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CKJ Review

CKJ REVIEW

Calciphylaxis diagnosis, management and future directions: a comprehensive update on behalf of the European Renal Association CKD-MBD Working Group

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ABSTRACT

Calciphylaxis, or calcific uraemic arteriolopathy, is a rare and life-threatening condition predominantly affecting people receiving dialysis. Characterized by painful necrotic skin lesions due to arteriolar calcification and thrombosis, calciphylaxis is associated with high morbidity and mortality. Diagnosis is frequently delayed due to misdiagnosis and an absence of specific diagnostic tests. Current treatment approaches are largely based on registry data and small uncontrolled studies. This update brings together the latest understanding of calciphylaxis pathogenesis, diagnostic approaches and management, highlighting recent advances and future directions. Pathophysiological mechanisms include vascular smooth muscle cell osteogenic transformation, loss of endogenous calcification inhibitors (fetuin-A, matrix Gla protein, pyrophosphate), systemic inflammation and thrombosis. The potential prognostic role of biomarkers, including the calciprotein particle crystallization test (T50) and plasma pyrophosphate, are also discussed. Management remains complex, with no proven treatments. A multifaceted, and multi-professional team approach is fundamental. Sodium thiosulfate remains widely used despite the lack of trial evidence. Recent investigational therapies, including SNF472 and INZ-701, target key calcification pathways and offer promise. The Better Evidence and Translation for Calciphylaxis (BEAT-Calci) adaptive platform trial represents a landmark step in evaluating multiple therapies systematically. National registries remain vital for informing prevalence estimates and improving real-world outcome data. Looking ahead, future research should prioritize the development and validation of diagnostic criteria, and prognostic tools integrating clinical risk factors with biomarkers. In addition, we propose the routine inclusion of patient-reported experience measures in calciphylaxis studies to better capture treatment impact in this vulnerable population.

Keywords: calcific uraemic arteriolopathy, calciphylaxis, CKD, kidney failure

INTRODUCTION

Calciphylaxis, also known as calcific uraemic arteriolopathy, is a rare but life-threatening condition associated with chronic kidney disease (CKD) and most commonly seen in people with end-stage kidney disease (ESKD) undergoing dialysis [1–3]. It is characterized by painful necrotic skin lesions resulting from arteriolar calcification and thrombosis involving the subcutaneous fat and dermis. Whilst reports of prevalence and incidence rates vary due to diagnostic challenges and recognized under-reporting to national registries, the largest national calciphylaxis dataset reported (from the USA) gives an incidence of 3.49 per 1000 patient-years among haemodialysis patients [3]. Calciphylaxis is associated with high morbidity and mortality; 1-year mortality ranges from 36% to 74% [4–6].

The clinical diagnosis and management of calciphylaxis remains challenging. Considering the rarity and the lack of awareness and standardized diagnostic criteria, the diagnosis is often delayed in clinical practice. Moreover, therapeutic decisions are complicated by a lack of evidence. The result is varying approaches and management strategies and inconsistencies in patient care and experience [7, 8].

This review aims to provide a comprehensive and up-to-date synthesis of the current landscape of calciphylaxis. We will explore the most up-to-date advances in pathophysiology, highlight the role of novel diagnostic and prognostic biomarkers and evolving research. Finally, we will propose a future research agenda, including prognostic tools and incorporating patient-reported experience measures.

PATHOPHYSIOLOGY AND RISK FACTORS

Cellular and molecular mechanisms of calciphylaxis

Calciphylaxis is mechanistically underpinned by calcification of the arterial medial layer, endothelial dysfunction with intimal fibrosis, and thrombosis (Fig. 1) [9, 10]. These processes impact small-to-medium-sized arteries, typically in the dermis and subcutaneous fat, although visceral calciphylaxis impacting other small-vessel beds in the colon and mesentery have been reported in the absence of cutaneous manifestation [11, 12]. Collectively, these processes drive ischaemia in the associated vascular distributions and result in the characteristic necrotic patches [13].

Vascular calcification

Vascular calcification (VC) is central to the pathophysiology of calciphylaxis. An active, highly cell-regulated process, VC is underpinned by phenotypic switching of vascular smooth muscle cells (VSMCs) to an osteoblast-like state in the arterial medial layer [14–16]. This osteogenic transdifferentiation is characterized by downregulation of smooth muscle markers (e.g. alpha-smooth muscle actin) and upregulation of osteogenic gene expression (e.g. RUNX2, BMP, osteopontin, alkaline phosphatase) [17, 18]. The precise pathways and mediators precipitating VSMC osteogenic transdifferentiation are poorly understood, limiting therapeutic innovation. Alongside emerging evidence of contributions from other cell types such as pro-inflammatory adipocyte [19], VC is suggested to have a multifactorial nature with roles for genetic predisposition, dysregulated calcium-phosphorus metabolism, systemic inflammation, alterations in extracellular matrix structure and reduction in local calcification inhibitor [20, 21].

In CKD, impaired phosphate excretion and FGF23–Klotho axis dysregulation drive hyperphosphataemia [22–24]. Elevated phosphate enhances PiT-1 activity and activates Wnt/β-catenin signalling, promoting VSMC osteogenic differentiation [23, 25, 26]. Most commonly, hypocalcaemia drives secondary hyperparathyroidism (SHPT), with elevated parathyroid hormone (PTH) increasing circulating calcium and phosphate through

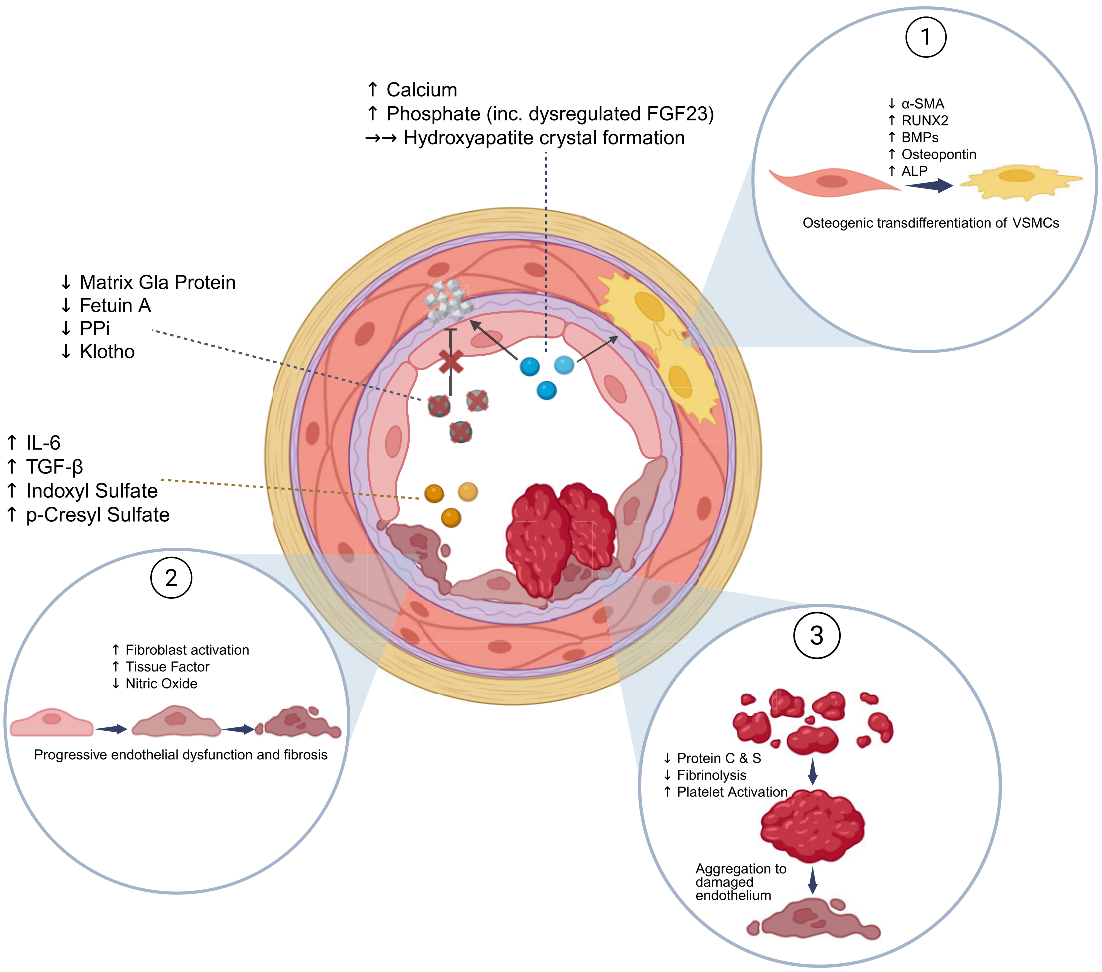

Figure 1: Pathophysiological mechanisms associated with calciphylaxis. (1) Osteogenic transdifferentiation of VSMCs; (2) endothelial dysfunction and intimal fibrosis; (3) hypercoagulability and thrombosis. These in turn are driven by systemic inflammation and uremia (IL-6, TGF-β, indoxyl sulfate, p-cresyl sulfate); reduction in innate calcification inhibitors (MGP, fetuin-A, PPi, Klotho); dysregulated calcium-phosphate homeostasis resulting in hydroxyapatite crystal formation. Created in BioRender.

bone resorption [27]. Concomitant hypercalcaemia, occurring in a smaller number of individuals or as a consequence of SHPT treatments, raises the calcium-phosphate product, leading to precipitation of mineral salts such as hydroxyapatite [28, 29]. Normally, fetuin-A binds phosphate and calcium, forming excretable calciprotein particles (CPM, CPP1). In uraemia, these accumulate and mature into pro-calcific CPP2, rich in hydroxyapatite [30]. High CPP levels and low T50 (the time for CPP1 to accumulate as CPP2) are seen in calciphylaxis [31–33]. Collectively, these changes increase hydroxyapatite formation [34].

CKD also creates a pro-inflammatory milieu. Uraemic toxins (indoxyl sulfate, p-cresyl sulfate) and cytokines [interleukin (IL)-1β, IL-6, transforming growth factor (TGF)-β] generate reactive oxygen species and endothelial dysfunction, which drive VSMC transdifferentiation through as-yet-unclear mechanisms [35–39]. Modulating inflammatory pathways may offer therapeutic opportunities; for example, targeting the TYMP–IL6–TF axis has been shown to improve skin microvascular integrity in calciphylaxis [40].

Uraemia and inflammation further impair synthesis of natural calcification inhibitors. Carboxylated Matrix Gla protein (MGP), a vitamin K–dependent inhibitor of VC, is inactivated by oxidative stress and vitamin K antagonism such as with warfarin [41]. Both fetuin-A synthesis and Klotho are suppressed by uraemia [42–46]. Inorganic pyrophosphate (PPi), an inhibitor of hydroxyapatite formation, is degraded in CKD. Some patients additionally harbour NT5E polymorphisms affecting pyrophosphatase and ENPP1, further reducing PPi generation and promoting calcification [47]. Collectively, these changes create a pro-calcific environment.

Endothelial dysfunction and intimal fibrosis

Alongside medial calcification, calciphylaxis is characterized by fibrotic changes to the intimal layer of dermal and subcutaneous arteries, driven by over-proliferation of extracellular matrix components and fibroblast activation. The derived fibrointimal dysplasia drives loss of nitric oxide, promotes upregulation of tissue factor and causes vascular stiffness [48]. Overall, these processes impair endothelial cell function and create a pro-thrombotic, pro-calcific environment.

Hypercoagulability and thrombosis

Advanced CKD is associated with deficiencies of protein C and protein S, while chronic systemic inflammation promotes

Table 1: Risk factors for calciphylaxis.

Risk factor	Proposed mechanism	Management strategy
Female sex	Higher fat mass and hormonal differences may predispose to VC	Not modifiable; maintain vigilance in high-risk females
Caucasian ethnicity	Possibly related to genetic, metabolic or lifestyle factors affecting mineral balance	Not modifiable; maintain awareness of increased risk
Obesity	Increases pro-inflammatory cytokines and fat necrosis; reduces peripheral perfusion	Encourage weight loss and optimize glycaemic control
Diabetes mellitus	Promotes vascular injury, endothelial dysfunction and chronic inflammation	Tight glycaemic control; manage comorbidities
Hypoalbuminaemia	Reflects malnutrition/inflammation; albumin also binds calcium and toxins	Improve nutrition; address inflammation and dialysis adequacy
Liver disease	Reduces synthesis of coagulation and calcification inhibitors (e.g. fetuin-A, protein C)	Optimize liver disease management; avoid hepatotoxic drugs
Warfarin therapy	Inhibits vitamin K–dependent activation of MGP, a key calcification inhibitor	Stop warfarin; consider alternatives (e.g. DOACs if safe)
Hyperphosphataemia	Drives VC by precipitating with calcium in soft tissues	Use phosphate binders; dietary phosphate restriction
Hypercalcaemia	Combines with phosphate to form insoluble calcium-phosphate complexes	Adjust calcium intake; review vitamin D and calcium therapy
Secondary hyperparathyroidism	Increases bone resorption and serum calcium/phosphate levels; promotes calcification	Control PTH with calcimimetics, vitamin D analogues or parathyroidectomy
Oversuppressed PTH levels	Adynamic bone turnover, lack of bone	Reduce PTH-lowering medication (avoid total parathyroidectomy)

platelet activation and suppresses fibrinolysis, collectively driving a hypercoagulable phenotype [37, 49]. Coupled with the pro-thrombotic environment generated by endothelial dysfunction, these processes are responsible for the intraluminal microthrombi observed in skin biopsies of calciphylaxis. The presence of these thrombi has been correlated with clinical pain score, suggesting the significant pain felt by patients with calciphylaxis could be driven at least in part by the thrombotic component [50]. Notably, in a proportion of cases of non-uraemic calciphylaxis the pro-coagulant environment is felt to have played a major role [51, 52].

Risk factors for calciphylaxis

Many of the risk factors for calciphylaxis are intrinsically linked with its pathogenesis, with modifiable and non-modifiable factors identified. Non-modifiable risk factors include female sex and Caucasian ethnicity, whose role as risk factors for calciphylaxis are not fully understood [53, 54]. Potentially modifiable factors include uncontrolled diabetes mellitus, obesity, secondary hyperparathyroidism (including lowering calcium-phosphate product), over-suppressed PTH (e.g. adynamic bone disease), malnutrition and hypoalbuminemia, liver disease, trauma from injection sites and warfarin therapy [11, 55, 56].

Table 1 summarizes key risk factors alongside their proposed mechanism and their suggested management. Notably, the majority of patients with multiple risk factors do not develop calciphylaxis and the precipitating stimulus, or combination of stimuli, remains elusive. Whilst there is a lack of evidence to recommend preventative strategies for calciphylaxis, addressing modifiable risk factors including severe obesity and uncontrolled diabetes, as well as optimizing dialysis adequacy, could be considered a sensible population approach.

Diagnosis

The diagnosis of calciphylaxis remains one of the most challenging aspects of its management; diagnostic delays remain common and contribute to poor outcome [6, 8, 57]. There is no diagnostic test for calciphylaxis; diagnosis relies on clinical judgement involving assessment of clinical features (described in Table 2) and risk factors (see Table 1). Adjunctive histopathology, and/or imaging can be used where appropriate, for example where the level of clinician uncertainty justifies further investigation.

Clinical features

The clinical presentation of calciphylaxis evolves through a characteristic but often under-recognized sequence, beginning with non-ulcerative changes and progressing to full-thickness skin necrosis. In the earliest stages, patients frequently report deep, localized pain in subcutaneous tissue, often described as a burning or stabbing feeling that can precede any visible skin changes by days or even weeks. On physical examination, firm nodules or indurated plaques may be palpated, typically in adipose-rich regions such as the thighs, abdomen or buttock [58]. Subtle violaceous colour changes may also develop, mimicking livedo reticularis or bruising [27]. Because the skin surface often remains intact at this stage, misdiagnosis is common, with pain easily misattributed to cellulitis, neuropathy or musculoskeletal discomfort [3].

As the disease progresses into its intermediate phase, the overlying skin develops more conspicuous changes, including retiform purpura, stellate ecchymosis, and increasing induration. The skin may appear mottled, indicating underlying vascular occlusion and ischaemia. In the advanced phase,

Table 2: Clinical features across the stages of calciphylaxis presented together with conditions in which symptoms crossover leading to potential misdiagnosis.

Phase	Clinical features	Possible differentials and common misdiagnosis
Early	• Deep, localized subcutaneous pain (often burning or throbbing) • Indurated nodules or plaques (more common in adipose rich areas such as the thigh) • Skin intact • Subtle bruising appearance/violaceous discolouration	• Cellulitis • Trauma or haematoma • Lipodermatosclerosis • Superficial thrombophlebitis
Intermediate	• Progressive retiform purpura • Worsening pain, often severe and disproportionate • Skin becomes firm—palpable nodules or plaques • Early necrotic tissue under intact epidermis	• Warfarin-induced skin necrosis • Cholesterol emboli
Advanced	• Full-thickness skin necrosis with black eschar • Ulceration with exposure of fat or muscle • Surrounding erythema and induration • Unpleasant odour • Secondary infection common • Systemic signs: fever, leucocytosis, sepsis	• Diabetic/vascular ulcer • Pressure ulcer • Necrotizing fasciitis • Pyoderma gangrenosum • Fournier's gangrene • Cutaneous malignancy

patients develop full-thickness ulceration with black eschar or exposed yellow necrotic fat. Advanced calciphylaxis wounds are highly susceptible to infection and can lead to systemic sepsis, a common terminal event in calciphylaxis. Recognizing the clinical features and their evolution, from deep subcutaneous pain through to ulceration, is essential for early diagnosis and improved outcomes [59].

Skin biopsy

When performed appropriately, skin biopsy can support the diagnosis of calciphylaxis. The biopsies should be deeper than usual punch biopsies, to contain sufficient subcutaneous tissue [60]. Dutta and colleagues analysed skin biopsies from 70 cases of calciphylaxis and found microvascular calcification in 86%, and necrosis in 73% of samples; fibrin thrombi correlated significantly with severe pain ($P = .04$), linking pathology to clinical symptom [61]. Findings support the diagnostic utility of skin biopsy, particularly in the context of clinical uncertainty, however sensitivity appears to vary with disease stage, emphasizing the need for careful timing and contextual interpretation [62, 63]. In particular, microvascular calcifications have been described in healthy skin biopsies from patients with ESKD and no calciphylaxis [64]. Furthermore, biopsy carries the risks of ulcer expansion, delayed healing and superimposed infection. Skin biopsy is likely unnecessary in patients with classic clinical features and identified risk factors; it may be required in people with atypical presenting features or in the absence of known risk factors [65] (Fig. 2).

Imaging

Imaging may play a useful adjunctive role in the diagnosis of calciphylaxis, particularly in the setting of clinical uncertainty or when skin biopsy is contraindicated. Plain radiographs may reveal a netlike pattern of subcutaneous VC, with up to 90% specificity reported, though sensitivity is limited [65]. Computed tomography (CT), including radiomics-enhanced approaches, show promise; one study ($n = 32$) reported 89% sensitivity and 80% specificity [66]. Bone scintigraphy has also demonstrated high sensitivity and specificity, but diagnostic reliability is limited by a lack of standardized interpretation [65, 67]. Similarly, experience with positron emission tomography and CT (PET-CT) imaging in calciphylaxis is limited. Magnetic resonance imaging, while poor at detecting VC, may help rule out differential diagnoses such as necrotizing fasciitis [68]. Overall, imaging supports, but does not replace, clinical diagnosis; its use should be carefully considered alongside assessment of clinical features and risk factors.

Management strategies

There are currently no approved treatments for calciphylaxis. Current management strategies involve a multifaceted approach incorporating risk factor mitigation, wound management, medical therapies (based largely on weak observational evidence), nutritional interventions and supportive care. Qualitative research capturing the patient experience of calciphylaxis has been lacking to date; one study (including nine participants) has highlighted the burden of this condition on quality of life, daily living and overall well-being [69]. Thus, a timely multispecialty, and multi-professional team approach is fundamental to good outcomes, with a focus on patient-centred holistic care [70].

Management of risk factors post-diagnosis

As described in Table 1, risk factors should be modified as much as possible. Sites of subcutaneous injection should be rotated to minimize trauma. Pain can affect appetite and dietary intake, increasing the risk of malnutrition and negatively impacting wound healing [71, 72]. Nutritional support, including the involvement of specialist dietitians, should be offered to: (i) minimize protein-wasting, (ii) address nutrient deficiencies (including increased protein requirements resulting from wounds) and (iii) support optimization of mineral balance. Efforts should also focus on controlling SHPT through first-line measures. Active vitamin D analogues should be discontinued wherever possible in those with calciphylaxis. Although there is no clinical evidence to suggest non-active vitamin D causes calciphylaxis or VC, discontinuation of vitamin D supplementation, in the presence of calciphylaxis, should be considered given

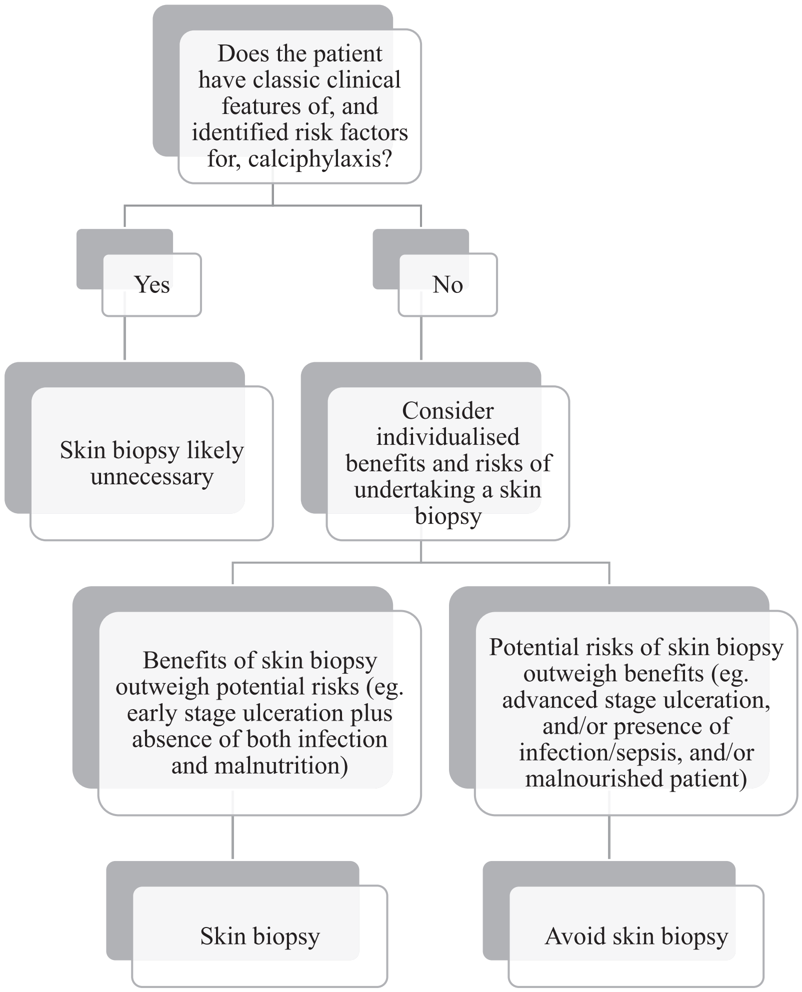

Figure 2: Algorithm outlining the clinical indication and considerations for undertaking skin biopsy.

it is an inducer of VC in animal models [73]. Calcium-phosphate product should be monitored routinely and optimized with the use of non-calcium-based phosphate binders to reduce serum phosphate [22, 50].

Warfarin should be stopped wherever possible. Warfarin impairs carboxylation of MGP, a key innate calcification inhibitor, through inhibition of vitamin K epoxide reductase [74]. This provides biological plausibility to support well-established observational data that identifies warfarin use as detrimental to clinical outcomes [1, 11]. Direct oral anticoagulants (DOACs), such as apixaban, are increasingly used in patients receiving dialysis and would offer a theoretical mechanistic advantage in patients with calciphylaxis who require anticoagulation. Two small retrospective case series have reported a generally favourable safety profile of DOAC use in calciphylaxis, however there remains paucity of robust data to support decision-making [75, 76].

Wound care

Sepsis from infected calciphylaxis wounds remains a leading cause of death [13]. High-quality wound care is therefore a cornerstone of management. Close monitoring of lesions and serial utilization of a modified wound assessment tool is recommended. Debridement can be atraumatic (using maggots), enzymatic or surgical. Risks of surgical debridement can be major and include poor post-operative wound healing, Koebnerization and extreme pain [77]. However retrospective studies have demonstrated beneficial outcomes with surgical debridement suggesting careful patient selection is key [11, 78].

Hyperbaric oxygen therapy, aiming to increase tissue oxygenation, has been utilized for calciphylaxis wound management [79]. A retrospective study by An *et al.* reported complete healing in half of patients after 44 sessions of hyperbaric oxygen therapy administered over a 2-month period [80]. However, pooled analysis in a systematic review by Udomkarnjananun *et al.* did not demonstrate benefit [77].

Although there is no evidence to support the use of prophylactic antibiotics, good infection control practices are critical. Involvement from plastics/tissue viability is recommended.

PHARMACOLOGICAL AND SURGICAL THERAPIES

Sodium thiosulphate

Sodium thiosulfate (STS), used off-label since 2004 for the management of calciphylaxis, is a chelating agent which binds calcium to form highly soluble calcium thiosulfate and thus reduces precipitation of mineral deposit [81–83]. STS may also reduce reactive oxygen species, endothelial dysfunction, CPPs and adipocyte contribution to VC [19, 83]. The most widely utilized dosing regimen is 25 g three times per week after each haemodialysis session [50, 84, 85]. Duration of therapy is controversial; some suggest a 4-week trial with cessation in non-responders, while case reports have documented use up to 2 years [86]. Though relatively safe, adverse effects include nausea, vomiting, QTc prolongation, headache, weakness and a raised anion gap metabolic acidosis [87]. Three randomized controlled trials (RCTs) evaluating the efficacy of STS in calciphylaxis have been attempted; none has reported, and there remains a paucity of high-quality evidence for the effectiveness of systemic STS. Intralesional STS at a dose of 1–3 mL of 250 mg/mL, injected weekly into clinically active calciphylaxis lesions, has been reported in those who cannot tolerate intravenous STS; evidence for efficacy is limited [77, 80–83, 85–88]. A recent meta-analysis by Wen *et al.* evaluated 19 retrospective cohort studies on the use of intravenous STS involving 422 patients with CKD experiencing calciphylaxis; no significant improvement in skin lesions or overall survival was demonstrated with STS [9]. This and other works have highlighted the significant heterogeneity in reporting of STS-related studies, and emphasized the clear need for a large, well-designed RCT [89].

Calcimimetics

Managing SHPT is a central component of calciphylaxis treatment. Cinacalcet, a calcium-sensing receptor (CaSR)-positive allosteric modulator (calcimimetic), reduces PTH production and release through enhancing the sensitivity of CaSR to extracellular calcium in the parathyroid gland [87, 90]. Calcimimetic treatment, alone or in combination, has shown beneficial effects in a number of calciphylaxis cases [70, 91, 92]. Although no significant reduction in death or major cardiovascular events was seen in patients with moderate-to-severe secondary hyperparathyroidism undergoing haemodialysis treated with cinacalcet in the EVOLVE trial, a secondary analysis indicated a lower incidence of calciphylaxis in patients treated with cinacalcet [93]. Recommendations for calcimimetic use in calciphylaxis follow KDIGO guidance for SHPT management [94].

Parathyroidectomy

Surgical parathyroidectomy has been demonstrated to improve both survival and wound healing in observational date [95]. Parathyroidectomy can be considered in patients with hyperparathyroidism refractory to medical management who have had careful pre-operative counselling and are felt to be at lower risk for a wound healing–related complications [96, 97].

Bisphosphonates

Case reports and retrospective series have described utilizing bisphosphonates in calciphylaxis. Bisphosphonates including pamidronate inhibit osteoclast-mediated bone resorption causing reduced hydroxyapatite crystal formation, alongside ameliorating pro-inflammatory cytokine production and macrophage activity [98]. However, there remain concerns about their potential toxicity in renal impairment and long-term risks of adynamic bone disease [99]. A 2019 systematic review by Udomkarnjananun *et al.* concluded that too little published data existed to be able to evaluate the efficacy of bisphosphonates in calciphylaxis and trials are needed [77].

Denosumab

The effect of denosumab, a RANK-ligand inhibitor which also inhibits osteoclast-mediated bone resorption, has not yet been reported in calciphylaxis. While attenuation of VC was seen in a murine model treated with denosumab, a secondary analysis of the SALTIRE2 trial failed to demonstrate attenuation of coronary artery calcification progression [100, 101]. Additionally, severe hypocalcaemia is a well-recognized adverse effect of denosumab use in dialysis-dependent patients and concomitant loading with calcium-based medications and/or active vitamin D is utilized as a preventative strategy in this regard [102–104]. As such, denosumab's use in calciphylaxis, where limiting exogenous calcium loading is a key aim, is likely to be challenging.

Vitamin K

Supplementation with vitamin K in calciphylaxis is an area of ongoing investigation. Vitamin K is essential for carboxylation of MGP [41, 105, 106], and has been reported to improve calciphylaxis in case reports [107, 108]. However, a systematic review by Vlasschaert *et al.* concluded that vitamin K supplementation did not consistently prevent VC progression, acknowledging significant heterogeneity in the reporting of included studies [109]. It is also worth considering that progression of VC cannot be relied upon as a surrogate marker for efficacy in calciphylaxis given its multifactorial nature. Recently, the VitaVasK study utilized vitamin K1 10 mg weekly in haemodialysis patients for 1 year and showed a significant reduction in VC characterized by a 72% reduction Agatston score ($P = .028$). It also confirmed a rapid decrease in circulating dp-ucMGP levels and a marked increase in serum phylloquinone (vitamin K1) concentration [110]. In a follow-up experimental study, Kaesler *et al.* discovered that altered vitamin K metabolism in dialysis patients may blunt the anti-calcifying properties of vitamin K2 and favour vitamin K1 in this specific context [111].

Magnesium

Magnesium attenuates the Wnt/β-catenin signalling pathway alongside replacing calcium in the structure of hydroxyapatite (thus increasing crystalline solubility and reducing calcification) and reducing CPP load [112, 113]. In murine models of CKD, a high-magnesium diet reduced aortic and soft tissue calcification [114, 115]. However, the MAGiCAL-CKD trial did not show a reduction in progression of VC in patients with CKD [116]. Zhan *et al.* undertook a meta-analysis of nine studies with a total of 496 patients evaluating the effect of magnesium supplementation on VC in CKD; while improvements were seen in magnesium and calcium levels in the supplementation group, VC burden was not reduced with magnesium treatment [117].

Hexasodium fytate

More recently, the CALCIPHYX trial has evaluated hexasodium fytate (SNF472), the hexasodium salt of the naturally occurring hydroxyapatite binder myo-inositol hexaphosphate (IP6). In an open-label, single-arm, phase 2 trial, improvements in wound healing, pain and health-related quality of life were seen in calciphylaxis patients treated with SNF472 three times weekly for 12 weeks [118]. The subsequent phase three international randomized, double-blind, placebo-controlled trial did not demonstrate a significant improvement in wound score compared with placebo, though there were numerically fewer (non-statistically significant) deaths (3% vs 15%) and calciphylaxis-related events (5% vs 33%) resulting in hospitalization in the SNF472 group [119]. Further adequately powered studies investigating hospitalization and mortality rates as primary outcomes, and studies investigating groups at high-risk of calciphylaxis and VC more broadly, are warranted.

Kidney replacement therapy

Modifications to dialysis schedule are frequently implemented in calciphylaxis management. An increment in the dialysis efficiency, obtained by an increase of the dialytic dose, has been associated with lesion improvement in observational studies, mostly due to better control of mineral bone disorder parameters [1, 70]. However, the additional burden of intensified dialysis must be carefully balanced against patient-specific needs. Use of low-calcium dialysate has been reported to help reduce calcium loading, and high-magnesium dialysate has been explored for its theoretical anti-calcific effects, and shown to reduce the calcification propensity, though robust clinical evidence is lacking [120, 121]. Overall, the evidence base for these interventions remains limited.

Although extensive ulcerations have traditionally been considered as a contraindication to kidney transplantation, the procedure has been documented as safe and effective [122].

Pain management and supportive care

Calciphylaxis is painful yet this is often undertreated [69, 123]. Alongside regular paracetamol and high-dose opiates, additional agents such as benzodiazepines and ketamine may be required. Early involvement of a pain-specialist team is recommended [124]. Additionally, supportive and palliative care team involvement is also suggested; given the high morbidity and mortality associated with calciphylaxis, supportive care services are beneficial in advising on pain management alongside facilitating holistic goals of care [125].

EMERGING RESEARCH AND FUTURE DIRECTIONS

Better evidence and translation for calciphylaxis (BEAT-Calci) trial

The BEAT-Calci trial is currently ongoing and represents a landmark effort in calciphylaxis research (NCT05018221). It is an innovative, multi-centre, adaptive international platform study designed to evaluate multiple potential treatments for calciphylaxis within a single, flexible trial framework. The trial allows for the simultaneous and sequential assessment of various interventions, including STS, vitamin K1, magnesium citrate, and medium cut-off and high flux dialysis membranes, based on evolving evidence and participant response. The trial's adaptive design enables the addition or removal of treatment arms over time, ensuring efficiency and responsiveness to early results. The primary outcome focuses on wound healing, measured using the 8-point BEAT-Calci Wound Assessment Scale, alongside secondary outcomes including pain reduction and mortality. The trial commenced in 2021 and has a recruitment target of 350; active participant follow-up is 26 weeks with passive follow-up extending up to 4.5 years.

Rheopheresis

Rheopheresis is a double-filtration apheresis which may reduce microvascular thrombosis and inflammation (associated with calciphylaxis) through targeting proinflammatory cytokines and high-molecular weight proteins [126, 127]. A retrospective multicentre study analysed eight patients with severe calciphylaxis who underwent rheopheresis after usual treatments had failed [128]; the study reported complete remission in five patients (63%) after a median of 25 sessions over 4 months. A prospective randomized controlled single-blind trial is now underway comparing the efficacy of rheopheresis versus sham apheresis as an adjuvant treatment to standard care in people with calciphylaxis undergoing haemodialysis (NCT04654000).

INZ-701

INZ-701 is a subcutaneous injection containing functional ENPP1, the enzyme responsible for generation of PPi which is a potent inhibitor of mineralization, and is currently in early phase investigation assessing safety and pharmacokinetics (NCT06283589). Preclinical studies in transgenic mouse models and rat models of CKD-induced VC have demonstrated reduction in ectopic calcification [129–131]. Although trials are not yet powered to assess clinical efficacy, the research represents a promising mechanistic-based approach to treating calciphylaxis.

Emerging prognostic biomarkers

Prognostic biomarkers in calciphylaxis are gaining attention as tools to refine risk stratification, facilitate earlier diagnosis and guide therapeutic decisions. Although still in the investigative stage, several candidates have emerged based on their biological relevance and early clinical associations.

Calciprotein particle crystallization test (T50)

The serum CPP crystallization test (also known as the T50 assay) developed in 2012 measures the half-transformation time from CPP1 to CPP2, reflecting the ability of serum to resist hydroxyapatite crystal formation (the final step in VC) [33]. As mentioned earlier, increased circulating CPP have been described in patients with calciphylaxis, suggesting that shortened T50 may indicate increased calciphylaxis risk [60]. T50 has been associated with cardiovascular events and mortality across all stages of CKD, including dialysis and transplant populations [132]. Interventions such as citrate-acidified dialysate, higher magnesium dialysate, phosphate binders, oral magnesium, etelcalcitide and spironolactone have been shown to improve T50 values [116, 132–134]. Though currently limited to research use, T50 or quantification of CPP may offer a future tool for risk stratification and monitoring in patients at risk of calciphylaxis.

Matrix Gla protein

MGP is a vitamin K–dependent protein characterized by five gamma-carboxyglutamic acid residues and three serine residues via the enzyme casein kinase that make it active (c-p MGP) [135]. Active MGP binds calcification crystals in blood vessels. In patients on vitamin K antagonists such as warfarin, MGP remains inactive, contributing to uncontrolled medial arterial calcification. Studies have shown that plasma dp-ucMGP is positively associated with VC and might be utilized as an early marker for VC [135]. Observational studies have shown that low levels of carboxylated MGP are associated with calciphylaxis development and may be predictive of lesion progression [74].

Pyrophosphate

PPi is a crucial inhibitor of VC, acting by blocking hydroxyapatite crystal formation. In advanced CKD, PPi levels are often reduced, contributing to increased risk of VC. While not yet validated as a prognostic biomarker in calciphylaxis, low PPi levels have been associated with increased mortality risk in people with calciphylaxis in a recent prospective study ($n = 70$) [136]. Currently challenges in PPi measurement and the absence of standardized assays currently limit its clinical application.

Interleukin-6

Elevated IL-6 levels correlate with increased VC and worse outcomes in people with CKD. The TYMP–IL6–TF axis has recently been identified as a modifiable contributor to calciphylaxis [137]. Clazakizumab (an IL-6 inhibitor) is shown to reduce inflammation (measured by high sensitivity C-reactive protein) in a phase 2 trial in people undergoing haemodialysis [138]. The POSIBIL6 Trial is a phase 2b/3 RCT aiming to recruit 2190 people undergoing haemodialysis to investigate the effect of clazakizumab on clinical end points (cardiovascular, death and major infection) (NCT05485961), though there are no trials specifically investigating IL-6-targeting treatments in calciphylaxis as yet.

National calciphylaxis registries

National calciphylaxis registries remain essential tools for improving our understanding of this rare and complex condition. The UK Calciphylaxis Study and UK Registry of Rare Renal Diseases, German Calciphylaxis Registry and the US-based Partners Calciphylaxis Biobank and Registry have led the way in systematically collecting real-world data on clinical presentation, risk factors, diagnostics, treatments and outcomes in calciphylaxis. In addition to providing critical insights into disease prevalence, calciphylaxis registries also inform clinical trial design and support the identification of participants. Alongside clinical trials, robust registry participation and consistent case reporting are fundamental to advancing knowledge and clinical care in calciphylaxis. There is an evident need for a common European registry, however regulatory and legal barriers need to be overcome to achieve this.

CONCLUSION

Calciphylaxis remains a devastating condition, marked by significant diagnostic uncertainty and limited treatment options. Despite increasing recognition of its complex, multifactorial pathophysiology and the emergence of clinical trials, there are still no approved therapies or reliable diagnostic tests. Current management is guided by registry data and small, uncontrolled studies [139].

The BEAT-Calci trial represents a major advance, offering an adaptive, collaborative platform for systematic therapy evaluation. National registries are addressing knowledge gaps by generating large-scale, real-world data on risk factors, outcomes and treatment responses. Emerging biomarkers, including the calciprotein particle crystallization test (T50) and PPi, may improve prognosis and risk stratification. Investigational agents such as SNF472 and INZ-701 signal a shift toward targeted, mechanism-based treatments.

Future research should focus on identifying novel mechanistic pathways which may represent potential therapeutic targets, and on validating prognostic tools that integrate clinical and biomarker data for diagnosis and risk assessment. Incorporating qualitative research and patient-reported outcomes is essential.

Progress will require sustained investment, international collaboration, and broad engagement in registries and trials to translate emerging insights into patient benefit. Given its rarity and limited local expertise, centralizing knowledge through national centres is recommended.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Chinnadurai R, Huckle A, Hegarty J *et al.* Calciphylaxis in end-stage kidney disease: outcome data from the United Kingdom Calciphylaxis Study. *J Nephrol* 2021;**34**:1537–45. https://doi.org/10.1007/s40620-020-00908-9
2. McCarthy JT, El-Azhary RA, Patzelt MT *et al.* Survival, risk factors, and effect of treatment in 101 patients with calci-

phylaxis. *Mayo Clin Proc* 2016;**91**:1384–94. https://doi.org/10.1016/j.mayocp.2016.06.025
3. Nigwekar SU, Zhao S, Wenger J *et al*. A Nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Neprol* 2016;**27**:3421–9. https://doi.org/10.1681/ASN.2015091065
4. Gabel CK, Nguyen ED, Chakrala T *et al*. Assessment of outcomes of calciphylaxis. *J Am Acad Dermatol* 2021;**85**:1057–64. https://doi.org/10.1016/j.jaad.2020.10.067
5. Panchal S, Holtermann K, Trivedi N *et al*. Calciphylaxis: an analysis of concomitant factors, treatment effectiveness and prognosis in 30 patients. *Int J Nephrol Renovasc Dis* 2020;**13**:65–71. https://doi.org/10.2147/IJNRD.S241422
6. Tan AJ, Xia J, Glennon CM *et al*. Assessment of diagnostic delay, morbidity, and mortality outcomes in 302 calciphylaxis patients over a 17-year period: a retrospective cohort study. *J Am Acad Dermatol* 2024;**91**:834–42. https://doi.org/10.1016/j.jaad.2024.06.058
7. Chinnadurai R, Sinha S, Lowney AC *et al*. Pain management in patients with end-stage renal disease and calciphylaxis- a survey of clinical practices among physicians. *BMC Nephrol* 2020;**21**:403. https://doi.org/10.1186/s12882-020-02067-2
8. Nigwekar SU, Kroshinsky D, Nazarian RM *et al*. Calciphylaxis: risk factors. *Am J Kidney Dis* 2015;**66**:133–46. https://doi.org/10.1053/j.ajkd.2015.01.034
9. Wen W, Portales-Castillo I, Seethapathy R *et al*. Intravenous sodium thiosulphate for calciphylaxis of chronic kidney disease: a systematic review and meta-analysis. *JAMA Netw Open* 2023;**6**:e2310068. https://doi.org/10.1001/jamanetworkopen.2023.10068
10. Bachu R, Patel TH, Hemmings S. Calciphylaxis in end-stage renal disease: a rare condition with high mortality. *Cureus* 2022;**14**:e26752.
11. Brandenburg VM, Kramann R, Rothe H *et al*. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. *Nephrol Dial Transplant* 2017;**32**:126–32. https://doi.org/10.1093/ndt/gfv438
12. Rivera-Nieves J, Bamias G, Alfert J *et al*. Intestinal ischemia and peripheral gangrene in a patient with chronic renal failure. *Gastroenterology* 2002;**122**:495–9. https://doi.org/10.1053/gast.2002.31387
13. Nigwekar SU, Kroshinsky D, Nazarian RM *et al*. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis* 2015;**66**:133–46. https://doi.org/10.1053/j.ajkd.2015.01.034
14. Vervloet M, Cozzolino M. Vascular calcification in chronic kidney disease: different bricks in the wall? *Kidney Int* 2017;**91**:808–17. https://doi.org/10.1016/j.kint.2016.09.024
15. Ding N, Lv Y, Su H *et al*. Vascular calcification in CKD: new insights into its mechanisms. *J Cell Physiol* 2023;**238**:1160–82. https://doi.org/10.1002/jcp.31021
16. Miyazaki-Anzai S, Masuda M, Keenan AL *et al*. Activation of the IKK2/NF-kappaB pathway in VSMCs inhibits calcified vascular stiffness in CKD. *JCI Insight* 2024;**9**:e174977. https://doi.org/10.1172/jci.insight.174977
17. Rong S, Zhao X, Jin X *et al*. Vascular calcification in chronic kidney disease is induced by bone morphogenetic protein-2 via a mechanism involving the Wnt/beta-catenin pathway. *Cell Physiol Biochem* 2014;**34**:2049–60. https://doi.org/10.1159/000366400
18. Kramann R, Brandenburg VM, Schurgers LJ *et al*. Novel insights into osteogenesis and matrix remodelling associated with calcific uraemic arteriolopathy. *Nephrol Dial Transplant* 2013;**28**:856–68. https://doi.org/10.1093/ndt/gfs466
19. Chen NX, O'Neill K, Akl NK *et al*. Adipocyte induced arterial calcification is prevented with sodium thiosulfate. *Biochem Biophys Res Commun* 2014;**449**:151–6. https://doi.org/10.1016/j.bbrc.2014.05.005
20. Faleeva M, Ahmad S, Theofilatos K *et al*. Sox9 accelerates vascular aging by regulating extracellular matrix composition and stiffness. *Circ Res* 2024;**134**:307–24. https://doi.org/10.1161/CIRCRESAHA.123.323365
21. Salera D, Merkel N, Bellasi A *et al*. Pathophysiology of chronic kidney disease-mineral bone disorder (CKD-MBD): from adaptive to maladaptive mineral homeostasis. *Clin Kidney J* 2025;**18**:i3–14. https://doi.org/10.1093/ckj/sfae431
22. Rodelo-Haad C, Rodriguez-Ortiz ME, Garcia-Saez R *et al*. The true cost of phosphate control in chronic kidney disease. *Clin Kidney J* 2025;**18**:i46–60. https://doi.org/10.1093/ckj/sfae434
23. Chen YX, Huang C, Duan ZB *et al*. Klotho/FGF23 axis mediates high phosphate-induced vascular calcification in vascular smooth muscle cells via Wnt7b/beta-catenin pathway. *Kaohsiung J Med Sci* 2019;**35**:393–400. https://doi.org/10.1002/kjm2.12072
24. Yamada S, Giachelli CM. Vascular calcification in CKD-MBD: roles for phosphate, FGF23, and Klotho. *Bone* 2017;**100**:87–93. https://doi.org/10.1016/j.bone.2016.11.012
25. Crouthamel MH, Lau WL, Leaf EM *et al*. Sodium-dependent phosphate cotransporters and phosphate-induced calcification of vascular smooth muscle cells: redundant roles for PiT-1 and PiT-2. *Arterioscler Thromb Vasc Biol* 2013;**33**:2625–32. https://doi.org/10.1161/ATVBAHA.113.302249
26. He F, Wang H, Ren WY *et al*. BMP9/COX-2 axial mediates high phosphate-induced calcification in vascular smooth muscle cells via Wnt/beta-catenin pathway. *J Cell Biochem* 2018;**119**:2851–63. https://doi.org/10.1002/jcb.26460
27. Nigwekar Sagar U, Thadhani R, Brandenburg Vincent M. Calciphylaxis. *N Engl J Med* 2018;**378**:1704–14. https://doi.org/10.1056/NEJMra1505292
28. Shanahan CM, Crouthamel MH, Kapustin A *et al*. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. *Circ Res* 2011;**109**:697–711. https://doi.org/10.1161/CIRCRESAHA.110.234914
29. Turek M, Stepniewska J, Rozanski J. The multifactorial pathogenesis of calciphylaxis: a case report. *Am J Case Rep* 2021;**22**:e930026. https://doi.org/10.12659/AJCR.930026
30. Smith ER, Holt SG. The formation and function of calciprotein particles. *Pflugers Arch* 2025;**477**:753–72. https://doi.org/10.1007/s00424-025-03083-7
31. Smith ER, Cai MM, McMahon LP *et al*. Serum fetuin-A concentration and fetuin-A-containing calciprotein particles in patients with chronic inflammatory disease and renal failure. *Nephrology* 2013;**18**:215–21. https://doi.org/10.1111/nep.12021
32. Rondbjerg AK, Gyldenlove M, Krustrup D *et al*. Cutaneous vascular calcifications in patients with chronic kidney disease and calcific uremic arteriolopathy: a cross-sectional study. *J Nephrol* 2023;**36**:1991–9. https://doi.org/10.1007/s40620-023-01707-8
33. Pasch A, Farese S, Gräber S *et al*. Nanoparticle-based test measures overall propensity for calcification in serum. *J Am Soc Neprol* 2012;**23**:1744–52. https://doi.org/10.1681/ASN.2012030240
34. Colboc H, Moguelet P, Bazin D *et al*. Localization, morphologic features, and chemical composition of calciphylaxis-related skin deposits in patients with calcific uremic arteriolopathy. *JAMA Dermatol* 2019;**155**:789–96. https://doi.org/10.1001/jamadermatol.2019.0381

35. Opdebeeck B, Maudsley S, Azmi A *et al.* Indoxyl sulfate and p-cresyl sulfate promote vascular calcification and associate with glucose intolerance. *J Am Soc Neprol* 2019;**30**:751–66. https://doi.org/10.1681/ASN.2018060609
36. Opdebeeck B, D'Haese PC, Verhulst A. Molecular and cellular mechanisms that induce arterial calcification by indoxyl sulfate and p-cresyl sulfate. *Toxins* 2020;**12**:58. https://doi.org/10.3390/toxins12010058
37. Lash JP, Go AS, Appel LJ *et al.* Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 2009;**4**:1302–11. https://doi.org/10.2215/CJN.00070109
38. López-Mejías R, González-Gay MA. IL-6: linking chronic inflammation and vascular calcification. *Nat Rev Rheumatol* 2019;**15**:457–9. https://doi.org/10.1038/s41584-019-0259-x
39. Sowers KH, Hayden MR. Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. *Oxid Med Cell Long* 2010;**3**:109–21. https://doi.org/10.4161/oxim.3.2.11354
40. Napoleon MA, Yang X, Zhang Y *et al.* Activation and targetability of TYMP–IL-6–TF signaling in the skin microenvironment in uremic calciphylaxis. *Sci Transl Med* 2025;**17**:eadn5772.
41. Roumeliotis S, Duni A, Vaios V *et al.* Vitamin K supplementation for prevention of vascular calcification in chronic kidney disease patients: are we there yet? *Nutrients* 2022;**14**:925. https://doi.org/10.3390/nu14050925
42. Cozzolino M, Gallieni M, Brancaccio D. Inflammation and vascular calcification in chronic kidney disease: the role of Fetuin-A. *Cytokine* 2009;**45**:70–1. https://doi.org/10.1016/j.cyto.2008.11.012
43. Shroff RC, Shah V, Hiorns MP *et al.* The circulating calcification inhibitors, fetuin-A and osteoprotegerin, but not matrix Gla protein, are associated with vascular stiffness and calcification in children on dialysis. *Nephrol Dial Transplant* 2008;**23**:3263–71. https://doi.org/10.1093/ndt/gfn226
44. Cianciolo G, Galassi A, Capelli I *et al.* Klotho-FGF23, cardiovascular disease, and vascular calcification: black or white? *Curr Vasc Pharmacol* 2018;**16**:143–56. https://doi.org/10.2174/1570161115666170310092202
45. Gao Y, Zhao CJ, Liu Q *et al.* Relationship between serum indoxyl sulfate and klotho protein and vascular calcification in patients with chronic kidney disease stages 3-5. *Int J Endocrinol* 2024;**2024**:8229604. https://doi.org/10.1155/2024/8229604
46. Lim K, Lu TS, Molostvov G *et al.* Vascular Klotho deficiency potentiates the development of human artery calcification and mediates resistance to fibroblast growth factor 23. *Circulation* 2012;**125**:2243–55. https://doi.org/10.1161/CIRCULATIONAHA.111.053405
47. Rothe H, Brandenburg V, Haun M *et al.* Ecto-5'-Nucleotidase CD73 (NT5E), vitamin D receptor and FGF23 gene polymorphisms may play a role in the development of calcific uremic arteriolopathy in dialysis patients—data from the German Calciphylaxis Registry. *PLoS One* 2017;**12**:e0172407. https://doi.org/10.1371/journal.pone.0172407
48. Garcia-Lozano JA, Ocampo-Candiani J, Martinez-Cabriales SA *et al.* An update on calciphylaxis. *Am J Clin Dermatol* 2018;**19**:599–608. https://doi.org/10.1007/s40257-018-0361-x
49. Ichinose M, Sasagawa N, Chiba T *et al.* Protein C and protein S deficiencies may be related to survival among hemodialysis patients. *BMC Nephrol* 2019;**20**:191. https://doi.org/10.1186/s12882-019-1344-8
50. Gallo Marin B, Aghagoli G, Hu SL *et al.* Calciphylaxis and kidney disease: a review. *Am J Kidney Dis* 2023;**81**:232–9. https://doi.org/10.1053/j.ajkd.2022.06.011
51. Nigwekar SU, Wolf M, Sterns RH *et al.* Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol* 2008;**3**:1139–43. https://doi.org/10.2215/CJN.00530108
52. Pollock B, Cunliffe WJ, Merchant WJ. Calciphylaxis in the absence of renal failure. *Clin Exp Dermatol* 2000;**25**:389–92. https://doi.org/10.1046/j.1365-2230.2000.00671.x
53. Kochhar K, O'Dell B, Torrence G *et al.* Managing calciphylaxis: insights from real-world cases at a tertiary academic center. *Adv Skin Wound Care* 2025;**38**:E1–5. https://doi.org/10.1097/ASW.0000000000000263
54. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med* 2018;**378**:1704–14. https://doi.org/10.1056/NEJMra1505292
55. Mazhar AR, Johnson RJ, Gillen D *et al.* Risk factors and mortality associated with calciphylaxis in end-stage renal disease. *Kidney Int* 2001;**60**:324–32. https://doi.org/10.1046/j.1523-1755.2001.00803.x
56. Lal G, Nowell AG, Liao J *et al.* Determinants of survival in patients with calciphylaxis: a multivariate analysis. *Surgery* 2009;**146**:1028–34. https://doi.org/10.1016/j.surg.2009.09.022
57. Jeong HS, Dominguez AR. Calciphylaxis: controversies in pathogenesis, diagnosis and treatment. *Am J Med Sci* 2016;**351**:217–27. https://doi.org/10.1016/j.amjms.2015.11.015
58. Weenig RH, Sewell LD, Davis MDP *et al.* Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007;**56**:569–79. https://doi.org/10.1016/j.jaad.2006.08.065
59. Ghosh T, Winchester DS, Davis MDP *et al.* Early clinical presentations and progression of calciphylaxis. *Int J Dermatol* 2017;**56**:856–61. https://doi.org/10.1111/ijd.13622
60. Røndbjerg AK, Gyldenløve M, Krustrup D *et al.* Cutaneous vascular calcifications in patients with chronic kidney disease and calcific uremic arteriolopathy: a cross-sectional study. *J Nephrol* 2023;**36**:1991–9. https://doi.org/10.1007/s40620-023-01707-8
61. Dutta P, Chaudet KM, Nazarian RM *et al.* Correlation between clinical and pathological features of cutaneous calciphylaxis. *PLoS One* 2019;**14**:e0218155. https://doi.org/10.1371/journal.pone.0218155
62. Deinsberger J, Sirovina S, Bromberger S *et al.* Microstructural comparative analysis of calcification patterns in calciphylaxis versus arteriolosclerotic ulcer of Martorell. *Eur J Dermatol* 2021;**31**:705–11.
63. McMullen ER, Harms PW, Lowe L *et al.* Clinicopathologic features and calcium deposition patterns in calciphylaxis: comparison with gangrene, peripheral artery disease, chronic stasis, and thrombotic vasculopathy. *Am J Surg Pathol* 2019;**43**:1273–81. https://doi.org/10.1097/PAS.0000000000001302
64. Ruderman I, Hewitson TD, Smith ER *et al.* Vascular calcification in skin and subcutaneous tissue in patients with chronic and end-stage kidney disease. *BMC Nephrol* 2020;**21**:279. https://doi.org/10.1186/s12882-020-01928-0
65. Chewcharat A, Nigwekar SU. Ten tips on how to deal with calciphylaxis patients. *Clin Kidney J* 2025;**18**:sfaf098. https://doi.org/10.1093/ckj/sfaf098
66. Yu Q, Liu Y, Xie X *et al.* Radiomics-based method for diagnosis of calciphylaxis in patients with chronic kidney dis-

ease using computed tomography. *Quant Imaging Med Surg* 2021;**11**:4617–26. https://doi.org/10.21037/qims-20-1211
67. Groover M, Nutan F. Role of bone scan in diagnosis of calciphylaxis: a review. *JAAD Int* 2024;**14**:31–3. https://doi.org/10.1016/j.jdin.2023.09.010
68. X-k W, J-y H, Yang Q *et al.* Early diagnosis of necrotizing fasciitis: imaging techniques and their combined application. *Int Wound J* 2024;**21**:e14379.
69. Singh R, McCain S, Feldman SR *et al.* Characterizing the burden of calciphylaxis: a qualitative analysis. *Clin Exp Dermatol* 2023;**48**:371–3. https://doi.org/10.1093/ced/llac118
70. Borges L, Rosa P, Dias E *et al.* Successful treatment of calciphylaxis by a multidisciplinary approach. *BMJ Case Rep* 2014;**2014**:bcr2014204354. https://doi.org/10.1136/bcr-2014-204354
71. Pan Y, Wang H, Ye Y *et al.* The application of MDT model for calciphylaxis management in patients with end-stage renal disease. *Int Wound J* 2023;**20**:3717–23. https://doi.org/10.1111/iwj.14265
72. Ghaly P, Iliopoulos J, Ahmad M. The role of nutrition in wound healing: an overview. *Br J Nurs* 2021;**30**:S38–42. https://doi.org/10.12968/bjon.2021.30.5.S38
73. Carmo LS, Burdmann EA, Fessel MR *et al.* Expansive vascular remodeling and increased vascular calcification response to cholecalciferol in a murine model of obesity and insulin resistance. *Arterioscler Thromb Vasc Biol* 2019;**39**:200–11. https://doi.org/10.1161/ATVBAHA.118.311880
74. Nigwekar SU, Bloch DB, Nazarian RM *et al.* Vitamin K–dependent carboxylation of matrix Gla protein influences the risk of calciphylaxis. *J Am Soc Neprol* 2017;**28**:1717–22. https://doi.org/10.1681/ASN.2016060651
75. Garza-Mayers AC, Shah R, Sykes DB *et al.* The successful use of apixaban in dialysis patients with calciphylaxis who require anticoagulation: a retrospective analysis. *Am J Nephrol* 2018;**48**:168–71. https://doi.org/10.1159/000491881
76. King BJ, El-Azhary RA, McEvoy MT *et al.* Direct oral anticoagulant medications in calciphylaxis. *Int J Dermatol* 2017;**56**:1065–70. https://doi.org/10.1111/ijd.13685
77. Udomkarnjananun S, Kongnatthasate K, Praditpornsilpa K *et al.* Treatment of calciphylaxis in CKD: a systematic review and meta-analysis. *Kidney Int Rep* 2019;**4**:231–44. https://doi.org/10.1016/j.ekir.2018.10.002
78. Milas M, Bush RL, Lin P *et al.* Calciphylaxis and nonhealing wounds: the role of the vascular surgeon in a multidisciplinary treatment. *J Vasc Surg* 2003;**37**:501–7. https://doi.org/10.1067/mva.2003.70
79. Biglione B, Cucka B, Iriarte C *et al.* A retrospective review of outcomes after hyperbaric oxygen therapy for the treatment of calciphylaxis. *J Am Acad Dermatol* 2024;**90**:45–51. https://doi.org/10.1016/j.jaad.2023.07.1031
80. An J, Devaney B, Ooi KY *et al.* Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. *Nephrology* 2015;**20**:444–50. https://doi.org/10.1111/nep.12433
81. Cohen GF, Vyas NS. Sodium thiosulfate in the treatment of calciphylaxis. *J Clin Aesthet Dermatol* 2013;**6**:41–4.
82. Ross EA. Evolution of treatment strategies for calciphylaxis. *Am J Nephrol* 2011;**34**:460–7. https://doi.org/10.1159/000332221
83. Hayden MR, Goldsmith DJ. Sodium thiosulfate: new hope for the treatment of calciphylaxis. *Semin Dial* 2010;**23**:258–62. https://doi.org/10.1111/j.1525-139X.2010.00738.x
84. Singh RP, Derendorf H, Ross EA. Simulation-based sodium thiosulfate dosing strategies for the treatment of calciphylaxis. *Clin J Am Soc Nephrol* 2011;**6**:1155–9. https://doi.org/10.2215/CJN.09671010
85. Peng T, Zhuo L, Wang Y *et al.* Systematic review of sodium thiosulfate in treating calciphylaxis in chronic kidney disease patients. *Nephrology* 2018;**23**:669–75. https://doi.org/10.1111/nep.13081
86. Vaz J, Rosa E, Magalhaes L *et al.* Sodium thiosulfate treatment for calciphylaxis: is there an optimal duration of therapy? *Hemodial Int* 2025;**29**:238–41. https://doi.org/10.1111/hdi.13196
87. Raymond CB, Wazny LD. Sodium thiosulfate, bisphosphonates, and cinacalcet for treatment of calciphylaxis. *Am J Health Syst Pharm* 2008;**65**:1419–29. https://doi.org/10.2146/ajhp070546
88. Chewcharat A, Nigwekar SU. Ten tips on how to deal with calciphylaxis patients. *Clin Kidney J* 2025;**18**:sfaf098. https://doi.org/10.1093/ckj/sfaf098
89. Wen W, Portales-Castillo I, Seethapathy R *et al.* Intravenous sodium thiosulphate for vascular calcification of hemodialysis patients-a systematic review and meta-analysis. *Nephrol Dial Transplant* 2023;**38**:733–45. https://doi.org/10.1093/ndt/gfac171
90. Deen J, Schaider H. The use of cinacalcet for the treatment of calciphylaxis in patients with chronic kidney disease: a comprehensive review. *Aust J Dermatol* 2019;**60**:e186–e94. https://doi.org/10.1111/ajd.12992
91. Russo D, Capuano A, Cozzolino M *et al.* Multimodal treatment of calcific uraemic arteriolopathy (calciphylaxis): a case series. *Clin Kidney J* 2016;**9**:108–12. https://doi.org/10.1093/ckj/sfv120
92. Liu ALC, Ng GX. Calciphylaxis in a renal transplant patient. *Proceedings of UCLA Healthcare* 2015;**19**. Retrieved from https://escholarship.org/uc/item/305108d3 (9 September 2025, date last accessed).
93. Floege J, Kubo Y, Floege A *et al.* The effect of cinacalcet on calcific uremic arteriolopathy events in patients receiving hemodialysis: the EVOLVE Trial. *Clin J Am Soc Nephrol* 2015;**10**:800–7. https://doi.org/10.2215/CJN.10221014
94. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl (2011)* 2017;**7**:1–59.
95. Duffy A, Schurr M, Warner T *et al.* Long-term outcomes in patients with calciphylaxis from hyperparathyroidism. *Ann Surg Oncol* 2006;**13**:96–102. https://doi.org/10.1245/ASO.2006.03.042
96. Girotto JA, Harmon JW, Ratner LE *et al.* Parathyroidectomy promotes wound healing and prolongs survival in patients with calciphylaxis from secondary hyperparathyroidism. *Surgery* 2001;**130**:645–50; discussion 645–51. https://doi.org/10.1067/msy.2001.117101
97. Nigwekar SU, Sprague SM. We do too many parathyroidectomies for calciphylaxis. *Semin Dial* 2016;**29**:312–4. https://doi.org/10.1111/sdi.12502
98. Fernandez Canabate S, Alvarez CL, Ortega Valin L *et al.* Sodium thiosulfate and pamidronate for treatment of calciphylaxis: case report. *Colomb Med* 2018;**49**:288–91. https://doi.org/10.25100/cm.v49i4.4134
99. Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. *NDT Plus* 2008;**1**:135–47.
100. Helas S, Goettsch C, Schoppet M *et al.* Inhibition of receptor activator of NF-kappaB ligand by denosumab at-

tenuates vascular calcium deposition in mice. *Am J Pathol* 2009;**175**:473–8. https://doi.org/10.2353/ajpath.2009.080957
101. Geers J, Bing R, Pawade TA *et al*. Effect of denosumab or alendronate on vascular calcification: secondary analysis of SALTIRE2 randomized controlled trial. *J Am Heart Assoc* 2024;**13**:e032571. https://doi.org/10.1161/JAHA.123.032571
102. Chen CL, Chen NC, Hsu CY *et al*. An open-label, prospective pilot clinical study of denosumab for severe hyperparathyroidism in patients with low bone mass undergoing dialysis. *J Clin Endocrinol Metab* 2014;**99**:2426–32. https://doi.org/10.1210/jc.2014-1154
103. Kunizawa K, Hiramatsu R, Hoshino J *et al*. Denosumab for dialysis patients with osteoporosis: a cohort study. *Sci Rep* 2020;**10**:2496. https://doi.org/10.1038/s41598-020-59143-8
104. Bird ST, Smith ER, Gelperin K *et al*. Severe hypocalcemia with denosumab among older female dialysis-dependent patients. *JAMA* 2024;**331**:491–9. https://doi.org/10.1001/jama.2023.28239
105. Crotty R, Nazarian RM, Song PI *et al*. Heparin, warfarin, or calciphylaxis? *Am J Hematol* 2014;**89**:785–6. https://doi.org/10.1002/ajh.23679
106. Nigwekar SU, Bloch DB, Nazarian RM *et al*. Vitamin K-dependent carboxylation of matrix Gla protein influences the risk of calciphylaxis. *J Am Soc Neprol* 2017;**28**:1717–22. https://doi.org/10.1681/ASN.2016060651
107. Christiadi D, Singer RF. Calciphylaxis in a dialysis patient successfully treated with high-dose vitamin K supplementation. *Clin Kidney J* 2018;**11**:528–9. https://doi.org/10.1093/ckj/sfx126
108. Wajih Z, Singer R. Successful treatment of calciphylaxis with vitamin K in a patient on haemodialysis. *Clin Kidney J* 2022;**15**:354–6. https://doi.org/10.1093/ckj/sfab209
109. Vlasschaert C, Goss CJ, Pilkey NG *et al*. Vitamin K supplementation for the prevention of cardiovascular disease: where is the evidence? A systematic review of controlled trials. *Nutrients* 2020;**12**:2909.
110. Saritas T, Reinartz S, Kruger T *et al*. Vitamin K1 and progression of cardiovascular calcifications in hemodialysis patients: the VitaVasK randomized controlled trial. *Clin Kidney J* 2022;**15**:2300–11.
111. Kaesler N, Schreibing F, Speer T *et al*. Altered vitamin K biodistribution and metabolism in experimental and human chronic kidney disease. *Kidney Int* 2022;**101**:338–48. https://doi.org/10.1016/j.kint.2021.10.029
112. Montes de Oca A, Guerrero F, Martinez-Moreno JM *et al*. Magnesium inhibits Wnt/beta-catenin activity and reverses the osteogenic transformation of vascular smooth muscle cells. *PLoS One* 2014;**9**:e89525. https://doi.org/10.1371/journal.pone.0089525
113. Weglicki WB. Hypomagnesemia and inflammation: clinical and basic aspects. *Annu Rev Nutr* 2012;**32**:55–71. https://doi.org/10.1146/annurev-nutr-071811-150656
114. Leenders NHJ, Bos C, Hoekstra T *et al*. Dietary magnesium supplementation inhibits abdominal vascular calcification in an experimental animal model of chronic kidney disease. *Nephrol Dial Transplant* 2022;**37**:1049–58. https://doi.org/10.1093/ndt/gfac026
115. Diaz-Tocados JM, Peralta-Ramirez A, Rodriguez-Ortiz ME *et al*. Dietary magnesium supplementation prevents and reverses vascular and soft tissue calcifications in uremic rats. *Kidney Int* 2017;**92**:1084–99. https://doi.org/10.1016/j.kint.2017.04.011
116. Bressendorff I, Hansen D, Schou M *et al*. The effect of magnesium supplementation on vascular calcification in CKD: a randomized clinical trial (MAGiCAL-CKD). *J Am Soc Neprol* 2023;**34**:886–94. https://doi.org/10.1681/ASN.0000000000000092
117. Zhan Y, Zhang R, Li G. Effect of magnesium on vascular calcification in chronic kidney disease patients: a systematic review and meta-analysis. *Ren Fail* 2023;**45**:2182603. https://doi.org/10.1080/0886022X.2023.2182603
118. Brandenburg VM, Sinha S, Torregrosa JV *et al*. Improvement in wound healing, pain, and quality of life after 12 weeks of SNF472 treatment: a phase 2 open-label study of patients with calciphylaxis. *J Nephrol* 2019;**32**:811–21. https://doi.org/10.1007/s40620-019-00631-0
119. Sinha S, Nigwekar SU, Brandenburg V *et al*. Hexasodium fytate for the treatment of calciphylaxis: a randomised, double-blind, phase 3, placebo-controlled trial with an open-label extension. *EClinicalMedicine* 2024;**75**:102784. https://doi.org/10.1016/j.eclinm.2024.102784
120. Bressendorff I, Hansen D, Pasch A *et al*. The effect of increasing dialysate magnesium on calciprotein particles, inflammation and bone markers: post hoc analysis from a randomized controlled clinical trial. *Nephrol Dial Transplant* 2021;**36**:713–21. https://doi.org/10.1093/ndt/gfz234
121. Bressendorff I, Hansen D, Schou M *et al*. The effect of increasing dialysate magnesium on serum calcification propensity in subjects with end stage kidney disease. *Clin J Am Soc Neprol* 2018;**13**:1373–80. https://doi.org/10.2215/CJN.13921217
122. Nordheim E, Hovd M, Dahle DO. Kidney transplantation and hyperbaric oxygen treatment for calciphylaxis. *Kidney Int* 2025;**107**:1113. https://doi.org/10.1016/j.kint.2025.03.003
123. Wen W, Krinsky S, Kroshinsky D *et al*. Patient-reported and clinical outcomes among patients with calciphylaxis. *Mayo Clinic Proc Innov Qual Outcomes* 2023;**7**:81–92.
124. Chinnadurai R, Sinha S, Lowney AC *et al*. Pain management in patients with end-stage renal disease and calciphylaxis-a survey of clinical practices among physicians. *BMC Nephrol* 2020;**21**:1–8. https://doi.org/10.1186/s12882-020-02067-2
125. Riemer CA, El-Azhary RA, Wu KL *et al*. Underreported use of palliative care and patient-reported outcome measures to address reduced quality of life in patients with calciphylaxis: a systematic review. *Br J Dermatol* 2017;**177**:1510–8. https://doi.org/10.1111/bjd.15702
126. Bouderlique E, Provot F, Lionet A. Rheopheresis for adjuvant treatment in resistant calciphylaxis. *Ther Apher Dial* 2018;**22**:413–4. https://doi.org/10.1111/1744-9987.12666
127. Naciri Bennani H, Jouve T, Boudjemaa S *et al*. Hemodialysis coupled with rheopheresis in calciphylaxis: a winning combination. *J Clin Apher* 2019;**34**:631–3. https://doi.org/10.1002/jca.21736
128. Robert T, Lionet A, Bataille S *et al*. Rheopheresis: a new therapeutic approach in severe calciphylaxis. *Nephrology* 2020;**25**:298–304. https://doi.org/10.1111/nep.13666
129. Albright RA, Stabach P, Cao W *et al*. ENPP1-Fc prevents mortality and vascular calcifications in rodent model of generalized arterial calcification of infancy. *Nat Commun* 2015;**6**:10006. https://doi.org/10.1038/ncomms10006
130. Reichenberger EJ, O'Brien K, Hatori A *et al*. ENPP1 enzyme replacement therapy improves ectopic calcification but does not rescue skeletal phenotype in a mouse model for craniometaphyseal dysplasia. *JBMR Plus* 2024;**8**:ziae103. https://doi.org/10.1093/jbmrpl/ziae103
131. O'Brien K, Laurion L, Sullivan C *et al*. Recombinant ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) decreases vascular calcification and prevents osteomala-

cia in a rat model of chronic kidney disease. *JBMR Plus* 2025;**9**:ziaf065.
132. Pluquet M, Kamel S, Choukroun G *et al*. Serum calcification propensity represents a good biomarker of vascular calcification: a systematic review. *Toxins* 2022;**14**:637. https://doi.org/10.3390/toxins14090637
133. Lorenz G, Mayer CC, Bachmann Q *et al*. Acetate-free, citrate-acidified bicarbonate dialysis improves serum calcification propensity-a preliminary study. *Nephrol Dial Transplant* 2018;**33**:2043–51. https://doi.org/10.1093/ndt/gfy134
134. Ter Meulen KJ, Dekker MJE, Pasch A *et al*. Citric-acid dialysate improves the calcification propensity of hemodialysis patients: a multicenter prospective randomized cross-over trial. *PLoS One* 2019;**14**:e0225824. https://doi.org/10.1371/journal.pone.0225824
135. Fusaro M, Gallieni M, Porta C *et al*. Vitamin K effects in human health: new insights beyond bone and cardiovascular health. *J Nephrol* 2020;**33**:239–49. https://doi.org/10.1007/s40620-019-00685-0
136. Chewcharat A, Bouchouari H, Krinsky S *et al*. Role of plasma inorganic pyrophosphate in calciphylaxis: a prospective study: TH-OR39. *J Am Soc Nephrol* 2023;**34**:12. https://doi.org/10.1681/ASN.20233411S112a
137. Napoleon MA, Yang X, Zhang Y *et al*. Activation and targetability of TYMP–IL-6–TF signaling in the skin microenvironment in uremic calciphylaxis. *Sci Transl Med* 2025;**17**:eadn5772. https://doi.org/10.1126/scitranslmed.adn5772
138. Chertow GM, Chang AM, Felker GM *et al*. IL-6 inhibition with clazakizumab in patients receiving maintenance dialysis: a randomized phase 2b trial. *Nat Med* 2024;**30**:2328–36. https://doi.org/10.1038/s41591-024-03043-1
139. Seethapathy H, Brandenburg VM, Sinha S *et al*. Review: update on the management of calciphylaxis. *QJM* 2019;**112**:29–34. https://doi.org/10.1093/qjmed/hcy234

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