INTRODUCTION

Acute lower respiratory infections (ALRI) predominantly pneumonia is a substantial cause of mortality and morbidity in children less than five years of age. In developing countries an estimated 146-159 million per year new episodes of pneumonia are observed ***(Iqbal et al., 2010).***

Zinc is a micronutrient with important roles in growth and in the immune, nervous and reproductive systems. Regular dietary intake of zinc is necessary because the human body cannot produce zinc and does not have an adequate mechanism for storing or releasing it ***(Mayo et al., 2014).***

The prevalence of zinc deficiency in many low-income countries is extremely prevalent amongst children ***(World Bank, 2012).***

Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity and increases the susceptibility to infectious diseases such as diarrhea and respiratory infection ***(Tuerk, 2009).***

Zinc has been reported to prevent acute lower tract infection and reduce child mortality and Zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia, the leading cause of death in children ***(Lassi et al., 2010).***

Intervention studies suggest that zinc deficiency leads to deaths due to diarrhea, pneumonia, and malaria, which are leading causes of mortality in this age group ***(Wazny, 2013).***

Zinc influence pneumonia pathology may be related to the effects of zinc on the thymus and T cell immunity, thus modulating host immunity to pneumonia ***(Baum et al., 2003).***

Aim of the Work

The aim of this study is to assess the Serum Zinc status in children suffering from acute lower respiratory infection and to evaluate the relationship between Serum zinc status and severity of acute lower respiratory infection and to assess the effect of zinc on the prevention of acute lower respiratory infections.

RESEARCH QUESTIONS

1- Is serum zinc level lowered in children suffering from acute lower respiratory infection compared to controls?

2- Is there a difference in serum zinc between children regarding their age?

3- Is there a difference in serum zinc between male and female children?

4- Is there a relation between serum zinc levels and severity of lower respiratory infection?

5- Is there a relation between serum zinc levels and nutrition?

Chapter (1)

ZINC IN CHILDREN

I. Fundamentals:

Zinc is an essential micronutrient. Regular dietary intake of zinc is necessary because the human body cannot produce zinc and does not have an adequate mechanism for storing or releasing it ***(Mayo et al., 2014).***

Zinc is essential for maintaining the structure and form of protein molecules; it is in many cases fundamental to their function as enzymes or structural proteins. Diverse physiological processes including cell replication are impacted by zinc deficiency. Of particular relevance to public health, zinc is necessary for immune defense systems, growth, intestinal function, and brain development ***(Mary, 2013).***

II. Zinc Homeostasis:

Zinc is found in all body tissues and fluids and the total body zinc content is estimated at 2 g (30 mmol). Approximately 60% of the total body zinc content is found in skeletal muscle and 30% in bone mass.

The choroid of the eye and prostatic fluid has high concentrations of zinc. Plasma zinc represents approximately 0.1% of total body zinc content Zinc is absorbed in the small intestine and is excreted via the kidneys, skin and intestine (in faeces). There are no body stores of zinc and so daily intake of zinc is needed to maintain adequate body levels ***(Food and Agriculture Organization of the United Nations, 2002).***

On the cellular level, 30–40% of zinc is localized in the nucleus, 50% in the cytosol and the remaining part is associated with membranes. Cellular zinc underlies an efficient homeostatic control that avoids accumulation of zinc in excess. The cellular homeostasis of zinc is mediated by two protein families; the zinc-importer (Zip) family, and the zinc transporter (ZnT) family ***(Lichten and Cousins, 2009).***

The same transporter families also regulate the intracellular distribution of zinc into the endoplasmic reticulum, mitochondria, and Golgi apparatus ***(Taylor et al., 2008).***

Finally, metallothioneins (MTs) play a significant role in zinc homeostasis by complexing up to 20% of intracellular zinc. One MT molecule can bind up to seven zinc ions ***(Krezel and Maret, 2007).***

a. Normal Zinc levels:

Zinc circulates at a concentration of (60-120 µg/dL at 0-10 years) and (66-110 µg/dL at > or =11 years) with 70% loosely bound to albumin with the remainder bound tightly to α_2-macroglobulin (18%) and other proteins or amino acids, especially histidine and cysteine (Gibson et al., 2008). Urinary excretion typically ranges from 0.5 to 0.8 mg/day. The primary stores of zinc include the liver and kidney. Most of the body zinc stores are intracellular where zinc is bound to metalloproteinase ***(Maverakis et al., 2007).***

Table (1): Zinc requirements daily reference intakes

Infants		Males	
0 - 6 months	2 Zinc(mg/day)	9 - 13 years	8 Zinc(mg/day)
7 - 12 months	3 Zinc(mg/day)	14 - 18 years	11 Zinc(mg/day)
		19 - 30 years	11 Zinc(mg/day)
Children		31 - 50 years	11 Zinc(mg/day)
1 - 3 years	3 Zinc(mg/day)	51 - 70 years	11 Zinc(mg/day)
4 - 8 years	5 Zinc(mg/day)	> 70 years	11 Zinc(mg/day)
Pregnancy		Females	
< 18 years	13 Zinc(mg/day)	9 - 13 years	8 Zinc(mg/day)
19 - 30 years	11 Zinc(mg/day)	14 - 18 years	9 Zinc(mg/day)
31 - 50 years	11 Zinc(mg/day)	19 - 30 years	8 Zinc(mg/day)
		31 - 50 years	8 Zinc(mg/day)
Lactation		51 - 70 years	8 Zinc(mg/day)
< 18 years	14 Zinc(mg/day)	> 70 years	8 Zinc(mg/day)
19 - 30 years	12 Zinc(mg/day)		
31 - 50 years	12 Zinc(mg/day)		

(Bhowmik et al., 2010)

b. Dietary Sources of Zinc:

Red meat and poultry are the main sources of zinc ***(Beattie, 2012).***

Oysters, crab, lobster and other shellfish (oysters contain more zinc per serving than any other food). Pulses, nuts and legumes. Wholegrain cereals. Fortified breakfast cereals. Dairy products such as cheese.

Phytates in wholegrain bread, cereals, legumes and some other foods inhibit zinc absorption and so affect the bioavailability of zinc from plant foods ***(National Institutes of Health, 2013).***

Table (2): Zinc rich foods

FOODS THAT ARE HIGH IN ZINC

Foods	Milligrams per Serving (mg)	Percent Daily Value (DV)
Oysters, cooked, breaded and fried, 3 ounces	74.0	493
Beef chuck roast, braised, 3 ounces	7.0	47
Crab, Alaska king, cooked, 3 ounces	6.5	43
Beef patty, broiled, 3 ounces	5.3	35
Fortified breakfast cereal	3.8	25
Lobster, cooked, 3 ounces	3.4	23
Pork chop, loin, cooked, 3 ounces	2.9	19
Baked beans, canned, vegetarian, ½ cup	2.9	19
Chicken, dark meat, cooked, 3 ounces	2.4	16
Yogurt, fruit, low fat, 8 ounces	1.7	11
Cashews, dry roasted, 1 ounce	1.6	11
Chickpeas, cooked, ½ cup	1.3	9
Cheese, Swiss, 1 ounce	1.2	8
Instant plain oatmeal prepared with water	1.1	7
Milk, low-fat or non-fat, 1 cup	1.0	7
Almonds, dry roasted, 1 ounce	0.9	6
Kidney beans, cooked, ½ cup	0.9	6
Chicken breast, roasted, skin removed, ½ breast	0.9	6
Cheese, cheddar or mozzarella, 1 ounce	0.9	6
Peas, green, frozen, cooked, ½ cup	0.5	3
Flounder or sole, cooked, 3 ounces	0.3	2

(USDA National Nutrient Database, 2011)

c. Dietary promoters and inhibitors of zinc absorption:

Zinc is found widely in the food supply, but its bioavailability from different foods is highly variable. Rich sources of zinc include: oysters, red meat, liver and cheese. Zinc in animal products, crustacea and mollusks are more readily absorbed than from plant foods. Cereal grains, legumes and nuts are rich in phytate (the main storage form of phosphorous in plants), which bind zinc in the intestine and reduce its absorption. The early cases of zinc deficiency were associated with high phytate-containing foods: unleavened bread from unrefined wheat flour as a dietary staple, and beans. The molar ratio of phytate to zinc in the diet has been proposed as a predictor of zinc bioavailability, and ratios greater than 15 have been associated with suboptimal zinc status ***(Samman, 2007*****).**

Table (3): Dietary determinants of zinc bioavailability

Estimated absorption	***Type of diet***
Low	• Diet high in unrefined cereal grain
	• High-phytate soya-protein products as the primary protein source
	• Phytate : zinc molar ratio >15
	• Calcium >1 g/day
Moderate	• Mixed diet containing animal or fish protein
	• Lacto-ovo, ovovegetarian or vegan diets that are not based on unrefined cereals
	• Phytate : zinc molar ratio <10
	• Bioavailability of zinc is improved if the diet includes animal protein sources

High	• Refined diets, low in cereal fibre
	• Phytate : zinc molar ratio <5
	• Dietary protein primarily from animal foods

(Samman, 2007)

d. Zinc Metabolism and excretion

Zinc is absorbed in the small intestine, primarily via transporter-mediated processes. Rich sources of dietary zinc include meat, fish, shellfish, nuts, seeds, legumes, and whole-grain cereals. However, plant sources are considered to be less bioavailable because of the presence of phytic acid that binds to zinc-forming insoluble complexes, which thus inhibits zinc's absorption ***(Hunt, 2003).***

Unlike other micronutrients such as iron, there is no storage form of zinc in the body that can be readily mobilized when intakes are inadequate, which emphasizes the need for a regular dietary supply ***(King et al., 2001).***

A highly effective homeostatic mechanism responds to alterations in zinc intake, up regulating absorption and conserving losses via the gastrointestinal tract, kidneys when intakes fall and skin. By using isotope tracer techniques, it was predicted that when dietary zinc fell from 12.2 to 0.23 mg/d in a group of adult men, fractional zinc absorption could increase to virtually 100%, with urinary excretion falling from 0.36 to

0.006 mg/d and fecal excretion falling from 11.8 to 0.23 mg/d ***(King et al., 2001).***

III. Functions of Zinc:

- Zinc is a key micronutrient that is present in all organs, tissues and body fluids. After iron, it is the second most abundant trace element in the body and mediates a wide variety of physiological functions. It is a necessary component of numerous metalloproteins, including those important for DNA replication and cell division, and is crucial for maintaining immunological integrity, predominantly cellular immunity and antioxidant activity. Because of its role in maintaining cell integrity and immunity, it is considered to play a key role in cells that have a rapid turnover and a critical role in the control and prevention of infections ***(Cuevas and Koyanagi, 2005)***.
- On the cellular level, the function of zinc can be divided into three categories: (1) catalytic, (2) structural, and (3) regulatory (3).
- Catalytical: Nearly 100 different enzymes depend on zinc for their ability to catalyze vital chemical reactions.
- Structural: Zinc plays an important role in the structure of proteins and cell membrane.
- Regulatory: Zinc finger proteins have been found to regulate gene expression by acting as transcription factors. Zinc also plays a role in cell signaling and has been found to influence hormone release and nerves impulse transmission ***(Bhowmik et al., 2010).***

- In the brain, zinc is stored in specific synaptic vesicles by glutamatergic neurons and can modulate brain excitability ***(Hambidge and Kreb, 2007).*** It plays a key role in synaptic plasticity and in learning ***(Nakashima and Dyck, 2009).***

Table (4): Summarized role of zinc in the body

Benefits	**Mechanism**
Zinc boosts the immune system	Zinc is a component in thymic hormone which controls and facilitates the maturation of lymphocytes. Zinc also plays a role in cell division and DNA replication, thereby aiding in the production of immune system cells.
Zinc cuts short the common cold	Zinc gluconate lozenges taken at the first sign of a cold reduce duration and symptom severity Zinc, an antiviral agent and astringent, is released into the saliva, relieving cough, nasal drainage and congestion.
Zinc boosts brain activity	Enhancing memory and thinking skills. Patients deficient in zinc had a harder time on standard memory tests and lower cognition
Zinc heals and protects skin	Zinc is essential for healthy skin. Topical zinc preparations used as an astringent to treat diaper rash, itching and chapped lips and skin. Zinc sulfate used for treating acne, cold sores and burns. Zinc stimulates cell division, healing and proper connective tissue formation
Zinc stimulates taste, smell	Zinc activates areas of the brain that receive and process information from taste and smell sensors.
Zinc improves appetite	Insufficient zinc has been linked to anorexia, which responds well to zinc replacement treatment.
Zinc improves mood	Zinc sulfate effective in reducing fatigue and mood swings.
Testosterone and men's health	Stimulate testosterone production. Inhibits the aromatase enzyme that converts testosterone into excess estrogen. Increase sperm count and motility.
Zinc and pre-menstrual syndrome	Trace amounts of zinc regulate the secretion of many hormones, including progesterone. Some women's PMS symptoms may be improved by zinc supplementation.

(Bhowmik et al., 2010)

Functions of Zinc in organs and systems:

III.a. Zinc and Development:

Several zinc-dependent enzymes are involved in the synthesis of nucleic acids and proteins and, hence, in the fundamental processes of cell replication, differentiation and growth ***(Stefanidou et al., 2006).***

Zinc is essential for brain development and central nervous system function and is present in synaptic vesicles in a group of glutamatergic neurons in the brain .Zinc is concentrated in specific neuronal structures, notably in the nerve terminals of the hippocampus, cortex and pineal body, and deficiency alters autonomic nervous system regulation as well as hippocampal and cerebellar development ***(Georgieff, 2009).***

III.b. Zinc and immunity:

Zinc affects multiple aspects of the immune system. Zinc is crucial for normal development and function of cells mediating innate immunity, neutrophils, and natural killer cells. Macrophages also are affected by zinc deficiency. Phagocytosis, intracellular killing, and cytokine production all are affected by zinc deficiency. Zinc deficiency adversely affects the growth and function of T and B cells. The ability of zinc to function as an anti-oxidant and stabilize membranes suggests that it has a role in the prevention of free radical-induced injury during inflammatory processes ***(Prasad, 2008).***

Apoptosis is potentiated by zinc deficiency. Zinc deficiency adversely affects the secretion and functions of cytokines, the basic messengers of the immune system. Zinc functions as an antioxidant and stabilizes membranes ***(Shankar and Prasad, 1998).***

Zinc has been used successfully to restore immune function in the zinc-specific malabsorption syndrome known as acrodermatitis enteropathica as well as other morbidities. Some immunological dysfunction in the elderly such as decreased interferon- α (IFN- α) production can be corrected with zinc. Impaired immune response to diphtheria vaccination in hemodialysis patients has been linked to zinc deficiency and is correctable with zinc therapy. The subject of zinc and immunodeficiency has been extensively reviewed in a number of publications. hyperzincuria is a clinical manifestation of HIV and zinc therapy has been shown to increase the CD4+ cell count and reduce the incidence of bacterial infections in HIV-infected patients. Zinc salts are increasingly gaining favor as non-prescription drug for reducing the duration and severity of common colds ***(Bozalioglu et al., 2005).***

Zinc has an effect on cell mediated immunity, and has a role as an antioxidant and anti-inflammatory agent ***(Prasad, 2009) (figure 1 and 2).***