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Nutritional supplements in eating disorders

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Eating disorders (EDs) are a series of differentiated nosological entities sharing the common link of a continuous alteration in food intake or in food intake-related behavior.

Within this classification, the following disorders are noteworthy: anorexia nerviosa (AN) and bulimia nerviosa (BN). Anorexia nervosa is a chronic disorder characterized mainly by negative or decreased food intake accompanied by a distortion of body image and intense accompanying fear of weight gain. The estimated vital prevalence of this disorder in adolescence is approximately 0.5%-1%.1 The primary feature of BN is the presence of binge eating accompanied by compensatory behavior (in the form of intense exercise and the use of laxatives and diuretics, etc.). The prevalence of BN is estimated to be between 2% and 4% in young women, and it generally starts at somewhat later stages than AN.

It is believed that biological, psychological, and environmental factors, as well as genetic vulnerability, influence the pathogenesis of EDs. A variety of therapies exist, both biological and psychological, whose effectiveness is supported by the scientific literature. Nonetheless, we find these therapies only partially effective and new targets as well as new treatments should be sought. Although the etiopathogenesis of EDs is unclear, some of the neurobiological dysfunction found suggests that diet and nutrient supplementation could be relevant in their treatment. We review in this article new treatments focusing on nutritional deficits.

Keywords: Anorexia Nervosa, Bulimia Nervosa, Tryptophan, Omega 3 Fatty Acids

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Suplementos nutricionales en trastornos de la conducta alimentaria

Se consideran Trastornos de la Conducta Alimentaria (TCA) a una serie de entidades nosológicas diferenciadas que tienen como nexo común una alteración continuada en la ingesta o bien en la conducta relacionada con la ingesta.

Dentro de dicha clasificación destacan los siguientes trastornos: Anorexia Nerviosa (AN) y Bulimia Nerviosa (BN). La AN es un trastorno de curso crónico caracterizado principalmente por una negativa o disminución de la ingesta acompañado de una distorsión de la imagen corporal con el consecuente miedo intenso a la ganancia de peso. Se estima una prevalencia vital en la adolescencia de dicho trastorno de aproximadamente el 0,5-1%1. En la BN la presencia de atracones de comida y la posterior conducta compensatoria (en forma de ejercicio intenso, uso de laxantes, diuréticos…) es lo que prima en el paciente. La prevalencia se estima entre un 2 y un 4% en mujeres jóvenes, iniciándose generalmente en etapas algo posteriores que la AN.

Se cree que en su patogenia influyen factores biológicos, psicológicos y ambientales así como una cierta vulnerabilidad genética. Existen distintos tratamientos con eficacia avalada por parte de literatura científica, tanto terapias biológicas como psicológicas, a pesar de ello, nos encontramos con una efectividad parcial de dichas terapias siendo necesaria la búsqueda de nuevas dianas así como de nuevos tratamiento. Aunque la etiopatogenia de los TCA no esté clara, algunas de las disfunciones neurobiológicas encontradas permitirían considerar que la dieta y la administración de nutrientes podría ser relevante en el tratamiento de estos trastornos. Proponemos en este artículo una revisión de nuevos tratamientos enfocados al déficit nutricional.

Palabras clave: Anorexia Nerviosa, Bulimia Nerviosa, Triptófano, Omega 3

INTRODUCTION

The relevance of anorexia nervosa, bulimia nervosa, and unspecified eating disorders among psychiatric disorders has grown in the last decade due to the high frequency, increasing incidence, seriousness, and clinical and social transcendence of these disorders.

Eating disorders (EDs) are a series of differentiated nosological entities sharing the common link of a continuous alteration in food intake or in food intake-related behavior.[1] Within this classification, anorexia nervosa (AN) and bulimia nervosa (BN) are noteworthy conditions.

Anorexia nervosa is a chronic disorder characterized mainly by negative or decreased food intake, a distortion of body image, and intense fear of weight gain. The estimated vital prevalence of this disorder in adolescence is approximately 0.5%-1%.[1] AN includes two subtypes, the restrictive subtype, in which binge eating and forced purging are not features, and the type characterized by binge eating and/or purging behavior.

In BN, the existence of binge eating accompanied by compensatory behavior (in the form of intense exercise and the use of laxatives and diuretics, etc.) is foremost in patients. Binge eating is defined as the consumption in a short period of time of a much greater quantity of food than what most people would eat. The prevalence of BN is estimated to be between 2% and 4% in young women, and BN generally starts at somewhat later ages than AN.[1]

Unspecified EDs are disorders that share clinical characteristics with the above disorders, but do not fulfill all the criteria laid out in the manuals in use.

All EDs have significant organic impact (reaching mortality rates of up to 5.1 deaths/1000 people in AN), including cachexia and cardiac, digestive, or neuropsychiatric disorders.[1,2] Some of these complications are related to deficiencies of certain micronutrients.[3-5]

Despite the importance and social impact of AN and BN, the etiology of these conditions remains unclear, although biological, psychological and environmental factors, as well as genetic vulnerability, are known to influence pathogenesis. Although the etiopathogenesis of EDs is unclear, some of the neurobiological dysfunction found suggests that diet and nutrient supplementation could be useful in the treatment of these disorders.

NEUROBIOLOGICAL BASES OF EATING DISORDERS

Due to the important social and health impact of this group of diseases, their psychobiological aspects have been thoroughly investigated in recent years with the aim of identifying predisposing, precipitating, and maintenance factors. However, malnutrition, electrolyte imbalances, and the frequent comorbidity of AN and BN with anxiety, mood disorders, or personality disorders, among others, make it difficult to find biological markers.

We will review some of the biological mechanisms that seem to be involved in the etiopathogenesis of EDs, with special emphasis on serotonergic dysfunction, which appears to be one of the most relevant abnormalities in these disorders.

NEUROTRANSMISSION IN EATING DISORDERS

A variety of neurotransmitters are involved in the regulation of appetite (Table 1). Specifically, serotonin tends to inhibit appetite, whereas norepinephrine tends to stimulate it (Table 2). In experimental studies in animals, it has been observed that massive food intake is associated with serotonergic hypoactivity, α2-noradrenergic hyperfunction, or both.[6] Another neurotransmitter apparently involved is dopamine, which decisively influences the satisfaction associated with food intake, which is usually altered in eating behavior disorders.[7]

Serotoninergic neurotransmission

Serotonin (5-HT) regulates the circadian rhythms of feeding by acting on the choice of macronutrients and on the mechanisms that regulate satiety. The administration of serotonergic agonists, both central and peripheral, leads to decreased food intake.[6] Changes at the level of 5-HT neurotransmission could account for the symptoms of anxiety, depression, impulsivity, or altered appetite typical of the eating disorders.[8-10]

Serotonin and the role of this molecule in the etiology and maintenance of EDs have been extensively investigated. Some data suggest that dieting originates greater deficits in tryptophan, the 5-HT precursor, in females than in males. This may explain why EDs are more common in females and may also relate to the fact that diet is the most important risk factor for the development of such disorders.[11] On the other hand, different studies have found lower levels of plasma tryptophan in EDs.[12-14] Some typical symptoms of EDs, such as the anxiety preceding binge eating, depressive symptoms, and feelings of hunger, increase with lower tryptophan levels.[15] This is related to the fact that plasma tryptophan levels are directly related to serotonin levels in the central nervous system and, consequently, lower tryptophan levels entail a deficit in serotonergic function.[16] Among patients with EDs, patients with BN seem to be more

Table 1 Relation between neurotransmitters and food intake

	SITE OF ACTION	EFFECT ON FOOD INTAKE
NOREPINEPHRINE		
α2 agonists	ventromedial hypothalamus	general increase
β agonists	perifornical region	reduction in carbohydrates
SEROTONIN		inhibition of food intake
1B agonists	ventromedial hypothalamus	reduction in carbohydrates
DOPAMINE		hedonic response
D2 agonists	perifornical region	overall decrease
Antagonists	perifornical region	increase in proteins
D2 agonists	brown fat	increased thermogenesis
GABA		
Agonists 1 and 2	all	overall increase
Partial antagonist	all	decrease in sweet carbohydrates
GALANIN		
Brief effect	ventromedial hypothalamus	increase in carbohydrates
Prolonged effect	ventromedial hypothalamus	increase in fats

Table 2 Antagonistic effects of the serotonergic and α2-noradrenergic systems on the hypothalamus

	Noradrenalina	Serotonin
Total food intake	+	–
Weight	+	–
Protein intake	–	+
Carbohydrate intake	+	–
Amount of food ingested	+	–
Frequency of food intake	no effect	no effect
Duration of food intake	+	–

vulnerable to the effects of lower plasma tryptophan levels, presenting more impulsivity, less ability to control food intake, and more symptoms of anxiety and depression, possibly related to the 5-HT hypofunction resulting from the tryptophan deficit.[17-20]

In AN, it is suggested that 5-hydroxyindolacetic acid (5-HIAA), a serotonin metabolite, decreases in the acute phases of AN, returning to normal levels with weight gain.[21] It could be hypothesized that the people who eventually manifest AN have a biological susceptibility in the form of a serotonergic activity dysfunction that can be destabilized by malnutrition. However, increases in 5-HIAA in cerebrospinal fluid (CSF) have also been reported, which could be associated with the presence of personality traits such as obsessiveness and perfectionism. Studies of peripheral serotonergic activity are also inconclusive. Research on plasma 5-HT levels, 5-HT reuptake and release, paroxetine receptor density, and monoamine oxidase activity, among other topics, has not clarified this issue as some findings indicate serotonergic hypofunction and others show no alteration.[8,21,22] Our group found that platelet MAO levels were approximately 40% lower in patients with EDs compared to control subjects.[9] Accordingly, most of the results of neuroendocrine stimulation tests (flattening of the prolactin response following the administration of serotonergic agonists) seem to indicate the existence of hypofunction.[10,23,24] At the pharmacological level, selective serotonin reuptake inhibitors (SSRIs) are useful in preventing relapses.[25]

In BN, most of the research points to diminished serotonergic activity. Several hypotheses have been proposed based on this model. For instance, pre-existing serotonergic dysfunction may predispose to BN. Another possibility is that BN is due to the nutritional changes derived from sustained food restriction and binge eating. Finally, it has been suggested that purging and binge eating behaviors could be due to the impulsivity of these patients. In this sense, impulsivity has been associated with serotonergic hypoactivity, as BN has been associated with the decrease in serotonin with depressive symptoms, a greater number of episodes of binge eating, strong impulsivity and, in general,

more severe BN.[26] In addition, the presence of self-injury behavior in patients with BN is associated with greater serotonergic dysfunction as measured by the response to the partial agonist m-CPP, which in patients with BN without this comorbidity again indicates the presence of more dysfunction in the most impulsive patients.[27] Consistent with these findings, substance abuse, impulsive behaviors, and depression often appear concurrently with BN. Some authors even suggest that the frequent association of BN with borderline personality disorder (BPD) could be related to the serotonergic hypofunction that appears in both entities, which is associated with impulsivity and affective instability.[28,29]

In studies of the serotonin metabolite 5-HIAA in cerebrospinal fluid, a negative correlation is observed between the frequency of binge eating and purging behaviors in BN and 5-HIAA levels.[30] However, some subsequent studies have not found evidence to support this hypothesis and it has been seen that in patients with BN in the recovery phase, CSF 5-HIAA levels were increased compared to controls.[31]

At the peripheral level, diverse investigations have been undertaken in BN to assess serotonergic activity in platelets. Studies on serotonin reuptake by platelets, platelet serotonin release, and the stimulation of 5HT receptors have not been conclusive.[2] With regard to platelet MAO, a marked decrease in activity has been observed in patients who practice more binge eating or have a more impulsive temperament.[34] The results obtained by our group confirm these findings, as there was more serotonergic hypofunction in patients with more severe BN, as shown by a greater decrease in platelet MAO.[9]

Neuroendocrine tests carried out in patients with BN indicate a decrease in serotonergic activity at both the pre- and postsynaptic levels, as demonstrated by the flattening of prolactin secretion after the administration of L-tryptophan, m-CPP, D-fenfluramine, and 5HT.[35] In stimulation with D-fenfluramine, it has also been observed that flattening of the prolactin response is more pronounced as the frequency of binge-eating increases.[36] Several investigations have evaluated the effects of an acute transient serotoninergic deficit induced by the tryptophan depletion test, and it was observed that depletion is associated with intensification of the typical BN symptoms, which supports the existence of central serotonergic dysfunction.[17,37]

To conclude, we point out the effectiveness of drugs that act by modifying serotonergic hypoactivity in EDs. SSRIs have proven useful in the treatment of BN and in the prevention of relapses in AN.[38-40] In fact, a positive correlation has been found between the normalization of 5-HT transmission and a reduction in binge-eating.[29]

Specific symptoms related to serotonergic dysfunction

- **Anxiety/Obsessive Symptoms/Depression**

  There is a known relation between anxiety and depressive symptoms and serotonergic dysfunction, and these symptoms are also identified in patients with AN and BN. In addition, malnutrition may enhance the reduction in 5-HT levels.[41-45]

- **Body image**

  The serotonergic system seems to be related to the modulation of memory. In this sense, different alterations in the 5-HT2A receptor have been observed that could be related to the tendency of patients with EDs to:

  • Pay more attention to external memories, which conditions their sensitivity to criticism.

  • Remember events with intense emotion.

  • Have reduced ability to inhibit memories.

  This dysfunction causes patients diagnosed with ED to consolidate negative memories of themselves and to have difficulties in inhibiting bad memories. In addition, it has also been observed that they have difficulties in recovering their own memories and are more affected by things outside the personal realm. These difficulties may explain, in part, the alteration in perception and distorted body image of these patients, although more studies are necessary to confirm this hypothesis.[46-49]

- **Impulsivity**

  Impulsivity is a multidimensional personality trait with a complex etiology. Among the EDs, patients with purging and binge-eating behaviors (BN and compulsive purging AN) are typically more impulsive. Impulsive behaviors have been associated with alterations in the serotonergic circuits: decreased serotonin in the prefrontal cortex is associated with hypoactivation of the 5-HT1B and 5-HT2A receptors, as well as serotonin transporter dysfunction.[50-54] In addition, a disturbance in the cortico-limbic and cortico-striatal circuit, which are also dependent on serotonin, has been suggested.[55,56]

Noradrenergic neurotransmission

Norepinephrine has a role in regulating appetite by acting on the hypothalamus to enhance food intake, acting on the α2-noradrenergic receptors. In this sense, it has been suggested that binge eating may depend on α2-noradrenergic hyperactivity of hypothalamic origin.[57] However, noradrenergic activity may be affected by other factors, such as intermittent dieting, malnutrition, physical activity, mood

disorders, water and electrolyte balance abnormalities, and neuroendocrine systems.[7]

A decrease in noradrenergic activity has been observed in both AN and BN, as indicated by low levels of norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in plasma, urine, and CSF. A flattening of the norepinephrine response to different stimuli has also been observed.[58] These disturbances normalize with weight recovery in most patients. In some patients with AN in remission, decreased norepinephrine levels persist in the CSF, indicating the existence of dysfunction prior to the onset of the disease.[59,60]

Dopaminergic neurotransmission

The dopaminergic system is associated with feelings of pleasure and reward, and with the positive hedonic processes referred to food, sexual activity, and certain substances, so dopaminergic dysfunction could explain the disturbance in this hedonic response in EDs.[61]

However, there have been no relevant findings to date. In patients with BN, one of the metabolites of dopamine, homovanillic acid, is decreased.[61] In a study in which the levels of HVA, the major dopamine metabolite, were measured in CSF, lower HVA levels were found in restrictive AN than in controls, compulsive-purging AN, and BN.[62] In functional tests, data have been found in AN that suggest dysfunction in the regulation of negative feedback. In patients with BN and no history of anorexia, a lower dopamine response was observed after clonidine stimulation, which did not occur in patients with a history of anorexia.[7] The bulimic episodes could be the consequence of a dysfunction in the dopaminergic system producing a decrease in the hedonic response to food intake. In studies carried out in recent years, the existence of dopamine hypersecretion at the presynaptic level, accompanied by a decrease in the sensitivity of the hypothalamic postsynaptic D2 receptors, has been proposed.[62]

THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

Hypercortisolism is a common finding in AN,[63] although its etiology is still unknown. The competence and functioning of the hypothalamic-pituitary-adrenal axis (HPA) have traditionally been evaluated using the dexamethasone suppression test (DST), and this axis has commonly been considered the biological transducer of the stress response. In patients with AN, it has been observed that there is no inhibition of the axis after DST.[64] Both normal and increased cortisol levels have been found in BN, and the results of functional tests are inconclusive.[9, 65]

On the other hand, a history of trauma has been associated with HPA axis abnormalities. Recently, new interest in DST has arisen thanks to the discovery of cortisol hypersuppression in post-traumatic stress disorder.[66] This finding is interpreted as an enhanced response to the usual stressful stimuli. It may also serve to characterize learned responses as manifestations of intolerance of stress, which also characterize impulsive personalities, such as BPD and impulsive forms of ED.[67] In fact, the findings in patients with BPD reveal a tendency to manifest hypersuppressive responses similar to those of post-traumatic stress disorder.[68,69]

These data allow a relation to be established between trauma and HPA axis dysfunction in these patients that is the opposite of what is found in depression.

GENETIC FACTORS

The data currently available allow us to affirm that there is a genetic vulnerability in EDs; a high concordance is found in homozygous twins that reaches up to 80% in some studies.[70-78] Various genes have been studied with inconsistent results: dopaminergic[79] and serotonergic[80] receptor genes, and the genes implicated in obesity.[81] Nonetheless, the relation with serotonergic dysfunction is evident in these disorders and it appears that the modifications in the gene encoding the serotonin transporter and the 5-HT2A receptor gene may be the most closely related.[82,83]

INFLAMMATORY FACTOR DYSFUNCTION IN EATING DISORDERS

A new line of research has recently opened in EDs and other mental disorders, involving the role of inflammation in their etiology.[84,85]

Our group has found a dysfunction in the inflammatory cascade in EDs that is greater in patients who are more impulsive and have a history of trauma, which would imply an increase in oxidative stress in these patients that could be managed by administering antioxidant products to regulate this function.[86]

OMEGA 3 FATTY ACID DISTURBANCES

Patients with EDs have a complex profile of membrane fatty acids. They do not have deficits in essential fatty acids, but they do have deficits in long-chain polyunsaturated fatty acids. Some studies support the idea of adipose tissue as a source of endogenous fatty acids capable of compensating the decreased intake of essential fatty acids, but unable to compensate for the deficit in the intake of polyunsaturated fatty acids such as omega 3 or omega 6

fatty acid.[87] Other psychiatric disorders, such as major depression, bipolar disorder, schizophrenia, or attention deficit and hyperactivity disorder, also seem to be associated with a deficit in omega 3 fatty acids that could be involved in the pathogenesis of these disorders.[88] In EDs in which there is also inadequate dietary intake, the deficit in omega 3 fatty acids may increase.[87,89,90]

Given the role of the omega 3 fatty acids in the control of inflammation and protection against oxidative stress, a deficit in omega 3 fatty acids could be related to findings indicating an inflammatory dysfunction and increase in oxidative stress in different psychiatric disorders, including EDs, as was pointed out earlier. Therefore, it is postulated that the administration of polyunsaturated fatty acids may act to prevent neuronal damage, as in other mental disorders, stabilizing the cell membrane and acting as an anti-inflammatory agent.[91]

In the EDs, neurocognitive alterations, difficulties in processing and executive function, and in emotional processing are identified that may depend on disorders in the different systems involved.[92-94]

NUTRITIONAL DEFICITS IN EATING DISORDERS

Given the role of some nutrients in common symptoms in patients diagnosed with EDs, we consider it important to point out the main nutritional deficiencies that we find in this type of patients.

The pattern of food intake of patients with EDs is erratic and conditions altered neuronal mechanisms in the dorsal striatum and its connections with the frontal circuits.[95] Decreased brain volume and thinning of the cerebral cortex have also been reported in relation to these patterns.[96] These behaviors imply a deficit in both AN and BN of different nutrients: electrolytes, vitamins, and minerals, among others.[3]

- **Electrolyte disturbances:** Electrolyte abnormalities are a consequence of purgative behaviors, such as self-induced vomiting and incorrect use of laxatives, diuretics, or enemas. Vomiting may cause hypokalemia and/or hypochloremic alkalosis. Laxative abuse can cause hypomagnesemia and hypophosphatemia. These anomalies may require emergency supplementation to address individual needs.[3]

- **Calcium**: Hypocalcemia is common in patients diagnosed with ED. Calcium insufficiency is often not reflected by the plasma calcium levels, as the body's homeostasis tends to rely on the calcium in bone to compensate for plasma calcium deficits. This means that poor bone density is an indicator of long-term calcium deficits.[97]

- **Phosphorus.** Hypophosphatemia is a complication more typical of supplementation than of the nutritional deficit derived from restrictive or purging behavior in EDs. This complication is easily detectable and treatable, but extremely serious if not detected in time. Predictors of this complication are low body mass index (BMI), hypokalemia, low blood prealbumin levels, and high hemoglobin levels.[3,98,99]

- **Iron.** The nutritional poverty of the diet normally followed by patients with EDs may result in low plasma iron levels. In addition to diet, erythrocyte hemolysis in these patients may also contribute to iron deficiency.[100]

- **Vitamin A or retinol.** There is controversy regarding the data on retinol abnormalities in patients with EDs.[101] Elevated serum vitamin A levels are attributed to inadequate intake of other nutrients required for vitamin A metabolism. Decreased levels are associated with inadequate vitamin A intake.[3]

- **Vitamin B1 or thiamine.** Food restriction can lead to low plasma thiamine levels. This deficit can cause varied neuropsychological symptoms, such as worsening of depressive symptoms. These symptoms are more serious in conditions with comorbid ethanol abuse.[102]

- **Vitamin B9 or folic acid.** Folate deficiency has been reported in patients with EDs.[3] This vitamin is essential for human growth, nerve function, and for reducing levels of the amino acid homocysteine. Folate requirements increase in pregnant women, as folate helps in the growth of the fetus and placenta, as well as in preventing possible developmental defects.

- **Vitamin B12 or cobalamin.** Short-term cobalamin deficiency can produce symptoms of anemia (fatigue or weakness), or affective symptoms. Long-term deficiency is related with brain damage.

- **Vitamin C.** This vitamin is necessary for the growth and repair of tissues in all parts of the body and acts as an antioxidant.[3] The majority of fruits and vegetables contain vitamin C.

- **Vitamin D.** Anorexia nervosa is associated with loss of bone mass. This is the consequence of attaining an insufficient peak bone mass in adolescence followed by subsequent loss in the early adult years. An Italian study found a strong relation between vitamin D values and bone mineral density (BMD). Levels of 25OHD in excess of 20 ng/mL are related to significantly higher BMD values.[99]

In addition to administering vitamins, calcium, and iron, which is logical given the neurobiological aspects of EDs and the consequences of disturbances in food intake, and

knowing that pharmacological treatment is only partially effective in these patients, it would be useful to propose additional therapeutic strategies aimed at reversing both the potential biological dysfunction and the deficits inherent to erratic diets. On the other hand, having demonstrated the need for long-term treatments in these patients, the administration of more natural dietary supplements may be better accepted and improve adherence in patients with impulse control issues.

From the pharmacological point of view, the drugs regulating the serotonergic system have been the most widely used because of the benefit they have on bulimic behaviors, rumination about weight, affective instability, and the anxiety-depression symptoms of these patients. It should also be taken into account that the doses of serotonergic antidepressants used in bulimic patients are much higher than those used in depression, so reinforcement with dietary supplements could contribute to better regulation of the pharmacological guidelines.

Following this line of thought, tryptophan supplements or food rich in tryptophan, an essential amino acid in the biosynthesis of serotonin, seems to be of particular interest in the treatment of AN and BN.[103]

Moreover, some data suggest that the response to antidepressants is worse if tryptophan is deficient.[104] In fact, some clinical guidelines are particularly relevant regarding the relation between tryptophan levels and certain clinical symptoms, as well as the clinical therapeutic usefulness of tryptophan. Although supplementation with serotonin precursors is not being considered as monotherapy at present, tryptophan supplements are recommended as adjunctive treatment. In this sense, tryptophan administration not only aims to normalize the neurobiological mechanisms involved in this disorder, but also makes pharmacological treatment with serotonergic drugs more effective.[105-107]

Given the role of the omega 3 fatty acids in the control of inflammation and protection against oxidative stress, omega 3 deficits could be related to study findings indicating an inflammatory dysfunction and increase in oxidative stress in different psychiatric disorders, among them EDs, as pointed out earlier. Numerous studies show nutrient deficiencies in depression, obsessive-compulsive disorder, bipolar disorder, schizophrenia, and eating disorders, and improved affective symptoms and impulse control with supplementation.[108-110]

Therefore, it is postulated that the administration of polyunsaturated fatty acids may act to prevent neuronal damage, as in other mental disorders, stabilizing the cell membrane and acting as an anti-inflammatory agent.[91]

Dietary sources rich in polyunsaturated fatty acids are oily fish, perilla oil, flax seeds, chia seeds, sacha inchi, cannabis, and walnuts, among others. Due to the difficulties patients have in achieving normal food intake, several studies have shown the usefulness of adjuvant treatment with omega 3 fatty acids, resulting in a significant improvement in symptoms, especially anxiety.[111-113] Therefore, most studies suggest that treatment with omega 3 fatty acids may be beneficial, although more study is needed in this area.[114]

Zinc is another element involved in different central nervous system processes. Its mechanism of action is unknown, but zinc is believed to be involved in neurodevelopment and in synaptic transmission, especially by GABA receptors.[115,116] The effects of zinc deficiency are similar to the clinical manifestations of EDs, especially AN. In adults, zinc deficiency causes weight loss, sexual dysfunction (amenorrhea in women and impotence in men), nausea, vomiting, and skin lesions.[117,118] Moreover, zinc deficiency has been reported in patients diagnosed with AN.[119] Various studies have shown the usefulness of zinc supplementation, and zinc treatment might be useful in EDs, but there is still insufficient evidence to support this recommendation.[105-107,120,121]

Finally, arginine has been identified as an essential amino acid with special relevance in the synthesis of nitrous oxide, although the evidence is still not abundant. Nitrous oxide has an important role in vasodilatation and numerous studies have reported a relation between arginine and cardiovascular accidents, as well as the possible usefulness of arginine as adjuvant treatment.[122-124] Arginine's role in EDs is related to the fact that mortality in these patients is often related to cardiovascular disturbances. Recent studies have focused on investigating the role of arginine in patients with EDs,[125] but few studies have been published to date and the patient samples are small. Consequently, the benefit of arginine supplementation in these disorders is still lacking in scientific evidence.

CONCLUSIONS

The possible neurobiological implications of eating disorders, nutritional deficits resulting from abnormal food intake in eating disorders, the partial efficacy of pharmacological treatments, need for long-term treatment, and the benefits of dietary supplementation in AN and BN seem particularly relevant. Dietary supplementation can contribute fundamentally to the potential normalization of serotonergic system function, and supplements such as tryptop han and polyunsaturated fatty acids can have anti-inflammatory effects.

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