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META-ANALYSIS

Incidence of kidney stones in kidney transplant recipients: A systematic review and meta-analysis

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Abstract

AIM

To evaluate the incidence and characteristics of kidney stones in kidney transplant recipients.

METHODS

A literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from the inception of the databases through March 2016. Studies assessing the incidence of kidney stones in kidney transplant recipients were included. We applied a random-effects model to estimate the incidence of kidney stones.

RESULTS

Twenty one studies with 64416 kidney transplant patients were included in the analyses to assess the incidence of kidney stones after kidney transplantation. The estimated incidence of kidney stones was 1.0% (95%CI: 0.6%-1.4%). The mean duration to diagnosis of kidney stones after kidney transplantation was 28 ± 22 mo. The mean age of patients with kidney stones was 42 ± 7 years. Within reported studies, approximately 50% of kidney transplant recipients with kidney stones were males. 67% of kidney stones were calcium-based stones (30% mixed CaOx/CaP, 27%CaOx and 10%CaP), followed by struvite stones (20%) and uric acid stones (13%).

CONCLUSION

The estimated incidence of kidney stones in patients after kidney transplantation is 1.0%. Although calcium based stones are the most common kidney stones after transplantation, struvite stones (also known as "infection stones") are not uncommon in kidney transplant recipients. These findings may impact the prevention and clinical management of kidney stones after kidney transplantation.

Key words: Nephrolithiasis; Incidence; Kidney stones; Kidney transplantation; Transplantation

Core tip: The authors performed this meta-analysis to assess the incidence and characteristics of kidney stones in kidney transplant recipients. The estimated incidence of kidney stones in patients after kidney transplantation is 1.0%. Calcium based stones (CaOx and CaP) are the most common kidney stones after transplantation following by struvite stones and uric acid stones. The findings from this study may impact the management of kidney stone prevention after kidney transplantation.

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INTRODUCTION

Kidney stones are one of the most common metabolic disorders and urological problems with a prevalence of 7.2%-7.7% in the adult population, and a ten-year recurrence rate of ⩾ 30%[1-4]. The incidence of kidney stones is increasing especially in industrialized countries with an estimated global prevalence between 10%-15%[5-8]. Approximately 13% of men and 7% women will have a kidney stone during their lifetime[5,8].

Previous studies have shown that stone recurrence rates may be lower, when glomerular filtration rate (GFR) reduced[9,10]. Thus, patients with advanced chronic kidney disease (CKD) or end-stage kidney disease (ESRD) may encounter less stone disease[10], reported being as low as 0.68%[11]. After successful kidney transplantation, ESRD patients subsequently have significant improvement in renal function resulting in urinary excretion of metabolites that increases risk of stone disease. Studies have identified kidney stones in allograft kidney as one of the serious problems in kidney transplant recipients[12-40]. However, unlike the general population, the incidence and characteristics of kidney stones in kidney transplant recipients are not well studied. The aim of this meta-analysis was to appraise the incidence and types of kidney stones after kidney transplantation.

MATERIALS AND METHODS

Cheungpasitporn W and Thongprayoon C individually examined published studies and conference abstracts indexed in MEDLINE, EMBASE, and Cochrane Database from the inception of the databases through March 2016. The search strategy used is detailed in the supplementary material (Item 1). Further pertinent studies were retrieved by conducting a manual search using references from the articles that were reclaimed from the search strategy noted above. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses[41] and previously published guidelines[42,43].

The inclusion criteria were as follows: (1) randomized controlled trials or observational studies (case-control, cross-sectional, cohort studies, or case series); (2) patient population age > 18 years old; and (3) data on kidney stones in kidney transplant recipients were provided. The search was limited to English-language studies. Both published studies and conference abstracts were incorporated. Study eligibility was independently determined by the two investigators mentioned earlier. Differing decisions were settled by joint agreement.

A standardized information collection form was applied to derive the following data: The first author of each study, study design, year of publication, country where the study was conducted, number of kidney transplant recipients studied, number of patients with kidney stone, age and gender of patients with kidney stones, time of diagnosis after kidney transplantation, type of donor (Live or deceased donor), type and location of kidney stones, and period of follow-up.

Statistical analysis

MetaXL software (EpiGear International Pty Ltd)[44] was utilized for data analysis. The incidence rates (IRs) and 95%CIs of adverse effects were reported using a DerSimonian-Laird random-effects model[45]. A random-effects model was implemented due to the high likelihood of inter-study variances. The Cochran Q test was completed to assess statistical heterogeneity. The I^2 statistic was added to evaluate the degree of variation across studies related to heterogeneity instead of chance. An I^2 of 0%-25% represents insignificant heterogeneity, 26%-50% low heterogeneity, 51%-75% moderate heterogeneity and > 75% high heterogeneity[46]. To assess for publication bias funnel plots were used[47].

RESULTS

Our search strategy yielded 1554 articles. Of these, 1397 articles were excluded following the review of their title and abstract based on their relevance and the eligibility criteria. The remaining 157 articles underwent full-length review, and an additional 136 were excluded for failing to meet the criteria. Twenty one articles[12-29,36,38,40] met all inclusion criteria and were identified for the meta-analysis of kidney stones in kidney transplant recipients (Table 1). Supplementary Item 2 outlines our search methodology

Table 1 Main characteristics of the studies included in this meta-analysis

Ref.	Country	Year	Total number	No. of patients with kidney stone	Time of diagnosis	Sex of patients with stone	Age of patients with stone	Donors	Stone location	Stone composition	Mean follow-up time
Cho *et al*[12]	United States	1988	544	9	Mean 14.7 mo, Median 7 mo (range 3-42 mo)	6 male, 3 female	Mean 30 yr (range 8-65 yr)	6 living, 3 cadaveric	4 bladder, 3 kidney, 2 unknown	4 calcium oxalate/ calcium phosphate, 2 ammonium magnesium phosphate and carbonate appetite, 1 uric acid, 2 not studied	5 (range 1.5-15.5) yr
Hayes *et al*[13]	United States	1989	892	10	Mean 13 mo (range 4-49 mo)	7 male, 3 female	Mean 29 yr (range 17-53 yr)	3 living, 7 cadaveric	NR	NR	NR
Harper *et al*[38]	United Kingdom	1994	178	6	NR	4 male, 1 female	NR	4 living, 1 cadaveric	NR	1 uric acid, 2 calcium phosphate, 1 calcium oxalate, 1 Magnesium ammonium phosphate	NR
Shoskes *et al*[14]	United Kingdom	1995	812	2	Mean 3.5 yr (range 2-5 yr)	NR	Mean 40 yr	NR	2 ureter	NR	At least 1 yr
Benoit *et al*[36]	France	1996	1500	12	NR	7 male, 5 female	Mean 36 yr	2 living, 10 cadaveric	5 calyces, 6 ureter, 1 pyeloureteral junction	4 calcium oxalate and phosphate, 2 struvite	NR
Del Pizzo *et al*[15]	United States	1998	540 (445 renal transplant, 95 pancreas/ renal transplant)	4	NR	NR	NR	NR		NR	NR
Rhee *et al*[16]	United States	1999	1813 (1730 renal transplant, 83 pancreas/ renal transplant)	8	NR	4 male, 4 female	Mean 51 yr (range 34-60 yr)	2 living, 1 cadaveric, 5 pancreas/ renal	3 kidney, 1 ureter, 4 bladder	1 uric acid, 1 calcium oxalate, 1 calcium oxalate/ calcium phosphate, 1 calcium phosphate, 1 struvite stone, 3 unknown	Mean 68.6 mo (range 27-98 mo)
El-Mekresh *et al*[17]	Egypt	2001	1200	11	NR	NR	NR	NR	3 kidney, 4 ureter, 4 bladder	NR	NR
Kim *et al*[18]	United States	2001	849	15	Mean 17.8 mo (range 3-109 mo)	10 male, 5 female	Mean 41.5 yr (range 28-67 yr)	8 living, 7 cadaveric	11 bladder, 3 kidney, 1 multiple sites	5 mixed form of calcium oxalate and calcium phosphate, 1 calcium oxalate, 3 predominant calcium phosphate, 2 struvite, 2 mixed form of struvite and calcium phosphate, 2 not studied	Mean 58 mo (range 11-149 mo)

Klinger *et al*[19]	Austria	2002	1027	19 (4 diagnosis during transplant, 5 perioperative, 10 *de novo*)	For *de novo*: Mean 27.7 mo (range 13 to 48 mo)	8 male, 11 female	Mean 48.1 yr (range 26-72 yr)	1 living, 18 cadaveric	14 kidney, 3 infundibulum, 1 distal ureter, 1 staghorn	11 calcium oxalate, 2 uric acid, 1 calcium phosphate, 5 not studied	Mean 29 mo (range 14-48 mo)
Doehn *et al*[20]	Germany	2002	1500	11	NR	5 male, 6 female	Median 50 yr	11 cadaveric	NR	3 uric acid, 3 calcium oxalate, 2 magnesium ammonium stone, 3 not studied	Median 4 yr
Streeter *et al*[21]	United Kingdom	2002	1535	12	For renal calculi: Median 150 d (range 56-1280 d); For bladder calculi: Range 8 mo - 4 yr	NR	NR	NR	9 ureter, 3 bladder	NR	NR
Abbott *et al*[22]	United States	2003	42906	52	NR	NR	NR		35 kidney, 17 ureter	NR	1.89 ± 1.15 yr
Lipke *et al*[23]	United States	2004	500	7	9 mo (range 1.5-26 mo)	7 female	Mean 50 yr (range 8-73 yr)	4 living, 3 cadaveric	7 bladder	7 mixed between calcium oxalate and calcium phosphate	NR
Yigit *et al*[24]	Turkey	2004	125	5 (2 preoperative, 1 early posttransplant, 2 *de novo*)	For *de novo*: Mean 6.5 mo (range 6-7 mo)	3 male, 2 female	Mean 35.2 yr	NR	NR	2 calcium oxalate, 1 uric acid, 2 infectious	Mean 32.4 mo
Challacombe *et al*[25]	United Kingdom	2005	2085	21	3.7 (0.17-18) yr	8 male, 13 female	Mean 41 yr (range 15-64 yr)	3 living, 18 cadeveric	13 kidney, 7 ureter, 1 bladder	NR	NR
Ferreira Cassini *et al*[26]	Brazil	2012	1313	12 *de novo*	Range 6 mo to 13 yr	8 males, 9 females	Mean 45.6 yr (range 32-63 yr)	2 living, 15 cadaveric	6 calyces, 3 renal pelvis, 3 ureter	NR	NR
Stravodimos *et al*[27]	Greece	2012	1525	7	Mean 3.2 (2-7) yr	NR	NR	NR	5 kidney, 2 ureter	NR	Mean 8 yr
Cicerello *et al*[40]	Italy	2014	953	10	NR	4 male, 6 female	Mean 43 yr	NR	7 kidney, 3 ureter	NR	NR
Mamarelis *et al*[28]	Greece	2014	2045	9	Mean 3.1 yr (range 1-7 yr)	NR	NR	NR	6 kidney, 3 ureter	NR	6.6 yr (range 1-15 yr)
Rezaee-Zavereh *et al*[29]	Iran	2015	574	25	NR	NR	NR	NR	NR	NR	55 ± 53 mo

CaOx: Calcium oxalate; CaP: Calcium phosphate; NR: Not reported.

and selection process.

Incidence of kidney stones in kidney transplant recipients

The incidence of kidney stones after kidney transplantation within the 21 individual study ranged between 0.2% to 4.4% with an overall meta-analytical incidence of 1.0% (95%CI: 0.6%-1.4%)with evidence of a high level of heterogeneity (I^2 = 93%, P < 0.001; Figure 1).

We performed a sensitivity analysis limited only to the studies that provided data on time of kidney stone diagnosis after kidney transplantation; the estimated incidence of kidney stones was 0.9% (95%CI: 0.7%-1.2%), and there was evidence of a high level of heterogeneity (I^2 = 60%, P < 0.001; Figure 2). The mean duration to diagnosis of kidney stones after kidney transplantation was 28 ± 22 mo.

Subgroup analyses by geographic information were also performed. The estimated incidences of kidney stones were 0.9% (95%CI: 0.3%-1.7%; I^2 = 94%) and 0.7% (95%CI: 0.5%-0.9%; I^2 = 40%) in the United States and Europe, respectively. Data on the incidence of kidney stones in kidney transplant recipients in other geographical area were limited as shown in Table 1.

Characteristics of kidney transplant recipients with kidney stones

The mean age of patients with kidney stones was 42 ± 7

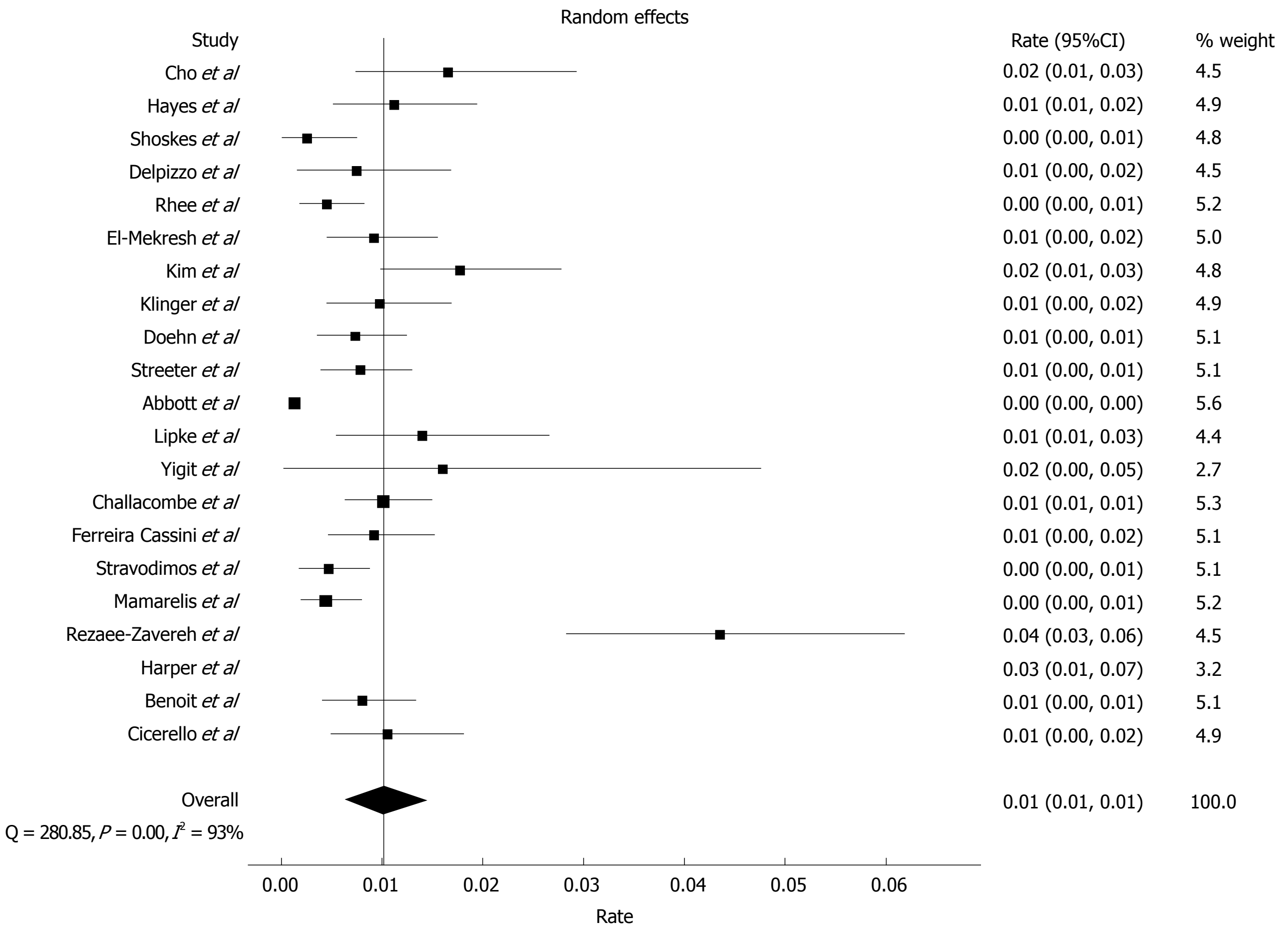

Figure 1 Forest plot of incidence of kidney stones in kidney transplant populations.

years. Within reported studies (Table 1), approximately 50% of kidney transplant recipients with kidney stones were males.

Types of kidney stones in kidney transplant recipients

Sixty-seven percent of kidney stones were calcium-based stones (30% mixed CaOx/CaP, 27%CaOx and 10%CaP), followed by struvite stones (20%) and uric acid stones (13%) as shown in Table 1.

Risk factors for kidney stones in kidney transplant recipients

Despite limited data on urinary supersaturation and risk factors for kidney stones, studies reported increased risk of kidney stones in kidney transplant recipients with hyperparathyroidism, hypercalciuria, hypocitraturia, hypophosphatemia, and urinary tract infection[28,38]. Harper *et al*[38] found that urinary excretion of magnesium and phosphate was at the lower range for all kidney transplant recipients with kidney stones. Uncommonly, urinary outflow obstruction and foreign bodies were also found as risk factors for kidney stones in kidney transplant patients[28,48].

Allograft failure in kidney transplant recipients with kidney stones

As in general patient populations, kidney stones can also cause acute kidney injury in kidney transplant recipients[49-52]. Since kidney transplant recipients can have obstructed kidney stones without any symptom of pain[26,28], prompt diagnosis and the removal of obstructed stones are the keys to preventing renal allograft failure[18]. Rezaee-Zavareh *et al*[29] reported no significant association between kidney stones after transplantation and graft survival (OR = 1.04; CI: 0.71-1.54). With the prompt removal of stones, Kim *et al*[18] found no significant changes in renal allograft function at diagnosis and after removal of kidney stones.

Evaluation for publication bias

Funnel plot evaluating publication bias for the incidence of kidney stones in kidney transplant recipients demonstrated slight asymmetry of the graph and thus suggested the presence of publication for positive studies regarding the incidence of kidney stones.

DISCUSSION

In this study, we demonstrated that an overall incidence of kidney stones in kidney transplant recipients was 1.0%. The mean age of recipients with kidney stones was 42, and half of stone formers were males. Calcium based (CaOx and CaP) stones were the most common types of kidney stones after kidney transplantation,

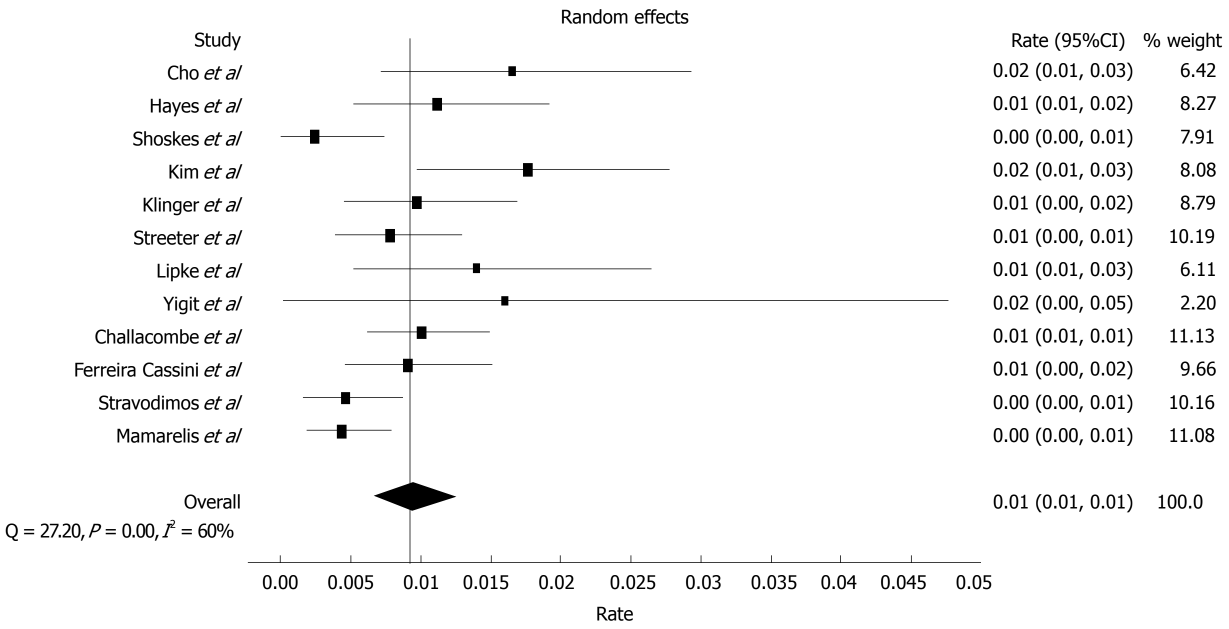

Figure 2 Forest plot of incidence of kidney stones in kidney transplant populations limited only to the studies that provided data on the time of kidney stone diagnosis after kidney transplantation.

followed by struvite stones and then uric acid stones.

The incidence of kidney stones after kidney transplantation from our meta-analysis is much lower than reported in the general adult populations[5-8]. Although the mechanisms behind the lower incidence of kidney stones after kidney transplantation, when compared with the general population, are only speculative, there are several plausible explanations. First, with the observation that new kidney stones are usually formed in transplanted allograft kidney but not in native non-functioning kidneys, kidney transplant recipients have significantly improved but still lower GFRs than those in healthy general populations, which may be "protective" for stone disease[9,10]. Second, transplanted kidneys are from healthy donors ideally without tubulointerstitial defects, one not uncommon cause of kidney stones. Third, it is possible that kidney stones after kidney transplantation are underdiagnosed since recipients may spontaneously pass them from the transplanted kidney/ureter without pain or awareness.

Calcium based (CaOx and CaP) stones are the most common types of kidney stones in the general population as well as after kidney transplantation as demonstrated in our meta-analysis. Interestingly, struvite stones (ammonium magnesium phosphate) or "infection stones" is more common in kidney transplant recipients (20%) than in the general population (10%-15%)[53]. Since struvite stones are associated with infection with urea-splitting bacteria and the principles of treating struvite stones are different than other stones types, including removal of all stone fragments and use of antibiotics[53], this information is important for future studies targeting prevention and management of kidney stones after kidney transplantation.

There are several limitations to our study. First, there were statistical heterogeneities in the analysis of the incidence of kidney stones. The potential sources of this heterogeneity included differences in diagnostic methodology of kidney stones and follow-up duration. However, a sensitivity analysis that limited studies to those that only provided data on time of kidney stone diagnosis still showed a similar incidence rate of kidney stones, consistent with the finding of our primary analysis. Second, most included studies were conducted in developed Western countries with the majority of the subjects being Caucasian. Thus, our findings may not represent renal transplant populations from other parts of the world. Lastly, the data on urinary supersaturation and risk factors for kidney stones were limted. Although struvite stones represent an association with urinary tract infection, it is still unclear the risk factors for other stone types after kidney transplantation, and future studies are needed.

Our meta-analysis demonstrates that the estimated incidence of kidney stones in patients after kidney transplantation is 1.0%. Although calcium based stones are the most common kidney stones after transplantation, struvite stones are the second common type. These findings may impact clinical prevention and management of kidney stones in kidney transplant recipients.

COMMENTS

Background

Renal stones are one of the most prevalent metabolic disorders and urological problems. However, with reduced kidney functions, patients with advanced chronic kidney disease (CKD) or end-stage kidney disease (ESRD) may encounter less stone disease. After successful kidney transplantation, ESRD patients have significant improvement in kidney functions and may develop kidney stones in their allograft kidney.

Research frontiers

The incidence and characteristics of kidney stones in kidney transplant recipients are not well studied. It is thus necessary to assess the incidence and types of kidney stones after kidney transplantation.

Innovations and breakthroughs

In this study, the authors demonstrated that an overall incidence of kidney stones in kidney transplant recipients was 1.0%. The mean age of recipients with kidney stones was 42, and half of stone formers were males. Calcium based (CaOx and CaP) stones were the most common types of kidney stones after kidney transplantation, followed by struvite stones and then uric acid stones.

Applications

The data in this study demonstrates an estimated incidence of kidney stones in patients after kidney transplantation of 1.0%. Calcium based stones and struvite stones are common types of kidney stones after transplantation. These findings may impact the clinical management of kidney stones prevention in kidney transplant recipients.

Terminology

CaOx: Calcium oxalate; CaP: Calcium phosphate; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; NR: Not reported.

Peer-review

This is a reasonable first meta-analysis of incidence of kidney stones in kidney transplant recipients. The results have potential clinical applications.

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