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Treatment of Calciphylaxis in CKD: A Systematic Review and Meta-analysis

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Background: Calciphylaxis is a life-threatening complication of chronic kidney disease (CKD). To inform clinical practice, we performed a systematic review of case reports, case series, and cohort studies to synthesize the available treatment modalities and outcomes of calciphylaxis in patients with CKD.

Methods: Electronic databases were searched for studies that examined the uses of sodium thiosulfate, surgical parathyroidectomy, calcimimetics, hyperbaric oxygen therapy, and bisphosphonates for calciphylaxis in patients with CKD, including end-stage renal disease. For cohort studies, the results were synthesized quantitatively by performing random-effects model meta-analyses.

Results: A total of 147 articles met the inclusion criteria and were included in the systematic review. There were 90 case reports (90 patients), 20 case series (423 patients), and 37 cohort studies (343 patients). In the pooled cohorts, case series, and case reports, 50.3% of patients received sodium thiosulfate, 28.7% underwent surgical parathyroidectomy, 25.3% received cinacalcet, 15.3% underwent hyperbaric oxygen therapy, and 5.9% received bisphosphonates. For the subset of cohort studies, by meta-analysis, the pooled risk ratio for mortality was not significantly different among patients who received sodium thiosulfate (pooled risk ratio [RR] 0.89; 95% confidence interval [CI] 0.71–1.12), cinacalcet (pooled RR 1.04; 95% CI 0.75–1.42), hyperbaric oxygen therapy (pooled RR 0.89; 95% CI 0.71–1.12), and bisphosphonates (pooled RR 0.77; 95% CI 0.44–1.32), and those who underwent surgical parathyroidectomy (pooled RR 0.88; 95% CI 0.69–1.13).

Conclusion: This systematic review found no significant clinical benefit of the 5 most frequently used treatment modalities for calciphylaxis in patients with CKD. Randomized controlled trials are needed to test the efficacy of these therapies.

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Calcific uremic arteriolopathy or calciphylaxis is a rare and serious disorder that presents with skin ischemia and necrosis and is characterized histologically by calcification of arterioles in dermis and subcutaneous adipose tissue.[1] Calciphylaxis most commonly occurs in patients with end-stage renal disease who are on dialysis, and confers a high mortality rate of 40% to 60%.[2] The incidence of calciphylaxis in hemodialysis patients has been estimated at 35 cases per 10,000 patients in the United States[3] and 4 cases per 10,000 patients in Europe.[4] Major risk factors include poorly controlled secondary hyperparathyroidism, diabetes mellitus, obesity, and warfarin therapy.[3,5] Although the pathophysiology of calciphylaxis has primarily been linked to longstanding hyperphosphatemia and hyperparathyroidism,[6] low parathyroid hormone levels confer an increased risk for calciphylaxis.[4]

To date, there are no evidence-based clinical practice guidelines for the prevention and treatment of calciphylaxis, only expert opinions derived from the limited literature.[4,7] Treatment modalities are not standardized, but they all focus on wound care with or without surgical debridement. Hyperbaric oxygen therapy is proposed to be the second line of wound care treatment[8] to improve oxygen delivery to hypoxic soft tissues and promote wound healing. Calcium-based phosphate binders and vitamin D analogues should be avoided, and patients with poorly controlled hyperparathyroidism should be prescribed a calcimimetic agent or undergo surgical parathyroidectomy. Sodium thiosulfate is frequently used an adjunctive treatment,

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with several proposed mechanisms, including calcium chelation, vasodilatory effects, and ability to restore endothelial function.[9] Although bisphosphonates have been used for the treatment of calciphylaxis, their mechanism of action is unknown, and includes inhibition of calcium crystallization and prevention of hydroxyapatite formation.[10,11] Other treatments described in case reports have included the use of apheresis[12] and tissue plasminogen activator.[13,14] At present, there are no approved treatments for calciphylaxis, and all drug therapies that have been tested fall under the off-label use.

To inform clinical practice and shed more light on this orphan serious and fatal disorder, we performed a systematic review of case reports, case series, and cohort studies to synthesize the available treatment strategies and outcomes of patients presenting with calciphylaxis.

METHODS

Data Source and Searches

The review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[15] The literature search was conducted in MEDLINE (1966 to July 2018), Scopus, and the Cochrane Central Register of Controlled trials to identify eligible studies. For the search, the following Medical Subject Heading terms were used: "calciphylaxis" and "calcific uremic arteriolopathy." We also manually reviewed the reference list in the retrieved articles. The search was limited to the English language and focused on adults (age ≥18 years) with all stages of CKD, including end-stage renal disease.

Study Selection

In the absence of randomized controlled trials for the treatment of calciphylaxis, we focused on retrospective and prospective cohort studies, case series, and case reports that reported on 1 or more of the following treatment modalities for calciphylaxis: sodium thiosulfate, surgical parathyroidectomy, calcimimetic agent (i.e., cinacalcet), hyperbaric oxygen therapy, and bisphosphonates. There were no restrictions on sample size or study duration.

We classified types of studies based on the presence or absence of a control group. Case reports or single cases consisted of reports of individual patients who received at least 1 of the previously mentioned treatment modalities. Case series consisted of multiple cases (>1 subject) in which patients received the same treatment modalities, and there was no control group.[16] Cohort studies entailed patients receiving treatment and a control group not receiving treatment.[17] For both case series and cohort studies that had multiple treatment modalities, we meta-analyzed each treatment modality separately according to the presence or absence of a control group.

The CAse REport (CARE) guidelines[18] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[19] were used to identify case reports and cohort studies, respectively. Only case reports with adequate information according to the CARE guidelines, and cohort studies with adequate methods according to the STROBE statement were included in the review. Two authors (SU and KK) independently screened the titles and abstracts of the electronic citations, and full-text articles were retrieved for comprehensive review, and were independently rescreened. Disagreements were resolved through consensus and arbitration by a third author (PS).

Data Extraction and Quality Assessment

The following study characteristics were extracted in duplicate: country of origin, year of publication, study design, number of patients, demographic data, dialysis modality, diabetes mellitus status, medication use (vitamin D analogues, calcium-based phosphate binders, and warfarin), laboratory test results (calcium, phosphorus, and parathyroid hormone level) at the time of diagnosis, and location of the calciphylaxis skin lesions (upper vs. lower extremities, proximal vs. distal).

The following outcomes of interest were extracted: characteristics of each treatment modality, impact on calciphylaxis skin lesions, all-cause mortality, and treatment-related adverse effects. The outcome of the calciphylaxis skin lesions were categorized into 3 groups: complete resolution of lesions, partial resolution or stable lesions, and worsening of lesions.

Data Synthesis and Analysis

The results of the case reports and case series were tabulated and synthesized qualitatively. The results of the case series were synthesized quantitatively by performing random-effects model meta-analyses to compute pooled means and rates with corresponding 95% CIs to describe patient characteristics and clinical outcomes. For the subset of cohort studies with analyzable and comparable data, the results were synthesized quantitatively by performing random-effects model meta-analyses to compute weighted mean difference for continuous variables, and pooled risk ratios (RRs) for binary variables. All pooled estimates are displayed with a 95% CI. Existence of heterogeneity among study effect sizes was examined using the I^2 index and the Q-test P value. An I^2 index greater than 75% indicate medium to high heterogeneity.

Categorical variables were presented as percentage and continuous variables as mean ± SD or median (with interquartile range). Statistical significance was met when P value was less than 0.05. Publication bias was formally assessed using funnel plots and the Egger test. The analyses were performed using the Comprehensive Meta-Analysis Software version 2.0 (www.meta-analysis.com; Biostat, Englewood, NJ).

RESULTS

Characteristics of the Studies

A total of 1646 potentially relevant citations were identified and screened; 577 articles were retrieved for detailed evaluation, of which 147 fulfilled eligibility criteria, including 37 cohort studies,[10,20–55] 20 case series,[8,56–74] and 90 case reports[75–164] (Figure 1). There were 856 patients, 90 originating from case reports, 423 originating from case series, and 343 originating from cohort studies. Details of the individual reports are shown in Supplementary Tables S1 to S3.

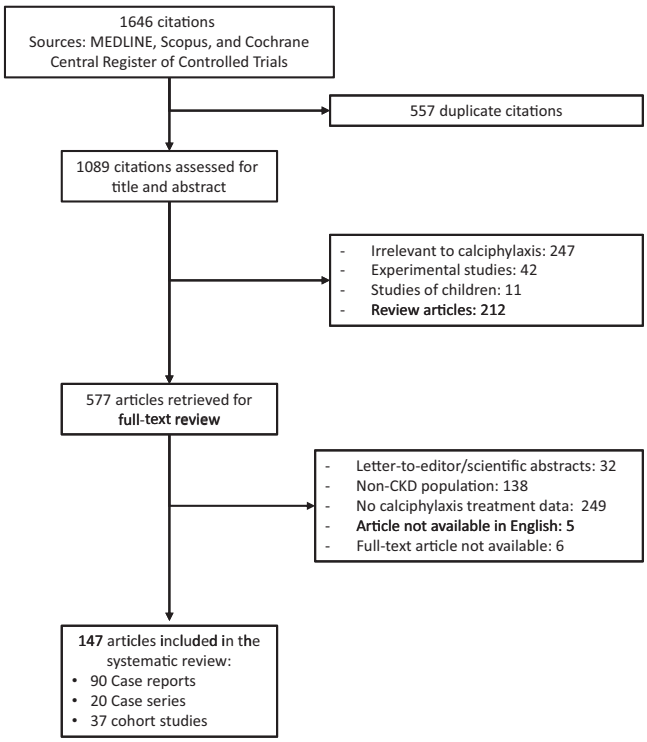

Figure 1. Flow diagram of study selection. CKD, chronic kidney disease.

Characteristics of Patients With Calciphylaxis and Risk factors

Table 1 displays the characteristics of patients (derived from case reports, case series, and cohort studies) at the time of diagnosis of calciphylaxis and notable risk factors for the disorder. In brief, 70% were women, with a mean age of 56 ± 13 years, and a mean body mass index of 29.7 ± 8.8 kg/m^2. Seventy-six percent of patients were on long-term hemodialysis for a mean of 4.3 ± 4.6 years. Diabetes mellitus was prevalent in 49% of patients. Forty-six percent of patients received calcium-containing phosphate binders, 54% received vitamin D analogues, and 41% received warfarin. Mean serum phosphorus was 6.1 ± 1.9 mg/dl. Distal lower extremities were the most common skin lesion sites (55.3%), followed by proximal lower extremities (39.3%), trunk (31.0%), distal upper extremities (7.2%), and proximal upper extremities (3.4%).

Treatment Modalities and Clinical Outcomes

Sodium thiosulfate was the most commonly prescribed treatment (50.3%) to patients with calciphylaxis (Table 1), with a mean treatment duration of 20 ± 26 weeks (median 12 weeks, interquartile range 8–24 weeks) and a cumulative dose of 1302 ± 2745 g (median 600 g, interquartile range 240–1350 g). Twenty-five percent of patients were treated with cinacalcet at a mean daily dose of 52 ± 31 mg for a mean duration of 27 ± 20 weeks (median 28 weeks, interquartile range 12–52 weeks). Twenty-nine percent underwent surgical parathyroidectomy. Fifteen percent of patients received hyperbaric oxygen therapy for a mean of 41 ± 24 sessions. Approximately one-third of patients had worsening of the skin lesions. The overall mortality rate was 46.9%.

The location of the calciphylaxis skin lesions dictated clinical outcomes (Supplementary Table S4). Lesions located in the proximal upper extremities (shoulder to elbow) were associated with the worst outcomes (50.0% had worsening skin lesions with a mortality rate of 70.0%), followed by truncal lesions (50.0% with worsening lesions and a mortality rate of 63.8%). Lesions located in the distal lower extremities (knee to foot) had the lowest likelihood of worsening calciphylaxis (33.5%), and lesions located in the distal upper extremities (elbow to hand) had the lowest observed mortality rate (46.9%).

Meta-analysis of Case Series

Table 2 displays the results of the meta-analysis of the case series. Patients who underwent surgical parathyroidectomy or received a calcimimetic had a high serum parathyroid hormone level with a weighted mean value of 640 pg/ml (95% CI 393–887) and 1000 pg/ml (95% CI 683–1316), respectively. Patients who received hyperbaric oxygen therapy had lower serum parathyroid hormone levels with a weighted mean of 202 pg/ml (95% CI 55–350) and had been on dialysis for a weighted mean of 8.4 years (95% CI 1.5–18.3). Patients prescribed sodium thiosulfate and bisphosphonates had a serum parathyroid hormone level that was within the clinical practice guideline goals with a

Table 1. Summary measures of clinical characteristics, risk factors, treatment modalities, and outcomes of patients with calciphylaxis (derived from case reports, case series and cohort studies)

Variables	Total population (n = 856)	Number of reported patients
Demographic and clinical characteristics		
Age, yr	56.3 ± 13.3	856
Male gender, %	29.7	829
Body mass index, kg/m^2	29.7 ± 8.8	239
Hemodialysis, %	75.9	801
Peritoneal dialysis, %	10.4	801
Chronic kidney disease not on dialysis, %	15.7	692
Dialysis vintage,[a] yr	4.3 ± 4.6[i]	414
Risk factors for calciphylaxis and laboratory data		
Diabetes mellitus, %	49.4	813
Calcium-containing phosphate binders, %	45.8	334
Warfarin use, %	40.8	472
Vitamin D analogues, %	53.7	334
Serum calcium,[b] mg/dl	9.1 ± 3.6	675
Serum phosphorus, mg/dl	6.1 ± 1.9	675
Serum albumin, g/dl	3.2 ± 0.7	427
Serum intact parathyroid hormone, pg/ml	584 ± 933[i]	671
Location of calciphylaxis skin lesions		
Proximal upper extremities,[c] %	3.4	442
Distal upper extremities,[d] %	7.2	442
Proximal lower extremities,[e] %	39.3	436
Distal lower extremities,[f] %	55.3	436
Trunk,[g] %	31.0	442
Treatment modalities		
Use of sodium thiosulfate,%	50.3	856
Cumulative dose, g	1115 ± 1866[i]	265
Treatment duration, week	19.8 ± 25.9[i]	98
Use of hyperbaric oxygen therapy, %	15.3	856
Treatment dose, atmosphere	2.4 ± 0.2	27
Number of sessions	40.8 ± 24.1	53
Surgical parathyroidectomy,[h] %	28.7	856
Use of cinacalcet, %	25.3	739
Daily dose, mg/d	51.6 ± 31.3	19
Treatment duration, week	27.4 ± 20.2[i]	9
Use of bisphosphonates, %	5.9	623
Clinical outcomes		
Amputations, %	10.2	432
Complete resolution of lesions, %	39.0	615
Partial resolution or stable lesions, %	31.1	615
Worsening of lesions, %	26.1	615
Mortality, %	46.9	853

Continuous data shown as mean ± SD.
[a]Dialysis vintage was calculated for the dialysis population.
[b]Serum calcium was corrected for the serum albumin.
[c]Upper extremities, proximal type: lesion located from shoulder to elbow.
[d]Upper extremities, distal type: lesion located from elbow to finger.
[e]Lower extremities, proximal type: lesion located from hip to knee.
[f]Lower extremities, distal type: lesion located from knee to toe.
[g]Trunk: lesion located in chest, abdomen, or buttock.
[h]Parathyroidectomy; total, subtotal, or near total parathyroidectomy.
[i]Median (with interquartile range) value for selected parameters: dialysis vintage 4.7 years (2.0–7.6), parathyroid hormone level 646 pg/ml (230–922), cumulative dose of sodium thiosulfate 600 g (240–1350), sodium thiosulfate treatment duration 12 weeks (8–24), and cinacalcet treatment duration 28 weeks (12–52).

weighted mean value of 431 pg/ml (95% CI 329–534) and 459 pg/ml (95% CI 98–1016), respectively.

In terms of clinical outcomes, patients who underwent surgical parathyroidectomy had the highest amputation rate, with a weighted mean of 41.1% (95% CI 24.3–60.2). The mortality rate was lowest in patients undergoing hyperbaric oxygen therapy with a weighted mean of 43.8% (95% CI 11.3–82.6).

Meta-analysis of Cohort Studies

In the 7 cohort studies on the use of sodium thiosulfate (151 patients), the pooled risk ratio for mortality was not different between patients who received sodium thiosulfate relative to those who did not (pooled RR 0.89; 95% CI 0.71–1.12, $P = 0.31$; Table 3). In the 20 cohort studies that examined the use of surgical parathyroidectomy (171 patients), the pooled RR for mortality was not significantly lower between patients who underwent parathyroidectomy relative to those who did not (pooled RR 0.88; 95% CI 0.69–1.13; $P = 0.31$; Table 4). Patients undergoing surgical parathyroidectomy were younger compared to those who did not (mean age difference −5.44 years; 95% CI −10.55 to −0.34, $P = 0.04$; Table 4). Serum albumin and parathyroid hormone levels were higher in patients who underwent surgical parathyroidectomy (mean difference 0.36 g/dl, 95% CI 0.03–0.70, $P = 0.04$ for serum albumin, and mean difference 148.01 pg/ml, 95% CI 2.74–293.29, $P = 0.05$ for parathyroid hormone level; Table 4). Patients undergoing parathyroidectomy had a lower risk of wound deterioration (pooled RR 0.75, 95% CI 0.57–0.99, $P = 0.05$; Table 4), compared to those who did not. In the 9 cohort studies (73 patients) that examined the use of cinacalcet, the drug had no impact on mortality (pooled RR 1.04, 95% CI 0.75–1.42, $P = 0.83$; Table 5). In the 10 cohort studies that examined the use of hyperbaric oxygen therapy (170 patients), there was no impact on mortality (pooled RR 0.89, 95% CI 0.71–1.12, $P = 0.32$; Table 6). Finally, in the 6 cohort studies (56 patients) that examined the use of bisphosphonates, including pamidronate, ibandronate, etidronate, alendronate, and risedronate, their use did not lower mortality compared to untreated patients (pooled RR 0.77, 95% CI 0.44–1.32, $P = 0.34$; Table 7).

Secondary analyses focusing on studies published in 2006 (the year that the use of cinacalcet for the treatment of calciphylaxis was first reported) and thereafter did not show a mortality benefit across all treatment modalities. Similarly, by meta-regression of the mortality rate against year of publication, there was no significant mortality rate change over time for any of the treatment modalities, including sodium thiosulfate (rate change = −0.11%; 95% CI −0.31 to 0.09, $P = 0.28$), surgical parathyroidectomy (rate change = 0.01%; 95% CI −0.01 to 0.04; $P = 0.76$), cinacalcet (rate change = −0.06%; 95% CI −0.22 to 0.10, $P = 0.61$), hyperbaric oxygen therapy (rate change −0.06%; 95%CI −0.17 to 0.06, $P = 0.32$), and

Table 2. Meta-analysis of clinical characteristics and outcomes of patients with calciphylaxis according to treatment modality (derived from case series)

Variables	Sodium thiosulfate			Surgical Parathyroidectomy			Cinacalcet			Hyperbaric oxygen therapy			Bisphosphonates		
	No. of studies	No. of patients	Weighted mean (95% CI)	No. of studies	No. of patients	Weighted mean (95% CI)	No. of studies	No. of patients	Weighted mean (95% CI)	No. of studies	No. of patients	Weighted mean (95% CI)	No. of studies	No. of patients	Weighted mean (95% CI)
Clinical characteristics															
Age, yr	14	321	58.5 (44.0–73.0)	11	54	53.3 (48.1–58.4)	3	12	53.3 (36.3–70.2)	5	61	57.7 (54.0–61.4)	1	3	58.5 (44.0–73.0)
Dialysis vintage, yr	8	228	2.9 (2.1–3.7)	7	33	7.3 (5.1–9.4)	2	10	3.5 (1.6–5.5)	3	18	8.4 (1.5–18.3)	–	–	–
Serum calcium, mg/dl	9	303	9.2 (8.8–9.7)	10	51	9.5 (9.0,10.0)	3	12	8.8 (6.5,11.1)	5	61	9.4 (8.7–10.0)	1	3	9.0 (7.9–10.3)
Serum phosphorus, mg/dl	9	303	5.7 (5.4–6.1)	10	51	5.7 (5.4–6.1)	3	12	5.3 (4.7–5.9)	5	61	6.6 (5.4–7.8)	1	3	6.3 (3.9–8.7)
Serum albumin, g/dl	4	269	3.0 (2.6–3.5)	2	12	3.4 (2.9–3.9)	1	2	3.5 (3.5–3.5)	2	14	2.8 (2.2–3.3)	1	3	3.1 (2.2–4.0)
Serum intact parathyroid hormone, pg/ml	10	305	431.3 (329.0–533.5)	8	38	640.1 (393.3–886.8)	3	12	999.6 (683.4–1315.7)	4	50	202.4 (55.1–349.8)	1	3	459.0 (97.7–1015.7)
Clinical outcomes															
Amputation, %	12	85	11.9 (6.5–20.9)	10	44	41.1(24.3–60.2)	3	12	10.4 (2.1–38.8)	4	52	9.3 (3.0–25.6)	–	–	–
Worsening of lesions, %	14	321	30.4 (24.3–37.3)	11	54	43.7 (24.4–65.1)	3	12	30.4 (4.9–78.9)	4	52	37.3 (25.3–51.2)	1	3	66.7 (15.4–95.7)
Mortality, %	14	321	44.4 (31.1–58.6)	10	44	44.9 (29.2–61.7)	3	12	62.8(8.2–97.0)	4	52	43.8 (11.3–82.6)	–	–	–

bisphosphonates (rate change −0.07%; 95% CI −0.34 to 0.20, $P = 0.61$).

Analyses of Treatment-Related Adverse Effects

Sodium thiosulfate resulted in a high anion gap metabolic acidosis in 19 (32.3%) of the 59 patients with available data. Hypernatremia occurred in 3 (18.8%) of 16 reported patients. Fifty-seven (24.7%) of 231 patients experienced nausea and vomiting. Among the 2288 sessions of hyperbaric oxygen therapy, the incidence rate of barotrauma was 0.2%, anxiety 0.2%, myopia 0.1%, and nausea and vomiting 0.1%. There were no treatment-related adverse effects reported for cinacalcet, bisphosphonates, and surgical parathyroidectomy.

DISCUSSION

The present systematic review and meta-analysis explores the benefits of 5 treatment modalities for calcific uremic arteriolopathy or calciphylaxis in patients with CKD, including end-stage renal disease. We focused on 2 clinical outcomes: wound healing and mortality. At time of diagnosis, most patients were on maintenance hemodialysis, with a preponderance of women and a mean age of 56 years. The significant laboratory abnormalities were hyperphosphatemia with a mean intact parathyroid hormone level at the upper limit of the recommendation by clinical practice guidelines.[165] Skin lesions located in the proximal upper extremity were associated with the highest mortality rate. Compared with cohort studies, wound healing and survival rates tended to be higher in uncontrolled studies (i.e., in case reports and case series) (Supplementary Table S5), reflecting in part publication bias. However, the mortality RR did not meet statistical significance in meta-analyses that included only studies with control groups (i.e., cohort studies).

Calciphylaxis was first described in 1961 by Selye and colleagues.[166] At first, it was demonstrated in rats with kidney failure as a hypersensitivity reaction to sensitizing agents. With more cases and knowledge in pathogenesis, it is now defined as a systemic process of vascular calcification, particularly in small dermal and subcutaneous arteries and arterioles, leading to microthrombi and tissue ischemia.[167] Patients commonly present with severe intractable pain in the involved skin areas. In more severe cases, tissue ischemia progresses to chronic ulcerated dry gangrene.[29,106,168] These lesions are frequently infected and lead to septicemia and the patient's death. In addition to skin involvement, calciphylaxis can involve internal organs, such as intestines, brain, and liver, leading to organ dysfunction.[80,169–172] The pathogenic mechanisms of vascular calcification are not fully elucidated. The

Table 3. Clinical characteristics and outcomes of patients with calciphylaxis treated with sodium thiosulfate relative to those who did not (derived from cohort studies)

Sodium thiosulfate	No. of studies	No. of patients	Weighted mean difference (95% CI)	*P*	I^2 index, %	Q-test *P* value	Egger's test *P* value
Age, yr	4	129	−0.16 (−5.43 to 5.11)	0.95	0	0.90	0.77
Dialysis vintage, yr	3	28	−0.52 (−1.76 to 0.72)	0.16	0	0.77	0.58
Serum calcium, mg/dl	3	28	−0.01 (−0.89 to 0.87)	0.98	0	0.99	0.09
Serum phosphorus, mg/dl	3	28	0.29 (−0.79 to 1.37)	0.60	0	0.75	0.90
Serum albumin, g/dl	3	28	0.27 (−0.29 to 0.83)	0.35	0	0.58	0.22
Serum intact parathyroid hormone, pg/ml	3	28	−1.47 (−35.44 to 32.51)	0.93	0	0.67	0.52
			Risk ratio (95% CI)				
Amputation	7	52	0.93 (0.29–2.97)	0.90	0	0.85	0.97
Worsening of lesions	4	28	0.66 (0.23–1.93)	0.45	39.9	0.17	0.69
Mortality	7	151	0.89 (0.71–1.12)	0.31	0	0.83	0.51
Mortality[a]	7	151	0.89 (0.71–1.12)	0.31	0	0.83	0.51

[a]Subgroup analysis of cohort studies published in 2006 and thereafter (the year that the use of cinacalcet for the treatment of calciphylaxis was first reported).

imbalance between promotors and inhibitors of vascular calcification is the most accepted hypothesis. Phosphate and calcium abnormal metabolism, uremic toxins, hypercoagulability, and endothelial dysfunction can trigger the transformation of smooth muscle cells into osteoblast-like cells[6] and initiate the process of calcific uremic arteriolopathy. This theory, however, faces some scrutiny among patients with calciphylaxis in the absence of uremia or abnormal mineral metabolism.[173] In the present study, we found that 46% and 54% of patients received calcium-containing phosphate binders and vitamin D analogues, respectively. These percentages are higher than in the general dialysis population where 34% to 38% of patients are taking a calcium-containing phosphate binder and 24% are taking a vitamin D analogue[174,175] and support the premise that calcium-phosphate-parathyroid hormone dysregulated metabolism has a role in the development of calciphylaxis.[3] Approximately 41% of patients in our systematic review were taking warfarin at the time of diagnosis of the calciphylaxis. This high prevalence rate of vitamin K antagonist use supports its role as a promotor of vascular calcification, potentially through the inhibition of vitamin K-dependent Matrix Gla-protein, a potent inhibitor of arterial calcification.[176] In addition, most of the patients in our review were overweight, were women, and had diabetes mellitus, which are also known risk factors for calciphylaxis.[5]

The rationale for using sodium thiosulfate for the treatment of calciphylaxis is based on the proposed pathogenesis of the disease.[9,177] Thiosulfate forms highly soluble complexes with calcium and decreases calcium-phosphate precipitation in the vascular wall. Other mechanisms include an antioxidant and vasodilatory effect, resulting in decreased tissue ischemia and pain relief. Sodium thiosulfate is typically prescribed i.v. at a dose of 25 g thrice weekly after hemodialysis. In our systematic review, the mean sodium thiosulfate treatment duration was 20 weeks with a cumulative dose of 1155 g, the equivalent of 45 doses. We estimated an average weekly dose of 56 g. In our analysis, there was no demonstrable benefit of sodium thiosulfate on wound healing and mortality, which is consistent with a recently published systematic review of case reports and case series.[178] The common side effects reported in our data synthesis included nausea and vomiting, high anion gap metabolic acidosis, and hypernatremia, consistent with previous reports.[177]

Table 4. Clinical characteristics and outcomes of patients with calciphylaxis who underwent surgical parathyroidectomy relative to those who did not (derived from cohort studies)

Parathyroidectomy	No. of studies	No. of patients	Weighted mean difference (95% CI)	*P*	I^2 index, %	Q-test *P* value	Egger's test *P* value
Age, yr	15	137	−5.44 (−10.55 to −0.34)	**0.04**	64.0	<0.001	0.87
Dialysis vintage, yr	9	66	0.74 (−0.88 to 2.36)	0.37	52.6	0.03	0.79
Serum calcium, mg/dl	12	112	−0.14 (−0.66 to 0.37)	0.58	30.7	0.15	0.89
Serum phosphorus, mg/dl	12	112	0.35 (−0.14 to 0.85)	0.16	0.0	0.96	0.42
Serum albumin, g/dl	6	51	0.36 (0.03 to 0.70)	**0.04**	0	0.57	0.04
Serum intact parathyroid hormone, pg/ml	13	123	148.01 (2.74 to 293.29)	**0.05**	75.5	<0.001	0.95
			Risk ratio (95% CI)				
Amputation	7	49	1.35 (0.49–3.70)	0.56	0	0.91	0.48
Worsening of skin lesions	17	143	0.75 (0.57–0.99)	**0.05**	0	0.93	0.33
Mortality	20	171	0.88 (0.69–1.13)	0.31	3.0	0.42	0.82
Mortality[a]	10	84	1.05 (0.72–1.54)	0.80	14.1	0.31	0.47

Boldface indicates statistical significance.
[a]Subgroup analysis of cohort studies published in 2006 and thereafter (the year that the use of cinacalcet for the treatment of calciphylaxis was first reported).

Table 5. Clinical characteristics and outcomes of patients with calciphylaxis treated with cinacalcet relative to those who did not (derived from cohort studies)

Cinacalcet	No. of studies	No. of patients	Weighted mean difference (95% CI)	*P*	I^2 index, %	Q-test *P* value	Egger's test *P* value
Age, yr	8	73	−2.02 (−8.63 to 4.60)	0.55	0	0.88	0.43
Dialysis vintage, yr	6	53	0.33 (−0.53 to 1.19)	0.46	2.1	0.40	0.12
Serum calcium, mg/dl	7	67	−0.001 (−0.41 to 0.40)	0.99	0	0.99	0.31
Serum phosphorus, mg/dl	7	67	0.47 (−0.52 to 1.46)	0.35	39.5	0.13	0.94
Serum albumin, g/dl	5	46	0.02 (−0.64 to 0.68)	0.96	63.34	0.03	0.64
Serum intact parathyroid hormone, pg/ml	7	67	313.53 (−32.40 to 659.45)	0.08	90.54	<0.001	0.92
			Risk ratio (95% CI)				
Amputation	3	21	1.18 (0.23–6.03)	0.85	0	0.41	0.39
Worsening of skin lesions	5	44	0.86 (0.32–2.28)	0.76	0	0.61	0.56
Mortality	9	73	1.04 (0.75–1.42)	0.83	0	0.51	0.96
Mortality[a]	9	73	1.04 (0.75–1.42)	0.83	0	0.51	0.96

[a]Subgroup analysis of cohort studies published in 2006 and thereafter (the year that the use of cinacalcet for the treatment of calciphylaxis was first reported).

Although sodium thiosulfate is a promising treatment for calciphylaxis, the optimal dose and treatment duration need to be formally examined in a randomized controlled trial.

By restoring the abnormal calcium-phosphate-parathyroid hormone metabolism, surgical parathyroidectomy is believed to improve calciphylaxis-related outcomes. This is based on previous cohorts and case reports.[23,32,33,63] However, more recent studies[179,180] suggest that surgical parathyroidectomy might not be suitable for every patient with calciphylaxis, especially those who are at risk for postoperative complications. Moreover, recurrent or *de novo* calciphylaxis has been described following surgical parathyroidectomy.[65,181,182] Our results show that patients who underwent parathyroidectomy had higher serum parathyroid hormone levels and tended to be younger and healthier with higher serum albumin levels (Table 4). These differences in patient characteristics might have led to better wound healing. At present, surgical parathyroidectomy should be reserved for patients with poorly controlled hyperparathyroidism unresponsive to calcimimetics,[183] and with careful preoperative evaluation.

Medical parathyroidectomy can be achieved through the use of cinacalcet, an oral calcimimetic.[184] The results derived from our systematic review of case reports and case series show that patients treated with an oral calcimimetic had a lower rate of worsening skin lesions and lower mortality rate compared to those who were not. However, the results derived from our meta-analysis of cohort studies did not demonstrate a mortality benefit. Although cinacalcet has been shown to reduce the incidence of calciphylaxis in hemodialysis patients according to a *post hoc* analysis from the largest randomized controlled trial of cinacalcet,[185] this was not observed in a large case-control study of hemodialysis patients.[3]

Hyperbaric oxygen therapy is an adjunctive consideration for wound care in patients with calciphylaxis. It increases the amount of dissolved oxygen and its delivery to the local tissue. The exact mechanism of wound healing promoted by hyperbaric oxygen therapy is unclear, but the hypotheses include enhancing fibroblast function and angiogenesis, increasing neutrophil bactericidal activity, and direct toxicity of high oxygen tension to anaerobic microorganisms.[6] Patients are required to breathe in the

Table 6. Clinical characteristics and outcomes of patients with calciphylaxis who received hyperbaric oxygen therapy relative to those who did not (derived from cohort studies)

Hyperbaric oxygen therapy	No. of studies	No. of patients	Weighted mean difference (95% CI)	*P*	I^2 index, %	Q-test *P* value	Egger's test *P* value
Age, yr	7	163	1.69 (−3.17 to 6.56)	0.50	0	0.97	0.24
Dialysis vintage, yr	4	40	0.33 (−1.05 to 1.71)	0.64	0	0.85	0.30
Serum calcium, mg/dl	6	62	0.24 (−0.33 to 0.81)	0.41	0	0.67	0.64
Serum phosphorus, mg/dl	6	62	0.93 (0.52 to 1.34)	**<0.001**	0	0.55	0.02
Serum albumin, g/dl	5	48	0.29 (−0.19 to 0.76)	0.24	15.6	0.32	0.06
Serum intact parathyroid hormone, pg/ml	6	62	144.90 (−83.28 to 373.09)	0.21	48.9	0.08	0.92
			Risk ratio (95% CI)				
Amputation	3	21	2.02 (0.40–10.31)	0.40	0	0.71	0.06
Worsening of skin lesions	6	47	0.87 (0.48–1.60)	0.66	0	0.75	0.76
Mortality	10	170	0.89 (0.71–1.12)	0.32	0	0.64	0.67
Mortality[a]	10	170	0.89 (0.71–1.12)	0.32	0	0.64	0.67

[a]Subgroup analysis of cohort studies published in 2006 and thereafter (the year that the use of cinacalcet for the treatment of calciphylaxis was first reported).

Table 7. Clinical characteristics and outcomes of patients with calciphylaxis who received bisphosphonates therapy relative to those who did not (derived from cohort studies)

Bisphosphonates therapy	No. of studies	No. of patients	Weighted mean difference (95% CI)	*P*	I^2 index, %	Q-test *P* value	Egger's test *P* value
Age, yr	3	43	−1.72 (−8.90 to 5.45)	0.64	0	0.37	0.96
Dialysis vintage, yr	–	–	–	–	–	–	–
Serum calcium, mg/dl	2	37	0.25 (−0.30 to 0.79)	0.38	0	0.37	NA
Serum phosphorus, mg/dl	2	37	0.17 (−1.12 to 1.46)	0.79	0	0.92	NA
Serum albumin, g/dl	–	–	–	–	–	–	–
Serum intact parathyroid hormone, pg/ml	2	37	−57.73 (−201.47 to 86.01)	0.43	0	0.96	NA
			Risk ratio (95% CI)				
Amputation	1	23	0.06 (0.01–0.99)	**0.05**	0	1.00	NA
Worsening of skin lesions	5	51	0.50 (0.13–1.86)	0.30	26.6	0.24	0.16
Mortality	6	56	0.77 (0.44–1.32)	0.34	0	0.54	0.67
Mortality[a]	5	54	0.80 (0.46–1.39)	0.43	0	0.46	0.73

Boldface indicates statistical significance. NA, not available.
[a]Subgroup analysis of cohort studies published in 2006 and thereafter (the year that the use of cinacalcet for the treatment of calciphylaxis was first reported).

hyperbaric chamber with 100% oxygen, usually at 2.5 atmospheres absolute. In our synthesis of the data, patients received a mean of 35.8 sessions of hyperbaric oxygen therapy. The most common adverse effect is middle ear barotrauma,[186] which can be prevented by pretreatment maneuvers.[187,188] Claustrophobia is another psychological barrier to hyperbaric oxygen therapy, which can be solved by using a multiplace chamber. Our results did not demonstrate efficacy of hyperbaric oxygen therapy for treatment of calciphylaxis in the pooled cohort studies.

Bisphosphonates are the most frequently used medications for the treatment of osteoporosis.[189] Similar to sodium thiosulfate and cinacalcet, the off-label use of bisphosphonates has been reported to effectively treat calciphylaxis.[105,115,190] Proposed mechanisms of action include inhibition of hydroxyapatite crystallization, reduction of macrophage activity, and a decrease of proinflammatory cytokines.[189] Overall, bisphosphonates might reduce the capacity of calcium to accumulate in the arterial wall, thus inhibit vascular calcification.[10] In our systematic review, the use of bisphosphonates was reported in 37 patients. This number is too small to evaluate their true efficacy and potential harm, especially in the setting of decreased glomerular filtration rate, and their role requires careful study.

In clinical practice, treatment of calciphylaxis is multifaceted and multidisciplinary.[5] Data from a large nationwide registry in Germany[4] show that common therapeutic strategies for calciphylaxis include surgical wound management (29.2%), discontinuation of vitamin K antagonist (25.4%), discontinuation or reduction of calcium-containing phosphate binders (23.8%), administration of sodium thiosulfate (21.5%), administration of vitamin K (17.7%), intensifying dialysis treatment (16.9%), and reduction or discontinuation of vitamin D analogues (16.2%). However, these treatment patterns are largely based on expert opinions without sufficient high-level clinical evidence. Based on a recent survey conducted at the International Consensus Conference on Calciphylaxis, the opinions on diagnosis and management of calciphylaxis were very diverse.[191] Some strategies, such as surgical wound management and intensifying dialysis treatment, had very high heterogeneity in details.

In our systematic review, we selected 5 frequently used interventions to help inform clinical practice. We found no randomized controlled trials, which limit the robustness of our findings. National registries on calciphylaxis are being established to help collect high-quality data and inform clinical practice in terms of natural history of disease and treatment trends and measures of efficacy.[3,4,192,193] Ongoing clinical trials identified at the ClinicalTrials.gov Web site (accessed on September 19, 2018), a database of funded clinical studies, for the treatment of calciphylaxis are summarized in Supplementary Table S6.

Our study has several strengths and limitations. We focused on the most frequently used treatment modalities and described their pattern of use, but found no clear clinical benefit of any specific therapy. In addition, variable patient characteristics likely resulted in patient selection bias regarding the pursuit of surgical versus medical treatment. Patients who received surgical interventions were more likely to be deemed fit to undergo surgery. However, due to the lack of randomized controlled trials, our analysis is descriptive and our results are inconclusive. Moreover, the reports frequently described multimodal treatment approaches and protocols, rendering the assessment of the efficacy of each modality impossible to ascertain.

In conclusion, in the present systematic review, although sodium thiosulfate, surgical parathyroidectomy, hyperbaric oxygen therapy, cinacalcet, and bisphosphonates failed to demonstrate a mortality benefit in the pooled cohort studies, the results are

inconclusive, as they are not derived from randomized controlled trials, and their potential benefit cannot be ruled out. Multicenter randomized controlled trials are urgently needed to demonstrate the true efficacy of these treatment modalities, individually or combined, for this vexing and life-shortening orphan disease.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

SU: first author, study design, review of citations and articles, analysis, manuscript preparation; KK: review of citations and articles; KP: study design; SE-O: manuscript review and edits; BLJ: manuscript review and edits; PS: corresponding author, review of citations and articles, analysis, manuscript review and edits.

SUPPLEMENTARY MATERIAL

Table S1. Cohort studies included in the systematic review.
Table S2. Case series included in the systematic review.
Table S3. Case reports included in the systematic review.
Table S4. Clinical outcomes according to location of calciphylaxis.
Table S5. Clinical outcomes of patients with calciphylaxis (derived from case reports, case series, and cohort studies) according to treatment modality ever received.
Table S6. Ongoing calciphylaxis clinical studies registered at clinicaltrials.gov (September 2018).
Supplementary material is linked to the online version of the paper at http://www.kireports.org/.

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