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Zinc Deficiency and Depression

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Abstract

Zinc deficiency has multiple effects, including neurological and somatic symptoms. Zinc deficiency can lead to depression, increased anxiety, irritability, emotional instability, and induced deficits in social behavior. Clinical studies have shown that low levels of zinc intake contributes to the symptoms of depression and patients suffering from depression have a lower serum zinc level. Also the animal studies have shown an important role of dietary zinc deficiency in the induction of depressive-like symptoms. Moreover, both preclinical and clinical studies have indicated the potential benefits of zinc supplementation as an adjunct to conventional antidepressant drugs or as a stand-alone intervention. This chapter focuses on the role of the zinc deficiency in the pathogenesis of depression, changes in animal behavior induced by dietary zinc restriction, the role of zinc supplementation in the treatment of depression, and the possible mechanisms involved in these relationships. Both clinical and preclinical studies related to these findings will be discussed.

Keywords: zinc, zinc deficiency, depression, zinc supplementation, biomarkers of depression

1. Introduction

Depression is a mental disorder associated with functional impairment, disability, morbidity, and mortality. Despite the extensive research, its pathophysiology is still poorly understood. Current pharmacotherapy, although effective is usually costly, requires time and has potential side effects [1, 2]. Thus, there is a strong need to investigate alternative prevention

or treatment strategies. Both clinical and preclinical studies have indicated the important role of zinc in the pathophysiology and treatment of depression.

Early studies exploring the role of zinc in depression focused on demonstrating its antidepressant activity, and then, they tried to explain whether zinc enhances the effect of antidepressants and which mechanisms are involved in the antidepressant effects of zinc. Current studies, however, are mostly focused on examining whether serum zinc concentration might be a biomarker of depression or if experimentally induced zinc deficiency can be a new useful animal model of depression.

This review summarizes the most important data concerning the role of zinc and particularly zinc deficiency in the development or treatment of depression.

2. Dietary zinc intake and depressive symptoms (Table 1)

The first study indicating a relationship between dietary zinc deficiency and depression was performed by Amani et al. [3]. This study recruited 23 young women diagnosed with moderate-to-severe depression and 23 age matched healthy volunteers. All of the women involved in this study completed the food frequency questionnaire (FFQ) and a 24 h-food recall questionnaire to confirm the sources of zinc and daily zinc intakes in the diet. Analyses of the obtained results showed that both the daily zinc intake and the serum zinc concentration in the depressive group were lower than that found in the healthy women. Moreover, an inverse correlation between the depression scores and serum zinc concentration was found [3].

A few other papers published recently indicated that women seem to be more vulnerable to zinc deficiency than men. Maserejian et al. [4] examined the relationship between dietary zinc restriction and depressive symptoms in a large group of men and women. They analyzed cross-sectional, observational epidemiological data from the Boston Area Community Health (BACH) Survey. The final group of samples used in the analyses involved 2163 women and 1545 men from three racial/ethnic groups such as Hispanic, non-Hispanic black, and non-Hispanic white. To ascertain the diet from multiethnic populations, all of the participants completed the Food Frequency Questionnaire (FFQ). This questionnaire included also data on the vitamin and mineral supplements used. The depressive symptoms were assessed by the abridged Center for Epidemiologic Studies Depression scale (CES-D). Interestingly, it turned out that a zinc deficient diet influences the severity of depressive symptoms in women but not in men [4].

In the same year (2012), Jacka et al. [5] reported the data from a study on a large randomly selected, population-based groups of women ($n = 1494$, aged 20–94 years). Similarly, the aim of this study was to determine the relationship between the dietary intake of zinc as well as magnesium and folate and clinically determined depressive and anxiety symptoms. Habitual dietary intake was assessed using FFQ. The current depressive and anxiety depression were measured using the Structured Clinical Interview for DSM-IV-TR, non-patients edition, and the General Health Questionnaire-12 (GHQ-12) was used to assess the psychiatric symptoms. As reported in the results, the intake of both zinc and magnesium was inversely related to

GHQ-12 scores and each standard deviation increase in the intake of these nutrients was associated with a standard deviation decrease in GHQ-12 scores. The relationship between nutrient intakes and anxiety disorder was not significant [5].

Authors	Participants (women/men)	Measurement	Effect
Marcellini et al. [8]	(485/367)	FFQ, GDS, M-MSE, PSS	Low zinc intake associated with low zinc plasma level and psychological disorders
Amani et al. [3]	(308/0)	FFQ, serum Zn	Inverse relationship between depression symptoms and both dietary zinc deficiency and zinc serum level
Roy et al. [6]	(2030/0)	FFQ, CES-D	Zinc deficiency diet influences the severity of stress and symptoms of depression.
Jacka et al. [5]	(1046/0)	FFQ, GHQ-12,	Increase in zinc intake induced decrease in psychiatric symptoms but not anxiety
Maserejian et al. [4]	(2163/1545)	FFQ, CES-D	Zinc deficiency is associated with depression in women but not in men
Yary and Aazami [7]	(173/229)	FFQ, CES-D	Inverse relationship between dietary zinc intake and depression
Lehto et al. [10]	(0/2317)	CES-D	No effect of dietary zinc intake on the incidence of depression
Markiewicz-Zukowska et al. [9]	(52/48)	AMTS, GDS, SRH, ADL Serum Zn	Low serum zinc levels correlate with mental disorders and depression

ADL, Activities of Daily Living; AMTS, Abbreviated Mental Test Score; CES-D, Center for Epidemiologic Studies Depression scale; FFQ, Food Frequency Questionnaire; GDS-Geriatric Depression Scale; GHQ-General Health Questionnaire; M-MSE, Mini Mental State Examination; PSS, Perceived Stress Scale; SRH, Self-Rated Health.

* Analysis of cross-sectional, observational epidemiological data from the Boston Area Community Health (BACH) Survey.

Table 1. A summary of the influence of dietary zinc deficiency on the depressive symptoms.

Zinc intake as a causative factor in the induction of depressive symptoms was also considered in the context of prenatal depression. The study by Roy et al. [6] was conducted on pregnant

women (2030 samples, recruited between 2002 and 2005 year) from the clinics in London, Ontario (Prenatal Health Project). The main aim of this study was to analyze the relationship between zinc intake, sociodemographic factors, and psychosocial stress, as well as the development of depressive symptoms. As in other studies, the zinc intake was assessed using FFQ and nutrient supplement data. The level of psychological stress was evaluated using a standardized composite score, and the depressive symptoms were measured using a CES-D scale. The results showed that low zinc intake, social disadvantage, and stress were correlated with higher CES-D scores, but higher zinc intake was found to buffer the impact of stress on the depressive symptoms during pregnancy [6].

Another study indicating that long-term zinc deficiency may induce the symptoms of depression was carried out on 402 postgraduate students with a mean age of about 32 years (229 men and 173 women) [7]. The CES-D questionnaire was used to measure the prevalence of depressive symptoms among participants, while the dietary intake of zinc among the postgraduate students was evaluated using the FFQ. The results of this study show an inverse relationship between dietary zinc intake and depression in postgraduate students [7].

The statistics showed that zinc deficiency is common not only among the children but also in the elderly. In the ZINCAGE project older people from five countries: Italy, Greece, Germany, France, and Poland were recruited to investigate the relationship between nutritional aspects in Northern and Southern European Countries, zinc status, and psychological dimensions (mood, perceived stress and cognitive functions) [8]. The FFQ was typically used to estimate the intake of zinc. Evaluation of mood, the perceived stress level, and cognitive function was meanwhile performed using the: “Mini Mental State Examination”, Geriatric Depression Scale (GDS), and “Perceived Stress Scale.” The study involved 853 people who were divided into four age groups. The first group included 359 people between 60–69 years old, the second 225 at the age of 70–74 years, the third 153 at the age of 75–79 years, and the last 116 age of 80–84 years. Eighty-two percentage of the total samples showed no cognitive decline, 72% (according to GDS) of samples showed no depression, and all of the samples had a normal perceived stress level. Interestingly, however, a relevant correlation between all of the psychological dimensions studied in the project and the plasma zinc values or nutritional assessment was found. This phenomenon was not correlated with the age, which indicates that a normal zinc diet can help maintain proper plasma zinc levels and a good psychological condition in the elderly [8].

These findings were confirmed in another screening study. A research group from Bialystok (Poland) [9] conducted a nearly 2-year (from October 2010 to May 2012) study among 100 nursing home residents (aged 60–102 years) to determine the zinc status among the older individuals in correlation to their mental and physical performance. The participants were subjected to the Abbreviated Mental Test Score (AMTS), Self-Rated Health (SRH), Geriatric Depression Scale (GDS), and Independence in Activities of Daily Living (ADL). Also anthropometric variables and fitness scores were evaluated. The serum zinc level was measured by flame atomic absorption spectrometry. Almost one-third of the participants had zinc deficiency. Cognitive functions were impaired in 45% of them, and 48% of the participants showed depressive symptoms. Moreover, it was found that elderly patients with normal cognitive

function and without symptoms of depression had a higher serum zinc level than patients with mental disorders and depression [9].

One paper has so far showed no effect of dietary zinc intake on the incidence of depression [10]. This study was performed on 2317 Finnish men aged 42–61 years to estimate the correlation between dietary zinc intake and depression in a prospective setting in initially depression-free men during a 20-year follow-up. Nutrient intake was quantitatively evaluated by 4-day food record at the baseline. The severity of the depression was measured using the Human Population Laboratory Depression Scale. Participants who at the baseline had elevated depressive symptoms were excluded (n = 283) from the study. In this prospective setting, depression has been defined as a hospital discharge diagnosis of a unipolar depressive disorder [10]. Generally, ~3% of the participants received a hospital discharge diagnosis of depression during the 20-year follow-up, with the analysis adjusted for age, baseline depression severity, smoking, alcohol use, physical exercise, and the use of zinc dietary supplements not being associated with an increased depression risk in men [10]. However, as the author indicated, these observations may not be generalizable to women [10]. What is more, looking at the results of Maserejian et al. [4] and the other data described earlier, the present findings may simply confirm that zinc deficiency may play a greater role in the induction of depression in women.

3. Zinc level as a marker of depression (Table 2)

The biological markers (biomarkers) are defined as cellular, biochemical, or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids. Biomarkers should be fixed and concern specific features of the disease which occurs permanently, regardless of the stage/phase of the illness (a trait marker) or changes, depending on the stage (a state marker) [11]. Appropriately chosen biomarkers would be more objective and, as such, would significantly enhance the traditional patient symptoms-based assessment of depression. Biomarkers of depression could be used to support the presence or absence of the disease, provide individualized treatment, monitor treatment progress (or indicate the risk of the drug resistance), and predict the onset of future disease or its relapse. A clinically useful biological marker should be characterized by a high level of sensitivity and specificity (preferably above 80%), and its determination should be easy to make and relatively cheap [12]. Some potential candidate markers of depression have been reported, for example, see [13], but none of them have yet been used in clinical practice.

Authors	Disorder	Results
Hansen et al. [11]	MDD	Reduced serum zinc level in depressed patients
Little et al. [14]	Mood disorder	Higher prevalence of zinc deficiency in outpatients with mood disorder
Amani et al. [3]; Maes et al. [15, 16]; McLoughlin and Hodge [18]; Siwek et al. [19]	MDD	Reduction in the blood zinc level in depressed patients

Authors	Disorder	Results
Maes et al. [15, 16]; Siwek et al. [19]; Wójcik et al. [20]	MDD	Negative correlation between severity of depressive symptoms and serum zinc level
Wójcik et al. [20]	–	Lower zinc level in women with antepartum depression
Wójcik et al. [20]; Brownlie and Legge [21]	–	Lower zinc level in women with postpartum depression
Roosbeh et al. [22]	MDD	Lower zinc level in depressed patients with end-stage renal disease undergoing hemodialysis
Marcellini et al. [8]	–	Lower zinc level in late life
Stanislawska et al. [23]	MDD	Negative correlation between postmenopausal women and the severity of depressive symptoms and serum zinc concentration
Crayton and Walsh [24]; Irmish et al. [25]; Nguyen et al. [26]	MDD	No differences in the zinc concentration between depressed and healthy people
Salustri et al. [27]	MDD	Increase in the peripheral blood level of zinc in the course of depression
Manser et al. [28]	MDD	Significant differences between serum zinc level in depressed male and women
McLoughlin and Hodge [18]	MDD	Antidepressant therapy normalized lower zinc level in depressed patients
Maes et al. [16]	MDD	The zinc levels in the treatment-resistant depressed patients were significantly lower than its concentration in the depressed patients and healthy volunteers
Maes et al. [16]; Siwek et al. [19]	MDD	Lack of normalization in zinc level after antidepressants treatment or its correlation with the severity of depression
Stanley and Wakwe [29]	MDD, BD, schizophrenia	Reduction in serum zinc level across all of the investigated groups
Gonzales-Estecha et al. [30]	BD	Significant increase in serum concentration in the manic and no changes in depressed phase when compared to the healthy volunteers
Siwek et al. [31]	BDI, BDII	Significantly decreased peripheral blood zinc level in depressive phase in BDI patients compared with healthy control no changes in BDII subgroups

MDD, major depressive disorder; BD, bipolar disorder.

Table 2. A summary of the clinical studies on the relationship between the zinc level and depression.

The first clinical report that suggested the potential role of zinc in the pathophysiology of depression and role of zinc as a marker of this disease was published in 1983 by Hansen and colleagues [11]. In this paper, the reduced serum zinc concentration in patients suffering from

recurrent major depressive disorder and the negative correlation between the severity of depressive symptoms and the zinc level was described [11]. One of the preliminary studies also showed a significantly higher prevalence of zinc deficiency in outpatients with mood disorder than healthy controls [14]. The reduction of the blood zinc level in depressed patients has been confirmed in many other reports [3, 15–19]. Similarly, some studies have shown a negative correlation between the severity of depressive symptoms and serum zinc [15, 16, 19, 20]. The lower zinc level has also been observed in women with antepartum [20] and postpartum depression [20, 21], and in depressed patients with end-stage renal disease undergoing hemodialysis [22] or in late life [8]. Furthermore, in postmenopausal women, the negative correlation between the severity of depressive symptoms and the serum zinc concentration was noted [23]. To this date, only three studies have reported no differences in the zinc concentration between depressed and healthy people [24–26] and one report even shows an increase in the peripheral blood level of zinc in the course of depression [27]. It is also little data that show a significant differences between serum zinc in depressed male and women [28].

Support of the hypothesis that the zinc level might be a specific and sensitive marker of depression comes from the findings that the zinc level, lower in depressed patients, may be normalized to control levels after successful antidepressant therapy [18]. However, this effect was not observed in all of the studies. Maes et al. [16] showed that the zinc levels in the treatment-resistant depressed patients were significantly lower than its concentration in the remaining depressed patients and healthy volunteers. The next study by Maes et al. [17] performed on a larger group of patients, and a study by Siwek et al. [19] gave similar findings. A lack of normalization of the zinc level after antidepressants treatment or its correlation with the severity of depression was found. Based on this evidence, it has been suggested that a lower serum zinc level may be a sensitive (79%) and specific (93%) marker of drug resistance [16, 17].

To date, most studies on the role of zinc in the depression included patients diagnosed with major depressive disorder (MDD). Unfortunately, very little is known about the importance of zinc in the development (or treatment) of bipolar disorders (BD). So far, there are only three publications on this topic. In an early study, including patients diagnosed with MDD, BD and schizophrenia, a reduction in the serum zinc level across all of the investigated groups was observed [29]. A subsequent study, whose aim was to analyze the changes of trace elements exclusively in bipolar patients, indicated a significant increase in serum concentration in the manic and no changes in depressed phase when compared to the healthy volunteers [30]. Finally, a recent published study investigated in detail the issue concerning the concentration of zinc in bipolar disorder, with a special focus on the subtypes (BDI, BDII), and the phases and stages of the disease. It was found that a significantly decreased peripheral blood zinc level in the depressive phase in BDI patients (especially with stage 3 and 4) compared with the healthy control. However, both in remission and the manic phase, the zinc concentration was similar to that seen in the matched controls. In BDII subgroups, these alterations have not been noted [31].

Most of the clinical data come from studies of peripheral blood samples. Some researchers urged caution in interpreting such results. It is believed that the changes in the peripheral zinc concentration may not reflect zinc availability in the central nervous system, particularly in

the brain. However, in healthy individuals, a clear correlation between the cerebrospinal fluid (CSF) and serum zinc level was demonstrated [32]. It has also been proved that zinc penetrates the blood–brain barrier [33]. So far, there are no studies to compare the concentrations of zinc in blood and/or CSF in depressed patient and healthy people. It is known that the hippocampal zinc concentration in suicide victims (where there is evidence for an association between suicidal behavior and depression) did not differ from that measured in sudden death controls [34, 35]. However, these data do not undermine the role of zinc in the pathophysiology of depression. For example, they may indicate that, in the course of depression, only subtle changes are present in the zinc level in the central tissues, which cannot be measured via the currently available analytical methods. Alternatively, these changes can occur in specific areas of the brain or even only in selected areas of certain brain structures that have not yet been investigated.

In conclusion, we can argue that the study of zinc in the context of depression and as a potential biomarker of the disease has great meaning and a future. Based on the presented research, we can argue that the serum zinc concentration may be a state marker of depression in treatment responder patients. Similarly, in drug-resistant depression, a reduced level of zinc may be a trait marker. While, in bipolar patients, an increased zinc level may be a state marker in mania. Unfortunately, due to the fact that alterations of zinc concentration are not specific only to depressive disorders, the measurement of this trace element in the blood of a patient cannot be a useful clinical marker of MDD or BD. It seems, however, that the determination of the serum zinc level could be in the future a component of multifactorial tests and assist diagnosis of the disease.

4. Zinc supplementation in the therapy of depression (Table 3)

There are still a limited number of clinical reports examining the effect of zinc supplementation on depressive symptoms. However, the available evidence suggests potential benefits of zinc supplementation as an adjunct to antidepressants therapy or as a stand-alone therapy for the prevention of depressive symptoms.

The first report indicating the beneficial effect of zinc supplementation in the therapy of depression was published in (2003) by Nowak et al. [36]. This placebo-controlled, double-blind pilot study was conducted in patients who fulfilled DSM-IV criteria for major (unipolar) depression. The recruited patients were divided into two groups: one receiving zinc supplementation (6 patients; 25 mg Zn/day) and the second (8 patients) a placebo. Both groups were treated with standard antidepressant therapy (clomipramine 125–150 mg; amitriptyline 125–150 mg; citalopram 20 mg; fluoxetine 20–40 mg). The efficacy of antidepressant therapy and the patient's status was evaluated before the treatment and 2, 6, and 12 weeks after it began using the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI). In this study, antidepressants significantly reduced HDRS scores by the 2nd week of treatment in both groups, and BDI scores at the 6th week in the zinc-treated group. Zinc supplementation significantly augmented this reduction after 6- and 12-week (HDRS) and at 12 week (BDI) of

treatment when compared with the placebo. Although the observed effect of zinc was delayed, its potency was quite robust [36].

Authors	Participants (placebo/Zn group)	Supplementation (dose)	Duration (weeks)	Treatment (dose)	Measurement	Efficacy
Nowak et al. [36]	(8/6) MDD	Zinc hydroaspartate (25 mg Zn/day)	12	TCAs, SSRI	HDRS, BDI	Yes
Siwek et al. [37, 19]	(30/30) MDD	Zinc hydroaspartate (25 mg Zn/day)	12	TCAs	CGI, BDI, HDRS, MADRS	Yes
Ranjbar et al. [38, 39]	(17/20 or 21) MDD	Zinc sulfate (25 mg Zn/day)	12	SSRI	HDRS, BDI	Yes
Nguyen et al. [26]	396 (88/ 97/84/100) Healthy woman	Micronutrient supplements with zinc sulfate (~20 mg Zn/week or ~10 mg Zn/day)	12	No	CES-D, FFQ, serum Zn	No
Sawada and Yokoi [40]	(15/15) Healthy women	Multivitamins + zinc gluconate (7 mg Zn/day)	10	No	CMI, POMS	Yes
Di Girolamo et al. [43]	674 children	10 mg ZnO/day for 5 day/ week	6 months	No	Depression, anxiety, hyperactivity and conduct disorder	No
Maserejian et al. [4]	(2163 women/ 1545 men)	Multivitamins (0.1–15 mg Zn/day) or zinc supplements (>15 mg Zn/day)	NA	No or SSRI, SNRI, serotonin modulators	FFQ, CES-D	Yes

BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression scale; CGI, Clinical Global Impression; CMI, Cornell Medical Index (somatic symptoms and mental symptoms); FFQ, Food Frequency Questionnaire; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; POMS, Profile of Mood State (depression dejection and anger hostility score); NA, not applicable.

* The final group of patients.
** Analysis of cross-sectional, observational epidemiological data from the Boston Area Community Health (BACH) Survey.

Table 3. Summary of studies on the efficacy of zinc supplementation in the treatment or prevention of depressive symptoms.

The second report of the benefit of zinc supplementation in antidepressant therapy was published by Siwek et al. [37]. This group performed a placebo-controlled, double-blind study of zinc supplementation in imipramine therapy in sixty, 18–55-year old, unipolar depressed patients fulfilling the DSM-IV criteria for major depression but without psychotic symptoms. The participants were randomized into two groups treated with imipramine (approximately

140 mg/day) and receiving once daily either a placebo or zinc supplementation (25 mg Zn/day) for 12 weeks. In this study, the BDI, HDRS, CGI, and MADRS scales were used. Analyses of the results obtained from this study showed no differences in CGI, BDI, HDRS, and MADRS scores between zinc-supplemented and placebo-supplemented antidepressant treated non-resistant patients. However, they indicated that zinc supplementation reduced depression scores and augmented the efficacy and speed of the onset of response to antidepressant treatment in the patients previously non-responsive to antidepressant therapy [19, 37].

A study by Ranjbar et al. [38, 39] presented a double-blind randomized clinical trial on 39 patients (aged 18–55 years) diagnosed with MDD. The participants of this study were randomly assigned to groups receiving zinc supplementation (25 mg Zn/day) or a placebo. The patients from both groups received SSRIs (citalopram 20–60 mg/day or fluoxetine 20–60 mg/day) for 12 weeks. The severity of depression was measured using the BDI [38] and HDRS [39] at the baseline and after 6 and 12 weeks of treatment. At the end of the study, the BDI and HDRS scores were significantly lower in the SSRI and zinc-treated group than the group receiving the SSRI and the placebo.

The report published by Sawada and Yokoi [40] showed in turn that young women taking multivitamins and zinc supplements exhibited a significant reduction in depression and anxiety symptoms than women taking only multivitamins. This randomized, double-blind, placebo-controlled study was performed among 30 women in the aged of 18–21 years. The subjects were randomly assigned to receive multivitamin capsules or multivitamins and zinc once daily for 10 weeks. The Cornell Medical Index was used to evaluate somatic symptoms (A-L score) and mental symptoms (mood and feelings, including anxiety, sensitivity, anger and tension, M-R score). Additionally to ascertain the mood state during the previous week, the Profile of Mood State (POMS) questionnaire was used. Analyses of the data highlighted that women taking multivitamins and zinc showed a significant decrease in anger-hostility and depression-dejection scores (on the POMS). No changes were found in the M-R (mental symptoms) on the CMI between women taking multivitamins and zinc and multivitamins only. Despite this, as the authors themselves make clear, these findings are only preliminary and do not suggest that zinc supplementation may be effective in reducing anger and depression [40].

Another paper published in 2012 by Maserejian et al. [4] (the study design and population was described in detail in the Section 2) revealed that dietary, supplemental, and total zinc were significantly associated with the presence of depressive symptoms but only in women and not in men. Moreover, there was a statistically significant interaction between the total zinc intake and use of SSRIs in the development of depressive symptoms. No statistically significant interactions were observed for use of SNRIs, TCAs, or antipsychotics [4].

In the same year (2012), Sandstead [41] published the results from six randomized controlled comparative treatment experiments performed on Chinese and Mexican-American low-income children (6–9 years); middle-income US premenopausal women; middle-income US adolescents, and middle-income US men. These findings illustrated that subclinical zinc deficiency changes the brain function and that zinc and micronutrient treatment improves altered brain functions [41]. Recently, the beneficial effect of zinc monotherapy (30 mg Zn,

12 weeks) in the relief of depressive symptoms in overweight or obese subjects was also reported [42].

Two studies have so far shown no effect of zinc supplementation on the improvement of depressive symptoms [26, 43]. These studies, however, differ significantly from the one previously described with respect to both the participants and the length and quality of applications. The first study by DiGirolamo et al. [43] examined the effect of zinc supplementation on the mental health of school-age children in Guatemala. Zinc as a ZnO (10 mg/day for 5 days/week) was applied for 6 months. Outcome measures at the end of the study included internalizing problems such as depression or anxiety and externalizing (hyperactivity and conduct disorder) problem behaviors. Generally, no difference in mental health outcomes between the zinc and placebo groups was found, although increases in serum zinc concentrations were associated with decreases in depression and anxiety among the children who were at risk of zinc deficiency [43]. The second study of Nguyen et al. [26] investigated the impact of combinations of micronutrient supplements on symptoms of depression rather than the effect of zinc supplementation as a stand-alone therapy.

Because of these methodological limitations in the existing studies, further well-designed, adequately powered research is required.

The data described earlier are clinical verification of the results obtained in preclinical studies. The beneficial effects of zinc treatment have been in fact reported in several preclinical test and models of depression. Zinc administration induced an antidepressant-like effect in the forced swim test (FST) both in mice and rats and in the tail suspension test (TST) in mice [44–49]. Zinc was also active in different models of depression such as: (a) the olfactory bulbectomy (OB) (a reduction in the number of trials in the passive-avoidance test and a decreased OB-induced hyperactivity in rats) [48]; (b) the chronic mild stress (CMS) model of depression (zinc reversed the CMS-induced reduction in the consumption of sucrose in rats) [50]; and (c) chronic unpredictable stress (CUS) (zinc treatment prevented deficits in the fighting behavior of chronically stressed rats) [51]. Moreover, zinc has been found to intensify the effects of standard antidepressants (imipramine, fluoxetine, paroxetine, bupropion or citalopram) in the FST, the TST, and CUS [44, 49, 51–53].

5. Experimental zinc deficiency as an animal model of depression

Analysis of the clinical data makes it possible to address a very important question concerning the relationship between zinc deficiency and depression, namely to establish whether zinc deficiency is the cause or an important risk factor for depression or if zinc deficiency is a consequence of pathological processes underlying depression [54, 55]. In order to answer this question, several animal studies have been conducted. It is well established that the subjection of animals to procedures such as chronic stress, removal of olfactory bulbs, and several other leads to observed, depressive-like behaviors. In principle, these changes in animal behavior in some extent should correspond with human behaviors observed in depressive patients, that is, olfactory bulbectomy in rodents serves as a model of agitated depression, and chronic mild

stress modulates anhedonia in laboratory animals. Several tests are used to evaluate the pro-depressive effects of a particular procedure, with the most popular being the open-field test, social interaction, FST, TST, and sucrose intake test.

Several data published recently indicated that experimentally induced zinc deficiency may be one of the procedures used to modulate depressive symptoms in both mice and rats. According to the data in the so-called “experimentally induced zinc deficiency” model two factors play an important role: the amount of zinc in the feed and the time of exposure to zinc restriction. Whittle et al. [56] showed that feed containing 40% of zinc in the daily requirement (~ 12 mgZn/kg) is sufficient to produce depressive-like behavior in mice, which is observed as increased immobility time in the TST and FST [56]. In this study, mice were treated with zinc deficient diet for 7 weeks. Mlyniec et al. [57, 58] showed that 4 or 10 weeks of zinc deficiency (0.2 mgZn/kg) in mice induced depressive-like behavior observed in TST and FST. Interestingly, the same studies showed that mice subjected to a zinc deficient diet for 2 weeks displayed antidepressant-like activity in the TST and FST [57, 58]. The explanation of these differences requires further studies. The more, that in contrast to the results obtained by Mlyniec et al. [58], 2 weeks exposure to zinc deficiency (0.37 mgZn/kg) induced the depressive-like behavior in young rats, measured as and increased immobility time in the FST [59, 60]. In studies conducted by Tassabehji et al. [61], 3 weeks of zinc deficiency (10 mgZn/kg) led to increased immobility time in the FST and decreased sucrose intake in adult rats. Similar results were obtained by Doboszewska et al. [62] who showed that 4 or 6 weeks consumption of feed low in zinc (3 mg Zn/kg) caused the decreased intake of sucrose solution and increased immobility time in the FST. Additionally, 4 or 6 weeks zinc deficiency significantly reduced social interaction in adult rats [62].

As shown above, the behavioral disturbances induced by zinc deficiency overlap with depressive-like behaviors induced by well-known experimental procedures. Additionally, some of these procedures, such as stress, are causally related to a lower serum zinc level in rats. However, the physiological role of zinc is very complex and involves the activity of zinc on many receptors and enzymes, with some of these molecular events possibly being considered as key factors engaging in depression or depressive-like behaviors. Zinc is an inhibitor of glutamate N-methyl-D-aspartate receptors (NMDAR), therefore zinc released with glutamate from glutamate terminals determines the correct functioning of the glutamate system [63, 64]. In pathological states, when the glutamate concentration is radically increased in the synaptic cleft, the overstimulation of NMDAR may lead to atrophy and neural cell death. The overstimulation of NMDAR leading to atrophy cell death is named excitotoxicity [65, 66]. The role of glutamate transmission in behavioral abnormalities induced by zinc deficiency was indicated by Doboszewska et al. [62]. They showed that zinc deprivation led to a significantly enhanced expression of GluN1, GluN2A, and GluN2B subunits of NMDAR in the hippocampus and GluN2B subunit in the prefrontal cortex (PFC) [62, 67]. In the same study, zinc deficiency radically decreased the level of brain-derived neurotrophic factor (BDNF), whose concentration in the physiological range is a crucial factor for normal neurotransmission and the survival of neurons. A decreased level of BDNF has been noted in both clinical and preclinical studies,

respectively, in depressive patients and animals subjected to procedures inducing depressive-like behaviors [68].

One of the factors modulating the glutamate transmission is glucocorticoids [69]. The enhanced level of glucocorticoids may potentiate glutamate enhanced transmission in the hippocampus, leading to neuronal death [70]. Only 1 week of zinc deprivation is enough to decrease the serum zinc level in rats with a concomitant increase level of glucocorticoids serum levels [69–71]. These data indicate on hyperactivation of the hypothalamic-pituitary-adrenal axis (HPA-axis) in a zinc deficient condition. However, the causative relationship between zinc deficiency and HPA-axis overstimulation is unknown. The enhanced activation of the HPA-axis disrupts hippocampal function which is a brain structure sensitive to a higher level of glucocorticoids and involved in the development and expression of depression [72]. Moreover, a similar effect of the overstimulation of the HPA-axis on hippocampal function has been observed under stressful conditions [72].

6. Conclusions

The importance of zinc as the life-threatening factor for humans was first described in 1963 by Prasad et al. [73, 74]. Zinc deficiency still remains a substantial global health problem. Statistics show that two billion people worldwide are not getting enough zinc via their diet. Zinc deficiency is accountable for physical and intellectual retardation, preventing children from developing to their full potential. Marginal zinc deficiency is also evident in older people. A recent study showed a significant relationship between zinc deficiency and cognitive impairment, increased susceptibility to stress and something that should be emphasized, to depressive symptoms. Taking into account that depression is the most serious mental illness associated with decreased productivity and quality of life and well-being, evidence about the causative role of zinc deficiency in the development of this disease is very important.

Recent clinical research, indicated that the serum zinc level in patients was significantly lower than in the control group. Other studies have also shown that low serum zinc levels are normalized during treatment with antidepressants [54]. This suggests that the measurement of the serum zinc level could be in the future a component of multifactorial tests and assist diagnosis of the disease. This is of particular importance, especially now, when effective markers of the disease are needed. This problem also applies to mental illnesses. The next significant aspect is the pharmacotherapy of depression. Current treatments for depression are costly, have potential side effects, and require time and commitment. However, most alarming is the fact that antidepressants are effective only in 60% of patients. Treatments with zinc in laboratory animals have antidepressant effects, and zinc supplementation enhances the effectiveness of antidepressants in animal tests and models of depression. Also, clinical studies examined the effects of zinc supplementation as an adjunct to antidepressant drug therapy. Both preclinical and clinical studies indicated that zinc supplementation could be an adjunct increasing the effectiveness of tricyclic antidepressants but especially, selective serotonin reuptake inhibitors rather than selective noradrenaline reuptake inhibitors [38]. These results,

therefore, suggest that zinc supplementation may be effective but only for drugs with a specific mechanism of action. To ensure the benefits of zinc supplementation as an adjunct to conventional antidepressants or as an intervention in the prevention of depression or as a marker of depression more, high-quality trials are needed.

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