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The role of zinc in acute pyelonephritis

Ruolo dello zinco nella pielonefrite acuta

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INTRODUCTION

Urinary tract infection (UTI) is a common disease among infants and children [1, 2]. UTI might affect the lower urinary tract (cystitis) or the upper urinary tract (acute pyelonephritis) [3]. Acute pyelonephritis is the most severe and dangerous form of UTI. Delay in diagnosis and treatment may results in renal scar and chronic renal failure [1-5]. The prevalence of renal scar formation following acute pyelonephritis is reported as high as 10%-65% [3]. Several risk factors such as vesicoureteral reflux, urinary tract obstruction, nephrolithiasis, and dysfunctional voiding syndrome increase the chance of developing acute pyelonephritis and its complications [1]. Given the role of some trace elements like zinc in various infectious diseases, the following questions arose: What is the status of serum zinc level in children with acute pyelonephritis? Do zinc play a role in the pathogenesis of acute pyelonephritis? Trace elements are mineral nutrients that are fundamental for the normal physiological functioning of the body. Zinc element is crucial for free radical detoxification, antioxidant defense, and immune system function in humans [6-8]. Nowadays, zinc deficiency is a major risk factor for morbidity and mortality, particularly in developing countries [9]. It increases the chance of occurrence of different infectious diseases such as skin and respiratory infections, diarrhea, malaria, and tuberculosis [10,11]. Due to the high prevalence of acute pyelonephritis, it is important to identify the factors involved in its pathophysiology. Therefore, this study was conducted to compare serum concentration of zinc in children with acute pyelonephritis and healthy children.

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PATIENTS AND METHODS

This case-control study was conducted at Qazvin Children Hospital affiliated to the Qazvin University of Medical Sciences in Qazvin, Iran in 2012-2013. This hospital is the only children's teaching hospital in Qazvin Province. In this study, 60 children with acute pyelonephritis (the case group) and 60 healthy children (the control group) were compared in term of serum zinc level. The ages of all children were between two months and 12 years. The sample size was calculated based on the following formula:

$$n = \frac{2\left(z\,1-\frac{\alpha}{2}+z\,1-\beta\right)^2\sigma^2}{(\mu_1-\mu_2)^2}$$

where $\alpha = 0.05$; $1-\alpha/2 = 0.95$; $\beta = 0.2$; $1-\beta$ (power) $= 0.8$; $\sigma = 8$; $\mu_1 = 83$ µg/dL; and $\mu_2 = 79$ µg/dL [12]. Consecutive sampling continued until the desired sample size was reached. The inclusion criteria for children with acute pyelonephritis (case group) were:

- first UTI;
- having clinical signs and symptoms of acute

pyelonephritis such as fever, chills, abdominal pain, flank pain, frequency, and dysuria;
- positive urine culture (urine culture more than10^5 colonies of a single pathogen in a midstream urine sample or clean catch method or 10^4 colonies of a single pathogen via urinary catheterization, or presence of any number of colonies of an organism in urine culture taken by suprapubic method);
- diagnosis of acute pyelonephritis confirmed by Tc-99m dimercaptosuccinic acid (DMSA) renal scan (gold standard) [1, 2].

Children were excluded from study if they had recurrent UTI, and in addition if there were risk factors, such as vesicoureteral reflux, structural abnormalities in the urinary system, neurogenic bladder, vaginal adhesion, constipation etc. Underlying diseases such as malnutrition and septicemia also were considered as exclusion criteria. Group matching was used to select the control group from healthy children who referred to the growth monitoring center of the hospital or underwent elective operations such as inguinal hernia surgery at the hospital's surgical ward. The two groups were matched for age and gender.

DMSA renal scan is the gold standard for the diagnosis of acute pyelonephritis in children. However, it is not routinely performed in clinical practice due to the limited availability of nuclear medicine departments. Acute pyelonephritis was diagnosed upon the observation of focal or diffuse areas of diminished uptake associated with preservation (or at time even bulging) of renal cortical outline in technetium-99m DMSA renal scan [1]. Abnormalities revealed on the DMSA renal scans were categorized into mild, moderate, and severe abnormalities based on kidney uptake [1, 13].

First, demographic information of subjects were recorded. Then three milliliters of blood was taken from the peripheral vessels of children in all the groups, and serum was obtained by centrifugation at 3,000 rpm for 5 minutes at 4°C. The serum was then poured into acid-washed tubes and stored in a refrigerator at -20°C until serum zinc assay. Serum zinc level was measured by using an atomic absorption flame spectrophotometer (GBC Scientific Equipment Pty Ltd, Australia) at the Biochemistry Department of Qazvin University of Medical Sciences (Qazvin, Iran). All the samples were measured in duplicates to improve accuracy.

Statistical analysis

Chi-square test, t-test, spearman and Pearson correlations were applied to analyze the obtained data. All analyses were performed with SPSS for Windows 16.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Ethics approval

The ethics committee of the research department in the Qazvin University of Medical Sciences (Project No: 303) approved the study. All parents were provided information regarding the research method in simple language. The children were included in the study after their parents agreed and signed the informed consent form.

RESULTS

The case group consisted of seven (11.7%) males and 53 (88.3%) females. The corresponding numbers in the control group were 12 (20.0%) and 48 (80.0%), respectively (P=0.317). The mean±SD age was 48.98±28.54 months in the case group and 60.91±40.81 months in the control group (P=0.066).

The two groups had no significant difference in terms of sex and age (P>0.05). Serum zinc level in the case and control groups were 70.73 ± 14.15 and 87.61 ± 12.68 µg/dL, respectively (P=0.001). There was significant difference between groups regarding serum zinc concentration (P=0.001) (Table 1, Figure 1).

Hypozincemia (serum zinc level less than 70 µg/dL) was observed in 51.7% and 8.3% of case and control groups, respectively (Table 2) (P=0.001). There was not any correlation between serum zinc level with inflammatory markers, severity of acute pyelonephritis, causative organism and duration of disease (P<0.05) (Table 3). *Escherichia coli* was the most common grown microorganism (%80). Based on DMSA renal scan, most of patients had mild acute pyelonephritis (75% of patients).

Table 1 - Comparison of serum zinc level in case and control groups.

Trace element (mean±SD) (µg/dL)	*Case group*	*Control group*	*P*
Zinc	70.73±14.15	87.61±12.68	0.001

T-Test.

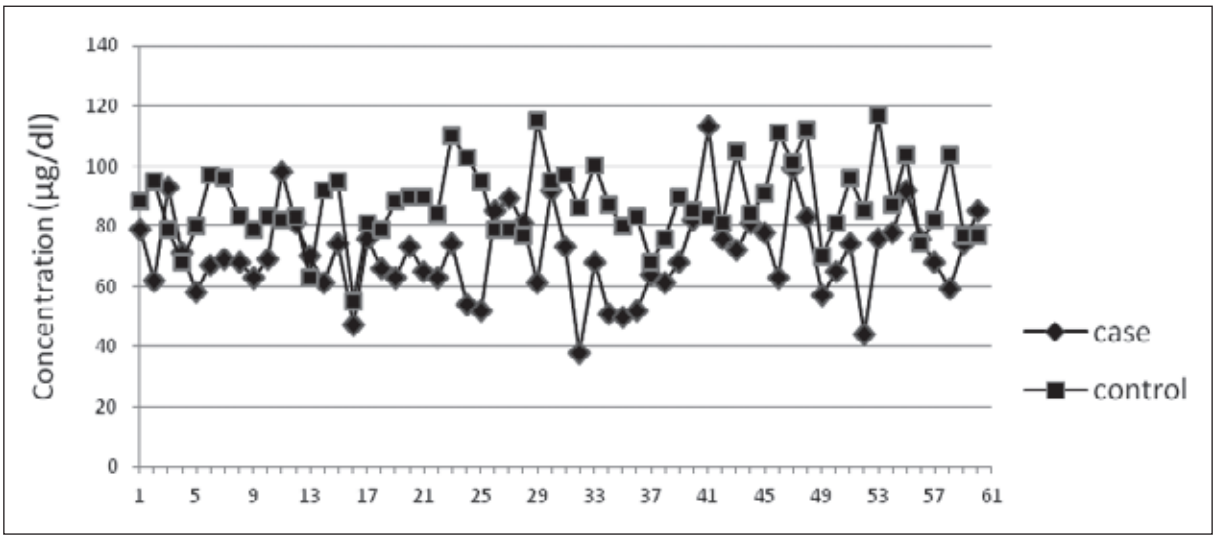

Figure 1 - Comparison of serum zinc level in case and control groups.

Table 2 - Comparison of serum zinc level according normal values in case and control groups.

Zinc (µg/dL)	*Case n (%)*	*Control n (%)*	*P*
Less than normal (70)	31 (51.7)	5 (8.3)	0.001
Normal (70-120)	29 (48.3)	55 (91.7)	
More than normal>120	0 (0)	0 (0)	

Chi-square test.

Table 3 - Correlation analysis between serum zinc level and inflammatory markers and other variables in case group.

Variables	*Zinc*	
	r	*P*
Fever	-0.037	0.83
WBC	-0.076	0.66
Neutrophil	0.091	0.60
ESR	-0.094	0.59
CRP	0.075	0.67
Severity of disease	-0.176	0.32
Causative organism	-0.173	0.33
Duration of disease	0.174	0.32

Spearman and Pearson analysis.

DISCUSSION

The present study demonstrated that there is a significant correlation between serum zinc level and acute pyelonephritis. According to literature review and as far as our knowledge is concerned, the present study is the first one that surveyed serum zinc concentration in children with acute pyelonephritis. In addition, studies on zinc changes in other bacterial infections are limited. Reduction in serum zinc concentration was approved by Cesur et al. on 60 patients with brucellosis and 15 healthy controls [12]. In addition, similar study on patients with brucellosis confirms these changes [14]. A study by Kassu et al. on 155 patients with tuberculosis and 31 healthy controls demonstrated that in patients with tuberculosis, serum zinc concentration decreases [15]. The results of our study are similar to those mentioned above. What is the underlying reason for these changes in acute pyelonephritis? Does acute pyelonephritis lead to a reduction in serum zinc level? Or zinc deficiency may be a risk factor for acute pyelonephritis?

Studies conducted on humans and animals have shown that hypozincemia occur shortly after infection or following injection of bacterial endotoxin. These metabolic reactions against infections are called acute phase responses. The acute phase response is mediated by cytokines such as interleukin-1 β and TNF α. Hypozincemia might be related to the redistribution of zinc from serum to other tissues, the decrease in zinc-carrier proteins and as a result an increase in the production of metallothionein in the liver. Metallothionein is a protein carrying zinc to the liver [15, 16]. In present study, correlation analysis showed that there is not any significant correlation between serum zinc level with inflammatory markers, severity of acute pyelonephritis, causative organism and duration of disease. Thus, it seems that these vari-

ables are not responsible for serum zinc reduction in our case group patients. On the other hand, due to the elimination of known risk factors of UTI in our study (*e.g.*, vesicoureteral reflux, urinary tract abnormality or obstructions, vaginal adhesion, constipation etc.), zinc deficiency may be a predisposing factor for acute pyelonephritis.

Zinc is one of the major nutritionally essential elements in the human body. This element is essential for structural formation and the functioning of several macromolecules and over 200 enzymes, most of which contribute to the immunological processes [7]. By damaging the epithelial line of defense, reducing antioxidant activity and damaging the immune system's functionality, zinc deficiency increases the chance of contracting infectious diseases such as tuberculosis; lower respiratory tract diseases and diarrhea [11, 17, 18].

Some studies have pointed out the role of zinc supplementation in the prevention and treatment of bacterial diseases [19-21]. According to our results, the question arises whether the prescription of zinc along with antibiotics to children with acute pyelonephritis can accelerate the recovery and also prevents its serious complications such as renal scar. Numerous human and animal studies have highlighted the role of inflammation and free radicals in the development of renal scar. They have also underlined the effects of various antioxidants on the prevention of renal scar development in patients with acute pyelonephritis [5, 22]. Ayazi et al. suggested that prescription of vitamin A to children with acute pyelonephritis prevents the development of renal scar significantly [5]. Similar results have been reported following the consumption of selenium [22].

Our findings showed that there is a significant relationship between serum zinc reduction and acute pyelonephritis. The main limitation of the present study was the failure in measuring the serum zinc level after complete recovery in case group. Further studies are suggested to be conducted on this topic with larger sample sizes while also measuring serum zinc level before and after treatment.

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Conflict of interest

We declare no conflict of interest.

Funding

None

Keywords: zinc, acute pyelonephritis, children.

SUMMARY

This study was conducted to determine the serum concentration of zinc in children with acute pyelonephritis. Serum zinc levels of 60 children with acute pyelonephritis and 60 healthy children were compared. Acute pyelonephritis was diagnosed using Tc-99m dimercaptosuccinic acid (DMSA) renal scan. Serum zinc levels were measured by the atomic absorption flame spectrophotometry. The levels in question in the case and control groups were 70.73±14.15 and 87.61±12.68 µg/dL, respectively (P=0.001). There was no correlation between serum zinc level with inflammatory markers, severity of acute pyelonephritis and duration of the disease. This study showed that there is a correlation between serum zinc level and acute pyelonephritis. Zinc would therefore appear to play a certain role in the pathogenesis of acute pyelonephritis.

RIASSUNTO

Il presente studio è stato condotto al fine di determinare la concentrazione sierica di zinco in bambini affetti da pielonefrite acuta. I livelli sierici di zinco rilevati in 60 bambini con pielonefrite acuta sono stati confrontati con quelli riscontrati in altrettanti bambini sani. La diagnosi di pielonefrite acuta è stata posta utilizzando la scintigrafia renale con ^{99m}Tc acido dimercaptosuccinico (DMSA). I livelli sierici di zinco, determinati mediante spettrofotometria ad assorbimento atomico, sono risultati pari a 70,73±14,15 nei bambini con pielonefrite e a 87,61±12,68 µg/dL, (P=0,001). Non è stata evidenziata nessuna correlazione tra livelli sierici di zinco e marcatori infiammatori, gravità della pielonefrite acuta e durata della malattia. Questo studio ha indicato una correlazione tra concentrazione sierica di zinco e pielonefrite acuta, suggerendo dunque un qualche ruolo dello zinco nella patogenesi della pielonefrite acuta.

REFERENCES

[1] Bensman A., Dunand O., Ulinski T. Urinary tract infection, In *Pediatric Nephrology* (Avner E.D., Harman W.E., Niaudet P., Yoshikawa N., Eds) 2009, 1007-1025. Springer, Berlin.
[2] Elder J.S. Urinary tract infection, In *Nelson textbook of pediatrics* (Kliegman R.M., Stanton B.F., Geme III J.W.S., Shor N.F., Behrman R.E., Eds), 2011, 1829-1838. Saunders, Philadelphia.
[3] Sheu J.N., Chen M.C., Lue KH., et al. Serum and urine levels of interleukin-6 and interleukin-8 in children with acute pyelonephritis. *Cytokine* 36, 5-6, 276-282, 2006.
[4] Ayazi P., Mahyar A., Jahani Hashemi H., Daneshi MM., Karimzadeh T., Salimi F. Comparison of procalcitonin and C-Reactive protein tests in children with urinary infection. Iran *J. Pediatr*. 19, 4, 381-386, 2009.
[5] Ayazi P, Moshiri S.A., Mahyar A., Moradi M. The effect of vitamin A on renal damage following acute pyelonephritis in children. *Eur. J. Pediatr*. 170, 3, 347-350, 2011.
[6] Strachan S. Trace elements. *Current Anaesthesia & Critical Care* 21, 1, 44-48, 2010.
[7] Tapiero H., Townsend D.M., Tew K.D. Trace elements in human physiology and pathology. Copper. *Biomed. Pharmacother.* 57, 9, 386-398, 2003.
[8] Tapiero H., Tew K.D. Trace elements in human physiology and pathology: zinc and metallothioneins. *Biomed. Pharmacother*. 57, 9, 399-411, 2003.
[9] Black R.E., Allen L.H., Bhutta Z.A., et al. For the Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: Global and regional exposures and health consequences. *Lancet* 371, 9608, 243-260, 2008.
[10] Black R.E., Sazawal S. Zinc and childhood infectious disease morbidity and mortality. *Br. J. Nutr.* 85, 2, 125-129, 2001.
[11] Caulfield L.E., Black R.E. Zinc deficiency, In *Comparative quantification of health risks: Global and regional burden of disease attributable to select major risk factors* (Ezzati M., Lopez A.D., Rodgers A., Murray C.J.L. Eds), 2004. Geneva: World Health Organization.
[12] Cesur S., Kocaturk P.A., Kavas G.O., Aksaray S., Tezeren D., Ciftci U. Serum copper and zinc concentrations in patients with brucellosis. *J. Infect.* 50, 1, 31-33, 2005.
[13] Dalirani R., Yousefi Zoshk M., Sharifian M., Mohkam M., et al. Role of vitamin A in preventing renal scarring after acute pyelonephritis. *Iran J. Kidney Dis*. 5, 5, 320-323, 2011.
[14] Mobaien A., Hajiabdolbaghi A., Jafari S., et al. Serum zinc and copper concentrations in brucellosis patient. *Arch. Clin. Infect. Dis.* 5, 2, 96-100, 2010.
[15] Kassu A., Yabutani T., Mahmud Z.H., et al. Alterations in serum levels of trace elements in tuberculosis and HIV infections. *Eur. J. Clin. Nutr*. 60, 5, 580-586, 2006.
[16] Brown K.H. Effect of infections on plasma zinc concentration and implications for zinc status assessment in low-income countries. *Am. J. Clin. Nutr.* 68, 2, 425S-429S, 1998.
[17] Cuevas L.E., Koyanagi A. Zinc and infection: a review. *Ann. Trop. Paediatr.* 25, 3, 149-160, 2005.
[18] Fischer Walker C., Black R.E. Zinc and the risk for infectious disease. *Annu. Rev. Nutr.* 24, 255-275, 2004.
[19] Nenni V., Nataprawira H.M., Yuniati T. Role of combined zinc, vitamin A, and fish oil supplementation in childhood tuberculosis. *Southeast Asian J. Trop. Med. Public Health.* 44, 5, 854-861, 2013.
[20] Faiz U., Butt T., Satti L., Hussain W., Hanif F. Efficacy of zinc as an antibacterial agent against enteric bacterial pathogens. *J. Ayub Med. Coll. Abbottabad*. 23, 2, 18-21, 2011.
[21] Raqib R., Roy S.K., Rahman M.J., et al. Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. *Am. J. Clin. Nutr.* 79, 3, 444-450, 2004.
[22] Park J.S., Lee K.S., Jung H.C., Moon G.H. The suppressive effect of selenium on renal inflammation in a rat model of pyelonephritis with delayed treatment. *Urology* 68, 182, 2006.