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Vitamin Deficiency and Depression

Maddison Jeffries
Philadelphia College of Osteopathic Medicine

Philadelphia College of Osteopathic Medicine

Graduate Program in Biomedical Sciences

School of Health Sciences

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A Capstone in Neurobehavioral Science by Maddison Jeffries

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ABSTRACT

Depression, or major depressive disorder, has affected how people think, feel, and behave. As well as psychological problems, depression has also been a comorbid factor in other emotional and physiological disorders. The actual cause of depression is unknown. Researchers have worked to understand the connections and conditions a person may experience for depression to develop. One commonly researched path to depression is vitamin deficiency. A variety of vitamins like B6, B12, folate, and vitamin D have been linked extensively to depression as a possible cause. A continuation of research expands into how a deficiency of these vitamins causes depression. Low levels of these vitamins are associated with taking birth control and other medication, nutrition, diet, and disorders. Several research studies have led to understanding biological pathways and determined that vitamins such as B6, B12, and folate share a common pathway, homocysteine metabolism. Reduced levels of these vitamins have caused an increased level of homocysteine. An increased concentration of homocysteine is associated with depression, cerebrovascular disease, and monoamine neurotransmitters.

A combination of these effects has led to the creation of a hypothesis: high homocysteine levels can cause cerebral vascular disease and neurotransmitter deficiency resulting in a depressed mood. In this paper, depression is explored through the lens of homocysteine metabolism, the cause of the pathway's dysfunction, and if vitamin D is related. Additionally, treatment by vitamin supplementation will also be examined.

INTRODUCTION

Depression is a significant impairment in social and occupational functioning (9). Depression's cause is unknown but may have developed from a variety of conditions. Rather than a single force that has affected mood, research agrees that several elements, such as social, psychological, and biological factors, interact with one another to result in depression. (1, 21, 22). A factor commonly discussed is vitamin deficiency and nutrition that can lead to depression. Vitamins that act as catalyzing cofactors like folate, B6, and B12 are related to mood and cognitive performance, and a deficiency could negatively affect mental state (15). Other vitamins such as vitamin D and its metabolites are involved with various psychiatric disorders. Insufficient vitamin D levels are associated with anxiety and depression because of their brain and nervous system health. Like B vitamins associated with depression, nutrition and vitamin D are possible risk factors for developing depression-like symptoms. In addition to nutrition, however, sun exposure plays a crucial role in vitamin D and adds another environmental factor that can cause a deficiency and a risk for depression (23). Whether it is nutrition, sun exposure, or trauma experienced in early life when added to having certain genes, the environment's role can increase the risk of developing depression (24).

BACKGROUND

Vitamin Deficiency

Vitamin levels connected to depression include vitamin D, folic acid, vitamin B6 (pyridoxal phosphate), B12, zinc, and copper (3, 2,). Below normal vitamin B levels have influenced memory negatively and are connected to cognitive impairment and dementia. Vitamin B levels also contribute to an unstable mood, namely depression (2). Both vitamins B6 and B12 are involved in a metabolic pathway for homocysteine metabolism. Within the pathway are other substances that have a role in mood regulation and depression, specifically, homocysteine and S-Adenosylmethionine (SAM) (5). Homocysteine (Hcy) is an agent involved in the production of neurotransmitters and activation of NMDA receptors. Evidence has shown that dysfunction of these receptors and neurotransmitters, glutamate, and glycine, has provoked damage in the brain, namely the hippocampus (19). In the context of depression, the hippocampus is a commonly studied brain structure. The role of the hippocampus is stress regulation, involvement in cognitive processing, and connections with the limbic and prefrontal regions (9). Damage and reduction of a functional hippocampus have been used as a marker observed in depression. Persistent reduction during the lifespan could further increase vulnerability (9).

A deficiency in the B6 vitamin can directly impact function by causing abnormal homocysteine levels (5). Hyperhomocysteinemia is associated with many diseases and disorders related to heart, kidney, and cognitive function, including depression and

Alzheimer's. Also connected to homocysteine metabolism are complications with pregnancy and congenital disabilities (6).

Researchers have found that folate, a byproduct when homocysteine is converted to methionine by B12, has a lower serum level in patients with depression. A high prevalence of a deficiency has also been documented in patients with other psychiatric conditions such a bipolar disorder and cognitive dysfunction disorders (11,10, 15).

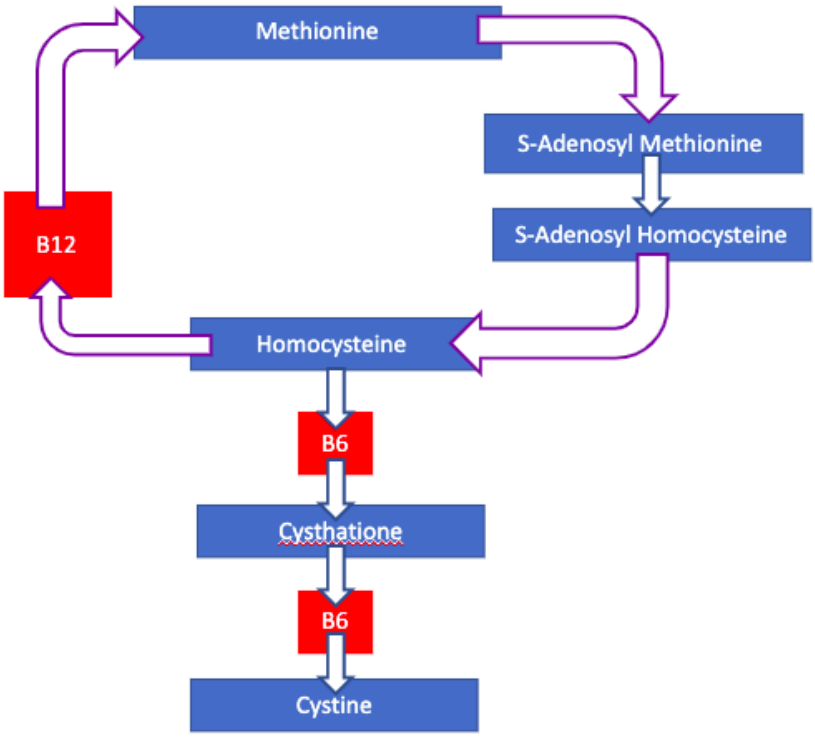

Figure 1. *Homocysteine Metabolism*
The biological pathway of homocysteine metabolism includes many different linkages to depression. A deficiency in B6 and B12 vitamins will lead to an increased level of homocysteine. Both methionine and S-Adenosyl Methionine have stress and antidepressant properties that are therefore decreased with a B vitamin deficiency.

Abnormal behavior has been observed when zinc and copper levels are affected. Vitamins like zinc and copper have played a role in glutamate receptors (NMDA), a

primary excitatory neurotransmitter in the cerebral cortex. A decreased level of zinc and copper will affect these receptors, leading to a decrease in impulses or abnormal NMDA activity, which could implicate abnormal behavior and cortical functioning (3).

Depression also has a relationship with vitamin D. Vitamin D's relationship has been related and driven by homeostatic, trophic, and immunomodulatory effects of vitamin D, suggesting a role in pathophysiology. A deficiency may also be attributed to a consequence of depression-related symptoms like reduced outdoor activities, sun exposure, and dietary changes. (12, 13). Receptors of vitamin D are distributed in many areas in the brain, including the limbic system, cerebellum, and cortex. These structures are involved in emotional processing and affective-related disorders such as depression (25 and 26).

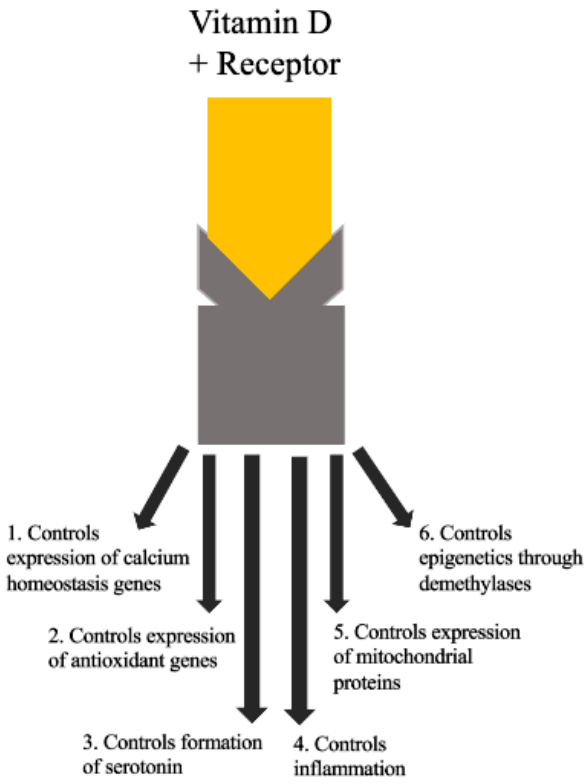

Figure 2. *Vitamin D's Role in Managing Depression-like symptoms*
The role of vitamin D has multiple relationships with managing phenotypic signs of depression. This includes control of calcium homeostasis, expression of antioxidant genes, control of serotonin formation, inflammation, mitochondrial function, and epigenetics through demethylases.

Developing depression is reduced in individuals with a high serum level of vitamin D. Control of mood associated with vitamin D ranges from calcium level control, expression of genes, serotonin manufacturing, control of inflammation, and mitochondrial function. In Figure 2, there are six controls of vitamin D that allow for mood regulation. These functions are critical to maintaining a normal and healthy number and function of neurons in the nervous system (27).

One of the mood controls that occur through absorption of vitamin D is calcium level homeostasis. Vitamin D typically maintains a low calcium level intracellularly.

When vitamin D levels are low, there will be a higher calcium level. Control of calcium levels associated with vitamin D is linked to various channels that buffer and extrude calcium, such as calbindin and parvalbumin. Most notably, however, is vitamin D's involvement with the channels in the hippocampus associated with calcium levels, L-type CaV1.2 and L-type CaV1.3. Deficient vitamin D levels impact these receptors, leading to elevated calcium levels in the hippocampus, which researchers have found linked to bipolar depression (27).

Depression has also been found to be related to antioxidant genes. For example, the antioxidant pathway NRF2. Dysfunction of this gene and pathway produces neurodegenerative, cardiovascular, pulmonary, and chronic inflammation problems, leading to depression-like symptoms (28 and 29). This pathway functions explicitly to defend against oxidative or electrophilic stress by triggering proteins through the expression involved in eliminating these agents (30). An article published on this pathway indicated that Nrf2-null mice have an endogenous state of oxidative stress and are vulnerable to depression due to the imbalance of toxic products in the cell (29). The NRF2 pathway is related to seasonal depression symptoms, likely from a decrease in the sun during the winter months (28).

Vitamin D also plays a role in the inflammatory process (28). Inflammation and depression have already been connected; in fact, low-grade inflammation will trigger a change in patients' mental and physical health already diagnosed with major depression. Likely, inflammation promotes susceptibility to depression (31). Typically, physical stress like damage to cells or infection causes inflammation; however, psychological stress can also initiate the inflammatory and adaptive immune systems (31 and 32).

Another aspect of vitamin D's linkage to depression is that it controls the expression of mitochondrial proteins. A deficiency of vitamin D leading to a lower level of mitochondrial function will directly impact mood (28). If the mitochondria and oxidative phosphorylation are compromised, neurons cannot meet their energy demand. Chronic stress inhibits mitochondrial OXPHOS, dissipates membrane potential, and damages the organelle in many brain regions, influencing the hippocampus, the cortex, and the hippocampus. Successful adaptation to stressful conditions is also compromised with mitochondrial dysfunction. Exposure to many different situations that exert stress can lead to ROS production, increased proinflammatory cytokines, and decreased antioxidant enzymes, which are other controls of mood associated with vitamin D (33).

Vitamin D controls the expression of DNA demethylases, which control gene transcriptions to maintain regular neuronal activity and prevention of depression (28).

Finally, vitamin D is also involved in the formation of serotonin. Vitamin D is directly responsible for the increased tryptophan hydroxylase 2 (TPH2) level while repressing tryptophan hydroxylase 1 (TPH1). This enzyme has direct involvement in the synthesis of tryptophan to serotonin. Additionally, to vitamin D is involved in serotonin synthesis, vitamin B6 and B12 are also involved and are shown in Figure 3 to be essential for synthesizing tryptophan to 5-HTP and 5-HTP to serotonin.

In addition to serotonin synthesis, Vitamin D's role, indicated in Figure 2, in mood regulation relates to the function of the homocysteine metabolism (14). Figure 3 provides a comprehensive overview of vitamin deficiency and how the vitamins discussed relate to each other, relate in function, and depression. Together they have

combined in significant ways and indicate that these are essential vitamins responsible for a regulated mood.

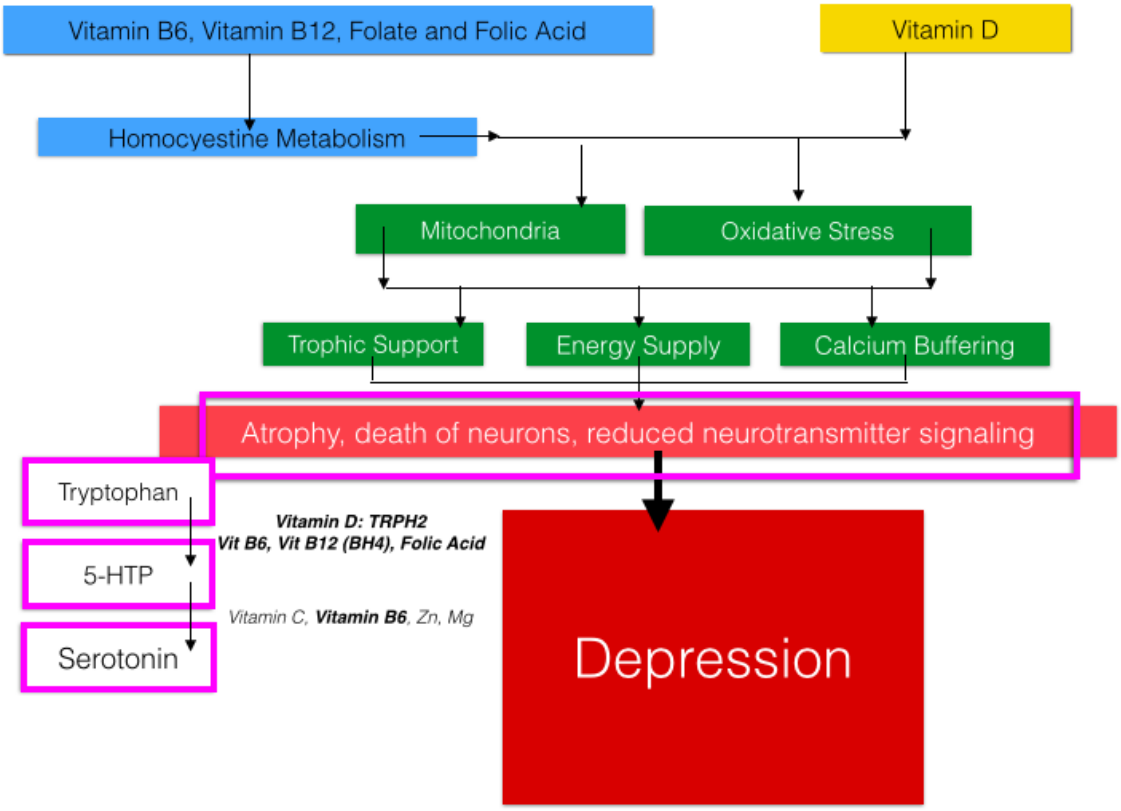

Figure 3. *Deficiencies of Vitamin D, Vitamin B12 and B6, and Folate/Folic Acid and their Involvement in Depression*

Vitamin B6, B12, and Folate are components of the homocysteine metabolism. All three, folate taking the form of folic acid also are involved in the synthesis of serotonin. The three of these vitamins also share a relationship with Vitamin D. Vitamin D regulates the expression of TRPH2, the enzyme and rate limiting step responsible for serotonin synthesis. Vitamin D's roles for mood regulation have similar, or nearly identical, outcomes as the homocysteine metabolism.

Adverse Effect of Depression Caused by Medication

Medications that have caused depression as an adverse effect are treatments for acid reflux, allergies, anxiety, birth control, blood pressure, and pain. Additionally, a patient prescribed more than one medication with an adverse effect of depression has an

increased likelihood of developing depression (7, 22). Researchers have found that homocysteine is affected by the use of birth control. Birth control's influence on homocysteine levels has also induced sporadic ovulation and hormonal changes. These risks and others like vascular disease are more likely to occur in users of oral contraceptives (OC). OCs made primarily with synthetic estrogen have caused B6, B12, and folate (19, 8, 22). In the absence of B12, conversion from Hcy to SAM, which has antidepressant properties, is affected (19).

Across the life cycle, hormonal fluctuation increased the risk of depression in women, specifically ovarian hormones. OC use and depression have shown a decreased tryptophan oxidase resulting in a vitamin B6 deficiency. OC use has been known to cause zinc and copper deficiencies, nutrients involved in cortical functioning. Zinc and copper are associated with glutamate receptors; decreased levels of these nutrients may produce abnormal behavior and cortical functioning (21).

Researchers have shown that mood-related disorders such as depression are more frequently related to women and are connected to alterations with sex hormone production. This includes birth control, undergoing hormonal replacement therapy, and menopause. Estrogen imbalance significantly can contribute to depression and induce long-lasting effects on brain function and gene expression (34).

Medical Conditions, Genetics, and Vitamin Deficiency

Studies that investigated Autism have shown that many children diagnosed have a low B6 vitamin (3). And a decreased folate level is associated with depression and alcohol addiction (16). Methylenetetrahydrofolate reductase (MTHFR) is an enzyme

involved in homocysteine metabolism. MTHFR polymorphisms have shown a significant impact in developing diseases and disorders when there is a reduction of enzyme activity. Specifically, MTHFR dysfunction has been linked to anxiety, depression, positive or negative symptoms of schizophrenia, Autism, and bipolar disorders (20).

Also associated with Autism is vitamin D. A vitamin D deficiency could be explained by nutrition and or exposure to light, but it also can be considered a risk factor for impaired brain development (35). Additionally, vitamin D deficiency in Autism can disrupt the serotonin pathway. Autism's link to serotonin is serotonin's promotion for prosocial behavior and emotional, social cue assessments, common symptoms or issues within the Autism community (36).

Diseases like cystic fibrosis, Crohn's disease, and celiac disease can cause a vitamin D deficiency (43). More generally, irritable bowel syndrome (IBS) is associated with a vitamin d deficiency. Vitamin D deficiency has been linked to depression and colorectal cancer, sclerosis, and several other pathologies when combined with inflammatory bowel diseases (37). Therefore, a deficiency of vitamin D increases the risk of depression and other additional medical problems.

Diet and Depression

As discussed in the previous sections, vitamins are essential in mood regulation. An essential part of maintaining the correct balance of nutrients and vitamins is diet. Food patterns that lead to vitamin deficiency and then to depression are the same that occur during depression. Diet during a depressive episode or major depressive disorder commonly included poor appetite, skipping meals, and an increased desire for sweet

foods (50). Researchers had found that a reduced risk of developing depressive symptoms was associated with a healthy diet (46). Diet alone is related to inflammation, oxidative stress, and brain plasticity, all of which are factors in depression. Specific diets with high consumption of processed food, a high intake of refined grains, and food with high sugar and high-fat content like the Western diet have been associated more closely with depression than alternative lifestyles (45). Decreased vitamin levels linked with the Western diet are commonly the vitamins discussed in this paper, such as vitamin D and B-vitamins (47). Previous studies have shown that diet may have a significant effect on the treatment and the prevention of depression.

Additionally, the Mediterranean diet is noted as the diet that significantly improved mental health in adults with depression (49). The diet has high nutrient levels of B vitamins, vitamin D, and folic acid, which are all vitamins involved directly in serotonin synthesis (44). Therefore, an unhealthy diet has been considered a predisposing factor for depression based on vitamin deficiency, and a change in diet could directly result in mental health.

Vitamin Supplement Treatment

Antidepressants have come with a range of complications and adverse effects that could call for new strategies or interventions. Vitamin supplementation for patients with depression has been a subject of research to understand and identify vitamin pathways and their relationship to depression. Vitamin supplementations are defined by "ad-on" strategies with antidepressant treatment and delaying the onset of depression (14 and 38). Researchers have found that treatment with vitamins B6, B12, and folic acid reduced

depressive episodes. Supplementation with these vitamins has also reduced the risk of a recurring episode. Furthermore, a study highlighted that there was mood improvement associated with higher B6 levels. Regarding B12, the study noted that adolescents with a borderline level of B12 deficiency started to develop signs of cognitive changes indicating the importance of B12 in cognitive function (50). Previous research has implicated and suggested that folate supplementation improved the efficacy of antidepressants. Most researchers and studies have used folic acid as a supplement and found reduced symptoms of depression and improved cognitive function. (10, 11, 16, 50). Since then, there has been an expansion in the research of vitamin supplementation. Evidence has supported that supplementation may be more helpful for the long-term management of depression (15). Low folate levels in patients with depression have also been linked to poor response to antidepressants, and the additional supplement of folate has been shown to improve a better treatment outcome (16 and 50). Trials involving folate and vitamin B12 have suggested that a treatment of 0.8 mg of folic acid a day or 0.4 mg of vitamin B12 a day have demonstrated decreased depression symptoms (50).

Vitamin D supplementation in combination with antidepressants was also used to treat and reduce depressive symptoms effectively. In a study, researchers found that vitamin D supplementation had increased the blood vitamin serum levels and improved the mood of participants either mildly or moderately (38). Deficiency of this vitamin is expected in the elderly, adolescents, individuals that are obese and do not get enough outdoor exercise, are homebound with limited sun, and people with chronic illness. These groups of people are known as a risk for depression and may benefit from vitamin D supplementation for treatment and prevention (26 and 39). Another benefit of adding

vitamin D supplementation to treatment is depression's multifactorial origins. Depression's origins are related to other purposes of vitamin D, such as inflammation reduction, antioxidant influence, and involvement with mitochondrial function (39).

Adding vitamin D as a treatment has numerous benefits in treating someone with gastrointestinal disorders. Syndromes like irritable bowel syndrome (IBS) can lead to a vitamin D deficiency, and quality of life may improve with vitamins added to the treatment (37). A person diagnosed with autism may be treated with a supplement of B6. Studies have shown that patients had increased appropriate behaviors when provided supplements compared to children who did not receive a supplement (3). Due to their deficiency, these disorders could lead to depression, so supplementation with the other appropriate medication may reduce the risk of depression.

In addition to depression treatment, research has also proved that nutritional and herbal supplementation is an effective method for treating anxiety and anxiety-related conditions without the side effects of medication (48). The conclusion drawn in a literature review shows that psychological conditions could be treated or alleviated by a more natural treatment than traditional Western medicine.

COVID-19, Stress, and Vitamin Deficiency

Health problems such as stress, anxiety, depressive symptoms, insomnia, denial, anger, and fear rose during the outbreak of the COVID-19 pandemic (41). The pandemic resulted in stress worldwide to people without and people with mental illness. Based on estimates in a previous study, exposure to recent significant life stress has been considered a risk factor for major depressive disorder (40). A recent study comparing the

prevalence of mood disorders and depression-like symptoms before the pandemic found a three-fold higher symptom prevalence during the pandemic. An increased amount of stressors such as stay-at-home orders, unemployment, and concern about the virus could have caused physical, emotional, and psychological harm, which indicated that the COVID-19 pandemic itself could be considered a traumatic event (42).

The social signal transduction theory of depression is a hypothesis that could be applied to this impact of the pandemic. According to this theory, experiences of social threat and adversity can increase inflammation, and that this inflammation could have a role in depression through proinflammatory cytokines (40). Due to constrictions of the pandemic, fewer people were going outside, and therefore not getting enough sun exposure. Lack of this for the human body could result in a vitamin D deficiency, a biological factor that mediates the response to stress (41).

RESEARCH STRATEGIES

Strategies involved were using a search engine such as PubMed, Google Scholar, and the Philadelphia College of Osteopathic Medicine library's online database.

DISCUSSION

When it comes to depression, there has never been a single force responsible for the disorder; instead, it occurs due to the combination of several elements. Vitamin deficiency has proved to be an element contributing to depression, and vitamin supplementation can be a possible add-on treatment for depression through years of research. The most notable vitamins were vitamins B6, B12, and folate and are components of homocysteine metabolism. A deficiency of these vitamins has led to dysregulation of homocysteine metabolism associated with moods. In homocysteine metabolism, products such as methionine and S-Adenosyl Methionine have direct effects on mood regulation. When the products are not formed or have decreased levels, depression symptoms could develop. As well as homocysteine metabolism, vitamin B6 is also related to the synthesis of serotonin. Therefore not only could a B6 deficiency cause depression from influencing the homocysteine metabolism, but it could further cause damage in the serotonin synthesis pathway.

Another vitamin that has a strong link to serotonin synthesis is vitamin D. In serotonin synthesis, vitamin D regulates the rate-limiting step and, therefore, directly affects the serotonin levels. Vitamin D is also involved in several other processes linked to the development of depression, such as antioxidants, mitochondrial proteins, and more. The metabolic processes and the vitamins involved can be affected by medication, including oral contraceptives, nutrition, medical conditions, and genetics.

Treatment for depression with supplements of vitamin B6, B12, and folic acid have reduced depressive episodes. The addition of vitamins to the treatment plant for

someone diagnosed with depression also reduced the risk of recurrent depressive episodes. Folate significantly has improved the use of antidepressants, and most researchers found that folic acid had reduced signs of depression and improved cognitive function. Vitamin D supplementation in combination with antidepressants had also been effective in reducing depressive symptoms.

RECOMMENDATIONS FOR FUTURE STUDIES

Vitamin deficiency and depression remain a topic in research that still needs to be studied. In this paper, many studies were brought together to show how a vitamin deficiency can change the processes in the body that are responsible for mood regulation. However, in this topic, many studies explain that adding vitamin supplementation into treatment for depression does not create any significant positive result. In addition to whether or not vitamins help symptoms of depression, an area not discussed in this paper, dosage volume, needs to be further researched. Several reviews have suggested that dosage needs should be evaluated, and dosage regarding the severity of depressive disorders should be further expanded.

Discussed in this paper were the ways that vitamin levels are affected. Vitamin levels are affected by oral contraceptives, causing depression-like symptoms, and remains to have little research. In most studies, there is no definite answer as to why oral contraceptive use causes these vitamin level fluctuations, and, therefore, no real explanation exists for why they may cause depression.

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