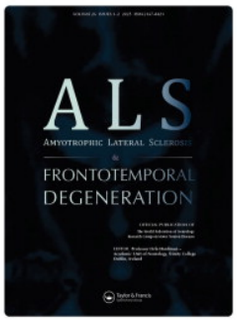

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BRIEF REPORT

ALSUntangled #78: Zinc

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Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). In this review, we assess the utilization of dietary zinc supplements for modulating ALS pathology and progression. Studies in mouse models of ALS have demonstrated that high-dose zinc supplementation may be harmful, but moderate doses could potentially be beneficial. Clinical data is limited, and only one trial has explored zinc supplementation within PALS. This study reported potential benefits in slowing ALS progression but lacked statistical analyses and failed to report quantitative evidence. Numerous case reports from individual patients at varying doses have demonstrated no benefit. Zinc supplements at moderate doses are generally low cost and not associated with severe complications, but further research is required to determine the safety and efficacy of zinc supplementation within PALS. Therefore, we cannot at this time, endorse zinc supplementation to slow ALS progression.

Keywords: *Zinc, supplement, antioxidant*

ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS (PALS). Within this review, we examine the use of zinc supplementation to slow ALS progression, for which we have had 84 requests (1).

Overview

Zinc is an elemental metal with essential roles in various physiological processes including protein, lipid, and nucleic acid metabolism, enzyme

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function, and gene transcription (2,3). Consequently, the normal functioning of zinc is important for numerous processes within the human body but is especially relevant for immune response, reproduction, and wound repair (4–6). At optimal levels, zinc additionally plays a key role in cellular antioxidative activity through both increasing the activity of proteins with antioxidative functions and directly antagonizing transition metal-catalyzed reactions (7).

Due to the complexity and importance of zinc-dependent processes, dysregulation of zinc homeostasis has significant detrimental consequences (8,9). While most Americans consume enough zinc to meet the estimated average daily requirement of 8–11mg, up to 15% do not (10). Zinc deficiency can present with numerous symptoms, including growth impairment, inflammation, gastrointestinal symptoms, and sexual dysfunction (5,8). Deficiency also has a wide array of neurological implications that can result in cognitive decline, depression, and has been linked with progression of neurodegenerative diseases (2,11). Zinc toxicity is significantly rarer but occurrences still have significant negative implications for human health (12). Acute overdose of zinc leads to nausea, vomiting, abdominal pain, metabolic imbalances, and, in rare cases, severe neurological symptoms. Chronic zinc toxicity additionally manifests adverse health effects, including impaired immune function, alterations in lipoprotein homeostasis, zinc-induced copper deficiency and resultant neurological symptoms (12,13). Furthermore, high levels of zinc are known to be neurotoxic and induce neuronal cell death, including within motor neuron populations (14,15). Therefore, maintaining proper zinc homeostasis is crucial for overall health, as both deficiency and excess can lead to significant physiological and neurological disturbances.

Within the context of ALS, the modulation of zinc homeostasis and the potential for therapeutic zinc supplementation remains speculative, but clinical data has reported links between zinc dysregulation and ALS. One observational study reported that, on average, PALS have poor dietary intake and consequently have inadequate levels of zinc (16). Additionally, several studies have noted correlations between PALS with lower zinc intake and increased symptom severity (17,18). However, the evidence from these studies is insufficient to prove causality, and the ALS-related factors that directly interfere with food intake make establishing a definitive relationship between zinc levels and ALS pathophysiology difficult. It is very plausible that this reported correlation is simply the result of generally poor nutritional intake; malnutrition alone is known to accelerate ALS progression. Therefore, further research is needed to clarify the role of zinc in ALS pathogenesis and progression, as well as to determine whether zinc supplementation may offer any therapeutic benefits.

Mechanistic plausibility

Oxidative stress is thought to play a significant role in ALS pathology and progression (19). In numerous studies including a large meta-analysis of randomized controlled trials, zinc supplementation has demonstrated the capacity to reduce plasma concentrations of oxidative products in humans (20–22). Zinc utilizes several mechanisms to exercise its antioxidative effect, which include the upregulation of metallothionein (MT) expression and its role as a cofactor in copper/zinc superoxide dismutase (SOD1) enzymatic function (23,24).

MTs are a family of metal-binding proteins that are known for their role in zinc homeostasis and protective antioxidant properties (25). MTs contain a zinc-specific binding site that is highly responsive to reduction-oxidation (redox) activity and exhibits the dynamic capacity to release or sequester zinc depending on the cellular environment (11). This ability to rapidly modulate free zinc availability enables MTs to serve as a buffering mechanism to counterbalance oxidative stress due to the antioxidative functions of free zinc (11). MTs additionally combat oxidative stress through direct scavenging of free oxygen radicals, such as hydroxyl radicals (26). Zinc supplementation can modulate MT's antioxidative activity because expression of MTs is induced by high levels of zinc (27,28). Therefore, stimulation of MTs via zinc supplementation presents a plausible mechanistic avenue through which a major contributing factor to ALS pathology, oxidative stress, might be decreased.

SOD1 is a cytosolic enzyme responsible for catalyzing superoxide radicals into molecular oxygen and hydrogen peroxide, which protects cells against oxidative damage (29). The activity of SOD1 is dependent on the binding of metal cofactors, particularly zinc and copper. Copper directly catalyzes the enzymatic function in the active site of SOD1, while zinc binding increases both the structural stability and enzymatic proficiency (30). This increased structural stability from zinc binding significantly decreases SOD1 misfolding, which is a hallmark of SOD1 ALS pathology (31). This link between zinc-induced structural stability and ALS has been furthered by preclinical data that demonstrated that under zinc-deficient conditions, wild type SOD1 adopts a mutant-like conformation that predisposes SOD1 for oligomerization and increases cellular stress similar to SOD1 proteins with pathogenic mutations (31). Therefore, without adequate zinc, SOD1 cannot effectively function as an antioxidant enzyme and the

decreased stability may increase the protein's propensity for misfolding, both of which contribute to ALS pathology and progression. Zinc supplementation could potentially mitigate these effects by protecting the antioxidative function and stability of SOD1 and consequently represents a mechanism that could be theoretically beneficial in PALS.

Due to zinc's role in MT expression and SOD1 stability and activation, which both modulate factors believed to be important within ALS pathology and progression, we assign zinc supplementation a TOE "Mechanisms" grade of B (Table 1).

Pre-clinical

Currently, two preclinical studies have evaluated the use of zinc supplements in mouse models of ALS. The first study was conducted by Groeneveld et al. in 2003 and examined the effect of two doses of zinc supplementation, 75 and 375 mg/kg/day, on onset and progression of ALS within a transgenic mouse model overexpressing human SOD1 with a G93A mutation (32). Starting at day 50, zinc sulfate supplements were given in drinking water. The study found that 375 mg/kg/day zinc supplementation significantly decreased the survival of transgenic mice compared to the untreated group, while the survival of the 75 mg/kg/day dose group did not significantly vary from the control group. Additionally, neither group significantly varied in the onset or progression of ALS symptoms. While MTs were upregulated in all transgenic groups, zinc supplementation did not result in a further increase in MT expression in the spinal cord regardless of treatment group (32). Of note, this group did not add copper supplements to their treatment regimen, which might have influenced the toxicity of high dose zinc treatments.

The second study was conducted by Ermilova et al. and examined the effect of more moderate doses of zinc supplementation, 12 and 18 mg/kg/day. This study utilized a similar methodology to Groenveld et al. by using the G93A mutant SOD1 transgenic mouse model, oral zinc sulfate supplements dissolved in drinking water, and starting supplementation at day 50. However, this study utilized a zinc-deficient diet for all animal groups to isolate the effect of zinc supplementation and also utilized copper supplementation to mitigate zinc-induced copper deficiency (33). The researchers found that 12 mg/kg/d of moderate zinc supplementation provided a protective effect by delaying disease onset and progression and extending survival compared to the control group. The higher dose group (18 mg/kg/d) recapitulated the findings of Groeneveld et al. and demonstrated decreased survival. However, this decrease was reversed when co-administered with 0.3 mg/kg/d copper supplements, which increased survival rates to approximately the equivalent of the 12 mg/kg/d group (33). This suggests that high zinc doses may accelerate ALS disease progression by causing copper deficiency.

While both preclinical studies provide insight into the effects of zinc supplementation in ALS models, they also have factors that significantly limit their conclusions. Groeneveld et al. utilized exceedingly high doses of zinc that are approximately 15 and 75 times greater than the recommended zinc intake for rodents (34). This high level of intake raises the likelihood that the observed negative effects were due to zinc toxicity and not modulation of ALS pathology. Ermilova et al. utilized more moderate doses of zinc supplementation but introduced a complicating factor by using a zinc-deficient diet to isolate the effect of supplementation. This may have exaggerated any beneficial effects by correcting an induced deficiency, which makes it difficult to separate the effect of zinc repletion from other variables. Therefore, while preclinical experimentation with zinc supplementation in the context of ALS has shown some promise in increasing survival and slowing disease progression, due to the complicating factors discussed above, we assign a TOE "preclinical" grade of C (Table 1).

Data in PALS

Cases

Within the Patients Like Me (PLM) community of 13,991 PALS, 28 reported using zinc supplements as a treatment for ALS. Of these, six male PALS completed detailed treatment reports. Four of these individuals ranged in age from 55 to 65 years old, and two did not report their ages. Unfortunately, we do not know if any of these PALS had genetic forms of ALS (ex. mSOD1).

Table 1. Table of evidence for zinc supplementation as an ALS treatment.

Category	Grade	Explanation
Mechanism	B	Zinc supplementation acts on two biological mechanisms that are theoretically relevant to ALS progression
Preclinical	C	Zinc supplementation has been shown to decrease the rate of disease progression in mouse models of ALS
Cases	F	The only reports available show no benefit
Trials	D	One publication reported benefits in a limited trial but failed to provide quantitative results and statistical analyses.
Risks	A	No exposed ALS patients have reported side effects from supplementation

The reported daily doses of zinc supplementation were 10, 15, 30, and 440 mg, while two individuals did not specify their dosage. All six participants rated zinc supplementation as having no effectiveness in treating their ALS symptoms but reported no significant side effects associated with their zinc supplementation regiments (35). No more details are available on these patients. This is a very small sample size and it lacks diversity, meaning the results may not be generalizable to all PALS.

Trials

To date, only one small pilot trial has reported evaluating zinc supplementation in PALS. This study by Levine et al. consisted of ten patients with sporadic ALS on stable doses of riluzole receiving 90 mg/d of Optizinc, a zinc methionine sulfate complex, and a 2 mg/day copper supplement for three months. Eight patients completed the study and tolerated the treatment well, with zinc and copper levels maintained within acceptable ranges. ALS progression as assessed by monthly ALS-FRS-R scores was reported to show some slowing over the course of treatment (36). However, the quantitative evidence and statistical analyses of this difference were not reported, which, in addition to the small sample size, significantly limits the strength of any conclusions drawn from this trial.

Due to PLM case reports showing no benefit of zinc supplementation and the only trial that has examined zinc supplementation in PALS reporting limited evidence, we assign a TOE "cases" grade of F and a "trials" grade of D (Table 1).

Dosing, risks and costs

Zinc supplements can be purchased in various formulations and dosages, but optimal dosing for PALS has not been established. For healthy adults, the recommended daily allowance (RDA) of zinc is 8 mg/day for females and 11 mg/d for males, with a safe upper limit of 40 mg/d according to the U.S. Food and Drug Administration (10) which maintains a website listing RDA and safe upper limits for many different vitamins and minerals (37). We are not aware of a list like this one from other countries. Zinc is considered relatively non-toxic, especially if taken orally, but side effects, including zinc-induced copper deficiency and impaired immune function, can occur when taking amounts in great excess of the RDA (13). However, one trial found that a dose of 90 mg/day of zinc was well tolerated in PALS but additionally utilized copper supplements to avoid deficiency. Therefore, further studies are needed to determine the safety of zinc supplementation in PALS, especially at doses exceeding the RDA. It is critical to note that zinc over supplementation can cause copper deficiency, which is a well-known cause of a motor neuron disease mimicking ALS (38). Depending on the retailer and dose, zinc supplements generally cost approximately $10 per month (39).

No PALS exposed to zinc supplementation reported any adverse effects in the above described case reports or trials. Thus, we assign a TOE "risks" grade of A (Table 1) but again advise caution regarding the potential risk of zinc-induced copper deficiency.

Conclusion

Zinc has plausible mechanisms for modulating ALS progression, specifically with its roles in oxidative stress reduction and stabilization of SOD1 structure and function. Preclinical data has demonstrated potential benefits in slowing ALS progression at moderate doses in mouse models, but high doses without additional supplementation of copper were shown to be harmful. Clinical data on zinc supplementation in PALS is limited, but numerous case reports and a small pilot trial provide some insight. The case reports indicated no benefit from zinc supplementation, while the pilot trial reported potential benefits in slowing ALS progression. However, this trial lacked statistical analyses and had a very small sample size, which significantly limits the strength of its findings. Based on the current lack of substantial clinical evidence supporting the potential benefits of zinc supplementation in PALS, we cannot endorse zinc supplementation as a treatment for ALS at this time.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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