

Investigating the Effect of Zinc Deficiency on the Risk of Urinary Tract Infection in Children

Fariba Zabihi¹, Mina Mostafavi², Mohammad Esmaili², *Massoud Issapour Cheshani³

¹Department of General Surgery, Mashhad University of Medical Sciences, Mashhad, Iran.

²Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

³Department of Urology, Islamic Azad University, Mashhad Branch, Mashhad, Iran.

Abstract

Background

Urinary Tract Infection (UTI) is a common infectious disease among children. Deficiency in micronutrients such as zinc, is believed to play a role in predisposing children to UTI. However, rare studies have been conducted on this subject. The present study aimed to compare the serum zinc level between children with UTI and normal controls.

Materials and Methods: In this case-control study, which was conducted on children with UTI who referred to 17th Shahrivar and 22th Bahman hospitals, Mashhad- Iran, during 2016-2017, patients suspicious of UTI were assessed by urine culture. The urine sample of the patients who were not toilet-trained was collected using urinary bags, and those who were toilet trained were asked to collect the clean catch mid-stream urine. Demographic data, urinary symptoms, type of cultured microorganism, and colony count were recorded. Data were analyzed using SPSS V. 20.0.

Results: Overall, 104 children (52 cases and 52 controls) were included. The groups had significant differences regarding sex, age, and weight ($P<0.05$). Serum zinc level was 60.0 ± 17.1 $\mu\text{g/dl}$ in the case group and 83.0 ± 15.7 $\mu\text{g/dl}$ in the control group ($P=0.001$). After being adjusted for demographic factors, the zinc deficiency proved to be a significant predictor of UTI (OR= 8.633, 95% confidence interval=3.084-24.171, $P<0.001$).

Conclusion

According to the results of our study, serum zinc level was markedly lower among patients with UTI. Zinc deficiency can put the children at an eight times higher risk for developing UTI, independent of age and gender.

Key Words: Children, Micronutrients, Zinc Deficiency, Urinary Tract Infection.

*Please cite this article as: Zabihi F, Mostafavi M, Esmaili M, Issapour Cheshani M. Investigating the Effect of Zinc Deficiency on the Risk of Urinary Tract Infection in Children. Int J Pediatr 2020; 8(9): 11959-966. DOI: **10.22038/ijp.2020.47133.3819**

*Corresponding Author:

Massoud Issapour Cheshani, MD, Department of Urology, Islamic Azad University, Mashhad Branch, Mashhad, Iran.

Email: massoodissapour@yahoo.com

Received date: Jun.10, 2020; Accepted date: Jul.22, 2020

1- INTRODUCTION

Urinary Tract Infection (UTI) is a common problem in pediatric care, listed as the second prevalent infection after common colds (1). The incidence of the condition is 0.18 and 1.28 per 100,000 boys and girls, respectively (2). The prevalence of pediatric UTI cases ranges from 2-5 % (3). Although the condition is more prevalent among girls in general, it is more prevalent among boys during the early infancy period (4). Furthermore, 5.3 % of the infants with the febrile disease are diagnosed with UTI (2). Symptoms of UTI include fever, nausea, vomiting, anorexia, and flank pain. However, characteristic adult symptoms may be absent in children (5). The condition may present with symptoms such as jaundice, growth retardation, weight loss, and fever with unknown origin (5-7). Early diagnosis and management of UTI are necessary to prevent further complications (8, 9).

The complications of UTI include bacteremia, sepsis, hypertension, scar formation, and renal failure (10). The incidence of transient and permanent renal failure due to UTI is estimated to be 40 and 5 %, respectively (11). Several risk factors are associated with the occurrence of UTI, such as urinary tract obstruction, vesicoureteral reflux, nephrolithiasis, dysfunctional voiding syndrome, and posterior urethral valve (12).

Current evidence suggests that nutritional deprivation may make children susceptible to UTI (13, 14). Zinc is among the top listed micronutrient with immunological activity. It plays a crucial role in cellular growth and metabolism (15). Furthermore, it is crucial for immunity and free radical scavenging (16). Several studies have reported that this trace element also has antibacterial properties (17), and investigated its role in different infectious disorders (18). Although some studies have assessed the relationship between zinc level and UTI in different groups of

patients, only a few studies have assessed it in children, and this issue still needs deep investigation among the pediatric population (13, 17, 19, 20). Therefore, this study aimed to assess the serum zinc level in UTI patients compared to children without UTI or any other urinary problems.

2- MATERIALS AND METHODS

2-1. Study design and population

This case-control study was conducted on children with UTI who referred to 17th Shahrivar and 22th Bahman hospitals, Mashhad, Iran, during 2016-2017. Considering a confidence level of 90%, a power of 80%, and a mean zinc level of 106.9 ± 23.7 in healthy controls and 95.4 ± 21.8 in UTI cases, a sample size of 52 patients was calculated according to previous studies (21).

2-2. Methods

Patients who were suspicious of UTI were assessed for urine culture. Urine samples were collected using urinary bags in patients who were not toilet-trained, and those who were toilet-trained were asked to collect the clean catch mid-stream urine. To collect mid-stream urine, girls were positioned in the lithotomy position, perineum was cleaned using water and soap, the labia were opened, and the child was allowed to urinate for a volume of 200 ml. For boys, only the glans and phallus were cleaned with soap and water, and mid-stream urine was collected.

2-3. Laboratory measurements

In the case of mid-stream examination, those with colony counts $>100,000$, or those with colony counts $>10,000$ along with UTI symptoms, and single organism culture results were considered positive. In the case of urinary bag examination, the urinary culture was considered positive if contained $>10,000$ colonies while the patient being symptomatic (22).

Furthermore, fasting blood sugar, serum urea, and creatinine were assessed to rule out diabetes and renal failure. Data were collected in pre-designed simple checklists. We collected demographic data including age and gender, anthropometric data including weight, and clinical data, including urinary symptoms, type of cultured microorganism, and colony count. To assess serum zinc level, 1 ml samples of venous blood were gathered and sent to the laboratory. Blood serum was separated and stored at -70°C . The plasma level of elemental zinc was measured in all participants using the flame technique using the atomic absorption spectrophotometer (Perkin-Elmer Norwalk 3030, Zeeman Ltd., USA). According to previous similar studies, we set the cutoff point of $70\ \mu\text{g}/\text{dl}$ as a zinc deficiency level and the range of $70\text{-}120\ \mu\text{g}/\text{dl}$ as a normal level (21).

2-4. Ethical Consideration

The patients' parents were completely informed about the study and were asked to sign written consent before commencing the study. The Ethics Committee of the Islamic Azad University of Medical Sciences approved the study protocol.

2-5. Inclusion and Exclusion Criteria

We included patients aged <5 years who had a positive urine culture test along with UTI symptoms. The control group was selected among children who were referred for elective surgeries and had no UTI symptoms with a negative urine culture. The exclusion criteria were receiving zinc supplementation in the past two months, immunosuppressive therapies, uncircumcised boys, other localized infections than UTI, malnutrition, chronic

diarrhea, and celiac. We also excluded subjects with systemic diseases including diabetes mellitus, genital anomalies according to physical examination, chronic renal disorder according to the history and laboratory findings, mental retardation or cerebral palsy, neurologic problems, renal stones, long term catheterization or ureteral stents, and dysfunctional voiding according to history and physical examination.

2-6. Data Analyses

Data were entered in Statistical Package for the Social Sciences (SPSS) V. 20.0. Central and dispersion indices were calculated. Data were compared using independent samples t-test. In the case of qualitative data, the Chi-square test and Fisher's exact test were used. For further analyses, a binary logistic regression model was used to adjust the groups for confounding variables. The significance level was considered <0.05 .

3- RESULTS

Overall, 104 subjects in two cases ($n=52$) and control ($n=52$) groups were studied. Females composed $36/52$ (69.2%) of the case group and $23/52$ (44.2%) of the control group ($P=0.010$). The mean age was 26.5 ± 20.5 and 34.3 ± 16.8 months in the case and control group, respectively ($P=0.035$). According to **Table. 1**, the control group had a mean serum zinc level of $83.0 \pm 15.7\ \mu\text{g}/\text{dl}$, while it was $60.0 \pm 17.1\ \mu\text{g}/\text{dl}$ in the case group ($P=0.001$). The results of urine cultures showed that the most common microorganism was *Escherichia coli* ($n=39$, 75.0%), followed by *Klebsiella* ($n=6$, 11.5%), and *Proteus* ($n=2$, 3.8%) (**Figure.1**).

Table-1: Comparison of demographic parameters and serum zinc level between patients and controls.

Feature		Case group	Control group	P-value
Gender, Number (%)	Male	16 (30.8)	29 (55.8)	0.010
	Female	36 (69.2)	23 (44.2)	
Age, months (mean ± SD)		26.5 ± 20.5	34.3 ± 16.8	0.035
Weight, kg (mean ± SD)		11.0 ± 4.6	13.7 ± 3.2	0.001
Zinc, µg/dl (mean ± SD)		60.0 ± 17.1	83.0 ± 15.7	0.001

Case group: children with UTI, Control group: children without any urinary problem, SD: Standard deviation, UTI: Urinary Tract Infection.

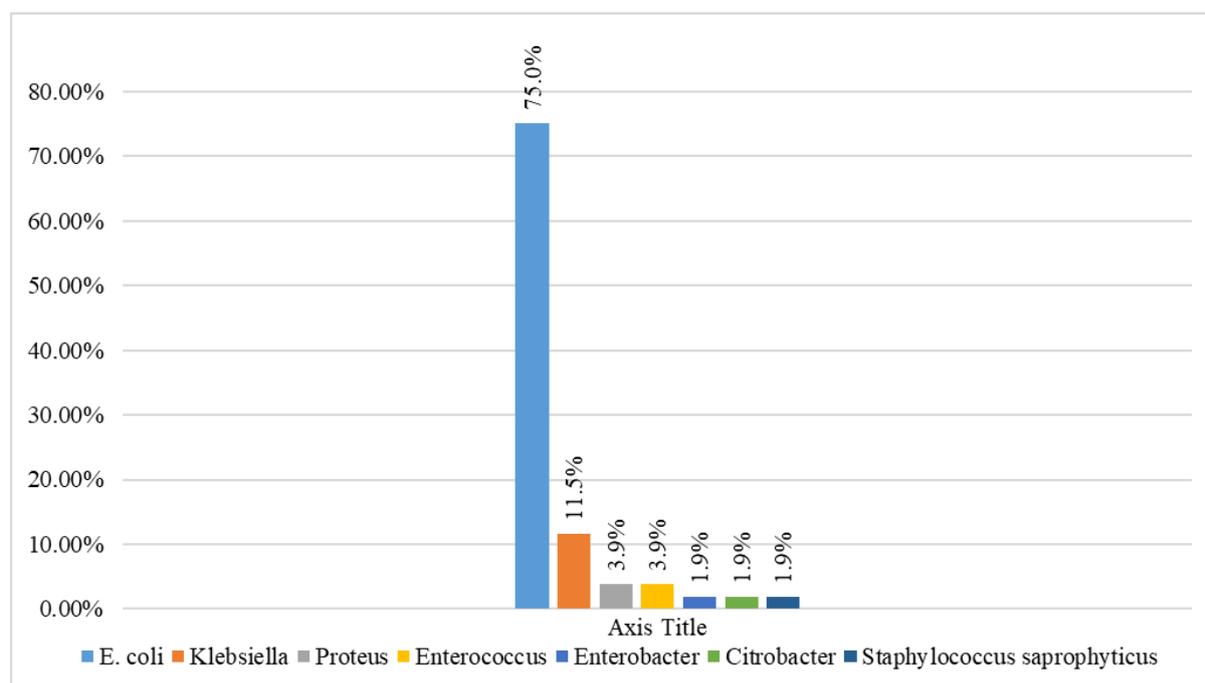


Fig.1: Frequency of the isolated bacteria from urine cultures in children with UTI. UTI: Urinary Tract Infection.

Table.2 shows the comparison of serum zinc level between different genders, age groups, and weights. The results showed that the zinc level was significantly higher in the control group in both genders ($P < 0.001$). However, only the participants of the control group with above one year had a significantly higher zinc level compared to the case group ($P < 0.001$). Furthermore, the zinc level was significantly higher in the control group compared to the case group only in those weighing ≥ 10 kg ($P < 0.001$). Moreover, we found a significant association between zinc level and UTI, since age, gender, and

body weight was significantly different between the UTI group and controls. Therefore, a logistic regression model was used to adjust for age, sex, and weight and assess the association of zinc level and UTI regardless of these possible confounding factors (**Table.3**). The results of multivariate logistic regression showed that weight and zinc levels were significant and independent predictors of UTI. As shown in the table, the risk of developing UTI was about eight times higher in children with zinc deficiency compared to normal cases (odds ratio=8.633, 95% CI =3.084-24.171, $P < 0.001$).

Table-2: The association between serum zinc level in the study groups and demographic variables.

Variables		Zinc serum level $\mu\text{g/dl}$ (mean \pm SD)		P-value
		Case	Control	
Age	≤ 1 years	64.9 \pm 17.4	77.1 \pm 17.4	0.090
	> 1 years	56.9 \pm 16.4	84.1 \pm 15.9	< 0.001
Gender	Male	65.1 \pm 15.6	84.9 \pm 14.7	< 0.001
	Female	57.7 \pm 17.5	80.5 \pm 16.9	< 0.001
Weight	< 10 kg	62.0 \pm 15.1	78.4 \pm 14.8	0.052
	≥ 10 kg	58.0 \pm 19.0	83.4 \pm 15.8	< 0.001

Case group: children with UTI, Control group: children without any urinary problem, SD: Standard deviation, UTI: Urinary Tract Infection.

Table-3: Multivariate binary logistic regression model for adjusting the effect of confounding factors on the association between zinc deficiency and UTI.

Variables	Odds ratio	95% confidence interval		P-value
		Lower bound	Upper bound	
Sex (male)	0.567	0.203	1.582	0.279
Age (> 1 years)	0.841	0.170	4.170	0.833
Weight (< 10 kg)	13.035	2.307	73.647	0.004
Zinc deficiency	8.633	3.084	24.171	< 0.001

UTI: Urinary Tract Infection.

4- DISCUSSION

The present study aimed to compare the serum level of zinc between pediatric cases with UTI and those with no urinary problems. Our results showed that UTI cases had significantly lower serum zinc levels and were at an eightfold risk of UTI. Furthermore, it was observed that the weight of patients also associates with their susceptibility to UTI. Consistent with our results, Noorbakhsh et al. reported that serum zinc level was significantly lower in UTI cases. However, they found that other trace elements, such as vitamins A and D, showed no notable difference (13). Their sample included children below five years, which was similar to our study. Mahyar et al. reported the reduction of serum zinc levels to be significantly associated with the risk of developing pyelonephritis (20). Inflammatory cytokines are reported by some studies to be linked with zinc deficiency in infections (23, 24). However, others argued that zinc deficiency is not associated with inflammatory cytokines, and its relationship with UTI is regardless

of inflammation markers (20). Zinc is an important micronutrient, which plays a crucial role in cellular growth and differentiation through the synthesis of proteins and nucleic acids. It is a key cofactor for around 200 enzymes (16). Zinc deficiency can bring impaired immunity, as it is important for the development and function of T-lymphocytes. Furthermore, this micronutrient has a role in the production of cytokines, including interleukin-2, interferon- γ , and tumour necrosis factor- α (25, 26). The dearth of this nutritional element increases the chance of infectious diarrhea, tuberculosis, and lower respiratory infection (27). It is believed that zinc supplementation can lower the risk of different infections in children through improving the immune system (28). Studies reported that zinc prescription could ameliorate the symptoms of lower respiratory tract infection (29, 30). Zinc spray has been successfully used in the treatment of respiratory infections (30). Further studies

reported that zinc sulphate could be used to prevent diarrhea and pneumonia (31, 32). It can also lower the burden of infectious diarrhea in children aged below five years (33). This micronutrient makes children resistant to infectious diseases like influenza (34). Yousefichaijan et al. reported that zinc supplementation with a dosage of 1 mg/kg/day along with antibiotic treatment could notably improve urinary symptoms such as dysuria and frequency (26). These results further confirm our findings. A study by Mohsenpour et al. on female adults was also in line with our outcomes since they reported that females with zinc deficiency are more susceptible to recurrent UTIs compared to those having normal zinc levels (35).

This finding supports that serum level of zinc is not only important in immune regulation of children, but also is a key factor in preventing recurrent UTI in adult females. Our study was among the few investigations on the role of the zinc deficiency in urinary tract infections, which could strongly associate zinc deficiency with the risk of UTI. However, it had some limitations. First, our study groups were not well-matched and showed significant differences in their demographic characteristics, which we tackled this shortcoming using logistic regression for adjustment. Furthermore, we assessed only children <5 years old, and other age ranges were not assessed, which can be a limitation as well.

5- CONCLUSION

Our results showed that zinc deficiency is strongly associated with the risk of UTI, as the serum zinc level was significantly lower in UTI patients. Zinc levels of lower than 70 µg/dl can potentially put children at an eight-fold risk for the development of UTI. However, zinc deficiency may be a result of cytokine release in infectious diseases like UTI.

Further, investigations are needed to complete the results of this study.

6- CONFLICT OF INTEREST: None.

7- REFERENCES

1. Yousefi P, Dorreh F, Gazerani N. Effect of ablution the genital area on result of urine culturing among 3-12 years old girls referring to Amir Kabir hospital, Arak, Iran. *Iranian Journal of Clinical Infectious Diseases*. 2010;5(3):133-6.
2. Schweich P. *Fever in young infants*. Oski's Pediatrics 4th ed Philadelphia: Lippincott, Williams and Wilkins. 2006:701-2.
3. Salo J, Ikäheimo R, Tapiainen T, Uhari M. Childhood urinary tract infections as a cause of chronic kidney disease. *Pediatrics*. 2011;128(5):840-7.
4. Riccabona M. Urinary tract infections in children. *Current opinion in urology*. 2003;13(1):59-62.
5. Yosefi P, Dorreh F. Urinary tract infection due to salmonella in an otherwise healthy child. *Iranian journal of kidney diseases*. 2014;8(2):155.
6. Yousefichaijan P, Kahbazi M, Rasti S, Rafeie M, Sharafkhah M. Vitamin E as adjuvant treatment for urinary tract infection in girls with acute pyelonephritis. *Iranian journal of kidney diseases*. 2015;9(2):97.
7. Chaijan PY, Sharafkhah M. A comparison between bacterial resistance to common antibiotics in breast-fed and bottle-fed female infants with urinary tract infection. *Archives of Clinical Infectious Diseases*. 2012;7(4):113-5.
8. Yousefi P, Cyrus A, Moghaddasi Z, Dorreh F, Aravand A. The frequency of recurrence of urinary tract infection (UTI) in 1-month to 12-year-old children without congenital abnormalities referred to Arak Amir Kabir Hospital. *ZUMS journal*. 2011;19(76):66-76.
9. Taneja N, Chatterjee SS, Singh M, Singh S, Sharma M. Pediatric urinary tract infections in a tertiary care center from north India. *Indian journal of medical research*. 2010;131(1):101-6.

10. Freedman AL, Project UDiA. Urologic diseases in North America Project: trends in resource utilization for urinary tract infections in children. *The Journal of urology*. 2005;173(3):949-54.
11. Williams G, Craig JC. Long- term antibiotics for preventing recurrent urinary tract infection in children. *Cochrane Database of Systematic Reviews*. 2019(4).
12. Leroy S, Vantalou S, Larakeb A, Ducou-Le-Pointe H, Bensman A. Vesicoureteral reflux in children with urinary tract infection: comparison of diagnostic accuracy of renal US criteria. *Radiology*. 2010;255(3):890-8.
13. Noorbakhsh S, Nia SJ, Movahedi Z, Ashouri S. Does the Trace Element Deficiency (Vit A, D & Zinc) Have Any Role in Vulnerability to Urinary Tract Infection in Children: A Case-Control Study: Tehran, Iran. *The Open Urology & Nephrology Journal*. 2019;12(1).
14. Gammoh N, Rink L. Zinc in infection and inflammation. *Nutrients*. 2017;9(6):624.
15. Brunton LL, Knollmann B, Hilal-Dandan RG. *Gilman's the pharmacological basis of therapeutics*. new York City. USA: McGraw-hill Education; 2018.
16. Kliegman RM, Md KM, Md HB, Jenson M, Behrman RE. MD. *Pediatrics Nutrition and Nutritional Disorders*. Nelson Essentials of Pediatrics. 2006:532-5.
17. Bohan AJ. Antibacterial Activity of Zinc Oxide Nano Particles against Bacteria Isolated from Infants with Urinary Tract Infection. *Al-Mustansiriyah Journal of Science*. 2018;29(2):34-42.
18. Caulfield LE, Black RE. Zinc deficiency. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. 2004;1:257-80.
19. Mohsenpour B, Ahmadi A, Baneh AM, Hajibagheri K, Ghaderi E, Afrasiabian S, et al. Relation between serum zinc levels and recurrent urinary tract infections in female patients: A case-control study. *Medical journal of the Islamic Republic of Iran*. 2019;33:33.
20. Mahyar A, Ayazi P, Farzadmanesh S, Oveisi S, Chegini V, Esmacily S. The role of zinc in acute pyelonephritis. *Le Infezioni in Medicina*. 2015.
21. Javadi Nia S, Noorbakhsh S, Izadi A, Soheyli pour F, Tabatabaei A, Shokrollahi MR. Comparison of vitamin A, D & zinc serum levels between children with urinary tract infection and control group in two University Hospital. *Tehran University Medical Journal*. 2013;71(4):244-9.
22. Okarska-Napierała M, Wasilewska A, Kuchar E. Urinary tract infection in children: Diagnosis, treatment, imaging—Comparison of current guidelines. *Journal of pediatric urology*. 2017;13(6):567-73.
23. Kassu A, Yabutani T, Mahmud Z, Mohammad A, Nguyen N, Huong B, et al. Alterations in serum levels of trace elements in tuberculosis and HIV infections. *European journal of clinical nutrition*. 2006;60(5):580.
24. Brown KH. Effect of infections on plasma zinc concentration and implications for zinc status assessment in low-income countries. *The American journal of clinical nutrition*. 1998;68(2):425S-9S.
25. Abrams S, Motil K, Hoppin A. Zinc deficiency and supplementation in children and adolescents. *Uptodate Wellesley*. 2007;15(3).
26. Yousefichaijan P, Naziri M, Taherahmadi H, Kahbazi M, Tabaei A. Zinc supplementation in treatment of children with urinary tract infection. *Iranian journal of kidney diseases*. 2016;10(4):213.
27. Cuevas LE, Koyanagi A. Zinc and infection: a review. *Annals of Tropical Paediatrics*. 2005;25(3):149-60.
28. Yousefi P, Moghaddasi Z, Tabaei A. Therapeutic effects of zinc supplementation in children with urinary tract infection. *Koomesh*. 2011;12(2):204-8.
29. Hensley C, Davidson R. Reduction in duration of lower Respiratory tract infection by zinc gluconate in a double blind study. *Virol*. 2005;25:20-4.
30. Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults.

The American journal of medicine. 2001;111(2):103-8.

31. Lazzerini M, Gray D. Oral zinc for treating diarrhoea in children. Commentary. International journal of epidemiology. 2008;37(5):938-40.

32. Rahman MJ, Sarker P, Roy SK, Ahmad SM, Chisti J, Azim T, et al. Effects of zinc supplementation as adjunct therapy on the systemic immune responses in shigellosis. The American journal of clinical nutrition. 2005;81(2):495-502.

33. Sabri M, Houle S, Dozois CM. Roles of the extraintestinal pathogenic Escherichia

coli ZnuACB and ZupT zinc transporters during urinary tract infection. Infection and immunity. 2009;77(3):1155-64.

34. Sandstead HH, Prasad AS. Zinc intake and resistance to H1N1 influenza. American journal of public health. 2010;100(6):970.

35. Mohsenpour B, Ahmadi A, Mohammadi Baneh A, Hajibagheri K, Ghaderi E, Afrasiabian S, et al. Relation between serum zinc levels and recurrent urinary tract infections in female patients: A case-control study. Medical journal of the Islamic Republic of Iran. 2019;33:33-.