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Is diet important in bipolar disorder?

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Summary

In recent years it has been increasingly indicated that diet/nutrition is important in the pathogenesis, course and effectiveness of treatment of various mental disorders. Most of the research published so far has focused on the role of nutrition and nutrients in the development and treatment of depression. The results indicated a relationship between diet and risk of depression. Few studies have examined the relationship between diet and bipolar disorder (BD), although it can be assumed that some of the observations related to people with depression may be related to BD. The authors present an overview of the relationship between diet and bipolar disorder and the use of dietary interventions in the treatment of BD. They also discuss the use of nutrients, including polyunsaturated fatty acids, N-acetylcysteine, vitamin D, folic acid, and zinc, in the treatment of BD. For patients, the supplementation of mood disorders treatment with dietary recommendations, supplementation with selected nutrients, supplementation of micronutrients, may provide – in addition to indirect and direct effect on brain function – the possibility of greater co-participation in the treatment, enhancing the sense of control, coping, which may have a significant effect on the course of BD and the effectiveness of its treatment.

Key words: bipolar affective disorder, diet

Introduction

The prevalence of bipolar affective disorder (BD) is estimated at 1–4% of the population [1]. BD is often associated with impaired functioning in various areas (occupational, personal, family, social), major disability and increased morbidity [2] as well as a reduction of life expectancy by as much as 10–20 years compared to the general population [3]. Of the somatic diseases, BD is most commonly (20–80%)

associated with obesity, metabolic syndrome, cardiovascular and respiratory diseases and endocrine disorders [4, 5], with cardiovascular diseases being estimated as the cause of death of almost 40% of patients with BD [1]. The relationships between diet and many somatic diseases are well-known and documented [6, 7]. Awareness of these relationships has led to a number of therapeutic and preventive activities in recent years with regard to modifying dietary habits and weight control in order to limit the prevalence of obesity and its consequences.

Effect of diet/nutrition on mental health

According to Beyer and Paynet [8], the effects of diet/nutrition on mental health are due to the fact that in order for the brain to function and maintain its morphology (structure) it is necessary to provide energy (constituting a significant part of the total energy contained in food) and a number of nutrients (lipids, vitamins, macro – and micro-elements, antioxidant reactions cofactors, neurotrophic agents synthesis catalysts and many others). Hence, the manner of nutrition and the closely related development of food habits indirectly influence the origination and progression of many mental disorders, and thus could also be the target of therapeutic intervention and prevention.

The increased interest in these issues in various fields of study (human nutrition, food biochemistry, nutrigenomics, psychiatry) has led to the development of a separate trend in research – the so-called nutripsychiatry emphasizing the role of diet in the development, progression, and effectiveness of the treatment of mental disorders [9]. Most of the research published to-date is about the role of nutrition and nutrients in the development and treatment of depression. The results have indicated a relationship between diet and the risk of developing depression. Meta-analysis of observational studies shows that the Mediterranean-style diet has protective effects against depression (as well as stroke), while dietary habits defined as the Western dietary pattern increase the probability of depression [10, 11]. In a meta-analysis by Lai et al, a diet rich in fruits, vegetables, and fish was linked to a reduction in the risk of depression, and a diet with a higher carbohydrate content and a high content of high-processed products was associated with a higher risk of it occurring [12]. A systematic review of randomized clinical trials (RCT) has indicated a positive effect of dietary intervention on reducing depressive symptoms [13]. The results of RCT, recently published in the *BMC Medicine* journal, have shown that significantly better outcomes were achieved in patients with depression (treated with pharmacotherapy or psychotherapy) in the group that included diet counseling compared to the group offered social support [14].

Taking into account individual dietary components and their effects on depression, beneficial effects in the treatment of depression have been demonstrated with the use of omega-3 fatty acids [15], zinc [16, 17], N-acetylcysteine [18], B vitamins (including folates) [19], vitamin D [20]. There are still no well-planned and performed interven-

tion studies in large patient groups that would allow for greater statistical output of published results and thus reliable, unequivocal information.

So far, few studies have looked at the relationship between diet and BD, although it can be assumed that some of the observations about people with depression may be related to patients with BD. In a review of such studies [21] (until February 2015), Lopresti and Jacka discussed the results presented in five articles. A review of the literature carried out by the authors after two years (until February 2017) did not disclose new articles in this field.

Elsmlie et al. [22] have found that BD patients consume more carbohydrates, and BD women also have a higher total energy intake. Larger seafood consumption has been associated with a lower incidence of BD in a study conducted by Noaghiula and Hibbelna [23]. Kilbourne et al. [24] reported that data from the National Veterans Registry has indicated that people with BD more frequently reported eating only one meal per day and having difficulty in sourcing food and cooking. In an Australian study, patients with BD had a higher energy consumption rate and more often consumed products typical of Western diets [25]. In ambulatory BD patients in Japan, a higher symptoms severity has been observed in the group who reported less frequent consumption of Mediterranean diet products [26].

The review authors have emphasized that the interactions between diet and BD are not fully understood. Perhaps the improper diet in BD has a causal meaning, may aggravate the course of the disease, may also be part of the lifestyle. There is a relationship between the pharmacological treatment used in BD and obesity [27], so this improper diet may be the result of undesirable drug effects. Preferred consumption of sugar-rich and fatty products by patients with BD has been seen by Lopresti and Jacka [21] as self-medication (sugar can reduce stress-induced cortisolemia, which is often seen in patients with BD). The diet-BD interaction is probably complex and multi-factorial.

Importance of diet in BD

The comorbidity of somatic diseases and BD described above is associated with therapeutic difficulties, drug resistance and a more severe course of BD [28]. In this context, the right diet/nutrition in BD may lead to a reduction in the risks associated with diet-related diseases, but may also have a beneficial effect on the course of BD. For example, patients with BD and type 2 diabetes or glucose intolerance show a greater risk of adverse (chronic) BD than patients without glycemic control disorders [29] and weight changes (loss and gain) are associated with the incidence of manic and depressive phases [28].

Diet (its composition and quality) may also cause/sustain biological disorders associated with the onset, development, and treatment of BD. We include among them monoaminergic transmission, inflammatory processes, oxidative stress, mitochondrial

activity, neuroplasticity and neurogenesis [21, 30, 31]. Numerous preclinical studies indicate the effect of diet/nutrition on these mechanisms, although such correlations have not been established in BD studies.

The monoaminoergic theory assumes the importance of serotonergic, noradrenergic, and dopaminergic transmission disorders in the pathogenesis of affective disorders. Animal studies have shown that high-fat diets may directly affect monoaminoergic transmission [32, 33]. Such diets in animals also caused ineffectiveness of fluoxetine in the treatment of stress-related behaviors [34]. In humans, high-fat diets with high carbohydrate snacks reduced serotonergic transmission in the hypothalamus [35]. The reported positive effect of ketogenic diet on mood stabilization in BD [36] may be related to an increase in dopaminergic activity in the mesolimbic system [37]. In recent years, attention has been paid to the importance of inflammatory processes in the pathogenesis of BD [38, 39]. Mediterranean diet and increased intake of fruits and vegetables are associated with decreased inflammation [40, 41], whereas diets dominated by Western dietary patterns are considered "pro-inflammatory" diets associated with an increased concentration of inflammatory markers such as interleukin-6 and C-reactive protein [42].

Brain-derived neurotrophic factor (BDNF) affects the growth and differentiation of neurons. There was an increase in serum BDNF levels in people using the Mediterranean diet [43] and the influence of dietary components (zinc and flavonoids) on BDNF activity [44]. Animal studies have demonstrated a decrease in BDNF expression in the brain and a deterioration in the quality of new hippocampal neurons produced in rodents on the high-fat diet [45, 46]. In a review of the literature on the diet/nutrition of animals and humans [47], it has been found that diet composition (fat and carbohydrate content), frequency of food consumption and their calorific value affect neurogenesis in the hippocampus. In longitudinal studies conducted in Australia by Jacka et al. [48], a reduced volume of the left hippocampus was found in people who ate according to the so-called "Western diet" compared to those who ate properly.

Oxidative stress and mitochondrial dysfunction are also associated with BD pathogenesis. Beyer and Payne [8] point out that the brain is an organ whose function and structure are largely dependent on the energy supplied, and damage to the mitochondria (responsible for the neuron's energy production) may lead to increased oxidative stress, further damaging mitochondria. Studies show that diets may significantly influence mitochondrial function by reducing oxidative stress and protecting mitochondrial DNA from oxidative damage. Mediterranean diet and increased fish intake are associated with decreased levels of oxidative stress markers in serum [49] and urine [50]. Animal studies indicate that a ketogenic diet can protect mitochondria from exposure to oxidative stress [51].

Nutrients, vitamins, micronutrients in bipolar disorder

The role of selected nutrients in the development, progression and potential treatment of BD has been discussed by Beyer and Payne in 2015 [8]. Studies in this area are few, conducted in small groups, non-randomized. These restrictions apply to studies on the use of various diets and the studies of the effects of particular nutrients (including dietary supplements) on BD. The results obtained so far are ambiguous, with little practical potential.

In recent years, a lot of attention has been paid to nutraceuticals, which are nutrients that, through their involvement in metabolic processes, have a proven and beneficial effect on health and are used in treatment. Sarris et al. [52] in 2011 carried out a systematic review of the literature on the use of nutraceuticals in the treatment of BD and subsequently, in 2017, on the use of nutraceuticals in the treatment of depression, including depression in BD [53]. In 2014, Rakofsky and Dunlop [54] divided the nutrients used as nutraceuticals into two groups: essential nutrients, that is, those that people need to obtain from the diet (e.g., omega 3, folic acid), and nonessential ingredients (e.g., n-acetylcysteine, inositol). Nutraceuticals may work in similar mechanisms such as normotimics (lithium salts, valproates), perhaps in some patients nutraceuticals provide (or allow to reproduce) missing components to maintain their physiological concentrations. It is also possible that, by supplementation, an increased amount of a particular compound leads to intracellular responses, which results in a reduction in the severity/relapse of the disease. It is believed that an additive or synergistic effect of nutraceuticals with normotimics is possible [54].

Based on the literature of the aforementioned reviews [52–54], we present selected compounds that are implicated in the pathogenesis, progression, and treatment of BD.

Polyunsaturated omega 3 (PUFA omega 3) (eicosapentaenoic, docosahexaenoic) fatty acids are essential for brain development and function, including neuronal maturation, migration and synaptogenesis, plasticity, neurogenesis, and neurotransmission [55]. It is stressed that in the western diet there is too little omega 3 fatty acids. A number of epidemiological and intervention studies have concerned the relationship between consumption of products that are the source of PUFA omega 3 in diet or supplementation with these acids and the occurrence or severity of depression [56]. There are also studies showing that it is advisable to increase the content of this ingredient in the diet of BD patients (see also study summary in [8]). In the treatment of depression, doses of 1–2 g eicosapentaenoic acid daily have been used to reduce the symptoms of depression, including bipolar one [53]. Although we have no clear evidence of their therapeutic effect in BD, it is indicated that PUFA omega 3 have no side effects and their consumption is beneficial to general health.

One of the major endogenous antioxidant compounds in the brain is glutathione. Oral supplementation of glutathione alone is not effective (it is mostly hydrolyzed and weakly penetrates the blood-brain barrier), but it has been found that N-acetylcysteine

(NAC) should be given. NAC provides l-cysteine essential for the synthesis of glutathione, but it also exhibits antioxidant activity itself [57].

In clinical trials, patients with BD have been given either 500 or 1000 mg of NAC twice daily for standard treatment for acute depressive episodes and during the maintenance therapy period, with a reported reduction in symptoms of depression and improved functioning and quality of life [58, 59]. Although NAC is well tolerated, chronic tolerance data are limited.

Systematic reviews with meta-analysis have confirmed the association of low vitamin D levels with depression [60] and have demonstrated the efficacy of vitamin D supplementation in reducing the symptoms of depression in patients with clinically more severe depression [61]. This has not been reported in individuals with symptoms of mild depression [62]. However, the authors of the review indicate that there is still no clear evidence from controlled trials concerning the use of vitamin D in the prevention and treatment of depression to determine whether this association is not accidental. There are very few studies on the role of vitamin D in patients with BD although it has been established that vitamin D deficiency in the outpatient group of patients with BD is 4.7 times higher than in the general population [63].

It is believed that folic acid and other folates can be important in the treatment of depression, which is explained by, among others, their contribution to the synthesis of neurotransmitters and the effect on DNA methylation [64]. Many studies have reported that people with depression have lower plasma and erythrocyte folate concentrations compared to healthy individuals and patients with other mental disorders [65]. Lower folate levels have been associated with a worse response to pharmacological antidepressant therapy. It should be remembered that the effectiveness or ineffectiveness of folic acid can be attributed to the chemical form of this vitamin – since folic acid, unlike natural folate, must be converted into a metabolically active form to cross the blood-brain barrier and approximately 30% of the population has a genetically determined deficit of the enzyme necessary for this transformation [66]. It is recommended to consider the administration of folic acid in the form of levomefolic acid which is more bio-available and thus possibly more effective [67]. Studies on the concentration of folic acid and its intake in BD patients are very few. Some authors report that conclusions from the studies of patients with depression [68] may also be relevant to patients with BD. A study of augmentation of lithium with folic acid (200 μg/d) in BD treatment has been conducted, its authors proposing considering supplementation with folic acid during the maintenance therapy [69]. In 2009, Behzadi et al. [70] presented encouraging results of the addition of folic acid to valproates used in the treatment of mania. Recently published studies have described the beneficial effects of the addition of levomefolic acid to standard treatment in a group of ten patients with type I bipolar disorder suffering from depression. [71].

An essential role in the pathogenesis of affective disorders is also attributed to the circulation (delivery, absorption, intra – and extracellular concentrations etc.) abnor-

mality of some micronutrients. Research results show that the levels of micronutrients in BD patients differ from controls, but within normal limits. In patients with BD, reduced zinc levels have been observed in the depressive phase, but in the mania/hypomania period, serum zinc concentrations were similar to healthy subjects [72]. Serum magnesium concentrations in patients with BD during periods of depression, mania and hypomania were significantly higher in comparison with healthy subjects, while in the remission period they normalized and did not differ in comparison to the control group [73]. There were no statistically significant differences in the serum copper concentration between patients in various phases of BD and controls. Most of the participants have copper level within normal range. The copper concentration was related to the number of episodes – lowering with the increasing number of episodes [74].

There are no known results of controlled studies of zinc or magnesium intake in the treatment of BD. In the treatment of depression, 15–30 mg of zinc has been added daily to the antidepressant [53].

Many reports have highlighted the good tolerance of nutraceuticals and the low rate of therapy abandonment. However, the potential for interactions, side-effects, over-dosage, and, as mentioned above, the lack of data on the long-term effects of their use in treatment should not be forgotten. An impediment in evaluating the effect of nutraceuticals is that most of these are not registered drugs and the content of active ingredient in particular preparations may vary widely. It seems that in considering the diet in BD it is also important to assess not only what the patient's diet contains but also what has been excluded, because both what is and what is not consumed affects the body. Finally, it is important to note that research into the relationship between diet and psychiatric disorders raises issues such as microbiota [75, 76], starvation (ketogenesis) [77], the effect of fermented foods [78], the use of functional foods (such as so-called psychobiotic yoghurts) [79, 80], but we are not aware of studies of these factors in patients with bipolar affective disorder.

As the Australian psychiatrists emphasize in their extensive guidelines for the treatment of mood disorders [81], it is important to consider the subjective feeling of the patient that the use of supplementation of selected nutrients, microelements, and dietary modifications in the treatment of BD (apart from pharmacotherapy) is beneficial. For some patients, the possibility of such an active participation in treatment gives a sense of coping, a sense of control [82].

Conclusions/recapitulation

In recent years, interest in the importance of diet and its components in the pathogenesis, treatment and even prevention of BD has increased. Diet, eating habits, taking into account the contribution of nutrients with a possible beneficial effect on BD treatment, are potential goals of intervention – –nutrition counseling – in the treat-

ment of BD. Unfortunately, there is still a lack of well designed, long-term follow-up studies in large patient groups that provide reliable and unequivocal information on the effects of selected BD nutrition strategies. It appears, however, that the obtained data are sufficient for assessing possible nutrient deficiencies and dietary habits in BD patients and for considering supplementation or dietary modifications (with obvious known benefits to somatic health). At the same time making changes in diet can improve the effectiveness of BD treatment by increasing the patient's sense of control and coping. Further nutritional studies in BD are needed to clarify the extent to which past dietary habits of patients and the introduction of dietary interventions may affect the pathophysiology, progression and treatment of this illness.

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