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. Characterised 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 crystallisation 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 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 prioritise 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: calciphylaxis, calcific uraemic arteriolopathy, CKD, kidney failure

Introduction

Calciphylaxis, also known as calcific uraemic arteriolopathy (CUA), 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 characterised 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 recognised under-reporting to national registries, the largest national calciphylaxis dataset reported (from the United States) 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 36-74%(4-6).

The clinical diagnosis and management of calciphylaxis remains challenging. Considering the rarity and the lack of awareness and standardised 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 experiences(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 (*Figure 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 characterised 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 adipocytes(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 inhibitors(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 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 (IL-1β, IL-6, TGF-β) generate reactive oxygen species and endothelial dysfunction, which drive VSMC transdifferentiation through as-yet-unclear mechanisms(35-38),(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 vascular calcification, 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 characterised 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 (NO), 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 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-supressed PTH (eg. adynamic bone disease), malnutrition and hypoalbuminemia, liver disease, trauma from injection sites, and warfarin therapy (11, 55, 56).

Table 1 summarises 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 optimising 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 outcomes(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-recognised sequence, beginning with non-ulcerative changes and progressing to full-thickness skin necrosis. In the earliest stages, patients frequently report deep, localised 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 buttocks(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 ischemia. In the advanced phase, 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. Recognising 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 ($p = 0.04$), linking pathology to clinical symptoms(61). Findings support the diagnostic utility of skin biopsy, particularly in the context of clinical uncertainty, however sensitivity appears to vary with disease stage, emphasising 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)*(figure 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 vascular calcification, 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 standardised interpretation(65, 67). Similarly, experience with positron emission tomography, and computed tomography (PET-CT) imaging in calciphylaxis is limited. Magnetic Resonance Imaging (MRI), while poor at detecting VC, may help rule out differential diagnoses such as necrotising 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 9 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 minimise 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) minimise protein-wasting, ii) address nutrient deficiencies (including

increased protein requirements resulting from wounds), and iii) support optimisation 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 vascular calcification, discontinuation of vitamin D supplementation, in the presence of calciphylaxis, should be considered given it is an inducer of vascular calcification in animal models.(73) ~~while~~ Calcium-phosphate product should be monitored routinely and optimised 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 matrix-Gla protein, a key innate calcification inhibitor, through inhibition of vitamin K epoxide reductase(74). This provides biological plausibility to support well-established observational data which 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 in 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 utilisation 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, Koebnerisation 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 utilised 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 two-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 deposits(81-83). STS may also reduce reactive oxygen species, endothelial dysfunction, CPPs, and adipocyte contribution to VC(19, 83). The most

widely utilised dosing regimen is 25grams three times per week after each haemodialysis (HD) session(50, 84, 85). Duration of therapy is controversial; some suggest a four-week trial with cessation in non-responders, while case reports have documented use up to two years(86). Though relatively safe, adverse effects include nausea, vomiting, QTc prolongation, headache, weakness, and a raised anion gap metabolic acidosis(87). Three randomised controlled trials (RCTs) evaluating the efficacy of STS in calciphylaxis have been attempted; none have reported, and there remains a paucity in high-quality evidence for the effectiveness of systemic STS. Intralesional STS at a dose of 1–3mL of 250mg/mL, injected weekly into clinically active calciphylaxis lesions, has been reported in those who cannot tolerate intravenous STS; evidence for efficacy is limited(83, 88)(82, 87)(81, 86)(80, 85)(80, 85)(80, 85)(80, 85)(80, 85)(80, 85)(80, 85)(77, 82)(77, 82)(77, 82). 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 emphasised 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 glands(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 data(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 complication(96, 97).

Bisphosphonates

Case reports and retrospective series have described utilising 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 vascular calcification 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-recognised adverse effect of denosumab use in dialysis-dependent patients and concomitant loading with calcium-based medications and/or active vitamin D is utilised 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 utilised vitamin K1 10mg weekly in haemodialysis patients for one year and showed a significant reduction in vascular calcification characterised by a 72% reduction Agatston score ($p=0.028$). It also confirmed a rapid decrease in circulating dp-ucMGP levels and a marked increase in serum phylloquinone (vitamin K1) concentrations(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 two 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 randomised, double-blind, placebo-controlled trial did not demonstrate a significant improvement in wound score compared to placebo, though there were numerically fewer (non-statistically

significant) deaths (3% vs 15%) and calciphylaxis-related events (5% vs 33%) resulting in hospitalisation in the SNF472 group(119). Further adequately powered studies investigating hospitalisation 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 four months. A prospective randomised 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 inorganic pyrophosphate (PPi) that 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 crystallisation test (T50)

The serum calciprotein particle (CPP) crystallisation 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 vascular calcification)(33). As mentioned earlier, increased circulating CPP have been described in patients with calciphylaxis suggesting 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

Matrix Gla protein (MGP) is a vitamin K-dependent protein characterised 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 utilised as an early marker for vascular calcification(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

Inorganic 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 standardised assays currently limit its clinical application.

Interleukin-6

Elevated interleukin-6 (IL-6) levels correlate with increased VC and worse outcomes in people with CKD. The TYMP–IL-6–TF axis has recently been identified as a modifiable contributor to calciphylaxis(137). Clazakizumab (an IL6 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 2,190 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 crystallisation test (T50) and inorganic pyrophosphate (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, centralising knowledge through national centres is recommended.

Acknowledgements

The CKD-MBD Working Group is an official body of the European Renal Association.

Data availability statement

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

Conflict of Interest Statement

SH, SM, CA, MK, and JMT have no conflicts of interest.
AB received consultancy/advisory board fees from CSL Vifor and Bayer. PMF received consultant fees and grant/other support from Allena Pharmaceuticals, Alnylam, Amgen, AstraZeneca, Bayer, Boehringer, Gilead, EG Stada, Novartis, Novo Nordisk, Otsuka Pharmaceuticals, Rocchetta, Vifor Fresenius, and royalties as an author for UpToDate. DC has received speaker fees from Alnylam, AstraZeneca, Amgen, Astellas, Bayer, Boehringer Ingelheim, Chiesi, CSL-Vifor, MSD, Novartis, Stada, Takeda and UCB. MdB has received consultancy fees from Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, CSL Vifor, Kyowa Kirin Pharma, Lilly, Sanofi Genzyme. MdB has received research grant funding from CSL Vifor. MF has received consultancy fees from Amgen and Abiogen, sponsorship to attend meetings from Amgen and Abiogen, and advisory board fees from Amgen. MH had provided consultancy to Resverlogix. DH has received speaker fees from UCB Nordic. MK has received advisory and/or lecture fees from Amgen and Vifor Pharma. SS has received sponsorship to attend medical education conferences from Sanifit, Novartis, AstraZeneca, and CSL Vifor. SS has received speaker fees from AstraZeneca, Bayer, Chiesi, Sanofi-Genzyme, Novartis, CSL Vifor, GSK, Menarini, Medscape, and Boehringer-Ingelheim. SS has received advisory/consultancy feed for AstraZeneca, Novo Nordisk, Amicus, Stada, Santhera, Novartis, Bayer, Sanofi-Genzyme, Vifor Pharma, Boehringer-Ingelheim, GSK, Inozyme Pharma, Inozyme Pharma Inc., Sobi and Purespring. SS has also received research grants from Amgen, Johnson & Johnson, AstraZeneca, CSL Vifor, Sanofi-Genzyme, and Novartis.

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Risk Factor	Proposed Mechanism	Management Strategy
Female sex	Higher fat mass and hormonal differences may predispose to vascular calcification.	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 vascular calcification 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)

Table 1: Risk factors for calciphylaxis

Phase	Clinical features	Possible differentials and common misdiagnosis
Early	• Deep, localised 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 discoloration	• 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 • Necrotising fasciitis • Pyoderma gangrenosum • Fournier's gangrene • Cutaneous malignancy

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

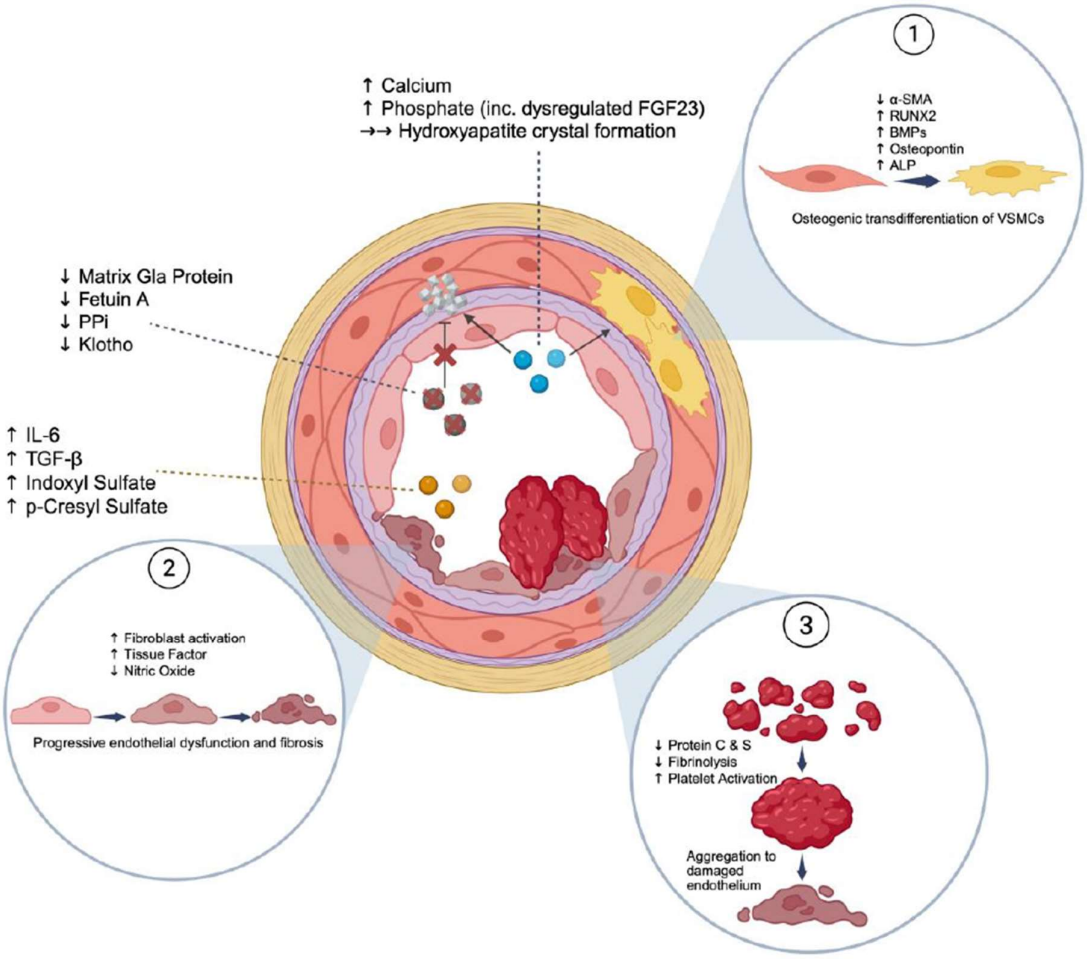

Figure 1: Pathophysiological mechanisms associated with calciphylaxis. 1. Osteogenic transdifferentiation of vascular smooth muscle cells (VSMCs); 2. Endothelial dysfunction and intimal fibrosis; 3. Hypercoagulability and thrombosis. These in turn are driven by systemic inflammation and uremia (IL-6, TGF-β, indoxyl sulfate, p-cresyl sulfate); reduction in innate calcification inhibitors (matrix Gla protein, fetin A, inorganic pyrophosphate (PPi), Klotho); dysregulated calcium-phosphate homeostasis resulting in hydroxyapatite crystal formation. Created in BioRender.

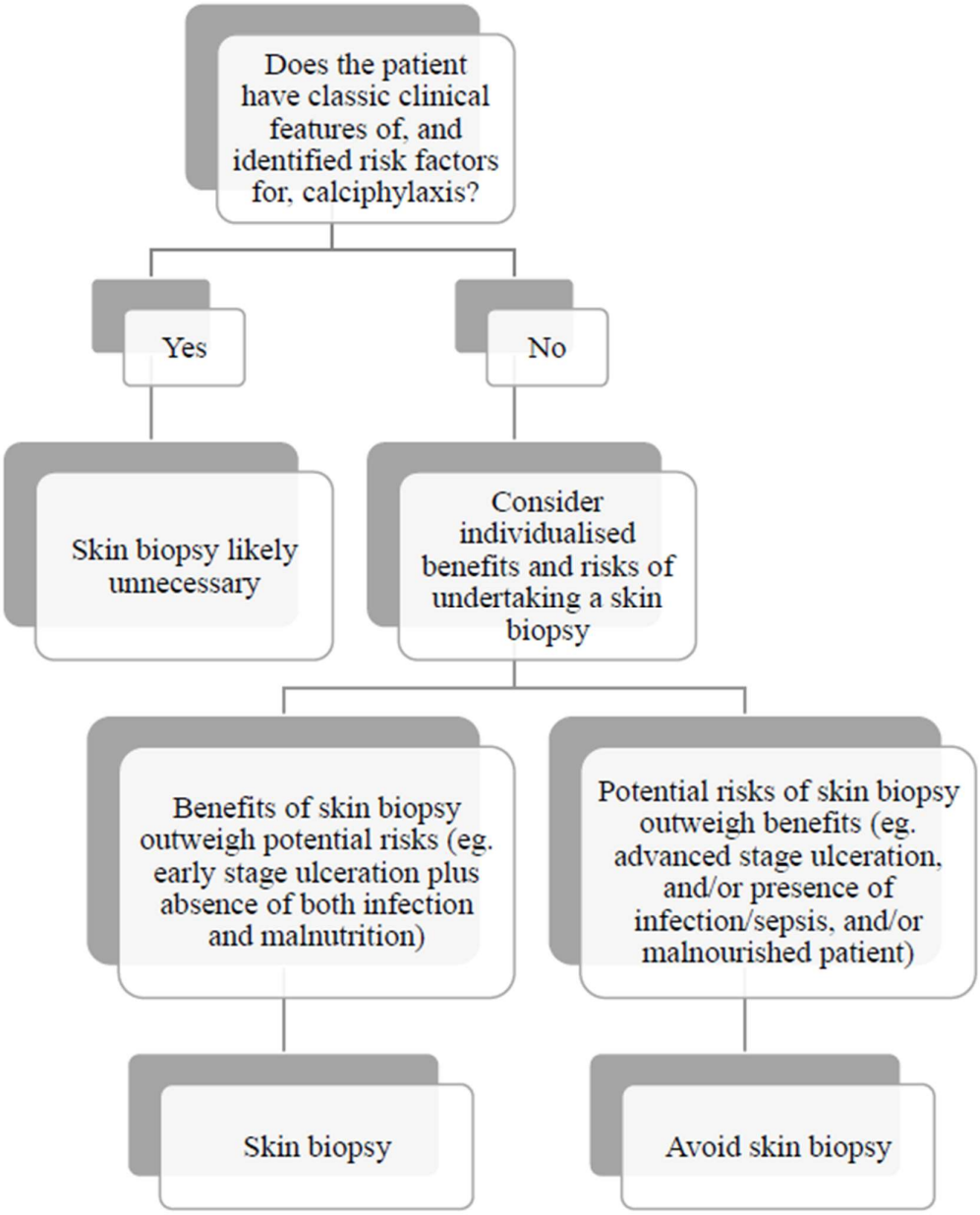

Figure 2: Algorithm outlining the clinical indication and considerations for undertaking skin biopsy