

RESEARCH ARTICLE

In vitro effects on calcium oxalate crystallization kinetics and crystal morphology of an aqueous extract from *Ceterach officinarum*: Analysis of a potential antilithiatic mechanism

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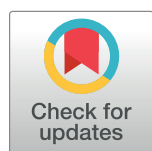
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Abstract

Ceterach officinarum Willd is a plant widespread throughout Europe and used in southern Italy as a diuretic. Beliefs in the benefits of *C. officinarum* aqueous extract in the treatment of calcium oxalate kidney stones are widely held. Little is known, however, about the actual mechanism of its antilithiatic action. Our results in this *in vitro* study corroborate *C. officinarum* aqueous extract as a good source of antioxidants with a high antioxidant effects. Our results also demonstrate a major impact of *C. officinarum* aqueous extract on *in vitro* induced calcium oxalate crystallization kinetics and crystal morphology, showing its critical role in kidney stone formation and/or elimination. We show that progressively increasing doses of *C. officinarum* aqueous extract cause a sequence of effects. A powerful inhibitory action on calcium oxalate monohydrate (COM) growth and aggregation is first observed. *C. officinarum* aqueous extract also appears highly effective in stimulating nucleation increasing the number and reducing the size of COM crystals, which become progressively thinner, rounded and concave in a dose-dependent manner. These shape-modified COM crystals are known to be less adherent to renal tubular cells and more easily excreted through the urinary tract preventing kidney stone formation. Further, *C. officinarum* aqueous extract promotes the formation of calcium oxalate dihydrate (COD) rather than the monohydrate so that, at the highest concentrations used, only COD crystals are observed, in significant greater numbers with a clear reduction in their size, in a dose-dependent manner. Furthermore, AFM analyses allowed us to reveal the presence of *C. officinarum* component(s) on the surfaces of COD and modified COM crystals. The crystal surface adsorbed component (s) are shown to be similarly active as the total aqueous extract, suggesting a trigger factor which may direct crystal modification towards COD forms. In urolithiasis pathogenesis COD crystals are less dangerous than the COM forms due to their lower affinity for renal tubular cells. Our results are important in understanding the mechanisms which guide the modification induced by *C. officinarum* on the crystallization process. Based on these data, together with no adverse toxic effect being observed on the *in vitro* model of human intestinal enterocytes, *C. officinarum* aqueous extract could represent an attractive natural therapy for the treatment of urolithiasis.



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The effectiveness of citrates and pyridoxine in the treatment of kidney stones

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ABSTRACT

The prevalence of nephrolithiasis is increasing across all demographic groups. Apart from the morbidity associated with an acute occurrence, preventative treatment is essential for stone disease, which can become a long-term problem. Simple interventions like fluid intake optimization and dietary modification are effective for most stone types. However, patients with specific metabolic abnormalities may require pharmaceutical therapy if lifestyle changes are insufficient to reduce the risk of stone recurrence. The treatment of citrates and/or pyridoxines may help eliminate or prevent recurrences of kidney stones, especially when they are composed of uric acid, calcium oxalate, calcium phosphate, or the latter two together. In cases of struvite stones, which often necessitate a surgical approach, acetohydroxamic acid emerges as a valuable second-line treatment option. Thiol-binding agents may be needed for cystinuria, as well as lifestyle modifications. Successful treatment reduces stone recurrence and the need to remove stones surgically.

KEYWORDS: citrates, kidney stones, pyridoxine, calcium

Impiego del citrato nel paziente con nefrolitiasi

cap.6

Uso del citrato nella nefrolitiasi

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ABSTRACT

Il Citrato è un acido tricarbossilico ed è un metabolita intermedio del Ciclo di Krebs. Contribuisce al metabolismo ossidativo del rene e del fegato. I suoi sali alcalini rappresentano basi potenziali e contribuiscono pertanto alla riserva alcalina. Viene completamente filtrato dal glomerulo, con una frazione escreta pari al 10-40%. L'insufficienza renale, l'acidosi metabolica, la deplezione potassica ed alcuni farmaci inducono ipocitraturia. Il Citrato ha una spiccata affinità per il calcio con cui forma complessi solubili e svolge anche un'interferenza negativa con i processi di cristallizzazione dei sali di calcio. Si ha dunque un'inibizione termodinamica, la prima, e cinetica, la seconda. Inoltre l'azione alcalinizzante ha mostrato effetti positivi sulla mineralizzazione ossea. Si tratta pertanto del più importante e fisiologico inibitore ionico e questo giustifica il suo largo impiego nella prevenzione della nefrolitiasi calcica. Inoltre l'effetto alcalinizzante sulle urine è alla base del suo impiego anche nella NL urica e cistinica. L'ipocitraturia ha una incidenza significativa nei pazienti con NL calcica, sia quella secondaria di cui si è detto sopra, sia quella idiopatica, a volte familiare. Nella prevenzione delle recidive viene utilizzato in dose di 0.1 mmol/kg/die, diviso in 2-3 dosi, in forma di sale tripotassico o di potassio-magnesio. Nella calcolosi urica l'aumento del pH a valori mantenuti costantemente intorno a 6.5 può indurre la chemiolisi di calcoli renali. Il suo effetto sull'osso, mediato dall'aumento della riserva alcalina, è stato dimostrato sia attraverso una riduzione dei marker di riassorbimento scheletrico che da un miglioramento dei dati densitometrici.

PAROLE CHIAVE:

citrato, citrato di potassio, ipocitraturia, nefrolitiasi calcica.

ABSTRACT

Citrate is a tricarboxylic acid and an intermediate metabolite of Krebs cycle. It contributes to oxidative metabolism of both kidney and liver. Alkaline sodium or potassium salts have the potential to increase alkaline reserve. In the kidney citrate is completely filtered at the glomerulus, undergoing to 10-40% tubular resorption. Renal insufficiency, even early, metabolic acidosis, potassium depletion induce hypocitraturia. Its importance in nephrolithiasis stems from its ability to form soluble complexes with calcium and to interfere with crystal formation, thus exerting a dual inhibition, thermodynamic and kinetic. Moreover, its alkalizing property has shown benefits of bone mineralization. The alkalizing effect is also useful in uric acid and cystine stone disease. Hypocitraturia has a significant incidence in the course of calcium nephrolithiasis, either secondary to aforementioned causes, or in idiopathic and/or familial forms. Citrate is used in the prevention of stone recurrences and given as tripotassic or potassium-magnesium salt, 0.1 mmol/kg/day in 2-3 dosages. In uric acid disease, in addition to prevention, it can induce dissolution of renal stones, provided urine pH is maintained at higher than 6.5 values. As concerns its effects on bone, it was shown to induce both decreases in marker of bone resorption and increases in bone mineral density.

KEYWORDS:

citrate, potassium citrate, hypocitraturia, calcium nephrolithiasis

[Intervention Review]

Citrate salts for preventing and treating calcium containing kidney stones in adults

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ABSTRACT

Background

Kidney stones affect people worldwide and have a high rate of recurrence even with treatment. Recurrences are particularly prevalent in people with low urinary citrate levels. These people have a higher incidence of calcium phosphate and calcium oxalate stones. Oral citrate therapy increases the urinary citrate levels, which in turn binds with calcium and inhibits the crystallisation thus reduces stone formation. Despite the widespread use of oral citrate therapy for prevention and treatment of calcium oxalate stones, the evidence to support its clinical efficacy remains uncertain.

Objectives

The objective of this review was to determine the efficacy and adverse events associated with citrate salts for the treatment and prevention of calcium containing kidney stones.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 29 July 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included randomised controlled trials (RCTs) that assessed the efficacy and adverse events associated with citrate salts for the treatment and prevention of calcium containing kidney stones in adults treated for a minimum of six months.

Data collection and analysis

Two authors assessed studies for inclusion in this review. Data were extracted according to predetermined criteria. Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes.

Main results

We included seven studies that included a total of 477 participants, most of whom had oxalate stones. Of these, three studies (247 participants) compared potassium citrate with placebo or no intervention; three (166 participants) compared potassium-sodium citrate

with no intervention; and one (64 participants) compared potassium-magnesium citrate with placebo. Overall, quality of the reporting of the included studies was considered moderate to poor, and there was a high risk of attrition bias in two studies.

Compared with placebo or no intervention, citrate therapy significantly reduced the stone size (4 studies, 160 participants: RR 2.35, 95% CI 1.36 to 4.05). New stone formation was significantly lower with citrate therapy compared to control (7 studies, 324 participants: RR 0.26, 95% CI 0.10 to 0.68). The beneficial effect on stone size stability was also evident (4 studies, 160 participants: RR 1.97, 95% CI 1.19 to 3.26). Adverse events were reported in four studies, with the main side effects being upper gastrointestinal disturbance and one patient reported a rash. There were more gastrointestinal adverse events in the citrate group; however this was not significant (4 studies, 271 participants: RR 2.55, 95% CI 0.71 to 9.16). There were significantly more dropouts due to adverse events with citrate therapy compared to control (4 studies, 271 participants: RR 4.45, 95% CI 1.28 to 15.50). The need for retreatment was significantly less with citrate therapy compared to control (2 studies, 157 participants: RR 0.22, 95% CI 0.06 to 0.89).

Authors' conclusions

Citrate salts prevent new stone formation and reduce further stone growth in patients with residual stones that predominantly contain oxalate. The quality of reported literature remains moderate to poor; hence a well-designed statistically powered multi-centre RCT is needed in order to answer relevant questions concerning the efficacy of citrate salts.

PLAIN LANGUAGE SUMMARY

Citrate salts for preventing and treating calcium containing kidney stones in adults

Kidney stones are one of the most common disorders of the urinary tract. They typically affect people aged 40 to 60 years of age and are twice as common in men than women although recent data suggest the risks are more equal. Calcium stones are the most common type of kidney stone and occur in two major forms: calcium oxalate and calcium phosphate. Kidney stones can cause severe abdominal pain and may require urgent treatment; they are one of the main causes of unscheduled admissions in urological practice.

Following treatment even first time stone formers have a risk for recurrence which increased with each subsequent stone. This increased risk of recurrence of stones is mainly attributed to altered composition of urine i.e. low citrate levels. Various prevention strategies including increased fluid intake and oral citrate supplements have been tried to modify the chemical composition of the urine. Citrate therapy is believed to stop crystals from growing into stones. The uncertainty of the true benefit of citrate therapy prompted this review.

We included seven studies (477 participants) in this review. Citrate salts significantly reduce stone size, prevent new stone formation, and results in stone size stability. People experienced more side effects, such as gastrointestinal disturbance, when using citrate salts than when using placebo, however the need for retreatment for stone removal was significantly less with citrate therapy.

Effect of potassium citrate supplement on stone recurrence before or after lithotripsy: systematic review and meta-analysis

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Abstract

This meta-analysis summarizes the available evidence on the effectiveness of citrate supplement for preventing the recurrence of nephrolithiasis in patients undergoing extracorporeal shock wave lithotripsy (SWL). Electronic searches were conducted using Medline-PubMed, Web of Science, Embase, BVS (Scielo, Lilacs), and Google Scholar literature databases. The authors worked in pairs to select studies that met the following criteria: randomized controlled trials that were conducted in adults and assessed the effect of potassium citrate supplement before or after SWL therapy for urolithiasis. Our primary aim was to assess the stone-free rate among the groups included in the studies. Fixed effect was used in the meta-analysis with 95% confidence interval (95% CI). Heterogeneity was analyzed by the I^2 value. A total of 2505 references were initially selected. Of those, four were subjected to meta-analysis contributing five samples. These four studies included 374 participants who were followed for a period of 12 months after SWL. Mean potassium citrate dosage was approximately 55 mEq/day (18 mmol). The results showed that citrate supplement significantly protected against the recurrence of nephrolithiasis during 1 year after SWL [RR; 95% CI 0.21 (0.13, 0.31)]. The heterogeneity was not significant across the analyzed studies ($p = 0.224$). The quality of the analyzed studies was generally low. The available evidence shows that citrate supplement effectively reduces the recurrence of nephrolithiasis in patients undergoing SWL. However, statistical analysis of a larger trial conducted with methodological rigor is warranted.

Keywords: Lithotripsy; Potassium citrate; Stone recurrence; Urolithiasis.



Evaluation of the efficacy of *Phyllanthus niruri* standardized extract combined with magnesium and vitamin B6 for the treatment of patients with uncomplicated nephrolithiasis

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Abstract

Introduction. The aim of our study was to assess the efficacy of *Phyllanthus niruri* standardized extract, combined with magnesium and B6 vitamin, used to treat uncomplicated nephrolithiasis.

Methods. We included in the present study 48 patients with uncomplicated nephrolithiasis, with the maximum calculi diameter of up to 15 mm, confirmed by non-contrast-enhanced computer tomography. Each patient followed a three-month therapeutic regimen with the above mentioned combination, with imaging assessment of the calculi after treatment.

Results. Per patient: The mean age of the patients was 48 years. The median number of calculi was 1 and the mean dimension was 5.5 mm. The stone-free status after treatment was not correlated with gender ($p=0.7$), side location ($p=0.8$) or with the number of calculi ($p=0.3$), but we found a correlation with the location in the upper or middle calyx (54.5% vs 13.8%, $p=0.008$) and with the maximum diameter ($p=0.001$).

Per stone: 60 calculi were analyzed, 8.3% being located in the upper calyx, 36.7% in the middle and 55% in the lower one. After treatment, 40% were absent, 21.7% showed lower dimensions and 38.3% remained unchanged, with the mean reduction of 1.7 mm. We identified a cut-off value of ≤ 3 mm (AUC 0.9, CI:0.8-0.9, $p<0.0001$) for the prediction of stone-free status after treatment.

Conclusions. The current treatment had the highest efficacy in achieving stone-free status for patients with calculi ≤ 3 mm, located in the middle or upper calyx. A higher duration of the treatment might show improved results.

Keywords: antilithogenic, *Phyllanthus*, kidney calculi, triterpenes

Can *Phyllanthus niruri* Affect the Efficacy of Extracorporeal Shock Wave Lithotripsy for Renal Stones? A Randomized, Prospective, Long-Term Study

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Purpose: *Phyllanthus niruri* is a plant used in Brazilian folk medicine for the treatment of urolithiasis. We assessed the efficacy of *P. niruri* after extracorporeal shock wave lithotripsy for renal stones.

Materials and Methods: We prospectively evaluated 150 patients with renal stones that were as large as 25 mm and composed of calcium oxalate. All patients received 1 to 3 extracorporeal shock wave lithotripsy sessions by Dornier Lithotriptor S. After treatment 78 of 150 patients (52%) underwent therapy with Uriston®, a *P. niruri* extract (2 gm daily) for at least 3 months (group 1). Otherwise 72 of 150 patients (48%) were used as a control group (group 2). No significant difference in stone size between the 2 groups was found. Stone clearance was assessed after 30, 60, 90 and 180 days by abdominal x-ray and ultrasound scan.

Results: Stone-free rate (stone-free defined as the absence of any stone or residual fragments less than 3 mm) was 93.5% in group 1 and 83.3% in group 2 ($p = 0.48$) at the end point of the followup (180 days). For lower caliceal stones (56 patients) the stone-free rate was 93.7% in the treatment group and 70.8% in the control group ($p = 0.01$). Re-treatment need for group 1 was 39.7% and for group 2 it was 43.3% ($p = 0.2$). No side effects were recorded with extracorporeal shock wave lithotripsy or *P. niruri* therapy.

Conclusions: Regular self-administration of *P. niruri* after extracorporeal shock wave lithotripsy for renal stones results in an increased stone-free rate that appears statistically significant for lower caliceal location. Its efficacy and the absolute lack of side effects make this therapy suitable to improve overall outcomes after extracorporeal shock wave lithotripsy for lower pole stones.

Key Words: kidney calculi, lithotripsy

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Effect of *phyllanthus niruri* on metabolic parameters of patients with kidney stone: a perspective for disease prevention

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ABSTRACT

Phyllanthus niruri (*P.niruri*) or stone breaker is a plant commonly used to reduce stone risk, however, clinical studies on this issue are lacking.

Objective: To prospectively evaluate the effect of *P. niruri* on the urinary metabolic parameters of patients with urinary lithiasis.

Materials and Methods: We studied 56 patients with kidney stones <10mm. Clinical, metabolic, and ultrasonography assessment was conducted before (baseline) the use of *P. niruri* infusion for 12-weeks (*P. niruri*) and after a 12-week (wash out) Statistical analysis included ANOVA for repeated measures and Tukey's/McNemar's test for categorical variables. Significance was set at 5%.

Results: Mean age was 44±9.2 and BMI was 27.2±4.4kg/m². Thirty-six patients (64%) were women. There were no significant changes in all periods for anthropometric and several serum measurements, including total blood count, creatinine, uric acid, sodium, potassium, calcium, urine volume and pH; a significant increase in urinary potassium from 50.5±20.4 to 56.2±21.8 mg/24-hour (p=0.017); magnesium/creatinine ratio 58±22.5 to 69.1±28.6mg/gCr24-hour (p=0.013) and potassium/creatinine ratio 39.3±15.1 to 51.3±34.7mg/gCr24-hour (p=0.008) from baseline to wash out. The kidney stones decreased from 3.2±2 to 2.0±2 per patient (p<0.001). In hyperoxaluria patients, urinary oxalate reduced from 59.0±11.7 to 28.8±16.0mg/24-hour (p=0.0002), and in hyperuricosuria there was a decrease in urinary uric acid from 0.77±0.22 to 0.54±0.07mg/24-hour (p=0.0057).

Conclusions: *P.niruri* intake is safe and does not cause significant adverse effects on serum metabolic parameters. It increases urinary excretion of magnesium and potassium caused a significant decrease in urinary oxalate and uric acid in patients with hyperoxaluria and hyperuricosuria. The consumption of *P.niruri* contributed to the elimination of urinary calculi.

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Keywords:

Kidney Calculi; Disease; Urolithiasis

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Reactive oxygen species, inflammation and calcium oxalate nephrolithiasis

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Abstract: Calcium oxalate (CaOx) kidney stones are formed attached to Randall's plaques (RPs) or Randall's plugs. Mechanisms involved in the formation and growth are poorly understood. It is our hypothesis that stone formation is a form of pathological biomineralization or ectopic calcification. Pathological calcification and plaque formation in the body is triggered by reactive oxygen species (ROS) and the development of oxidative stress (OS). This review explores clinical and experimental data in support of ROS involvement in the formation of CaOx kidney stones. Under normal conditions the production of ROS is tightly controlled, increasing when and where needed. Results of clinical and experimental studies show that renal epithelial exposure to high oxalate and crystals of CaOx/calcium phosphate (CaP) generates excess ROS, causing injury and inflammation. Major markers of OS and inflammation are detectable in urine of stone patients as well as rats with experimentally induced CaOx nephrolithiasis. Antioxidant treatments reduce crystal and oxalate induced injury in tissue culture and animal models. Significantly lower serum levels of antioxidants, alpha-carotene, beta-carotene and beta-cryptoxanthine have been found in individuals with a history of kidney stones. A diet rich in antioxidants has been shown to reduce stone episodes. ROS regulate crystal formation, growth and retention through the timely production of crystallization modulators. In the presence of abnormal calcium, citrate, oxalate, and/or phosphate, however, there is an overproduction of ROS and a decrease in the antioxidant capacity resulting in OS, renal injury and inflammation. Cellular degradation products in the urine promote crystallization in the tubular lumen at a faster rate thus blocking the tubule and plugging the tubular openings at the papillary tips forming Randall's plugs. Renal epithelial cells lining the loops of Henle/collecting ducts may become osteogenic, producing membrane vesicles at the basal side. In addition endothelial cells lining the blood vessels may also become osteogenic producing membrane vesicles. Calcification of the vesicles gives rise to RPs. The growth of the RPs is sustained by mineralization of collagen laid down as result of inflammation and fibrosis.

Keywords: Reactive oxygen species (ROS); nephrolithiasis; NADPH oxidase; Randall's plaque (RP); oxidative stress (OS)

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RESEARCH ARTICLE

WILEY

Efficacy of black seed (*Nigella sativa* L.) on kidney stone dissolution: A randomized, double-blind, placebo-controlled, clinical trial

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Preclinical studies have shown beneficial effects of black seed (*Nigella sativa* L.) in the prevention and treatment of renal stones. Hence, we designed a study to evaluate the renal-stone-dissolving efficacy of black seed. Sixty patients with renal stones were randomly enrolled in two arms of a randomized, triple-blind, placebo-controlled, clinical trial. The patients were treated by black seed capsules (500 mg) or placebo two times per day for 10 weeks. Patients were assessed in terms of size of renal stones by using sonography before and after intervention. In the black seed group, 44.4% of patients excreted their stones completely, and the size of the stones remained unchanged and decreased in 3.7% and 51.8% of patients, respectively. In contrast, in the placebo group, 15.3% of the patients excreted their stones completely, 11.5% had reduction in stone size, 15.3% had increase in stone size, and 57.6% had no change in their stone size. The difference in the mean size of renal stones after the study was significant between the two groups ($p < 0.05$). *N. sativa* L., as compared with placebo, is demonstrated to have significant positive effects on disappearance or reduction of size of kidney stones.

KEYWORDS

black seed, herbal medicine, *Nigella sativa*, Persian medicine, urinary stones

Mini Review Article

Renal injury, nephrolithiasis and *Nigella sativa*: A mini review

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Renal failure

Abstract

Objective: The incidence and prevalence of kidney stone is increasing worldwide. After the first recurrence the risk of subsequent relapses is higher and the time period between relapses is shortened. Urinary stones can be severely painful and make a huge economic burden. The stone disease may increase the vulnerability of patients to other diseases such as renal failure. Medicinal herbs are rich sources of antioxidants which are increasingly consumed globally for their safety, efficacy and low price. *Nigella sativa* is a spice plant that is widely used for prevention and treatment of many ailments in Muslim countries and worldwide. This review aims at investigation of the effects of *Nigella sativa* on renal injury and stone formation.

Materials and Methods: The scientific resources including PubMed, Scopus, and Google scholar were searched using key words such as: nephrolithiasis, urolithiasis, kidney/renal stone, renal injury, renal failure, urinary retention and black seed, black cumin, *Nigella sativa* and thymoquinone.

Results: *N. sativa* and its main component, thymoquinone showed positive effects in prevention or curing kidney stones and renal failure through various mechanism such as antioxidative, anti-inflammatory, anti-eicosanoid and immunomodulatory effects. The putative candidate in many cases has been claimed to be thymoquinone but it seems that at least in part, particularly in kidney stones, the herbal melanin plays a role which requires further investigation to prove.

Conclusion: *N. sativa* and its components are beneficial in prevention and curing of renal diseases including nephrolithiasis and renal damages.

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Multivitamins co-intake can reduce the prevalence of kidney stones: a large-scale cross-sectional study

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Abstract

Background: This research aimed to explore the association between changes in the intake of common individual vitamins and combinations of vitamins and the prevalence of kidney calculi.

Methods: We used data from NHANES to investigate the association between nine common vitamins and kidney stone prevalence. Participants were clustered into several vitamin exposure patterns using an unsupervised K-means clustering method. We used logistic regression models and restrictive cubic spline curves to explore the influence of vitamins.

Results: The regression model exposed that compared to lower intake, high intake of vitamin B6 [Q4: OR (95% CI) = 0.76 (0.62, 0.93)], vitamin C [Q4: OR (95% CI) = 0.73 (0.59, 0.90)] and vitamin D [Q4: OR (95% CI) = 0.77 (0.64, 0.94)] individually exerted protective effects against the prevalence of kidney stones. Furthermore, the restrictive cubic spline analysis showed that the protective effect against the prevalence of kidney stones is enhanced as the intake of vitamin B6 and vitamin D increased. Moreover, with the increase in vitamin C intake, its protective effect may turn into a risk factor. Regarding mixed exposure, Cluster 4 exhibited a significant protective effect against kidney stones compared with Cluster 1 [Model 3: OR (95% CI) = 0.79 (0.64, 0.98)].

Conclusions: Our research revealed that high levels of vitamin B6 and vitamin D intake were linked to a lower prevalence of kidney stone. With the gradual increase in intake of vitamin C, the prevalence of kidney calculi decreased first and then increased. In addition, the co-exposure of nine vitamins is a protective factor for kidney stone disease.

Keywords: Antioxidant; Cross-sectional study; Kidney calculi; Prevalence; Vitamins.