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# Effects of vitamins A, C, and D and zinc on urinary tract infections: A systematic review and meta-analysis

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**REVIEW ARTICLE**

## Abstract

Urinary tract infection (UTI) is responsible for a significant portion of the overall expenses of health care as well as mortality rates globally. We searched through the available research to evaluate whether micronutrient supplements affect the frequency and intensity of UTI in children Papers that investigated the effects of vitamins D and C, zinc, and multiple micronutrient supplementations (MMS) on the incidence and severity of UTI in pediatric patients were pooled together. A random effects model was used to conduct a meta-analysis of data. Vitamin D supplementation reduced the risk of UTI and shortened the duration of symptoms in children. If a clinical diagnosis or laboratory investigation was used to confirm UTI, the relative probability of UTI with vitamin D was remote from the null than using the self-report. If vitamin C was administrated, the frequency of UTI was reduced, and the period of clinical manifestations was cut to half. It was not possible to determine the impact of using zinc supplements. According to the findings of the current review, taking micronutrient supplements such as zinc, vitamins C and D, and multiple micronutrient supplementation could assist in preventing UTI and lessen its clinical outcome in pediatric patients. More research is required to establish the effect of individual or combination of micronutrients on the treatment outcomes of UTI.

*Keywords*: urinary tract infection; meta-analysis; vitamin A, vitamin C, vitamin D; zinc

## Introduction

Urinary Tract Infection (UTI) is one of the most common bacterial infections in childhood. Even though this kind of sickness rarely results in death, the patient still suffers greatly (Sheerin and Glover, 2019, Yang *et al.*, 2022). The incidence of UTI varies from 1.8 to 7.5% in childhood (2). UTI is more common in boys under 3 months than girls. In the United States, UTI is responsible for 7 million clinic visits annually, leading to considerable healthcare and social service expenditures (Sheerin, 2011. Compared to males, only very young children and older females could have a higher incidence of UTI. A high incidence of UTI and recurrent UTI is observed in females aged 1–50 years (Kasper *et al.,* 2018). Urinary tract abnormalities, such as those occurring after kidney transplantation or because of end-stage renal disease, are the leading cause of recurrent UTI. In addition, many


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instances of recurrent UTI were observed for which the underlying cause could not be identified (Freire *et al.,* 2020).

Bacteria are main etiologic agents that cause UTI (Olin and Bartges, 2015), although fungi and viruses may occasionally cause UTI (Rolston, 2001) in children. An uncomplicated UTI is the most common type that manifests itself even when no structural or functional issues are observed in the urinary system. A more challenging UTI type develops when an anomaly in the urinary system elevates the risk of infection (Byron, 2019).

Other pathogenic bacteria, such as Proteus mirabilis, Staphylococcus saprophyticus (especially isolated frequently in younger females), Enterococcus faecalis, Klebsiella pneumoniae, and Pseudomonas aeruginosa, are of lesser importance, compared to Escherichia coli, which is the most common uropathogenic (75–90% of isolates) in both community and hospital infections (Byron, 2019; Sheerin, 2011; Stamm, 2008). Uropathogenic bacteria express fimbrial adhesions, which attach to glycolipids and glycoproteins on the surfaces of epithelial cells.

Bacteria can live in the urinary system because they can withstand constant urine flow. This allows them to thrive. Bacteria produce a wide array of new compounds in addition to the toxins, hemolysin, and colony-necrotizing substances they produce normally. Because of these chemicals, the epithelium's barrier function is compromised, making it simpler for bacteria to infiltrate and contribute in spreading the sickness (Behzadi, 2020). In addition, uropathogens have the potential to penetrate host epithelial cells, where they may multiply and act as a source of recurrent infection (Byron, 2019).

Before typically generating an infection, uropathogens first colonize the skin around the urethra and perineum. Evidence shows that normal microbiota, such as Staphylococcus epidermidis, Lactobacillus spp., and Corynebacteria, may prevent bacterial colonization (Matulay *et al.,* 2016). Also, the natural defense mechanism of the bladder is able to stop the progression of bacterial colonization and development of the sickness. In the urinary system, inert surfaces, such as stones and catheters, provide a breeding ground for bacterial colonization (Kasper *et al.*, 2018). Female anatomy, age, sexual activity, some type of contraception, and menopause are risk factors for UTI. Other risk factors include having a compromised immune system, urinating using a catheter, or having recently undergone a urinary surgery (Storme *et al.,* 2019).

The following course of antibiotic treatment was recommended by the clinical knowledge summaries published by the National Health Service (NHS): (1) 7 days of ciprofloxacin, co-amoxiclav, or cephalexin; (2) 14 days of trimethoprim for males and nonpregnant females; and (3) 7–10 days of cefalexin for pregnant females. In order to effectively treat serious infections, inpatient hospitalization was required with intravenous fluids and parenteral broad-spectrum antibiotics.

Over the past several decades, the extensive use of antibiotics has led to an increase in antibiotic-resistant bacterial infections, which, in turn, have increased the prevalence of antibiotic-resistant bacterial illnesses in specially in pediatric patient. In addition, it would be beneficial to have a workable approach for preventing and treating UTI because of the chronic nature of these infections and the likelihood of antibiotic resistance.

In recent years, several approaches to deal with antibiotic resistance have been established (Khameneh *et al.,* 2016, 2019a, 2019b). Complementary and alternative medicine (CAM) has shown promise as a viable treatment for managing antibiotic-resistant bacterial infections (Bazzaz *et al.,* 2016, 2019) in pediatric patient. It contains various components, some natural compounds, and vitamins, minerals, and probiotics (Baker *et al.*, 2018). Today, this type of medical practice has attracted much attention in the more developed countries. According to the available data, only 1.8% of children in the United States get this type of therapy. On the other hand, the actual therapeutic frequency is anticipated to be higher.

Some of the best natural choices for long-term prevention include probiotics, medicinal herbs, vitamins, and other constituents that have been shown to prevent UTI (Farhadi *et al.,* 2019; Li and Liao 2022; Loubet *et al.,* 2020; Poulios *et al.,* 2021). These elements are found in dietary supplements. Vitamins and minerals could be useful in treating UTI, and their efficacy could be increased if combined with conventional antibiotic treatment. We would be in a better position to guide public health programs if we understood the role of nutrition in preventing and treating UTI in pediatric patients. A previous study has shown that lower nutritional levels are associated with an increased risk of contracting infectious diseases (Calder *et al.*, 2020). However, the participants in these experiments were not humans, and the researchers did not consider the impact of dose or different micronutrients when determining the most effective micronutrient package to prevent or treat UTI.

This study proposed to compile and analyze data from randomized controlled trials concerning the application of micronutrient supplementation in managing UTI in children. We investigated the efficacy of micronutrient supplements in both (1) preventing UTI and (2) reducing the period for which clinical manifestations persisted in pediatric patients with UTI.

## Material and Method

### Search strategy

In the databases of medical literature, Medline and EMBASE, we searched for studies published as recently as January 2021. Keywords and MSEs used were urinary tract infections (MSEs) and micronutrients (including ascorbic acid, niacin, and zinc, children, pediatric), respectively. This search had no restrictions based on the year of publication, age range, language, or ailment (however, articles without standard translation were excluded during full-text review). Corresponding author, Dan Li, resolved disagreement, if any, on the mode of selection of papers. In addition, we conducted a manual search of the works mentioned in the papers that were included and prepared systematic reviews. After analyzing titles and abstracts of the studies, we reviewed entire versions of the papers that satisfied our requirements. Randomized controlled studies were considered for inclusion if they explored the impact of micronutrient supplementation on the incidence of UTI or the severity of UTI symptoms in pediatrics.

### Inclusion and exclusion criteria

Studies that were conducted *in vitro* were excluded from the present investigation. All observational studies, case reports, and case series (both prospective and retrospective) were also not included in the present analysis. The included papers were combined to complete point estimates with confidence intervals (CIs), standard errors, $P$-values, data on the study methodology, demographic features, exposures, outcomes, variables, and findings.

In order to carry out this meta-analysis, we pooled the findings of at least four other researches that had previously calculated the same exposure–outcome relationships. In cases where more than one approach was used to arrive at a conclusion, the method that produced the most accurate or objective data was selected. According to the study on the incidence of infection, reverse transcription-quantitative polymerase chain reaction (RT-PCR) and serology were favored over clinical diagnosis. At the same time, self-reporting of patient was the least preferred diagnosis technique. Only the highest-quality categories that satisfied the inclusion criteria were considered for meta-analysis if multiple exposure doses were recorded.

### Evaluation of the Level of Quality

While conducting this meta-analysis, the researchers evaluated methodologies of the studies using a JBI critical appraisal tools checklist. Inclusion and exclusion criteria were articulated; study participants and study environment were described in depth; a measurement method that was valid and reliable was used; objective and standard criteria were applied; confounding factors were identified; strategies to mitigate their effects were implemented; outcomes were measured accurately; and appropriate statistical analysis was be carried out. The data were compiled using the studies that provided affirmative responses to a minimum of four of the questions.

### Gathering of Information

Two different reviewers carried out the data extraction process in an impartial manner while following a specified protocol (including name of the first author, published year, country, study design, age of participants, sample size of control and patient groups, study population, and serum level of vitamin D in both control and patient groups). Two independent reviewers went through the process of reading and analyzing all the provided material. If results of the reports were presented in different units, then units of vitamins A, C, and D were converted into nmol/L using the SI unit's conversion calculator (http://unitslab.com/node/84).

### Statistics with analytical focus

Mean values, standard deviation (SD) of serum levels of vitamins A, C, and D and zinc, sample size, and age of participants in both control and pediatric patient groups were analyzed to determine whether there was a statistical connection between these variables and the risk of developing a UTI.

As a part of this study's process of transforming the data, the concentrations of vitamins A, C, and D and zinc were converted from different units (such as ng/mL) into nmol/L, and the standard error of mean (SEM) was converted into SD. These changes were made to better analyze the results of this research.

Heterogeneity tests, such as the Cochran 2 and $I^2$ statistics, were used to reduce variation in the amounts of vitamins A and D and zinc consumed between studies. The fixed effects model was used if no statistical heterogeneity between the trials was discovered. In order to accurately describe fixed and random effects, we used a strictly standardized mean difference (SSMD) with CI 95%. SSMD with CI 95% was used to evaluate the level of vitamin D and risk of UTI in children of varied ages.

In order to conduct sensitivity analysis, we first isolated the findings of each research from the whole research. In the course of our research, a subgroup analysis based on different age ranges was also carried out. Egger's test and Begg's test were used to determine bias in the studies. Comprehensive Meta-*Analysis* (CMA), version 2, was used to conduct statistical tests. For measurements, $P < 0.05$ was considered statistically significant.

## Results and Discussion

A total of 85 titles were revealed while investigating the designated databases. After deleting the titles with similar themes, assessment of subjects and abstracts was conducted for 55 titles. Of the 12 original papers, systematic review included only eight papers, although all original publications were read and analyzed in detail. Twenty-four studies were rejected due to the absence of a control group; 21 studies were excluded because of the mismatch of patient populations of the two groups, and four studies were case reports or reviews. Since many factors could induce UTI, we searched for researches examining the influence of vitamins and mineral supplementation.

We analyzed evidence on how various micronutrients in humans affect the onset and progression of UTI. Vitamins C and D and multiple micronutrient supplements were shown to reduce the risk of UTI in children. Vitamins C and D and zinc were found to hasten the healing process after the onset of UTI. According to the findings of our study, vitamin D supplement lowers the overall risk of developing UTI by 3% and 18% if the UTI is detected by a laboratory testing or a clinical diagnosis in pediatrics. This is consistent with the findings of previous studies, most of which centered on children.

The present study focused on the examination of children for UTI. Although some regular exposure to sun is sufficient to prevent vitamin D insufficiency, approximately half of the global population has deficiency of vitamin D (Van Schoor and Lips, 2017). Vitamin D affects the activity of macrophages, dendritic cells, and T cells, all of which play a role in controlling the immune system (Lei *et al.,* 2017). Vitamin D stimulates the synthesis of interleukin (IL)-4, IL-5, and IL-10, and in turn favors T-helper 2 (Th2) response and reduces the activity of T-helper 1 (Th1) cells (Boonstra *et al.,* 2001; Lemire *et al.,* 1995). In addition, vitamin D stimulates the production of antioxidative enzymes necessary for preventing oxidative stress caused by various illnesses (Lei *et al.,* 2017).

It is essential to indicate that the present research included the countries with temperate climates and high incomes; hence, our findings are only relevant to this particular setting. Moreover, vitamin D baseline levels and adverse events associated with supplements were rarely recorded in the studies.

Evidence indicates that vitamin C helps to minimize the probability of acquiring UTI and lowers the severity of clinical manifestations in UTI patients. The results of previous studies were consistent with these findings. Hence, vitamin C is an essential ingredient to boost immunity in the body and repairing of injured tissues in case of an accident or traumatic event in pediatric patients.

Owing to its anti-inflammatory and antioxidant properties, vitamin C is a useful supplement for accelerating the body's natural healing process (Hemilä, 2003; Padayatty and Levine, 2016, Bai B et al 2023). Low levels of vitamin C negatively affect the body and result in stressful conditions. Presently, deficiency of vitamin C, known as scurvy, is not as widespread as it was in the past. Nonetheless, recent research has shown that low levels of vitamin C may develop adverse reaction in the body (Borran *et al.,* 2020; Borrelli *et al.,* 1996; Montorsi *et al.,* 2016).

Tables 1–3, and Figures 1A and 1B. A meta-analysis was carried out to assess the influence of micronutrients on the frequency of UTI and the period of clinical manifestations in pediatric patient. It was discovered that no significant dose–response correlation was discovered between vitamin C and incidence of UTI or duration of clinical manifestations. The included studies did not identify any adverse events related to vitamin C. No indication was evidenced that zinc supplementation substantially lowered the time it took for UTI to disappear.

Zinc deficiency, which affects more than 20% of the world's population, may be avoided by consuming zinc supplements in quantity appropriate to one's needs (Wessells and Brown, 2012). Zinc is found in hundreds of enzymes and transcription factors, and it plays a crucial role in the expression of genes, division of cells, and functioning of the immune system (Table 3). Zinc regulates the growth and functioning of epithelial cells and leucocytes (Read *et al.,* 2019). Moreover, it regulates the generation of T cells, cytokines, and reactive oxygen species (ROS) (Prasad, 2009; Tanumihardjo *et al.,* 2016). In addition, zinc stimulates appetite. Deficiency of zinc may lead to anorexia and, as a result, a potential cause of lower intake of macronutrients and micronutrients necessary for a robust immune response. Because the studies analyzed for this review used various formulations, it was impossible to conclude the preventive effects of these medications. Zinc levels tend to diminish with age, and

**Table 1. Vitamin A and UTI.**

| Author and year | Type of study | Objective | Results |
|---|---|---|---|
| Yilmaz, Bahat *et al.*, 2007 | In order to look at how vitamin A supplementation affects chronic bladder infections (recurrent UTI)? | In a trial that was controlled by placebo and carried out in a double-blind manner, 24 individuals were examined. In addition to antimicrobial treatment, a single dose of 200,000 international units (IU) of vitamin A was given to 12 patients. Both patient and control groups, each consisting of 12 patients , were monitored for up to a year to determine whether or not lower UTI had been eliminated and how often UTI occurred. Vitamin A and beta-carotene concentrations in the serum were measured at regular intervals. | The infection rate in the group that received vitamin A supplements dropped from 3.58 per 6 months to 0.75 per 6 months during the first 6 months of the follow-up period, and then it rose to 1.75 per 6 months over the succeeding 6 months. In the placebo group, these values were 2.75, 2.83, and 2.66, respectively. |

**Table 2. Vitamin C and UTI.**

| Author and year | Type of study | Objective | Results |
|---|---|---|---|
| Castello *et al.*, 1996 | The impact of ascorbic acid on the pH of urine was investigated in individuals with spinal cord injuries. | To evaluate difference in urine pH between the initial value, which was taken before treatment, and the final value taken after treatment with either a placebo or ascorbic acid, 500 mg/6 h. | No discernible change in the urine pH was observed. The usage of ascorbic acid did not result in any clinically significant benefits. |
| Ochoa-Brust *et al.*, 2007 | The participants in the clinical trial were randomly assigned to one of the two treatment groups: Group A received an oral treatment consisting of ferrous sulfate (200 mg per day), folic acid (5 mg per day), and ascorbic acid (100 mg per day) for a period of 3 months; Group B received an oral treatment consisting of ferrous sulfate (200 mg per day) and folic acid (5 mg per day) for a period of 3 months.<br>Every patient had a clinical examination, and over the course of 3 months, a urine culture was performed once a month on each of the patient. | The purpose of this study was to investigate the effectiveness of daily consumption of 100 mg of ascorbic acid in the prevention of UTI. | A 25% incidence of UTI is reported worldwide. The incidence of UTI was substantially lower in Group A (12.7%), compared to Group B (29.1%) ($P = 0.03$; odds ratio = 0.35; 95% confidence interval = 0.13–0.91).<br>The daily consumption of 100 mg of ascorbic acid played a significant role in the decrease of UTI, which contributed to an overall improvement in the health of pregnant females. |
| Borran *et al.*, 2020 | Kidney transplantation patients were randomly assigned to receive either vitamin C or a placebo.<br>A total of 19 patients were randomly assigned to one of the two groups: placebo group (n = 10) or vitamin C group (n = 9).<br>Patients in the treatment group were given a single dose of vitamin C infusion that was equivalent to 70 mg/kg. In another part of the experiment, only diluent solution was given to the participants. Information records were kept pertaining to bacteriuria throughout the first hospitalization after transplantation. | Finding out whether intravenous high dose of vitamin C was effective in preventing UTI after kidney transplantation was the goal of this study. | 11.1% of the patients in the vitamin C group had bacteriuria during their first hospitalization after receiving a transplant, which was much lower than 60% of the patients who experienced it in the placebo group ($P = 0.02$).<br>Vitamin C was a safe medication with a potential to function as a preventative therapy in UTI that occurred after kidney transplantation.. |

**Table 3. Zinc and UTI.**

| Author and year | Type of study | Objective | Results |
|---|---|---|---|
| Mohsenpour *et al.*, 2019 | Correlation between the amount of zinc in the serum and the frequency of UTI. | The blood zinc levels of 48 patients who suffered from recurrent UTI were evaluated and compared to the serum zinc levels of the same number of participants in the control group. | A relation between age and blood zinc level was observed; however, it wasn't very strong ($r = -0.205$, $P = 0.045$). Mean serum zinc levels in the test group and the control group were 96.83 (±11.25) microgram/deciliter and 76.72 (±17.06) microgram/deciliter ($P = 0.001$), respectively. Level of zinc dropped with age; in addition, the group with recurrent UTI had lower zinc levels than the control group ($P = 0.010$, $R^2 = 0.377$). |

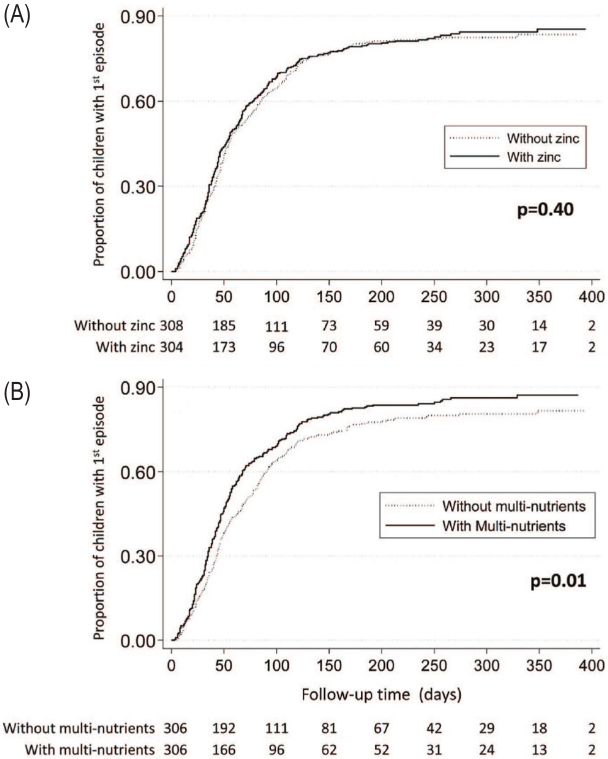


**Figure 1. (A) Correlation between the serum zinc level and the frequency of UTI; (B) correlation between the serum multivitamins level and the frequency of UTI.**

according to one study, patients with recurrent UTI have lower zinc levels than normal individuals (Mohsenpour *et al.*, 2019). Inadequate intake of micronutrients or significant dietary deficiencies could be the potential reasons for contravening preventive effects in the study cohort. In many instances, the intake of micronutrients is at or below the recommended daily requirement, which means that it is not adequate to make up for any prior deficiencies).

The positive effects of vitamin C and zinc supplements showed no dose–response correlation. Our review had certain limitations because of the amount and quality of readily accessible source material. Since most of the study was conducted there, our findings are solely relevant.and show that our capacity to identify important associations between studied micronutrients could not be possible because categorizing the outcomes of interest in many studies relied on participants' reports. Some of the included studies had a significant risk of bias or other limitations, in part, because assessment of the outcomes relied on participants' self-reporting. In addition, owing to insufficient data, we were unable to determine how the presence of micronutrients affected the severity of clinical manifestations. A lack of statistically significant dose–response correlations was observed in most investigated connects between exposure and outcome.

## Conclusion

According to the present meta-analysis of studies conducted worldwide, intake of zinc and vitamins A, C, and D could have a marginally positive effect on the incidence and clinical course of UTI in pediatric patients. Vitamins A, C, and D and zinc can marginally reduce the risk of UTI in children; hence, it is recommended to consume foods containing high amounts of these nutrients in countries with a low level of hygiene. Further research is required on the impact of single and combination of micronutrients on UTI and its therapy.

## Competing interests

The authors declared that they had no conflict of interest to report.

## Availability of data

Please contact corresponding author for data requests.

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