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Review Article

The Role of Trace Minerals in Depression a Review of Selenium Iron and Copper

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Abstract

Depression is currently being reduced with selective nutrition therapies such as supplementations with selected nutrients. Adequate nutrition has an important role in mental health status because the brain needs both macro- and micronutrients for its development and functioning. In particular, deficiency levels of omega-3 polyunsaturated fatty acids (n-3 PUFA), selenium, iron, zinc, magnesium, manganese, iodine, potassium, sodium, molybdenum, cobalt, chromium, lithium, essential amino acids, B-vitamins, vitamin C and copper are emerging as a potentially modifiable risk factor for mental illness and their deficiencies or toxicities have been implicated in a number of mental health conditions over the lifespan, from developmental disorders and mental retardation in childhood, to depression, bipolar disorder, schizophrenia and borderline personality disorder, stress, hostility and aggression in adulthood, and cognitive decline, dementia and Alzheimer's disease in late adulthood.

Keywords: *Depression; Selenium; Major Depressive Disorder (MDD)*

Introduction

A biochemical study was done in Turkey [4] showed that intake of retinol, thiamine, riboflavin, pyridoxine, folate, ascorbic acid, sodium, potassium, magnesium, calcium, phosphorous, iron, zinc, and fiber ($p < 0.05$) were lower in depression patients when compared to their normal counterparts. Fasting blood glucose levels, serum cobalamin, and folic acid ($p < 0.05$) in depression group were lower than controls. Studies have indicated that daily supplementations with these key nutrients are effective in alleviating depression symptoms [5]. There exist adequate evidence that deficiencies of trace elements are prevalent among depression and anxiety patients but supplementation of zinc, iron, magnesium, calcium lithium and chromium can improve effects of anti-depressants and lower their side effects [6]. Another study in 2018 [7] reported that zinc, iron, copper and selenium intakes may be inversely associated with depression.

Selenium: Selenium is vital to trace mineral necessary for smooth performance of selenium transport-proteins that are used in antioxidant system required especially by the Central nervous system and peripheral nervous system [8,9]. Selenium acts as a cofactor necessary for the maintenance of the activity of glutathione peroxidase, an enzyme required for catalyzation of degrading process of organic hydroperoxides. Deficiency of selenium results in loss of glutathione peroxidase (GSH-Px) activity which could lead to damage of cell membranes as a result of pilling up unwanted delete free radicals in the body [10]. The recommended daily allowance of selenium is 0.01 to 0.04 parts per million (ppm) and optimum balance between oxidative stress and antioxidant system is key in maintaining the nerve structures and effective functioning of the brain and the nervous system. The brain is vulnerable to oxidative stress because it has lipid-rich area especially in neuronal membranes and is metabolically active [11].

Vitamins A, C, E and selenium are major non-enzymatic antioxidants in foods, and there is emerging evidence that these antioxidant vitamins are protective against cognitive decline and mental disorders including anxiety disorders, attention-deficit or hyperactivity disorder, autism, bipolar disorder, depression, schizophrenia, and substance abuse [12]. Low blood levels of antioxidant vitamins are

observed in subject with various mental disorders. Selenium plays a major role in anti-oxidation system. It has been documented widely that selenium requirement per day stands at 55 µg per day [13] and serum selenium levels of between 70 µg/L and 90 µg/L are said to be optimal [14].

Since it has neuromodulatory role in brain function some studies have reported a relationship between selenium levels and depression. Research depicted an association between low serum selenium and reduced brain synthesized neurotrophic factor (BDNF) presence [15]. The BDNF that has been majorly associated with the pathophysiology of major depressive disorder [16] and it is possible that BDNF concentrations could explain the relationship between selenium deficiency and depression. In research done on mice [17] the provision of m-trifluoromethyl-diphenyl diselenide (m-CF_3-PhSe)$_2$, a multi-target selenium-based substance, decreased depressive symptoms [15]. Observational studies on selenium and depression are narrated below [17-19].

A research report of 2015 experiments that worked on the relationship between selenium and depressive symptomology or risk of depression provided contradictory results [20]. These findings were from a cross sectional study done among middle-aged population in West Texas that showed contrary relationship between selenium level and depression that was determined by the Geriatric Depression Scale [10]. Low selenium intake less than 8.9 µg/day was associated with higher risk of developing depression as was observed in a nested case-control research of 1494 women between the ages of 20 - 89 years [18]. However, contradictory results were seen in two cross-sectional studies done among aged population in rural China [21]. A study of patients on hemodialysis reported no significant association between levels of selenium and depression scores when the researcher controlled for chronic kidney disease and cognitive ability [20].

Conversely, in a cross-sectional study using toe nail biomarkers from 3735 participants aged 20 - 32 years, it was found out that higher levels of selenium exposure as assessed through toenail clippings were associated with the presence of elevated depressive symptoms which mean selenium toxicity may also aggravate depression symptoms [21]. The fact that an "optimal range" with respect to depressive outcomes may exist for selenium levels was supported in (2014) [22] cross-sectional study that implicated increased depressive symptomology below and above the serum selenium range of 82 and 85 µg/L.

Intervening with selenium supplementation in human beings have reported similar inconsistent findings as seen in a randomized control trial among 166 Iranian women which indicated that selenium supplementation during pregnancy was associated with increased selenium serum levels as well as lower scores on the Edinburgh Postnatal Depression Scale (EPDS) compared to those receiving placebo after 8 weeks of treatment [23]. Another study which was a randomized control trial to evaluate the effect of selenium supplementation on mood using the Profile of Moods States-Bipolar Form (POMS-BI) questionnaire found that giving of selenium supplements significantly elevated plasma selenium levels without influence on mood scores after bi-annual supplementation [24].

Selenium just like other micro-minerals when deficient, patients usually present with signs of malaise, anorexia, anemia, infection, skin lesions, and neuronal tissues. This symptom mars diagnosis of selenium deficiency. Signs of excess intake of trace minerals are have been observed as flu-like and psychiatric symptoms, fever, coughing, nausea, vomiting, diarrhea, anemia, and neuropathy [10]. Some reports have shown that selenium deficiency patients may show lowered mood status [25] and provision of selenium therapy for some patient's populations shows that selenium enhances mood and reduces anxiety [25].

In human beings, heart muscle appears to be the most vulnerable to poor selenium intakes [26]. This manifests with plasma membrane deterioration as normal cells get replaced by fibroblasts leading to cardiomyopathy. The condition is characterized by an enlarged heart with fibrous tissues replacing the muscles. Sometimes prolonged use of total parenteral nutrition for patients with dysfunctional bowel due to surgery may develop selenium deficiency and such cases should be supplemented with selenium in order to raise serum levels above 70 ng/mL. Serum monitoring should be done on bi-annual basis to checks the effectiveness of supplementation.

Studies in psychoneuroimmunology and brain biochemistry explored the possibility of communication pathways that could explain the association of selenium with nutritional intake, central nervous system and immune function thereby affecting psychological health

status. These reports may indicate more acceptance of the therapeutic effect of dietary selenium among those health workers dealing with depression and other mental health patients. It has been emphasized that, nutrient value of diet and meal patterns can affect brain and behavior either positively or negatively [26].

Iron: Much as low iron levels cause anemia because red blood cells require iron as a part of hemoglobin, iron is also critical for proper nerve and brain cell functions [27]. Severe iron deficiency in young children can cause irreversible damage to cognition and result in lower IQ and developmental delays, particularly during a critical period of human development in utero and up to 16 months of age. Lacking enough iron in the brain and nerves, there occur problems with neurotransmitter signaling, the formation of nerve insulation called myelin, and brain energy metabolism. Slowed central neuron processing is the critical problem of iron deficiency in the brain, which can be a primary cause of all sorts of behavioral disorders and increase in psychiatric problems that have become a global health concern [27]. Iron deficiency increased risk of psychiatric disorders including mood disorders, attention deficit disorders and autism disorder among children [28]. Self- reported anemia episodes were reported to be correlated to self- reported depression according to Japanese study [29].

Sometimes iron deficiency will present as anxiety, depression, irritability, and even poor concentration and general restlessness. Iron deficiency has a much higher prevalence in attention deficit hyperactivity disorder (ADHD), and the symptoms can improve with iron supplementation. Populations with iron deficiency have higher rates of psychiatric disorders (particularly ADHD) and developmental disorders, and there is a growing body of evidence the iron deficiency causes the problems and is not just a chance association [30].

Iron deficiency can contribute to depression because of its relationship with dopamine, one of the neurotransmitters in the brain that trigger elevated mood. Iron is required to produce dopamine in the brain [27,31].

Levels of Iron in the umbilical artery are important during fetus growth and development, and this also helps in developing the IQ of the child; infantile anemia is associated with iron deficiency and this is implicated in poor development of cognitive ability [32]. It has also been reported that women are two times more clinically depressed than men. The gender incidence has been observed to start early at puberty stage and gets prominent among the reproductive women of 25 - 45 years age bracket and this could be due to menstruation and blood loss at childbirth [32]. These findings insinuate the possibility of iron in the etiology of depression. In Iron deficiency anemia such symptoms like apathy, depression and palpitation have also been observed [32]. Our bodies use tyrosine amino acid from protein-rich foods to produce dopamine, but this only happens in the presence of iron [31].

Deficiency of dopamine neurotransmitters can lead to depression, anxiety, and other psychiatric disorders. Thus it has been reported that perhaps pathophysiological processes and signs of iron deficiency occur earlier even before anemia sets in. the phenomenon was narrated in a report of a study of women without anemia who experienced unexplained fatigue and when they were supplemented with iron for one month the fatigue subsided by 29% as compared to reduced fatigue of 13% in the placebo group [31]. It can then be said that there is subclinical iron deficiency which is also called non-anemic iron deficiency (NAID). This situation is likely to be more prevalent than iron deficiency anemia [31]. The NAID is said to be more difficult to diagnose because it requires complicated procedures and more often it is not easy to relate its symptoms with iron deficiency. A study done in the Netherlands, reported NAID cases to be at between 14% in men and 9% in women when they used serum ferritin as the indicator for iron status [31]. Iron as a trace element is therefore key in depression and mental health.

Copper: More recent studies such as that done by [33] that looked at serum copper in depression concluded that there is no potential role of copper and depression. The findings were similar to those recorded in 2016 among patients with bipolar disorder stages that included mania, hypomania, depression and remission. There was no significant difference in serum copper in all the above stages [33]. These findings were contradictory to the older reports apart from one that indicated higher serum copper, chromium and aluminum among the depressed than the control [34]. Some Studies [35-37] asserted that hyper-cupremia is associated with many psychiatric illnesses such as schizophrenia, depression, autism, involuntary movements of body parts and memory loss.

Hyper-cupremia above 140 mcg/dl is associated with hypertension in both laboratory animals and humans and its ability to be seized by melanin (skin pigment) could explain the high incidences of hypertension in dark-skinned people. Excess copper may overexcite the heart and this can lead to an individual developing myocardial infarction and other heart diseases. Treatment of copper toxicity involves copper intake restriction and administration of copper absorption inhibitors such as zinc, molybdenum and manganese which lower copper absorption in the gastro-intestinal tract while accelerating its excretion in the bile.

Food rich in iron, zinc, molybdenum and manganese could be suitable for this phenomenon. Copper as a nutrient stimulates the nervous tissue and most tissues of the body, and its effects are similar to the same dose of amphetamines (nervous system stimulant used to treat Attention Deficit Disorder) [35,37]. Other neurological disorders which are associated with high copper levels are: mumbling, autism, childhood hyperactivity, tinnitus, hypertension, eclampsia (convulsions due to pressure and proteinuria in pregnant women), premenstrual tension, psychiatric depression, abnormal blinking or spasms of the eyelids, psoriasis, arthritis, tardive dyskinesia, insomnia, senility, and functional hypoglycemia. Copper toxicity has similar symptoms that occur during cerebral intoxications with lead, bismuth, mercury, and aluminum and continuous hyper-cupremia could lead to memory deficit [35].

Nutritional treatment with zinc, manganese, vitamin C and molybdenum supplementation is suggested to have the ability to counteract the excess copper load in the body. When the body has Copper toxicity and zinc deficiency simple schizophrenia occurs as explained in the dopamine theory [37]. In 1976 a researcher [38] reported that up to a 40% reduction of copper occurred in liver when sheep were exposed to zinc supplementation at 420 mg/kg body weight [37]. The kind of association was also reported in humans [38,39]. Manganese nutrient has been discovered to be antagonistic just like zinc in copper reduction and this suggests manganese-zinc combination therapy in zinc toxicity.

Studies of poultry, rabbits, guinea pigs, and monkeys have implicated that there was a substantial reduction in serum copper activity resulting from vitamin C supplementation [40]. Similar findings were also seen when men were exposed to high intake of ascorbic acid. Since high intake of trace elements results in disease and toxicity, an optimum balance is necessary for good health [40]. More studies are still encouraged on hyper-cupremia and specific mental illnesses to confirm or dispute these studies on copper.

Conclusion

There is a connection between selenium and iron on brain integrity and behavior that has been observed in many studies. The studies suggest that supplementation or dense meal of these nutrients to depression patients may be useful for their management and recovery. Copper status on the other hand appears controversial although many studies suggest nutritional treatment of hypercupremia with zinc, manganese, vitamin C and molybdenum supplementation. The controversies call for more studies to prove or disagree with the findings observed so far. There should be also other studies on suitable meals, supplements and lifestyles that could help patients living with depression.

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