Evidence-Based Research on the Role of Zinc and Magnesium Deficiencies in Depression

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Targeted mineral supplementation has the potential to augment treatment response and yield improvement in clinical symptoms.

Minerals are critical in supporting several key functions related to mood disorders, including neurotransmitter synthesis, cellular metabolism, and immunocompetence. While micronutrient deficiencies were presumably thought to occur in lower-income countries, micronutrient depletion has emerged as a form of “type B” malnutrition in industrialized countries despite food surpluses. Modern-day malnutrition has been attributed to poor dietary patterns, marked by excess intake of refined sugars and the absence of nutrient-dense foods.

The significance of various nutrients for mental health status has been established, but whether poor nutritional status is a causative agent or an effect of poor mental health continues to be debated. However, the prevalence of poor nutrition among depressed persons is indisputable—nutritional deficiencies have frequently been associated with the incidence and increased risk of depressive symptoms. Related content: Micronutrients and Depression

In a population study that included 13,486 children and adolescents, excess consumption of low nutritional content foods was correlated with increased aggression, violent behaviors, and psychiatric distress.¹ Earlier clinical studies also indicated a positive correlation between rates of depression and poor nutrition. In a study that comprised 184 elderly participants, researchers found that up to 50% had identified nutritional inadequacies and comorbid depression.²

The role of micronutrients in the pathophysiology of depression

Current research illustrates the vast array of mental health complications that may arise because of micronutrient deficiencies, including impairments in cognitive function and neuromotor performance, effects on brain morphology, and disruption of neurochemical pathways. Micronutrients are vital in enzymatic reactions responsible for neurotransmitter synthesis and preservation, and mineral deficits have been identified in the pathophysiology of depressive symptoms.³

Minerals are essential in the enzymatic activation of brain-derived neurotrophic factor (BDNF), a protein that regulates neuronal plasticity and promotes the maturation and differentiation of new neurons within the CNS and the peripheral nervous system. Animal studies have shown that stress can reduce BDNF expression and activity in the hippocampus, and clinical studies have echoed similar findings in which serum BDNF levels are reported to be lower in depressed patients than in controls.⁴,⁵ Augmentation strategies that can facilitate BDNF expression have been emerging as an area of interest among researchers.

Augmentation strategies with zinc

As one of the most abundant trace minerals in the brain, zinc supports several physiological functions and possesses immuno-modulation properties. Zinc also activates hippocampal neurogenesis through the upregulation of BDNF, while inhibiting glutamate and N-methyl-D-aspartate (NMDA) activity.

The bioavailability of zinc can influence CNS function through a variety of mechanisms, and diets scarce in zinc have been known to result in behavioral disturbances and diminished brain function. In a meta-analysis that evaluated 17 studies with 1643 depressed and 804 control participants, peripheral serum zinc concentrations were approximately -1.85 μmol/L lower in depressed participants.⁶ Moreover, low serum plasma zinc levels have been associated with impairments in information processing and impulsivity in humans.⁷

Treatment with citalopram, a potent SSRI, in combination with zinc was found to induce a significant increase in presynaptic/extracellular zinc levels within the brain.⁸ It was hypothesized that the antidepressant effect of zinc is dependent on serotonin transmission; thus, a robust serotonin-enhancing mechanism may be influential in supporting zinc’s therapeutic effect. Zinc has
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Magnesium as a modulator of stress-response systems

Magnesium is a divalent cation that occupies a fundamental role in intermediary metabolic processes in living systems. It functions as a central regulator of metabolism and modulator of calcium and potassium transport. Like other trace minerals, magnesium works its way into the human system via the food chain. It is second only to potassium in terms of its abundance in mammalian tissues, and it is involved in over 300 vital biochemical reactions within the human body. Like zinc, magnesium is critical for enzymatic, hormonal, and neurotransmitter processes. The first report of magnesium’s role in depression surfaced almost a century ago. In 1921, magnesium became the first medically acknowledged substance to be utilized as an intervention for depressive illness. Magnesium was successfully used to treat 220 of 250 study participants who had initially presented with agitated depression. Since that benchmark study, empirical evidence in support of magnesium’s efficacy has continued to emerge.

Evidence suggests that magnesium can mitigate depressive symptoms, whereas magnesium insufficiency may aggravate stress responses. The repletion of magnesium levels is often associated with improvement of symptoms typically following antidepressant therapy and/or recovery from depression. Perhaps most exciting are data from clinical trials that have distinguished magnesium as an effective adjunct in the treatment of depression and anxiety; in these settings, it modulates stress response mechanisms.

Under circumstances of burden, the human brain activates a sequential neurobiological stress management reaction that prepares the individual to cope with imminent threat. Long-term exposure to ecological and/or psychological pressures can trigger the chronic hyperarousal of the body’s adaptive stress response mechanisms, as evidenced by elevated serum cortisol levels. Under normal conditions, an appropriate stress response is activated when the hypothalamus emits corticotrophin-releasing hormone (CRH) to signal the adrenocorticotropic hormone (ACTH) to release cortisol from the adrenals. Activation of this pathway triggers a negative feedback loop to suppress the production of CRH until the body reestablishes homeostasis. However, in conditions in which chronic stress is prevalent, such as in depression and anxiety, hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and persistent elevated cortisol levels cause neurons to demyelinate, degrade, and eventually die.

Magnesium aids in modifying the stress response via the HPA axis by reducing the secretion of ACTH, modulating adrenocorticotropic sensitivity to ACTH, and preventing stress hormones from entering the brain. However, in the presence of chronic stress exposure coupled with magnesium deficiency, the HPA axis is unable to respond appropriately and efficiently. Although scientific research is limited, the available evidence supports magnesium as a promising adjunct therapy. The efficacy of oral magnesium and imipramine was compared in elderly persons with type 2 diabetes, hypomagnesemia, and comorbid depression. Study participants were randomized to either 450 mg of supplemental magnesium or 50 mg of imipramine daily for 12 weeks. Magnesium supplementation was found to be comparable to imipramine, with similar levels of improvement as assessed by depression scales.

A cross-sectional study of 402 Iranian students also demonstrated a relationship between inadequate consumption of dietary magnesium and depressive symptoms that persisted even after adjustments for potential confounders such as sex, age, BMI, socioeconomic status, lifestyle activity, and other factors. Data were collected through self-reported questionnaires, including the Center for Epidemiologic Studies Depression scale and the semiquantitative food frequency questionnaire. Earlier clinical studies also illustrated magnesium’s ability to decrease symptoms of MDD and chronic fatigue syndrome by exhibiting a synergistic effect in tandem with some antidepressant therapy.

While the exact role of zinc in the pathophysiology of depression remains unclear, the inverse relationship between zinc and depression has been frequently established in studies that evaluated zinc status in depressed patients. Zinc supplementation has been an effective adjunct to pharmacological interventions, whereby a meta-analysis of randomized, controlled studies that included over 450 depressed patients who received zinc in addition to imipramine reported a reduction in depressive symptoms.

Persons who are susceptible to zinc insufficiency include those with gastrointestinal disorders or dietary restriction as seen in anorexia nervosa, alcoholics, vegetarians, and pregnant or lactating women. These conditions alter normal physiology and result in poor dietary absorption and expedited losses in the context of circumstances that require increased zinc bioavailability.

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compounds.\textsuperscript{17,18} Heiden and colleagues\textsuperscript{19} observed that magnesium, when administered with lithium, benzodiazepines, and neuroleptics, significantly reduced dosing requirements for all of the compounds. It appears that magnesium can be effective not only by itself, but also as an adjunct to standard treatment regimens.

A number of clinical disorders have been associated with diets deficient in magnesium, including diabetes, metabolic syndrome, inflammation, and hypertension. Thus, the decline of dietary magnesium intake over the past century should be of concern—approximately 45% of the US population are estimated to consume less than the recommended daily allowance.\textsuperscript{20}

**Evaluating the role of nutraceuticals in clinical practice**

Depression is a disabling, chronic illness: the majority of patients have unresolved symptoms despite first-line antidepressant treatment. The pathophysiology of depressive disorders involves a variety of dysfunctional biochemical mechanisms, such as monoamine impairment, BDNF activity, and neuroendocrinological changes.\textsuperscript{21} Minerals are vital in achieving optimal cognitive function. They function as part of larger cellular processes by mobilizing neurotransmitter synthesis, activating hundreds of key enzymes, modulating the activity excitatory receptors, and regulating immunological responses.

Inadequate levels of zinc and magnesium have direct, observable effects on biomarkers of mood and behavior. Targeted mineral supplementation has the potential to augment treatment response and yield improvement in clinical symptoms. Alterations in other minerals, including chromium, copper, iron, and lithium, are also key participants in neurochemical reactions that influence mood and behavior. The identification of mineral and other micronutrient deficiencies should be an integral part of the assessment, treatment, and prevention of mood disorders.

Adjunctive use of nutraceuticals may improve the therapeutic efficacy of pharmacological treatment by modulating underlying neurobiological mechanisms. Additional research studies that evaluate micronutrient therapy in large-scale populations will help strengthen our understanding of the clinical application of minerals in the treatment of depression.

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**Disclosures:**

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**References:**


