A Systematic Scoping Review of Comparative Effectiveness Studies in Kidney Stone Disease

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OBJECTIVE To review the status of comparative effectiveness studies for kidney stone disease with focus on study outcome, type, population, time trends, and patient-centered approaches.

METHODS A systematic scoping review was performed for articles published between January 1, 2005, and March 30, 2021, using keywords relevant to kidney stone disease. Studies published in English that compared two or more alternative methods for prevention, diagnosis, treatment, monitoring, or care delivery were included. Two reviewers independently reviewed abstracts and an arbitrator resolved discrepancies. Nine reviewers abstracted information from full-length studies. Descriptive statistics were summarized, and linear regression was performed to evaluate temporal trends of study characteristics.

RESULTS We reviewed 1773 abstracts and 707 full-length manuscripts focused on surgical intervention (440); medical expulsive therapy (MET) (152); analgesic control (80); and homeopathic, diagnostics, and/or prophylaxis (84). Randomized controlled trials were common across all outcome categories, including surgery (41.6%), MET (60.2%), analgesic control (81.3%), homeopathic (41.2%), diagnostic (47.6%), and prophylaxis (49.1%). Patient-reported outcomes were utilized in 71.7% and 95% of MET and analgesic control studies, respectively, but in the minority of all other study themes. Over time, meta-analyses and multicenter studies increased [$P < .001$].

CONCLUSION Surgical and MET themes dominate published comparative literature in kidney stone disease. There is substantial variation in use of patient-reported outcomes across surgical themes. Multicentered studies and those generating higher level evidence have increased over time but opportunities exist to improve collaborative, high-quality, and patient-centered research in kidney stone disease. UROLOGY 183: 3–10, 2024. © 2023 Elsevier Inc. All rights reserved.

American Urological Association (AUA) guidelines for the management of stone disease (2014) were established to guide providers caring for first-time and recurrent stone formers, with a particular focus on patients' preferences and goals.[1,2] AUA guidelines are based upon structured literature review and supported by consensus opinions, with the strength of recommendations based upon the level of evidence available. Many current recommendations for both medical and surgical management of kidney stone disease depend upon expert opinion alone, suggesting significant gaps in the evidence base across the spectrum of diagnosis, secondary prevention, and surgical intervention of kidney stone disease.

The goals of comparative effectiveness research (CER) in kidney stone disease are to support shared decision-making by providing stakeholders (ie, patients, caregivers, providers, payers, policymakers) with information that can be used to make decisions about the benefits/tradeoffs between two or more tests, treatments/interventions, care delivery systems, or policies.[3] High-quality CER resulting in robust findings to broadly support clinical care and influence guideline creation requires well-designed, resource-intensive, and often prospective clinical investigation. Thus, high-impact clinical investigation must target gaps within the literature. To this

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end, we performed a systematic scoping review of the CER literature for kidney stone disease.

Having a clearer understanding of the landscape of the current published literature and its deficiencies will help to guide researchers, funding agencies, and stakeholder-directed groups to establish research agendas in years to come. In this scoping review, we examine the status of comparative effectiveness studies for kidney stone disease with a focus on study outcome, type, population, time trends, and patient-centered approaches to propose future directions for research opportunities.

METHODS

Article Identification

A systematic scoping review was performed to characterize the current state of CER in kidney stone disease, in accordance with the PRSIMA-Scoping Review guidelines.[4] The scoping review protocol was registered in the Open Science Framework (www.osf.io) and can be found at: https://osf.io/c5wxp/?view_only=9146348d6bfb445fb471111a9df68651. A systematic review of three separate databases (PubMed, Cochrane, and EMBASE) was performed on March 30, 2021 by a research librarian for full-text articles related to comparative effectiveness in kidney stone disease. The search was performed for articles published between January 1, 2005 and March 30, 2021 to provide an overview of contemporary literature related to our topic. Search terms specific for kidney stone disease (ie, "urinary calculi" or "kidney calculi") and CER (ie, "therapy" or "intervention") were utilized, with a full review of all search terms listed in Supplementary Figure 1.

We included studies that (1) compared two or more alternative methods for prevention, diagnosis, treatment, monitoring, or care delivery[3]; (2) focused on kidney or ureteral stones, exclusive of bladder calculi; and (3) were written in English (as comprehensive translation services were not available at the time of the review).

Abstract Review

Two reviewers (JE, PD) independently reviewed all abstracts using the Rayyan platform for intelligent systematic review (www.rayyan.ai)[5] to determine inclusion for full-text review. A third reviewer (GT) resolved discordant assessments. Duplicate abstracts and those not meeting eligibility criteria were removed. Articles receiving two affirmative indicators from the abstract reviewers were included in the full-text review, using EndNote to export citations to a research librarian at our primary data site for acquisition of full-text articles. Full-text articles were shared via the Box.com cloud-based file-sharing platform.

Article Review and Abstraction

Nine reviewers reviewed the included articles. Articles that did not meet inclusion upon review of the entire manuscript were excluded at this stage. A study flowchart of the article review process is shown in Figure 1. REDCap[6] was used to record the following characteristics of each article: journal type, study theme, study type, study duration, participant follow-up duration, number of centers involved, location of study, outcomes, funding, cohort size, use of stakeholders in study design, and populations included. Supplementary Figure 2 includes a list of all abstracted variables and corresponding categories. Ten study themes were defined for categorization, nine of which were based off of kidney stone research study needs identified in 2015 by the National Institutes of Health.[7] We added a homeopathic theme following abstract review, acknowledging the presence of such studies within the first 10 articles reviewed.

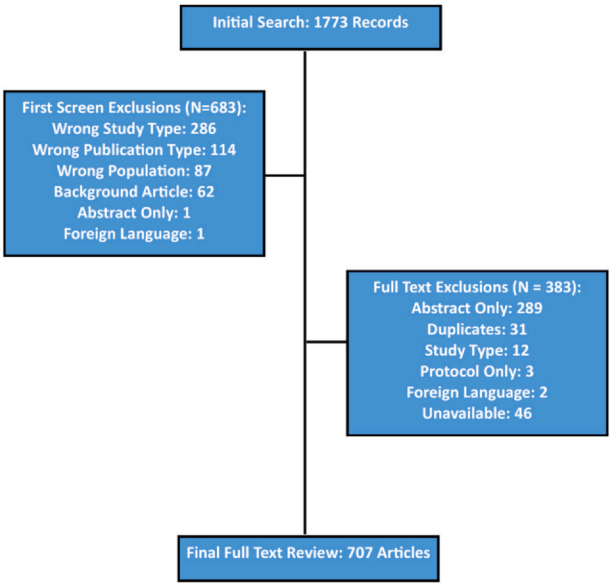

Figure 1. Inclusion/exclusion flow chart for scoping review. (Color version available online.)

These 10 themes included: surgical intervention, medical expulsive therapy (MET), imaging diagnostic tests, metabolic diagnostic tests, analgesics, medical prophylaxis for calcium or idiopathic stone disease, medical prophylaxis for uric acid stone disease, medical prophylaxis for rare (ie, genetic) stone disease, dietary intervention, and homeopathic intervention. Reviewers indicated "unspecified" if study design aspects were not reported. Studies modeling cost did not have cohort size entered. For meta-analyses, the study duration was defined as the interval for article inclusion and the location of study was based off the authors' institution. Turkey and Russia were considered to be in Asia for purposes of study location. Unless reported in the study methods, number of centers was taken from the number of different affiliated organizations for authors listed on the title page. Patient-reported outcomes (PROs) were defined as any outcome that was reported directly from the patient, including validated and nonvalidated questionnaires, symptom diaries, or pain scales. *Structured* PROs included use of validated questionnaires or pain scales.

Descriptive and comparative statistics were completed using Stata v15.0 (College Station, TX). Statistical significance for comparative statistics was defined as a *P*-value < .05.

RESULTS

The initial search yielded 1773 studies, of which 683 were excluded on abstract review and 383 excluded on full-text review, resulting in 707 full-text articles for data abstraction (Fig. 1). An overall summary of included studies, stratified by study design, study content (journal type, research themes, study outcomes), and study populations, is displayed in Tables 1-3. All studies had journal type, study theme, study type, number of centers involved, and location of study and reported at least one outcome. Most studies were randomized controlled trials (RCTs) (360/707, 50.9%), arose from a single center (540/707, 76.4%), and were published in urologic journals (445/707, 69.4%). A small proportion of studies (95/707, 13.4%) were funded by nonprofit and/or government sources (Table 1). The number of studies published per year increased over the assessment period, with the most voluminous year of productivity noted in 2020 (81 studies, 11.5%). Most included studies were published after 2015 (365/707, 51.6%). Surgical themes were the most commonly represented (440/707, 62.2%), followed by MET (152/707, 21.5%) and pain (80/707, 11.3%). The remainder of the themes are documented in Table 2 as are the reported study outcomes. Most studies measured PROs (354/707, 50.1%) but less than one-third of studies utilized a structured format for PRO reporting (224/707, 31.7%). Only two studies described including patient stakeholders in the study design (Table 3).

When evaluating study theme stratified by study design, RCTs were the most common study design across all study

Table 1. Summary of included studies, study design.

	N	%
Study type		
Meta-analysis	117	16.55
RCT	360	50.92
Prospective observational	69	9.76
Retrospective	145	20.23
Other	16	2.26
Number of centers involved		
Single center	540	76.38
Multi-institution (2-5 centers)	110	15.56
Multi-institution (6-10 centers)	24	3.39
Multi-institution (> 10 centers)	22	3.11
Unknown	11	1.56
Location of study[*]		
North America	73	10.33
South America	5	0.71
Europe	90	12.73
Asia	500	70.72
Africa	48	6.79
New Zealand/Australia/Pacific Islands	2	0.28
Study duration		
0-6 mo	60	8.49
7-12 mo	107	15.13
13-24 mo	156	22.07
25-48 mo	114	16.12
> 48 mo	159	22.49
Not specified	111	15.7
Follow-up duration		
0-3 mo	511	72.28
4-6 mo	32	4.53
7-12 mo	23	3.25
13-24 mo	9	1.27
25-48 mo	11	1.56
> 48 mo	117	16.55
Not specified	4	0.57
Funding		
Unfunded	209	29.56
Not profit/Government grant	95	13.44
Unknown	384	54.31
Industry grant	12	1.7
Combination nonprofit + Industry	7	0.99

RCT, randomized controlled trial.
[*] As more than one response could be indicated, percentages may total > 100%.

Table 2. Summary table of included studies, study content.

	N	%
Journal type		
Urology	445	62.94
Nephrology	9	1.27
Non-Urology/Nephrology	188	26.59
Both Urology/Nephrology	65	9.19
Research themes[*]		
Surgical	440	62.23
MET	152	21.50
Imaging	19	2.69
Metabolic evaluation	3	0.42
Analgesic control	80	11.32
Medical prophylaxis (CaOx, Idiopathic)	29	4.10
Medical prophylaxis (UA)	5	0.71
Medical prophylaxis (Genetic/Rare kidney stone type)	2	0.28
Diet	17	2.40
Homeopathic medicine	16	2.26
Diagnostic (any)[†]	21	2.97
Prophylaxis (any)[‡]	47	6.65
Outcomes[*]		
Imaging	533	75.39
Patient-reported event	262	37.06
Validated questionnaire	42	5.94
Diary	49	6.93
Nonvalidated questionnaire	69	9.76
Biological	223	31.54
Surgical complication	383	54.17
Medical complication	155	21.92
Cost	69	9.76
Observed event[§]	434	61.39
Pain scale	136	19.24
Other	138	19.52
Any PRO[**]	354	50.07
Structured PROs[††]	224	31.68

CaOx, calcium oxalate; MET, medical expulsive therapy; PRO, patient-reported outcome; UA, uric acid.
[*] As more than one response could be indicated, percentages may total > 100%.
[†] Diagnostic themes include imaging and metabolic evaluation.
[‡] Prophylaxis themes include any medical prophylaxis or diet.
[§] Not patient-reported, that is, hospital visit, surgical intervention, stone passage, acute kidney injury defined by diagnosis code as opposed to serum studies, blood transfusion, urinary tract infection.
[**] Patient-reported event, validated and nonvalidated questionnaires, diary, or pain scales.
[††] Validated and nonvalidated questionnaires, diary, or pain scales.

Table 3. Summary table of included studies, study populations.

	N	%
Age		
Pediatric	47	6.65
Adult	430	60.82
Lifespan	57	8.06
Unspecified	173	24.47
Rare stone disease		
Exclusively rare stone disease	4	0.57
Exclusively nonrare stone disease	33	4.67
Combination	11	1.56
Not specified	659	93.21
Rare stone type		
Medication-induced	1	6.67
Genetic based	11	73.33
Other	1	6.67
Unspecified	2	13.33
Disability		
Included population	1	0.14
Excluded population	29	4.1
Exclusive population	3	0.42
Unspecified	674	95.33
Gender		
Male only	9	1.27
Female only	4	0.57
Both males and females	607	85.86
Unspecified	87	12.31
Race[*]		
Asian	28	3.96
Black	12	1.70
Hawaiian/Pacific Islander	1	0.14
Native American/Alaskan Native	2	0.28
White	16	2.26
Not specified	667	94.34
Ethnicity		
LatinX	11	1.56
Not Latinx	1	0.14
Not specified	692	97.88
Both Latinx and non-LatinX	3	0.42

[*] As more than one response could be indicated, percentages may total > 100%.

themes. Meta-analyses were the second most common study design for analgesic control (65/80, 81.3%) and MET (100/166, 60.2%). In contrast, retrospective cohort studies were the second most frequent study design for surgery, homeopathic medicine, and diagnostics (Table 4). Stratifying study theme by specific design aspects (Supplementary Table) revealed little differences in the distribution of themes by study center or by studies that were unfunded, funded by government or nonprofit grants, or whose funding source was unspecified. While industry funding did seem to comprise a greater proportion of MET and prophylactic studies, the overall small number of industry-funded studies included either solely or in combination with nonprofit funding (N = 19) limits further comparisons. Studies on analgesic control used a high proportion of any PRO (76/80, 95.0%) or structured PROs (72/80, 90.0%), mostly attributable to use of pain scales. A full stratification of PRO use by study theme is shown in Supplementary Table.

The majority of studies focused on adult patients (430/707, 60.8%). A large proportion of cohorts were unspecified with regards to age, inclusion of rare stone disease, or inclusion of patients with disability: Age - 173/707 (24.5%); Rare Stone Disease - 659/707 (93.2%); Disability - 674/707 (95.3%) (Table 3). Retrospective cohort studies comprised most pediatric studies (24/47, 51.1%) while RCTs were the most common study design in studies of adults (268/430, 62.3%). Studies including both children and adults (ie, lifespan studies) accounted for 57 total studies, of which 26 (45.6%) were RCTs and 14 (24.6%) were retrospective cohort studies. Patients with disabilities were the exclusive focus of only three surgical studies (one meta-analysis, one RCT, one retrospective cohort study). Patients with rare kidney stone disease were the exclusive focus of four studies, all of which were RCTs focused on kidney stone prevention.

Meta-analyses increased over the evaluation period while RCTs had the most consistent decrease (Fig. 2A). Single-center studies became less common, although still predominated, over the study period (Fig. 2B). No substantial trends were seen with regards to study location, study theme, included populations, or use of PROs (data not shown).

DISCUSSION

In this scoping review, we identified 707 original CER studies in kidney stone disease, most of which focused on surgery and MET. Most studies were conducted at a single center, were RCTs, and were published in urologic journals. Study type and use of PRO measures varied across study themes. Overall, few studies utilized structured PROs. Assessment of specific subgroups (pediatrics, rare stone disease, patients with disabilities) was limited due to the lack of specific definitions in many studies' inclusion/exclusion descriptions. Pediatric studies used retrospective designs more than adult studies, which indicated a potential limitation in the quality of studies conducted in this

Table 4. Stratification by surgical theme and study design.

	Surgical		MET		Pain		Homeopathic		Diagnostic		Prophylaxis	
	N	%	N	%	N	%	N	%	N	%	N	%
Meta-analysis	72	16.36	34	20.48	10	12.50	1	2.94	3	14.29	7	13.21
RCT	183	41.59	100	60.24	65	81.25	14	41.18	10	47.62	26	49.06
Prospective observational	52	11.82	7	4.22	2	2.50	1	2.94	2	9.52	5	9.43
Retrospective	125	28.41	11	6.63	3	3.75	2	5.88	6	28.57	5	9.43
Other	8	1.82	14	8.43	0	0.00	16	47.06	0	0.00	10	18.87
Total	440		166		80		34		21		53	

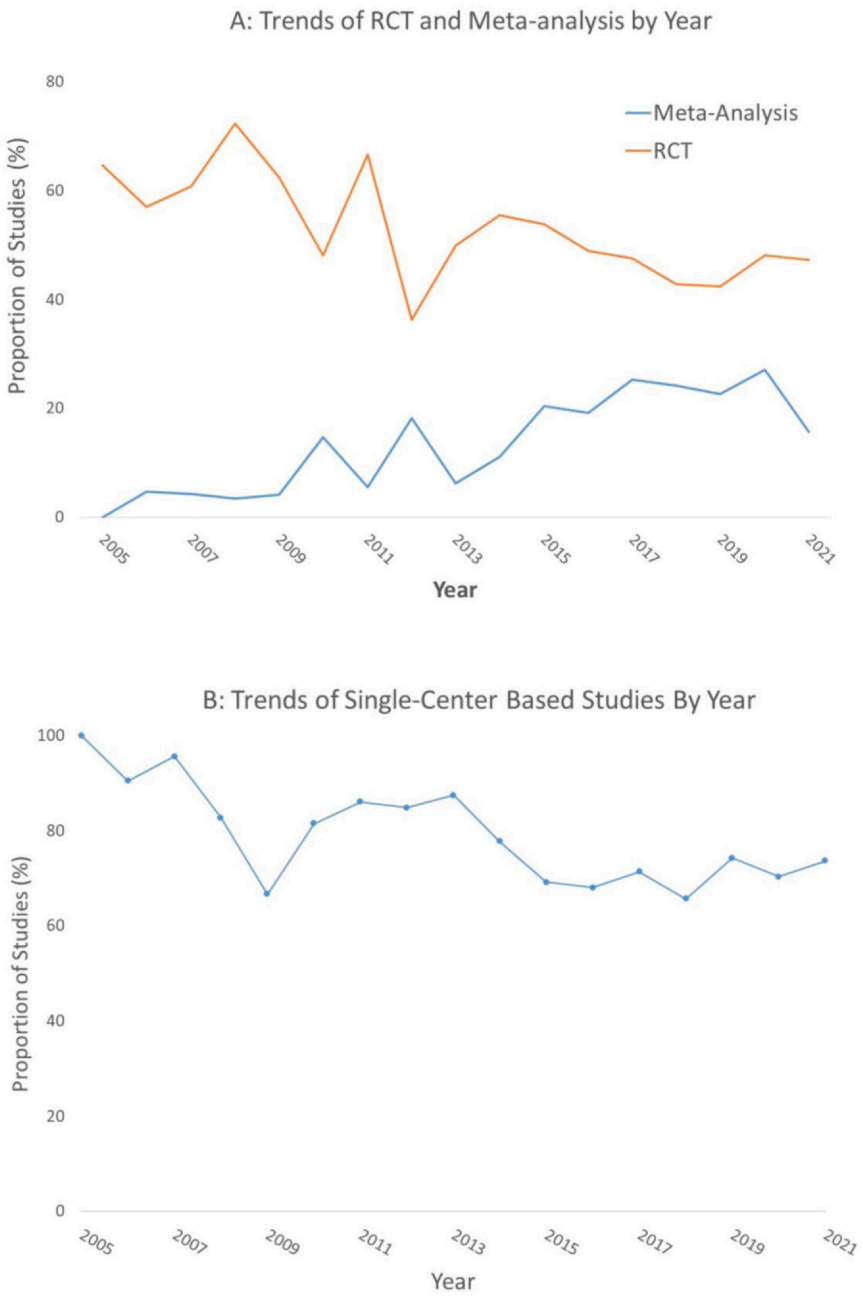

Figure 2. **(A)** Trends of RCT and meta-analysis by year. **(B)** Trends of single-center based studies over time. RCT, randomized controlled trial. (Color version available online.)

population. Over the course of the review period, meta-analysis and multicenter studies became more common, indicating increasing appetite and ability to enhance knowledge generation through collaborative efforts.

The majority of studies in our review, including most RCTs, examined surgery and MET in patients with stone disease. However, the evidence base supporting surgery and MET in the AUA guidelines is weak.[1] In spite of a large volume of CER dedicated to surgical management and expulsive therapy, only 18 of the 42 recommendations from the AUA guidelines on surgical management are level of evidence A or B. There is only one recommendation for ureteral stenting supported by grade A evidence (ie, unlikely to change with future research). Thus, the abundance of focus in the literature on surgery and MET has not translated into a strong evidence base supporting clinical decision-making. Meanwhile, themes that have not been studied as extensively have even less strong evidence supporting shared-decision making. For instance, only 9 of the 27 recommendations related to medical management and diagnostics in the AUA guidelines are level of evidence A or B. Only 1 recommendation is grade A evidence, pertaining to serum laboratory monitoring while on certain medical prophylactic medications.[2] Our findings reveal that the number of studies dedicated to certain themes does not

necessarily translate to strong evidence supporting clinical decision-making. Additionally, we saw trends toward more collaborative research in our study, albeit without an increase in the number of prospective or randomized trials, indicating further opportunities for improvement in clinical trial design for kidney stone disease. Meanwhile, we identified several understudied areas, such as diagnostic evaluation and prevention. These themes deserve additional attention within the research space, potentially bolstered by dedicated funding support. Finally, we would note in areas of heavy focus yet uncertainty (ie, MET), the landscape of current comparative investigation has seemingly been saturated. If no further gains in comparative effectiveness are to be made, we believe additional work should focus on implementation or optimization of treatments where evidence is supported.

The prevalence of stone disease has risen globally, with a disproportionate increase in stone incidence and prevalence in women and children as well as Black and Hispanic populations in the United States.[8,9] Notably, these populations also have unexplained variations in treatment decisions and outcomes.[10,11] Accordingly, there is a growing need to expand the evidence base to care for vulnerable populations. This review revealed deficiencies in this evidence base, particularly for PROs. Additionally, this review highlights the importance of defining cohorts clearly in future studies, particularly in the context of rare stone disease and disability and conducting more prospective studies. Our study identified inconsistent description of cohorts including age, rare stone disease, and inclusion of disability, further exacerbated by the lack of standardized reporting of ethnicity and race. Additionally, genetic causes of stone disease were poorly described and the inclusion or exclusion of these patients was poorly reported. To address these limitations, traditionally underrepresented groups within kidney stone disease should be intentionally included in future trials. Strategies to address these gaps could include stakeholder engagement, to further define the unmet needs of these populations and potential barriers to recruitment, as well as dedicated efforts from funding agencies to support research focused on these populations.[12]

Future efforts to amplify the patient voice and experience in kidney stone disease research should focus on PROs, an essential component to assess effective, patient-centered care delivery. Our current study found about half of studies utilized PROs, when considering a broad definition of this outcome. However, validated PROs were included in less than one-third of studies. These findings are concerning, as interpreting and comparing PROs across studies is limited if these outcomes are reported in a nonvalidated or unstructured format. These data echo previously reported findings, including a systematic review on PROs in RCTs for kidney stone disease, which found that a majority (67%) of RCTs failed to utilize any validated PROMs in secondary outcomes.[13] We would call on investigators to consider use of structured PROs as valuable primary or secondary outcomes for prospective investigation. Furthermore, clinicians who build PRO collection into routine clinical care and the electronic health record may also have access to these data even in retrospective study investigation. Such structural shifts in clinical assessments could have powerful implications when leveraging large, electronic health record-based data sets.

Our study has limitations. First, our selection of studies could be biased due to several factors. We selected only English-language articles, included articles of lower study quality (ie, retrospective chart reviews), and excluded studies prior to 2005. Thus, we may have failed to characterize landmark historical articles, or those that were published in non-English journals. Second, our study was designed as a scoping review, intended to provide information on the breadth of the published literature for CER in kidney stone disease. Thus, we did not formally assess study quality.

Nonetheless, our review provides valuable data for researchers interested in the current landscape of data related to CER in kidney stone disease. Moving forward, the research community needs to focus efforts to standardize reporting and include study samples that are representative of those living with the disease. Key experiences of the individuals with unique and potentially more challenging kidney stone disease, such as those with genetic stone disease or significant comorbidity, must be included. Validated PROs are generally underutilized and study focus remains heavily distorted toward MET and surgical therapy. Finally, our review suggests the current landscape is barren with respect to stakeholder-engagement efforts at the level of research design and development. Patient and caregiver-focused efforts to contribute to these studies can enhance the impact and feasibility of resource-intensive endeavors and should be an aspiration for researchers striving to develop meaningful CER trials for kidney stone disease.

CONCLUSION

Surgical and MET themes dominate published comparative literature in kidney stone disease. There is substantial variation in use of PROs across surgical themes. Multicentered studies and those generating higher level evidence have increased over time but there are opportunities to include patient-centered research across kidney stone disease. Future efforts should be directed with engagement from all stakeholders for design, planning, execution to address desired questions.

Declaration of Competing Interest

Jonathan S. Ellison: paid consultant for Alnylam Pharmaceuticals (not active, but present w/in past 24 months); paid contributor for UpToDate (active). Gregory Tasian: Gregory Tasian is on the Scientific Advisory Board of, is a consultant for, and receives research funding from Dicerna Pharmaceuticals and Alnylam Pharmaceuticals. David I. Chu: This work is supported in part by a research grant from the National Institute of Diabetes and Digestive and Kidney Diseases (K23 DK125670) to Dr David I. Chu. Ryan Spiardi: This work is supported in part by a research grant from NIH T32 research grants supporting Dr Ryan Spiardi (NIH 5T32DK7006-48 & NIH 5T32DK7006-49). None of the other authors have any financial interests to disclose.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.urology.2023.08.042.

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EDITORIAL COMMENT

The field of Endourology has driven innovation in technological advancements and surgical techniques over the last 5-10 years. Where we as a field have not been as successful is in answering the questions and evaluating the clinical outcomes that may be most pertinent to the average stone patient. In this review, Dangle and colleagues sought to describe the current state of the endourology literature and identify strengths and opportunities for further research and advancement. Several important themes emerged. Surgical outcomes research continues to rely heavily on retrospective series, while the randomized controlled trials that have been performed are largely single-center. As this review suggests, utilizing multicenter study designs with consortiums or research partnerships will facilitate trial enrollment and completion while yielding stronger evidence with which to better inform clinical practice. The authors highlight areas of research that are saturated, including medical expulsive therapy and evaluation of the use ureteral stents, as well as areas that are lacking. As the authors highlighted, these topics include stone prevention, rare stone disease, validated patient-reported outcome (PRO) measures, epigenetics and nephrolithiasis in underserved patient populations.

As we decide where to focus our resources and attention, reviews such as this one can provide direction. There is a need for multicenter randomized controlled trials examining surgical techniques and laser technologies, pharmacologic and dietary prevention and PRO measures. For example, word of mouth and expert opinions have guided the adoption of new laser techniques but are limited by the heterogeneity of stone disease. In a subset of patients, nephrolithiasis can be conceptualized as a chronic disease with varying pathogenic mechanisms including dietary intake, nephrogenic factors, and urinary and gastrointestinal microbiome variations. We lack a true understanding of the factors that incite stone disease and reproducible clinical methods to achieve durable disease prevention, especially in disadvantaged or underserved populations. Finally, we need to focus on developing and validating PRO measures that are meaningful to both surgeon and patient. Validated questionnaires such as WISQOL and USSQ[1,2] have laid the foundation upon which we must expand.

The authors have described our opportunity to focus on clinically relevant and unanswered questions. In the next 10+ years, I hope we find ourselves with a better understanding of stone disease and better tools for treatment and prevention.

Declaration of Competing Interest

None Declared.

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