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The Role of Zinc in the Pathophysiology and Treatment of Depressive Disorders: A Literature Review

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ABSTRACT

Background. Depression is one of the most common mental disorders worldwide and represents a major public health concern. Increasing evidence suggests that dietary factors, including trace elements such as zinc, may play a role in the development and course of depressive disorders. Zinc is involved in numerous biological processes within the central nervous system, including neurotransmission, neuroplasticity, immune regulation, and oxidative balance.

Aim. The aim of this study was to review the current literature on the role of zinc in the pathophysiology and treatment of depressive disorders, with particular emphasis on underlying biological mechanisms, clinical findings, and potential therapeutic implications.

Material and methods. The studies cited in the presented review were selected from Pubmed and Google Scholar. The search included studies between 2020 and 2026. The key words used for the search included: depression; zinc; zinc deficiency; zinc supplementation

Results. The available literature indicates that zinc deficiency is frequently observed in patients with depression and is associated with greater severity of symptoms. Experimental and clinical studies suggest that zinc influences key mechanisms implicated in depression, including NMDA receptor modulation, regulation of brain-derived neurotrophic factor (BDNF), dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, and inflammatory processes. Furthermore, zinc supplementation may enhance the efficacy of antidepressant therapy and improve clinical outcomes, particularly when used as an adjunctive treatment.

Conclusions. Zinc appears to play a significant role in the pathophysiology of depression and may represent a promising target for adjunctive therapeutic strategies. However, further well-designed randomized controlled trials are required to establish optimal supplementation protocols and to better define the clinical applicability of zinc in depressive disorders.

Keywords: depression; zinc; zinc deficiency; zinc supplementation

Introduction

Depression is among the most common health conditions worldwide. According to current estimates, it affects approximately 5% of the adult population globally and is associated with reduced quality of life, increased morbidity, and an elevated risk of suicide [1,2].

Despite the availability of pharmacological and psychotherapeutic interventions, a considerable proportion of patients do not achieve full remission, and treatment resistance remains a major clinical challenge. Therefore, increasing attention has been directed toward identifying additional modifiable factors that may influence the course of depression. In recent years, growing evidence has suggested that diet may play an important role in both depressive symptoms and clinically diagnosed depression [2].

In particular trace elements, such as zinc have emerged as potentially important contributors to mental health [3,13].

Material and Methods

This study is a narrative review of the literature focusing on the role of zinc in the pathophysiology and treatment of depressive disorders, with particular emphasis on biological mechanisms, clinical findings, and potential therapeutic implications.

A comprehensive search of electronic databases, including PubMed and Google Scholar, was conducted to identify relevant studies published in recent years.

The search strategy included combinations of the following keywords: “zinc”, “depression”, “zinc deficiency” and “zinc supplementation”.

Eligible studies included review articles, systematic reviews, meta-analyses, and original research papers, particularly randomized controlled trials and observational studies examining the association between zinc levels and depressive symptoms, as well as the effects of zinc supplementation.

A total of 21 studies were ultimately selected, including articles published between 2020 and 2026.

DISCUSSION

Biological Role of Zinc in the Central Nervous System

Zinc plays an important role in numerous processes occurring in the central nervous system. Maintaining proper zinc homeostasis is essential for normal brain function, as both deficiency and excess of this element may contribute to neuronal damage and the development of disorders, including depression [4].

In the central nervous system, zinc is mainly concentrated in brain regions associated with cognition and emotional regulation, such as the hippocampus, cerebral cortex, and amygdala. It exists in several forms, including protein-bound zinc, vesicular zinc, and free zinc ions (Zn^{2+}), and plays a key role in synaptic transmission and plasticity. In particular, vesicular zinc is co-released with glutamate from presynaptic terminals of glutamatergic neurons, modulating neuronal excitability and signaling [4,8].

Zinc homeostasis in the brain is tightly regulated by zinc transporters, including the ZnT and ZIP families, as well as metallothioneins. These systems control intracellular zinc levels and ensure proper distribution across neuronal compartments [8,9]. Zinc also enters neurons

through various ion channels, including NMDA and AMPA receptors, highlighting its role in excitatory neurotransmission [9].

In addition, zinc is involved in neurogenesis, regulation of oxidative stress, and immune responses within the CNS. It contributes to antioxidant defense mechanisms and modulates neuroinflammatory processes, partly through the regulation of cytokine production and microglial activation [5,7].

Given its diverse functions, dysregulation of zinc homeostasis may disrupt neuronal function, synaptic plasticity, and redox balance, thereby contributing to the pathogenesis of various disorders, including depression [6].

Zinc and the Pathophysiology of Depression

The pathophysiology of depression is complex and involves multiple interacting mechanisms, including abnormalities in neurotransmission, impaired neuroplasticity, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, and chronic low-grade inflammation [9,14]. A growing body of evidence suggests that zinc plays a significant role in many of these processes.

One of the key mechanisms linking zinc to depression involves the modulation of glutamatergic neurotransmission. Zinc acts as a neuromodulator at excitatory synapses, particularly through the regulation of N-methyl-D-aspartate (NMDA) receptors. It has been shown that zinc deficiency may lead to overactivation of NMDA receptors, resulting in excitotoxicity and neuronal damage, which are implicated in the development of depressive symptoms [6,9].

Zinc is also involved in neuroplasticity through its influence on brain-derived neurotrophic factor (BDNF), a key regulator of neuronal survival and synaptic plasticity. Reduced zinc levels have been associated with decreased BDNF expression, potentially contributing to impaired neurogenesis and structural brain changes observed in depression [5,9].

Another important mechanism involves the regulation of the HPA axis, which plays a central role in the stress response. Dysregulation of the HPA axis, often manifested as hyperactivation and elevated cortisol levels, is commonly observed in patients with depression. Zinc deficiency has been shown to enhance HPA axis activity, potentially exacerbating stress-related neurobiological changes and depressive symptoms [9,14].

Experimental studies also suggest that zinc deficiency may induce molecular and proteomic changes similar to those observed in major depressive disorder [10].

Moreover, zinc plays a key role in immune and inflammatory regulation. Low zinc levels are associated with increased production of pro-inflammatory cytokines, such as IL-6 and TNF-α, which have been linked to the development of depressive symptoms [15,18].

Zinc also contributes to the maintenance of redox balance in the central nervous system. Its deficiency may increase oxidative stress, thereby promoting neuronal damage and the progression of depressive disorders [6,7].

Taken together, these findings suggest that zinc is involved in multiple pathways associated with the pathophysiology of depression. Alterations in zinc homeostasis may contribute to the development and progression of depressive disorders through effects on neurotransmission, neuroplasticity, stress response, inflammation, and oxidative balance.

Zinc Levels in Patients with Depression

Numerous clinical studies have demonstrated that patients with depression often present with lower serum zinc levels compared to healthy individuals [11,15]. This association has been observed across various population groups, including women, older adults, and individuals with chronic diseases.

Meta-analyses and observational studies further indicate that lower zinc concentrations are associated with greater severity of depressive symptoms [11,20]. Additionally, altered levels of inflammatory markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP), have been reported in patients with reduced zinc levels, suggesting a link between zinc deficiency, inflammation, and depression [15].

Dietary factors also appear to influence zinc status. Inadequate zinc intake has been associated with a higher risk of depressive symptoms, further supporting the role of nutrition in mental health [12,19,21].

Zinc Supplementation in Depressive Disorders

Recently, increasing attention has been paid to the potential role of zinc supplementation in the treatment of depression. A growing body of evidence suggests that zinc supplementation may enhance the effectiveness of antidepressant therapy and alleviate depressive symptoms [16,17]. Studies indicate that zinc deficiency may reduce the efficacy of antidepressants, whereas supplementation may help restore their therapeutic effects [17]. Clinical trials also suggest that zinc supplementation may be beneficial, particularly as an adjunct to standard pharmacological treatment [16].

Furthermore, zinc may exert antidepressant effects through multiple mechanisms, including modulation of neurotransmission, reduction of inflammation, and improvement of neuroplasticity [9,14].

Despite these promising findings, further well-designed randomized controlled trials are needed to determine the optimal dosage, duration of treatment, and patient populations that may benefit most from zinc supplementation.

Limitations of Current Evidence

Despite the growing evidence supporting the role of zinc in depression, several limitations should be considered. Many of the studies conducted to date are observational in nature, which limits the ability to establish a causal relationship.

Moreover, the interpretation of clinical findings may be challenging, as serum zinc levels may not accurately reflect zinc concentrations in the brain. Differences in study populations, study designs, and methods used to assess zinc levels may further contribute to the heterogeneity of the available data [20].

In addition, the effects of zinc supplementation may depend on various factors, such as coexisting conditions, previous or concurrent treatments, and patient adherence [19,20]

Therefore, further research is necessary to better understand the role of zinc in depression and to determine its therapeutic potential.

Summary

Zinc is an essential trace element involved in multiple processes critical for proper brain function, including neurotransmission, neuroplasticity, stress response, immune regulation, and oxidative balance.

A growing body of evidence indicates that patients with depression often present with reduced zinc levels, which are associated with increased severity of symptoms. Both experimental and clinical studies suggest that zinc deficiency may contribute to the development and progression of depressive disorders through various biological mechanisms.

Moreover, zinc supplementation shows potential as an adjunct to standard antidepressant therapy, possibly enhancing treatment efficacy and improving patient outcomes.

Despite these promising findings, current evidence is limited by methodological heterogeneity and the predominance of observational studies. Therefore, further research is needed to clarify the role of zinc in depression and to determine its therapeutic potential in clinical practice.

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