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Review

Zinc as a marker of affective disorders

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Abstract:
Depression is considered as a chronic and recurring illness with functional impairment, significant disability, morbidity and mortality. Despite the extensive research carried out on depression, its pathophysiology is still poorly understood. An important problem concerning research into depressive disorder is the lack of biological markers which could improve diagnosis or indicate a risk of developing depression or risk of relapse. Several reports indicated decreased zinc concentrations and even its deficit in clinical depression, so the measurement of the concentration of this element in the blood of patients was suggested as a useful and specific clinical marker of depression. The reported results indicated that the serum zinc level might be a marker of depression as a state (state marker) in treatment responsive patients. However, in drug-resistant depression a decreased concentration of zinc may be a marker of traits (trait marker). It seems, however, that the measurement of the concentrations of zinc might be in the future a component of the battery of tests; of markers of immune activation and oxidative stress rather than itself alone.

Key words:
zinc, marker, depression, affective disorders

Introduction

Zinc is a cofactor and structural element of more than 300 enzymes and other proteins. It is necessary for DNA replication and transcription, protein synthesis, stabilization of cell membranes, transmembrane transport and regulation of the immunological system [53]. Zinc deficiency, in addition to neurological and so-

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matic symptoms, is accompanied by psychopathological symptoms that largely coincide with depression symptoms such as: poor appetite, reduced sense of taste, decreased libido, decrease in immunity, reduction and mood liability, irritability and cognitive impairment [43, 50]. These findings indicate the involvement of zinc turnover disturbances in depression symptoms and suggest the important role of this ion in the etiopathogenesis and therapy of depressive disorder.

Hypotheses indicating the role of zinc in the etiology of depression are based primarily on the effect of zinc on the modulation of the excitatory neurotransmitter systems' activity and related to these – neuronal plasticity [38]. The pathophysiological processes and related to these clinical symptoms of depression can be related to the excitatory processes associated with increased glutamate activity through the N-methyl-D-aspartate (NMDA) receptors and alterations in the homeostasis of the pro- and anti-apoptotic factors [32]. Glutamate receptors, especially NMDA, are considered as targets for new antidepressants, although even now NMDA antagonism is used in the treatment of treatment resistant depression [7, 51]. Zinc is a key modulator and inhibitor of the NMDA receptor activity [4, 51]. Brain structures in which functional and structural alterations in depression were observed (the hippocampus, amygdala, and cortex) are also the area where high concentrations of glutamatergic neurons, sequestering zinc, are found [32, 53]. Moreover, NMDA receptors localized in these areas are characterized by a high level of NR2A subunit protein level, which make these receptors very sensitive to an inhibitory effect of zinc and indicate its involvement in the mechanisms of neuronal plasticity [32].

Apart from NMDA receptor modulation, zinc is also an antagonist of group I (mGluR1) and group II (mGluR2) metabotropic glutamate receptors and an enhancer of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) ionotropic receptor involved in the mechanism of antidepressant activity [37, 57]. Another link between zinc and the pathogenesis of depression may be associated with the zinc sensing G-protein-coupled receptor 39 (GPR39), a member of the ghrelin receptor family [33]. GPR39 is expressed in the hippocampus (and in the cortex) and mediates metabotropic signaling triggered by zinc release. The GPR39 receptor is involved in apoptotic processes, zinc deficiency-induced depression-like behavior and the antidepressant mechanism [23, 25]. Another possible mechanism of the involvement of zinc in depression and antidepressant activity is the antagonism of glycogen synthase kinase-3 (GSK-3) [11]. Inhibition of the GSK-3 activity is one of the mechanisms of action of lithium, antidepressants and mood stabilizers (e.g., [8]).

Zinc is an essential element of the antioxidative mechanisms responsible for blood-brain barrier integrity (BBR). Zinc deficiency exacerbates loss in BBR integrity and increases its permeability for toxic substances [28]. Zinc is related to protection against oxidative damage. In animal studies, co-administration of zinc attenuates neurochemical changes that are associated with oxidative stress, such as: an increase in lipid peroxidation and a reduction in glutathione peroxidase or reductase activity or lithium-induced reductions in catalase and glutathione S-transferase activities [3].

Zinc exhibits antidepressant-like activity in both clinical and preclinical studies. Zinc (as chloride, sulfate or hydroaspartate salts) was found to be active in the forced swim test (FST), tail suspension test (TST), and in olfactory bulbectomy, chronic unpredictable stress (CUS) and chronic mild stress (CMS) models of depression (see [47, 50, 52] for review). Moreover, in the FST and CUS, zinc enhances the antidepressant effect of imipramine and citalopram (see [48, 50, 52] for review). In the controlled placebo study performed by Siwek et al. [39] (60 unipolar depressed patients, 18–55 year old, fulfilling the DSM-IV criteria for major depression without psychotic symptoms) zinc supplementation of imipramine treatment significantly reduced depression scores and improved the treatment outcome in drug-resistant patients. However, in non-resistant patients, no significant differences in the depression rating scores were demonstrated between the zinc-supplemented and placebo-supplemented groups. In a previous, placebo controlled, double blind pilot study conducted by the same authors, zinc supplementation in standard various antidepressant therapies (tricyclic antidepressants, selective serotonin reuptake inhibitors) significantly reduced the scores in the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS) after 6- and 12-weeks when compared with the placebo [30]. The recent study confirmed the antidepressant augmenting properties of zinc in major depressed patients [34]. In this randomized, double-blind, placebo controlled trial the zinc-supplemented group received

zinc orally in addition to selective serotonin reuptake inhibitor antidepressants for 12 weeks. Symptoms of depression were evaluated using the HDRS on arrival, weeks 6 and 12. In this study zinc supplementation significantly reduced HDRS sores at 12th week compared to placebo [34]. No effect of zinc supplementation on the improvement of depressive symptoms was also reported [5, 27]. However, these studies differ from that previously described with respect to both the patients and the length and quality of applications. Study by DiGirolamo et al. [5] examined the effect of six months of zinc supplementation on the mental health of school-age children and the second study [27] investigated the impact of combinations of micronutrient supplements including zinc on symptoms of depression.

The important role of zinc in the pathophysiology of depression might also be emphasized by the studies reporting alterations in the brain and serum zinc level during episodes of depression and in experimental models of depression (see [46] for review).

Zinc as a marker of depression – clinical study

The serum zinc level decreased in a stressed group (CUS) of rats rather than in the non-stressed controls, but no such alterations were demonstrated in other models, such as CMS and OB [31]. Zinc deficiency in rodents, which is recently under extensive investigation as a putative model of depression, robustly reduces serum zinc concentration (e.g., [22, 24]). On the other hand, antidepressant treatment or electroconvulsive shock (ECS) was associated with significant alterations in zinc concentrations in different brain structures and serum. Chronic ECS treatment induces a robust increase in the zinc level in the hippocampus and a slight increase in the cortex and cerebellum, while chronic treatment with citalopram or imipramine slightly increases the zinc level only in the hippocampus [29]. It is worth mentioning that chronic treatment with ECS, imipramine or citalopram induces a hippocampal/cortical increase in the presynaptic/synaptic zinc level in rats [14, 44, 54]. Moreover, chronic treatment with citalopram, but not with imipramine or ECS, increases the serum zinc level in rats [29].

Zinc as a marker of depression – clinical study

Some data has indicated that decreased zinc concentrations and even its deficit are linked to clinical depression (analyzed in [46]). As early as 1983, the case of recurrent major depressive disorder co-occurring with a low serum zinc level was described [10]. In the study conducted in 1989 on 31 Karachi patients suffering from depression, a significantly lower serum zinc level was observed in depressed women compared to healthy controls [20]. Such correlation was not found in men [20]. Little et al. [15], in the same year, in a group of ambulatory patients, observed a higher prevalence of zinc deficiency in depressed people. Also, a study conducted amongst the Iranian population showed a significantly higher prevalence of zinc deficiency in 144 people suffering from depression, compared to 161 healthy volunteers (65% *vs.* 50%). The average serum zinc level in patients was significantly lower than in the control group [35]. McLoughlin and Hodge [21] examined serum zinc levels in 14 untreated patients with a first depressive episode in comparison to the group of 14 healthy volunteers. The average concentration of serum zinc in patients was significantly lower than in the control group. In 9 patients, in whom the blood test was repeated after reaching a clinical improvement, the average zinc levels increased to values similar to that observed in the control group. In another study carried out on 35 patients suffering from depression, the serum zinc level was measured twice, both before treatment and after clinical improvement, and then compared with 35 healthy volunteers [31]. No statistically significant differences in the concentrations of zinc between these two groups were found. Clinical improvement, however, resulted in a statistically significant increase in the average zinc level in treated patients. In 1994, Maes and colleagues [16] compared the zinc concentration in the serum of 48 hospitalized patients diagnosed with unipolar affective disorder to the group of 32 healthy volunteers. Patients were divided into three subgroups depending on the severity of their symptoms: patients with a major depressive episode and melancholic symptoms, patients with a diagnosis of major depression without melancholic symptoms, and asymptomatic patients diagnosed with minor depression. In all three subgroups, the zinc levels were significantly lower than the control group, and it was lowest in the case of major depression. In

addition, a negative correlation between the level of zinc and severity of depression, measured by HDRS, was demonstrated. Another study by Maes et al. [19] confirmed these significantly lower concentrations of serum zinc in 31 depressed patients when compared to the control group (n = 15). However, no correlation between the level of zinc and severity of depression, the length of a depressive episode or the presence of melancholic features was observed. Nonetheless, the zinc levels in patients with treatment-resistant depression were significantly lower than zinc level in the remaining depressed patients and healthy volunteers. The subsequent treatment with antidepressants for 5 weeks (trazodone alone or in combination with fluoxetine and pindolol), did not induce significant changes in the level of zinc, regardless of the degree of response to treatment. An observation reported by Maes et al in 1999 [17], carried out on 48 patients diagnosed with major depression and 15 healthy volunteers, gave similar results. Lack of normalization of the level of zinc in the course of treatment or its correlation with the severity of depression measured by the HDRS was found. It should be noted that in both studies, a significant percentage of patients were those with treatment-resistant depression and in both lower levels of zinc, recorded in drug-resistant patients, showed higher intensity when compared with patients responding well to treatment, and was a sensitive (79%) and specific (93%) marker of drug resistance [17, 19]. In the Polish study conducted in 1999 by Nowak et al. [29] in 19 patients with a diagnosis of major depression, in the course of unipolar affective disorder the serum zinc level was measured 3 times: before treatment and at 2 and 6 weeks of treatment. The results were compared with a group of healthy volunteers (n = 16). Before starting the treatment, the zinc concentration in the blood in patients was significantly decreased, (12% less than the average level obtained in the control group), and was negatively correlated with the severity of depression as measured with HDRS. Effective antidepressant therapy resulted in the normalization of the level of zinc. A negative correlation between serum zinc and the severity of depression measured by the Geriatric Depression Rating Scale (GDS) was also demonstrated in a group of 66 long-term care residents [9].

Similarly, a negative correlation between the severity of depression (measured by BDI scale) and the concentration of zinc was observed in 23 female students who were diagnosed with a depressive disorder and selected from the group of 308 Iranian women aged 20-25 years [1]. In one recent study, published in 2010 and carried out in Poland by Siwek et al. [40], 30 patients who met the criteria for major depressive disorder (DSM-IV-TR) and were treated with imipramine, serum zinc concentrations were compared with a group of 25 healthy volunteers four times: at the start of treatment, and then after 2, 6 and 12 weeks. The study showed that the concentration of zinc in the serum of patients suffering from acute symptoms of depression was significantly lower (by 22%) than in healthy volunteers. The zinc concentration increased gradually in the subsequent time points until the end of the observation. There was no statistically significant correlation between serum zinc and the baseline severity of depression measured by the BDI, HDRS and MADRS. However, there was a significant negative correlation between serum zinc and the severity of depression at the end of the observation, as measured by the MADRS. The zinc concentration in the serum of patients that at the end of the observation met the criteria for remission or therapeutic response increased significantly and did not differ significantly from the concentrations found in healthy subjects. It was, however, significantly higher than in patients who did not meet the above criteria. As in the two studies of Maes et al. [17, 19], a significant percentage of subjects included in the study (n = 11) did not respond positively to at least one previous adequate medical therapy during the current episode. In this subgroup, drug resistant patients, the initial concentration of zinc was significantly (by 14%) lower than in the subset of non-drug resistant. Furthermore, at the end of the observation, the concentration of zinc in the drug-resistant patients, as opposed to the non-drug-resistant patients, did not increase substantially and was still lower than in the control group [40, 41]. It should be mentioned, however, that recently a lack of alterations in serum zinc in depression was indicated (13 depressed patients and 13 controls [36], 88 patients and 88 controls [12]).

Postpartum mood disorders are another area of zinc research. The negative correlation between serum zinc levels and scores in the Edinburgh Postnatal Depression Scale (EPDS), measured on the 3rd and 30th day after delivery, was demonstrated in a group of 61 women [56]. A significantly higher (by 45%) EPDS score with 24% lower serum zinc concentrations was found on the 3rd day after childbirth when compared with the 30th postpartum day [56].

The study of bipolar disorders demonstrated reduced levels of serum zinc [45] while it was increased during the manic phase of such patients [6].

Conclusions

The lower zinc level observed in depression could be caused by three different reasons (Fig. 1). First, by nutritional deficiencies: primary, inducing the development of depressive symptoms or secondary to depression, resulting from the reduced appetite, the typical picture of the disease. Patients suffering from depression tend to have lower levels of zinc in the blood than healthy subjects. However, only a few reports indicate the existence of actual zinc deficiency or different eating habits in people suffering from depression more often than in the general population. Grieger et al. [9] found an association between serum zinc and a poor nutritional status measured with the Mini Nutritional Assessment in geriatric long-term care residents. Amani et al. [1] found that in young depressed female (Iranian students), the daily zinc intake was about two thirds of the healthy control zinc consumption. The Beck questionnaire scores and dietary zinc intakes were inversely correlated. Another study of the Iranian population showed higher rates of zinc deficiency in patients with depression compared to healthy volunteers [35]. On the other hand, in most clinical trials, serum zinc, although lower than in healthy subjects, generally fell within the normal range and does not indicate a deficiency of zinc. Maes and coworkers [18] showed no correlation between the reduction in the level of serum zinc and weight loss or reduction in appetite in patients diagnosed with major depression. Second, an explanation for the reduction in the level of zinc in the blood of depressed patients could be hyperstimulation of the hypothalamic-pituitary-adrenal (HPA) axis, and the associated hypercortisolism [13]. There is also no relationship between the level of zinc in the blood and cortisone [16]. The most convincing seems to be a third concept, whereby a lower zinc level is the result of inflammatory and acute phase response (e.g., [2]) and is associated with oxidative stress (e.g., [42]). So far, depressed patients showed a positive correlation between reduced levels of zinc with a decrease in the overall level of protein, albumin and transferrin and negative correlation with increased levels of neopterin, IL-6 and CD4/CD8 ratio [19, 55]. The above data show that low levels of zinc in serum in depression may be due to a decrease in the level of the main zinc transporter, albumin, or can be caused by an excessive uptake of zinc from the bloodstream by the liver synthesizing metallothionein. Both the decrease in the level of albumin, as well as the synthesis of metallothioneins, are phenomena induced by IL-1 and IL-6 [16, 17]. Therefore, these findings raise the hypothesis that alterations in serum zinc may be the result of depression-related mechanisms rather than their cause [52]. Most of the clinical studies (but not all) indicate a reduction in the zinc concentration in the serum of patients diagnosed with major depressive disorder. Based on the previous data, we can argue that the serum zinc level is a marker of depression as a state (state marker) in treatment responder patients. However, in drug-resistant depression a decreased concentration of zinc may be a marker of traits (trait marker). Due to the fact that a reduction in the concentration of zinc is not a phenomenon specific to depression, its scale is varied, and taking into account the negative results of the research in this area, the measurement of the concentration of this element only in the blood of patients cannot be a useful specific clinical marker of depression. It seems, however, that the measurement of the concentrations of zinc might be in the future a component of the battery of tests; of markers of immune activation and oxidative stress.

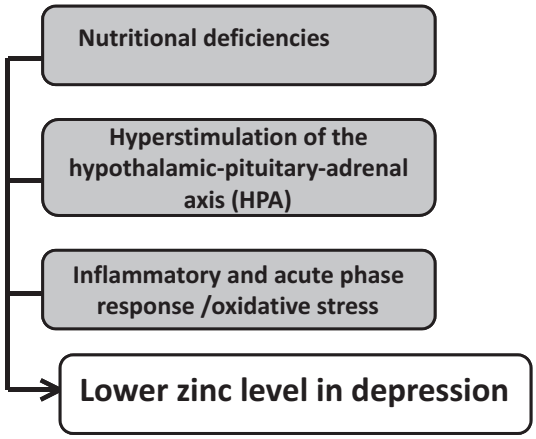

Fig. 1. The possible causes of lower zinc level in depression

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