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Review Article

Zinc Deficiency in Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is a major public health concern necessitating novel strategies for prevention and treatment. Zinc is an essential trace element involved in a myriad of vital biological processes, including crucial brain processes. Zinc deficiency is a major global health concern. Cross-sectional surveys show that patients with MDD frequently suffer from insufficient zinc supply. Emerging evidence from randomized trials supports the role of zinc in treating MDD. This clinical data is supported by neurobiological evidence generated using animal models linking zinc deficiency with neuronal dysfunction and depressive-like behavior. Importantly, zinc might link inflammation with glutamatergic and serotonergic dysfunction in depression.

This brief review summarizes the most important clinical and basic science evidence for zinc's role in depression and draws conclusions for the clinical practice.

Keywords: Zinc Deficiency; Major Depressive Disorder; Mental Health

Introduction

Major depressive disorder (MDD) is a significant public health concern imposing a substantial burden of functional disability and mortality. In the United States in 2010, the estimated annual economic losses of MDD exceeded 200 billion dollars [1]. MDD is highly prevalent in the general adult population throughout the world. The global 12-month prevalence of MDD is around 5% [2]. Moreover, large-scale longitudinal studies suggest that MDD is a predictor of poor physical health, increasing the risk for illnesses such as diabetes, obesity, heart disease, cancer, and Alzheimer's disease [3]. MDD will be the leading cause of global disease burden by 2030 [4].

Despite intensive research, the pathophysiology of depression is still understood poorly. Therefore, a causal medical treatment is still lacking [5]. Virtually all the available monoamine-based antidepressant drugs have a broadly comparable modest clinical efficacy and a response rate of approximately 50%; their onset of action is delayed by several weeks [6]. Moreover, considerable tolerability and safety issues, including adverse side effects such as nausea, dizziness, insomnia, sexual dysfunction, and weight gain, burden antidepressant drugs [7]. Psychotherapeutic interventions can alleviate MDD. However, the efficacy and response rate are comparable to antidepressant effects [8]. Moreover, the access to evidence-based psychotherapy is limited. Therefore, more efficient, available, and safe means for the prevention and treatment of MDD are urgently required.

Clinical and preclinical research provides evidence for the importance of zinc in MDD's pathophysiology and treatment. Zinc

might have antidepressant properties, act as an antidepressant drug enhancer, or serve as a biomarker. This brief review summarizes the recent literature supporting zinc's role in the pathogenesis, prevention, and treatment of MDD.

Zinc and human health

Zinc is an essential trace element vital for brain development and function [9,10]. Significant dietary sources of zinc are oysters, beef, crab, lobster, pork chop, baked beans, chicken, and pumpkin seeds [11]. Physiological serum zinc levels are considered to range from 0.66 to 1.10 µg/mL in adults [12], although the validity of serum zinc measurements has been questioned (see sections six and seven) [11]. Zinc cannot be stored in meaningful amounts in the body and thus requires a constant supply [13]. The ubiquitous importance of zinc is highlighted by the fact that around 10% of the human genome encodes zinc-binding proteins [14].

Zinc has various crucial functions in the brain's physiology. It influences neurotransmission and sensory processing and activates pro-survival and pro-death signaling pathways. Moreover, metal-binding proteins and an extensive array of zinc transporters tightly regulate cerebral cellular zinc levels [15]. Zinc is indispensable for survival, and zinc deficiency is linked to numerous health issues [13]. Zinc deficiency in children can cause growth retardation [11]. It has been estimated to cause stunted growth in one-third of the global population [16]. Moreover, zinc deficiency can cause impaired immune function, improper skin and bone health, and cognitive impairment [17]. Mutations in ZIP4, the principal intestinal zinc transporter, cause acrodermatitis enteropathica, a severe disorder leading to failure to thrive, dermatitis, hair loss, enteropathy, and, if untreated, eventually results in death [18].

Epidemiology and etiology of zinc deficiency

Zinc deficiency is a major global health problem, affecting especially developing countries, and is, thus, designated by the World Health Organization (WHO) as a significant disease-contributing factor [19]. The WHO estimates that zinc deficiency affects > 30% of the world population, with prevalence rates varying significantly from < 5% to > 70% between various world regions [20]. In developing countries, zinc deficiency is among the ten significant factors contributing to disease burden [21]. Almost 60% of all child deaths in Africa are attributed to zinc deficiency [22].

The required dietary intake of zinc increases from 3 mg/day in children to 8 mg/day in women and 11 mg/day in men. These requirements are even higher in pregnant and lactating women [13].

In developing regions, zinc deficiency commonly occurs due to malnutrition; however, it is often associated with aging and multimorbidity in developed regions. Inherited forms of zinc deficiency are rare conditions [23]. Individuals with an acquired zinc deficiency often display a combination of unfavorable factors, such as nutritional lack of meat intake, excess phytates (present in legumes, seeds, soy products, and whole grains), or oxalates (found in spinach, okra, nuts, and tea) [13]. Moreover, chronic conditions such as alcohol abuse, chronic intestinal diseases, diabetes, liver disease, sickle cell disease, HIV infection, parenteral nutrition, a strictly vegan diet, and anorexia nervosa can impede the absorption or be associated with an inadequate intake of zinc [13].

Zinc and depression

Numerous studies reported an association between zinc deficiency and depressive symptoms. A meta-analysis of 17 human observational studies found that blood zinc concentrations are approximately 0.12µg/mL lower in depressed subjects than in healthy controls [24]. Interestingly, a population-based epidemiological survey including > 5,500 individuals detected an association between zinc deficiency and depression in women but not in men [25]. A 20-year prospective follow-up study found no association between the risk of depression and zinc intake in middle-aged men [26]. On the other hand, cross-sectional studies in female adolescents and postmenopausal women reported a link between zinc deficiency and depression severity [27-29]. However, a recent Iranian study found a high prevalence of zinc deficiency and an association between inadequate zinc supply and depression in an elderly cohort (age ≥ 60 years), including both men and women [30]. Interestingly, another Iranian study with adolescent females found a weak correlation between dietary zinc intake and serum zinc concentrations, with only the former but not the latter correlating with depressive symptoms [31]. A US population survey including almost 15,000 adults found that meeting the recommended daily allowance of zinc intake was associated with a lower risk for depression [32].

A randomized controlled trial (RCT) found that serum zinc levels are inversely associated with the systemic immune response

in depressed individuals and interact with the antidepressant's sertraline clinical efficacy [33]. A recent comparative dose-response meta-analysis of observational studies and randomized controlled trials, including a total of 13 observational studies and 8 RCTs, concluded that zinc intake was associated with a 28% reduced risk of depression, that zinc supplementation lowers depressive symptom scores of depressed patients, and that even zinc monotherapy has a beneficial effect superior to adjunctive therapy [34]. Another recent meta-analysis, including five RCTs, found that zinc supplementation combined with antidepressant drugs might effectively treat patients with depression [35].

Neurobiology of zinc in depression

The neurobiology of zinc is a well-studied research area, and there are several excellent reviews covering it in-depth, e.g., by Krall and colleagues [15]. Numerous studies using experimental rodent models reported causal relationships between zinc depletion and depression-like and sickness-behavior. In the cerebral cortex and hippocampus, zinc ions regulate synaptic transmission and may act as neurotransmitters [36]. They modulate many ligand- and voltage-gated ion channels [37]. Chronic administration of a zinc-deficient diet results in a reduction in hippocampal neurogenesis in mice [38]. It increases neuronal apoptosis in mice, indicating that zinc deficiency is associated with a decline of structural plasticity in the hippocampus [38]. Zinc transporters are highly regulated genes during neuronal differentiation, and low zinc levels are associated with decreased cell survival, altered neuronal differentiation, and perturbed synaptic function [39].

Zinc transporters (ZincTs) and zinc sensing GPR39 receptors might play a crucial role in depression. Zinc transporter 3 knockout (KO) mice have significantly fewer proliferating progenitor cells and immature neurons after the hypoglycemia challenge, hinting toward zinc's essential role in hippocampal neurogenesis, a process critical for mood control [40]. Moreover, GPR39 receptors have been implicated in the serotoninergic system's homeostasis. GPR39 interacts with 5-HT1A and GalR1 to form heteroreceptor complexes with a considerable signaling diversity [41]. Liquid chromatography-mass spectrometry (LC-MS) studies demonstrated a significant reduction in tryptophan and tyrosine but not in glutamate levels in the hippocampus of GPR39 KO mice, indicating a possible role of the GPR39 receptor in monoaminergic neurotransmission, which plays an essential role in the pathophysiology of depression [42]. Furthermore, experiments conducted with GPR39 KO mice show that GPR39 is required for the antidepressant effect of monoamine-based antidepressants [43].

Zinc might influence depression by modulating the N-methyl-D-aspartate (NMDA) receptor's activity [44]. The NMDA receptor is a type of ionotropic glutamate receptor, the other being the AMPA receptor and kainate receptors. Ample evidence shows that glutamate homeostasis and transmission are disrupted in MDD, and thus, the NMDA receptor has become a therapeutic target of interest in MDD research [45]. A zinc-deficient diet upregulates NMDA receptor complexes, but antidepressants normalize their levels and reverse depression-like behavior in mice [46]. Zinc's antidepressant effects might be mediated through its interaction with NMDA receptors and the L-arginine-nitric oxide (NO) pathway [47].

Another theory potentially explaining zinc's antidepressant properties is its antioxidant and anti-inflammatory activities. Neuroinflammation, including microglia and astrocyte activation, might be crucial in depression [48]. Lipopolysaccharide injection (LPS) induces sickness and depressive-like behavior in experimental rodents [49]. Zinc induces the expression of the anti-inflammatory regulator A20 in BV2 microglial cells and thus inhibits LPS-induced microglial activation and protects the viability of HT-22 hippocampus cells [50]. Zinc supplementation in rodents prevents LPS-induced behavioral impairment, inflammatory cytokine expression (interferon-gamma), hippocampal astrocyte activation, and astrogliosis [51,52].

Interestingly, the inflammation may link the serotonergic and glutamatergic dysfunction in depression in a zinc-dependent manner, as zinc levels are decreased by stress and inflammation [53]. Moreover, reduced zinc levels may lead to an activation of the hypothalamic-pituitary-adrenal (HPA) axis [54]. In addition, the enzyme indoleamine 2,3-dioxygenase (IDO) is induced by pro-inflammatory cytokines. It metabolizes tryptophan into quinolinic acid, which acts as an NMDA receptor agonist. An increase in IDO activity might reduce tryptophan available for 5-HT synthesis, potentially aggravating depressive symptoms [55]. The increase in quinolinic acid results in excess NMDA receptor activity, causing an extra glutamate release and neurotoxicity. With zinc already decreasing in the pro-inflammatory state, it cannot effectively inhibit the NMDA receptor, and hyperactivity ensues, perpetuating and aggravating the depressed condition (Figure 1) [44].

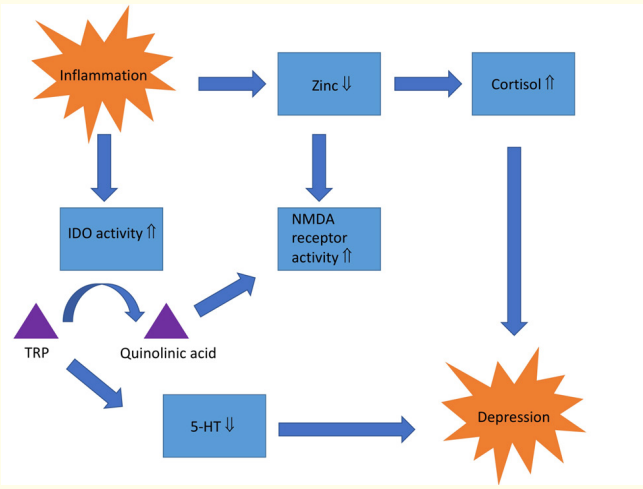

Figure 1

Figure 1. The link between glutamatergic and serotonergic transmission in depression through zinc. Inflammation may link the Glutamatergic and Serotonergic Systems. During inflammation, zinc levels decrease, resulting in the HPA axis activation with increases in glucocorticoids. This process might result in symptoms of depression. Simultaneously, pro-inflammatory cytokines increase the enzymatic activity of IDO. IDO increases the turnover of tryptophan to quinolinic acid, an NMDA receptor agonist. This event raises the release of glutamate and Ca+2, increasing the risk for neuronal damage. Because tryptophan (TRP) is converted to quinolinic acid, less tryptophan is available to produce serotonin (5-HT). This lack can aggravate symptoms of depression; adapted after [56].

Management of zinc deficiency

Treatment of zinc deficiency usually starts with oral supplementation [13]. Adults' clinical manifestations can generally be effectively remedied with a 1-2 weeklong treatment of a 2 to 3 mg/kg or 20-40 mg daily intake. Oral supplementation efficiently diminishes zinc deficiency symptoms, regardless of whether the deficiency is detectable in test results [13].

However, short-term oral supplementation treatment is not practical for all conditions. For instance, zinc supplements must be taken long-term when treating illnesses impairing effective zinc absorption, such as acrodermatitis enteropathica [57,58]. In life-long treatments of zinc supplementation, doses are determined by serial serum zinc levels of the patient. Generally, reactions to supplementation treatment and serum zinc levels should be examined for all patients after three to six months.

Notably, a high intake of zinc supplements may cause genitourinary complications due to iron and copper absorption damage. Therefore, it is necessary to regularly examine levels of copper and concurrent copper in long-term treatments, especially with high doses. Moreover, high doses of zinc supplementation (e.g., 50 mg/day) frequently cause gastrointestinal symptoms, abdominal discomfort, nausea, and diarrhea [13].

Conclusions and Recommendations

There are several methodological limitations to the reviewed literature. First, the relatively high error margin for measuring zinc status must be considered. While the measurement of serum zinc levels is a valuable biomarker in population surveys, its reliability as an indicator of the individual zinc status has not been demonstrated conclusively [59]. Zinc nutritional status is difficult to assess reliably with laboratory tests because of its complex distribution throughout the organism as a component of diverse proteins and nucleic acids [60]. Plasma or serum zinc levels are the most used indices for evaluating zinc deficiency. Still, these levels do not necessarily reflect cellular zinc status due to rigorous homeostatic regulatory mechanisms [61]. Thus, the clinical effects of zinc deficiency can be present in the absence of abnormal laboratory indices [11].

The relationship between zinc deficiency and depressive symptoms might be explained by reverse causation, whereby depression influences the intake because of a decrease in appetite or poor dietary habits [62]. Reduced zinc levels might also be a side effect of the increased inflammatory and oxidative processes implied in depression, rather than being causally involved in MDD's pathogenesis [37]. More prospective studies are needed to investigate a potential causal link between zinc intake and mood regulation. Moreover, more basic research is required better to understand zinc's impact on neuroinflammation and neurotransmission.

Clinicians must consider risk factors (such as insufficient caloric intake, alcohol abuse, and gastrointestinal diseases) and symptoms of zinc deficiency (such as growth retardation in children) when determining the need for zinc supplementation [11];

however, despite the emerging evidence, it is still unclear whether depression should be regularly considered a symptom of zinc deficiency. Therefore, zinc supplementation in all patients with MDD cannot be recommended currently. However, serum zinc might be measured as a part of laboratory routine work-up in patients with MDD alongside other essential micronutrients such as folic acid and vitamin B12 [63]. Clinicians should consider supplementation in patients with MDD who display deficient serum levels, show accompanying clinical signs of zinc deficiency, or have sociodemographic risk factors.

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