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Review

Low Serum Zinc Level is Associated with Urinary Tract Infection in Children: A Systematic Review and Meta-analysis

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ABSTRACT

To review the relationship between serum zinc (Zn) levels and urinary tract infections (UTIs) in children. Databases with published papers from 2015 up to July 2025 from PubMed Central, SpringerLink, EBSCOhost, and ScienceDirect were used in this investigation. The data were processed quantitatively using the Review Manager 5.4 software application. The risk of bias qualitatively was assessed using the New Ottawa Scale and Agency for Health Research and Quality requirements as the threshold. Four out of five studies (80%) reported that lower levels of Zn were found in children with UTIs compared to control subjects. Our analysis results showed that there was an inverse correlation between serum Zn levels and UTIs in children [p<0.0001; mean difference: -10.49, 95% confidence interval (-13.32 to -7.66)]. Low serum Zn levels correlated significantly with UTIs in children.

Keywords: Zinc, urinary tract infection, children

Introduction

Trace elements such as zinc (Zn) are essential for cell proliferation and biochemical reactions in the body. Zn has a significant impact on gene transcription, protein metabolism, lipid metabolism, nucleic acid metabolism, and complement activity (1). Skeletal muscle (approximately 60%), bone (about 30%), skin (about 5%, predominantly in the epidermis), and liver (about 5%) have the greatest tissue Zn concentrations. Additionally, blood serum contains a small quantity of Zn (about 0.1% of total Zn reserves). However, the element is not specifically stored in the human body (2).

Zn homeostasis is regulated by transcriptional pathways and transmembrane transport, which in part, shield the body from the negative consequences of too much or too little Zn in the diet (2). The human body cannot produce Zn, so sufficient levels must be obtained externally. The amount of Zn consumed in food rises with age, from 2 mg/day for children to 9 mg/day for adult females and 11 mg/day for adult men, which makes Zn supplementation now a common practice in primary healthcare services in many developing regions' health policy decisions (3).

Zn deficiency (ZnD) is a health problem with up to 17.3% of the world's population and up to 30% of those

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in South Asia potentially being at risk (4). ZnD usually manifests as growth impairment, sexual dysfunction, inflammation, gastrointestinal urinary symptoms, or cutaneous involvement. ZnD triggers thymic atrophy and lymphopenia, which both suppress innate and adaptive immune responses. It hinders macrophage phagocytosis, intracellular killing activity, and cytokine production; neutrophil and natural killer cell host defence; and T and B cell proliferation, cytokine production, and antibody secretion. These consequences lead to an increased susceptibility to a wide range of infectious agents and a longer duration of infection (5).

Urinary tract infection (UTI) is one of the most common infections in childhood. It can impact either the lower urinary tract (cystitis) or the upper urinary tract (pyelonephritis). Unfortunately, especially in newborns and young children, it may be challenging to differentiate between cystitis and pyelonephritis based solely on clinical symptoms and indicators (6). It is important to diagnose and treat UTIs early in order to avoid more complications.

Around 5% of girls who have not had their periods and 20% of boys get a UTI during the first two months of life in febrile newborns. Uncircumcised males have a ten-fold to twelve-fold higher risk of UTI during their first six months (7). Through to the time they reach seven years old, 1.7% of boys and 7.8% of girls, on average, are predicted to have experienced a UTI. Of the 16-year-old populations, 3.6% of boys and 11.3% of girls will have experienced a UTI at some stage, while the recurrence rates range from 30% to 50% on average (8-10). Inadequate host defences may be the reason for recurrent UTIs (a UTI occurring after the resolution of a previous episode) in certain patients (11). The two major host variables in the pathophysiology of UTIs include a failure in innate immune responses and urothelial barrier function, such as pro-inflammatory cytokine production or protective glycoprotein impairment (12). Thus far, the literature has presented contradictory results from the limited number of studies which have examined children's Zn status during UTIs (13-17). Therefore, evaluating the association between serum Zn levels and pediatric UTIs was the aim of this investigation.

Materials and Methods

The authors independently found articles published from 2015 until July 2025 on PubMed Central, SpringerLink, EBSCOhost, and ScienceDirect, by using titles and abstracts. There was also a manual assessment of the references for every eligible study.

This evidence-based study is structured on the Preferred Reporting Item for Systematic Review and Meta-study 2020 statement. We used a word mesh combining "Zn," "UTI" and "pediatric" to search for the journals used in this study. Overall, the researchers searched for and evaluated the papers included independently. Every issue which arose during the literature search was resolved by consensus. Result journals which mentioned the relationship between serum Zn levels and UTIs were included in this study. We detailed (participants, exposure, comparison and outcome): P: children with UTI, E: low serum Zn levels, C: control subjects, O: incidences of UTI in children. Four conditions had to be met to be included in this systematic review study: (1) observational studies investigating the association between serum Zn levels and UTIs, including case-controls, cross-sectional design, and cohorts; (2) child-related research; (3) non-recurrent UTI; (4) study in human. We did not include conference abstracts, letters, editorial comments, reviewed publications, or items which were published more than 10 years ago in our selection.

Every researcher extracted data individually from the verified articles, compiling it into an Excel spreadsheet. In order to reach a final decision, additional researchers settled any disagreements. The primary author, location, year of publication, number of subjects and population, study design, type of UTIs, diagnostic approach of the studies, and a description of the relationship between serum Zn levels and pediatric UTIs were the data which we gathered from each study.

The Newcastle-Ottawa Scale (NOS) was used to assess the included studies' risk of bias. In order to conduct case-control and cross-sectional research, we examined eight domains: non-response rate, exposure determination, case representativeness, control selection, control definitions, case-control comparability, and adequate case definition (18). Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, comparability of cohorts on the basis of the design or analysis controlled for confounders, assessment of outcome, long enough follow-up for outcomes to occur and adequacy of follow-up of cohorts were the eight domains for cohort studies which we evaluated. The Agency for Health Research and Quality criteria were used as a criterion to assess the quality of the studies (19).

Data on serum Zn (µg/dL) were collected both from the children with UTIs and the controls. The findings from individual studies are summarized in the summary tables, and

data for these variables were pooled as relative frequencies and presented as means and standard deviations. Data analysis and graphical plotting was performed using the Review Manager 5.4 software application. Publication bias was assessed using funnel plot visualization and interpreted qualitatively when fewer than 10 studies were included.

Results

The database searches and screening processes are shown in Figure 1. A total of 687 articles (PubMed Central: 72, SpringerLink: 290, EBSCOhost: 86, and ScienceDirect: 239) were identified in accordance with the key terms from the published literature. Of these, 435 articles were excluded before screening, and the remaining 256 articles were further screened by their title and abstract. Four out of five studies (80%) reported that lower levels of Zn were found in children with UTI compared with the control subjects. Only one study stated that the mean difference (MD) between the controls and the cases was not statistically significant (p=0.98). From that one study, the findings may have been related to the weights in the various age groups, gestational age, the severity of leukocytosis and thrombocytosis, the severity of increases in erythrocyte sediment rates or C-reactive protein (CRP), or the durations of hospitalization. The details of the studies included are shown in Table I.

Four studies were further reviewed quantitatively. One research from the prior qualitative evaluation was excluded due to differences in the unit measurements of serum Zn levels. We compared a total of 212 children with UTIs and 212 children as control. This figure shows the pooled analysis of four studies [Mahyar et al. (13), Zabihi et al. (17), Amoori et al. (20), Seifollahi et al. (21)] comparing MDs between those children with UTI and the controls. The pooled MD was -10.49 (95% confidence interval: -13.32, -7.66), indicating that children with UTIs had significantly lower values compared to the controls. The test for overall effect was statistically significant (Z=7.27, p<0.00001), supporting a strong association. However, there was high heterogeneity among the studies (I^2= 93%, p<0.00001), suggesting variability in the study results which may have resulted from differences in the study designs, populations, or their measurement methods. The data analysis and graphical plotting is shown in Figure 2.

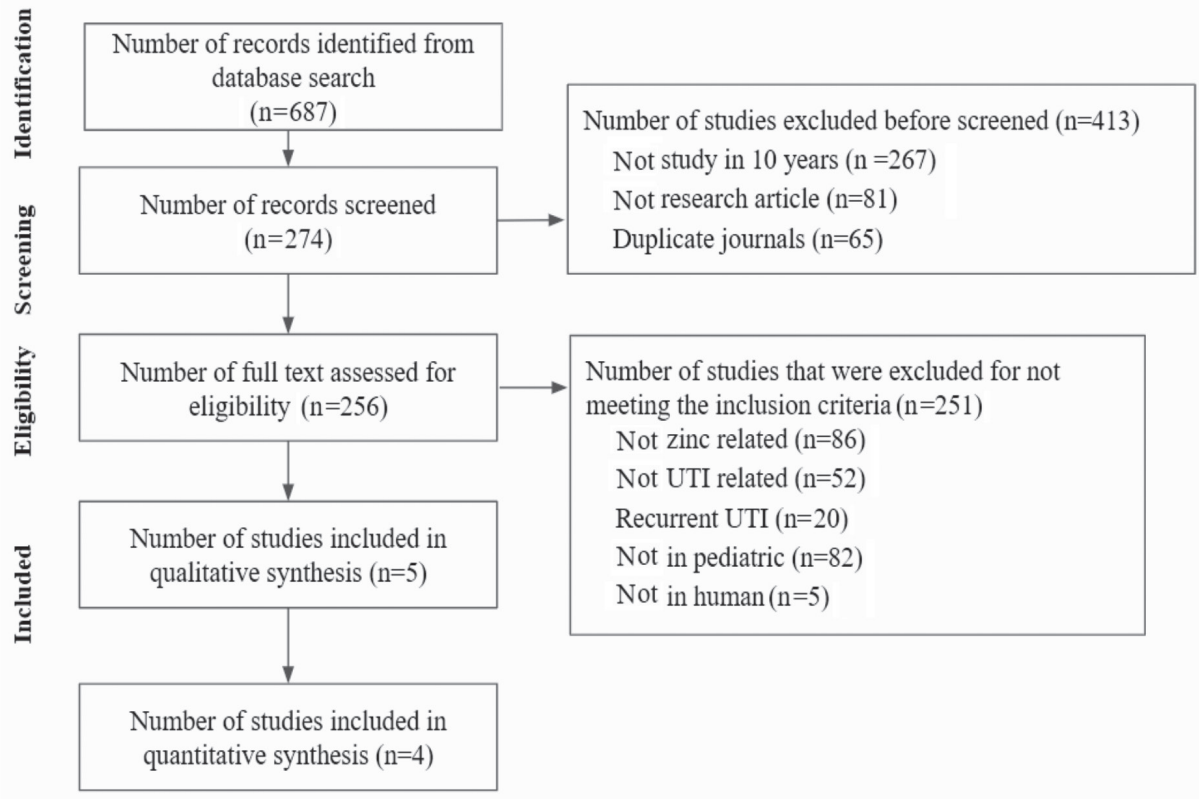

Figure 1. PRISMA study flow diagram

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses, UTI: Urinary tract infection

Table I. Descriptive information for selected research studies regarding the relationship between the levels of serum zinc and urinary tract infections in children

No	Primary author, Year	Population	Study design	Cut-off serum zinc level	Result zinc & UTI
1	Mahyar et al. (13), 2015	120 children (60 cases and 60 controls) aged 12 months-2 years old	Case control, non-RCT	70-120 µg/dL	Serum zinc levels in the case and control groups were 70.73±14.15 and 87.61±12.68 µg/dL, respectively (p=0.001).
2	Zabihi et al. (17), 2020	104 children (52 cases aged 26.5±20.5 months and 52 controls aged 34.3±16.8 months)	Case control, non-RCT	70-120 µg/dL	Serum zinc level was 60.0±17.1 µg/dL in the case group and 83.0±15.7 µg/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).
3	Amoori et al. (20), 2021	120 children (60 children with febrile UTI and 60 healthy children) aged 3 -120 months old	Case control, non-RCT	60-90 g/dL for <1 years old children and 80-110 g/dL for 1 to 10 years old children	Not statistically significant, the mean value was 95.05±11.34 µg/dL in the control group and 94.98±12.24 µg/dL in the case group; (p=0.98).
4	Noorbakhsh et al. (16), 2019	65 children (25 proven UTI cases and 40 controls without infection) aged <5 years old	Cohort study, non-RCT	≥65 µg/dL were considered normal	Lower serum levels for zinc in UTI cases as compared to the normal children (95.43 vs. 106.9 µg/dL; p=0.05).
5	Seifollahi et al. (21), 2024	80 children (40 cases and 40 controls)	Case control, non-RCT	63.8-110 µg/dL	Significant difference between the 2 groups regarding serum zinc levels (p<0.001). Twenty-four children were deficient with (mean ± SD) µg/dL serum level 75.02±56.00 and 7 children were deficient with serum level, 71.40±141.72 for the healthy children.

Diagnostic of UTI in these studies was based on positive urine culture
UTI: Urinary tract infection, RCT: Randomized controlled trial OR: Odds ratio SD: Standard deviation

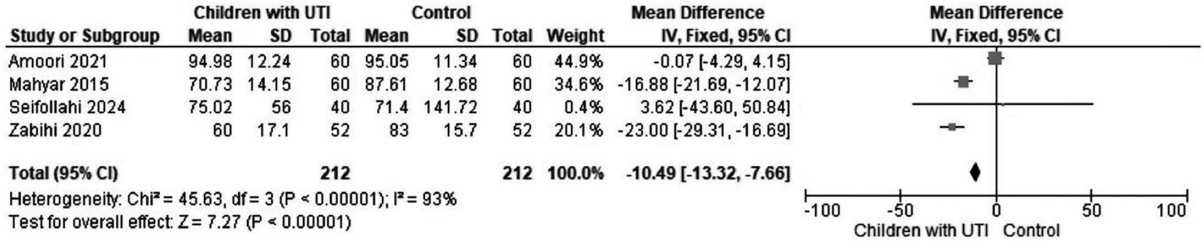

Figure 2. Forest plot of 4 studies assessing the serum zinc levels in children with urinary tract
UTI: Urinary tract infection, SD: Standard deviation, CI: Confidence interval

Finally, five studies were identified for this review. Quality assessment of these studies was performed by NOS. Risk of bias is shown in Table II (case-control study, non-randomized control trial) and in Table III (cohort study, non-randomized control trial). Among the five studies included, two [Mahyar et al. (13), Zabihi et al. (17)] were graded as fair quality due to limitations in selection and comparability. For Mahyar et al. (13) although UTI diagnosis was rigorous, the lack of adjustment for nutritional and socio-economic confounders limited comparability. Similarly, Zabihi et al. (17) reported significant baseline differences between the cases and the controls (age, sex, weight), and despite adjustments, these imbalances introduced residual bias. In contrast, three studies [Amoori et al. (20), Noorbakhsh et al. (16), and Seifollahi et al. (21)] achieved good quality, with more balanced groups and stricter exclusions of confounding factors, thereby fulfilling most NOS criteria and so resulting in a lower risk of bias. Overall, the evidence base appears reasonably strong, with a low-to-moderate risk of bias, although further well-designed studies with broader controls of potential confounding factors would strengthen the conclusions.

Table II. Risk of bias of the case-control studies included. Newcastle-Ottawa Scale and the Agency for Health Research and Quality guidelines were used to evaluate the risk of bias and establish the threshold for defining the research quality

Study	Selection				Comparability	Exposure			Interpretation†
	1	2	3	4	5	6	7	8	
Mahyar et al. (13), 2015	*		*		*	*	*	*	Fair quality
Zabihi et al. (17), 2020	*		*		*	*	*	*	Fair quality
Amoori et al. (20), 2021	*		*	*	*	*	*	*	Good quality
Seifollahi et al. (21), 2024	*		*	*	*	*	*	*	Good quality

1) Is the case definition adequate?
2) Representative of the cases,
3) Selection of controls,
4) Definition of controls,
5) Comparability of cases and controls on the basis of the design or analysis controlled for cofounders,
6) Ascertainment of exposure,
7) Same method of ascertainment for cases and controls,
8) Non-response rate.

†: Thresholds for converting the Newcastle-Ottawa Scales to AHRQ standards (good, fair, and poor):
• Good quality: 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Fair quality: 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Poor quality: 0 or 1 star in the selection domain or 0 stars in the comparability domain or 0 or 1 star in the outcome/exposure domain.
AHRQ: Agency for Healthcare Research and Quality

Table III. Risk of bias of the cohort study included. Newcastle-Ottawa Scale and the Agency for Health Research and Quality guidelines were used to evaluate the risk of bias and establish the threshold for defining the research quality

Study	Selection				Comparability	Exposure			Interpretation†
	1	2	3	4	5	6	7	8	
Noorbakhsh et al. (16), 2019	*		*	*	*	*	*	*	Good quality

1) Representativeness of the exposed cohort,
2) Selection of the non-exposed cohort,
3) Ascertainment of exposure,
4) Demonstration that outcome of interest was not present at start of study,
5) Comparability of cohorts on the basis of the design or analysis controlled for confounders,
6) Assessment of outcome,
7) Was follow-up long enough for outcomes to occur?
8) Adequacy of follow-up of cohorts.

†: Thresholds for converting the Newcastle-Ottawa Scales to AHRQ standards (good, fair, and poor):
• Good quality: 3 or 4 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Fair quality: 2 stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain.
• Poor quality: 0 or 1 star in the selection domain or 0 stars in the comparability domain or 0 or 1 star in the outcome/exposure domain.
AHRQ: Agency for Healthcare Research and Quality

Discussion

Many children suffer from UTIs, which are linked to serious morbidity. The prevalence rate is up to 30%. UTI is the most dangerous bacterial infection in children under three months old. One in six cases of febrile newborns is caused by a UTI. This condition can cause short-term consequences, such as acute kidney injury, renal abscess and sepsis. Hypertension, end-stage renal disease, preeclampsia, renal scarring, and recurrent infection are the possible long term consequences (22).

An estimated half a million infant and child deaths annually are attributed to ZnD. In five Indian states, a cross-sectional study revealed that 43.8% of infants aged six to sixty months had insufficient Zn. The most frequent causes of ZnD were determined to be insufficient dietary intake, minimal consumption of animal products, restricted Zn bioavailability from cereals, and recurrent diarrheal illnesses which resulted in intestinal Zn loss (23).

To the best of our knowledge, this is the first systematic review and meta-analysis regarding the association between serum Zn levels and non-recurrent UTI in children. In this systematic review and meta-analysis, we aimed to see the relationship between Zn and UTI in children by comparing the serum in those children with UTI and the controls. We

found significantly lower serum Zn levels in those children with UTI than in the controls. This finding is in line with three previous studies (8,17,21). The study by Amoori et al. (20) found contrasting results which showed that there was no relation between low serum Zn levels and UTI in children. Another slightly different study had a similar finding with this meta-analysis which showed that serum Zn levels played a role in recurrent UTI in children (12).

Nonetheless, some studies stated that there was no correlation between Zn deficit and inflammatory cytokines, and the association between ZnD and UTI was independent of inflammation indicators. Through the production of proteins and nucleic acids, Zn contributes significantly to cellular development and differentiation. Some studies have pointed out the role of Zn supplementation in the prevention and treatment of bacterial diseases (13).

The specific mechanism by which ZnD contributes to the pathogenesis of UTIs in humans has not been fully elucidated. Zn itself plays a role in immune system functioning in terms of defending against infections. It helps epithelial cells and leukocyte regulation. Zn homeostasis, intracellularly and extracellularly, is needed for optimal immune response and also to prevent further tissue damage (24). Antioxidant levels are downregulated and oxidative stress is elevated in UTI patients' serum cations. Copper, calcium, and Zn are decreased while indicators of oxidative stress such malondialdehyde are elevated in UTIs (15,25).

In the study by Hancock et al. (26), research was carried out on the antimicrobial and anti-biofilm effects of Zn on *Escherichia coli, Klebsiella*, and urinary tract pathogens. It was found that divalent Zn could apply its antimicrobial mechanism by preventing the above mentioned organisms from forming biofilms. Thus, it is possible to draw the conclusion that stones in the urinary system or the development of biofilm in the urinary tract are the cause of UTIs (26).

A previous systematic and meta-analysis reported that supplemental medicines containing Zn and dietary intake were also shown to have positive effects during infection, specifically in the respiratory and gastrointestinal systems (27). Previous studies have also stated that there was an inverse relation between Zn and inflammatory markers (interleukin-6, tumor necrosis factor-alpha, and CRP). Low levels of Zn were linked to decreased macrophage activation and impaired lymphoid tissue development (28).

Zn is the second most abundant trace element in the body, after iron. One in ten of the proteins found in the human body is a Zn protein. More than 300 enzymes and 1,000 transcription factors depend on Zn activity. Zn is an essential micronutrient involved in many cellular processes such as protein synthesis, nucleic acid metabolism including deoxyribonucleic acid synthesis, gene transcription, cell proliferation and differentiation, and mitosis (5).

The amount of Zn needed rises with age, starting from 2 mg/day for children, which makes Zn intake is an important supplementation (3). Zn can be found in a wide range of dietary and supplementary groups, but its content and bioavailability vary greatly (3). This micronutrient cannot be synthesized in the human body. Therefore, supplementation and foods which contain high Zn are needed in order to maintain adequate serum levels in the body (5,29). Some foods contain high levels of Zn, such as red meat, offal, oysters and shellfish, fortified cereals, and whole-grain products. Of all the foods, oysters provide the highest amount of Zn per serving. However, since beef is so widely consumed in Western nations, it accounts for 20% of total dietary Zn intakes. Zn is also found in eggs and dairy products. Zn is found in beans, nuts, and whole grains, but because plant-based diets are high in phytates, the bioavailability of Zn is reduced (29).

Through this study, the researchers want to enhance the understanding of the role of Zn in maintaining urinary tract health and its implications on more effective prevention strategies for children. Our findings also emphasize the importance of Zn nutrition. This study can be a reference for health guidelines and health promotion in order to raise awareness about the importance of adequate Zn supplementation.

Study Limitations

The limitation of this study was the small number of available studies. This limited evidence base reduces the generalizability of our findings and weakens the strength of our conclusions. Further large-scale, prospective studies are required in order to confirm the associations between serum Zn levels and pediatric UTI. Moreover, while our findings raise the possibility that Zn supplementation may serve as an adjuvant preventive or therapeutic strategy, this implication should be validated through well-designed randomized controlled trials.

Conclusion

This systematic review and meta-analysis demonstrated a significant association between low serum Zn levels and UTI in children. These findings highlight the potential role of Zn status in pediatric urinary health. However, given the

limited number of available studies, the evidence should be interpreted with caution. Further large-scale, prospective studies and randomized controlled trials are warranted in order to confirm this association and to explore whether Zn supplementation could serve as an effective adjuvant strategy in reducing the incidence of pediatric UTI.

Footnotes

Authorship Contributions

Concept: S.Y.U., J.C., M.O., Data Collection or Processing: S.Y.U., J.C., M.O., Analysis or Interpretation: S.Y.U., J.C., M.O., Literature Search: S.Y.U., J.C., M.O., Writing: S.Y.U., J.C., M.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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