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Review Article

Nutrition in Depression: Eating the Way to Recovery

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Abstract

Depression is a very frequent and debilitating mental disorder, which in recent years has become one of the leading causes of disability and a public health crisis, with a severe rise in prevalence, and very large direct and indirect economic costs. This situation has sparked a surge in the research for treatment alternatives for this disorder, in particular, lifestyle modifications, such as dietary interventions. Indeed, nutritional intake may have a significant impact in the neurobiology of mood regulation, chiefly by intervening in brain monoamine metabolism and modulating chronic, low-grade neuroinflammation. This review discusses current views on the role of dietary modifications for the treatment of depression, a form of "eating the way" to recovery, contrasting molecular neurobiological hypotheses and prominent epidemiological data.

Keywords: *Depression; Mental Health; Nutrition; Diet; Monoamine Metabolism; Chronic Inflammation*

Introduction

Depression is a very frequent and debilitating disease, currently estimated by the World Health Organization (WHO) to affect 350 million people worldwide, corresponding to 4.4% of the global population [1]. Indeed, in recent years, depression has evolved into a public health crisis, as it is responsible for greater levels of disability than cardiovascular disease, diabetes mellitus, arthritis and asthma [2].

Furthermore, the sum of the direct and indirect economic costs associated with depression currently exceed US$ 210.5 billion per year [3], and are projected to reach over US$ 6 trillion by 2030 [4].

This alarming outlook has kindled the research into novel therapeutic alternatives for depression. Notwithstanding the important improvements in the effectiveness of the therapy for depression in recent years, the direct treatment-related costs remain a substantial portion of the economic burden of this disease, at 45% [3]. In addition, depression has been linked to a myriad of chronic illnesses such as cardiovascular disease, metabolic disorders and cancer, among many others, all of which also entail a great economic and lifestyle burden [5].

Thus, the therapy of depression represents a potential target for cost reduction in this context. The treatment of depression may be conceptualized to consist of three elements: Pharmacotherapy, psychotherapy, and lifestyle modifications. Of these, the latter may be a useful low-cost option for the augmentation of other treatment modalities [6]. Although the benefits of regular physical activity have been well-established in the management of depression, nutritional interventions have also shown promising preliminary findings [7]. As posited by the adage, "an army marches on its stomach", and this review aims to discuss current views on dietary modifications for the treatment of depression, a form of "eating the way" to recovery.

The Role of Nutrition in Mood Regulation

The current understanding of the neurobiology of depression centers on the monoamine hypothesis, wherein decreased signalling by serotonin (or 5-hydroxytryptamine, 5HT), norepinephrine (NE) and dopamine (DA) in key areas of the brain results in the various symptoms of depression [8]. Much of the pharmacologic alternatives for the treatment of depression act through the modulation of this monoaminergic signalling [9], and although efforts have been made to elucidate the possible impact of nutrition in this context, its effects remain uncertain.

Tryptophan, the precursor for 5HT synthesis, and tyrosine, a precursor for NE and DA synthesis, are abundantly found in certain foods (Figure 1). Tryptophan may be particularly important, as it is an essential amino acid, and thus cannot be synthesized in the human body [10]. Despite various fruits and vegetables being rich in 5HT, this neurotransmitter is unable to cross the blood-brain barrier (BBB), and thus unavailable to the brain directly from dietary consumption. In contrast, tryptophan can readily cross the BBB and undergo conversion in the 5HT in neurons, through the sequential action of tryptophan hydroxylase and 5-HTP decarboxylase, respectively, in the presence of pyridoxal phosphate, derived from vitamin B_6 [11]. Because tryptophan is not abundant even in protein-rich foods, diets poor in this amino acid have been hypothesized to predispose to depression. This impact on serotonergic metabolism may go beyond depression, and also be present in other related conditions, such as anxiety, post-traumatic stress disorder, chronic pain, epilepsy, Parkinson's disease, Alzheimer's disease, schizophrenia, and drug addiction [12]. Nevertheless, implications of nutrition in NE and DA metabolism remain widely unknown.

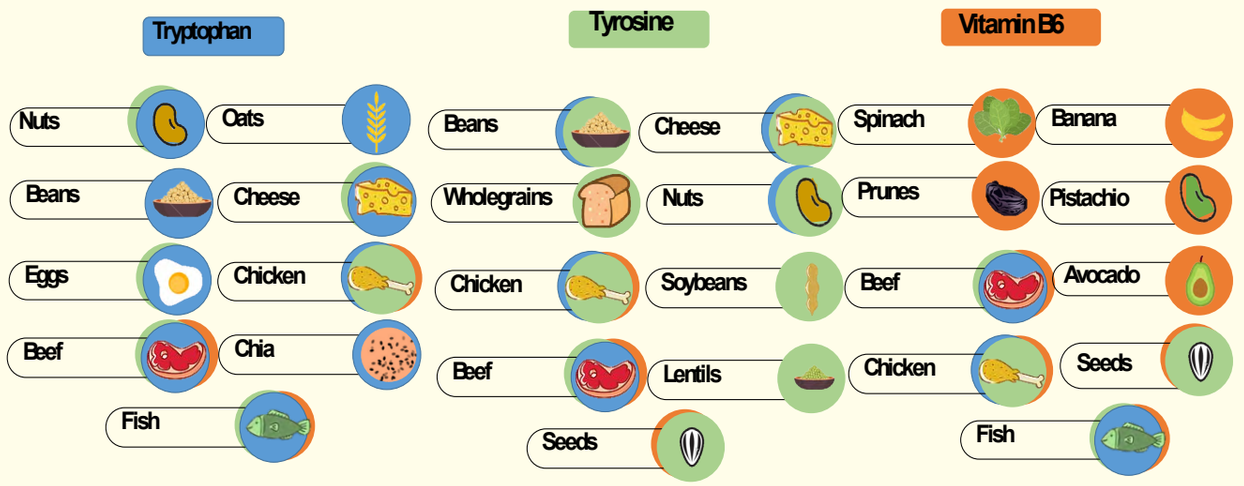

Figure 1: *Selected foods containing monoamine neurotransmitter precursors tryptophan and tyrosine; and vitamin B6, an important cofactor in their metabolism.*

Chronic, low-grade inflammation also appears to play a substantial role in the neurobiology of depression, by disrupting monoaminergic transmission and inhibiting neurotrophic signalling, among many other mechanisms [13]. Furthermore, low-grade inflammation has been identified as a common pathophysiologic component in a myriad of chronic non-communicable conditions, including cardiovascular disease, diabetes mellitus, and the metabolic syndrome [14]; as well as various mental disorders, such as depression, bipolar disorder, schizophrenia and dementia [15]. The close link between Westernized diets and chronic inflammation-related conditions has sparked interest in nutrition as an active component in the development of these disorders. Indeed, dietary patterns with abundant carbohydrates and lipids may intervene in the neurobiology of depression [16].

For example, foods with high glycemic indexes-typical of Westernized diets-seem to provide a temporary relief of depressive symptoms [17], possibly through an insulin-mediated improvement of the bioavailability of tryptophan in neurons [12]. However, these foods also entail short-term troublesome symptoms, cravings and anxiety in particular. Therefore, foods with low glycemic indexes and complex carbohydrates may be more apt at providing moderate yet long-term effects on mood and energy levels [18].

Dietary lipids may also participate in mood regulation, with the brain being rich in structural and functional lipid components, including phospholipids, sphingolipids and cholesterol. The glycerophospholipids in this organ consist of high proportions of polyunsaturated fatty acids (PUFA) derived from linoleic acid and α-linolenic acid, both essential fatty acids (FA). The most abundant PUFA in the brain is docosahexaenoic acid, an omega-3 FA derived from α-linolenic acid; and arachidonic acid and docosatetraenoic acid, both omega-6 FA derived from linolenic acid [19]. Dietary patterns may shift the omega-3/omega-6 balance in favour of the latter, resulting in a pro-inflammatory net effect, involved in the inflammatory process found in various diseases [20]. In depression, the predominance of omega-6 FA may promote neuroinflammation and dysregulation of neurotransmission and neurotrophic mechanisms (Figure 2) [21]. Moreover,

omega-3 FA act as membrane-stabilizing agents in neurons, by preserving the functionality of the Na^+/K^+ ATPase pumps, ion channels and caveolin proteins, ensuring maintenance of functional membrane potentials [22].

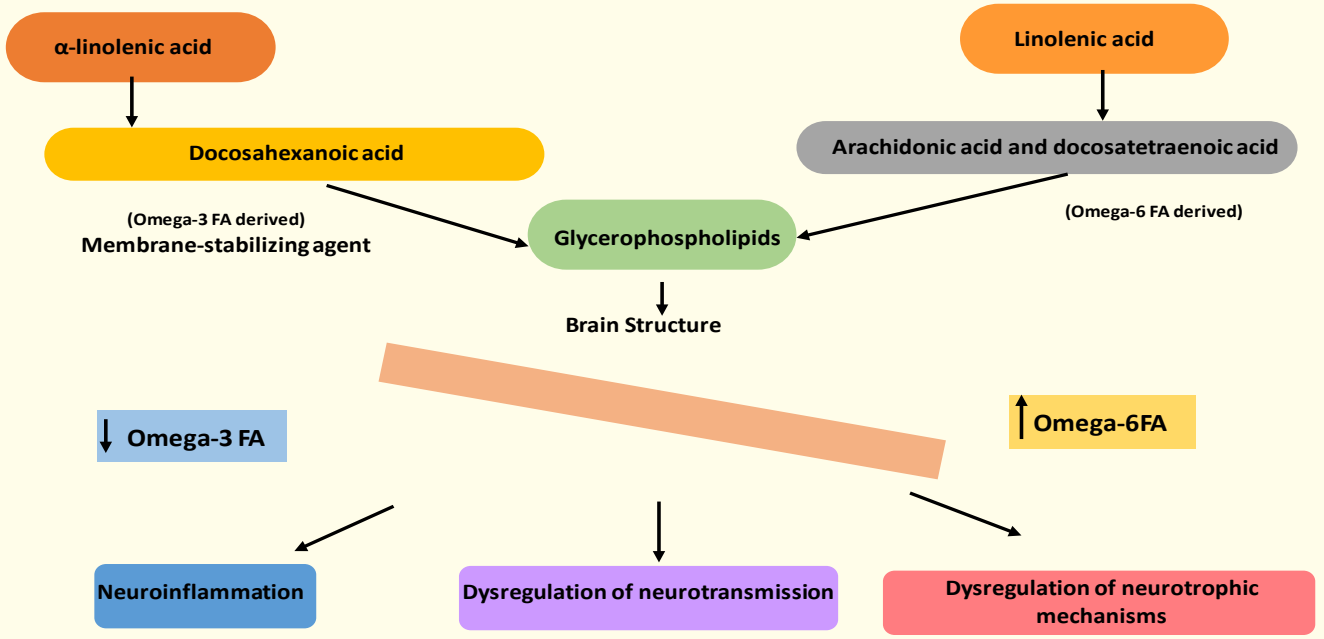

Figure 2: *Role of dietary fatty acids in the physiology of neurotransmission.*

In addition to macronutrients, micronutrients are also key for a healthy brain metabolism. Vitamins from the B complex and minerals such as calcium, iodine, magnesium, iron, lithium and zinc appear to be able to promote overall mental well-being, mood and cognitive functions by facilitating monoamine metabolism and activating the BDNF/TrkB neurotrophic system [23]. In particular, zinc also appears to have antioxidant properties [24], and aid taste perception, a sensory modality classically altered in depression [25]. Indeed, zinc is present in the presynaptic vesicles in glutamatergic neurons in the prefrontal cortex and amygdala, which regulate serotonergic activity in these areas; as well as in serotonergic neurons in the raphe nuclei, where it is a cofactor for tryptophan hydroxylase [26].

Finally, novel research has propelled the concept of the gut-brain axis (GBA), where the composition of the gut microbiota could modulate brain neurotransmission. The GBA appears to consist a neural, a metabolic, and an immune-endocrine pathway [27,28]. Through these pathways, the gut microbiota can provide precursors for neurotransmitter synthesis, regulate brain-derived neurotrophic factor (BDNF) synthesis, and regulate neuroinflammation [29-32]. Because the diet is a powerful modulator of gut microbiota, the GBA has become yet another element to ponder in the impact of diet on mental health [33].

Notwithstanding these pathophysiological and molecular phenomena, their clinical impact in the management of depression remains controversial, discussed in the following section.

Nutritional Interventions in Depression

Numerous studies have assessed the impact of nutritional interventions on various chronic diseases [34,35], yet these reports remain scarce regarding mental disorders. However, recent years have seen a surge in research in this area, in particular regarding depression. Table 1 summarizes some of the most representative research available to date. In particular, García-Toro., *et al.* [36] ascertained better outcomes in patients that followed lifestyle modifications in addition to medication-encompassing changes in diet, exercise, smoking habits, exposure to green areas and social media use-than in those with medication only.

Authors	Methodology	Intervention	Results
Kiernan M., *et al* (2001)	Psychological weight-specific measures as well as measures of psychological distress were obtained in 264 overweight adults that were followed for a year.	The participants were divided into a control group, a diet-only group and a diet plus exercise program group.	Men in the diet and exercise program presented greater psychological improvement than women from the same group, although both genders showed an increase in aerobic capacity.
García-Toro., *et al* (2012)	80 patients on antidepressant pharmacotherapy divided into two groups: Active intervention and control intervention.	Active intervention consisted of avoidance of sweet or sugary drinks, regular eating hours and including specific ítems such as fruit, cereal, nuts and fish in the regular di*et al*ong with other lifestyle interventions.	Patients under active intervention had a better response to treatment than the control group, and the base pharmacological prescription reduction was greater.
Sánchez-Villegas., *et al*. PREDIMED Study (2013)	2,513 patients were divided in three groups: control group with general recommendations of low-fat diet, Mediterranean Diet supplemented with extra virgin olive oil and Mediterranean Diet with supplemented mixed nuts. The patients were followed for 3 years.	Mediterranean Diet supplemented with mixed nuts consisted of 30 gr/day of mixed nuts including walnuts, hazelnuts and almonds.	There was no significant difference between groups, although an inverse relation with depression was observed for the Mediterranean Diet+nuts group. However, a statistically significant lower risk of developing depression was found in Type 2 diabetic patients in comparison with the control group.
Look AHEAD Research Group (2014)	5,145 diabetic patients between 45 and 76 years old, divided into two groups: Intensive lifestyle intervention or diabetes general support and education, followed for 9,8 years.	Calorie goals between 1,200-1,800 kcal/day with less than 30% coming from fat and more than 15% from proteins as well as a strict exercise plan.	Patients were 15% less likely than patients from the control group to develop mild or major depression according to the Beck Inventory.
Stahl S., *et al*. (2014)	95 elderly patients with subsyndromal depressive symptoms received coaching on dietary practices for 2 years.	Dietary practices coaching: General nutrition guidelines review, including the U.S. Department of Agriculture Food Pyramid summed up with help for the preparation of weekly menus and food intake review since prior visit	There was a 40% improvement regarding depression symptoms measured with the Beck Inventory and there was a low incidence of major depression episodes.
Jacka., *et al* SMILES Study (2017)	67 patients diagnosed with depression were divided into a diet intervention group and a control group. The Montgomery-Åsberg Depression Scale was used at 12 weeks.	Personalised dietary advice and nutritional counselling support (ModiMedDiet)	32.3% of the intervened group achieved remission with statistically significant difference when compared to the control group.

Table 1: *Studies assessing nutritional interventions for the prevention and treatment of depression.*

On the other hand, although the Predimed Study [37] found no changes when assessing a nutritional intervention in its general population, it appeared to have a significant effect in diabetic subjects, in association with an improvement of serum insulin levels and HOMA values. This finding supports the role of chronic inflammation in depression through one of its essential components, insulin resistance [37].

The Predimed Study, as well as the Look AHEAD trial, propose nutritional intervention not only as a therapeutic measure, but also as a prevention tool. In the Look AHEAD trial [38], patients with type 2 diabetes mellitus were treated with an intensive lifestyle intervention in which calorie goals, a minimum amount of weekly exercise, and behavioural strategies were set, including group and individual sessions to assess ways to improve adherence. Similar to this initiative, counselling was the pivotal consideration taken by Stahl., *et al.* [39] and Jacka., *et al.* [40] in studies with populations with subsyndromal and major depression diagnoses, respectively. In these studies, personalized nutrition considerations were offered, providing not only general nutritional content recommendations, but also considering the preparation of meals and adapting to the socioeconomic circumstances of each patient. Their results emphasize the benefits of dietary counselling, including greater adherence to treatment and better outcomes.

Numerous lifestyle intervention models include physical activity alongside dietary changes. Physical activity has been described to improve neurogenesis, immune function, stress regulation and circadian rhythms, as well as regulate antioxidant pathways and epigenetic modulation [41,42]. Furthermore, physical activity may intervene in synergy with dietary intake to attenuate and regulate chronic inflammation [43]. These effects appear to be more significant in mood regulation in men, as reported by Kiernan., *et al.* [44]; although further research is required to better characterize these epidemiologic caveats.

Regarding dietary supplements, current evidence is scarce, yet promising. Vitamin D supplementation appears to have clinically significant mood-regulating properties in subjects with Major Depressive Disorder [45]. Vitamin D is a neurosteroid with abundant receptors throughout the brain, and is a facilitator of hippocampal neurogenesis, neurotransmitter release, and neuroprotective and neurotrophic signalling [46]. On the other hand, S-Adenosyl Methionine is an important cofactor involved in one-carbon metabolism -along with folic acid, vitamin B6 and B12-, responsible for methylation monoamines [47]. It is an endogenous sulfur-containing compound and clinical trials have shown that it is an effective antidepressant [48]. Similarly, the amino acid-based compound N-Acetyl Cysteine has glutamate modulatory effects, and anti-inflammatory, antioxidant, and neuroprotective activity [49].

Lastly, newer treatment alternatives have surfaced with the consideration of the gut microbiota as a therapeutic target. Studies performed in rodents have shown that in numerous models of stress induction, intervention with probiotic supplements reduces depressive behaviour [50]. Moreover, recent studies performed in human patients have found that intervention with a multispecies probiotic for 4 weeks resulted in reduced depressive symptoms when compared to the control group [51].

Conclusions

Evidence available to date suggests nutrition bears a significant role in the prevention and treatment of depression, alongside other lifestyle modifications. This is important when considering that, despite common beliefs, dietary recommendations can be cost-effective, as demonstrated by the SMILES trial [40].

However, further research is required to formally recommend particular dietary styles with these purposes. Replication of epidemiological-interventional studies in larger sample sizes, and more sophisticated study designs are necessary, as well as identifying predictors to nutritional intervention may be especially useful.

Currently, a multinational trial titled MooDFOOD is underway in Europe, with the purpose of determining if food-related behaviour changes and multi-nutrient supplements are effective for preventing depression [52]. Other ongoing trials are performing more in-depth studies on the role of omega-3 FA [53], l-theanine [54], B12 vitamin and folate acid [55] in this context. Indeed, the future appears bright for a novel perspective in the treatment of depression.

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