



VITAMIN B12 AND FOLIC ACID SERUM LEVELS IN PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER: AN OVERVIEW

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Abstract

Background: Obsessive–compulsive disorder (OCD) is a mental disorder in which a person has certain repeated thoughts (called "obsessions") or feels the need to perform repeated behaviors (called "compulsions") to a level that causes distress or impairs general functioning. Amounts of evidence show that folate and vitamin B12 are important nutrient elements involved in the physiological and pathological functions of the neuropsychiatric system. The incidence of neuropsychiatric findings in patients with vitamin B12 deficiency has been investigated worldwide. More recently, folate and vitamin B12 have been reported in a large amount of literature as treatments or supplements for the treatment of psychiatry disease. **Aim of work:** To shed the light on the role of vitamin b12 and folic acid in OCD patients hoping to improve lately the assessment of symptoms severity and thus reducing the morbidity and mortality rates. **Methods:** Our study was a review article, interpreted in Al-Azazy Hospital mental health and addiction treatment during the period from august 2022 till January 2023. Approval was asked from the institutional review board (IRB). Many studies related to our subject were collected, analyzed and a narrative review of our findings was performed. **Conclusion:** We concluded that vitamin B12 and folic acid levels can be associated with certain neuropsychiatric disorders as OCD. We recommend paying attention to this fact which should be investigated in more in-depth and high-quality studies. Our findings can provide a starting point for further research.

Key words: Obsessive; Compulsive; Vitamin B12; Folic.

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Introduction:

Vitamin B12 and folic acid are water-soluble vitamins. Both play an important role in the formation of red blood cells and a key role, especially vitamin B12, in the functioning of the brain and nervous system. Several psychiatric and neurologic illnesses have been associated with vitamin B12 and folic acid deficiency, such as mood disorders, dementia, paranoid psychoses, violent behavior, and demyelinating myelopathy. Psychiatric manifestations may occur in individuals who have not yet developed hematologic or neurologic abnormalities at the time of presentation (1). There are prior evidences in regard to the relationship between folic acid deficiency and depressive disorders, which emphasized the importance of vitamin B12 and folate in carbon transfer metabolism required for the production of

serotonin. It is indicated that vitamin B12 and folic acid levels can be related to certain neuropsychiatric disorders like obsessive-compulsive disorder (OCD) (2). Previous studies showed that, there is a significant deficiency of vitamin B12 in OCD patients which is negatively correlated with the disease severity. Therefore, this suggests that taking vitamin B12 supplements will help in the resistant cases of OCD. As well as, evaluating the levels of Vitamin B12 will help in management of OCD (2).

Aim of work:

To shed the light on the role of vitamin b12 and folic acid in OCD patients hoping to improve lately the assessment of symptoms severity and thus reducing the morbidity and mortality rates.

Methods:

Our study was a review article, interpreted in Al-Azazy Hospital mental health and addiction treatment during the period from August 2022 till January 2023. Approval was asked from the institutional review board (IRB). Many studies related to our subject were collected, analyzed and a narrative review of our findings was performed.

The article:

OCD: a great concern worldwide:

Obsessive-compulsive disorder (OCD) is a mental disorder in which a person has certain repeated thoughts (called "obsessions") or feels the need to perform repeated behaviors (called "compulsions") to a level that causes distress or impairs general functioning. The person is unable to control either the thoughts or activities for more than a short period of time. Common compulsions include hand washing, counting of things, and checking to see if a door is locked. These activities occur to such a degree that the person's daily life is negatively compromised (3). The causes are not well known. There appear to be of a genetic cause, with both identical twins more often affected than both non-identical twins. Risk factors include a history of child abuse or another stress-inducing event. Some cases have been documented to occur following infections. The diagnosis is based on the symptoms and requires ruling out other drug-related or medical causes (4). Obsessive-compulsive disorder affects about 2.3% of people at some point in their lives while rates during any given year are about 1.2%. It is unusual for symptoms to begin after the age of 35, and half of people develop problems before 20. Males and females are affected about equally, and OCD occurs worldwide (4).

Serum vitamins in OCD:

Vitamin E:

Vitamin E is a group of eight fat soluble compounds that include four tocopherols and four tocotrienols. Vitamin E deficiency, which is rare and usually due to an underlying problem with digesting dietary fat rather than from a diet low in vitamin E, can cause nerve problems. Vitamin E is a fat-soluble antioxidant which may help protect cell membranes from reactive oxygen species (5). Vitamin E deficiency is rare in humans, occurring as a consequence of abnormalities in dietary fat absorption or metabolism rather than from a diet low in vitamin E. One example of a genetic abnormality in metabolism is mutations of genes coding for alpha-tocopherol transfer protein (α -

TTP). Humans with this genetic defect exhibit a progressive neurodegenerative disorder known as ataxia with vitamin E deficiency (AVED) despite consuming normal amounts of vitamin E (6). Large amounts of alpha-tocopherol as a dietary supplement are needed to compensate for the lack of α -TTP. Vitamin E deficiency due to either malabsorption or metabolic anomaly can cause nerve problems due to poor conduction of electrical impulses along nerves due to changes in nerve membrane structure and function. In addition to ataxia, vitamin E deficiency can cause peripheral neuropathy, myopathies, retinopathy, and impairment of immune responses (5). There is a significant relationship of OCD and oxidative stress, and consequently, an involvement of free radicals and of the antioxidant defence so patient with OCD had slightly lower concentrations of plasma vitamin E compared to normal persons (7).

Vitamin C:

Vitamin C is an essential nutrient for humans. Vitamin C functions as a cofactor in many enzymatic reactions in animals (including humans) that mediate a variety of essential biological functions, including wound healing and collagen synthesis. In humans, vitamin C deficiency leads to impaired collagen synthesis, contributing to the more severe symptoms of scurvy (8). Another biochemical role of vitamin C is to act as an antioxidant (a reducing agent) by donating electrons to various enzymatic and non-enzymatic reactions. Doing so converts vitamin C to an oxidized state - either as semidehydroascorbic acid or dehydroascorbic acid. These compounds can be restored to a reduced state by glutathione and NADPH-dependent enzymatic mechanisms (9). Several authors found lower vitamin C concentrations in people with OCD and cognitive impairment, including Alzheimer's disease and dementia, compared to people with normal cognition. The cognitive testing, however, relied on the Mini-Mental State Examination, which is only a general test of cognition, indicating an overall low quality of research assessing the potential importance of vitamin C on cognition in normal and impaired people (7).

Vitamin D:

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and many other biological effects. In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2

(ergocalciferol). Vitamin D deficiency is found worldwide in the elderly and remains common in children and adults (10). Deficiency results in impaired bone mineralization and bone damage which leads to bone-softening diseases, including rickets in children and osteomalacia in adults. Low blood calcifediol (25-hydroxy-vitamin D) can result from avoiding the sun. Being deficient in vitamin D can cause intestinal absorption of dietary calcium to fall to 15%. When not deficient, an individual usually absorbs between 60 and 80% (10). Many studies showed that patients with psychological and neurological diseases as OCD, ADHD, cognition, and dementia have lower vitamin D levels, and that there was a small association between low vitamin D levels at the time of birth and later development of these diseases. Several small randomized controlled trials of vitamin D supplementation indicated improved the psychological symptoms in these patients (7).

Vitamin B6:

Vitamin B6 is one of the B vitamins, and thus an essential nutrient. The term refers to a group of six chemically similar compounds, i.e., "vitamers", which can be interconverted in biological systems. Its active form, pyridoxal 5'-phosphate, serves as a coenzyme in more than 140 enzyme reactions in amino acid, glucose, and lipid metabolism (11). Vitamin B6 is involved in many aspects of macronutrient metabolism, neurotransmitter synthesis, histamine synthesis, hemoglobin synthesis and function, and gene expression. Vitamin B6 generally serves as a coenzyme (cofactor) for many reactions including decarboxylation, transamination, racemization, elimination, replacement, and beta-group interconversion. It acts a cofactor in the biosynthesis of five important neurotransmitters: serotonin, dopamine, epinephrine, norepinephrine, and gamma-aminobutyric acid (11). The classic clinical syndrome for vitamin B6 deficiency is a seborrheic dermatitis-like eruption, atrophic glossitis with ulceration, angular cheilitis, conjunctivitis, intertrigo, and neurologic symptoms of somnolence, confusion, and neuropathy (due to impaired sphingosine synthesis) and microcytic anemia (due to impaired heme synthesis). Lower vitamin B6 concentrations in people with OCD and cognitive impairment is proved in many studies (7).

Vitamin B12 and folate in OCD is a debate through decades:

Amounts of evidence show that folate and vitamin B12 are important nutrient elements involved in the physiological and pathological functions of the neuropsychiatric system. The incidence of neuropsychiatric findings in patients with vitamin B12 deficiency has been reported to be 4–50%. More recently, folate and vitamin B12 have been reported in a large amount of literature as treatments or supplements for the treatment of psychiatry disease (12). The interaction among folate, vitamin B12, genetic factors, and metabolism of neurotransmitters have significance in patients with OCD. As the research on folate and its carbon unit metabolism, and other psychiatric disorders has been progressed, researchers have been attempting to determine the correlation between them with OCD, whereas inconsistent results were achieved (13). Thus, several studies were conducted to investigate the epidemiological evidence of serum levels of folate, homocysteine, and vitamin B12 in OCD. Obsessions in OCD patients lead to nearly constant fear, repulsion, anxiety, and the need for repetition. The result is that OCD commonly occurs with other psychiatric disorders (7).

It is proposed that majority of OCD children have another axis I disorder. Of these the most common appear to be other anxiety disorders at rates of 50% and depressive disorders at rates of 40%. OCD patients obtain clearly high points on the CDI depression scale and the STAI-2 showing continuous anxiety and there is a clear positive correlation identified by many authors. Although vitamin B12 and folic acid levels in adults with OCD have been studied, no such research on children and adolescents with OCD has been performed up to now (13). Observations on the antidepressant effects of folate supplementation may support the importance of these nutrients in psychopathology. Although comorbidity of depressive and anxiety disorders is common, there are few studies addressing the effect of impaired one-carbon metabolism in anxiety disorders – especially in obsessive-compulsive disorder (OCD). OCD shows a prevalence of 1%–3% globally, and it follows a chronic course with increased rates of comorbidity (12). Thus, it is a global burden on the patients as well as on their families, i.e., it decreases the quality of life for both of these parties. Due to the role of OCD in the quality of life of patients and their families, as well as providing an alternative route of augmentation

for pharmacotherapy, further studies investigating the roles of vitamin B12, folate and homocysteine may be worthwhile to carry out (7).

The findings of several studies in this issue demonstrated that vitamin B12 and folic acid levels were significantly lower in patients compared to healthy controls. Folic acid levels in OCD patients are low (14). Türksoy et al. found low vitamin B12 levels, high homocysteine levels and indifferent folic acid levels in patients with OCD. There are other studies in the literature reporting OCD symptoms in patients with vitamin B12 deficiency. When evaluated together all these findings suggest that one carbon metabolism, which involves vitamin B12, folic acid and homocysteine, may contribute to the aetiology of OCD (13). One carbon metabolism maintains the methylation processes of neurotransmitters, proteins, and neural membrane phospholipids and is required for DNA synthesis. These metabolic pathways may play a central role in the occurrence of neuropsychiatric symptoms. Folic acid and vitamin B12 deficiencies cause a decrease in methylation reactions that leads to a decrease in neurotransmitter levels and as a result intracellular biochemical pathways are adversely affected (7). Besides, a significant increase in homocysteine levels may occur which may be toxic. Increased levels of homocysteine cause DNA damage, mitochondrial dysfunction and stress in endoplasmic reticulum and also increases influx of calcium into the cell by activating NMDA receptors. Apoptotic signals are activated and intracellular oxidative stress increases (12).

The problem in the era of COVID-19:

Psychiatric disorders, including OCD, represent one of the most important therapeutic challenges worldwide. Over the past decade, the prevalence of these disorders has increased, and this trend has intensified in the current pandemic period COVID-19. Because of the varied etiology and multifaceted nature of these pathologies, treatment of the associated symptoms is often complex (15, 16). Conventional antidepressant treatment options may not always be appropriate for the needs of all patients affected by OCD because they do not directly address hidden pathogenic factors, which include nutritional deficiencies, oxidative stress, inflammation, neuroprotection, and neurogenesis. Furthermore, there are limited treatment options for patients with OCD who do not respond to conventional therapy (14). Nutrition is the focus of

a new field, nutritional psychiatry, which aims to identify the dietary components of particular importance to mental health. Thus, targeting dietary imbalances by prescribing dietary modification/supplementation with medical foods and supplements may offer a variety of complementary strategies for treating patients who do not respond adequately to antidepressants and mood stabilizers (7).

Consistent with this approach, many articles agree, although not always at a highly homogeneous level, that folic acid and vitamin B12, taken as dietary supplements, may be beneficial in managing the symptoms of patients with depressive and mood disorders. Supplementation with folic acid and vitamin B12 may be related to the severity of the disorder: less severe, mildly symptomatic, and borderline disorders could be treated by oral supplementation with vitamin B12, and folic acid alone (12). This approach could be effective also in the treatment of early-stage depressive disorders and/or transient conditions. Other disorders that might benefit from supplementation with folic acid, and vitamin B12 as a first-line treatment include subthreshold depression, seasonal mood disorders, anxious-depressive syndromes, and those disorders associated with the current COVID-19 pandemic, a persistent, global, and pervasive event that has been shown to cause a set of interrelated mental disorders, including sleep and mood disorders, and post-traumatic stress syndromes (15).

The initial additional treatment not only relieves symptoms with little or no side effects but may also enhance subsequent pharmacological treatment if the symptoms worsen. The available experimental evidence has generally demonstrated a favorable safety profile for these compounds (17). The mechanism of action of these substances, the clinical findings, and their favorable safety profile suggest that early and prompt dietary modification/supplementation with vitamin B12, and folic acid can be a useful and safe option to curb symptoms such as mood swings, stress, and fatigue, and may also improve and prolong the efficacy of conventional pharmacological treatment. Taken together, the safety and efficacy of these compounds could influence clinical decision making in psychiatric and psychological disorders (7). To improve the results in terms of speed of efficacy, it is advisable to use orodispersible mixtures. Indeed, this product is

known to have a better bioavailability, which corresponds to a higher efficacy of the components and a faster effect, since the orodispersible formula has the property of quickly entering the bloodstream. However, given the heterogeneity of the studies reviewed here and methodological concerns, further controlled clinical trials are needed to validate the findings and to explore the full range of potential benefits or adverse effects of these compounds (15).

Conclusion and recommendations:

We concluded that obsessive-compulsive disorder (OCD) is one of the commonest mental disorders so early accurate diagnosis must be the major goal of the physician while facing these cases from the first second to avoid the probable dangerous sequences and to provide better understanding of the etiology and treatment for OCD patients. We also concluded that vitamin B12 and folic acid levels can be associated with certain neuropsychiatric disorders as OCD. Moreover, B12 and folic acid deficiency are shown to have an impact on brain functions and cause non-specific psychiatric symptoms. We recommend paying attention to the fact that clinicians should be vigilant about serum levels of vitamin B12 and folic acid in patients with OCD, which should be investigated in more in-depth and high-quality studies. Our findings can provide a starting point for further research.

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