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Does a Healthy Diet Have a Protective Effect on the Development of Depression? – A Review Article

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Abstract

Background: *Depressive disorder is one of the most common mental disorders all over the world experienced by 3.8% of the world's population, including 5% of adults and 5.7% of adults over 60 years old. Depression can be characterized by various symptoms like depressed mode, loss of interest, weight loss or gain, feeling worthless, or excessive guilt. Studies show that depression risk factors may be lowered by following a healthy diet, like the Mediterranean diet, consumption of fish and vegetables, vitamin D_3, probiotics, or antioxidants.*

Objectives: *The purpose of this paper was to summarize known factors with protective effect on the development of depression and possible intervention in daily habits of patients who are suffering from the disorder.*

Material and Methods: *The conclusions of the article were formulated by analysing the available literature mostly from 2019–2024 in PubMed and Google Scholar database. The articles were selected based on the following search criteria in various combinations: "depression", "diet", "antioxidants", "gut microbiota", "Mediterranean diet", "omega-3", "vitamin D". 120 articles were considered, where 40 references were chosen and 80 rejected. The selection of articles was conducted according to the subject of the review paper and appropriate search criteria.*

Results: *In controlled studies, patients with diagnosed major depressive disorder were reported to have low levels of bacteria representing intestinal gut microbiota, vitamin D_3, and omega-3 acids. Following the Mediterranean diet, full of vegetables, fruits, nuts, whole grains, and olive oil as a main source of dietary fats, patients were reported to have reduced symptoms of depression and anxiety. A correlation was shown between the imbalance of oxidative stress and the antioxidant defence and depressive disorders.*

Conclusions: *The findings suggest a strong connection between healthy lifestyle, dietary intervention and development of a depressive disorder.*

Key words: *antioxidants, depression, gut microbiota, Mediterranean diet*

Literature review

Introduction

Depressive disorder also known as depression is one of the most common mental disorders. Around 3.8% of the world's population experiences depression, including 5% of adults, and 5.7% of adults over 60 years old. It is 50% more common among women than men and affects more than 10% of pregnant women and the ones who have just given birth. Every year more than 700,000 people die from suicide [1]. There are two main diagnostic classification systems, the International Statistical Classification of Diseases and Related Health Problems (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM), which identify depression based on clinical picture. The criteria described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) to diagnose a major depressive disorder in adolescents characterise it as a period of at least 2 weeks, during which there is a change from previous functioning, at least one of the symptoms is depressed mood or loss of interest or pleasure, and five or more following symptoms from the list are present: depressed mood, loss of interest/pleasure, weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feeling worthless or excessive/inappropriate guilt, decreased concentration, thoughts of death/suicide [2]. Among adolescents, depressive disorders are also a significant problem, with many declaring feeling sadness, loneliness, pessimism, sleep disorders, predisposition to alcohol abuse or suicidal thoughts [3, 4]. People who enter adolescence with low self-esteem are more likely to exhibit symptoms of depression twenty or more years later which shows how mental health at an early age affects the mentality in adulthood [5]. Moreover, early life experience may affect brain development and predispose to depression which shows the importance of the prevention of depression starting from the early age [6]. Studies show that depression risk factors can be lowered with a balanced and healthy diet like the Mediterranean diet, consumption of fish and vegetables, vitamin D, some probiotics, bifidobacterium adolescentis NK98 and Lactobacillus reuteri NK33 and antioxidants [7, 8, 9].

Gut microbiota

The intestinal microbiota can communicate with the central nervous system through neural pathways, immune stimulation, hormonal response or bacterial metabolites. It has the ability to imitate and produce a variety of neuroactive molecules, such as serotonin, melatonin, histamine, acetylcholine or catecholamines. Moreover, produced in carbohydrate fermentation short-chain fatty acids, neurotrophins and proteins secreted by microbiota also interact with the central nervous system (CNS). The changes around the intestinal microbiota are communicated to the central nervous system through the vagus nerve, which connects the gastrointestinal tract with the brain [10]. The gut microbiota consists of over 50 bacterial phyla, which mainly include strict anaerobes but facultative anaerobes and aerobes as well. It is dominated by Basteroidetes and the Firmicutes, the rest are Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria and Cyanobacteria. The latest analysis suggests that the total number of human gut bacteria can involve even 35,000 bacterial species [11]. Bifidobacterium and Lactobacillus, which are included in the intestinal microbiota, potentially increase the production of short-chain fatty acids (SCFAs). SCFAs are the ligand of G-protein-coupled receptor43 (GPR43), which is necessary to produce glucagon-like peptide 1 (GLP-1) – the regulator between microbiota and brain with a proven antidepressant effect [12]. Moreover, patients with a diagnosed major depressive disorder presented a low level of Bacteroidetes with an overrepresentation of the Alistipes, which is also noticed in chronic fatigue syndrome [10]. Chronic stress and stressful life may affect not only mental health but also disturb the gut microbiota, and have a negative impact on the microbiota-gut-brain axis. Long-time taking antibiotics while killing pathogens also causes damage to the beneficial microorganisms, induces the dysfunction of the microbiota-gut-brain axis and increases the risk of mental health disorders. Infants who take antibiotics during the first year of life are more likely to develop depression later in life [13]. The gut microbiota is dependent on dietary habits, eating food rich in fibre, reducing saturated fats and simple sugars, eating regularly and supplementation of natural probiotics [14]. Probiotics are defined as "live micro-organisms" whose role is to improve

the barrier function of the gut microbiota, modulate the host's microbiota, inhibit the colonization of pathogens, produce bacteriocins, metabolites which decrease the pH unfavourable to bacterial growth [15].

Mediterranean diet

Studies have shown that the Mediterranean diet is associated with a lower risk of depression. In a randomized controlled trial (HELFIMED), adults with self-reported depression were randomized to receive food packages every 2 weeks, Mediterranean diet cooking workshops for 3 months and supplement fish oil for 6 months. After 3 months, correlations were reported between healthy diet habits and lower depression, anxiety, less stress and an increase in positive emotions. With higher consumption of vegetables and nuts, a greater diversity of fruits, a reduction in negative emotions and mental health problems was observed. Patients from the group of Mediterranean diet were reported to experience a reduction of 60% in severe levels of depression, 72% of anxiety and 69% of stress [16]. In another study – the SMILES in a single-blind, randomized controlled trial, a group of people with moderate to severe depression was getting individual nutritional consulting sessions run by a clinical dietician for 12 weeks. They were introduced to a modified Mediterranean diet called "ModiMedDiet". People who were following the diet for 3 months achieved significantly better improvement in depressive symptoms than the ones who did not follow it [17].

Mediterranean diet is a diet rich in vegetables, fruits, whole grains, seeds, nuts and olive oil as a main source of dietary fat. Consumption of low-fat dairy products, white meat and eggs is moderated while reducing red meat, processed products and sweets to a minimum [18]. In SUN (Seguimiento Universidad de Navarra, Spain), a project was organized, a dynamic cohort study based on graduates of a Spanish university with no depression disorder in the beginning, with a new clinical diagnosis of depression by a physician or reported use of an antidepressant drug during the study. The dietary intake was reassessed at the baseline and after 10 years of following the diet, which quality was described by three scores: Mediterranean Diet Score

(MDS), Pro-vegetarian Dietary Pattern (PDP) and Alternative Healthy Eating Index-2010 (AHEI-2010). The group of 15,093 participants reported 1,050 new cases of depression after a median follow-up of 8.5 years. The participants who in the beginning had reported a moderate adherence to the MDS were already correlated with a lower risk of developing depression. Moreover, during the study, graduates who followed the recommendations in the second to fifth quintile of adherence showed a 25–30% reduced risk of developing depression [19].

Antioxidants

Studies show that there is a correlation between the imbalance of oxidative stress and the antioxidant defence and depressive disorder. It was proven that antioxidants have the ability to transfer reactive oxygen species (ROS) and reactive nitrogen species (RNS) by scavenging radicals and inhibiting the oxidative stress (OS) pathway, which additionally protects neurons from damage and may lead to remission of depression [20]. Reactive oxygen and nitrogen species can regulate levels and activity of serotonin, noradrenaline, dopamine and glutamate, the main neurotransmitters connected to the neurobiology of depression. A depressive disorder is associated with lower levels of endogenous antioxidant compounds, which are vitamin E, zinc, coenzyme Q10 or enzyme like glutathione peroxidase [21].

Studies show a correlation between antioxidant depressive disorder and the level of antioxidant and oxidant stress. The study was based on 278 elderly participants – 144 with diagnosed depression and 134 without, using a Block 1998 food frequency questionnaire that was administered between 1999 and 2007, and examined the correlation between clinically diagnosed depression and intake of antioxidants, fruits and vegetables. All participants of the study were above 60 years old. People with depression were reported to have a lower level of vitamin C, lutein and beta-cryptoxanthin compared to the rest of the participants. Moreover, consumption of fruits and vegetables, which is the main determinant of antioxidants intake, was significantly lower in the group with a depressive disorder [22].

In another randomized study between 40 healthy participants and 67 depressed, patients from Government Medical College, Nagpur, India, tested the antioxidant influence of selective serotonin re-uptake inhibitors (SSRIs), first-line drugs for the treatment of major depression. SSRIs are proven to act against 5-hydroxytryptamine (5-HT) re-uptake, increase the retention time of monoamine (5-HT) in the synaptic gap and might have a role in antioxidant defence. Participants were not taking any other drugs for a preceding month and were newly diagnosed, without any treatment for depression before. Patients were randomly placed into groups treated with fluoxetine (20 mg/day) or citalopram (20 mg/day). In total 62 participants completed the study, 32 taking fluoxetine and 30 citalopram. The study showed the concentrations of serum malondialdehyde (MDA) and serum superoxide dismutase (SOD) activities were higher and plasma ascorbic acid lower compared to the healthy control group before the treatment, which may suggest a high level of oxidative stress. After 4 and 12 weeks of drugs intake, serum MDA and serum SOD levels reduced and plasma ascorbic acid increased in both groups [23].

The majority of biological mechanisms related to depressive disorders are connected with the production and release of cytokines like interleukin (IL)-1b, IL-2, IL-6, interferon-γ (INT-γ), tumour necrosis factor (TNF)- α. People suffering from depression showed higher levels of them in their blood plasma. Hypotactically it may be the influence of the damage to the blood-brain barrier (BBB) for which responsible is oxidative stress and pro-inflammatory signals, which prevent the brain from functioning properly [24].

In the group of 80 people in the age group of 20–60 years old, who were patients of a private psychiatric clinic, 40 were diagnosed with an anxiety disorder (GAD), 40 with depression. Differences in levels of vitamin A (β-carotene), C and E were analysed and compared to a healthy control group consisting of 20 people. It was reported that patients with anxiety disorder and depression had lower levels of those vitamins in the beginning. The group of patients with diagnosed depression was subdivided into control and experimental groups. Patients from the control group were given a daily dose of 10–20 mg of escitalopram while patients from the experimental group were given additional supplementation of vitamins: vitamin A 600 mg/day,

vitamin C 1000 mg/day and vitamin E 800 mg/day in the form of a capsule or tablet twice a day. The group of patients with GAD was subdivided similarly. People from the control groups were treated by a psychiatrist and the experimental group received alprazolam 1–2 mg/day and the same amount of vitamins as the group with a depressive disorder. After the 6-week supplementation, participants of the study from experimental groups were seen to have reduced symptoms and increased antioxidant blood levels, except for vitamin E in the group with a depressive disorder. People who received at the same time antioxidants combined with psychotropic treatment were reported to achieve better results, which shows the usefulness of adjuvant therapy [25].

Omega-3

Omega-3 fatty acids, known as n-3 or ω-3 fatty acids, belong to a group of polyunsaturated fatty acids (PUFA), which have a molecule with a last double bond at the third carbon atom counting from the methyl group side. The group consists of α-linolenic acid (ALA) and its derivatives: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [26]. Sources of omega-3 PUFAs are mainly seafood, but also vegetable oils, including rapeseed and linseed oils, walnuts, flaxseed, canola, linseed, sunflower seed, fish oil and microalgae [26, 27, 28].

In the study based on 28 children diagnosed with depression at the Schneider Children's Medical Center of Israel, Child Psychiatry Clinic, and the Beer-Sheva Mental Health Center at the ages of 6 and 12 a correlation between omega-3 fatty acids and the disease was analysed. The trial lasted weeks, where ratings were made in the beginning and after 2, 4, 8, 12 and 16 weeks by using the Childhood Depression Rating Scale (CDRS), Childhood Depression Inventory (CDI) and Clinical Global Impression (CGI). Patients were receiving two capsules of 500 mg or one 1000 mg a day with omega-3 acids. The placebo was olive oil or safflower oil. Capsules of 500 mg omega-3 acids consisted of 190 mg eicosapentanoic acid and 90 mg docosahexaenoic acid, whereas 1000 mg capsules contained 400 mg eicosapentanoic acid and 200 mg

docosahexaenoic acid. 20 participants completed at least 1-month rating, 10 received active capsules and 10 placebo. Among the children from the group which was taking active capsules with omega-3 acid fats, 7 out of 10 were reported to have a greater than 50% reduction in CDRS scores, 4 of 10 achieved remission in criteria of Emslie and colleagues, when at the same time none of the placebo group achieved that. Results from the self-rating CDI were similar, also CGI results showed a positive effect of omega-3 acids on the course of depression [29].

Very long-chain omega-3 fatty acids (w-3 PUFA) intake and consumption of seafood may reduce depressive disorder symptoms also among adults [30, 31, 32]. The protective effect of ω-3 PUFAs against the development of symptoms of depression is correlated with lower levels of pro-inflammatory mediators, which suggests their anti-inflammatory mechanism, suppression of pro-inflammatory and promotion of anti-inflammatory paths. Moreover, they suppress NFκB signalling, formation of the inflammasome, transcription of cyclooxygenase-2 and inhibit the production of IL-1β and chemokine MCP-1 [33].

Fish are rich in omega-3 polyunsaturated fatty acids, in particular, docosahexaenoic acid (DHA), some studies reported their low levels among patients with a depressive syndrome. In the group of 3 204 Finnish adults, depressive symptoms were rated by using the Beck Depression Inventory (BDI) and fish consumption by its frequency. 21-item BDI helped to divide the groups depending on the activity of the disease while fish consumption was checked by a response options questionnaire. There was a correlation between high consumption of fish and minor activity of depression. The likelihood of having mild to severe activity of depression was statistically 31% higher in the group of adults who consumed the fish rarely [34].

It is known that omega-3 PUFA deficiency decreases glucose uptake by brain cells and the activity of cytochrome oxidase, which is also reported in major depression and measures the functional activity of neurons, by 30% or more. Omega-3 PUFA's ability to inhibit the production of pro-inflammatory cytokines, while reducing the production of pro-inflammatory prostaglandins (PGEj) and leukotrienes (LTB4) has potential positive effects on the treatment of

depression which is associated with high levels of pro-inflammatory cytokines, like interleukin Iβ, IL-12, IL-6 or interferon-γ [35].

Vitamin D

Around 20% of vitamin D needed for organisms is provided by dietary intake and the other 80% is synthesized in the skin from ultraviolet rays. From 7-dehydrocholesterol it turns into calcidiol, the serum form, which is hydroxylated with the 25-hydroxylase enzyme (CYP2R1) in the liver and re-hydroxylated with the 1-α-hydroxylase (CYP27B1) enzyme in kidneys and brain into the active form of vitamin D – 1,25 (OH)2 cholecalciferol, known also as calcitriol [36]. From diet, vitamin D can be gained in two forms – vitamin D2 (ergocalciferol) whose sources are yeast, mushrooms and plants and vitamin D3 (cholecalciferol) obtained from foods of animal origin, like oily fish, animal oils and cod liver. Beyond its role in the maintenance of bone homeostasis, vitamin D has pleiotropic functions, which are mediated by vitamin D receptors (VDRs). VDR and enzymes of vitamin D metabolism are expressed by neurons and glial cells in the prefrontal cortex and hippocampus. Moreover, they are expressed as well in immune cells, like CD4+ or CD8+ T cells, and calcitriol inhibits the synthesis of interleukins by activated microglia [37].

During an 8-week double-blind randomized clinical trial, 56 patients with mild to moderate depression were allocated into two groups: intervention with supplementation of 50,000 IU/2 weeks and placebo. It was shown that an increase in the serum 25(OH)D was correlated with improved patients' mood status [38]. In another study based on 89 children and adolescents with depression and 43 control subjects without any DSM-5 diagnosis, participants completed a sociodemographic form, Childhood Depression Inventory, State-Trait Anxiety Inventory 1–2 and had measured levels of serum folate, vitamin B12 and 25-OH vitamin D, homocysteine. The patients were reported to have clearly low levels of vitamin D and B12, whereas the level of homocysteine was high [39].

Based on data collected from United Kingdom (UK) Biobank, between participants aged between 40 and 69 years old from 22 different assessment

centres in the United Kingdom in the years 2006–2010, it can be assumed that people with vitamin D insufficiency and those with vitamin D deficiency are more likely to develop depression. Participants after they provided information about the sociodemographic, medical situation and lifestyle, used a questionnaire and had blood samples collected. Associations between the level of vitamin D and depression were measured at the baseline and during observation in order to investigate incident and chronic depression changes. Around 8.5% of participants reported depression at the beginning of the study, which differed across vitamin D doses – 11.4% deficient, 9.0% insufficient and 7.4% sufficient. Strong evidence of correlation between levels of vitamin D levels and depressive disorder at the baseline and increased risk of depression among the ones with vitamin D insufficiency or deficiency were reported. Moreover, a negative association between depression at the beginning for every unit increase in vitamin D was reported. All these findings may suggest that lower levels of vitamin D are the predisposing factor to develop depression [40].

Conclusions

With the introduction of a literature review of 40 articles, there is proof that a healthy balanced diet, full of fruits, vegetables omega-3, and vitamin D may have a protective effect on developing a depressive disorder. Changing dietary habits can lead to a reduction of depressive symptoms and have a positive influence on the prognosis of the diagnosed patients. Incorporating dietary interventions into public health policies and pharmacological treatment of a depressive disorder could offer a cost-effective and accessible tool to support mental health. These findings suggest a strong connection between healthy lifestyle and development of a depressive disorder, but further high-quality and interventional studies are needed to guide evidence-based recommendations for the patients.

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