

# Beneficial effects of zinc on reducing severity of depression

## Abstract

There are many causes and factors that lead towards depressions including hypertension, illness, chronic diseases, physical illness, some medications, but one of the major causes regarding nutritional point of view for depression is zinc deficiency. Zinc is a trace mineral which is required by our body in a minute amount. From many researches zinc has been entitled as an important element for normal physiological as well as pathological functioning. Zinc has a lot of biological functions in our body like in immune system, growth and development, reproductive system, diarrhea, respiratory infections, wound healing, hair loss, decreased levels of t helper cells and many more. Zinc acts as antioxidant, anti-inflammatory and also in the process of apoptosis. Zinc plays fundamental role in cellular metabolism and modulates the synaptic activity of cells. Zinc also plays its role at molecular level by regulating the expression of genes. Zinc deficiency can cause many clinical problems. It can affect our neurological system as well as neurodegenerative system and hence it can be a cause of depression, anxiety, dementia, Alzheimer's disease, and many more. Therefore, this article aimed to highlight the important role of zinc in reducing the severity of depression.

**Keywords:** depression, zinc deficiency, beneficial effects, neurological, neurodegenerative

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## Introduction

In this living planet, Zinc considered to be essential for living organizations. It is 23<sup>rd</sup> most plentiful element in the earth with atomic number 30 and atomic weight 65.37. Shining metal, bluish-white and amphoteric nature are characteristics of zinc. During waste or production of steel, zinc can be free. Mineralized form of zinc is almost 55. It has to be in oxidation states, Zn (0) and Zn (+2) in Group IIB of the periodic table. Zinc chloride, zinc sulfate and zinc oxide are example of zinc compounds.<sup>1</sup>

## Functions of zinc in human body

Zinc is necessary for normal of plants as well as animals.<sup>2</sup> Zinc has also important role in biological processes.<sup>3</sup> Besides role of zinc in immune function, normal growth, brain function, it is good for normal delivery.<sup>4,5</sup> Growth retardation, loss of hair, hyper keratization of epidermis, and testicular atrophy, lower respiratory infections, and diarrhea in children decreased testosterone levels, oligospermia, decreased activity of t helper cells are due to the lack of Zinc.<sup>2,4,6</sup>

Zinc is best for health, tissue growth, wound healing, bone mineralization, improve immunity, increase memory and ability of thinking are increased due to zinc.<sup>7,8</sup> Zinc is good for treatment of disorder in teenagers known as Acne Vulgaris<sup>1</sup> Zinc is beneficial for dropping stress in diabetic person.<sup>9</sup> The usage of supplementation of zinc reduce fecal episodes and is useful on acute diarrhea.<sup>10,11</sup> Respiratory infection such as common cold, pneumonia can be reduced.<sup>12</sup> In chronic disease, free radicals are involved in inflammation and oxidative stress due to its antioxidants and anti-inflammatory properties. Regulation in genes expression and cellular membranes are facilitated by zin.<sup>13,14</sup> Intake of zinc in pregnant women can also increase nerve and brain functions in fetus, refining memory and learning skills.<sup>15</sup> The existence of preterm infants in pregnant women can be reduced due to zinc and it is verified by many researches.<sup>16</sup>

## Bioavailability

Talking about bioavailability, bioavailability of a nutrient is the amount which is ingested then utilized by our physiological functions or stored.<sup>17</sup> Zinc is available for animal and humans in the form of inorganic and organic salts. Zinc sulfate, zinc ammoniate, zinc chloride, zinc oxide and zinc carbonate includes in inorganic salts whereas organic salts includes zinc citrate, zinc lactate, zinc acetate, zinc gluconate, zinc stearate, zinc picolinate, and zinc ascorbate. Zinc in amino acids are investigated as zinc methionine complex, zinc lysine-complex, and zinc histidine complex.<sup>18</sup> Zinc binds with proteins obstinately in the presence of neutral pH so the availability of protein in the diet also effects the absorption of zinc. Zinc bioavailability dependent on the presence of intestinal lumen which is a dietary component. For example, without any food when we consume zinc in supplements, iron inhibits its absorption in our body and for that the molar ratio of iron and zinc is 25:1 below this ration the inhibitory effect is minimal. On the other hand phytate and nucleic acid i.e phosphorus containing compounds can decrease the absorption of zinc, whereas calcium might have inhibitory effect towards zinc.<sup>19</sup> Zinc oxide does not cause eye or skin problems, cancer, genetic toxicity, reproductive toxicity so it is also known as non-toxic element but its powder can be dangerous and can cause zinc fever or zinc ague.<sup>20</sup>

## Prevalence of depression

Depression will be ranked 2nd global disease by 2020 according to WHO. The depression prevalence rate was 7.2% from 1994 to 2014.<sup>21</sup> About 350 million people including children, female and male suffered from depression by 2018.<sup>22</sup> Depression is common mental disorder in Pakistan due to chronic illness and irregularities. In Pakistan, the worsening state of retrieval from chronic illness is due to depression. In general population, depression in female is 10-25% and male is 5-12% and risk is up to 25-33% in chronic patient.<sup>23</sup>

## Food sources of zinc and factors contributing to depression

Soybeans, kidney beans and chickpeas contain 1.0-2.0mg/100g. Vegetables 0.1-0.8mg/100g. Seeds and nuts (pumpkin, sesame, almond) contain 2.9-7.8mg/100g and eggs 1.1-1.4mg/100g of zinc. Beef and poultry liver kidney contains 4.2-6.1 mg/100g of zinc. Fruits contain 0-0.2mg/100g. Whole grain cereal (wheat, brown rice, maize) contains 0.5-3.2.<sup>18,24</sup>

There are many studies regarding factors of depression which are disability, Hypertension is the main factor for depression<sup>25</sup> disruption in sleep and previous depression<sup>26</sup> chronic illness or chronic disease in people cause surge in depression<sup>27</sup> Physical illness, change in white matter of the brain, female gender, various medicines, advancing years of life are also the factors of late life depression.<sup>28</sup> Depression in older adults can vary in many ways like physical disorder or represented symptoms. Pain, slow movement and weight loss are diseases involved in depression. Memory loss can be one of the problems in older adults.<sup>29</sup> The person with set of symptoms which lose their functionality is known as Major Depressive Disorder (MDD). Depressive mood and not having fun in life are the symptoms of this disorder.<sup>30</sup> After an increase of glucorticoids from HPA-axis dysregulation, signs of depression are visible. HPA-axis are activated by reduction in zinc.<sup>31</sup> HPA-axis dysregulation caused by depressive symptoms that includes indolamine 2, 3-dioxygenase metabolize tryptophan to quinolinic acid, rise in IDO activity will lead to low tryptophan for 5-HT synthesis.<sup>32</sup>

## Review literature

### Mechanism of zinc in depression

Decreased levels of zinc will lead to low electrical or chemical signals to another neuron or targeted cell which will eventually increase NMDA (N-methyl-D-aspartate) receptor. NMDA receptor will show a response to glutamate, which is an excitatory neurotransmitter and can be poisonous if produced too much in brain.<sup>33</sup> For the NMDA receptor to function properly, glycine which is a co-transmitter of glutamate must be present.<sup>34</sup>

At this time, the neuroprotective or inhibitory neurotransmitter levels are low such as GABA (gamma-Aminobutyric acid), BDNF (Brain-derived neurotrophic factor) and other nerve growth factor NGF (nerve growth factor). Glutamate is higher in nervous system, so calcium mediated stimulation of the nerves is primed. Higher levels of these can cause excitotoxicity. This mechanism is the cause of seizures, migraines, dementia, anxiety, depression, and bipolar disorder. This all process is done in hippocampus, antidepressants plays their role in repairing adaptation and recovery by elevating the levels of BDNF.<sup>33</sup>

Zinc deficiency also shows its effects on endocrine pathway of depression. Diet low in zinc causes high level of cortisol production causing hyperactivity of hypothalamic pituitary adrenal axis leading to depression. Increased levels of cortisol show a relation between zinc deficiency and depression. Zinc sensing receptors GPR39 play a major role in treatment of depression.<sup>35</sup> When zinc binds with GPR39 it triggers downstream cyclic MP-response element which depends on gene transcription and causing high levels of brain derived neurotrophic factor (BDNF) in parts of brain.<sup>36</sup>

## Experimental studies

In a study 2 months old male rats were used in light dark box test-pb0.001 for three weeks where on group of rats was given 30ppm of zinc which in adequate requirement of zinc, second group was gives 1 ppm of zinc which is lower than the adequate requirement ant the third was given 180ppm of zinc supplements. After the trial time group 2 with deficient zinc gave traces of depression along with elevated anxiety level, anorexia- pb0.001 and anhedonia which is decreased intake of saccharin water. After this decreased behavioral melancholy was seen as 10mg/kg fluoxetine (antidepressant drug) was given to each group had under gone forced swim test in which group 1 and group 3 gave results by pb0.05 while group 2 was ineffective. Hence depression and immunity to anti-depressants is caused due to inadequate zinc intake.<sup>37</sup>

In a study, zinc showed a role in neuronal plasticity regulations. Blot method was used for six weeks in order to observe the diet low in zinc content with elevated immobility time in the forced swim test by twenty-four percent which resulted in depression related behavior. Similarly when zinc deficient diet was given for six weeks in a biochemical study gave results in the frontal cortex had a decreased protein expression in it up to 49% BDNF and 53% GPR39 accordingly. This trial proves that zinc sensing receptor tend to decrease the protein level which results in depression pathogenesis.<sup>38</sup>

In a double blind study, researchers took 60 patients completing the DSM-IV requirement for serious depression in 20 males and 40 females between 18 years to 55 years old (with this 9 male and 16 females i.e. 25 healthy volunteers). In order to check the serum zinc level in the subjects four times blood samples were taken once before starting then after 2, 6, 12 weeks accordingly. The low concentration of zinc by 14% was seen in treatment resistant patients, secondly as compared to the normal people the depression patients had a low zinc level in blood by 22%, thirdly with or without giving zinc supplements an increase in zinc was seen over the time in all groups during imipramine treatment, lastly between serum zinc level along with concomitant and Montgomery-Asberg Depression Rating Scale a negative interaction was seen in the 12th week of imipramine treatment. Hence the tidemark for depression is serum zinc.<sup>39</sup>

In a randomized and a double blind clinical trial, 44 patients were with major depression accepting placebo and zinc supplementation were randomly given to the group. Daily supplementation with 25mg add on to antidepressant were received patients in zinc group. For 12 weeks received placebo with antidepressant, while the patient in placebo group, Selective Serotonin Reuptake Inhibitors. By Beck Depression Inventory at baseline, the severity of depression was measured and was repeated at the 6th and 12th week. During the study ANOVA was measured used to contrast and way the changes. Group in which zinc supplementation was given at the end week of the 6 and 12 it was compared to the baseline and the mean score of Beck test reduced remarkably. On the other hand, the results of placebo group at the end of 12th week were reduced. Thus the the study indicates that depressive disorders in patients with placebo and antidepressants are improved by zinc supplementation, with Selective Serotonin Reuptake Inhibitor antidepressant drug.<sup>40</sup>

In 2013, a study on 2317 finish men aged from 42 to 61 was conducted to check whether zinc supplementation had any kind of coalition with depression or not. By keeping a four day food record

zinc intake was evaluate at baseline. Raised depressive symptoms were showed among those individuals who were at baseline. Thoroughly, during the 20-year continuation 60 individuals were diagnosed with depression in hospital discharge. Findings suggested that a low dietary intake may not longwise prior depression in men. In men of middle age, depression may not be suppressed by consuming dietary zinc with adequate dietary zinc intake.<sup>41</sup>

Yary et al.<sup>42</sup> in 2012 investigated the relationship of dietary zinc and depression in postgraduate students. The study was administered on 402 members including 229 men and 173 women. The inverse relationship was found between the intake of dietary zinc and depression. The study of the results indicate that long term intake of zinc may regulate the symptoms of depression.<sup>42</sup>

In a study the researcher finds the connection between zinc plasma level and depression prevalence in patients on hemodialysis (HD). Beck Depression Inventory (BDI) was used while fasting samples were used for zinc plasma level detection. For this 135 patients with approximate (mean) age of 52.45 (standard deviation: 15.33) years were taken who were at hemodialysis due to end stage renal disease (ESRD). As a result the depressed patients had a mean level of (67.46±29.7 vs. 85.26+40.05) zinc plasma mean level which is clearly less than the normal level. However according to BDI scoring system (BDI>14) all the patients had some extent of depression which is 76% of depressed patients exactly.<sup>43</sup>

In 2015, researcher find outs relationship between mental and physical abilities and zinc levels in old people is examined. The method included recording Geriatric Depression Scale (GDS), independence in Activities of Daily Living (ADL), Abbreviated Mental Test Score (AMTS), Self-Rated Health (SRH) and measuring Anthropometric variables and fitness score (FS) of 100 people from nursing home in Bialystok (Poland) were selected in time period from October 2010 and May 2012 with age between 60 to 102 years. The results indicated a comparatively higher impact in old people of zinc levels in body with relation to mental health than others. It also indicated relation of SRH, (BMI) body mass index and GDS with 45% people with damaged cognitive functions (AMTS≤8), depressive instincts in 48% (GDS≥1). The overall zinc deficiency was seen in 28% examined people, weak body type of 90% examined people (FS<70) and 61% people were able to perform daily routine activities (ADL = 6). Hence the examined community had a border line zinc levels in them which leads to obesity and impaired mental health.<sup>44</sup>

In a double-blind study the effectuality of anti-depressant therapy by zinc supplementation was investigated. With the placebo controlled trial of zinc supplementation with DSM-4 major depression. For this study from a hospital university both sexes of 44 patients aged 18-55 years were inducted. For 12 weeks the group of zinc supplemented obtained orally zinc sulfate (25 mg elemental zinc per day) increment to their particular serotonin reuptake inhibitor anti-depressant. On arrival, 6 and 12-weeks symptoms assess by using Hamilton Depression Rating Scale (HDRS). Completed the study by 20 patients in zinc group and 17 patients in Placebo group. Those taking zinc supplements at baseline, there were no consequential difference in any changing between the patients administer to acquire placebo. As compared to placebo zinc supplementation remarkably reduced HDRS at 12th week. Between zinc supplemented group and placebo supplemented group there was no remarkable differences detecting in plasma level. Decreasing depressive symptoms zinc supplementation in simultaneity with anti-depressant might be favorable. Although, on

inflammatory processes its affect does not be revealed to moderate through impact of zinc.<sup>45</sup>

In 2013, researcher examine the status of zinc in older patients hurting from a vast range of psychiatric disorders. From 100 psychiatric patients aged 64 years blood sample and clinical data for zinc study were collected. The Alsberg and Montgomery Depression Scale used to evaluate the symptoms of psychiatric and cognitive. In patients with depression the frequency of zinc deficiency was contrast with the frequency of patients without depression. From a population study the frequency in a control group of eight hundred eighty-two older persons evaluated. Between the patient group and control group there was a remarkably difference in the frequency of zinc deficiency. In the patient group the frequency of zinc deficiency is higher in patients without depression than as a main diagnosis in patients with depression. In psychogeriatric patients zinc deficiency is evacuate ordinarily and become visible to be even more preeminent in patient's distress from other psychiatric disorder than depression.<sup>46</sup>

In 2016, a study was conducted to investigate zinc effect in mice induced by chronic restraint stress (CRS). The role of zinc was observed after three weeks of CRS exposure. Weight was reduced and corticosterone was raised. It was indicated that the zinc level was low in CRS and reduced movement distance. It can be normalized by Zinc 30mg/kg and also with a combination of imipramine 5mg/kg and Zinc 15mg/kg for three weeks.<sup>47</sup>

Lehto et.at. Find outs the association between zinc intake and depression during plenty years' follow-up in depression men. This study consists of 2317 men from Finland with aged 42 to 61 years. Baseline study was assessed by four-day food record of zinc intake. 283 people were excluded from study because they have alleviated depression symptoms. During follow-up, 60 men were cleared with depression diagnosis. Zinc RDI for men >9mg/day including 2189 of participants. The study suggests that middle aged men with dietary zinc intake may not have significance for prevention of depression.<sup>41</sup>

In a study, research finds out the efficiency of zinc supplementation in depression. Six databases studies were used. Zinc was compared with anti-depressants. The study concluded that zinc supplementation shower better result in lowering depressive symptoms that antidepressant therapy.<sup>48</sup>

Yary et al.<sup>42</sup> Finds out the relationship between zinc and depression in post-graduate students including men (55%) and women (43%). It showed an inverse relationship between zinc and depression. The study concluded that result remains the same regardless of physical activity, age or gender.<sup>42</sup>

In a study researcher finds out bipolar disorder in blood serum of patients by measuring zinc concentration. 129 patients included in this study with bipolar disorder type I and type II. Flame atomic absorption spectrometry was used to test the level of zinc. The study concluded that patients in the depressive phase with BD type I have a lower level of zinc.<sup>39</sup>

In 2017, research finds out a comparison between Major Depressive Disorder and control group patients. In this study 69 patients with depressive stage, 45 patients in active stage and 50 in the control group. Electro thermal atomic absorption spectrometry was used to measure zinc concentration. The conclusion of this study confirmed a positive correlation between zinc deficiencies in the depressive stage.<sup>49</sup>



In 2015, in order to find the reason for depression in young girls a study was conducted in which 849 girls with age of 12-18 year participated. Beck Depression Inventory (Korean version) was used. 16 and above score indicated depression in the patient. Every candidate's dietary patterns were evaluated of last one year. The results showed that 13.6% girls were prevalent and 116 had depression symptoms. The cause of depression included deficiency of zinc, potassium, vitamin C,  $\beta$ -carotene and copper also directly associated with green

vegetable and one to three fruit servings. Thus, caution is required regarding dietary choices in this population.<sup>50</sup>

In an experimental study 77 volunteers were taken and were told for follow up on their lifestyle changes. Intervention records were made before and after the changes and that showed that volunteers those were suffering from depression were having low levels of zinc and selenium that can be cured by Mediterranean diet (Table 1).<sup>51</sup>

**Table 1** Original studies regarding role of zinc in depression

Dietary Intervention	Study Subjects	Duration of Treatment	Treatment Effect	Study Reference
30ppm zinc 1ppm zinc 180ppm zinc	3 groups of rats	3 weeks	Decreased melancholy Depression, Elevated anxiety levels Decreased melancholy	Tassabehji et al. <sup>37</sup>
25mg zinc	44 patients	12 weeks	Decreased depression	Ranjbar et al. <sup>40</sup>
30mg/kg zinc	Mice	3 weeks	Reduced weight Corticosterone raised	Ding et al. <sup>47</sup>
>9mg/day	2317 men	4 days	Zinc is an anti-depressant	Lehto et al. <sup>41</sup>
25mg elemental zinc supplementation/d	44 patients	12 weeks	Zinc supplementation lowered depression levels in patients	Ranjbar et al. <sup>45</sup>
Alsberg and Montgomery Depression Scale	100 psychiatric patients 882 normal people		psychiatric disorders and depression both are elevated by zinc deficiency	Grønli et al. <sup>46</sup>
4-d food record zinc intake	2317 men	20 year followup	Suppression of depression in middle aged men with adequate dietary zinc intake.	Markiewicz- Żukowska et al. <sup>44</sup>

## Conclusion

It is concluded that zinc deficiency is majorly present in people having depression. Zinc supplementation with adequate amount and duration act as an anti-depressant in patients who have depressive disorder. The long term use of zinc can regulate the symptoms of depression. Even in bipolar disorder zinc levels are low and supplementation can be beneficial to those people. Zinc deficiency can gain weight and lower the serotonin levels. Along with the zinc deficiency certain more vitamins and minerals are also associated in causing depression, so cautions for dietary considerations are required.

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## Conflict of interest

The author declares that there is no conflict of interest.

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