İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2022;22(3):166-171
DOI: 10.26650/jchild.2022.1086003

RESEARCH ARTICLE / *ARAŞTIRMA MAKALESİ*

The Association Between Serum and Urine Zinc Concentrations and Recurrent Urinary Tract Infections in Children

Çocuklarda Tekrarlayan İdrar Yolu Enfeksiyonlarının Serum ve İdrar Çinko Konsantrasyonları İle İlişkisi

Yüksel Hakan Aydoğmuş[1], Aslı Çelebi Tayfur[2], Aysun Çatlık Yılmaz[2], Bahar Büyükkaragöz[2], Sibel Tekgündüz[3]

[1]University of Health Sciences, Keçiören Training and Research Hospital, Department of Pediatrics, Ankara, Turkiye
[2]University of Health Sciences, Keçiören Training and Research Hospital, Department of Pediatric Nephrology, Ankara, Turkiye
[3]University of Health Sciences, Keçiören Training and Research Hospital, Department of Pediatric Hematology, Ankara, Turkiye

ORCID ID: Y.H.A. 0000-0003-2978-8738; A.Ç.T. 0000-0002-6280-4587; A.Ç.Y. 0000-0003-0774-4419; B.B. 0000-0002-6342-1975; S.T. 0000-0003-4937-1681

Citation/Atıf: Aydogmus YH, Celebi Tayfur A, Catlık Yilmaz A, Buyukkaragoz B, Tekgunduz S. The association between serum and urine zinc concentrations and recurrent urinary tract ınfections in children. Çocuk Dergisi - Journal of Child 2022;22(3):166-171. https://doi.org/10.26650/jchild.2022.1086003

ABSTRACT

Objective: Two major host factors in the pathogenesis of urinary tract infection are a defect in innate immune responses and a decrease in urothelial barrier function (UTI). Even in the cases of moderate zinc deficiency, innate and adaptive immune system functions are impaired. The aim of this study was to assess the association between serum zinc concentration, urinary zinc/creatinine ratio, and recurrent UTIs in children.
Methods: In this study, children with recurrent UTIs and healthy children were enrolled. The patient group was divided into subgroups based on the nature of recurrent UTIs. Group 1 consisted of patients who had had ≥2 acute upper UTIs or 1 episode of upper UTI plus ≥1 episode of lower UTI. Group 2 consisted of the patients who had had ≥3 acute lower UTIs but no acute upper UTIs. The demographic characteristics, serum zinc levels, and urine zinc/creatinine ratios of the patients with recurrent UTIs were compared to those of the control group.
Results: Thirty-three patients with recurrent UTIs and 33 healthy children were enrolled in the study. The mean serum zinc level and mean urine zinc/creatinine ratio of patients with recurrent UTIs were 6.6±1.66 umol/l and 16.44±13.04 umol/g, respectively. There was no statistically significant difference between patients and controls and between patients in Group 1 and patients in Group 2 in terms of serum zinc concentration and urine zinc/creatinine ratio, respectively.
Conclusion: Further studies are needed to identify the impact of zinc deficiency on the recurrence of UTI in children.

Keywords: Children, recurrent urinary tract infection, serum zinc concentration, spot urine zinc/creatinine ratio, zinc

ÖZ

Amaç: Doğal immünite cevabındaki defekt ve ürotelyal bariyerdeki fonksiyon bozukluğu idrar yolu enfeksiyonu patogenezinin iki ana unsurunu oluşturmaktadır. Doğal immunite ve kazanılmış immunitenin fonksiyonları orta derecede çinko eksikliği durumlarında etkilenmektedir. Bu çalışmada çocuklarda serum çinko konsantrasyonu, idrar çinko/kreatinin oranı ve tekrarlayan idrar yolu enfeksiyonları arasındaki ilişkiyi değerlendirmeyi amaçladık.
Yöntem: Tekrarlayan idrar yolu enfeksiyonu olan çocuklar ve sağlıklı çocuklar çalışmaya dahil edildi. Hasta grubu tekrarlayan idrar yolu enfeksiyonu alt gruplarına ayrıldı. Grup 1 en az iki veya daha fazla akut üst idrar yolu enfeksiyonu geçiren ya da bir kez üst idrar yolu yanında bir ya da daha fazla alt idrar yolu enfeksiyonu geçiren hastalardan oluşturuldu. Grup 2 ise sadece üç ve üçten fazla alt idrar yolu enfeksiyonu geçiren hastalardan oluşturuldu. Kontrol grubu ile tekrarlayan idrar yolu enfeksiyonu tanısı alan hastalar demografik özellikleri ve serum çinko ve idrar çinko/kreatinin oranlarıyla karşılaştırıldı.
Bulgular: Otuz üç tekrarlayan idrar yolu enfeksiyonu olan hasta ve 33 sağlıklı çocuk çalışmaya dahil edildi. Ortalama serum çinko düzeyi ve ortalama idrar çinko/kreatinin oranı tekrarlayan idrar yolu enfeksiyonu olan hastalarda sırasıyla 6,6±1,66 umol/l ve 16,44±13,04 umol/g saptandı. Kontrol grubu ve hasta grubu arasında anlamlı istatistiksel fark saptanmadı. Grup 1 ve Grup 2 arasında anlamlı istatistiksel fark saptanmadı.
Sonuç: Çinko eksikliğinin çocuklarda tekrarlayan idrar yolu enfeksiyonlarına etkisini saptamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Çinko, tekrarlayan idrar yolu enfeksiyonu, çocuk, serum çinko konsatrasyonu, spot idrar çinko/ kreatinin oranı

Corresponding Author/Sorumlu Yazar: Yüksel Hakan Aydoğmuş **E-mail:** drhakanay@gmail.com

Submitted/Başvuru: 11.03.2022 • **Revision Requested/Revizyon Talebi:** 02.11.2022 • **Last Revision Received/Son Revizyon:** 03.11.2022 • **Accepted/Kabul:** 04.11.2022 • **Published Online/Online Yayın:** 29.12.2022

INTRODUCTION

The essential trace element zinc is an metal moiety of many enzymes required for structural, catalytic and biochemical functions as well as the formation and maintenance of proteins and the regulation of gene expression (1). Infants, children, adolescents, pregnant and lactating women, and the elderly have increased requirements (1,2). It is estimated that more than 20% of individuals worldwide are actually zinc deficient, especially in underdeveloped countries (3). The acquired zinc deficiency can occur as a result of poor dietary intake, dietary phytate rich nutrition, long-term parenteral nutrition without supplementation, malabsorption or excessive loss secondary to gastrointestinal disorders, chronic diarrhea, intestinal fistulae, chronic diuretic use and high ostomy outputs (1,2).

Zinc deficiency may present in the form of skin disorders, diarrhea, short stature with impaired development, hypogonadism, cognitive dysfunction, anorexia, impaired taste and smell, altered wound healing, and bacterial infections (1,2). The immune system is highly proliferative, and thus particularly susceptible to zinc deficiency. The innate and adaptive immune system function is impaired even in cases of moderate zinc deficiency (1,2,4). Zinc deficiency is associated with impaired phagocytic function, thymic atrophy, lymphocyte depletion, decreased immunoglobulin production, a reduction in the T4+/T8+ ratio, and decreased interleukin (IL)-2 production (4). Moreover, individuals with zinc deficiency may be vulnerable to certain infections secondary to damage to the epithelial line of defense and reduction in the antioxidant activity (5).

Urinary tract infections (UTIs) are one of the most common bacterial infections in children affecting around 1.7% of boys and 8.4% of girls by the age of seven years (6). A subset of these children (12-30%), will develop recurrent UTIs. Recurrent UTIs in some patients are caused by host defense deficiencies (7). A defect in innate immune responses and urothelial barrier function like secretion of pro-inflammatory cytokines and protective glycoproteins impairment are two main host factors in the pathogenesis of UTIs (8,9). There are few studies in the literature investigating the zinc status in children during UTIs displayed conflicting results so far (5,10-14). We aimed to assess the correlation between serum and urinary zinc concentrations and history of recurrent UTIs in children in this study.

MATERIALS AND METHODS

This study was conducted at Department of Pediatric Nephrology and Department of Pediatrics, University of Health Sciences, Keçiören Training and Research Hospital between March 2017 and September 2017. Patients who were followed-up with recurrent UTIs and healthy children were enrolled in this study.

Patients with chronic diseases (diabetes mellitus, hypertension, chronic kidney disease, nephrotic syndrome, malignancy, obesity, malnutrition, infectious or inflammatory disease), neurogenic bladder, comorbid urinary tract anatomic abnormalities [vesicoureteral reflux (≥grade 3), obstructive uropathy, ureterocele] or dysfunctional elimination syndrome were excluded. Moreover, children who had received glucocorticoids, cytotoxic drugs, zinc supplementation and/or nephrotoxic drugs in the last 6 months and those who had had a UTI diagnosis in the last 1 month, and lastly, children with incomplete toilet training were excluded from the study.

A lower UTI was defined as when urinary symptoms including dysuria, frequency, urgency, malodorous urine, incontinence, haematuria, and suprapubic pain were present without high grade fever and high levels of inflammatory markers in children ≥2 years of age with leukocyturia and a positive urine culture (6). An upper UTI was considered as occuring with the presence of clinical signs of UTI with high grade fever, lumbar or abdominal pain, and high levels of inflammatory markers in children with leukocyturia and a positive urine culture (5, 6). Recurrent UTIs were defined as the presence of ≥2 episodes of an upper UTI, or 1 episode of an upper UTI plus ≥1 episode of a lower UTI or ≥3 episodes of a lower UTI (15).

The patient group was divided into subgroups according to the nature of recurrent UTIs. (Group 1 consisted patients who had had ≥2 acute upper UTIs or 1 episode of upper UTIs plus ≥1 episode of lower UTIs, Group 2 consisted the patients who had had ≥3 acute lower UTIs but no acute upper UTIs). The control group consisted of age and sex-matched healthy children.

Data including age, gender and anthropometric measurements (body weight and height), were noted. Body mass index (BMI) was calculated using the formula: body weight (kg)/height^2 (m) (16). Urinary ultrasound, voiding cystourethrography, and/or 99mTc-dimercaptosuccinic acid (99mTc-DMSA) scintigraphy findings were recorded.

Blood samples obtained by venipuncture and mid stream clean-catch urine samples were collected from patients and controls. The trichloroacetic acid was added to the blood sample to precipitate the proteins and centrifuged at 10000 rpm for 10 minutes. Before the analysis of urine samples, flat glass tubes were washed with hydrochloric acid and then deionized water. The urine samples added to 0.5 ml deproteinized solution were centrifuged at 10000 rpm for 10 minutes. The supernatants of blood and urine samples were frozen in 2 ml samples at below −20°C, and thawed to room temperature immediately prior to zinc level analysis. The measurements of serum and urine zinc levels were performed by the colorimetric method using Abbott C16000 (USA) autoanalyser and Randox Zinc kit (ZincZn CE). All of the urine samples were assayed for creatinine for the purposes of normalization. Creatinine levels of the urine samples were studied by photometric method using Architect C16000 (USA).

The demographic features and the serum zinc levels and urine zinc/creatinine ratios of the patients with recurrent UTIs were compared with those of the control group. The patient groups (Groups 1 and 2) were also compared according to the demographic characteristics as well as the serum zinc levels and urine zinc/creatinine ratios.

Statistical Analysis

All statistical analyses were performed using SPSS (version 22, SPSS Inc., Chicago, IL, USA). To compare continuous variables we used the Student t test or the nonparametric Mann-Whitney U test. Categorical data were presented as the frequency or percentage (%) and continuous data as the mean±SD or median [minimum–maximum]. A p value <0.05 was considered statistically significant.

The study was approved by the the Ethical Committee of University of Health Sciences Ankara Kecioren Training and Research Hospital (22.02.2017/1348). Informed consent was obtained from the legal caregivers of each child before enrollment.

RESULTS

A total of 33 patients (29 females, 4 males) with a mean age of 125±44 months (range: 49-197 months) and 33 healthy children (23 females, 10 males) with a mean age of 132±51 months (range: 49-204 months) were included in this study. There were 16 patients (13 females, 3 males) in Group 1 and 17 patients (16 females, 1 male) in Group 2 (Table 1). There were no statistical differences between Group 1 and Group 2 in terms of gender or number of patients.

Table 1: Group 1 and group 2 gender distribution

	Male	Female	Total
Group 1	3	13	16
Group 2	1	16	17

The mean serum zinc levels and mean urine zinc/creatinine ratios of patients with recurrent UTIs were 6.6±1.66 umol/l (range: 3.1-9.2 umol/l) and 16.44±13.04 umol/g (range: 3.71-51.29 umol/g), respectively. The mean serum zinc levels and mean urine zinc/creatinine ratios of the control group were 7.15±2.16 umol/l (range: 2.9-11.2 umol/l) and 13.8±12.14 umol/g (range: 4.6-70.53 umol/g), respectively (Table 2). The mean serum zinc levels of patient and control groups were lower than the reference values of the commercial kit (reference values for serum zinc level: 9.18-18.4 umol/l).

There was no significant difference between girls and boys with rUTI in serum zinc level and urine zinc/creatinine ratio (p=0.353, p=0.979, respectively). No relationship was observed between BMI and serum zinc level, and between BMI and urine zinc/creatinine ratio within patients with rUTI (p=0.992, r= 0.16 and p=0.781, r=0.05, respectively).

There were no statistically significant differences between patients and controls in respect to serum zinc concentration and urine zinc/creatinine ratio (Table 2, p=0.24 and p=0.45, respectively). There was also no statistically significant difference between patients in Group 1 and Group 2 in serum zinc concentration or urine zinc/creatinine ratio (Table 2, p=0.43 and p=0.49, respectively). No significant difference was detected between patients in Group 1 and controls and between patients in Group 2 and controls in terms of both serum zinc concentration and urine zinc/creatinine ratios (Table 3, p=0.2 and p=0.2; p=0.57 and p=0.97, respectively).

DISCUSSION

Multiple studies have assessed the association of zinc deficiency with infections such as upper and/or lower respiratory tract infections and diarrhea (17-20). Zinc supplementation has been shown to reduce the duration and limit the complications of diarrhea in children by increasing intestinal fluid absorption, supporting mucosal integrity, and enhancing immune response (20). The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommend zinc supplementation in children aged 6 months to 5 years with acute gastroenteritis (21). The efficacy of zinc in community-acquired pneumonia remains controversial. Adjunctive zinc

Table 2: Serum zinc levels and urine zinc/creatinine ratios of children with recurrent urinary tract infections and healthy children

		Mean±std	Range	P value
Serum Zinc Level (umol/l)	**Patient (n=33)**	6.6± 1.66	3.1-9.2	0.242
	Control (n=33)	7.15± 2.16	2.9-11.2	
Urine Zinc/Creatinine Ratio (umol/gr)	**Patient (n=33)**	16.44±13.04	3.71- 51.29	0.453
	Control (n=33)	13.8±12.14	4.6- 70.53	

Table 3: Serum zinc levels and urine zinc/creatinine ratios of children in Group 1 and Group 2

		Mean±std	Range	P value
Serum Zinc Level (umol/l)	**Group 1 (n=16)**	6.35±1.77	3.1-8.7	0.439
	Group 2 (n=17)	6.81±1.57	3.6-9.2	
Urine Zinc/Creatinine Ratio (umol/gr)	**Group 1 (n=16)**	16.21±10.82	4.57-46.85	0.494
	Group 2 (n=17)	16.64±15.17	3.71-51.29	

supplementation failed to show a statistically significant effect on treatment duration and length of hospitalization in many studies (17,18). In our study, although serum zinc levels were found to be lower in the patient group, no statistical difference was found.

There are few studies in the literature which investigate the zinc levels in children with UTIs or the effects of zinc supplementation during UTIs. A case-control study showed lower serum zinc levels in women with recurrent UTIs than in age-matched controls (11). Few other pediatric studies demonstrated lower serum zinc levels in children with active UTIs compared to the controls (12,14). Moreover, Zabihi et al. showed that zinc deficiency increased the risk of UTIs in children by 8 fold (14). Zinc supplementation ameliorated severe dysuria and frequency in children with UTI in a study (13). On the other hand, in the study by Amoori et al., serum zinc levels were not found to be related to febrile UTI recurrences. Therefore, the authors concluded that prescribing zinc supplements to treat or prevent UTIs needs further investigation (10). Similarly, in a randomized, double-blind, placebo-controlled clinical trial performed in children with first nephrolithiasis, adjuvant treatment with zinc was found not to be more effective than consecutive treatment (22). Therefore, the effect of adjuvant zinc in the treatment of nephrolithiasis, which is one of the causes of rUTIs, has not been demonstrated. In addition to adjuvant treatment with zinc, several interventions to prevent UTI recurrences have been tried. The most established and accepted intervention at present is low dose long-term antibiotic prophylaxis. Although showing some promise, alternative interventions, such as Vaccinium Macrocarpon (cranberry), *Lactobacillu*s and Probiotics, circumcision, surgical management of vesicoureteral reflux, deliberate colonization of the urinary tract with *Escherichia-coli* (*E. coli)* 83972, treating constipation and dysfunctional voiding, administration of synthetic substitutes that reproduce natural surface glycosaminoglycan(s) anti-adherence effect on uroepithelial cells and *E. coli* isolate NU14 DeltawaaL as a candidate for developing a live-attenuated vaccine, have not provided a definitive effective answer (23).

Plasma or serum zinc levels are under tight homeostatic control and very sensitive to inflammation, cytokines and hormones (24,25). Individual age, infections, stress, hypoalbuminemia, time of day and recent food intake can modify circulating zinc levels (24-29). Experimental studies have shown hypozincemia occur shortly after infection or following injection of bacterial endotoxin probably due to an internal redistribution of zinc (25,26). In our study, patients with chronic inflammatory diseases or infections as well as underlying renal abnormalities were not included in order to exclude the effects of these conditions on zinc levels. Indeed, the zinc status of the patients were determined at least 1 month after a UTI.

To our knowledge, our study is the first study evaluating zinc status in children with recurrent UTIs. Moreover, urine zinc/creatinine ratios were assessed for the first time in children with rUTIs. The measurement of zinc in a sample of urine collected during 24 hours can be helpful for diagnosis of zinc deficiency in healthy individuals (30). However, to our knowledge, there is only one study in the literature investigating the role of urine zinc/creatinine ratio in determining zinc status in the body. De Portela et al suggested that urine zinc/creatinine ratios could be an indicator of dietary zinc intake in healthy women (31).

Mean serum zinc levels of the patient groups and control group were lower than the reference values of the commercial kit in our study. Dietary factors may be responsible for the decreased availability of zinc; phytate in cereals markedly impairs the absorption of both zinc and iron (30,32). Low dietary zinc intake and zinc deficiency are common, particularly in countries with low socioeconomic status (3,32). Similarly, zinc deficiency was observed in 27.8% of the cases in a study including 1063 healthy children aged 5-16 years living in the Central Anatolia region (33). Turkish soil selenium (Se) and zinc concentrations are lower than in other countries. Wheat, like other cereal species, has very low concentration and availability of zinc. In Turkey, wheat is still the major source of daily calorie intake (33,34). The age distribution of the patients and healthy children enrolled in the study was in the period where nutritional needs were high. Furthermore, dietary factors like high consumption of wheat and other cereals might be the major cause of zinc deficiency in our study group.

Gender factor demonstrated no significant effect on serum zinc level and urine zinc/creatinine ratio of the patients in our study. However, the number of male patients was very low compared to that of female patients. Few studies have reported that males are more vulnerable to zinc deficiency than females, presumably because of a higher requirement for zinc due to a higher growth rate and a greater proportion of muscle per kilogram body weight, as muscle contains a higher content of zinc than fat (35, 36). Comprehensive epidemiological studies are required to assess the gender factor in association with zinc levels in body fluids and/or tissues.

Some studies have shown a significant decrease in erythrocyte and hair zinc levels in patients with overweight/obesity (37-39). In contrast, urinary zinc level was found to be higher in these patients (39). Cortisol induces the gene expression of metallothionein and the zinc transporter Zip14, which favors the redistribution of plasma zinc for various tissues such as hepatic and adipose, leading to the development of hypozincemia in obesity (37). Children with obesity were not included in our study. Nevertheless, there was no correlation between BMI and serum zinc concentrations and urine zinc/creatinine ratio in the patients with recurrent UTIs.

It is known that effects of zinc deficiency on specific functions often become apparent before plasma zinc levels decrease. However, plasma or serum zinc determination remain the most informative and easy to use index in large-scale studies (40). Urinary zinc excretion and hair zinc can provide useful information on zinc status in zinc-supplemented persons, but whether these reflect zinc status in depleted persons is not clear (41). It is generally recommended to obtain

blood samples early in the morning from fasting individuals for measuring plasma zinc concentrations. Zinc levels in the body of patients and controls were assessed with serum zinc levels and urine zinc/creatinine ratio in our study. We measured serum zinc levels and spot urine zinc and creatinine levels only once in each child. Moreover, we did not query the dietary factors including consumption proportion of cereals in daily nutrition charts or the time interval between recent food intake and blood and urine sampling. These situations can be considered as a limitation of our study. The low mean serum zinc levels in patient and control groups might be attributed to poor dietary intake, but improper sample collecting time or increased tissue zinc uptake while growing up might have also contributed. Another limitation of this cross-sectional study is the rather small numbers of children with recurrent UTIs and healthy controls.

CONCLUSIONS

Our study is the first cross-sectional study investigating serum zinc concentrations and urinary zinc excretions in children with history of recurrent UTI. Our study failed to show a significant difference of serum zinc level and urine zinc/creatinine ratio between patients with recurrent UTIs and the control group. Moreover, these levels did not significantly differ between patients with history of upper or lower UTIs. We believe that further studies are needed to confirm these preliminary results and identify impact of zinc deficiency on reoccurrence of UTI in children.

Ethics Committee Approval: The study was approved by the the Ethical Committee of University of Health Sciences Ankara Kecioren Training and Research Hospital (22.02.2017/1348).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Y.H.A., A.Ç.Y.; Data Acquisition- A.Ç.T., B.B.; Data Analysis/Interpretation- S.T.; Drafting Manuscript- Y.H.A., A.Ç.Y., B.B.; Critical Revision of Manuscript- A.Ç.T., S.T.; Final Approval and Accountability- Y.H.A., A.Ç.T., A.Ç.Y., B.B., S.T.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

REFERENCES

1. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. J Res Med Sci 2013;18(2):144-57.
2. Yanagisawa H. Zinc deficiency and clinical practice--validity of zinc preparations. Yakugaku Zasshi 2008;128(3):333-9.
3. Gupta S, Brazier AKM, Lowe NM. Zinc deficiency in low- and middle-income countries: prevalence and approaches for mitigation. J Hum Nutr Diet 2020;33(5):624-43.
4. Wessels I, Fischer HJ, Rink L. Dietary and Physiological Effects of Zinc on the Immune System. Annu Rev Nutr 2021;41:133-75.
5. Mahyar A, Ayazi P, Farzadmanesh S, Sahmani M, Oveisi S, Chegini V, et al. The role of zinc in acute pyelonephritis. Infez Med 2015;23(3):238-42.
6. Tullus K, Shaikh N. Urinary tract infections in children. Lancet 2020;395(10237):1659-68.
7. Becknell B, Schober M, Korbel L, Spencer JD. The diagnosis, evaluation and treatment of acute and recurrent pediatric urinary tract infections. Expert Rev Anti Infect Ther 2015;13(1):81-90.
8. Chowdhury P, Sacks SH, Sheerin NS. Minireview: functions of the renal tract epithelium in coordinating the innate immune response to infection. Kidney Int 2004;66(4):1334-44.
9. Svanborg C. Urinary tract infections in children: microbial virulence versus host susceptibility. Adv Exp Med Biol 2013;764:205-10.
10. Amoori P, Valavi E, Fathi M, Sharhani A, Izadi F. Comparison of Serum Zinc Levels Between Children With Febrile Urinary Tract Infection and Healthy Children. Jundishapur Journal of Health Sciences 2021;13.
11. 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. Med J Islam Repub Iran 2019;33:33.
12. Noorbakhsh S, Nia S, 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;12:23-6.
13. Yousefichaijan P, Naziri M, Taherahmadi H, Kahbazi M, Tabaei A. Zinc Supplementation in Treatment of Children With Urinary Tract Infection. Iran J Kidney Dis 2016;10(4):213-6.
14. Zabihi F, Mostafavi M, Esmaeili M, Issapour Cheshani M. Investigating the Effect of Zinc Deficiency on the Risk of Urinary Tract Infection in Children. International Journal of Pediatrics 2020;8(9):11959-66.
15. National Collaborating Centre for Ws, Children's H. National Institute for Health and Clinical Excellence: Guidance. Urinary Tract Infection in Children: Diagnosis, Treatment and Long-term Management. London: RCOG Press Copyright © 2007, National Collaborating Centre for Women's and Children's Health.; 2007.
16. Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. J Chronic Dis 1972;25(6):329-43.
17. Fataki MR, Kisenge RR, Sudfeld CR, Aboud S, Okuma J, Mehta S, et al. Effect of zinc supplementation on duration of hospitalization in Tanzanian children presenting with acute pneumonia. J Trop Pediatr 2014;60(2):104-11.
18. Sakulchit T, Goldman RD. Zinc supplementation for pediatric pneumonia. Can Fam Physician 2017;63(10):763-5.
19. van Wouwe JP, van Gelderen HH, Bos JH. Subacute zinc deficiency in children with recurrent upper respiratory tract infection. Eur J Pediatr 1987;146(3):293-5.
20. Zou TT, Mou J, Zhan X. Zinc supplementation in acute diarrhea. Indian J Pediatr 2015;82(5):415-20.
21. World Health O. Clinical management of acute diarrhoea: WHO/UNICEF joint statement. Geneva: World Health Organization; 2004.
22. Yousefichaijan P, Cyrus A, Dorreh F, Rafeie M, Sharafkhah M, Frohar F, et al. Oral Zinc Sulfate as Adjuvant Treatment in Children With Nephrolithiasis: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Iran J Pediatr 2015;25(6):e1445.

23. Tewary K, Narchi H. Recurrent urinary tract infections in children: Preventive interventions other than prophylactic antibiotics. World J Methodol 2015;5(2):13-9.
24. Brown KH, Rivera JA, Bhutta Z, Gibson RS, King JC, Lönnerdal B, et al. International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull 2004;25(1 Suppl 2):S99-203.
25. Gammoh NZ, Rink L. Zinc in Infection and Inflammation. Nutrients 2017;9(6).
26. Gaetke LM, McClain CJ, Talwalkar RT, Shedlofsky SI. Effects of endotoxin on zinc metabolism in human volunteers. Am J Physiol 1997;272(6 Pt 1):E952-6.
27. Hambidge KM, Goodall MJ, Stall C, Pritts J. Post-prandial and daily changes in plasma zinc. J Trace Elem Electrolytes Health Dis 1989;3(1):55-7.
28. Hotz C, Lowe NM, Araya M, Brown KH. Assessment of the trace element status of individuals and populations: the example of zinc and copper. J Nutr 2003;133(5 Suppl 1):1563s-8s.
29. Katayama K, Kawaguchi T, Shiraishi K, Ito T, Suzuki K, Koreeda C, et al. The Prevalence and Implication of Zinc Deficiency in Patients With Chronic Liver Disease. J Clin Med Res 2018;10(5):437-44.
30. Johnson PE, Hunt CD, Milne DB, Mullen LK. Homeostatic control of zinc metabolism in men: zinc excretion and balance in men fed diets low in zinc. Am J Clin Nutr 1993;57(4):557-65.
31. de Portela ML, Weisstaub AR. Basal urinary zinc/creatinine ratio as an indicator of dietary zinc intake in healthy adult women. J Am Coll Nutr 2000;19(3):413-7.
32. Prasad AS. Zinc deficiency. Bmj 2003;326(7386):409-10.
33. Vuralli D, Tumer L, Hasanoglu A. Zinc deficiency in the pediatric age group is common but underevaluated. World J Pediatr 2017;13(4):360-6.
34. Aras N, Nazli A, Zhang W, Chatt A. Dietary intake of zinc and selenium in Turkey. Journal of Radioanalytical and Nuclear Chemistry 2001;249:33-7.
35. Gibson RS, Manger MS, Krittaphol W, Pongcharoen T, Gowachirapant S, Bailey KB, et al. Does zinc deficiency play a role in stunting among primary school children in NE Thailand? Br J Nutr 2007;97(1):167-75.
36. Smit Vanderkooy PD, Gibson RS. Food consumption patterns of Canadian preschool children in relation to zinc and growth status. Am J Clin Nutr 1987;45(3):609-16.
37. Morais JBS, Severo JS, Beserra JB, de Oiveira ARS, Cruz KJC, de Sousa Melo SR, et al. Association Between Cortisol, Insulin Resistance and Zinc in Obesity: a Mini-Review. Biol Trace Elem Res 2019;191(2):323-30.
38. Suliburska J, Cofta S, Gajewska E, Kalmus G, Sobieska M, Samborski W, et al. The evaluation of selected serum mineral concentrations and their association with insulin resistance in obese adolescents. Eur Rev Med Pharmacol Sci 2013;17(17):2396-400.
39. Tinkov AA, Skalnaya MG, Ajsuvakova OP, Serebryansky EP, Chao JC, Aschner M, et al. Selenium, Zinc, Chromium, and Vanadium Levels in Serum, Hair, and Urine Samples of Obese Adults Assessed by Inductively Coupled Plasma Mass Spectrometry. Biol Trace Elem Res 2021;199(2):490-9.
40. Hess SY, Peerson JM, King JC, Brown KH. Use of serum zinc concentration as an indicator of population zinc status. Food Nutr Bull 2007;28(3 Suppl):S403-29.
41. King JC, Brown KH, Gibson RS, Krebs NF, Lowe NM, Siekmann JH, et al. Biomarkers of Nutrition for Development (BOND)-Zinc Review. J Nutr 2015;146(4):858s-85s.