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Nutritional supplements in depressive disorders

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There is increasing evidence about the role of nutrients in mental health. An adequate intake of nutrients contributes to better overall health and mental health in particular. Major depression is a severe mental illness with a high prevalence for which effective treatments exist but not in all cases the patient's remission is achieved. Therefore, it is increasingly aimed at optimizing the supply of nutrients necessary for adequate brain functioning as adjunctive therapy to antidepressant treatment in depressive disorders. In this article we review those nutrients that have been related to depression: Omega-3 fatty acids, B vitamins, s-adenosylmethionine, tryptophan, magnesium, zinc and probiotics.

Keywords: Nutritional supplements, Depression, Depressive disorder, Major depressive disorder

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Suplementos nutricionales en trastornos depresivos

Cada vez hay más evidencia que demuestra el papel de los nutrientes en la salud mental. Una adecuada alimentación contribuye a una mejor salud general y salud mental en particular. La depresión mayor es una enfermedad mental grave con una alta prevalencia para la que existen tratamientos eficaces pero no en todos los casos se consigue la remisión del paciente. Por ello, cada vez se apunta más hacia la optimización en la aportación de nutrientes necesarios para un adecuado funcionamiento cerebral como terapia coadyuvante al tratamiento antidepresivo. En este artículo revisamos aquellos nutrientes sobre los que se ha estudiado su implicación en dicha patología: ácidos grasos omega-3, vitaminas del grupo B, s-adenosilmetionina, triptófano, magnesio, zinc y probióticos.

Palabras clave: Suplementos nutricionales, Depresión, Trastorno depresivo, Trastorno depresivo mayor

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INTRODUCTION

The pharmacological approach to mental diseases has achieved a moderate decrease in the load of such diseases, but there is still much important room for improvement. Furthermore, the indicators point to an increase of such load worldwide in the coming years, that these data are generally underevaluated[1] and that the prevalence is considered to be greater due to the increased life expectancy and to better detection of the cases. The WHO indicates that major depression will be the second cause of incapacity in the year 2020, following ischemic heart diseases.[2] Major depressive is a serious disease having a high prevalence, although this varies according to the study considered. It has been estimated to be 13-16% during the lifetime for women and 5-8% for men.[3]

Within the developed world and increasingly more in emerging economies, the inhabitants are more overfed and also at the same time more undernourished, not even reaching the minimum daily requirements of different essential nutrients for the good functioning of our brain and body in general.[4] These deficiencies together with sleep alterations, alcohol consumption, tobacco, drugs and/or insufficient physical activity often lead to deficient health of the population.[5] One closely related aspect is the globalization of the food industry that has radically varied the diet of many persons with great repercussion on their health.[6]

The mechanisms by which nutrition affects mental health are varied: a) the human brain has a high metabolic rate, so that it uses an elevated proportion of nutrients and energy, b) its adequate structure and functioning depend on the adequate supply of nutrients such as amino acids, fats, vitamins, minerals and other micronutrients c) eating habits modulate the functioning of the immune system which in turn affects the risk of depression, d) the antioxidant defense system that has been observed to be altered in mental diseases functions with the support of cofactors and phytochemicals that we eat and e) neurotrophic factors,

with their important role in plasticity and neuronal maintenance, are affected by the intake of nutrients. Thus, the scientific evidence seems to consider diet as an added factor as well as one that is key to the approach of mental diseases. That is why it is necessary to wake up to the reality that deficient nutrition and/or chemical unbalance can be contributing to the appearance and/or maintenance of many of the mental diseases.

Considering this viewpoint, we are going to explore depression somewhat more in depth from the approach of an emerging discipline such as Nutritional Psychiatry.[5] In general, we need to extend our field of view and include depression among those diseases that include the presence of a poor diet among their possible etiological factors and whose symptoms we could attempt to improve with the use of an adequate diet and/or nutritional supplements.[7] It is also known that patients with depression have a greater likelihood of having a food intake that is low in amount and of poor quality. However, the reverse relationship has also been demonstrated since in both cross-sectional and prospective studies, it has been seen that a diet having better quality is directly related with a lower risk and lower prevalence of depression,[8] with an effect size that reveals clinical importance and not just a simple statistical significance.[5]

Up to now, treatments for depression (both pharmacological and psychotherapy) have been fairly efficient, although a subgroup of patients does not completely improve their symptoms and the functional remission is also not complete in a percentage of them. Thus, the nutrition approach in these patients would be a recommendable option.[9] For example, the remission rates with the use of a single first line antidepressant are 30 to 40% and it has been observed that use of coadjuvant therapies improves remission rates of depression. Currently, there is scientific evidence that supports the use of certain nutritional supplements (nutraceutics) as coadjuvant therapy for depression.[10]

In 2015, the "International Society for Nutritional Psychiatry Research" defined those nutrients as important for prevention or management of certain mental conditions, among them depression.[10] Standing out among these nutrients are omega 3 fatty acids, group B vitamins, s-adenosylmethionine (SAMe), tryptophan, magnesium, zinc and probiotics.

OMEGA-3 FATTY ACIDS

Omega-3 fatty acids (ω-3) are essential components of the cell membranes, the most representative ones being eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is the most abundant ω-3 in the brain since it accounts for 10-20% of all the fatty acids of its composition. The ω-3, characterized for having a double bond in position 3 of its molecule, has been shown to have certain antiinflmmatory activity, on the contrary to the ω-6 that are precursors of proinflammatory eicosanoids, such as prostaglandins and thromboxanes. It has been found that adequate nutritional support of ω-3 favors the cell membranes fluidity, which influences the correct functioning of the neurotransmission.[11] In fact, it has been verified that societies with elevated consumption of ω-3 have a lower incidence and prevalence of depression.[12]

DHA is associated with the stability of the neuronal membrane and with the functioning of the dopaminergic and serotonergic neurotransmission, which would connect it with its possible role in depressive symptoms. On the contrary, EPA has great importance in balancing neuronal and immune functioning since it antagonizes the arachidonic acid of the membrane and reduces prostaglandin E_2 synthesis (PGE_2).[11] This antagonism of PGE_2 leads to the reduction of the synthesis of the P-Glycoprotein that is involved in the resistance to antidepressant treatment, an antidepressive action mechanism that EPA shares with the amitriptyline, for example. Another possible action mechanism of ω-3 in depression is the regulation of the calcium flow through the calcium channels, which also stabilizes and provides fluidity to the cell membranes.[13]

Both EPA and DHA must be supplied to the individual externally through diet or nutritional supplements although, in general, the intake of ω-3 in the Western societies has drastically decreased in the last century, while the intake of ω-6 has increased, this increasing the ω-6/ω-3 ratio, resulting in a proinflammatory condition. Evidence indicates that a supplement with ω-3 could be an antidepressant treatment option[14] perhaps because of its capacity to offset the effect of the eicosanoids derived from a high intake of ω-6 and inhibit the secretion of proinflammatory cytokines, resulting in a decrease of the release of cortisol by the adrenal gland, affecting así a the mood changes associated with the cortisol levels.[13]

In fact, an abnormal composition of fatty acids in the cell membranes has been found in patients with major depression, postpartum depression, bipolar disorder or anxiety disorders and the intake of polyunsaturated fats is increasingly considered as a physiological determinant of an optimum mental health.[15] There is a Cochrane review on the use of ω-3 for the treatment of depression in adults. It summarizes that those studies that evaluate the effect of the ω-3 compared to the placebo show a mild to moderate benefit of ω-3 in the improvement of the depressive symptoms measured through the 17-item HDRS scale (difference of means: -0.32, CI 95%: -0.12,-0.52).[16] Rates of remission and response, quality of life and drop-out rates

were similar in both groups. When they were compared against antidepressant drugs, the differences were not significant,[12,16] so that their efficacy would be comparable. The review also concluded that the scientific evidence reviewed had a low and very low quality, so that more studies on this with better methodological quality are needed.

The not very strong results described up to date may be due to the different combinations and doses of ω-3 used up to date. In the work published in 2013, the efficacy of DHA versus EPA and placebo in the treatment of depression as coadjuvant therapy was compared and the authors described a greater reduction in the score on the HDRS-17 items scale in the patients who took EPA.[17]

GROUP B VITAMINS

The evidence suggests that folate deficiency is causally related with the depressive symptoms since said molecules play an important role in the methylation processes and in the synthesis of neurotransmitter in the CNS. Furthermore, depressed patients with low levels of folates have a lower likelihood of responding to antidepressant treatment, greater likelihood of relapse[18] and worse cognitive performance.[19] On the contrary, an adequate intake of folates has been shown to be a protector against the development of depressive symptoms.[20]

There are currently three commercial folate formulations available for their possible concomitant use with antidepressant therapy: 1) folic acid, 2) folinic acid, 3) l-methyfolate. Both folic acid and folinic acid need the methylene tetrahydrofolate reductase (MTHFR) that converts them into L-methyfolate that is the active form capable of crossing the blood-brain barrier (BBB)[21] and capable of activating the enzyme that synthesizes dopamine, norepinephrine and serotonin.[19] The three presentations available are well tolerated and have shown mild to moderate efficacy as coadjuvants to the antidepressant treatment, benefiting both patients with low levels of folates and those with normal levels from them.

It must be kept in mind that in some patients, deficiency of L-metylfolate is due to a genetic deficiency that prevents the correct synthesis of MTHFR so that the external supply of folates should be directly in form of L-methylfolate.[21]

It has been observed that patients having low folate levels in blood have a mean longer time for improvement of the depression than the normofolateemic (3.5 versus 5 weeks; $p<0.001$). The relapse rates are also associated with low folate levels in blood (42.9% in low folate levels versus 3.2 in normal folate levels.[22]

A greater increase in the blood levels of folates during antidepressive treatment significantly correlates with a greater decrease in the Hamilton depression scale score. Furthermore, a greater concentration of folate in blood is observed after the treatment in responding than in non-responding patients.[23, 24]

Folates below 13.6 nmol/liter of blood are considered low levels. Folate deficiency increases the levels of homocysteine (Hcys) and decreases SAMe, which implies a reduction of the methylation capacity, which finally alters neurotransmitter synthesis.[25] Furthermore, this deficit alters the synthesis of a cofactor, as BH4, which in turn activates the tryptophan hydroxylase and thyrosinahydroxilase enzymes, necessary for the synthesis of 3 very important monoamines in mood regulation, as are serotonin, dopamine and norepinephrine.[18]

It has also been described that the high levels of Hcys are significantly related with the presence of depressive symptoms.[26-28]

In regards to intervention trials with:

- Folic acid or folinic acid. The duration of the trials carried out at present varies from 6 to 52 weeks. None of the studies includes patients with low levels of folates in blood. In general, it has been observed that the dose-dependent response and the patients have null or low incidence of adverse effects.
- L-methylfolate. In the studies L-methylfolate was used in periods between 4 weeks and 6 months, both a potentiation therapy and monotherapy. Significant adverse events did not appear in any case. In general, the results were favorable for L-methylfolate in both monotherapy and coadjuvant therapy compared to placebo in terms of higher response to treatment and lower response time.[19] L-methylpholate seems to significantly decrease depressive symptoms, even in patients resistant to SSRI and in those with more serious symptoms at baseline.[29]

The advantages of the use of L-methylfolate versus folic or folinic acid are that:

- It has a seven times greater bioavailability
- It obtains a level in CSF that is three times greater than the levels in blood due to its capacity to cross over the BBB.
- It reduces in a more effective way the levels of Hcys.
- It does not mask the anemia due to lack of vitamin B12
- It has a lower likelihood of causes a decrease in the "Natural Killer" cells

- It has a lower likelihood of causing the cancerigenic cells to proliferate in the colon, which has been described in supplements with folic acid.[21]

The daily dose of L-methylfolate recommended as an antidepressant therapy supplement is 15 mg. The use of this strategy has shown results similar to other potentiation strategies such as the use of lithium or antipsychotics and is well tolerated by the patients.

It must be kept in mind that a supplement with folic acid can mask a vitamin B12 deficiency so that special care must be taken in patients with anemia.

S-ADENOSYL METHIONINE

L-methylfolate and S-Adenosyl methionine (SAMe) are found to be involved in a common metabolic pathway that is the *methylation cycle or carbon-1.* In fact, L-methyfolate is an intermediate molecule in the conversion of folic acid to SAMe, a molecule that finally serves as a donor of methyl groups required in different processes (methylation of DNA, of phospholipids, of RNA, synthesis of neurotransmitters, etc.) essential for cell metabolism. Specifically, the L-methyfolate bonds to Hcys to form methionine that is metabolized to SAMe. It has been verified that patients with depression have low levels of SAMe in the CSF.

In addition to those described in the previous paragraph, another hypothesis that could explain the possible antidepressive effect of the folates and SAMe is based on that fact that through the methylation of the plasma phospholipids, SAMe can alter the neuronal membrane fluidity, which would affect the functionality of certain membrane proteins, including the monoamine receptors and transporters.[30]

At present, the use of SAMe has been evaluated both by parenteral pathway at a dose of 150-400 mg/day, as by oral pathway at a dose of 1600 mg/day, with studies that are not inferior compared to 150 mg of imipramine.[31]

There is a study in which it has been seen that SAMe administered as coadjuvant to escitalopram compared with placebo shows greater antidepressant efficacy but only in the case of male patients.[32] There are no conclusive studies comparing SAMe with selective serotonin reuptake inhibitors (SSRI) antidepressants that are the antidepressants used most at present.

In regards to the tolerability ad safety of SAMe it is well-tolerated in general but cases of increase of anxiety symptoms and possible masking of manic and hypomanic symptoms in patients with bipolar depression have been described.[33]

A Cochrane review on the use of SAMe in depressed adults found that its effect is not greater than the placebo and concludes that given the absence of high quality evidence at present, firm conclusions based on said evidence cannot be obtained. Thus, the review recommends that the use of SAMe in depression should be investigated further, including antidepressant comparators of all the available pharmacological groups.[34] Furthermore, it recommends paying special attention to the possible induction of mania.

TRYPTOPHAN

Tryptophan and tyrosine are two important amino acids for mood and emotional regulation since they are precursors of serotonin (tryptophan) and dopamine, epinephrine and norepinephrine (tyrosine), respectively. The main difference between them is that tryptophan is essential and should be supplied externally while tyrosine can be synthesized in the body from phenylalanine.[35]

According to the monoamine hypothesis of depression, a depletion of these amino acids could lead to insufficient synthesis of neurotransmitters and with this to a depressive mood state.[36]

The daily intake of tryptophan recommended by the WHO is 4 mg/kg. Furthermore, it is important to know that entry of tryptophan into the brain depends on the amount of free tryptophan in blood and on the concentration of other amino acids that compete with tryptophan for the transporter that they use for passage of the BBB. The enzyme that catalyzes the passage of tryptophan to 5-hydroxytryptophan (5-HTP) (tryptophan hydroxylase) can be inhibited by different factors such as stress, insulin resistance, vitamin B6 deficiency or magnesium deficit.[37] After, the 5-HTP is decarbonized to form serotonin (or 5- hydroxytryptophan or 5-HT) that once released into the synaptic cleft will affect brain functioning and the behaviors associated with the serotoninergic system.

The shortage of tryptophan to initiate this pathway may be due to an insufficient intake or activation of the IDO enzyme (indolamine-2,3-dioxygenase) that degrades tryptophan to kynurenine. This enzyme can be activated by certain proinflammatory cytokines or by treatment with corticosteroids. In effect, it has been verified that treatment with cytokines is often accompanied by depressive symptoms.[38]

In general, patients with depression have tryptophan deficits in relationship to healthy subjects,[39,40] although other authors have found normal levels in depressed patients.[41] The evidence points to the existence of lower levels of tryptophan in blood of patients with melancholic or psychotic depression than those who do not have this type

of depression, suggesting different endophenotypes of the disease.

There are authors who state that the proportion of tryptophan compared to other amino acids that compete for the same transporter, which would be a good predictor of the response to treatment with tryptophan, is more important than the blood concentration of triptophan.[42]

In regards to intervention studies with tryptophan in depression, we could state that in a review of 111 works in this regards, only two of them met the quality criteria required to be included. These were: a) be randomized, b) include patients with unipolar depression or dysthymia, c) compare preparations of tryptophan or 5-HTP versus the placebo and d) that the clinical results were evaluated by scales.[43] In both studies, the preparations of tryptophan or 5-HTP showed superiority to the placebo in the relief of depressive symptoms, although the level of evidence is low.

Although a favorable profile of side effects has been shown, it is important to keep in mind the possibility that a serotoninergic syndrome can be precipitated in the patient if the tryptophen (or 5-HTP) is administered together with other serotoninergic agonists such as the SSRI. It seems that if the dose of tryptophan does not exceed 50 mg/kg there is no risk of said syndrome in the concomitant administration with SSRI.[37]

MAGNESIUM

Magnesium is a mineral that acts as a cofactor in multiple enzyme reactions so that it is involved in the correct functioning of the cardiovascular, endocrine, osteoarticular, nervous systems, among others. On the level of the nervous system, magnesium affects different biochemical processes and the correct fluidity of the neuronal membrane. In fact, magnesium deficiency gives rise to multiple psychiatric and neuromuscular manifestations such as agitation, tetany, seizures, headache, anxiety, insomnia, tiredness, depression, etc.[44] Experimentally, it has been seen that magnesium deficiency causes behaviors consistent with depression and an inverse relationship has been seen between magnesium intake in the diet and depressive symptoms.[45]

A magnesium deficit can be due to an inadequate intake but also to poor intestinal absorption or to an excess of loss through the kidneys. It has even been postulated that the passage of large amounts of magnesium (together with other micronutrients) from the mother's blood to the fetus could contribute to the development of post-partum depression.[46] Furthermore, sustained depletion of magnesium is associated with activation of inflammatory processes which worsens the depressive symptoms.[47,48]

A significant decrease in magnesium blood levels has been demonstrated in patients with depression, which correlates with the intensity of the clinical symptoms measured with the Hamilton Rating scale for depression.[49] Similar results are obtained when analyzing the levels of magnesium in cerebrospinal fluid.[50] It is believed that the depressive states that frequently occur in alcoholic patients are due to the increase of urinary excretion and deficient intestinal absorption of magnesium caused by the ethanol.[51]

In regards to the antidepressive effect of the use of magnesium supplements, it seems that said mineral modulates the NMDA receptor activity of glutamate.[52] Indeed, given the limitations of the monoaminergic hypothesis of depression and the low rates of remission with conventional antidepressants, the glutamertergic hypothesis has been gaining strength in recent years.[53,54] In addition, it has been seen that magnesium interacts with the hypothalamic-pituitary adrenal (HPA) axis, whose function is generally altered in depressed patients.[55]

In addition, lack of magnesium makes it possible for the calcium and sodium ions to move into the postsynaptic neuron and for the potassium ions to move out, which causes a larger amounts of reactive species of oxidative and nitrosative stress to be produced with the consequent neuronal damage.[44]

Favorable results in animal models of depresión[56-58] gave rise to the study of the clinical applicability of magnesium in the treatment of depression. However, the reality is that few and not very promising quality studies have been performed with magnesium in depression. There is a randomized study in pregnant women that did not find that supplementation with magnesium or zinc decreases anxious-depressive symptoms after giving birth.[59]

The daily recommended intake of magnesium is 300 mg but it this is associated with antidepressants, it would be somewhat less since it seems that part of the effect of the antidepressive drugs is that it causes an increase of plasma levels of magnesium.

ZINC

Zinc is one of the most abundant trace elements in the body and is essential in multiple metabolic processes since it acts as a cofactor of up to 300 enzymes,[60] many of them having an important role in the brain functioning.[61] In regards to mental health, it has been seen that the zinc deficiency increases the levels of lipid peroxidation, affects cell survival[62] and in general, influences brain homeostasis, leading to alterations in behavior, in learning processes and in depressive states.[63] Significantly lower blood levels of zinc have been found in depressed patients than in healthy

controls[64] which in turn correlate with the severity of the disease,[65] a fact also observed in patients with perinatal depression.[66]

In fact, the benefit of supplementation with zinc to antidepressant treatment in animal models has been demonstrated.[67] However, although there are some positive studies with zinc supplements in patients with depression,[68] the evidence is still poor.

The relationship between zinc deficiency and depression is not totally known but there are several hypotheses in this regards. The first one involves the immune system since we know that zinc is necessary for hormonal regulation and of the cellular immune response, both involved in the physiopathology of depression,[63] since it is known that the activation of inflammatory processes is associated to depressive symptoms.[48,69] In the second place, it has been seen that zinc deficiency activates the HPA (hypothalamic-pituitary-adrenal) axis which in turn affects the mood state. The possible antidepressive effect of zinc (as with magnesium) would also be mediated by the activation on the NMDA receptor,[70] since significant alterations have been observed in the interaction between zinc and the NMDA receptor in post-mortem samples of suicide victims.[71]

The study conducted by Ranjbar et al., found that the use of 25 mg/day of zinc as therapy coadjuvant to treatment with SSRI significantly decreases the score on the BDRS scale at 12 weeks.[72] Said study only included 38 patients randomized to two groups and was not duly replicated. As occurs in the case of magnesium, the scientific evidence is still not conclusive in relationship with the antidepressive efficacy of zinc as a coadjuvant therapy.

PROBIOTICS

One factor clearly influenced by nutrition that has been significantly related with depression is gut microbiota, which has encouraged the use of probiotics in the promotion of mental health (the so-called psychobiotics).[73-75] An unhealthy diet has been observed to be related with altered microflora, greater gut permeability, low level systemic inflammation and alteration of BBB.[76] The important role played by intestinal flora in the bidirectional communication between the gut and brain has been described[77] and the scientific community is increasingly convinced that our gut plays an important role in our mental health.[78] In 2016, a metaanalysis was published that summarized the evidence of the relationship between probiotics and depression. Said work included 5 randomized clinical trials with a control group, one of which included non-depressed individuals.[79] The studies were heterogeneous in regards to the probiotic strains evaluated (*Lactobacillus Casei, Lactobacillus Acidophilus, Lactobacillus Rhamnosus, Lactobacillus Bulgaricus, Lactobacillus Brevis, Lactobacillus Helveticus, Lactobacillus Salivarius, Lactobacillus Pentosus, Lactococcus Lactis, Bifidobacterium Breve, Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium Lactis, Bifidobacterium infantis and Streptococcus Thermophilus*), dose and duration of the intervention and type of scale used to measure the depressive symptoms. The metaanalysis found that the use of probiotics reduced the risk of depression in healthy subjects (difference of means=-0.30, p=0.005) and the depressive symptoms in depressed subjects (difference of means=-0.73, p=0.03) but only in the under 60 year old age group.

CONCLUSIONS

The evidence available at present supports the recommendation of some of the nutritional supplements for the prevention of depressive symptoms in healthy subjects, treatment in monotherapy of mild depressive symptoms and associated to antidepressants in major depressive disorder. The greatest experience is with ω-3 fatty acids. However, the level of evidence is scarce and thus both preclinical and clinical studies need to be performed that go deeper into the study of how nutritional supplements interact with the antidepressive medication.

On the other hand, it would be recommendable to perform prior blood work on the patient to evaluate possible deficiencies in the nicronutritients to be supplemented.

In a future time, it would be interesting to perform studies that identify biomarkers of clinical results for the use of nutritional supplements in depression.

In regards to the use of probiotics, more studies are needed that support their efficacy and that make it possible to determine the adequate composition of species and strains in the supplement to be used, and the time that treatment with probiotics should be maintained. It would be advisable for said studies to keep in mind the diet of the patients since this noticeably affects the composition and diversity of the gut flora.

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