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Serum Concentration on Mineral Zinc and Cognitive Changes in Children: a Review

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Abstract

Introduction: Micronutrient deficiencies in children in developing countries remain a public health problem, as they are persistently common. Among them, zinc is an essential trace element and plays a crucial role in biological functions and physiological processes in humans. Disorders of zinc balance during life appear to be an important factor correlated with the development of CNS diseases. This research aimed to conduct a literature review on the proportion of research involving zinc and brain development in children. **Methods:** A search was performed in the Pubmed, Scorpus, and Web of Science databases, and articles from the last 5 years were retrieved. According to the criteria, 7 articles were chosen to compose this review. **Results:** 57% revealed that children with ASD have low serum zinc levels, and 29% of the studies found lower plasma zinc levels in children diagnosed with ADHD. Revealing that attention to the levels of zinc in the plasma must be special, since mainly the levels of micronutrients, are decisive for a good biological, physiological, neurobiological, and behavioral development, acting on the personality and formation of the human being. **Conclusion:** In this perspective, we emphasize the importance of giving greater attention to the serum levels of adequate zinc in the human body, renewing the knowledge that adequate nutrition is of great importance for normal development from pregnancy to aging.

INTRODUCTION

Zinc is an essential trace element and plays a crucial role in biological functions and physiological processes in humans (Liu *et al*., 2017). Essentially present as a co-factor of more than 300 enzymes or metalloproteins, it is the second most abundant metal in the human body, with a concentration of 2 to 4 grams distributed throughout the body, plays an important role in many functions, including cell division, immune system, protein synthesis, and DNA synthesis (Ackland & Michalczyl, 2016, Wessels *et al*., 2017, Kawahara *et al*., 2018).

The most important biological processes regulated by zinc are gene expression, antioxidant defense, and apoptosis. It is necessary for normal growth and development since the uterus until puberty, and is usually ingested through food or breast milk, absorbed through various intestinal transporters and released into the bloodstream. Concentration in the diet, on the other hand, is important, since zinc imbalance can result not only from dietary intake, but also from impaired activity of zinc transport proteins and zinc-dependent regulation of metabolic pathways (Liu *et al.,* 2017).

The crucial role of zinc homeostasis in the central nervous system (CNS) has an influence on the function of learning, cognition and mood regulation (Kawahara et al., 2018, Portbury & Adlard, 2017). Zinc can modulate long-term synaptic plasticity (Bird et al., 2017). In addition, it can increase postsynaptic density in the pathways of activation of the brain-derived neurotrophic factor (BDNF) (Xu *et al*., 2011).

Adequate intake is crucial for cognitive function, especially in children and the elderly (Pavlica & Gebhardt, 2010, Brewer et al., 2010, Lovell *et al.,* 2006, Leven et al., 2006, Yasuda et al., 2011, Tyszka-Czochara et al., 2014). Changes in zinc level have been reported in diseases such as depression and Attention Deficit Hyperactivity Disorder (ADHD), Alzheimer's disease, Parkinson's disease, as well as ischemia, and traumatic brain injury (Portbury & Adlard, 2017).

Based on studies presented, disturbances in zinc balance during human life appear to be an important factor correlated with the development of CNS diseases. In this perspective, the present study aimed to conduct a literature review on the proportion of research involving zinc and brain development in children, considering this theoretical dimension to verify the existence of studies and the feasibility of working on these concepts.

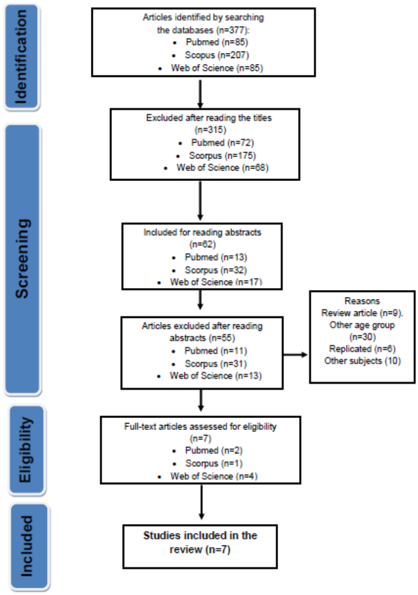
MATERIAL AND METHODS

A search was performed in the Pubmed, Scorpus, and Web of Science databases, looking for articles that would allow us to evaluate the action of the mineral zinc on cognitive development in children. Using the literature review technique, after searching for the regular words for indexing in MeSH, it was decided to use “Child”, “Zinc”, “Brain”, interspersed using only the Boolean operator “AND”, so that, when another operator was used, the searches returned material that did not meet the purposes or were not relevant to the scope of this review.

The inclusion criteria for the research were: publications from the last 5 years; in all languages; published until September 17, 2019. The exclusion criteria corresponded to studies carried out with adults, the elderly, animals and in vivo; review articles; congress proceedings; book chapters; other articles that do not address zinc as an element researched in cognition.

The inclusion process of the studies took place in two phases, the first being the evaluation of the titles and abstracts of the identified studies and the second, reading in full where the inclusion criteria were applied and later the number of included and excluded studies was determined, defining the final sample.

Figure 1: Flowchart of selection, inclusion, and exclusion of studies.



According to the criteria, 7 articles were chosen to compose this review (Table 1), on a scale of publications where in 2015 the research collected information on the association between ADHD and plasma zinc levels; in 2016 research already found that lead, a neurotoxic trace element is present in high concentrations in the blood of children with Autistic Spectrum Disorder (ASD), and also fulfilled the search for associations between learning disabilities related to other causes and serum levels of zinc. In 2018, the search for consolidating the presence of plasma zinc in learning performance was proposed, supplementing healthy children to analyze whether the results of Intelligence Quotient (IQ) tests were increased in children who received daily doses of zinc syrup; in 2019 we found research that aimed to specifically analyze the associations between plasma zinc concentration with gene expression and cognitive--motor performance in children diagnosed with ASD. Still from the perspective of experimental analyzes, knowing that iron and zinc are very important for the development of the CNS, they analyzed the cases of children with febrile seizure crises and found that they have low serum concentrations of these micronutrients. The characteristics of these studies are described in Table I.

There is a consolidation in which plasma zinc levels are reduced in children with ASD, as well as in the manifestations of ADHD. 57% dos artigos estudados nesta revisão revelam que crianças com TEA possuem níveis séricos de zinco reduzidos, e 29% dos estudos encontraram menores níveis de zinco no plasma de crianças diagnosticadas com TDAH.

Anthropometric nutritional status, IQ, and associations with febrile seizures also showed a strong association with lower plasma zinc levels in children. Revealing the importance that should be given to serum zinc concentrations and its relationship with the nutritional, intellectual, behavioral and psychological development of our children.

REFERENCE	OBJECTIVE (S)	STUDY DESIGN	RESULTS
Khodashenas et al., 2015.	Quantify the impact of zinc supplementation on the cognitive development of schoolchildren.	Randomized, double-blind, placebo-controlled study. 45 healthy children aged 6 to 8 years, divided into cases and controls. The cases received 20mg of zinc sulfate syrup, and the controls only placebo for 6 months. The Intelligence Quotient (IQ) assessment was analyzed before and after supplementation, the method chosen was Raven.	Memory and intellectual development in the experimental group were significantly higher than in the control group. Demonstrating the positive relationship between zinc administration in some aspects of intellectual development, personality characteristics and normal psychological state of children.
Viktorinova et al., 2015.	Investigate the levels of trace elements copper (Cu), zinc (Zn), Cu / Zn ratio, selenium (Se), and lead (Pb) in children with ADHD and healthy children.	58 cases of ADHD and 50 controls, aged 6 to 14 years, both sexes.	Lower Zn concentrations were found, and higher concentrations in the Cu / Zn and Cu ratios in the cases. Pointing out changes in plasma Cu and Zn levels related to ADHD cases.
Crăciun et al., 2016.	To investigate the total serum levels of zinc (Zn) and copper (Cu) in children with autism spectrum disorder (ASD).	28 children with ASD and 28 healthy controls, both according to age and sex.	The results indicate that children with ASD were characterized by ~ 10% and ~ 12% lower levels of the Zn and Zn / Cu ratio in whole blood, respectively, compared to controls. The results of the present study may be indicative of Zn deficiency in children with ASD, and confirm that a high dose of Cu in the blood is related to neurological changes, which is neurotoxic.
Taşkın et al., 2016.	Investigate zinc and vitamin B12 deficiencies in learning disabilities.	412 children between 4 and 18 years old, 206 with learning disabilities and 206 control cases.	The zinc levels in the cases were significantly low compared to the controls, but no association was found between vitamin B12 deficiency. It was concluded that simply giving oral zinc supplements to children with learning difficulties can be an alternative treatment.
Kusumastuti et al., 2018.	To analyze the effects of iron (Fe) and zinc (Zn) supplementation on appetite, nutritional status, and intelligence quotient (IQ) of young children.	Randomized experimental study. 68 children, aged between 30 and 59 months, were divided into four groups (G1- control, received placebo; G2-Zn 10mg; G3-Fe 7.5mg; G4-Zn + Fe in the doses presented, for 3 months). Appetite was assessed based on food frequency and energy intake, nutritional status by z score height-for-age and weight-for-age, whereas IQ score based on Wechsler Preschool and Primary Scale of Intelligence	Zinc and iron supplementation for three months had a positive effect on appetite, body weight and IQ score, but no significant effect on body height.
Abdel Hameed et al., 2019.	Evaluate the relationship between iron and zinc deficiencies with febrile seizures.	Cross-sectional study including 100 participants, 50 children with febrile seizures and 50 control cases, both admitted to the hospital at the University of Assiut, Egypt.	The zinc level was 68% lower in the cases and 36% lower in the controls. Showing that lower zinc levels appear to be predisposing factors for febrile seizures in children.
Meguid et al., 2019.	Investigar a ação da suplementação de zinco na concentração plasmática, expressão gênica e desempenho cognitivo-motor em crianças com desordem do espectro autista (ASD).	30 children with ASD, aged between 3 and 8 years, evaluated for 3 months. Supplied with zinc calculated according to body composition (between 15 and 20mg).	An increase in cognitive-motor performance, serum metallothionein concentration was observed, as well as a significant reduction in circulating serum copper levels after zinc supplementation.

Tabel 1: Articles included in the review.

DISCUSSION

Micronutrient deficiencies in children in developing countries remain a public health problem, as they are persistently common. They can be attributed to inadequate intake, low bioavailability of micronutrients, and anti-nutritional factors. They further increase the risk of disease and infection by weakening the immune system and further depleting nutrient reserves (Katona & Katona-Apte, 2008).

Zinc is an essential micro nutrient for the normal development of the central nervous system and is necessary for the formation and function of a variety of proteins, enzymes, hormones and growth factors that direct the proliferation and differentiation of stem cells during neurodevelopment (Gower-Winter & Levenson, 2012).

In normal neurons, free zinc is largely located in the presynaptic vesicles of glutamatergic neurons (Franco-Pons *et al.*, 2000), but it has also been observed to be located in neurons containing gamma-aminobutyric acid (GABA) (Wang *et* *al*., 2001). Regions rich in vesicular free zinc include the mossy fibers of the hippocampus, amygdala, and olfactory bulb. "Zincergic" neurons are also abundant in the cortex (Frederickson *et al*., 2000, Gower-Winter & Levenson, 2012). As for the hippocampus, it is not only one of the primary regions of the brain that support neurogenesis, but it has also been shown to contain high concentrations of zinc (Takeda *et al*., 2001).

In the brain, zinc regulates the activity of glutamic acid and the rate-limiting enzyme in GABA synthesis and facilitates the inhibitory effect of calcium on N-methyl-d-aspartate receptors, and these effects prevent the stimulation of neuronal discharge. (Rehman *et al*., 2018).

ASD is a neurodevelopmental and neurobehavioral pathology of greatest interest in neurobiology worldwide, responding to an epidemiological trend in the USA of about one in 40 individuals in recent years (Meguid *et al*., 2019). In addition to the known deficiencies in social communication and behavior, subjects with ASD suffer from motor disabilities (Takeda, 2014). Zinc bioavailability is crucial for Autism Spectrum Disorder (Yasuda *et al*., 2011), as it has been treated in recent years as one of the main concerns (Kambe et al., 2015, Andreini *et al*., 2006), particularly in regarding the relationship between zinc and copper (Cu) and the functionality of the gut-brain axis (Viktorinova et al., 2015). Meguid *et al.,* (2019), found a reduction in the severity of ASD symptoms after supplementing children with zinc daily; it was possible to notice that plasma zinc levels increased and copper levels decreased. A possible explanation can be recovered from studies showing that zinc is connected to the regulation of glutamate and GABA.

The study by Viktorinoca *et al*., (2015), provides insight into the excess of copper and lead, and low levels of zinc on neurological development, since copper participates in the metabolism of dopamine, noradrenaline, and epinephrine, its excess in blood flow provides symptoms of physical and mental fatigue, depression, and other problems such as schizophrenia, learning disabilities, hyperactivity and general behavioral problems. In addition, lead can cause dysfunction of some neurotransmitters, including dopaminergic, glutamatergic and cholinergic systems. These neurotransmitter systems, especially the dopaminergic system, have been linked to ADHD symptoms in children (Jeff *et al*., 2002, Costa *et al*., 2004), and zinc indirectly affects dopamine metabolism, hormones and actions needed to good neural development. Because they are antagonists, zinc and copper tend to disharmonize and this action is worrying because it causes changes in neuroprotective proteins and a greater proportion of neurotoxic actions (Craciun *et al*., 2016).

Among children with low academic performance, or even learning disability was found lower zinc levels than healthy children of the same age and sex (Taskin *et al*., 2016).

Kusumastuti et al., (2018), sought an association between increased appetite, nutritional status (weight and height), and IQ levels in children, and found a strong relationship with appetite and cognitive stimulation in healthy individuals supplemented with zinc and iron for a period of 3 months. taste buds (Kelishadi *et al*., 2014, Suziki *et al*., 2011, Yagi et al., 2013). As for stature stimulation, there were no changes because at 2 years of age, stature growth is slower in terms of speed than at an earlier age, so more time is needed to statistically increase height (Roche & Sun, 2003).

Another frequent neurological disorder in children is a febrile seizure that affects 2% to 5% of children between 3 and 60 months of age (Abdel Hameed *et al*., 2019, Hubaira et al., 2018). Alteration of brain synaptic neurotransmitters, increase in glutamate excitatory neurotransmitters, decrease in GABA inhibitory neurotransmitters, decrease in monoamines and hypoxemia that occurs due to iron deficiency may be responsible for inducing seizures (Yadav & Chandra, 2011). Zinc is abundantly located in the hippocampus, where a total of 5% to 15% of zinc is collected as a vesicle at glutamatergic synapses. Zinc acts as a neurotransmitter and improves the communication and locomotive function and the maturation of the neurological system, its deficiency decreases the zinc of the hippocampus and leads to the release of seizures (Rehman *et al*., 2018).

CONCLUSION

In general, the articles present the importance of maintaining adequate serum zinc levels in the human body, renewing the knowledge that adequate nutrition of micro and macronutrients is extremely important for normal development. As for childhood, this attention must be doubled, since especially the levels of micronutrients, are decisive for a good biological, physiological, neurobiological, and behavioral development acting on the personality and formation of the human being.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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