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Review Article

Supplementation of minerals in effective management of refractory major depressive disorders

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ABSTRACT

In the past two decades, rapid urbanization and globalization have adversely changed our lifestyle and diet habits. Our traditional healthy food habits have been replaced by processed foods with low nutritive value. These measures also saw a high prevalence of depression and other psychiatric disorders not only in western, urbanized countries but also in other developing countries as well. Long-term undernutrition due to deficiency of micronutrients such as iodine and iron can lead to increased chances of physical and mental disabilities. Undernourished children have less energy, decreased curiosity, and less interest in physical activities as well as they lack communication skills. These factors impair their physical, mental, and cognition. The aim of this article was to find the association of micronutrients especially minerals in patients with major depressive disorders. An adequate supply of nutrients is essential to regulate microbiome health and to improve the efficacy of other psychotherapeutic and psychopharmacological interventions. Lifestyle interventions in the form of dietary coaching could be used as promising, cost-effective, and practical intervention in depressed individuals. Nutritional interventions should be integrated in the multifactorial and treatment-resistant psychiatry patients.

Keywords: Micronutrients, Minerals, Trace elements, Psychiatry disorders, Nutrition

INTRODUCTION

Mental health is an increasing health problem across the world. In the United States in 2015, about 43.4 million adults were affected by any one of the mental illnesses.[1] Psychiatric disorders are highly heritable presenting with varying physical health problems. The pathogenesis behind the various psychiatry disorders is inflammation, oxidative injury, genetic predisposition, etc. The clinical manifestations in the patients may be sleep disorders, mood alterations, anxiety, decreased retention of memory, worst feature being stigmatization, and social isolation. Various treatment modalities such as chemotherapy, psychosocial counseling, and electrophysiological therapies have been in vogue till date. These remedies work better in the early stage of the disease. When the patient presents late, the efficacy is very questionable. The side effects of the drugs are also so high that the patients prefer to abstain from drugs. Diet and nutrition are considered to be key modifiable factors in the development and progression of almost all mental health disorders. A traditional diet with whole foods including vegetables, fruit, seafood, fish, whole grains, lean meat, and nuts is a good preventive measure of a number of diseases. Furthermore, our dietary habits modulate gut bacteria, the immune system and neurotransmitters involved in psychiatric disorders. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are essential for neuronal plasticity; it is modified by dietary factors.[2] In the UK, over the past six decades, there is decline in consumption of vegetables by 34% in vegetable and also fish consumption by 59%.[3]

THE ROLE OF DIET IN VARIOUS MENTAL DISORDERS

Food-containing selenium, zinc, and iodine[4] are thought to decrease the symptoms of depression and bipolar disorder (BD). Minerals may improve mental health and cognitive functions.[3] Selenium being an antioxidant, when prescribed along with antipsychotics, improves outcomes in patients with schizophrenia [Figure 1].[5] Essential fatty acids

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along with zinc are useful in ADHD. Among some young offenders, diets supplemented with vitamins, minerals, and essential fatty acids have resulted in significant and remarkable reductions in their anti-social behavior.[3] Long-term undernutrition due to deficiency of micronutrients such as iodine during pregnancy and iron occurring in early childhood can lead to physical and mental disabilities. Undernourished children have less energy, decreased curiosity, and less interest in physical activities as well as they lack communication skills.[6] Minerals carry out lot of essential activities in the body such as cofactor of enzymes involved in various metabolic reactions, muscle contraction, nerve conduction, structural role, etc. Serum levels of macrominerals (calcium, phosphorus, and magnesium) and trace elements (copper, iron, manganese, selenium, and zinc) play versatile roles in the biological system ranging from regulating metabolic reactions to acting as antioxidants.[7]

Calcium

Studies show that impaired function of calcium is seen in mood disorders, depression, anxiety, behavior, and personality changes. In depression, there is elevated platelet serotonin-stimulated intracellular calcium mobilization.[7,8] Hypocalcemia results in neurological symptoms such as seizures and alternations of mental status including neurosis, delusion, delirium, mental clouding, dementia, and retardation of the mental activity. In chronic hypocalcemia, chorea and parkinsonism are observed.[9]

Phosphorus

Phosphate is used as additive and preservative, hence, processed foods contain high amount of phosphorus. Our daily intake of phosphate food additives has doubled in the past three decades. Too much phosphorus can lower calcium levels in the body. Phosphorus reduces the absorption of other vital nutrients, precipitating ADHD in children.[10]

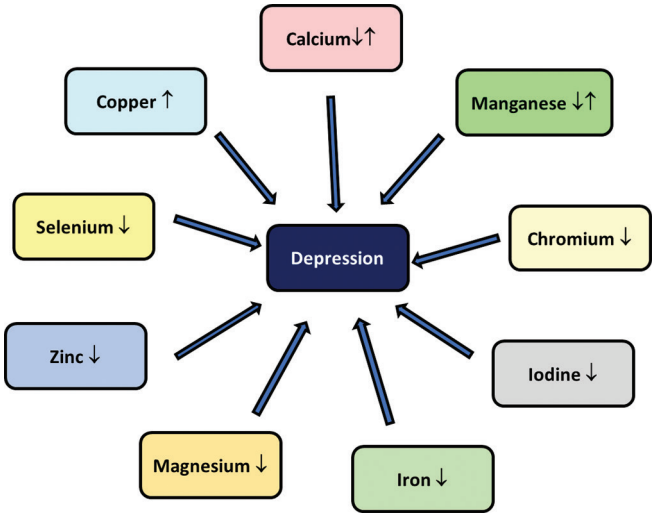

Figure 1: Trace elements involved in the progression of depression.[5]

Magnesium

Magnesium is vital to the brain functions such as stress response, recovery, and repair. Magnesium is considered to be one of nature's mood stabilizers.[11] Magnesium plays a critical role in the treatment of depression through to its regulatory effects on N-methyl-D-aspartate (NMDA) receptor [Figure 2]. The NMDA receptor plays a very important role in synaptic plasticity and memory.[12]

Magnesium deficiency is shown to lead to changes in the functioning capacity of central nervous system (CNS), especially in the synaptic potentiation and glutamatergic transmission in the limbic system and cerebral cortex, which are the centers for learning and memory. These regions in the brain play important roles in the etiopathogenesis of depression. Magnesium modulates adrenocorticotropic sensitivity to adrenocorticotrophic hormone and protects against the hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoid is demonstrated to exhibit neurotoxic effects in the hippocampus, and hippocampal cells are found to be lost in depression. Magnesium interacts with gamma-amino butyric acid (GABA) receptors and also keeps glutamate within healthy limits [Figure 3].[13]

Depression has diverse effects on different neurotransmitter or immune systems. Many elements have an effect on the monoaminergic system (copper and selenium) and glutamatergic or GABAergic system (copper and manganese). Appropriate levels of elements such as copper, selenium, and manganese regulate the immune system, which is also involved in depressive disorder.[5] Excess physical or mental stress causes excretion of calcium and magnesium in the urine, leading to decreased blood levels.[13]

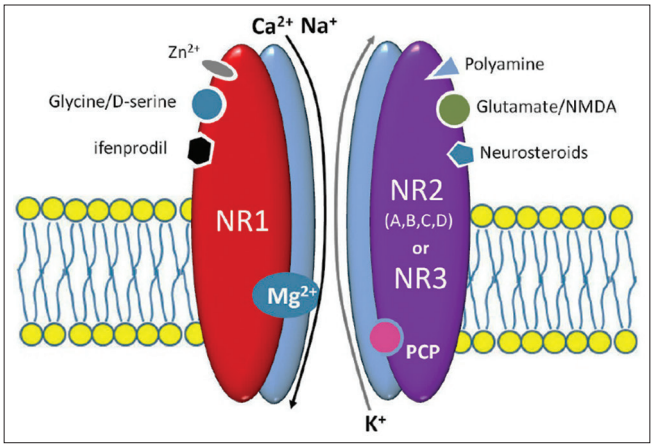

Figure 2: NMDA receptor with agonists and antagonists binding sites[12]

Selenium

Antioxidant property is seen through functioning of selenoproteins, in almost all the systems of the body.[7,14] Selenium alters dopaminergic, serotonergic, and noradrenergic systems to produce antipsychiatric effects. Its deficiency is linked to adverse mood states.[6,15] Selenium increases serotonin levels by inhibiting monoamine oxidase A.[16] Selenium has a role as antioxidant seem to preserve dopaminergic system from free radical injury, thus plays a crucial role in progression of neuronal degeneration.[14,17]

In animal models, selenium deficiency was shown to alter neurotransmitter turnover rate; and sodium selenite showed protective role against dopamine loss. Glutathione peroxidase has selenium as the cofactor; thus, it offers protection against altered levels and function of neurotransmitters, neuron loss, cell death, free radical generation, and amyloid beta peptide. The activity of the enzyme is decreased in depressed and irritable individuals.[3] Selenium supplementation was shown to reduce intractable epileptic seizures.[18] A study involving rodents found an association between selenium deficiency and decreased BDNF concentrations.[14] Selenium deficiency and resulting deregulation of thyroid function may play a role in the development of depression.[15,19] A low selenium concentration has been associated with an increased level of pro-inflammatory cytokines, IL-6, CRP, and GDF-5.[14]

Iodine

Deficiency of iodine affects energy metabolism, body temperature, growth, immune function, and brain performance (concentration, memory, and more). Iodine deficiency disorders lead to reversible brain damage of fetus and retarded psychomotor ability with lowered mental ability such as depression.[4,6]

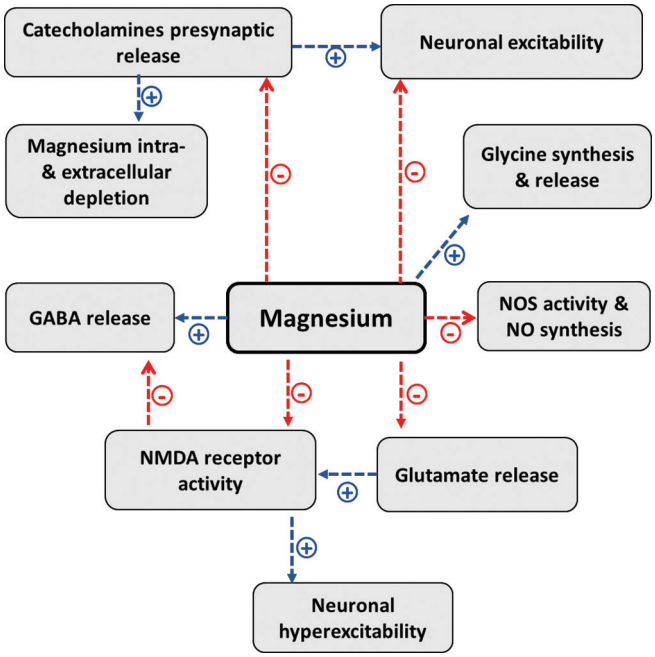

Figure 3: Functions of magnesium in the brain.[13]

Zinc

Zinc is found in high levels in the regions of the brain involved in emotions, learning, and memory. These zinc regions, where glutaminergic neurons are present, are the hippocampus, frontal cortex, amygdala, and olfactory bulb.[20] Along with pyridoxine, it helps in the synthesis of neurotransmitters, such as serotonin and dopamine.[7] It regulates gene expression in neurons and glial cells.[8,21] By its antioxidant role, it protects the brain cells against oxidative damage.[4] Following antipsychotic medications such as haloperidol or risperidone, magnesium, and zinc were found to increase.[22] Zinc supplementation by raising GABA levels may help improve to anxiety symptoms.[23] Zinc plays a very important role in neural development, learning and memory function, as well as mood disorders. Excessive activation of NMDA glutamate receptor and associated processes of excitotoxicity leads to mood disorders [Figure 4].

Zinc decreases the activation of NMDA glutamate receptors thus bringing out antidepressant effects. It was found that mice which were receiving selective serotonin reuptake inhibitors were found to have more number of receptors for zinc in their frontal cortex.[20] Lower serum zinc can be considered as a marker of treatment resistance.[24] When pro-inflammatory cytokines increase, zinc level decreases. Cytokines, which get elevated during stress and inflammation, cause formation of quinolinic acid from tryptophan. Quinolinic acid is found to favor NMDA receptor activity. There is less tryptophan to form serotonin; precipitating symptoms of depression especially when there is overactivity of HPA axis.[25,26]

Copper

Copper is a component of several metalloenzymes linked to dopamine synthesis, in biochemical pathways involving either antagonism of dopamine production or catalysis of its breakdown. Excess copper accumulation leading to decreased dopamine action is implicated in schizophrenia. In a study, ADHD children had a higher copper than zinc which was correlated with observations made by the teacher.[27] Increase in blood copper was associated with a decrease in sustained attention and short-term memory.[28] In a randomized controlled trial on 80 adults with ADHD, lower baseline copper levels were associated with better response to treatment with a vitamin-mineral supplement.[29] Copper in high doses increases free radical injury causing damage to DNA with decreasing cell proliferation.[30] Furthermore, increased copper in blood and brain induces symptoms of major

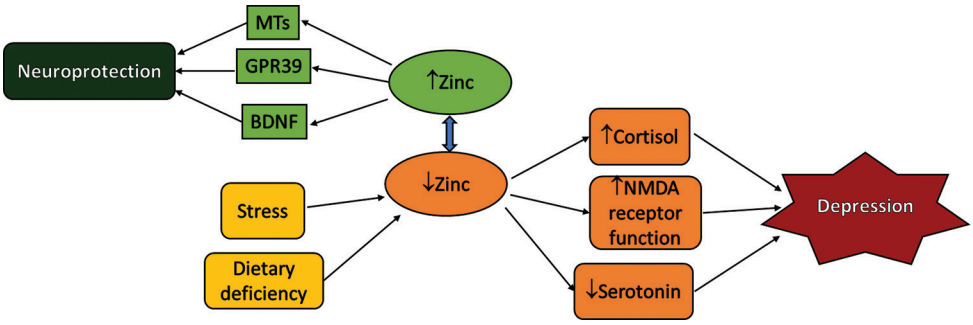

Figure 4: Role of zinc at normal and low blood levels.

depressive disorders. In very high levels, copper can cause extensive tissue destruction of various organs such as skeletal and cardiac muscles, liver, kidney, methemoglobinemia, hemolysis, and encephalopathy, resulting in death.[31]

Iron

Iron supplementation has been shown to have effect on lassitude, concentration, and mood; thus iron plays a crucial role in the formation and function of the CNS. Iron is a cofactor in the metabolism of tyrosine to dopamine. Thus, it plays a great role in the production of serotonin, norepinephrine, epinephrine, and dopamine. As a result, changes in iron metabolism are markers in patients with depression. Like zinc, iron also has effect on the frontal cortex; causes binding of dopamine and serotonin to their binding proteins.[8] In case of iron deficiency anemia (IDA), iron is utilized by the red blood cells, thus depriving brain of iron. This leads to impaired myelination in the brain and thus of the monoamine metabolism. IDA is associated with increased risks of dementia, anxiety disorders, depression, sleep disorders, and psychotic disorders. Iron deficiency results in mental and physical fatigue, difficulty in concentration and dizziness, low mood, and irritability and also triggers panic symptoms resulting in panic attacks.[4,32,33]

Serum levels of iron were reduced significantly in MDD patients.[7,34] In cases of IDA, there are altered levels of neurotransmitters, glutamate, and GABA in the brain resulting in impaired memory, learning, and behavior, thus causing emotional and psychological problems.[35] IDA patients are more predisposed to altered cognitive and neurological symptoms.[36-38] IDA interferes with cognitive and skills development as well as learning and behavior in children and adolescents.[6] Thus, IDA is associated with psychiatry disorders such as anxiety, depression, BD, restless legs syndrome, and dementia.[7]

Manganese

All other minerals, manganese is a component of various body enzymes, thus having a major role in homeostasis of brain function. Hypomagnesemia increases autoimmune reactions and macrocytosis, thus precipitating depression. Manganese levels are low in patients with MDD when compared with that of controls.[7] Individuals with manganese deficiency were found to have altered carbohydrate and lipid metabolisms, fertility, and bone problems. Superoxide dismutase (SOD) which takes part in antioxidant activity requires manganese for efficient function. In human, three types of SOD are present. SOD1 and SOD3 contain copper and zinc, while SOD2 contain manganese at their reactive center. It is involved in defense against reactive oxygen species.[7]

Electrolytes

Altered electrolyte metabolism may play a role in the pathogenesis of the affective disorders.[39] Several symptoms such as headache, vomiting, nausea, gait disturbances, dizziness, mild dementia, irritability, and involuntary muscle contractions are common among mild hyponatremia with serum sodium level of 125–130 mEq/L. When there is further decline in serum sodium level to 115–120 mEq/L, there may be convulsions, unconsciousness, and respiratory collapse.[9] Potassium imbalances rarely involve CNS and are predominantly associated with muscle symptoms. Hypokalemic cerebral symptoms may be mild and rare. Mild muscle weakness is the mostly observed manifestation of hyperkalemia and often observed in chronic adrenal deficiency.[9] Hyponatremia, hypokalemia, and hypercalcemia are common electrolyte alterations seen in patients with psychiatric disorders. Thus, correction of underlying electrolyte abnormality may improve the psychiatric symptoms and helpful for clinician for further treatment.[40]

Chromium

Chromium helps in the transport of tryptophan across the blood–brain barrier into the CNS, where tryptophan is converted to serotonin in the brain. Thus, chromium helps in the management of depression. Chromium also induces the production and release of norepinephrine. Studies have shown that chromium decreases the activity of serotonin receptor, 5-HT2A. Chromium also improves endothelial

function, lipid profile, and biomarkers of oxidative stress. It has a role as an antidepressant in atypical depression, a condition characterized by increased appetite, hyperphagia, and carbohydrate craving.[4]

Lithium

Lithium has been used in the management of psychiatry disorders. Studies have shown that lithium causes epigenetic changes in various genes which code for proteins such as signaling molecules, transcriptional enhancers, and transactivating factors, proteins involved in carcinogenesis such as cell adhesion molecules, oncogenes, and tumor suppressor genes.[40] BDNF, being a widely prevalent growth factor in the brain, has important role in the formation of plasticity of the brain. BDNF is involved in the formation and growth of new neurons, as well as in improving memory as shown by the increase in the size of hippocampus. In patients with major depressive and BD, epigenetic changes in BDNF alter its function. This is further evidenced by decrease in size of hippocampus with impairment of memory.[41,42] Lithium is found to promote intercellular communications and immune response; also regulates protein and nucleic acid metabolisms, thus enhancing cell growth. This improves the symptoms present in mental disorders.[43] In patients with Alzheimer's disease and other dementias, BDNF is found to cause destruction of amyloid-β.[44] Lithium, in trace amounts, has been shown to improve mood and slow the progression of dementia. Overall, lithium has neuroprotective, antioxidant, and regenerative roles in the brain. Lithium also modulates monoamine oxidase activity.[45,46] Lithium has been used in BD, depression, schizophrenia, aggression, impulse control disorder, eating disorders, ADHD, and in certain subsets of alcoholism. Lithium can be used in patients with cardiovascular, renal, endocrine, pulmonary, and dermatological comorbidity.[4]

ASSESSMENT OF MINERAL STATUS

All patients should be subjected to laboratory testing to assess mineral nutrient deficiency. Testing for dietary deficiencies of these nutrients gives the opportunity to manage in the form of drugs or dietary supplementation. This could provide an adequate nutrient supply for effective brain development, thus improving cognition and thus preventing or delaying the onset of psychiatric disorders later in life.[47]

CONCLUSION

Mental wellness requires a constellation of factors including healthy lifestyle choices in the form of supplementation of vitamins and minerals which can boost mental health. Even though micronutrients such as minerals could be dietary supplements, the appropriate quantity of intake of the dietary sources containing these minerals should be from the treating physician or nutritionist. Patients shall be encouraged to eat green leafy vegetables, colorful vegetables and fruits, beans and legumes, seafood, and whole grains.

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Authors' contributions

All the authors have contributed in writing and publishing this article.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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