional intervention was conducted under the supervision of a clinical nutritionist and a psychiatrist.

Discussion

The use of low-carbohydrate models is not limited to epilepsy therapies only. The ketogenic diet has also found its practical application in the treatment of other diseases such as obesity, diabetes, polycystic ovary syndrome (PCOS), insulin resistance, acne, neurodegenerative diseases [15–17].

Based on the presented case study, it should be pointed out that the diet may play an important role also in the course of bipolar affective disorder. The ketogenic diet seems to be the most promising, as it has a strong influence on the change in nervous system function, as shown in available literature [18]. Numerous studies confirm its high effectiveness in the treatment of epilepsy, whose etiopathogenesis bears some similarities to affective disorders [15, 19]. Many mental illnesses are linked to glucose hypometabolism, neurotransmitter imbalances, oxidative stress, and inflammation. There is evidence that the ketogenic diet may have a beneficial effect on the above-mentioned biopathologies [20, 21]. Preclinical studies and a series of described cases suggest that the described nutrition model shows antidepressant and mood stabilizing effects [13]. The ketogenic diet is most effective when combined with pharmacotherapy, especially in the treatment of resistant depression. The use of the diet in an episode of severe depression leads to improvement in somatic and psychiatric symptoms [22]. By

looking at the effects of some antiepileptic drugs, which are also effectively used in the treatment of BPAD, many similarities can be observed as compared to the effects of the ketogenic diet [23]. The following table shows the areas of activity of antiepileptic drugs and the ketogenic diet.

Table 1**. Mechanism of action of antiepileptic drugs in BPAD based on modified M. Jarema [24], and of the ketogenic diet [6, 25–28]**

Mechanism of action	Sodium channel blocking	Calcium channel blocking	$GABA_A$ receptor modulation	Increase in GABA	AMPA receptor blocking
Ketogenic diet	+	+	+	+	+ MCT fatty acids
Lamotrigine	+	+			
Oxcarbazepine	+	+			
Carbamazepine	+	+			
Valproic acid	+	+		+	
Topiramate	+	+	+	+	+
Zonisamide	+	+	+		

"+" – area of activity

Available literature presents a limited number of studies on the use of the ketogenic diet in mental illness. Murphy et al. [29], referring to an improvement in concentration and cognitive functions in children with epilepsy, indicate mood-stabilizing properties of the ketogenic diet. In a rat study, using the Porsolt test, it was observed that individuals fed high-fat and low-carbohydrate feed were less susceptible to negative moods, as were rats taking antidepressants. The researchers' conclusion emphasizes potential antidepressant properties of the ketogenic diet [29]. By extrapolating this study to the case of the male patient described here, similar conclusions can be drawn because the patient's permanent depression subsided. According to Sussman et al. [30], the ketogenic diet used in the prenatal period in mice affects the neuroanatomical structure of the progeny's brain (increased cerebellum volume, reduction of the hypothalamus and corpus callosum), reducing depressive and anxiety potential. An interesting study was carried out by Prins and Matsumoto [31], where the researchers demonstrated the influence of the ketogenic diet on the structural reconstruction of the brain and its function in patients with brain and spinal cord injuries. The effects of the ketogenic diet on the intellect were demonstrated in Kabuki syndrome mouse models. The authors of the study suggest that the influence of the diet on epigenetic modifications, by increasing the level of β-hydroxybutyrate, may be a strategy for the treatment of intellectual disabilities and related disorders [32]. Therefore, it can be used in patients with depression, affective disorders and schizophrenia. Patients diagnosed with BPAD are usually creative people, often exceptionally talented in artistic, scientific or business fields, but during the episodes of the illness (depression,

mania), cognitive (intellectual) dysfunctions are observed [33–36]. Ketogenic diet therapy can improve patients' functioning in this aspect. Studies carried out by IJff et al. [37] on children and teenagers with epilepsy have shown significantly lower levels of anxiety behavior and mood disorders after introducing the ketogenic diet. This group was assessed as more productive, also achieving better results of cognitive function tests. Improved behavior, social skills and ability to learn have also been observed in studies in people with autistic spectrum disorders [38, 39]. Neurobehavioral development and changes in the EEG record proportional to the improvement in clinical symptoms were shown by Zhu et al. [40] in 42 children with drug-resistant epilepsy who were on the ketogenic diet. According to Włodarczyk et al. [11], the ketogenic diet can improve the functioning and alleviate the symptoms of schizophrenic patients by increasing GABA synthesis. The authors indicate that such a dietary approach also prevents excessive weight gain, which is often observed with the introduction of some drugs. Kraeuter et al. [41] demonstrated the use of the ketogenic diet for the first time on an animal model of schizophrenia. The study showed normalization of pathological behavior in mice on a low-carbohydrate and high-fat diet. The authors conclude that the pathophysiology of schizophrenia is associated with abnormal glutamate neurotransmission, reduction of GABA and serious disorders of glucose metabolism. The ketogenic diet influences each of these elements, hence it may have a beneficial effect in normalization of pathophysiological processes in schizophrenia. The conducted studies demonstrate that the ketogenic diet may constitute a new, safe and effective management approach in schizophrenia [41]. According to Yudkoff et al. [42], ketosis reduces the concentration of the main excitatory neurotransmitter – glutamate, allowing more effective conversion of glutamine to GABA, the key inhibitory neurotransmitter. Studies carried out on mice on the ketogenic diet indicate a significant change in the levels of catecholamines – dopamine, norepinephrine and serotonin. The activity of the dopaminergic system, measured by the ratio of dopamine metabolites to dopamine content, was significantly higher in the regions of the motor and somatosensory cortex in animals on the ketogenic diet, compared to the same areas of the mouse brain on a standard diet. The results of these studies indicate activity of the ketogenic diet with regard to the mesocortical dopaminergic system [43]. Kraft and Westman [44] describe a case of a woman with diagnosed schizophrenia, in whom the introduction of the ketogenic diet resulted in sudden subsidence of symptoms such as hallucinations and crosstalk. Similar conclusions are presented by Jaramillo et al. [45], who have observed a positive effect of the ketogenic diet in patients with schizophrenia, noting an improvement in symptomatology after 14 days of the diet. Studies on rats given exogenous ketone bodies also seem interesting. The supplementation increased the concentration of β-hydroxybutyrate in blood and reduced anxiety behaviors [46].

Bipolar affective disorder and schizophrenia are associated with disorders of energy metabolism. More and more often researchers talk about mitochondrial dysfunction manifested on the level of cellular respiration, morphological changes in mitochondria, increased polymorphisms and mutations of mitochondrial DNA, decreased levels of

nuclear mRNA molecules and proteins involved in mitochondrial respiration, decreased high-energy phosphorus compounds, and decreased pH in the brain [47]. The domain of mitochondria is production of ATP, but they are also involved in controlling apoptosis, calcium homeostasis and detoxification of reactive oxygen species (ROS). Therefore, it is easy to assume that their dysfunction is linked to various diseases [48]. A study by Hasan-Olive et al. [49] showed an increase in mitochondrial biogenesis and bioenergetics through the PGC1α-SIRT3-UCP2 axis in mice on the ketogenic diet. Studies by Sullivan et al. [50] suggest that the ketogenic diet reduces production of free radicals by activating mitochondrial thermogenins (UCP). Whereas Bough et al. [51] indicate an improvement in cerebral metabolism as well as stimulation of mitochondrial biogenesis. This was presented on models of rats on the ketogenic diet, which had significantly higher number of mitochondria in the hippocampus compared to the control group. In another animal study, Bough [52] showed an increase in mitochondrial density of 46% in tissues of specimens on the ketogenic diet compared to the control group. Most of the mitochondria were located in areas involved in neural processes (such as dendrites and axons). It was also observed that 39 out of 42 genes encoding mitochondrial proteins increased after the introduction of a ketogenic diet model [52]. Nylen et al. [53] has also observed an increase in the number of mitochondria in mice fed ketogenically. According to Campbell's hypothesis [23], mitochondrial dysfunction plays a causal role in BPAD through disruption of the pyruvate dehydrogenase complex and/or mitochondrial carrier proteins that carry intracellular pyruvate. By bypassing this metabolic pathway, ketones provide an alternative substrate for oxidative phosphorylation. Ketosis reduces inflammation; therefore, this phenomenon is successfully used in metabolic diseases [54]. Literature more and more often indicates participation of inflammatory conditions also in the pathogenesis of BPAD [55]. Among patients with these disorders, a certain disharmony of the immune system is observed, defined as an imbalance between pro – and anti-inflammatory cytokines. In BPAD inflammation is mainly linked to the increase in concentration of interleukins: IL-2, IL-4, IL-6, as well as TNF-α (tumor necrosis factor α), CRP (C-reactive protein), complement components C3 and C4, and the immunological cellular response [56]. Brietzke and Kapczinski [57] indicate a significant increase in TNF-α, both in mania and depression, and its normalization during treatment. Lithium – a pioneering and effective drug used in the treatment of BPAD – shows strong anti-inflammatory effects, which may indicate high significance of these processes in the pathogenesis of mood disorders but also contribute to its increased pharmacological efficacy [58]. According to studies by Maalouf et al. [59], ketone bodies (β-hydroxybutyrate, acetoacetate) reduce production of glutamate-induced free radicals by increasing the NAD^+/NADH ratio and strengthening mitochondrial respiration in new brain cortex neurons. Studies by Jarrett et al. [60] confirm the antioxidant potential of the ketogenic diet, which is related, among others, to the increase of mitochondrial GSH (glutathione). Rats with diet-induced ketosis (determination of β-hydroxybutyrate in blood) showed a twofold increase in mitochondrial GSH in the hippocampus, compared to the control group. The results of

the study demonstrate that the ketogenic diet, by increasing GSH synthesis, enhances the antioxidant potential and mtDNA protection against damage activated by free radicals [60]. The antioxidant properties of the ketogenic diet have been demonstrated in a study by Greco et al. [61] on female rats with severe brain damage. The authors of the study emphasize that the alternative source of energy – ketone bodies, due to their antioxidant properties – prevents mitochondrial disorders mediated by oxidative stress. factor which influences brain function, well described in literature, is omega-3 polyunsaturated fatty acids. They have a proven effect in reducing the negative effects of affective disorder, as shown by numerous studies and meta-analyses. Researchers emphasize an improvement especially during the depressive state [62, 63]. The efficacy of omega-3 acids can be explained by their strong anti-inflammatory and neuroplastic effects [64]. Moreover, they are the key substrate in serotonin and dopamine synthesis; therefore, their mood-enhancing effects may be associated with this mechanism [65]. It is also mentioned that omega-3 acids affect the modification of G-protein signaling, which in turn translates into neurotransmitter reactions [66]. It is worth noting that fats, depending on their type, contain other anti-inflammatory and antioxidant substances. The most important antioxidants are alpha-tocopherol, beta-carotene, fat-soluble vitamins (A, D, E, K), coenzyme Q-10, phospholipids, as well as conjugated linoleic acid and alpha-lipoic acid (ALA). Due to their lipophilic character, they are better absorbed and used by the body compared to hydrophilic antioxidants [67]. All of the abovementioned effects of the ketogenic diet may be helpful in the treatment of mood disorders, including bipolar affective disorder.

There are also several other reasons why the ketogenic diet can be used as a mood stabilizer in BPAD. It should be noted that some pharmacological anticonvulsant effects may improve the clinical presentation in mood disorders, and the ketogenic diet is one of the available treatment methods for epilepsy. In patients with depression or mania cerebral hypometabolism is observed and the ketogenic diet has a positive effect on the energy profile in the brain. It is worth noting that extracellular changes occurring during the state of ketosis reduce intracellular sodium concentrations – which is a common property of all effective mood stabilizers [68]. The ketogenic diet also affects the composition of the gut microbiota, which may play a role in mood stabilization. According to Olson et al. [69], the antiepileptic effect of the diet is related to, among others, colonization of the *Akkermansia* and *Parabacteroides* species, which mediate a protective effect. New insights are presented by Heischmann et al. [70], who suggest that the effects of the ketogenic diet may be related to the tryptophan metabolic pathway. Studies in rats have shown that rodents on the ketogenic diet, as well as with caloric restrictions, had reduced plasma and hippocampal kynurenine values, compared to the control group. A premise for the potential benefits of the ketogenic diet is an analysis carried out by researchers from the Cambridge University, who monitored online entries and comments on the diet in bipolar affective disorder. According to the study, 141 entries (85.5%) indicated positive effects of the ketogenic diet on mood stabilization [71]. Phleps et al. [72] describe two cases of females with

BPAD type II who have experienced mood stabilization by maintaining the state of ketosis for 2 and 3 years respectively. The effects associated with the diet exceeded conventional pharmacological treatment (as in the described case of the male patient) and the improvement was clearly related to the state of ketosis. Neither female reported any negative effects. The authors state that the ketogenic diet is a potential option for mood stabilization in bipolar affective disorder type II. They also support the hypothesis that blood acidosis may stabilize the mood by reducing intracellular sodium and calcium [72]. The effective stabilizing effect of the ketogenic diet in bipolar disorder is described by Saraga et al. [73] using the example of a woman with BPAD type I. After introduction of the ketogenic diet, chronic depression, anxiety and manic symptoms subsided. Antipsychotic medication (sertindole) was also discontinued.

Unfortunately, despite the long history of its use in neurology, the role of the ketogenic diet in psychiatric disorders is not clear. Scientific evidence to date has significant limitations and further research is needed to verify the effects of the ketogenic diet on various psychiatric disorders [74]. However, it should be recognized that due to its potential pleiotropic effects, it represents a promising prospect in the study of mood disorders, especially in treatment-resistant cases [13].

Safety of the ketogenic diet

In recent years, scientists' views on low-carbohydrate and high-fat diets have changed significantly. In the past, fats and food cholesterol were believed to be the undisputed cause of cardiovascular diseases, while current research increasingly questions the paradigms that once existed.

An analysis carried out by Halton et al. [75] on 82,202 women did not show any relation between high fat intake and coronary heart disease; however, it noted an increased risk in people on a diet with higher glycemic load. Similar conclusions were presented in a large cohort study – PURE (Prospective Urban Rural Epidemiology), carried out in 18 countries at different stages of civilizational development, where the diet of 135,335 people between the ages of 35 and 70 was analyzed for an average of 7.4 years. No correlation was observed between high fat intake and increased mortality, including from cardiovascular causes. Whereas a higher mortality rate was found for people whose diet was richer in carbohydrates. The conclusions from this publication emphasize that the current dietary recommendations should be reconsidered [76]. Saturated fatty acids cause controversy in medical sciences, as they are blamed mainly for cardiovascular diseases. However, after a thorough analysis of current literature, it turns out that studies conducted on large population groups (meta-analyses, systematic reviews, cohort and clinical studies) to a large extent do not show a correlation between consumption of these fatty acids and cardiovascular risks. A meta-analysis of cohort studies published in 2019 in *Lipids in Health and Disease* does not provide evidence of a link between total fat intake, including saturated, monounsaturated and polyunsaturated fatty acids, and the risk of cardiovascular

diseases. However, it is important that such a relation was observed between the intake of fatty acids of trans configuration [77]. In turn, another meta-analysis [78] indicates that high saturated fatty acid intake among the Japanese population reduces the risk of intracerebral hemorrhage and ischemic stroke; however, this summary did not show such a correlation among the other studied subgroups. According to a meta-analysis of randomized controlled trials conducted by Hamley [79], replacement of saturated fatty acids mostly with polyunsaturated omega-6 fatty acids does not reduce the risk of coronary heart disease incidents, related mortality and total mortality. According to the authors, recommendations from previous studies related to the benefits of such a dietary procedure resulted from inappropriate inclusion of trials in scientific analyses [79]. Another meta-analysis of 15 prospective studies, including 476,569 individuals, shows a correlation between higher intake of saturated fatty acids and decreased risk of stroke and related death [80]. Medium and long-term effects of the ketogenic diet were monitored in a clinical trial conducted by Cicero et al. [81] on a group of 377 patients. The conclusions from this experiment are in line with the previously quoted literature. Researchers showed improvements in cardiovascular risk parameters such as anthropometric measurements, blood pressure, lipid levels, glucose metabolism. In addition, the participants were observed for 12 months. All obtained health benefits were maintained [81].

A systematic review and meta-analysis of observational studies carried out by de Souza et al. [82] does not show a correlation between consumption of saturated fatty acids and increased risk of mortality, cardiovascular disease, ischemic heart disease, ischemic stroke or type II diabetes, while pointing out the diversity and some methodological limitations of these observations. Nevertheless, researchers call for an in-depth analysis of the health effects of replacement of, among others, saturated fats with other alternative macroelements, as this ultimately translates into dietary recommendations. Another meta-analysis [83], taking into account 7,150 participants, does not provide evidence of a beneficial effect of a reduced or modified fat diet as part of secondary prevention of ischemic heart disease. Replacement of saturated fatty acids with polyunsaturated fatty acids was not associated with a decreased risk of ischemic heart disease. Interesting conclusions are presented in a meta-analysis by Siri-Tarino et al. [84], involving 347,747 patients, which argues that there is no connection between the consumption of saturated fatty acids and increased risk of coronary heart disease or other cardiovascular diseases [84].

There is also a Mediterranean model of the ketogenic diet, based on oil, fish and green vegetables. That variant improves glycemia, cardiovascular markers and can be used in non-alcoholic fatty liver disease [85, 86]. Such a dietary intervention can also be used directly in patients with BPAD, because according to a study by Łojko et al. [87, 88] more than half of such patients suffer from glucose metabolism disorders. In addition, these patients have increased fasting triglycerides and increased waist circumference. Dietary habits of patients with bipolar disorder in euthymia are also worse as compared to the control group.

However, nutrition based on a high-fat model such as the ketogenic diet can carry some risks, especially if it is not well planned. It is important to emphasize that this type of therapy requires monitoring of the patient's somatic condition, as well as follow-up ultrasound and laboratory examinations. The most common problems at the gastrointestinal level are diarrhea, constipation and vomiting [89]. Some literature also points to disorders caused mainly by energy and nutrient deficits (vitamins, minerals). Due to low protein and carbohydrate supply, low body weight and growth inhibition disorders (hypoproteinemia) may occur in children [90]. The ketogenic diet is also likely to contributed to reduced IGF-1, which may explain physical development disorders in children [91]. In some people elevated triglycerides, total cholesterol and low-density lipoprotein (LDL) levels can be observed, but usually these parameters return to normal limits within 12 months. The ketogenic diet may increase the risk of kidney stones, which occurs in 3–7% of patients, but an adequate content of citrates in the diet prevents the formation of stones (prophylactic alkalinization of urine). Literature also indicates cases of cardiomyopathy, pancreatitis as well as liver and renal dysfunction, especially in combined therapy with valproic acid [92]. In most cases, however, simultaneous use of valproate and the ketogenic diet appears to be safe [93]. Introduction of the ketogenic diet is linked to electrolyte disturbances, which can cause headache, fatigue, nausea, dizziness and fainting, gastrointestinal problems, decreased energy, and cardiac arrhythmias – the so-called carb flu (keto-flu) [94]. Hypoglycemia is also a frequently reported side effect [95]. In a study on rats, the ketogenic diet induced pH disturbances (acidosis), anemia and decreased levels of antioxidant enzymes [96]. The ketogenic diet may also have potential effects on the development of non-alcoholic fatty liver disease and insulin resistance, mainly in rodents [97]. Ketone bodies can attach to proteins using the same mechanism as sugars (glycation), forming adducts that promote inflammation [98]. A literature review by Batch et al. [99] indicates that the ketogenic diet results in lower blood pressure, weight loss, lower triglycerides, glycated hemoglobin and an increase in HDL (high density lipoprotein), but the authors point out an increase in LDL (low-density lipoprotein) and VLDL (very-low-density lipoprotein) fractions, which in turn may lead to increased cardiovascular risk. In addition, dietary restrictions may make it difficult to maintain the diet [99]. An updated expert report of 2018 on ketogenic nutritional therapies indicates low risk of serious side effects and the most common (gastrointestinal) symptoms are relatively easy to manage [92].

Recapitulation and conclusions

The ketogenic diet has been used in medicine for almost a hundred years to treat drug-resistant epilepsy, mainly in children. On the basis of the presented case and the analysis of available literature, it can be assumed that this diet may also have an effect in affective disorders and other mental illnesses. After the introduction of the ketogenic diet and cyclic one-day fasting (increased intensity of ketosis) by the patient, the mood

stabilized, depression completely subsided, the doses of lamotrigine were significantly reduced and quetiapine was completely discontinued. After 8 years, the patient entered into a state of total remission for the first time, lasting permanently. The effects of the diet are probably related to several mechanisms, including its influence on ionic channels (sodium, calcium) and increased blood acidity, similarly to pharmacological mood stabilizers. The potential effect of the diet can also be explained by the increase in GABA concentration, modulation of $GABA_A$ receptors and blocking of AMPA receptors by medium-chain fatty acids (MCT). The ketogenic diet positively influences glutamate metabolism and the whole nerve cell metabolism, which uses ketone bodies as energy sources. Ketosis stimulates the biogenesis of mitochondria, improves brain metabolism, acts as a neuroprotective factor, as well as increases glutathione synthesis and reduces oxidative stress. Moreover, numerous studies and meta-analyses indicate safety of the ketogenic diet and even promote its use in some metabolic disorders [43–46]. Based on the abovementioned reasons, it seems appropriate to conduct carefully-designed studies on a larger group of patients, assessing the impact of the ketogenic diet on the human psyche, with obligatory inclusion of patients with bipolar affective disorders, depression and schizophrenia. The pleiotropic properties of this diet can be potentially helpful in the treatment of various mental disorders, alleviating the course of the illness, improving the quality of patients' life and increasing the likelihood of remission.

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