Section A -Research paper

The link between Trace Elements assay and Pediatric Asthma

Usama Mahmoud Alkholy [1], Hossam El Din Salah Mohamed[2], Omnia Essam Abd El-Motaal Saleh[1*], Dalia Gameil [1]

[1] Pediatrics Department, Faculty of Medicine, Zagazig University

[2] Clinical pathology Department, Faculty of Medicine, Zagazig University

***Corresponding author:** Omnia Essam Abd El-Motaal Saleh

Email: omnia953ssam@gmail.com, **Mobile:** 01129177997

Article History: Received: 20.06.2023 **Revised:**02.07.2023 **Accepted:** 13.07.2023

Abstract:

Asthma is a multifactorial disease and its severity varies with the inflammatory grade. There are conflicting reports about the roles of trace elements in asthma. This study evaluate the effects of zinc (Zn), copper (Cu), and magnesium (Mg) concentrations in sera of patients with allergic asthma.

Keywords: Trace Elements, Pediatric, Asthma.

DOI: 10.53555/ecb/2023.12.1192

Introduction:

An imbalance between the oxidative forces and the antioxidant defense systems favoring an oxidative injury has been implicated in the pathogenesis of asthma **(1).**

Oxidative injury leads to increased lipid peroxidation, increased airway reactivity and secretions, production of chemoattractant molecules, and increased vascular permeability , which collectively lead to an augmentation of the existing inflammation that is a hallmark of asthma **(2)**.

Lungs are constantly exposed to oxygen as well as smoke and other inhaled pollutants that lead to generation of ROS **(3)**. It has been found that some trace elements such as Cu, Zn, and Mn may

play important roles in the genesis of asthma because they participate in oxidative stress reactions as cofactors of antioxidant enzymes **(4)**.

Cu/ Zn superoxide dismutase system contains Cu and Zn in its structure. These minerals are essential to SOD activity in reducing the harmful effects of ROS. Deficiency of these trace elements results in lowering the effects of antioxidant systems and thus to hyperactivity and inflammation in the respiratory tract **(5)**.

Zinc:

It has been shown to have a vital role as an anti-oxidant , microtubule stabilizer, anti-apoptotic agent, growth cofactor, and anti-inflammatory agent in various tissues **(6)** . Zinc deficiency is found in inflammatory diseases including asthma, where low zinc levels are risk factors of development, severity, and exacerbations of asthma **(7)** .

Zinc decreases oxidative stress by inhibiting reactive oxygen species (ROS) production via inhibition of pro-oxidant enzymes, such as NADPH oxidase and by activation of anti-oxidant enzymes including glutathione-related enzymes, catalase (CAT) and SOD **(7)**. Together $O_2^{\cdot-}$, H_2O_2, and ·OH are known as reactive oxygen species (ROS), and these are produced continuously in vivo under aerobic conditions. The NADPH oxidases are a group of plasma membrane associated enzymes, which catalyze the production of $O_2^{\cdot-}$ from oxygen by using NADPH as the electron donor. Zinc is an inhibitor of this enzyme. The dismutation of $O_2^{\cdot-}$ to H_2O_2 is catalyzed by an enzyme super oxide dismutase (SOD), which contains both copper and zinc. Zinc is known to induce the production of metallothionein, which is very rich in cysteine, and is an excellent scavenger of ·OH . Iron and copper ions catalyze the production of ·OH from H_2O_2. Zinc competes with both iron and copper for binding to cell membrane, thus decreasing the production of ·OH **(8)**.

Dysregulation of Zn homeostasis causes a shift in the Th1/Th2 balance towards a Th2 response, which may lead to increased inflammatory response. A fundamental abnormality in asthma is an exaggerated Th2 response to normally harmless environmental antigens. Th2 cells secrete cytokines that promote inflammation and stimulate B cells to produce IgE and other antibodies. These cytokines include IL-4, which stimulates the production of IgE; IL-5, which activates locally recruited eosinophils; and IL-13, which stimulates mucus secretion from bronchial submucosal glands and also promotes IgE production by B cells **(9, 10)**. Zinc also reduces the propagation of inflammation by inhibition of LTB4 production and expression of its receptors **(7).**

Inflammatory diseases can cause an increase in the demand for Zn as: Zn is essential for producing the thymic hormone thymulin necessary for regulating T-cell development and activation; and zinc is crucial for activation of natural killer cells, phagocytic cells and for

granulocytes, such as mast cells and eosinophils. As a result, greater demand for Zn by the immune system could be a contributing factor to the Zn deficiency noted in inflammatory diseases. Zinc deficiency itself is detrimental for inflammation as it results in dramatic increases in the number, size and activation state of mast cells **(11).**

Zinc deficiencies have been reported in many disorders, including asthma. Most of reports show a decrease of zinc concentration in the serum or induced sputum of children **(12, 13)**. **Siripornpanich et al (14)** and **Khanbabaee et al (12)** found zinc deficiency in the serum of asthmatic children together with increased oxidative stress and airway inflammation. They also found a correlation between zinc levels and breathing parameters such as FEV1 and FEV1/FVC and concluded that zinc deficiencies are related to severe asthma and to decreased pulmonary function. There are many reports showing that proper levels of zinc and other anti-oxidants and higher maternal intake of this element during pregnancy prognoses better pulmonary functions of the offspring and lower risk of developing asthma in childhood **(15, 16) .** Low zinc intake increases (up to five times) the risk of developing atopy, bronchial reactivity, and allergy-like symptoms **(17)**. Most of the symptoms of zinc deficiency can be easily reversed by zinc supplementation as it has been described by **Prasad (8)** who found that Zn supplementation diminished the number and symptoms of respiratory tract infections.

Copper:

In general, both copper deficiency and excess can lead to chronic inflammation **(18)** .According to most researchers, copper levels are elevated in asthma **(19, 20)** , even if no direct association between copper status and lung function can be found **(18)** and elevated Cu in serum, or parallel to decreased zinc can be a marker of inflammation and of immune status. copper activates phosphatidyl-inositol-3-kinase (PI3K), an enzyme activating itself inflammatory mediators, inflammatory cell recruitment, and airway remodeling **(21)** . It also stimulates IL-6 production and release **(22)** . As a consequence, copper ions might be some kind of second messenger in propagation of inflammation and response to inflammatory burden **(23)** .

Ceruloplasmin (CP) is the main carrier protein for copper. It not only plays a role in iron metabolism but is also one of the components of the antioxidant defense, acting as a free radical scavenger. CP levels are elevated during oxidative stress including the course of asthma **(20)** .**Winter et al. (23)** described that the increased levels of CP are rather a response to inflammatory burden as the highest levels of the protein were observed in asthma patients with systemic inflammation, severe or neutrophilic asthma.

Another important copper-containing enzyme is the Cu-Zn-superoxide dismutase (CuZnSOD), whose levels are decreased in asthma **(24)**, likely due to the decreased levels of zinc **(5)** or an oxidative degradation of the protein during inflammation rather than disturbances of copper levels.

As CuZnSOD is located intracellular in ciliated epithelium **(25)** ,any disturbance in copper levels and CuZnSOD can result in further progression of oxidative stress.

Magnesium:

The relation between Magnesium and asthma is well established over the years. Mg+2 has a significant role in causing muscle relaxation. Hypomagnesemia leads to muscle contraction and hypermagnesemia to muscle relaxation . Magnesium can induce bronchial smooth muscle relaxation in a dose-dependent manner by inhibiting calcium influx into the cytosol histamine release from mast cells, or acetylcholine release from cholinergic nerve endings. It also may increase the bronchodilator effect of β2-agonist by increasing the receptor affinity. It is also engaged in the promotion of nitric oxide and prostacyclin generation and smooth muscle stabilization There are studies documenting usefulness of Mg+2 in treating acute asthma **(26)** . Moreover, Mg2+ regulates the release of ACh and histamine, which have both been implicated in asthma **(27).**

Several studies have reported low serum Mg2+ levels or low erythrocyte Mg2+ levels in asthmatic patients **(28, 29)**. However, others could not detect a Mg2+ deficiency in patients with asthma, suggesting that Mg2+ levels may depend on the severity of the disease **(30)**. In 1940, Victor Haury was the first to treat bronchial asthma patients with Mg2+ injections to relieve asthmatic paroxysms. Since then, ∼25 randomized controlled studies have been published examining the effects of nebulized and intravenous Mg2+ administration in asthma patients **(31).**

References:

1. Sahiner, U. M., Birben, E., Erzurum, S., Sackesen, C., & Kalayci, O. (2011). Oxidative stress in asthma. World Allergy Organization Journal, 4(10), 151-158.
2. Fatani, S.H., 2014. Biomarkers of oxidative stress in acute and chronic bronchial asthma. Journal of Asthma, 51(6), pp.578-584.
3. Michaeloudes, C., Abubakar-Waziri, H., Lakhdar, R., Raby, K., Dixey, P., Adcock, I. M., ... & Chung, K. F. (2022). Molecular mechanisms of oxidative stress in asthma. Molecular aspects of medicine, 85, 101026.
4. Guo CH, Liu PJ, Lin KP, et al. Nutritional supplement therapy improves oxidative stress, immune response, pulmonary function, and quality of life in allergic asthma patients: an open-label pilot study. Altern Med Rev 2012; 17(1):42–56

5. Ariaee, N., Farid, R., Shabestari, F., Shabestari, M., & Azad, F. J. (2016). Trace elements status in sera of patients with allergic asthma. Reports of biochemistry & molecular biology, 5(1), 20.
6. Rajkumar, S., Bhat, N. K., Kumar, V., Bolia, R., Verma, P. K., Kumar, M., ... & Mirza, A. A. (2023). Association of serum zinc levels and symptom control of asthma in children and adolescents—a prospective observational study. European Journal of Pediatrics, 182(1), 141-147.
7. Zajac, D. (2021). Mineral micronutrients in asthma. Nutrients, 13(11), 4001.
8. Prasad, A. S. (2014). Impact of the discovery of human zinc deficiency on health. Journal of trace elements in medicine and biology, 28(4), 357-363.
9. Orihara K, Dil N, Anaparti V, Moqbel R (2010) What's new in asthma pathophysiology and immunopathology? Expert Rev Respir Med 4(5):605–629
10. Mims JW (2015) Asthma: definitions and pathophysiology. Int Forum Allergy Rhinol 5(Suppl 1):S2-6
11. Kakarash, T. A., & Al-Rabaty, A. (2012). Zinc status in children with bronchial asthma. Iraqi Postgrad Med J, 11, 698-703.
12. Khanbabaee, G., Omidian, A., Imanzadeh, F., Adibeshgh, F., Ashayeripanah, M., & Rezaei, N. (2014). Serum level of zinc in asthmatic patients: A case–control study. Allergologia et immunopathologia, 42(1), 19-21.
13. Ghaffari, J., Khalilian, A., Salehifar, E., Khorasani, E., & Rezaii, M. S. (2014). Effect of zinc supplementation in children with asthma: a randomized, placebo-controlled trial in northern Islamic Republic of Iran.
14. Siripornpanich, S., Chongviriyaphan, N., Manuyakorn, W., & Matangkasombut, P. (2022). Zinc and vitamin C deficiencies associate with poor pulmonary function in children with persistent asthma. Asian Pacific Journal of Allergy and Immunology, 40(2), 103-110.
15. Allan, K., & Devereux, G. (2011). Diet and asthma: nutrition implications from prevention to treatment. Journal of the American Dietetic Association, 111(2), 258-268.
16. Uysalol, M., Uysalol, E. P., Yilmaz, Y., Parlakgul, G., Ozden, T. A., Ertem, H. V., ... & Uzel, N. (2014). Serum level of vitamin D and trace elements in children with recurrent wheezing: a cross-sectional study. BMC pediatrics, 14, 1-8.

17. Devirgiliis, C., Zalewski, P. D., Perozzi, G., & Murgia, C. (2007). Zinc fluxes and zinc transporter genes in chronic diseases. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 622(1-2), 84-93.
18. Guo, C.H.; Liu, P.J.; Hsia, S.; Chuang, C.J.; Chen, P.C. Role of certain trace minerals in oxidative stress, inflammation, CD4/CD8 lymphocyte ratios and lung function in asthmatic patients. Ann. Clin. Biochem. 2011, 48, 344–351
19. Gray, R.D.; Duncan, A.; Noble, D.; Imrie, M.; O'Reilly, D.S.; Innes, J.A.; Porteous, D.J.; Greening, A.P.; Boyd, A.C. Sputum trace metals are biomarkers of inflammatory and suppurative lung disease. Chest 2010, 137, 635–641.
20. Verrills, N.M.; Irwin, J.A.; He, X.Y.; Wood, L.G.; Powell, H.; Simpson, J.L.; McDonald, V.M.; Sim, A.; Gibson, P.G. Identification of novel diagnostic biomarkers for asthma and chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 2011, 183, 1633–1643.
21. Yoo, E. J., Ojiaku, C. A., Sunder, K., & Panettieri Jr, R. A. (2017). Phosphoinositide 3-kinase in asthma: novel roles and therapeutic approaches. American journal of respiratory cell and molecular biology, 56(6), 700-707.
22. Grubman, A., & White, A. R. (2014). Copper as a key regulator of cell signalling pathways. Expert reviews in molecular medicine, 16, e11.
23. Winter, N.A.; Gibson, P.G.; Fricker, M.; Simpson, J.L.; Wark, P.A.; McDonald, V.M. Hemopexin: A novel anti-inflammatory marker for distinguishing COPD from asthma. Allergy Asthma Immunol. Res. 2021, 13, 450–467.
24. Lee, I. T., & Yang, C. M. (2012). Role of NADPH oxidase/ROS in pro-inflammatory mediators-induced airway and pulmonary diseases. Biochemical pharmacology, 84(5), 581-590.
25. Borgstahl, G. E., & Oberley-Deegan, R. E. (2018). Superoxide dismutases (SODs) and SOD mimetics. Antioxidants, 7(11), 156.
26. Singh AK, Gaur S, Kumar R. A randomized controlled trial of intravenous magnesium sulphate as an adjunct to standard therapy in acute severe asthma. Iran J Allergy Asthma Immunol. 2008;7:221–9.

27. Novelli, F., Malagrinò, L., Dente, F. L., & Paggiaro, P. (2012). Efficacy of anticholinergic drugs in asthma. Expert Review of Respiratory Medicine, 6(3), 309-319.
28. Amin, M., Abdel-Fattah, M., & Zaghloul, S. S. (2012). Magnesium concentration in acute asthmatic children. Iranian Journal of Pediatrics, 22(4), 463.
29. Hashimoto, Y., Nishimura, Y., Maeda, H., & Yokoyama, M. (2000). Assessment of magnesium status in patients with bronchial asthma. Journal of Asthma, 37(6), 489-496.
30. Kazaks, A. G., Uriu-Adams, J. Y., Albertson, T. E., & Stern, J. S. (2006). Multiple measures of magnesium status are comparable in mild asthma and control subjects. Journal of Asthma, 43(10), 783-788.
31. De Baaij, J. H., Hoenderop, J. G., & Bindels, R. J. (2015). Magnesium in man: implications for health and disease. Physiological reviews.