ISSN 2607-9917 www.bdd.rdplf.org Volume 8, n° 2, June 2025 https://doi.org/10.25796/bdd.v8i2.87068

*Bulletin de la Dialyse à Domicile*

*Home Dialysis Bulletin (BDD)*

*International bilingual journal for the exchange of knowledge and experience in home dialysis*

*(English edition) (version française disponible à la même adresse)*

# Calciphylaxis in 2024

## (La Calciphylaxie en 2024)

Pablo Antonio Ureña Torres [1], Denis Viglietti [1], Ziad A. Massy [1, 2]

[1]AURA (Association pour l'Utilisation du rein Artificiel en Région Parisienne), 75014 Paris, France
[2]Inserm Unit 1018, Team 5, CESP, Hôpital Paul Brousse, Paris-Saclay University (UPS) and Versailles Saint-Quentin-en-Yvelines University (UVSQ), Villejuif, France

**To cite:** Ureña Torres PA, Viglietti D, Massy Z. La Calciphylaxie en 2024. Bull Dial Domic [Internet]. 8(2):83-100. available: https://doi.org/10.25796/bdd.v8i2.87068

**Summary**

Calciphylaxis is a rare and potentially fatal disease manifested by progressive skin ulcerations due to calcification and obstruction of small-caliber arteries and arterioles. It mainly affects patients with chronic kidney disease treated by dialysis or renal transplantation but also individuals with normal kidney function, in which case it is often associated with chronic inflammatory diseases, neoplasia, primary hyperparathyroidism, and post-bariatric surgery. Necrotized ulcerations can become infected, leading to septic syndrome and a mortality rate of up to 80%. Its incidence varies from one case per 1,000 to one case per 1,500 hemodialysis patients per year, although this is probably underestimated. Clinical manifestations include very painful nodular or plaque-like indurations occurring in the extremities and central to the body. Lesions can also affect the fingers, penis, breasts, and visceral organs such as the lungs, intestines, and eyes. Its management is complex and requires a multimodal, individualized approach, involving close cooperation between nephrologists, dermatologists, surgeons, and other specialists. The aim of this review is to revise old and new aspects of this management while including the control of parameters of mineral and bone metabolism disorders, the replacement of vitamin K antagonists by alternative anticoagulants, the optimization of dialysis prescription, and the use of sodium thiosulfate, as well as new experimental therapies under development. We hope this review will help avoid common pitfalls and provide the highest quality care for patients with calciphylaxis.

**Keywords**: Calciphylaxis, Calcium, Phosphate, Vascular calcification, Parathormone

**Résumé**

La calciphylaxie est une maladie rare et potentiellement mortelle se manifestant par des ulcérations cutanées progressives dues à la calcification et obstruction des artères de petit calibre et des artérioles. Elle touche principalement les patients atteints de maladie rénale chronique traités par dialyse ou ayant reçu une greffe rénale, mais également des individus avec une fonction rénale normale, souvent associée à des maladies inflammatoires chroniques, néoplasies, hyperparathyroïdie primaire et post-chirurgie bariatrique. Les ulcérations nécrosées peuvent s'infecter et entraîner un syndrome septique, avec une mortalité pouvant atteindre 80 %. Son incidence varie de 1 cas pour 1000 à 1 cas pour 1500 patients hémodialysés par an, bien que cette estimation soit probablement sous-évaluée. Les manifestations cliniques incluent des indurations nodulaires ou en plaques, très douloureuses, survenant aux extrémités, au niveau central du corps. Les lésions peuvent également toucher les doigts, le pénis, les seins et les organes viscéraux tels que les poumons, les intestins et les yeux. Sa prise en charge est complexe et nécessite une approche multimodale et individualisée, impliquant une coopération étroite entre néphrologues, dermatologues, chirurgiens et autres spécialistes. C'est le but de cette revue, de réviser les aspects anciens et nouveaux de cette prise en charge, tout en incluant le contrôle des paramètres des troubles du métabolisme minéral et osseux, le remplacement des antagonistes de la vitamine K par des anticoagulants alternatifs, l'optimisation de la prescription de dialyse et l'utilisation du thiosulfate de sodium, ainsi que des nouvelles thérapies expérimentales en cours de développement. Nous espérons que cette revue aidera à éviter les pièges courants et à fournir des soins de la plus haute qualité aux patients atteints de calciphylaxie.

**Mots-clés** : Calciphylaxie, Calcium, Phosphate, Calcification vasculaire, Parathormone

**Correspondance :**

Pablo Antonio Ureña Torres, AURA – Paris Nord. 12, rue Anselme. 93400 Saint Ouen. France. E-mail : pablo.urena@auraparis.org





*journal officiel du Registre de Dialyse Péritonéale de Langue Française* **RDPLF** www.rdplf.org

www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

## Introduction

Calciphylaxis is a rare disease that is potentially life-threatening. It manifests essentially as progressive skin ulcerations resulting from the obstruction of small-caliber arteries and calcified arterioles. Calciphylaxis mainly affects subjects with chronic kidney disease (CKD) treated by dialysis or undergoing renal transplantation. However, it can exceptionally be seen in subjects with normal renal function, in which case it is often associated with chronic inflammatory diseases, neoplasia, and primary hyperparathyroidism, and after bariatric surgery [1-3]. The clinical manifestations of calciphylaxis are so disastrous, including superinfection of necrotic skin lesions and associated septic syndrome, that they often lead to death. The annual mortality rate can be as high as 80%. This is partly explained by the fact that most of these patients also present with other comorbidities, such as undernutrition and cardiovascular pathologies, including arterial and valvular calcification, ischemic heart disease, arrhythmia, hypertensive heart disease, and stroke [4].

## Incidence and epidemiology

The exact prevalence of calciphylaxis is still poorly defined, ranging from 0.03 to 4.0% in the literature, and varies widely from country to country [5-7]. Its incidence in hemodialysis patients is estimated at between one case per 1,000 and one case per 1,500 patients per year, based on small series and small international registries. However, it is highly likely that this incidence is underestimated, as certain skin lesions, particularly those that are minor and doubtful, often go undiagnosed in a significant proportion of patients. The most recent and largest study of calciphylaxis has recently been carried out using Fresenius Medical Care North America (FMCNA) data collected between 2010 and 2014. It reports 1,030 cases of calciphylaxis and a mean annual incidence of 3.49 cases per 1,000 patients per year (95% CI 3.30 to 3.72) [7]. The incidence of calciphylaxis is thought to be even higher in French Polynesia, where it is around 10 times higher, although these results have not yet been published.

## Diagnosis

### *Clinical*

The term “calciphylaxis” was first used by Selye in 1961 as a contraction of “calcification” and “phylaxis” to describe a supposedly adaptive response to aggression [8]. Indeed, Selye and his colleagues succeeded in inducing skin calcifications by injecting inducers or facilitators such as parathyroid hormone (PTH) and vitamin D or by inducing hypercalcemia in rats subjected to local trauma.

Today, the term calciphylaxis is synonymous with calcific uremic arteriolopathy (CUA). It describes a clinical entity characterized initially by the appearance of patchy nodular or cutaneous indurations that are highly analgesic and often accompanied by reticular livedo. These lesions occur on the extremities (Figure 1A), and when they appear distally, below the knees and elbows, they can be defined as peripheral. They may also occur in more central, fat-rich areas, such as the abdomen, thorax, buttocks, hips, and thighs, and may extend deep down to the skeletal muscles (Figure 1B). These are described as central lesions. They can also be observed on the fingers,

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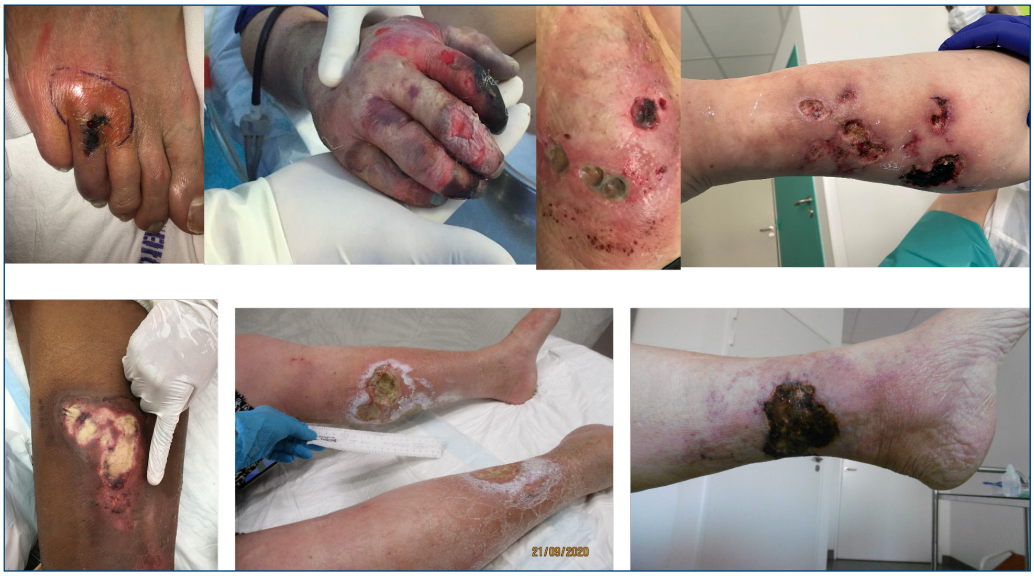
www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

particularly affecting the fingertips. More rarely, calciphylaxis lesions may be observed in the penis, breasts, and visceral organs such as the lungs, intestines, or eyes, with retinal arterial thrombosis [9, 10].




*Figue 1A. Peripheral calciphylaxis lesions*

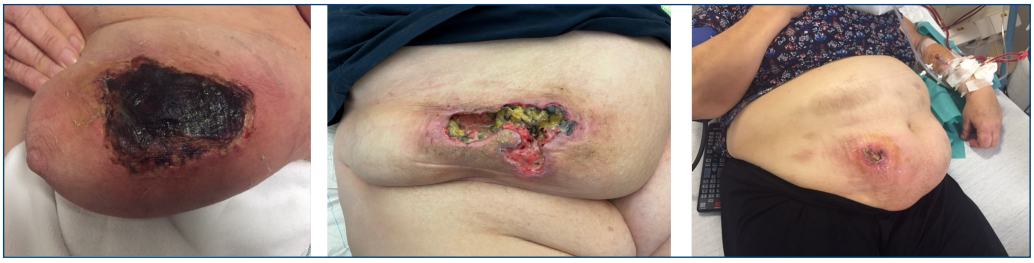


*Figure 1B. Central lesions*

Calciphylaxis lesions affecting the lower extremities pose the problem of differential diagnosis with four diseases: lesions of vasculitis, ulcerations in connection with diabetic arteriopathy, lesions resulting from cholesterol emboli, and lesions of necrotizing angiodermatitis [4, 11, 12]. Central lesions may pose the problem of differential diagnosis with lesions of cutaneous necrosis induced by vitamin K antagonists (VKAs) [2].

Skin ulcerations can occur and progress rapidly, spreading over large areas of the body and significantly limiting healing capacity. The major complication, to be avoided wherever possible, is superinfection of necrotic lesions.

### *Histology*

The characteristic histological lesions of calciphylaxis are calcification of the lamina media and intimal fibrosis of the arterioles of the dermis and hypodermis, resulting in a narrowing of the lumen. Calcification of nerve endings, adipocytes, and sweat glands is also frequently observed [13]. Fibrin thrombi may also be observed. If treatment of these lesions is not initiated early on, or if the lesions persist despite treatment, in most cases, the evolution is toward necrosis of adipose and cutaneous tissue, superinfection of the lesions, and septic complications in general.

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

Given the rarity of calciphylaxis, there is no standardized clinical procedure or radiological or biochemical analysis leading to its precise diagnosis. The very painful nature of the lesions and the association with advanced CKD and dialysis are very strong and characteristic features of calciphylaxis. The only way to make a precise diagnosis is by histological analysis of a lesion. Nevertheless, skin biopsy is still the subject of heated debate. On the one hand, opponents of skin biopsy argue that it causes additional trauma and creates a new focus for ulceration and necrosis, which can worsen the evolution of local lesions [14]. On the other hand, proponents of skin biopsy argue that it is the only way to formally diagnose calciphylaxis and exclude other pathologies such as vasculitis. However, it should be noted that the sensitivity diagnostic of biopsy is highly variable, ranging from 20-80%; that false negatives are frequent (47%); and that in a third of cases, samples are insufficient [15].

Vascular calcifications must be systematically detected using silver nitrate staining (von Kossa or alizarin red). Vascular calcifications may go undetected by conventional hematoxylin-eosin staining [13, 16]. A similar approach could also be proposed for skin biopsies in subjects with suspected vasculitis. The absence of calcification would formally exclude the presence of potential calciphylaxis. Skin biopsies should be taken at the margin of the main ulcerated lesion. If lesions are present over a large skin surface area, a whole-body bone scan three-phase technetium 99m (99mTc) methylene diphosphonate could be a good tool for early diagnosis and non invasive treatment of calciphylaxis before necrotic and ulcerated lesions develop. Indeed, the radioactive tracer is deposited in subcutaneous areas where a mineralization process is present [17-20].

## Pathophysiology

### *Risk factors*

Very few epidemiological data are currently available on calciphylaxis. The most important publications are retrospective case-control studies. The results show that the most important risk factors associated with the development of calciphylaxis are female gender, the presence of diabetes, peritoneal dialysis treatment, obesity, hypoalbuminemia, inflammatory and hypercoagulable states, autoimmune diseases, use of VKAs, treatment with intravenous iron, and increased phosphocalcic product in combination with the use of derivatives active vitamin D and/or excessive doses of calcium-based phosphate binders[4, 21, 22]. In the most recent and largest study on calciphylaxis, that of the FMCNA, it was observed that repeated insulin injections in diabetic subjects, with the recurrent traumatic skin lesions they can cause, increase the risk of calciphylaxis up to four-fold (odds ratio 3.74; 95% CI 2.28 to 6.25) [13, 23, 24].

Genetic predispositions could also contribute to susceptibility to developing calciphylaxis, as suggested by a recent study showing an unusually high incidence of calciphylaxis in dialysis patients from Māori and in Australia and New Zealand [25]. Polymorphisms in several genes involved in the metabolism of vascular, mineral, and bone tissues, such as the gene NT5E encoding the protein CD73, the vitamin D receptor, and the gene FGF23, have been associated with an increased risk of calciphylaxis [26, 27]. Given these genetic and geographical influences, obtaining a detailed regional and family history can provide valuable diagnostic information when evaluating suspected cases of calciphylaxis.

In most reported clinical cases, episodes of calciphylaxis are always associated with alterations

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

in phosphocalcic metabolism. These include an increase in phosphocalcic product, often in the context of secondary or tertiary hyperparathyroidism (HPTS). In a clinical case series from the University of Wisconsin, it was shown that parathyroidectomy (PTX), in emergency surgery, could dramatically improve certain calciphylaxis lesions[28]. In the FMCNA study, whose data were collected at the initiation of dialysis treatment, the median PTH value was significantly higher in the group developing calciphylaxis compared with the control group, even though PTH remained within the values recommended by the KDIGOs, i.e., between two and nine times the upper limit of normal [24]. However, it should be noted that in other series studied, the opposite was observed, with the development of severe de novo calciphylaxis in patients who had undergone PTX. Preliminary data from the German Calciphylaxis Registry also show that two-thirds of patients with calciphylaxis have a low PTH value [29, 30]. Both forms of bone damage—high bone remodeling, as in HPTS, and low bone remodeling, as in adynamic osteopathy (ABD)—cause alterations in mineral metabolism that predispose to or promote the onset of calciphylaxis. In both situations, high (HPTS) and low (ABD) bone remodeling, there is a tendency to increase the phosphocalciuc product and the risk of calciphylaxis [29, 30]. It is the bone's inability to buffer excess calcium ("calcium buffer") that creates a favorable environment for mineralization of extraskeletal soft tissue. Finally, it should be noted that there is a close correlation between the use of VKAs (warfarin) and the occurrence of calciphylaxis. The possible pathophysiological mechanisms involved in calciphylaxis when treated with VKAs are discussed below [23, 24].

### *Inhibitors of ectopic mineralization*

A number of recent observations suggest the existence of an undesirable local and/or systemic disturbance in the balance of factors promoting/inhibiting the extraskeletal mineralization process. Two prototypical calcification inhibitor molecules, Matrix Gla Protein (MGP) [24] and fetuin-A (alpha2-Heremans Schmid glycoprotein or AHSH) [29], are implicated strongly in calciphylaxis.

MGP is a 10 protein KD expressed exclusively in vascular wall smooth muscle cells and chondrocytes. To be fully active, MGP must undergo post-translational gamma-carboxylation, which is vitamin K-dependent. Vitamin K, such as the antagonist warfarin, inactivate MGP and may promote vascular calcification [31]. Mice disabled for the MGP gene (MGP-/-) show severe calcification of the lamina media of large-caliber arteries and the aorta. They die at around six to eight weeks of age from internal hemorrhage secondary to fully ossified rupture of the aorta [32]. The protective effect of MGP against vascular calcifications appears to be local (autocrine/paracrine), as its systemic overexpression does not prevent or regress MGP vascular calcifications-/-. Similarly, arterial tunica media calcifications can be induced by vitamin K antagonists. In rats, vascular calcifications induced by vitamin K antagonists can be partially reversed by administration of supra-physiological doses of vitamin K1 or K2 or by suspension of vitamin K blockade [33-35]. Administration of low doses of vitamin K1 or K2 cannot prevent the progression of vascular calcifications [36].

The second important molecule in the inhibition of vascular calcification and in the pathophysiology of calciphylaxis is fetuin-A. Fetuin-A is a 60 glycoprotein kD produced by the liver [37]. It is perhaps the most potent circulating inhibitor of vascular calcification. Its concentration plasma can reach 0.5 to 1.0 g/liter in normal subjects, representing a significant fraction of the alpha-2 band in blood protein electrophoresis [38]. Fetuin-A is a protein negatively regulated by the acute phase

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

reactant of inflammation. During an inflammatory process, systemic and local concentrations of fetuin-A drop dramatically, exposing the patient to the formation of vascular calcifications [37, 39]. It should be noted that the rare cases of calciphylaxis observed in subjects with normal renal function were always associated with active chronic inflammatory diseases or undernutrition, such as that observed after bariatric surgery [40, 41]. Animals invalidated for fetuin-A (fetuin A-/-) spontaneously develop massive calcification of soft tissues and internal organs [37]. A large number of dialysis-treated CKD patients have serum concentrations of fetuin-A below the normal reference value. This fetuin-A deficiency is associated with an increased relative risk of all-cause and cardiovascular mortality [42-45]. In eight well-characterized patients included in the German Calciphylaxis Registry, a circulating concentration of fetuin-A was found to be extremely low (ranging from 0.09 to 0.25 g/liter), with a parallel high serum concentration of C-reactive protein (CRP) [29].

### *The role of the endothelial cell*

A study by Ellis et al. published in 2018 calls into question the specificity of calcifications in calciphylaxis [11]. Indeed, the authors observed in asymptomatic dialysis patients the same vascular and extravascular calcifications as those described in calciphylaxis, with the same prevalence and locations. However, they observed a much higher prevalence of arteriolar thrombosis in patients with calciphylaxis than in asymptomatic patients. These data suggest that arteriolar in the dermis and hypodermis intimal calcifications are not sufficient to induce calciphylaxis lesions and that additional endothelial aggression would be required to lead to arteriolar thrombosis and lesions.

A recent study showed that over 80% of patients with calciphylaxis had microvascular complement activation, demonstrated by the presence of endothelial C5b-9 deposits in the injured vessels [46]. In 40% of cases, patients also showed microvascular C5b-9 deposits in the dermis, indicating systemic complement activation. These studies tend to bring closer to calciphylaxis the spectrum of thrombotic microangiopathies, such as atypical hemolytic uremic syndrome or anti-phospholipid syndrome, and could pave the way for complement-targeted therapies in calciphylaxis [47, 48].

## Treatments

### *General measures*

Therapeutic approaches are still very limited in cases of calciphylaxis, as previously reported. Available data concern only a few isolated clinical cases or small-series retrospective cases. The two meta-analyses recently published, including all prospective clinical studies and five randomized clinical trials, evaluated the various therapeutic strategies in calciphylaxis, including parathyroidectomy, cinacalcet, bisphosphonates, hyperbaric oxygenation, and sodium thiosulfate. They failed to demonstrate any clear clinical benefit from these five therapeutic approaches [49, 50].

When the diagnosis of calciphylaxis is confirmed in a uremic patient, one of the first steps to be taken is the implementation of multidisciplinary management involving nephrologists,

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

dermatologists, dieticians or nutritionists, vascular surgeons/plasticians, social workers, and pain and palliative care teams [51]. Early involvement of the wound care team is essential for the selection of the most appropriate dressings, the use of chemical debridement agents, and the application of negative wound pressure therapy if necessary. Surgical debridement by a specialist is strongly recommended for visibly infected or necrotic wounds without signs of granulation tissue. Wound debridement should be combined with negative pressure therapy, followed by skin grafting wherever possible [52]. Broad-spectrum antibiotic therapy should also be offered as soon as ulcerative lesions become progressive and necrotic. Nutritional support is essential to combat protein-energy malnutrition and enhance wound healing. Albumin levels should be normalized wherever possible, as they play an important role in inhibiting extraosseous mineralization [2]. Pain relief is crucial and requires the prescription of analgesics with different mechanisms of action, with the aim of minimizing opioid consumption [53]. The use of regional anesthetics should not be ruled out, such as sympathetic blockade in the lumbar region for refractory pain [54]. In a significant proportion of patients with calciphylaxis, it will be necessary to involve the palliative care team, not only for the management of symptoms such as pain, pruritus, and loss of appetite and sleep but also to improve the quality of end-of-life care.

### *High-pressure oxygenation*

Patients suffering from calciphylaxis could also benefit from treatment of lesions with high-pressure oxygen therapy (hyperbaric chamber). Basile et al. recently reported excellent results with this therapy in a small series of uremic patients [55]. The aim of this approach is to significantly increase local oxygen pressure and attempt to improve healing of ulcerated and necrotic tissue. In their study, affected areas were exposed to oxygen under a pressure of 2.5 times atmospheric pressure, in a closed chamber and for a duration of 90 minutes per session. The number of sessions required ranged from 20 to 108. Eight of the 11 patients showed complete healing of the ulcerated calciphylaxis legions. However, the use of hyperbaric oxygen therapy is limited due to its high cost; restricted access to hyperbaric chambers; logistical challenges associated with transportation; contraindications cardiac, neurological, or pulmonary; and potential discomfort, for example, in cases of claustrophobia.

### *Optimizing dialysis treatment*

Optimization of dialysis treatment as recommended by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative in 2015 is paramount [56]. The first objective of this therapeutic approach is to try to normalize the circulating concentration of the phosphocalcic product, for example by increasing the duration and frequency of dialysis sessions, the surface area of the dialysis membrane, and/or the convection volume. A few case reports have shown complete healing of ulcerative calciphylaxis lesions after switching from standard hemodialysis to short daily home hemodialysis (six sessions of 2.5 to 3 hours per week) [57, 58]. There is no formal indication for replacing peritoneal dialysis with another, more efficient, technique, unless the performance of peritoneal dialysis is inadequate. Nor are there any sound scientific arguments for transferring patients with calciphylaxis to on-line hemodiafiltration, especially as this method could be accompanied by greater loss of albumin and other extraosseous calcification-inhibiting proteins such as MGP.

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

### *Correction of mineral disorders and bone metabolism*

Phosphocalcic product control may also require the use of a calcium-depleted dialysis bath (< 1.25 mmol/litre); prescription of phosphate binder, preferably non-calcium-based. It is necessary to reduce, or even stop, treatment with natural and active vitamin D derivatives, or to adjust their dosage according to the PTH value and the phosphocalcic product.The ultimate goal is to normalize phosphatemia while avoiding hypercalcemia [59]. Emergency renal transplantation could be a strategy worth discussing, provided the patient has no contraindications. Three cases of recovery from calciphylaxis have been reported two to four months after renal transplantation [60].

When a patient presents with severe calciphylaxis and with clinical, biological, and radiological signs of high bone remodeling, it is legitimate to consider the indication of HPTS emergency surgery (parathyroidectomy PTX) to bring PTH within the values recommended by the KDIGO [59]. Six patients with calciphylaxis who underwent subtotal (3.5 glands) PTX all showed resolution of pain and healing of skin lesions, whereas lesions persisted in seven patients who received only medical management. Furthermore, all six parathyroidectomized patients survived, whereas five of the seven non-parathyroidectomized patients died as a result of calciphylaxis-related complications [28, 49]. Nevertheless, in some of these patients, especially when surgery is contraindicated, the prescription of an oral or injectable calcimimetic may represent another therapeutic alternative [61, 62]. The dose of this calcimimetic should be titrated to maintain PTH within the range recommended by the KDIGOs (two to nine times the upper limit of normal [ULN]). Excessive suppression of PTH (< 2 ULN or < 130 pg/mL) should be avoided, as it increases the risk of adynamic bone disease predisposing patients to vascular calcification and calciphylaxis [63]. A recent meta-analysis from observational studies showed that cinacalcet use did not decrease the risk of deterioration of the calciphylaxis wound, amputation, or mortality [49]. However, the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) study, which evaluated the effect of cinacalcet on the occurrence of major cardiovascular events and death, showed no benefit over the placebo, but among the 3,861 patients in the trial who received at least one dose of cinacalcet, only six developed calciphylaxis, compared with 18 in the group assigned to the placebo. The unadjusted relative risk of developing calciphylaxis was reduced by 69% [64].

Other strategies may be considered to reduce the rate of bone remodeling, including the use of bisphosphonates and denosumab. In the case of bisphosphonates, which are pyrophosphate analogues, it remains to be demonstrated whether their potential beneficial effect on the prevention of extraskeletal mineralization is exerted by its anti-bone resorption effects or by a directly local effect like that of pyrophosphates. In a prospective observational study involving 11 dialysis patients, treatment with pamidronate for two to four weeks delayed lesion progression and improved survival, compared with 12 other patients following a conventional therapeutic approach: lesion debridement and calcium-poor dialysate [65, 66]. However, given the significant risk of inducing low-remodeling bone pathology with their use, it is highly advisable to ensure that the patient does not have low bone remodeling before initiating bisphosphonate therapy, especially in patients with CKD. There are as yet no published data on denosumab. Very promising results have recently been published concerning this type of conservative management of calciphylaxis [67, 68].

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

### *Sodium thiosulfate*

Sodium thiosulfate is normally used as a chelating agent in cases of cyanide poisoning. It has a very high affinity for calcium and, therefore, when binding to calcium, forms a calcium thiosulfate compound that is much more soluble than the calcium phosphate compound and can be potentially eliminated by dialysis. Sodium thiosulfate also possesses antioxidant properties and could in this way interfere with and limit the local inflammatory process in calciphylaxis. Intravenous infusion of sodium thiosulfate reduces calcium deposits in adipocytes and arterial smooth muscle cells in patients with calciphylaxis [69, 70]. Sodium thiosulfate is generally used intravenously. In dialysis patients, it is recommended to start with a dose of 12.5 mg per dialysis, usually three times a week, gradually increasing to 25 mg per dialysis according to the patient's tolerance. It should be administered by slow intravenous infusion during the last 30 to 120 minutes of dialysis. It is also advisable to reduce the sodium concentration of the dialysate in order to attenuate the sodium load provided by sodium thiosulfate [71]. An observational study including 27 dialysis patients with calciphylaxis showed complete remission of lesions in 52% of patients and partial regression in 19% of cases [72]. Another study involving 53 dialysis patients with calciphylaxis observed complete healing of lesions in 26% of cases and improvement in 19% of patients [73].

In peritoneal dialysis patients, sodium thiosulfate can be added to the peritoneal dialysis fluid (25 g) and left to stagnate for the longest exchange time[74]. Two other forms of sodium thiosulfate administration have been tried, one by oral route and the other by intralesional injection. In studies evaluating oral sodium thiosulfate, at doses ranging from 1.2 to 2.6 grams per day, the results obtained are disputed: The lesions in two patients out of four improved, but diarrhea and digestive side effects were frequent [75]. For the intralesional route, trials have been carried out injecting 1 to 3 mL of sodium thiosulfate (250 to 750 mg) once a week, with results yet to be confirmed by larger studies [76].

The optimal duration of treatment with sodium thiosulfate has not been studied in controlled trials. It is most often adapted to the patient's tolerance and the evolution of the lesions. Adverse effects include gastrointestinal disorders such as nausea and vomiting, volume overload, hypocalcemia, QT interval prolongation, arterial hypotension, metabolic acidosis with increased anion gap, and peritonitis in the case of intraperitoneal administration.

All in all, the efficacy of sodium thiosulfate has been reported in numerous publications of single cases or small series of cases of calciphylaxis. However, the efficacy and benefits of treating calciphylaxis with sodium thiosulfate have yet to be scientifically proven in uremic patients, as suggested by a recent meta-analysis including 147 studies, some of them small randomized trials, and 860 dialysis patients with calciphylaxis. Compared with the standard therapeutic approach, sodium thiosulfate improved neither survival nor lesion healing nor the risk of amputation [49].

### *Vitamin K*

Despite the lack of scientific evidence, in patients with calciphylaxis treated with VKAs, it is strongly recommended to replace them with heparin or another latest-generation anticoagulant therapy. With regard to vitamin K supplementation, some cases of complete wound healing and ulcer closure have been reported following treatment with vitamin K1 (phylloquinone)[77]. Preliminary results from the trial VitK-CUA suggest that vitamin K1 may help relieve pain and

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

reduce total lesion area in calciphylaxis, even in the absence of cinacalcet or use of intralesional sodium thiosulfate [78] (*Nigwekar et al., Kidney Week 2023; November 2-5, Philadelphia, Pennsylvania. Poster TH-PO1156*). Given that there is a very high biological probability that treatment with VKAs may promote the onset of calciphylaxis, it will be extremely important to investigate, through future randomized studies, whether vitamin K supplementation can prevent or regress calciphylaxis lesions in uremic patients.

### *Rheopheresis*

Rheopheresis is double-filtration plasmapheresis designed to improve the blood rheology of micro-vessels [79-81]. During rheopheresis treatment, the plasma is separated from the blood by a filter first and then subjected to a second filter prior to restitution. In this way, the molecules of interest are retained by the second filter before the plasma is returned to the patient. The pore size of the two filters determines the nature of the proteins removed from the plasma before restitution. In this way, primary and secondary filters can be selected with pore sizes close to 300 nm and 25 nm, respectively. Rheopheresis with these two filters can then purify high proteins, molecular weight between 25 and 300 nm, involved in plasma viscosity, such as alpha-2-macroglobulin, fibrinogen, or LDL cholesterol. It can also purify secondary calciprotéines, which are estimated to be between 120 and 150 nm in size. Iterative sessions rheopheresis lead to a reduction in the plasma concentration of these molecules, with a decrease in plasma viscosity and an improvement in microcirculation (Fahraeus–Lindqvist effect) [80]. Therefore, rheopheresis could improve microcirculation in ischemic territories secondary to calciphylaxis. There are other theoretical advantages to using rheopheresis in calciphylaxis: 1) purification of secondary calciproteins with a benefit on inflammation and vascular calcifications, 2) increased NO and bradykinin production, and 3) reduced expression of adhesion molecules, such as ICAM-1 and VCAM-1[81, 82]. This technique is also attractive because of its ease of access for nephrologists. Rheopheresis can be carried out at the same time as dialysis, enabling incremental therapy without increasing patient care time. The safety and efficacy of rheopheresis have been demonstrated in other microcirculatory diseases, such as age-related macular degeneration (AMD) and arteritis of the lower limbs [79]. To date, few data are available on use of rheopheresis as an adjuvant treatment for calciphylaxis. Promising results have been reported in two patients with pejorative necrotic lesions [83, 84] and in a series case where five of eight patients with calciphylaxis had a complete cure after treatment with rheopheresis [85, 91]. Interest in this technique is growing, and the number of nephrology centers in France performing it is increasing. However, the level of evidence for the benefit of rheopheresis in calciphylaxis is not yet scientifically established. A French national retrospective study of cases of calciphylaxis treated by rheopheresis is currently underway, as a prospective randomized controlled trial to assess the efficacy of rheopheresis as adjuvant treatment in necrotizing calciphylaxis in hemodialysis patients (PHRC-N; RHEO-CAL; NCT04654000).

### *SNF472*

SNF472 is the brand name of the molecule hexasodium phytate, in other words, a salt hexasodium of myo-inositol hexaphosphate. SNF472 is a vascular calcification inhibitor. Preclinical studies using in vitro cell cultures have demonstrated SNF472's ability to bind to hydroxyapatite and prevent the formation and growth of hydroxyapatite crystals. Phase 1 and 2 clinical trials demonstrated

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

the safety and potential efficacy of SNF472 in attenuating hydroxyapatite crystallization in hemodialysis patients [77, 86]. In addition, SNF472 has been shown to significantly attenuate the progression of coronary artery calcification and aortic valve calcification in dialysis patients [87, 88].

In calciphylaxis, a recent Phase 3, open-label, randomized, controlled, double-blind clinical trial (CALCIPHYX) in 71 hemodialysis patients (37 patients assigned to SNF472 and 34 patients assigned to placebo) failed to meet the primary efficacy endpoints of 8-point modification of the Bates-Jensen wound assessment tool and pain on a visual analog scale. However, a post-hoc analysis revealed lower hospitalization and mortality rates in the SNF472 group compared with the placebo group [89]. SNF472 is currently administered like sodium thiosulfate, by slow intravenous route during dialysis (2-3 hours), three times a week. Nevertheless, preliminary data in animal models indicate that subcutaneous SNF472 could reach therapeutic concentrations [86], supporting further research into alternative administration strategies. Future studies are needed to assess the feasibility of subcutaneous or intraperitoneal formulations, which could potentially extend the accessibility of SNF472 to peritoneal dialysis and non-dialysis patients.

### *INZ-701*

Inorganic pyrophosphate (PPi) is a potent inhibitor of ectopic vascular calcification, and low PPi levels are associated with calciphylaxis and poorer survival [90]. Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) is an enzyme responsible for PPi generation, and strategies to increase ENPP1 activity could help restore PPi levels and reduce vascular calcification and calciphylaxis. INZ-701 is a fusion protein containing the functional enzyme ENPP1 and is currently under clinical investigation to assess its safety, pharmacokinetics, and pharmacodynamics in hemodialysis patients. By increasing PPi levels, INZ-701 promises to be a potential therapy for preventing or treating calciphylaxis.

### *Other therapeutic approaches*

Finally, other therapeutic approaches have been considered but remain to be validated by controlled studies. For example, concerning corticosteroids, Fine and Zacharias reported the complete cure of 36 cases of early calciphylaxis, characterized by non-ulcerated lesions [91]. These results should be treated with great caution, given the high risk of superinfection in calciphylaxis. Other approaches tested in calciphylaxis include: endothelin antagonists, including bosentan[92]; thrombolytic agents, such as tissue plasminogen activator [93]; topical cerium nitrate [94]; cryopreserved human amniotic membrane grafting [95]; plasma exchange [96]; cryofiltration plus apheresis [97]; and the use of larvae (Lucilia sericata) for wound detersion in association with pentoxyphyline[98].

## Conclusion

Calciphylaxis is a rare disease with disastrous complications in chronic kidney disease, associated with an extremely high risk of mortality. Its incidence is probably underestimated. Recent scientific advances have highlighted the important role of a deficiency in calcification-inhibiting factors (MGP and fetuin-A) in the pathophysiology of calciphylaxis. Generally, the

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www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

aim of management is to reduce the serum concentration of the phosphocalcic product. Treatment options include calcimimetics or parathyroidectomy in cases of clinically uncontrollable secondary hyperparathyroidism. VKAs should be discontinued and replaced by heparin or another anticoagulant therapy whenever possible. In the future, new therapeutic strategies, such as vitamin K supplementation, calcimimetics, bisphosphonates, anti-RANK-L antibodies (Denosumab), sodium thiosulfate, reopheresis, SNF472, and INZ-701 may find a real indication in daily clinical practice. However, given the current state of knowledge, the indication for these treatments must be considered with caution and on a case-by-case basis.

*Table I. Points to remember*

**Diagnostic criteria:**
- Terrain: Dialysis, obese, female, diabetic, treated with antivitamin K (AVK), vascular, undernutrition, elevated phosphocalcic product (Ca x P), severe secondary hyperparathyroidism
- Circumstances: shock, dehydration, sepsis, trauma, subcutaneous injections
- Lesions: Livedo, painful nodules, necrotic ulcerations
- Skin biopsy: useful in cases of diagnostic doubt
- Paraclinical examinations: soft-ray computed tomography (CT), ultrasound (breast), bone scan, plain X-ray, to look for small-vessel calcifications

**Therapeutic management:**
- Improvement of oxygenation and tissue perfusion:
  - o Sodium thiosulfate (STS) (intravenous or locally)
  - o Hyperbaric chamber
  - o Rheopheresis
  - o Treatment of upstream arterial lesions
  - o Daily dialysis to combat hypotension, volume variations, and hyperphosphatemia, and to provide parenteral nutrition
- Attenuate progression of microvascular calcifications:
  - o STS
  - o Permanent discontinuation of VKAs (heparin relay or new oral anticoagulants such as apixaban or rivaroxaban); vitamin K supplementation
  - o Dialysate low in calcium (1.25 mmol/liter)
  - o Discontinuation of vitamin D derivatives and calcium supplements
  - o Control of secondary hyperparathyroidism (calcimimetics, parathyroidectomy)
  - o Bisphosphonates as appropriate
- Pain management:
  - o Sodium thiosulfate
  - o Morphine derivatives
  - o Nitrous oxide for dressings
- Wound treatment:
  - o Dressings, detersion
  - o Antibiotic therapy
  - o Surgical debridement
  - o Skin grafting
- Combating undernutrition and grabatization:
  - o Enteral/parental feeding
  - o Physiotherapy, nursing
  - o Psychological support

## Authors' Contributions

*Pablo Urena designed the project and wrote the text, Denis Viglietti and Ziad Massy proofread the text and provided constructive feedback.*

## Ethical Considerations

*N/A*

## Patient Consent

*N/A*

www.bdd.rdplf.org Volume 8, n° 2, June 2025
https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

## Funding

*none*

## Conflicts of interest

*The authors declare that they have no conflict of interest with this publication*

*ORCIDids :*
Pablo Urena : https://orcid.org/0000-0001-6757-1906
Denis Viglietti : https://orcid.org/0000-0003-3025-1479
Ziad Massy : https://orcid.org/0000-0001-5771-5996

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https://doi.org/10.25796/bdd.v8i2.87068
ISSN 2607-9917

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