Evaluation of serum srace element levels in children with bronchial asthma

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Abstract

Background and objectives: The metabolism of several trace elements has been reported to alter in bronchial asthma and these elements might have specific roles in the pathogenesis and progress of this disease. The aim of the present study was to investigate serum levels of Zinc, Copper, Calcium, Iron and Magnesium in asthmatic children

Patients and Methods: The comparative study includes 56 asthmatic patients and 44 healthy non asthmatic control subjects. The trace elements concentrations were measured by means of an atomic absorption spectrophotometer, results were calculated from the calibration curve obtained by statistical analysis of concentration Vs Absorbance data for elements using fitting of straight line by least square.

Results: Mean(±SD**)** zinc level was significantly ($p<0.01$) decreased in asthmatic children (70.6±8.3 µg /dL) compared with controls non asthmatic children (78.3± 9.2 µg /dL),calcium and iron serum concentrations were significantly($p<0.001$) higher in asthmatic patient (10.98±2.53 mg/dL, (113.23 ± 45.47 µg/dl) respectively compared with controls (8.23±3.4mg/dL,83.25±29.43 µg /dL) respectively, on the other hand copper level was significantly ($p<0.01$) higher in asthmatic children (143±20.8µg/dl) in comparison to the control values (130±22.7 µg/dL). Magnesium concentration was significantly lower in comparison to the control values ($p<0.01$).

Conclusion: The results support that deficiency of Mg, Zn, Cu, Ca and Fe may play a role in the development of asthma

Key words: Trace Elements, Bronchial Asthma

Introduction

Elements are essential micro-nutrients and have a variety of biochemical functions in all living organisms. Some of them form an integral part of several enzymes[1,2]. Zinc and copper are key components necessary to maintain cellular homeostasis. The primary reason for this necessity is associated with the fact that hundreds of metaloenzymes require a metal element, as cofactors, to be functional [3].Zinc has many important roles in the body and its deficiency causes broad and nonspecific signs and symptoms, including suppressed immunity[4,5], decreased growth velocity, delayed sexual maturity and dysgusia [6,7]. Zinc, copper and magnesium are elements in the preservation of immune resistance. Zinc is known to be essential for all highly proliferating cells in the human body, especially the immune system. A variety of in *vivo* and in *vitro* effects of zinc on immune cells mainly depend on the zinc concentration. All kinds of immune cells show decreased function after zinc depletion. In monocytes, all functions are impaired, whereas in natural killer cells, cytotoxicity is decreased, and in neutrophil granulocytes, phagocytosis is reduced. The normal functions of T cells are impaired, but auto reactivity and all reactivity are increased. Iron metabolism is of crucial importance in the biology and pathophysiology of the lower respiratory

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As with many other factors involved in inflammation, it is very important that an appropriate iron balance is maintained. Local deficiency could impair growth and proliferation of cells responsible for the inflammatory response and tissue repair and the synthesis of mediators[8].Because calcium is the major second messenger regulating ASM contraction, investigators hypothesized that abnormalities in calcium homeostasis, manifested by increases in the flux of calcium or alteration in calcium regulatory proteins, may play a critical role in inducing ASM hyper reactivity in asthma[9]. Magnesium is the most abundant cation in the body and the second most common intracellular cation since magnesium intervenes in calcium transport fourth mechanisms and intracellular phosphorylation reactions. It constitutes an important determinant of the contraction and relaxation state of bronchial smooth muscle[10].Magnesium deficiency is associated with increased contractility of smooth muscle cells. Since contractility of bronchial smooth muscle is important in patients with asthma, magnesium deficiency could lead to bronchial smooth muscle contraction or lack of bronchial muscle relaxation[11].Bronchial asthma is a chronic inflammatory disease of the lung airways resulting in episodic airflow obstruction (airway hyper-responsivness). Different genetic and environmental factors are involved in the pathogenesis of asthma [12]. The rise in asthma and allergic disease among children is a matter of worldwide concern [13,14].Many authors have argued that the changes in diet may have been an important determinant of increased susceptibility to asthma [15,16].We believe that a reduction in antioxidant intake, reflected in the diet of pregnant women, would increase the susceptibility of the new born baby to allergens [17]. Chronic inflammation causes a characteristic decline in serum zinc levels in experimental studies. It is well known that zinc deficiency affects the regulation of T-cell lymphocytes, which may play some part in the nutritional status between asthmatic and healthy subjects. Asthmatic children, in particular, seem to be at a risk of zinc deficiency. The changes in trace element status may be the effect of chronic disease state and do not associate with the cause of disease [16, 17].The aim of the present study was to evaluate the serum of Mg ,Cu ,Co ,Zn and. Fe in serum of children with bronchial asthma

Methods

The study was performed on asthmatic children and healthy non asthmatic control subjects. A total of 100 sera sample were enrolled in the present study during their attendance to clinics and used for determination of trace elements. 56 of these samples were of asthmatic children their age range from (4-13) years as diagnosed by physician, while the others were for control group. Six milliliters of blood has been collected and allowed standing at room temperature until it has clotted. Restriction of cot may be assisted by gentle loosing it from the walls of the container. The separated serum, about 2-3 mL is centrifuged at 3000 r p m using T-centrifuge for removal of any suspended cells. All chemicals used were of analytical grade supplied by fluka Atomic Absorption Spectroscopic standard solutions of Zn,Cu,Fe,Ca and Mg of 1000ppm were prepared from certified standards Fluka. The internal standards were prepared from metal salts obtained from Fluka ,working standard solutions were prepared by diluting the stock solutions. All of sample series of standard solutions of Zn,Cu,Fe,Ca and Mg of 1000ppm were atomized in air-acetylene flame with a Hitachi 180-50 AAS. Results were calculated from the calibration curve of obtained by statistical analysis of concentration Vs Absorbance data for elements using fitting of straight line by least square.

Results

Table (1) showed the results of serum trace elements expressed as mean ±standard deviation. Serum zinc and magnesium of asthmatic patients are significantly lower ($p<0.01$) than the level in normal subjects. A significant increase ($p<00.01$) in serum copper, iron, and calcium levels were demonstrated in asthmatic patients as compared with that of the normal subjects

Table (1): Levels of trace elements in serum of asthmatic and control Subject

Elements	Mean±SD Asthms	Mean±SD Control	P value
Zn [µg/dl]	(70.6±8.3)	(78.3± 9.)	<0.01
Cu [µg/dl]	(143±20.)	(130±22.78)	<0.01
Fe [µg/dl]	(113.23 ± 45.47)	(83.25±29.43)	<0.0001
Ca [mg/dl]	(10.98±2.53)	(8.23±3.4)	<0.001
Mg [mg/dl]	(1.88±0.0 1)	(2.23±0.15)	<0.01

Discussion

Table (1) summarizes data on serum concentrations of zinc, copper, iron,calcium and magnesium elements in asthmatic children and in the control).It is clear from the results that a significant decrease ($p<0.01$)of zinc concentration in asthmatic children (70.6±8.3 Mg/dL) compared with controls non asthmatic children (78.3± 9.2Mg/dL),the results of this study support previous observation that there is low serum Zinc and Mg level in asthmatic children [18,19]. It is clear that profound variations in copper and zinc status occur during the course of acute and chronic inflammation. Zinc and magnesium are important elements in the preservation of immune resistance and both zinc and copper are required for numerous biochemical functions and for optimal activity of the immune system. Zinc plays an important role in DNA and protein involved with copper as cofactors in several important enzyme systems [20,21]. Significant higher levels of serum ceruloplasmin were observed in the asthmatic children compared to the controls and were correlated with the hypercupremia. Zinc and copper are involved in cell and tissue growth. Changes in patterns of dietary consumption, associated with development of a more affluent lifestyle, may have contributed to the rise in asthma over the past few decades[22,23].Plausible mechanisms have been proposed for the influence of dietary factors such as sodium, magnesium, antioxidants, selenium and fats on respiratory symptoms and lung function [24].There is now some epidemiological support for dietary antioxidant vitamins being risk factors for asthma in adults [25,26]. There are some defense mechanisms to escape from the effects of oxidant radicals. These defense systems prevent the

them. The most important antioxidant endogen systems are mitochondrial cytochrome oxidase, superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH-Px) systems. Also albumin, ceruloplasmin, ferritin and hemoglobin which are found in the extracellular space have antioxidant properties [27]. Glutathione peroxidase has selenium and Cu/Zn, and superoxide dismutase system has copper and zinc in their structure which diminishes the harmful effects of free oxygen radicals. Decreasing these trace elements causes the effects of antioxidant systems to be lower and this leads to hyperactivity and inflammation in the respiratory tract [28,29]. Our study was showed relatively low blood levels of zinc in subject with asthma. Chronic inflammation causes a characteristic decline in serum zinc levels in experimental studies [30].It is well known that zinc deficiency affects the regulation of T-cell lymphocytes, of allergies[31]. T cell derived inflammatory mediator interleukin-2 is also involved in the cellular control of copper levels [32].The mean values of copper were significantly higher in asthmatic children(143±20.8µg/dl) than normal subjects(130±22 µg/dl). In another study[36], serum copper has been found to be elevated while serum zinc level was found to be low. It is debatable whether an increase in the copper level has an impact upon SOD absorption; however, it is clear that a decrease in this element impairs the enzyme activity Such a condition may cause oxidative stressor may further increase the existing stress [33].An additional hypothetical explanation of a rise in susceptibility to asthma is that the change from Th2 to Th1 phenotype now occurs less frequently since, in healthier societies, children no longer suffer the infections that used to promote this change [34,35]. There is epidemiological support for this hypothesis with respect to atophy but little so far with respect to asthma [36]. Increased dietary magnesium has been shown to be associated with an independent beneficial effect on lung Another study has shown that a low intake of magnesium, which is involved in the relaxation of smooth muscle, is associated with reduced lung function, bronchial hyper -reactivity and self reported wheezing [38]. Our findings, indicated that serum iron was significantly higher ($P<0.001$)(113.23 ± 45.47 µg/dl) in asthmatic group than that in controls (113.23 ± 45.47 µg/dl) [Table 1] This results is in agreement with that found by others [39,40]. Whereas, Vural et al [41] reported that serum iron level in asthmatics not significantly different from control group .In fact, mediators, including NO released during chronic inflammation were shown to increase heme oxygenase expression in asthmatic patients .Heme oxygenase reaction, with its products bilirubin, carbonmonoxide and free iron, is interpreted as an antioxidant defense mechanism due to release of bilirubin .However, free iron, a catalyst during ROS production, is another product of this reaction and therefore may possess some inflammatory effects [39,40]. The usual source of iron in the lung is serum iron, which is derived from catabolized erythrocytes and absorbed iron. Metabolism of Iron is of a crucial importance in the biology and pathophysiology of the lower respiratory tract. As with many other factors involved in inflammation, it is very important that an appropriate iron balance is maintained. Excessive accumulation of iron exerts toxic effects through its ability to catalyze formation of highly reactive hydroxyl radicals Reports on serum iron levels in bronchial asthma are scare. In one report, no change was detected in serum iron levels in patients with asthma as compared to controls. However, significantly increased serum iron level in asthmatic patients was found in this study, and our finding was consistent with that reported by others[41] . Thus elevation of serum iron level in asthmatics may be variable with disease severity consistent.The present study also showed that., serum calcium concentration was significantly higher

of controls (8.23 ± 3.46 mg/dl). Calcium ions (Ca 2+) are fundamental to the processes responsible for the initiation and maintenance of contraction of ASM cells and development in understanding of signal transduction mechanisms relating to intracellular Ca 2+ release have extended the knowledge of excitation – contraction coupling mechanisms in ASM. Further more, these developments open up potential targets for the development of new drugs, with novel mechanisms of action for the treatment of asthma [41].Bronchial asthma specific changes in cell electrolyte composition (red cell and lymphocyte) impair cAMP metabolism and activate lipid peroxidation and this lead to BHR[42].It was suggested that abnormal intracellular homeostasis of bivalent cations in asthmatic patients may be due to hyperactivation of free radical oxidation of cell membrane lipids. Reported studies indicated that Ca 2+ ion was significantly higher in asthmatic platlets and polymorphonuclear lekocytes .Calcium in the cytoplasm is cytotoxic, so it is necessary to have mechanisms that regulate Ca2+ to avoid overload. Excessively generated oxidants in the mitochondria, such as in ischemia, – reperfusion injury, changes mitochondrial function and cause Ca 2+ leak from the

Conclusion

organelle, which leads to induction of apoptosis [43,44].

The results confirm that deficiency and efficiency of some essential trace elements may play a role in the development of asthma.

Recommendation:

In order to better understand the role of these trace elements in asthma ,further clinical studies are required enrolling larger number of patients and using more sophisticated techniques. Besides blood, urine and hair samples should also be obtained to allow clear conclusión.

References

1. Sommers, E., The toxic potential of trace elements in foods - a review, Environ. Res.Technology., 1974: 39 : 215 – 227
2. Tripathi, R.M. ; Raghunath, R. and Krishnamoorthy, T.M.,.Dietary intake of heavy metals in Bombay city, India, Sci. of Total Environ.1997: 208 : 49 – 159
3. Kietizmann,A. Immunotoxicology of Environmenta landOccupational tals.Toxicon. 2000,: 38:735-741
4. Fraker ,P.J; King ,T.and laakko T .The dynamic link between the integrity of the immune system and zinc status .J.nutr. 2000,: 130:1399-1406
5. Wapinar, R.A. Zinc defiency,malnutrition and gastrointestinal tract J.Nutr. 2000,:130:1388-1390
6. Cousimg, R.J and Hempe,M.Essential elementdefiency.Clin.Pediatr.J.Neonat.2 0 0 5 : 2 (4):45-48
7. Bashir,N.A. Serum zinc and copper levels in sickle cell anemia .Ann.Trop.Paediat. 2005:,15:291 -3
8. Mateos F, Brock JH,.Arellano JL. Iron metabolism in the lower respiratory tract. Thorax 1998 , 53:594 -600.
9. Amrani Y, Panettieri Jr RA(). Modulation of calcium homeostasis as a mechanism for alteringsmooth muscle responsiveness in asthma. Curr Opin Allergy Clin Immunol. 2002,: 2:39-45.
10. Dominguez LJ, Barbagallo M, Di Lorenzo G,. Bronchial reactivity and intracellular magnesium: a possible mechanism for the bronchodilating effects of magnesium in asthma. Clin Sci .1998:, 95:137-142.
11. de Valk HW, Kok PT, Struyvenberg A, et al. . Extracellular and intracellular magnesium concentrations in asthmatic patients. Eur Respir J.1993,:6:1122-1125.
12. Fraenkel DJ, Holgate ST.. Etiology of asthma: Pathology and ediators. In:C.W.. Biermann, D.S. Pearlman, G.G.Shapiro, W.W. Busse (eds) Allergy,Asthma and Immunology from Infancy to Adulthood. 3r ed . WB Saunders Company, Philedelphia, pp 443-72
13. Burney PGJ, Chinn S, Rhona RJ. Has the prevalence of asthma increased in children? Evidence from the national study of health and growth. B M J.1990;300: 1306-10
14. Omran M, Russell G, Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. BMJ.1996; 312: 334-36
15. Seaton A, Godden DJ, Brown K. Increasein asthma: a more toxic environment or a more susceptible population. Thorax1.994;49: 171-74
16. Seaton A, Soutar A, Mullins J. The increase in hay fever: pollen, particulate matter and SO2 in ambient air. Q J Med.1996;89: 279-84
17. Godden DJ, Devereux GS, Anderson WJ.Environmental lung disease: the role of diet. Monaldi Arch Chest Dis. 1999:, 54: 479– 84 .

18. Khoyl MS, Gas MA, Shimi S, Baz F,Tayeb H, Hamid MS.Zinc and copper status in children with bronchial asthma and atopic dermatitis. J Egypt Pub Health Assoc.1990; 65: 657-68
19. Konig P, Hillmann L, Cervantes C,Levine C, Maloney C, Douglass B,Johnson L, Allen S. Bone metabolism inchildren with asthma treated with inhaledbeclomethasone diproprionate, J Pediatr.1993:,122; 219-26
20. Beisel WR. Interrelationship between zinc and immune function Single nutrients and immunity.Am J Clin Nutr.1986,:35 (2);417-6811-
21. Burney P..A diet rich in sodium may potentiate asthma: idemiological evidence for a new hypothesis. Chest.1987; 91: 143S-148S
22. Godden DJ, Devereux GS, Anderson WJ.Environmental lung disease: the role of diet.Monaldi Arch Chest Dis.1999; 54: 479-84
23. Kennedy T, Ghio AJ, Reed W, Samet J,Zagorski J, Quay J, Carter J, Dailey L, Hoidal JR, Devlin RB. Copper-dependent inflammation and nuclear factor -kappa Bactivation by particulate air pollution.Am J Respir Cell Mol Biol; 1998:, 19(3): 366-78
24. Gitlin JD, Schroeder JJ, Lee-AmbroseLM, ousinsJ..Mechanism of ceruloplasmin biosynthesis in normal and copper deficient rats. Biochem J.1992;28: 835-39
25. Barber E, Cousins RJ. .Interleukin 1stimulated induction of ceruloplasminsynthesis in normal and copper deficientrats, J Nutr; 1988,118: 375-81
26. Soutar A, Seaton A, Brown K.. Bronchial reactivity and dietary antioxidants. Thorax; 1997:,52: 166-70
27. Bodner C, Godden D, Brown K, Little J,Ross S, Seaton A. Antioxidant intake andadult-onset wheeze: a case-control study. Aberdeen WHEASE Study Group Eur Respir J.1999; 13: 22-30
28. Halliwell B. Free radicals, antioxidantand human disease. Curiosity, cause orconsequence. Lancet.1994; 344: 721-24.
29. Pucheu S, Coudray C, Tresallet N, FavierA, Leiris J.. Effect of dietary antioxidanttrace elements supply on cardiac toleranceto ischemia-reperfusion in the rat. J MolCell Cardiol; 1995: 27: 2303-14
30. Raeve HR, Thunnisen FJ, Kaneko FT,Guo FH, Lewis M. Decreased Cu-Zn-SO Dactivity in sthmatic airway epithelium:correction by inhaled corticosteroidinvivo. Am J Physiol; 1997,: 272: 148-54
31. Milanion R, Marrela M, Gasprini R,Pasqualic-Cho M, Velo G.Copper and zinc body level in inflammation: an overview of the data obtained from animaland human studies. Agents Actions.1993;39:195-208.
32. Allen JI, Perri RT, McClain CJ, Kay NF. Altertions in human natural killer cellactivity and monocyotoxicity induced by zinc deficiency. J Lab Clin Med.1983;102 (4): 577-81
33. O'Dell BL. Interleukine 2 production is altered by copper deficiency. Nutr Rev; 1993:,51: 307-9
34. Vural H, Uzun K, Uz E, Koçyiğit A, Çu, zinc and various elements in serum of patients with bronchial asthma. J TraceElem Med Biol .2000:, 14; 88-91
35. Shaheen SO. Changing patterns of childhood infection and the rise inallergic disease. Clin Exp Allergy.1995;25: 1034-37
36. Shaheen S., Discovering the causes of atopy.Patterns of childhood infection and fetal growth may be implicated .B M J.1997; 314: 987-88
37. Shahean SO, Aaby P, Hall AJ, BarkerDJ, Heyes CB, Shiell AW,et al. 1996,. Measles and atopy in Guinea-Bissau Lancet 347:1792-96
38. Britton J, Pavord I, Richards K,Wisniewski A, Knox A,et al.Dietary magnesium, lung function, wheezing and airway hyperreactivity in a random adult population sample. Lancet. 1994: 344:357-62
39. Baker JC, Tunnicliffe WS, DuncansonRC, Ayres JG.() Dietary antioxidants and magnesium in type 1 brittle asthma: a case control study. Thorax.1999,: 54:115-18
40. Kocyigit A, Armutcu F, Gurel A, Ermis B. . Alterations in plasma essential trace elements selenium, manganese, zinc, copper and iron concentrations and the possible role of these elements on oxidative status in patients with childhood asthma. Biological Trace Element Research. 2003:, 96:1-11.
41. Vural H, Uzun K, Uz E, Kocyigit A, Cigli A, AkyolO. . Concentrations ofcalcium, zinc and variouselements in serum of patients with bronchial asthma. J Trace Elements Med Biol. 2000:,14:88–91
42. Neskoromnyi AF. . Role of magnesium and calcium ions in thepathogenesis of bronchial asthma. Klin Med.1994;72:47-51.
43. Kuroda S, Ishikawa K, Hanamitsu H, .Evidence for increased intracellular free calcium concentration in platlets of bronchial asthma patients. Intern Med.1995;34:722-727
44. Saik M i,. Sumita N.M, Jaluul O., Sobreiro L.F., Jacob-Filho W.,. Vasconcellos M.B.A,."Establishing a protocol for trace element in serum samples from healthy elderlypopulation in São Paulo city, SP, Brazil".J. Radioanal. Nucl. Chem2006**,:**269: pp.665-669