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Zinc Possible Correlation with Pneumonia: Review Article

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ABSTRACT

Background: One of the most important trace elements is zinc. Proliferating cells throughout the body, and the immune system in particular, rely heavily on zinc. Humans have between 2 to 4 micro grammes of zinc in their bodies, with about 95% of that amount being located within their cells. Although zinc is found in all bodily tissues and fluids, about 57% of the body pool is kept in skeletal muscles, 29% in bone, and 6% in skin.

Objective: Review of literature about zinc possible correlation with pneumonia.

Methods: We searched Science Direct, Google Scholar as well as PubMed for relevant articles on Zinc as well as Pneumonia. Only the most recent or thorough study was taken into account between May 2001 and April 2023. The authors also evaluated the value of resources culled from other works in the same genre. Therefore, documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research.

Conclusion: Zinc transporters control the levels of zinc in lung tissue, where it binds mostly to metallothionein (MT). Cigarette smoke contains significant concentrations of cadmium (Cd), a hazardous heavy metal and carcinogen, and ZIP8, a zinc transporter, is the primary entry site for Cd. Zinc lowers the cytotoxicity of Cd to alveolar epithelial cells after inhalation of Cd-containing gas by competing with Cd for binding to ZIP8 protein. Preventative zinc supplementation can lessen the likelihood of contracting pneumonia. Zinc supplementation has been shown to reduce the severity and duration of pneumonia.

Keywords: Zinc, Pneumonia, Interleukin, B cells.

INTRODUCTION

Serum zinc concentrations in healthy adults are kept within a small range (about 10-15 μmol; 70-98 g/dL) by homeostatic processes. When zinc consumption is kept constant (between 5 and 20 mg per day), blood levels of zinc is kept stable [(1)]. To maintain a sufficient zinc level, the mineral must be taken in on a daily basis through diet. Zinc is mostly absorbed by the cells of the jejunum and stored in the liver, bones, and muscles. Increased intercellular signaling and zinc homeostasis occur despite plasma zinc making up only 0.1% of total zinc storage [(2)].

Zinc and immunity:

Both innate and adaptive immunity play a role in protecting the body. Innate immune cells are the first to detect and destroy foreign invaders. Some of the first cells to respond to an infection are called polymorphonuclear cells (PMNs), macrophages (M), and natural killer cells (NK). Zinc deficiency impairs PMN chemotaxis and phagocytosis, whereas zinc supplementation restores these functions. Both zinc deficiency and excess have been demonstrated to impede the action of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, which are responsible for the destruction of pathogens following phagocytosis [(3)].

The levels of proinflammatory cytokines including interleukin (IL)-1beta, IL-6, and tumour necrosis factor (TNF)-alpha are elevated in the body when zinc is lacking. Zinc depletion affects NK cell lytic activity and NK cell recognition of major histocompatibility complex (MHC) class I. Reduced antibody production is another consequence of zinc deficiency's effect on the adaptive immune response, which includes thymic atrophy, lymphopenia of activated T cells, and a decrease in both immature and premature B cells [(4)].

Lymphocyte proliferation slows down in people who don't get enough zinc. Both CD4+ and CD8+ thymocyte numbers drop dramatically when zinc intake is low. In reaction to higher glucocorticoids caused by zinc deficiency, naive cells sustain high levels of apoptosis. In addition to being able to withstand zinc deprivation and thymic atrophy, mature CD4+ and CD8+ T lymphocytes also have larger quantities of the anti-apoptotic protein Bcl2. Zinc deficiency, interestingly, maintains some parts of innate immunity via maintaining myelopoiesis [(5-8)].

Zinc and inflammation:

The inflammatory response resolves and equilibrium is restored because inflammation is a necessary, protective response to tissue damage and infection. However, in other cases, the inflammation does not go away and becomes chronic, resulting in the dysfunction of the affected tissues [(3)].

NF-κB and other signaling pathways:

The NF-kappa B (NF-kappa light chain enhancer on activated B cells) signaling pathway is an important mediator of inflammation. This transcription factor controls several cellular activities, including proliferation, adhesion, tissue remodeling, immune responses (both innate and adaptive), inflammation, and stress responses. Then, it alters the production of inflammatory cytokines such TNF-alpha, IL-1 beta, IL-

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6, IL-8, and MCP (monocyte chemoattractant protein)-1. NF-B is one of the most versatile factors regulating gene expression [9].

Several studies, some of which are at odds with one another, examine zinc's effect on this process. Lipopolysaccharide (LPS)-induced nuclear factor (NF)-B signaling requires zinc, as found by **Haase *et al.*** [10]. Zinc, on the other hand, inhibits NF-B signaling pathways. Several potential methods of inhibition have been proposed. The regulation of protein A20 expression by zinc is a key inhibitory mechanism. The zinc-finger protein A20 is an anti-inflammatory factor known for its negative regulation of NF-B pathways activated by tumour necrosis factor receptors (TNFRs) and toll-like receptors (TLRs). Deubiquitination of receptor interacting protein 1 (RIP1) by A20 during TNFR signaling blocks RIP1's interaction with the key regulator of NF-B, IKK. Removing polyubiquitin chains from TNF receptor associated factor 6 also reduces TLR signaling (TRAF6). Although zinc chelator does not affect A20's deubiquitinase activity [3].

Zinc deficiency:

After iron, zinc is the most common trace element in the human body. It's a crucial vitamin for development and healthy immune system function. Zinc deficiency is difficult to diagnose but is common in many parts of the world, especially in developing countries. Causes include insufficient food intake, high demands, poor absorption, excessive loss, and inefficient use [11].

Meat, fish, legumes, nuts, and other meals all contain zinc, albeit its absorption varies depending on the substrate used to transport it. The World Health Organization recognises zinc deficiency as a major risk factor for disease because of its widespread prevalence, especially in developing nations [12].

Zinc deficiency increases the risk of development retardation, diarrhoea, and respiratory infections in children. Acute lower respiratory tract infection (ALRTI) susceptibility may be reduced by zinc's ability to regulate multiple immunological activities, including the protection of respiratory cells against damage and inflammation in the lungs [13].

Malnutrition is a leading cause of zinc shortage in impoverished countries, but in industrialized nations, zinc insufficiency is linked to ageing and several chronic diseases. Both inheriting and acquiring zinc deficiency are possible. It is possible to develop a shortfall due to inadequate intake, poor absorption, increased metabolic demand, or excessive loss [14].

The World Health Organization ranks zinc deficiency as the sixth largest cause of death and disease in poor countries. About a third of the global population may be affected. Zinc deficiency is responsible for about 16% of all cases of pneumonia, 18% of all cases of malaria, and 10% of all cases of diarrhoea. Severe zinc deficiency is uncommon, while mild to moderate shortage is common [3].

Aetiology of zinc deficiency:

There are varying degrees of zinc deficiency, which can be further classified as either mild (as is seen in the older population) or severe (which is more uncommon). Zinc insufficiency causes complicated immunological abnormalities, and its most extreme manifestation is seen in the rare autosomal recessive illness known as zinc malabsorption syndrome acrodermatitis enteropathica. Zinc deficiency can also occur from other sources, such as zinc-free parenteral feeding. This condition is fatal within a few years if left untreated, however a daily zinc dose of 1 milligram per kilogram of body weight can completely alleviate all symptoms [2].

Inadequate intake, increasing needs, malabsorption, increased losses, and reduced utilisation are all common factors contributing to zinc insufficiency. Secondary zinc deficiency may develop in people with malabsorption syndromes or inflammatory bowel illnesses due to the poor absorption and loss of zinc. Infection hinders zinc utilisation because of decreased zinc circulation, which lessens zinc availability to the tissues. Low zinc levels and elevated cadmium and lead levels have also been linked to maternal diets and cigarette smoking during pregnancy [11].

Clinical manifestations of zinc deficiency:

Negative effects of zinc deficiency include stunted development, loss of body mass, recurrent infections, weakened immune systems, frequent bouts of diarrhoea and pneumonia, acne, delayed wound healing, lack of appetite, and impaired sexual development in both sexes. Worldwide, malnutrition, diarrhoea, and pneumonia account for the bulk of paediatric morbidity and mortality. Dry, scaly, erythematous plaques appear on the face, scalp, extremities, and genitalia, indicating dermatitis. Psoriasiform features may be more prominent in lesions that persist over time. Common mouth conditions include cheilitis and angular stomatitis. There could be nail dystrophy. The baldness affects the entire body and worsens over time [11].

Zinc deficiency has been linked to growth retardation and stunting, nevertheless a meta-analysis of zinc studies indicated that supplementation enhanced length growth, especially in children under the age of 2 and in those who were stunted to begin with [15].

As zinc is involved in many various cellular processes, including the proliferation of inflammatory cells and the modulation of cutaneous inflammation, zinc deficiency is linked to delayed wound healing. Collagen synthesis necessitates zinc both during proliferation and during the maturation phase. In addition to speeding up re-epithelialization and bolstering wound strength, this element is also required for fibroblast and keratinocyte proliferation [11].

ZINC AND PNEUMONIA

In low- and middle-income nations, pneumonia is a leading killer of children under the age of five. Fifteen percent of all deaths in children younger than five years are attributed to pneumonia, and in low-income countries, that number rises to nineteen percent [(16)].

Micronutrient deficiencies (such as vitamins A, D, E, selenium, and zinc) can have serious consequences for lung growth and function [(17)].

Zinc deficiency now affects the health of individuals all over the world. As a result, studying how zinc homeostasis affects lung function stability is crucial. The lung is the entry point for air into and out of the body. The protective effects of zinc on lung tissue following exposure to hazardous chemicals (cadmium, cigarette smoke) are achieved through modulating the activities of specific cell types (macrophages, T lymphocytes and neutrophils) [(1)].

Zinc transporters control the levels of zinc in lung tissue, where it binds mostly to metallothionein (MT). Cigarette smoke contains significant concentrations of Cd, a hazardous heavy metal and carcinogen, and ZIP8, a zinc transporter, is the primary entry site for Cd. Zinc lowers Cd's cytotoxicity to alveolar epithelial cells by competing with Cd for binding to ZIP8 protein when Cd-containing gas is inhaled [(18)].

MT is a zinc-thiolate moiety-containing intracellular metal-binding protein with antioxidant properties (NO). The death of pulmonary endothelial cells can be prevented, lung endothelial cells can be protected, and vascular tension can be maintained by increasing the unstable zinc concentration in pulmonary artery endothelial cells, which is mediated by NO-induced S-nitrosylation of MT [(19)].

Therefore, zinc homeostasis is extremely important, because lung zinc levels can regulate several cellular processes (like neutrophils and macrophages).

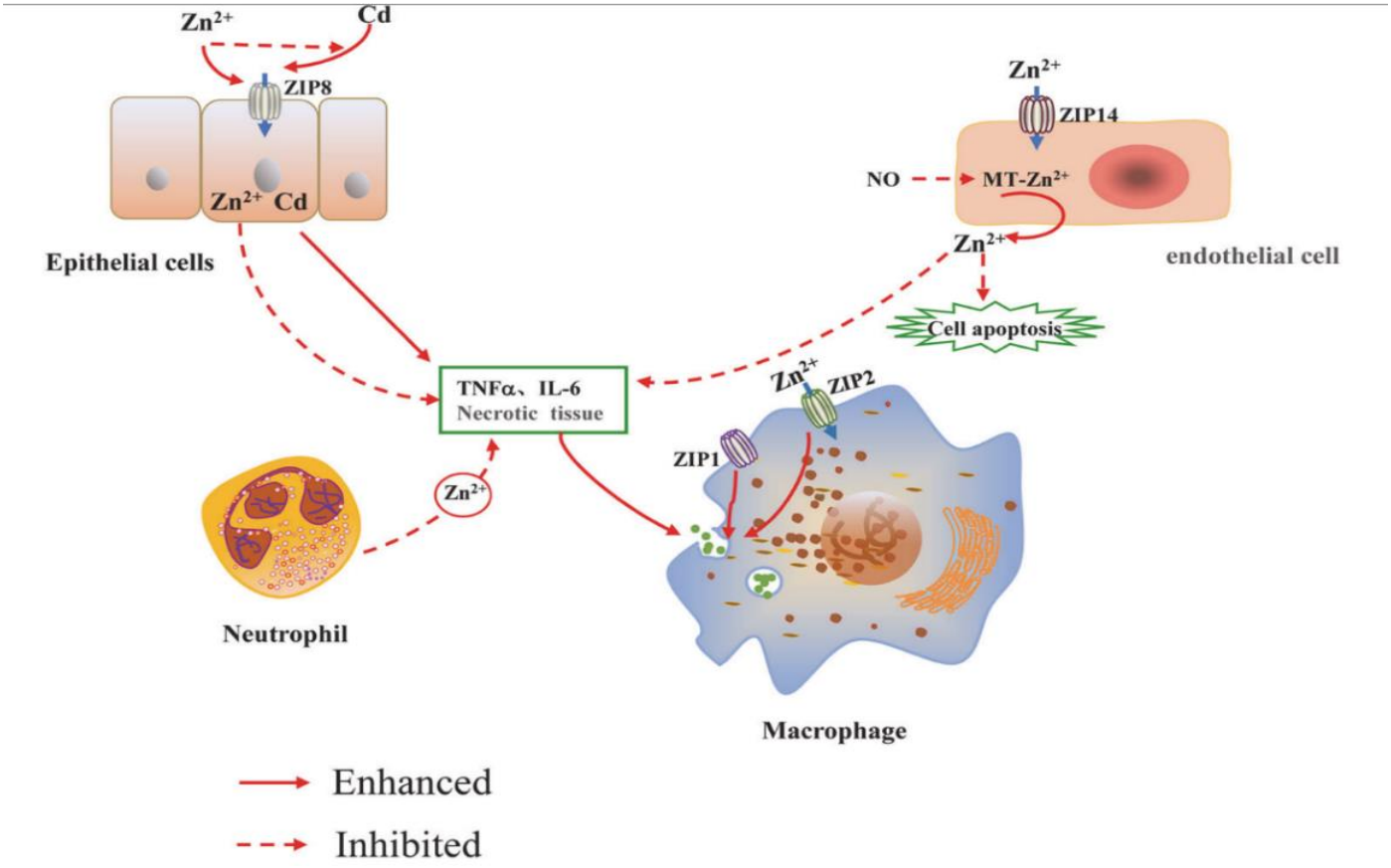

Figure (1): Lung zinc homeostasis regulation [(1)].

By modulating many signaling pathways, zinc slows the development of lung disease. As a result of increasing the activity of zinc finger protein A20, zinc is able to reduce inflammation by hastening the breakdown of receptor-interacting protein 1. The pro-apoptotic family members BAD and BAX are inhibited in tumour cells when zinc supplementation is used. Furthermore, p53-mediated apoptosis is improved, and the NF-B pathway is blocked, both of which prevent the recruitment of regulatory T lymphocytes. Zinc prevents inflammatory lung damage in obese patients by preventing the generation of the adipocytokine leptin and, in turn, preventing activation of the MAPK/NF-B pathways. The antioxidant and anti-inflammatory properties of zinc are due to its ability to stimulate the ERK/mTOR autophagy pathway [(1)].

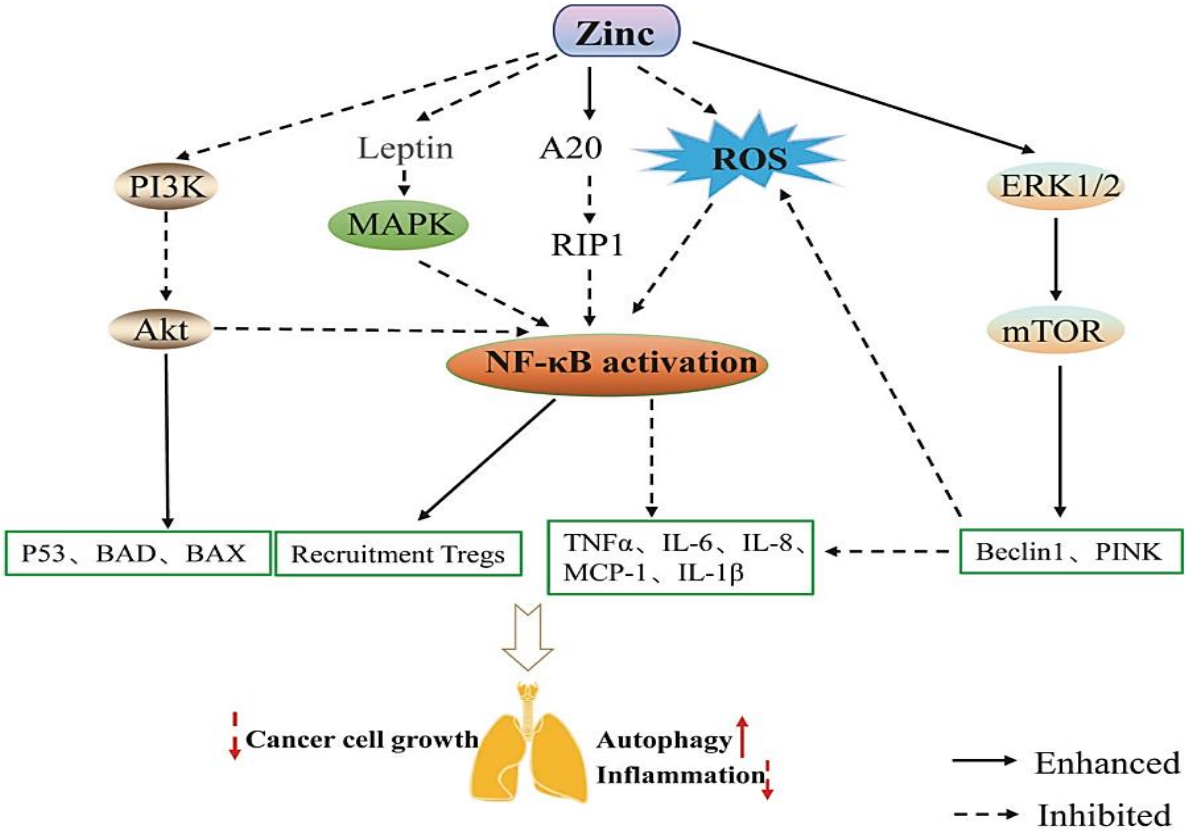

Figure (3): Lung disease progression can be slowed by zinc's influence on several signaling pathways [(1)].

Zinc supplementation and pneumonia:

Pneumonia is a very inflammatory disease that bacteria and viruses can cause. The World Health Organization (WHO) says that children with pneumonia may have trouble breathing, cough, have a high respiratory rate, have their chests draw in, have their nostrils flare, and have a decreased level of consciousness. Low and middle income countries have been found to have a higher incidence than high income countries, with 0.22 and 0.05 episodes per child-year, respectively [(20)].

It has been shown that zinc supplementation helps treat and prevent childhood pneumonia, and zinc deficiency among children with pneumonia has been recorded in numerous countries [(16)].

Preventative zinc supplementation can lessen the likelihood of contracting pneumonia. Taking a zinc supplement can lessen the impact of pneumonia and shorten its duration. The length of hospital stays and readmissions for patients with severe pneumonia have both been demonstrated to be decreased by zinc supplementation in trials [(11)].

A meta-analysis by **Yakoob and colleagues** [(21)] looking at 18 studies from developing countries found that zinc supplementation for prevention decreased the occurrence of diarrhea by 13% and pneumonia by 19% [(21)].

Pneumonia, diarrhea, dysentery, and malaria accounted for a combined 3.9 million deaths in 2015. Studies have indicated that zinc supplementation can reduce the severity and fatality rate of these diseases [(13)].

Zinc adjunct therapy was demonstrated to speed up recovery in randomised controlled research conducted in Bangladesh, however other investigations have found no impact [(22)]. No research has evaluated zinc adjunct therapy's effect on paediatric pneumonia mortality. Fewer studies have looked at zinc's efficacy as a medicinal agent for treating acute or chronic pneumonia in young children. Zinc supplementation during antimicrobial treatment significantly reduced the duration of pneumonia in young children in Bangladesh compared to a control group that received the same treatment but no zinc [(23)].

Rerksuppaphol and Rerksuppaphol [(20)] reported that zinc supplementation improved pneumonia treatment results by speeding up the recovery time from pneumonia and bringing oxygen and temperature levels back to normal. Zinc-treated children spent less time in the hospital than their placebo-treated counterparts. **Ahmed *et al.*** [(16)] found zinc treatment supplementation is thought to result in faster clinical recovery and shorter hospital stays for children with pneumonia.

Evidence suggests that zinc can protect against pneumonia, and it's also used to treat and prevent diarrhoea. Furthermore, it may play a significant role in the acute phase response to infection and help to boost the body's immune response via a defence cascade, beginning with the mobilisation and sequestration of zinc to metallothionein-rich tissue, rapid up-regulation of immune defence specific protein synthesis, activation of immune defence activity, and so on [(24)]. According to

research by **Sowmya and Chetty [25],** zinc sulphate helps children with pneumonia recover faster and experience less severe symptoms. The absolute number of annual deaths caused by acute lower respiratory tract infections in children could be drastically decreased as a result of these consequences. Zinc therapy has been shown to lessen the drug resistance that can result from using numerous antibiotic treatments, although further research is needed to confirm this.

CONCLUSION

The concentration of zinc in lung tissue, where it mostly binds to metallothionein, is regulated by zinc transporters (MT). Cigarette smoke is a major exposure route for the dangerous heavy metal and carcinogen cadmium (Cd), which is transported into cells mostly via zinc transporter ZIP8. Inhaling Cd-containing gas causes alveolar epithelial cells to be more cytotoxic, but zinc mitigates this effect by competing with Cd for binding to the ZIP8 protein. Zinc supplementation as a preventative measure has been shown to reduce pneumonia risk. The intensity and length of pneumonia can be diminished by taking a zinc supplement.

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