

REVIEW ARTICLE

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Calciphylaxis

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CALCIPHYLAXIS IS A RARE, LIFE-THREATENING SYNDROME OF VASCULAR calcification characterized by occlusion of microvessels in the subcutaneous adipose tissue and dermis that results in intensely painful, ischemic skin lesions. Once calciphylaxis has been diagnosed, the prognosis is generally poor (survival, <1 year).¹⁻³ The disorder, which is underrecognized,⁴ typically affects patients with end-stage renal disease (ESRD),^{2,5} a population with a high prevalence of extraskeletal calcifications. A clear majority of such calcifications do not represent calciphylaxis, which cannot be placed on a simple continuum of vascular calcification. However, an improved understanding of vascular calcification has helped to elucidate the pathogenesis of calciphylaxis and promising approaches to treatment.

Calciphylaxis also occurs in patients with earlier stages of chronic kidney disease,^{2,5} acute kidney injury,⁶ or prior receipt of a kidney transplant,⁷ and in rare cases, it occurs in patients with normal kidney function.^{2,5,8,9} We therefore prefer the name calciphylaxis to calcific uremic arteriolopathy, which is another name for this entity.¹⁰ This review presents the current understanding of calciphylaxis and provides a framework for its interdisciplinary management.

CLINICAL MANIFESTATIONS

Calciphylaxis causes painful skin lesions (Fig. 1A through 1H). The pain is somatic and may precede the appearance of skin lesions.¹¹ Although the pain may initially fluctuate in intensity,¹² it characteristically remains severe during the course of the disease and is frequently accompanied by tactile hyperesthesia.¹¹ The initial skin manifestations may include induration, plaques, nodules, livedo, or purpura.^{12,13} A dusky discoloration of the skin indicates an area of imminent necrosis. Because an arteriole supplies a 1-to-3-cm conical area of microvasculature in a funnel shape, there are frequently reticulate (netlike) areas of erythema (Fig. 1C) and livedo. Patients typically have multiple, bilateral lesions, with surrounding skin showing a leatherlike texture. The initial lesions rapidly progress to stellate, malodorous ulcers with black eschars.^{12,13} Sepsis originating from the resultant wounds is considered the most common cause of death.^{8,14,15} Approximately 50% of patients are bedridden or wheelchair-bound, and more than 70% require hospitalization for severe ulcers.¹⁴ Ongoing pain, anorexia, insomnia, and depression further compromise the quality of life.¹⁶

Extraskeletal calcifications (Fig. 1I and 1J) are often found on imaging studies, but the sequelae of cutaneous involvement are the predominant clinical manifestations. On rare occasions, extracutaneous vascular calcifications lead to skeletal myopathy, intestinal bleeding, or visual impairment.¹⁷

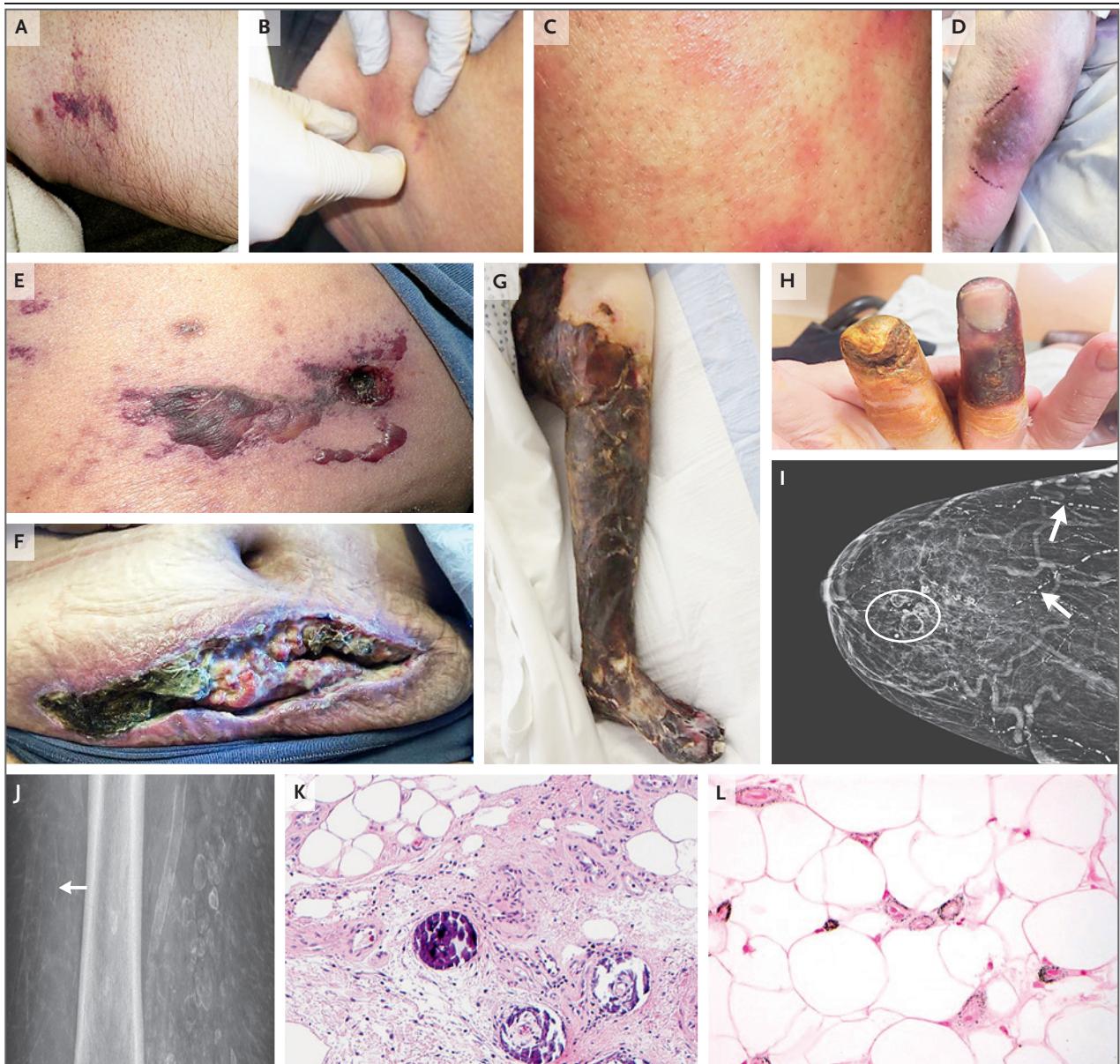


Figure 1. Clinical Manifestations, Radiographic Features, and Histologic Characteristics of Calciphylaxis.

Panels A through E show the early manifestations of calciphylaxis: a violaceous patch with surrounding retiform purpura (Panel A), a palpable subcutaneous nodule with overlying erythema (Panel B), a reticulate pattern of erythema (Panel C), an induration with dusky discoloration (Panel D), and multiple plaques with livedo (Panel E). Panels F, G, and H show late manifestations: a necrotic ulcer partially covered with a black eschar (Panel F), a leg with a mummified appearance (Panel G), and gangrenous fingers (Panel H). Panels A, B, E, and F show central involvement, and Panels C, D, G, and H show peripheral involvement. In Panel I, a mammogram from a patient with calciphylaxis involving the breast shows microvascular calcifications (arrows) and fat necrosis (oval). In Panel J, a radiograph from a patient with ulcerated calciphylaxis involving the thigh shows microvascular calcifications in a netlike pattern (arrow), subcutaneous extravascular calcifications, and a calcified femoral artery. A skin-biopsy section stained with hematoxylin and eosin (Panel K) shows coarse basophilic calcification, fibrointimal hyperplasia, and fibrin thrombus in dermal and subcutaneous microvessels with septal panniculitis. A skin-biopsy section with von Kossa stain (Panel L) shows fine arteriolar and interstitial calcifications. Pathological and radiographic findings by themselves are not diagnostic of calciphylaxis and should be clinically correlated.

CLINICAL CLASSIFICATION

Calciphylaxis can be classified as uremic (in patients with ESRD) or nonuremic (in patients with normal renal function or earlier stages of chronic kidney disease). The lesions in affected patients can be classified as central (involving central areas within subcutaneous adipose tissue such as the abdomen or thighs) or peripheral (restricted to peripheral sites that have limited adipose tissue, such as the digits). In addition, lesions can be nonulcerated (in the earlier stages of the disease) or ulcerated (in later stages).

The lesions are similar whether or not patients have kidney disease; however, 70 to 80% of lesions in patients with ESRD have a central distribution,^{1,14} as compared with approximately 50% of lesions in patients who do not have ESRD.^{8,14} Patients without ESRD have a better prognosis (1-year mortality, 25 to 45%^{8,9}) than those who have ESRD (1-year mortality, 45 to 80%¹⁻³), probably because of the differences in coexisting conditions and the location of lesions. Patients with central lesions are more likely to have a high body-mass index than patients without central lesions,¹ are more likely to be women,¹ and have a higher risk of death.¹⁸ The presence of ulcerated (late) lesions reduces the 6-month survival rate to 20%.³

HISTOPATHOLOGICAL FEATURES

Characteristic histologic features of calciphylaxis (Fig. 1K and 1L) include calcification, fibrointimal hyperplasia, and thrombosis in microvessels in the subcutaneous adipose tissue and dermis, often accompanied by necrosis of epidermal and adipose tissue, dermal–epidermal separation, panniculitis, proliferation of dermal endothelial cells, and extravascular calcifications.^{19,20} The mean diameter of the involved microvessels is 100 μm (range, 40 to 600).¹⁵ Calcified lesions consist of calcium and phosphate in a molar ratio of 1.7, which matches that of hydroxyapatite.²¹

EPIDEMIOLOGY

Calciphylaxis, although rare, has been reported worldwide, with an estimated annualized incidence of 35 cases per 10,000 patients undergoing hemodialysis in the United States,¹ 4 per

10,000 in Germany,⁵ and less than 1 per 10,000 in Japan.²² A report from the United States suggests an increasing incidence,²³ which may be due to an actual increase, heightened awareness of the disorder, or both. The interval from the initiation of dialysis to the appearance of calciphylaxis ranges from 30 months in the United States¹ and Germany⁵ to 105 months in Japan.²⁴

Patients treated with peritoneal dialysis have a higher incidence of calciphylaxis than those treated with hemodialysis^{25,26}; however, the underlying mechanisms are unclear. The incidence in kidney-transplant recipients and in patients with earlier stages of chronic kidney disease is unknown.

Several reports suggest that the mean age at the time of diagnosis is 50 to 70 years^{2,5,14,25}; very few patients are children.²⁷ Approximately 60 to 70% of patients with calciphylaxis are women.^{3,5,14} In a U.S. study involving 1030 patients with calciphylaxis who were dependent on hemodialysis, 49% were white and 28% were black,¹ a racial distribution approximating that of patients undergoing hemodialysis in the United States.

RISK FACTORS

Table 1 lists risk factors for calciphylaxis,^{1,8,17,25,28-31} which include obesity, diabetes mellitus, female sex, and dependence on dialysis for more than 2 years. Obesity and diabetes mellitus are also risk factors for calciphylaxis in patients without ESRD.^{8,9}

Elevations in phosphate and calcium levels increase the risk of subsequent calciphylaxis in patients undergoing dialysis.¹ Patients with calciphylaxis have high parathyroid hormone (PTH) levels at the start of treatment with dialysis,¹ and primary hyperparathyroidism⁸ and administration of recombinant PTH³¹ are risk factors for calciphylaxis in patients who do not have ESRD. At clinical presentation, however, approximately 45% of dialysis-dependent patients with calciphylaxis have PTH levels below the recommended target range.⁵ These observations suggest overuse of calcium and vitamin D supplements, leading to PTH suppression and adynamic bone (low bone turnover), which may exacerbate extraskeletal calcium depositions.³² Fibroblast growth factor 23 (FGF-23), a phosphaturic hormone, is increased

Table 1. Risk Factors for Calciphylaxis.*

End-stage renal disease
Female sex
Obesity
Diabetes mellitus
Hypercalcemia
Hyperphosphatemia
Hyperparathyroidism (both primary and secondary)
Oversuppressed PTH with adynamic bone disease (low bone turnover)
Elevated alkaline phosphatase
Vitamin K deficiency
Hepatobiliary disease
Thrombophilia (e.g., antithrombin deficiency, protein C deficiency, or lupus anticoagulant)
Autoimmune disorders (e.g., systemic lupus erythematosus)
Hypoalbuminemia
Metastatic cancers (e.g., colon or lung cancer)
POEMS syndrome
Genetic polymorphisms (e.g., rs4431401 and rs9444348)
Skin trauma (e.g., from subcutaneous injections)
Recurrent hypotension
Rapid weight loss
Exposure to ultraviolet light
Exposure to aluminum
Medications (e.g., warfarin, calcium, vitamin D, iron, and recombinant PTH)

* POEMS denotes polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes; and PTH parathyroid hormone.

in patients with ESRD and calciphylaxis⁵; however, the role of FGF-23 in vascular calcification remains controversial.^{33,34}

The use of warfarin, a vitamin K antagonist, increases the risk of calciphylaxis by a factor of 3 to 13.^{1,24,25,35} About 40 to 50% of patients with ESRD and calciphylaxis^{5,36} and 25% of those with calciphylaxis in the absence of ESRD have been treated with warfarin,⁸ and warfarin use is also linked with increased mortality among patients with this disease.³⁶ Even in the absence of warfarin use, vitamin K deficiency from malabsorption or other causes develops in 80% of patients with ESRD and calciphylaxis.³⁷

Most patients with one or even multiple risk

factors do not have calciphylaxis. A triggering event in patients with underlying risk factors probably induces calciphylaxis. Cutaneous calcifications develop in rats that have been sensitized with PTH extract, high-dose vitamin D, a high-phosphate diet, or nephrotoxic insults and then challenged with physical trauma or metal injections.³⁸ Repetitive trauma from subcutaneous injections is an example of a trigger reported in some cases of human calciphylaxis.¹ Most often, however, no obvious trigger is identified.

PATHOGENESIS

The pathogenesis of calciphylaxis is uncertain. Histologic analysis suggests that calcified, narrowed microvessels lead to chronic, low-grade ischemia, and further occlusion of vessels induced by endothelial injury and microthrombosis results in infarction.^{20,21} Thrombosis could be due to a local prothrombotic state,²¹ with or without systemic hypercoagulability.³⁹ The similarity of histologic features in patients with calciphylaxis, irrespective of their status with respect to ESRD, suggests a common final pathway.²⁰

The development of microvascular calcifications in patients with calciphylaxis (and in patients with other vascular calcifications) is likely to be an active, cell-mediated process that depends on the balance between the promoters and inhibitors of calcification (Fig. 2).^{21,40,41} Serum samples from patients with calciphylaxis show impaired inhibition of calcium phosphate precipitation,⁴² which is probably the result of a deficiency of calcification inhibitors. Matrix Gla protein (MGP) is an extracellular matrix protein synthesized by vascular smooth-muscle and endothelial cells. Carboxylated MGP is a potent inhibitor of calcification, with carboxylation dependent on vitamin K.⁴³ A deficiency of carboxylated MGP accelerates spontaneous arterial calcifications in mice.⁴³ Calciphylaxis in humans is characterized by relative reductions of carboxylated MGP in cutaneous tissue²¹ and the circulation.³⁷ Moreover, reduced circulating levels predict more extensive lesions and ulcer formation.³⁷ Carboxylated MGP, in addition to being a direct calcification inhibitor, inhibits the procalcifying factors bone morphogenetic protein 2 (BMP-2) and bone morphogenetic protein 4 (BMP-4).⁴⁴ As shown in Figure 2, in calciphylaxis, the deficiency of car-

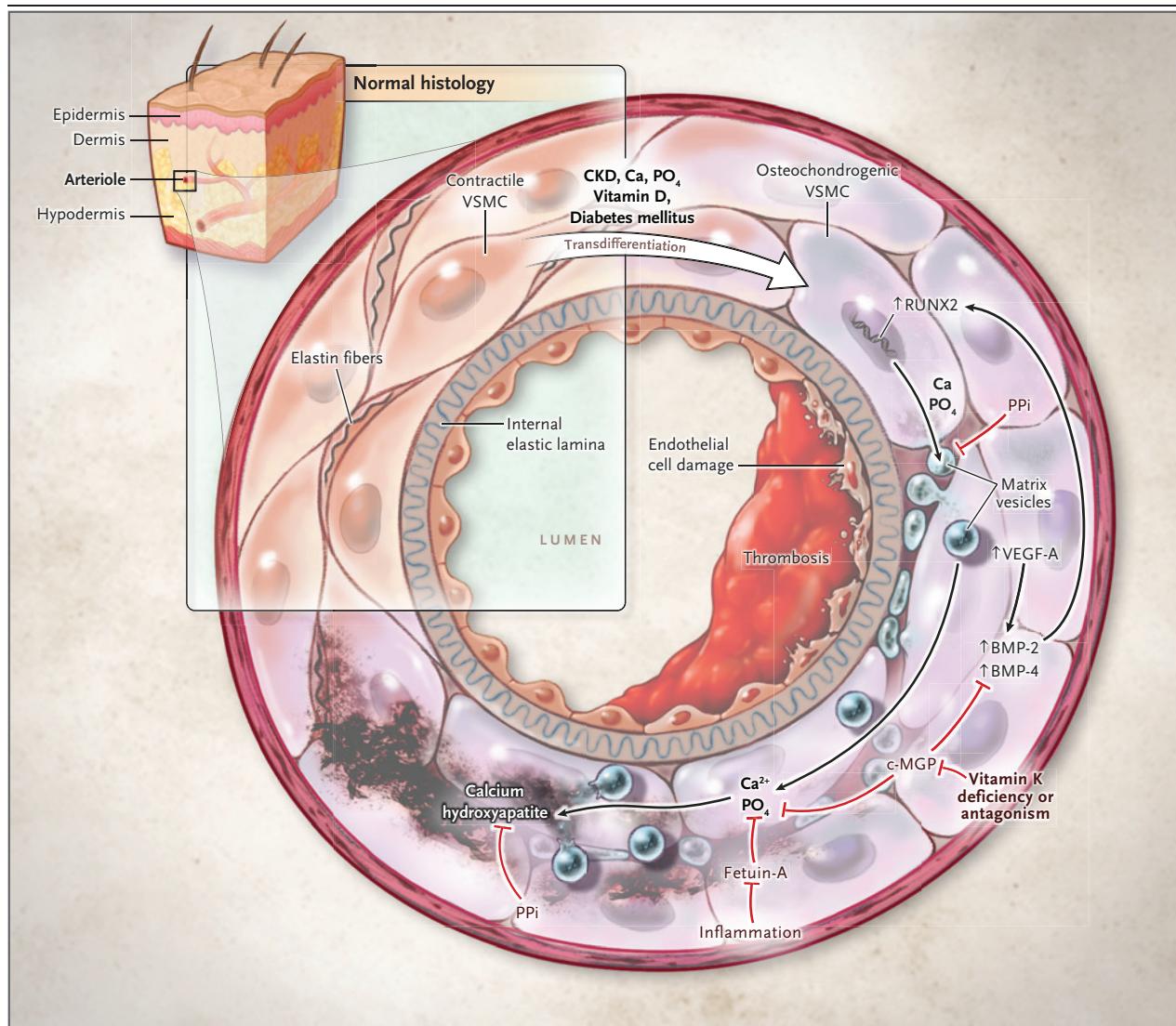


Figure 2. Proposed Pathogenesis of Calciphylaxis.

A representative arteriole from a skin section is magnified. The top left quarter of the arteriole represents normal histologic features, including an intact endothelial lining, internal elastic lamina, vascular smooth-muscle cells (VSMCs), and elastin fibers. In the presence of chronic kidney disease (CKD) and toxins from other sources, VSMCs are probably transdifferentiated from a contractile phenotype to an osteochondrogenic phenotype with up-regulated transcription factors such as runt-related transcription factor 2 (RUNX2). The transdifferentiated cells elaborate matrix vesicles containing calcium (Ca) and phosphate (PO₄), which nucleate crystalline hydroxyapatite in the extracellular matrix. Eventually, the balance between calcification promoters (e.g., bone morphogenetic protein 2 and 4 [BMP-2 and BMP-4]) and inhibitors (e.g., carboxylated matrix Gla protein [c-MGP], fetuin-A, and inorganic pyrophosphate [PPI]) determines whether the arteriole will calcify. Carboxylated MGP inhibits BMP-driven VSMC transdifferentiation and, by loading into matrix vesicles, prevents mineralization. Vitamin K deficiency or antagonism blocks MGP carboxylation, which then promotes VSMC transdifferentiation and matrix mineralization. The transdifferentiated VSMCs produce less MGP, resulting in a cascade effect. Adipocytes may influence this process by releasing vascular endothelial growth factor A (VEGF-A). Arteriolar calcification combined with endothelial destruction and thrombosis ultimately leads to clinical manifestations.

boxylated MGP probably promotes increased cutaneous expression of BMP-2²¹ and BMP-4⁴⁵ and further osteogenic transcription, as evidenced by increased runt-related transcription factor 2

(RUNX2).^{21,46} Another calcification inhibitor is fetuin-A, which is involved in the formation of calciprotein particles that transport mineral nanocrystals.⁴² Fetuin-A is down-regulated in

chronic inflammatory conditions, including chronic kidney disease.^{42,47} Calciphylaxis is characterized by a pronounced burden of circulating calciprotein particles, indicative of severe, functional fetuin-A deficiency.^{47,48}

The discovery of causal genes for mendelian traits with extensive calcifications may provide clues to the pathogenesis of calciphylaxis. Mutations of *NTSE*⁴⁹ and the gene encoding ectonucleotide pyrophosphatase and phosphodiesterase (*ENPP1*),⁵⁰ which are involved in the pathways that regulate the metabolism of pyrophosphate (a critical inhibitor of calcification),⁵¹ lead to arterial calcifications in humans. Polymorphisms in *NTSE* (rs4431401 and rs9444348) are overrepresented in patients with calciphylaxis.³⁰ In murine models, administration of an *ENPP1*-Fc fusion protein⁵⁰ or a small-molecule *ENPP1* inhibitor⁵² prevents cardiovascular calcifications — findings that highlight a promising pathway for the treatment of calcification disorders, including calciphylaxis.

Calcifications of the aorta, coronary artery, and femoral artery are common in patients with ESRD.³⁴ Nonetheless, cutaneous microvascular calcifications leading to clinical manifestations of calciphylaxis remain rare. Why calciphylaxis occurs primarily in the cutaneous microcirculation is unclear. Predominant involvement of subcutaneous panniculus and aggregation of lesions in body areas with abundant adipose tissue, such as the abdomen and thighs, suggest a role of adipocytes in the pathogenesis of calciphylaxis. Mature adipocytes exposed to high phosphate levels calcify and unidirectionally induce calcification of vascular smooth-muscle cells, probably through the release of adipokines.⁵³ Vascular endothelial growth factor A (VEGF-A) is a potential adipokine that has been shown to produce a procalcific response through BMP-4.⁵⁴ The relatively high prevalence of calciphylaxis (4%) among patients with the polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes (POEMS) syndrome underscores the possible role of VEGF-A in calciphylaxis, since the POEMS syndrome is characterized by marked elevations in VEGF-A.⁵⁵ Adipocytes also secrete MGP,⁵⁶ which may be inadequate or ineffective in patients with calciphylaxis. Whether differences in susceptibility to calciphylaxis are due to genetic or environmental variations in adipose tissue is unknown.

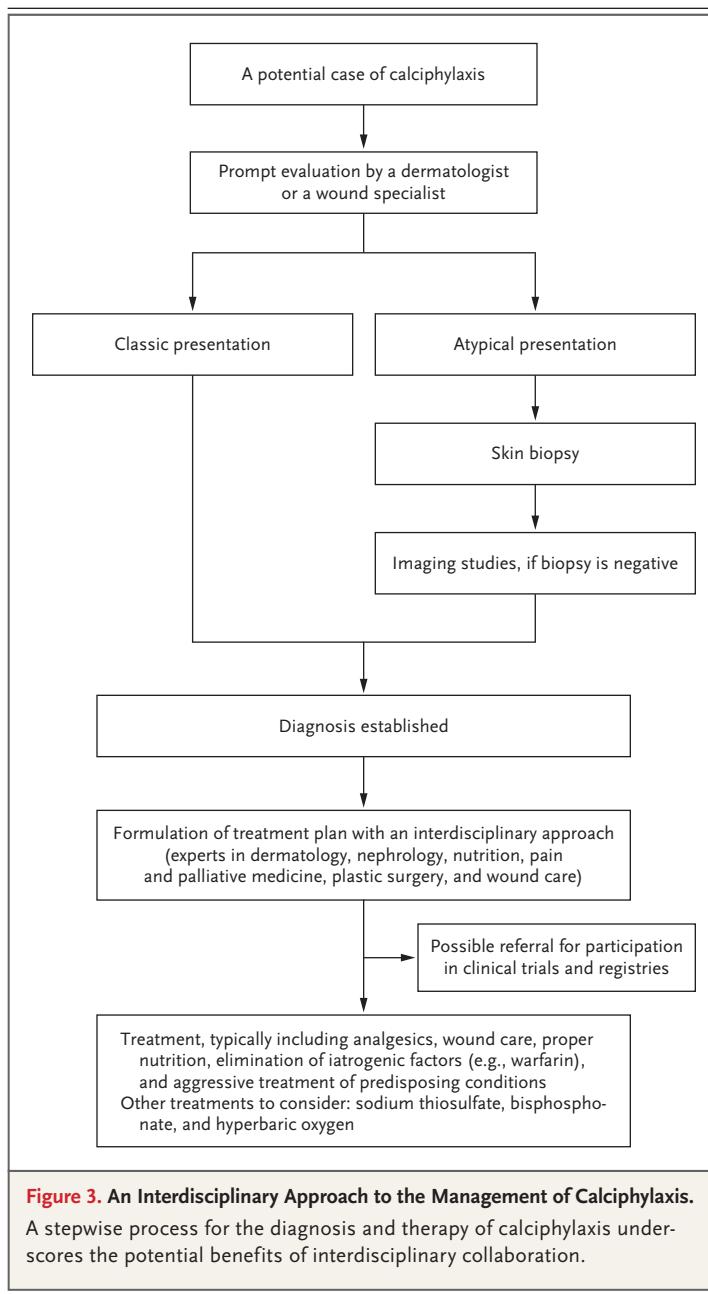
INTERDISCIPLINARY MANAGEMENT

Although there is no approved therapy for calciphylaxis, several approaches may be effective (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). However, the evidence in support of these approaches comes from uncontrolled, observational studies and case reports; for this reason, prospective clinical trials of repurposed and novel therapies are now under way (Table S2 in the Supplementary Appendix). Nonetheless, on the basis of expert opinion, we recommend an interdisciplinary approach (including specialists in dermatology, nephrology, nutrition, pain and palliative medicine, plastic surgery, and wound care) with the aim of expediting the diagnosis and treatment (Fig. 3).

DIAGNOSIS

Clinical suspicion is important for an early diagnosis. Elevations in serum calcium or phosphate levels are not specific. A recent analysis of data from the German Calciphylaxis Registry showed that 86% of dialysis-dependent patients with calciphylaxis had either normal or low plasma calcium levels, and 40% had either normal or low plasma phosphate levels.⁵ Many disorders mimic calciphylaxis (Table 2). These diagnoses can be eliminated by performing a meticulous clinical examination and evaluating histopathological features, laboratory findings, and imaging results (Table S3 in the Supplementary Appendix).

Skin biopsy is the standard method for confirmation of clinically suspected calciphylaxis; however, its role in practice is debated, given the risk of provoking new, nonhealing ulcers and infection.⁴ A biopsy is not needed for a patient with ESRD and the classic presentation of a painful necrotic ulcer covered with a black eschar. However, a biopsy should be strongly considered if a patient has early, atypical lesions or if calciphylaxis is suspected in a patient without ESRD. A biopsy is contraindicated for acral, penile, or infected lesions. A punch biopsy is safer than a large, excisional biopsy but has limited depth and can be nondiagnostic. The yield on biopsy can be improved with a double-punch technique, wherein a second punch is inserted through the center of the first to retrieve deeper subcutaneous tissue, and by biopsy of an active lesion margin rather than a central or necrotic area.

**Table 2. Differential Diagnosis of Calciphylaxis.**

Warfarin-induced skin necrosis
Atherosclerotic vascular disease
Venous stasis ulcer
Cellulitis
Cholesterol embolization
Dystrophic calcinosis cutis
Livedoid vasculopathy
Nephrogenic systemic fibrosis
Oxalosis
Pyoderma gangrenosum
Purpura fulminans
Necrotizing vasculitis
Martorell's ulcer

calciphylaxis: a stippled appearance of calcifications, involvement of capillaries, internal elastic lamina or perieccrine glands, or the presence of fibrointimal hyperplasia or thrombosis.^{15,19,20,57}

Although imaging studies (e.g., plain radiography, mammography, or nuclear bone scanning) are not routinely recommended for the diagnosis, they may support the diagnosis when a biopsy is inconclusive or contraindicated. In small, retrospective studies, a netlike pattern of subcutaneous calcification on plain radiographs (Fig. 1J) and increased heterogeneous radiotracer uptake in soft tissues on nuclear bone scanning have robust specificity (Fig. S1 in the Supplementary Appendix).^{58,59}

ANALGESIA AND WOUND MANAGEMENT

A clinician should first consider analgesic agents to address the severe pain that accompanies calciphylaxis. Adequate pain relief can be challenging because the pain may be unresponsive to high-dose opioids, and opioid toxicity may develop.¹¹ Concomitant treatment with gabapentin, ketamine, or the application of spinal anesthetic agents is used in refractory cases.¹¹

The primary goals of wound care are to remove exudate and necrotic tissue and prevent infection. Calciphylaxis wounds are particularly complicated because the ischemic tissue bed often heals poorly. Moreover, the lesions are extremely painful, making débridement difficult; thus, collaboration with a plastic surgeon and a

Specialized stains (e.g., the von Kossa stain, which uncovers phosphate within hydroxyapatite) are necessary to avoid missing subtle calcifications. Patients with ESRD may have cutaneous microvascular calcifications from causes other than calciphylaxis (e.g., metastatic calcinosis cutis or Mönckeberg's arteriosclerosis).^{19,20,57} The following features, combined with clinical manifestations, help to establish the diagnosis of

pain specialist is beneficial. Retrospective studies have suggested improved survival among patients who underwent operative débridement.^{2,14} However, patients who can tolerate débridement may be healthier than those who cannot, possibly accounting for the difference in survival. Corroborating data from prospective, controlled studies are lacking. Operative débridement accompanied by negative-pressure wound therapy is recommended for infected wounds and large necrotic areas with drainage, but such therapy can result in defective soft tissue lined by marginally viable tissue, requiring further excision. Once the wound has stabilized and granulation tissue is present, split-thickness skin grafting may be performed to close the wound.

Transcutaneous oxygen tension is reduced at lesion sites.⁶⁰ In a retrospective study involving 34 patients with predominantly peripheral disease, hyperbaric oxygen therapy was associated with complete healing in half the patients after 44 sessions of therapy administered over a period of 2 months.⁶¹ These findings provide support for the use of hyperbaric oxygen, particularly in patients with peripheral lesions.⁶¹ Attention to nutritional status is necessary to prevent or treat protein-energy wasting.⁶² There is no indication for prophylactic use of antibiotics.

ELIMINATION OF RISK FACTORS

Hypercalcemia and hyperphosphatemia should be corrected. Intake of vitamin D and calcium (including calcium-based phosphate binders) should be eliminated, and high levels of dialysate calcium should be avoided. The optimal PTH level for patients with calciphylaxis is unknown; however, extreme values (high and low) should be avoided. In a randomized trial involving more than 3500 patients being treated with hemodialysis, the administration of cinacalcet (a calcimimetic agent) decreased the median PTH level from approximately 690 pg per milliliter to 300 pg per milliliter.⁶³ Adverse-event analyses in that trial showed a reduced incidence of calciphylaxis (unadjusted relative hazard, 0.31; 95% confidence interval, 0.13 to 0.79) in the cinacalcet group. The low event rate for calciphylaxis in both study groups (0.3% [6 patients] in the cinacalcet group and 0.9% [18 patients] in the placebo group) precluded detailed analyses; furthermore, this trial did not address the role of cinacalcet once calciphylaxis is present. However, the possibility that a calcimimetic agent is helpful warrants further prospective examination in both preventive and treatment studies. Considering the risks associated with parathyroidectomy, including irreversible reduction of PTH levels and the hungry bone syndrome, requiring calcium and calcitriol, a calcimimetic agent is preferable to parathyroidectomy, the latter being reserved for refractory cases.⁶⁴

In patients with ESRD, increasing the length or frequency of dialysis sessions may accelerate wound healing.⁶⁵ Intensified hemodialysis (beyond the regular regimen of 4-hour sessions three times weekly) is warranted for treating bone and mineral abnormalities, including severe hyperphosphatemia, hypercalcemia, and hyperparathyroidism. A transition to hemodialysis is recommended for patients being treated with peritoneal dialysis, since hemodialysis may accelerate wound healing, presumably through better control of mineral metabolism.²⁶ A complete resolution of calciphylaxis in patients with ESRD has been achieved with kidney transplantation⁶⁶; however, transplantation is not a feasible treatment option for all such patients.

Iatrogenic factors, including treatment with warfarin, should be identified and discontinued, and best practices for the treatment of predisposing conditions should be instituted. If subcutaneous injections cannot be avoided, injection sites should be rotated to minimize repetitive trauma to one location.

PHARMACOTHERAPEUTIC AGENTS

Sodium thiosulfate is an agent with antioxidant and vasodilatory properties that also inhibits adipocyte calcification and blocks the ability of adipocytes to induce calcification of vascular smooth-muscle cells.^{48,53} In a study involving 53 hemodialysis-dependent patients with calciphylaxis who were treated with intravenous sodium thiosulfate (three times per week [with each dialysis session] for approximately 3 months), calciphylaxis completely resolved in 26% of the patients, and 19% had marked improvement in skin lesions.⁶⁷ In another study, involving 27 patients being treated with dialysis, complete remission was observed in 52% of the patients and partial remission in 19% after treatment with intravenous sodium thiosulfate.¹⁸ Lack of a con-

trol group and the retrospective nature of the study preclude definitive conclusions regarding the effectiveness of sodium thiosulfate.

Although successful use of sodium thiosulfate for the treatment of calciphylaxis was first reported more than a decade ago, only now are two ongoing trials investigating its safety and efficacy (Current Controlled Trials number, ISRCTN73380053; and ClinicalTrials.gov number, NCT03150420). Nevertheless, sodium thiosulfate is frequently used to treat calciphylaxis. A typical dose is 25 g in 100 ml of solution given intravenously three times a week during the last 30 to 60 minutes of hemodialysis. The optimal duration of the treatment course is unclear. Pharmacokinetic simulations may be used to estimate the dose for hemodialysis at various levels of intensity.⁶⁸ The dosing for patients undergoing peritoneal dialysis, patients who are not being treated with dialysis, and children is less standardized. Adverse effects include volume overload, hypocalcemia, QT-interval prolongation, hypotension, and metabolic acidosis. These adverse effects can be avoided with intralesional administration, which may be an alternative approach for patients with early and limited disease.⁶⁹

Bisphosphonates are pyrophosphate analogues that have been used successfully to treat patients with genetic *ENPP1* deficiency.⁷⁰ In a prospective series of 11 patients, bisphosphonates halted the progression of lesions in all the patients starting at 2 to 4 weeks after treatment initiation.⁷¹ Further investigation of bone-vascular cross-talk is needed to understand the role of bisphosphonates and other agents that modify bone (e.g., receptor activator of nuclear factor- κ B ligand inhibitor and antisclerostin antibody).

Decisions regarding anticoagulation therapy should be individualized after an assessment of the risk of bleeding versus the risk of thrombosis. If ongoing anticoagulation therapy is favored, the selection of an agent should be based on the patient's kidney function and the indication for anticoagulation.⁷²

In a study involving patients 60 to 80 years of age, vitamin K₁ supplementation (phylloquinone at a dose of 500 μ g per day) slowed the progression of preexisting coronary-artery calcification by 6% at 3 years of follow-up.⁷³ In healthy post-

menopausal women, vitamin K₂ supplementation (menaquinone-7 administered at a dose of 180 μ g daily for 3 years) reduced aortic stiffness (measured as carotid-femoral pulse wave velocity with the use of mechanotransducers) and common carotid-artery stiffness (measured according to the stiffness index β with the use of echotracking and oscillometry).⁷⁴ Moreover, vitamin K₁ supplementation (phytonadione administered at a dose of 2 mg daily for 12 months) slowed the progress of aortic-valve calcification (measured by means of computed tomography) by 57%, as compared with placebo, in patients with mild-to-moderate aortic stenosis.⁷⁵ The efficacy of vitamin K supplementation for calciphylaxis, however, is unclear, with no support for the superiority of a specific form of vitamin K (K₁ or K₂). A proof-of-concept study of vitamin K₁ supplementation (10 mg administered orally three times weekly after hemodialysis) is currently under way (NCT02278692).

SUMMARY AND FUTURE DIRECTIONS

Calciphylaxis is a complex disorder of microvascular calcification that is typically manifested as painful cutaneous lesions and results in poor outcomes. Currently, there are no approved therapies for calciphylaxis; however, ongoing trials are examining end points that include pain intensity and lesion characteristics. Although some risk factors for calciphylaxis are now better understood, animal models that recapitulate this rare human condition would be helpful to gain a better understanding of pathogenesis and to test novel therapeutic agents.

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REFERENCES

- Nigwekar SU, Zhao S, Wenger J, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Nephrol* 2016;27:3421-9.
- McCarthy JT, El-Azhary RA, Patzelt MT, et al. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. *Mayo Clin Proc* 2016;91:1384-94.
- Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. *Kidney Int* 2002;61:2210-7.
- Brandenburg VM, Evenepoel P, Floege J, et al. Lack of evidence does not justify neglect: how can we address unmet medical needs in calciphylaxis? *Nephrol Dial Transplant* 2016;31:1211-9.
- Brandenburg VM, Kramann R, Rothe H, et al. Calcific uremic arteriolopathy (calciphylaxis): data from a large nationwide registry. *Nephrol Dial Transplant* 2017;32:126-32.
- Honda Y, Endo Y, Tanizaki H, et al. Calciphylaxis associated with acute renal failure in multicentric Castleman's disease. *Eur J Dermatol* 2015;25:497-9.
- Vanparijs J, Sprangers B, Sagaert X, Kuypers DR. Chronic wounds in a kidney transplant recipient with moderate renal impairment. *Acta Clin Belg* 2013;68:128-31.
- Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol* 2008;3:1139-43.
- Kalajian AH, Malhotra PS, Callen JP, Parker LP. Calciphylaxis with normal renal and parathyroid function: not as rare as previously believed. *Arch Dermatol* 2009;145:451-8.
- Coates T, Kirkland GS, Dymock RB, et al. Cutaneous necrosis from calcific uremic arteriolopathy. *Am J Kidney Dis* 1998;32:384-91.
- Polizzotto MN, Bryan T, Ashby MA, Martin P. Symptomatic management of calciphylaxis: a case series and review of the literature. *J Pain Symptom Manage* 2006;32:186-90.
- Ghosh T, Winchester DS, Davis MDP, El-Azhary R, Comfere NI. Early clinical presentations and progression of calciphylaxis. *Int J Dermatol* 2017;56:856-61.
- Daudén E, Ofiñate MJ. Calciphylaxis. *Dermatol Clin* 2008;26:557-68.
- Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007;56:569-79.
- Case Records of the Massachusetts General Hospital (Case 7-2007). *N Engl J Med* 2007;356:1049-57.
- Riemer CA, El-Azhary RA, Wu KL, Strand JJ, Lehman JS. 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.
- Nigwekar SU. Calciphylaxis. *Curr Opin Nephrol Hypertens* 2017;26:276-81.
- Zitt E, König M, Vychytal A, et al. Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients. *Nephrol Dial Transplant* 2013;28:1232-40.
- Mochel MC, Arakali RY, Wang G, Kroshinsky D, Hoang MP. Cutaneous calciphylaxis: a retrospective histopathologic evaluation. *Am J Dermatopathol* 2013;35:582-6.
- Chen TY, Lehman JS, Gibson LE, Lohse CM, El-Azhary RA. Histopathology of calciphylaxis: cohort study with clinical correlations. *Am J Dermatopathol* 2017;39:795-802.
- Kramann R, Brandenburg VM, Schurgers LJ, et al. Novel insights into osteogenesis and matrix remodelling associated with calcific uremic arteriolopathy. *Nephrol Dial Transplant* 2013;28:856-68.
- Hayashi M. Calciphylaxis: diagnosis and clinical features. *Clin Exp Nephrol* 2013;17:498-503.
- Nigwekar SU, Solid CA, Ankers E, et al. Quantifying a rare disease in administrative data: the example of calciphylaxis. *J Gen Intern Med* 2014;29:Suppl 3:S724-S731.
- Hayashi M, Takamatsu I, Kanno Y, Yoshida T, Abe T, Sato Y. A case-control study of calciphylaxis in Japanese end-stage renal disease patients. *Nephrol Dial Transplant* 2012;27:1580-4.
- Zhang Y, Corapi KM, Luongo M, Thadhani R, Nigwekar SU. Calciphylaxis in peritoneal dialysis patients: a single center cohort study. *Int J Nephrol Renovasc Dis* 2016;9:235-41.
- Sprague SM. Painful skin ulcers in a hemodialysis patient. *Clin J Am Soc Nephrol* 2014;9:166-73.
- Araya CE, Fennell RS, Neiberger RE, Dharnidharka VR. Sodium thiosulfate treatment for calcific uremic arteriolopathy in children and young adults. *Clin J Am Soc Nephrol* 2006;1:1161-6.
- James LR, Lajoie G, Prajapati D, Gan BS, Bargman JM. Calciphylaxis precipitated by ultraviolet light in a patient with end-stage renal disease secondary to systemic lupus erythematosus. *Am J Kidney Dis* 1999;34:932-6.
- Amuluru L, High W, Hiatt KM, et al. Metal deposition in calcific uremic arteriolopathy. *J Am Acad Dermatol* 2009;61:73-9.
- Rothe H, Brandenburg V, Haun M, et al. Ecto-5'-nucleotidase CD73 (NT5B), 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(2):e0172407.
- Spanakis EK, Sellmeyer DE. Nonuremic calciphylaxis precipitated by teriparatide [rhPTH(1-34)] therapy in the setting of chronic warfarin and glucocorticoid treatment. *Osteoporos Int* 2014;25:1411-4.
- Mawad HW, Sawaya BP, Sarin R, Malaluke HH. Calcific uremic arteriolopathy in association with low turnover uremic bone disease. *Clin Nephrol* 1999;52:160-6.
- Scialla JJ, Lau WL, Reilly MP, et al. Fibroblast growth factor 23 is not associated with and does not induce arterial calcification. *Kidney Int* 2013;83:1159-68.
- Yamada S, Giachelli CM. Vascular calcification in CKD-MBD: roles for phosphate, FGF23, and Klotho. *Bone* 2017;100:87-93.
- Nigwekar SU, Bhan I, Turchin A, et al. Statin use and calcific uremic arteriolopathy: a matched case-control study. *Am J Nephrol* 2013;37:325-32.
- Santos PW, He J, Tuffaha A, Wetmore JB. Clinical characteristics and risk factors associated with mortality in calcific uremic arteriolopathy. *Int Urol Nephrol* 2017;49:2247-56.
- Nigwekar SU, Bloch DB, Nazarian RM, et al. Vitamin K-dependent carboxylation of matrix Gla protein influences the risk of calciphylaxis. *J Am Soc Nephrol* 2017;28:1717-22.
- Sely H, Gentile G, Prioreschi P. Cutaneous molt induced by calciphylaxis in the rat. *Science* 1961;134:1876-7.
- Dobry AS, Ko LN, St John J, Sloan JM, Nigwekar S, Kroshinsky D. Association between hypercoagulable conditions and calciphylaxis in patients with renal disease: a case-control study. *JAMA Dermatol* 2018;154:182-7.
- Moe SM, Chen NX. Calciphylaxis and vascular calcification: a continuum of extra-skeletal osteogenesis. *Pediatr Nephrol* 2003;18:969-75.
- Shroff R, Long DA, Shanahan C. Mechanistic insights into vascular calcification in CKD. *J Am Soc Nephrol* 2013;24:179-89.
- Schafer C, Heiss A, Schwarz A, et al. The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. *J Clin Invest* 2003;112:357-66.
- Luo G, Ducy P, McKee MD, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature* 1997;386:78-81.

44. Schurgers LJ, Uitto J, Reutelingsperger CP. Vitamin K-dependent carboxylation of matrix Gla-protein: a crucial switch to control ectopic mineralization. *Trends Mol Med* 2013;19:217-26.

45. Griethe W, Schmitt R, Jurgensen JS, Bachmann S, Eckardt KU, Schindler R. Bone morphogenic protein-4 expression in vascular lesions of calciphylaxis. *J Nephrol* 2003;16:728-32.

46. Nigwekar SU, Jiramongkolchai P, Wunderer F, et al. Increased bone morphogenic protein signaling in the cutaneous vasculature of patients with calciphylaxis. *Am J Nephrol* 2017;46:429-38.

47. 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 (Carlton)* 2013;18:215-21.

48. Sowers KM, Hayden MR. Calcific uremic arteriolopathy: pathophysiology, reactive oxygen species and therapeutic approaches. *Oxid Med Cell Longev* 2010;3:109-21.

49. St Hilaire C, Ziegler SG, Markello TC, et al. *NTSE* mutations and arterial calcifications. *N Engl J Med* 2011;364:432-42.

50. 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.

51. Lomashvili KA, Narisawa S, Millán JL, O'Neill WC. Vascular calcification is dependent on plasma levels of pyrophosphate. *Kidney Int* 2014;85:1351-6.

52. Pillai ICL, Li S, Romay M, et al. Cardiac fibroblasts adopt osteogenic fates and can be targeted to attenuate pathological heart calcification. *Cell Stem Cell* 2017;20(2):218-232.e5.

53. Chen NX, O'Neill K, Akl NK, Moe SM. Adipocyte induced arterial calcification is prevented with sodium thiosulfate. *Biochem Biophys Res Commun* 2014;449:151-6.

54. Mikhaylova L, Malmquist J, Nurminskaya M. Regulation of in vitro vascular calcification by BMP4, VEGF and Wnt3a. *Calcif Tissue Int* 2007;81:372-81.

55. Araki N, Misawa S, Shibuya K, et al. POEMS syndrome and calciphylaxis: an unrecognized cause of abnormal small vessel calcification. *Orphanet J Rare Dis* 2016;11:35.

56. Mutch DM, Rouault C, Keophiphatth M, Lacasa D, Clément K. Using gene expression to predict the secretome of differentiating human preadipocytes. *Int J Obes (Lond)* 2009;33:354-63.

57. Cassius C, Moguel P, Monfort JB, et al. Calciphylaxis in haemodialysed patients: diagnostic value of calcifications in cutaneous biopsy. *Br J Dermatol* 2018;178:292-3.

58. Paul S, Rabito CA, Vedak P, Nigwekar SU, Kroshinsky D. The role of bone scintigraphy in the diagnosis of calciphylaxis. *JAMA Dermatol* 2017;153:101-3.

59. Shmidt E, Murthy NS, Knudsen JM, et al. Net-like pattern of calcification on plain soft-tissue radiographs in patients with calciphylaxis. *J Am Acad Dermatol* 2012;67:1296-301.

60. Wilmer WA, Voroshilova O, Singh I, Middendorf DF, Cosio FG. Transcutaneous oxygen tension in patients with calciphylaxis. *Am J Kidney Dis* 2001;37:797-806.

61. An J, Devaney B, Ooi KY, Ford S, Frawley G, Menahem S. Hyperbaric oxygen in the treatment of calciphylaxis: a case series and literature review. *Nephrology (Carlton)* 2015;20:444-50.

62. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008;73:391-8.

63. The EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;367:2482-94.

64. Nigwekar SU, Sprague SM. We do too many parathyroidectomies for calciphylaxis. *Semin Dial* 2016;29:312-4.

65. Baldwin C, Farah M, Leung M, et al. Multi-intervention management of calciphylaxis: a report of 7 cases. *Am J Kidney Dis* 2011;58:988-91.

66. Nordheim E, Dahle DO, Syse IM, Åsberg A, Reisæter AV, Hartmann A. Resolution of calciphylaxis after urgent kidney transplantation in 3 patients with end-stage kidney failure. *Transplant Direct* 2016;2(11):e113.

67. Nigwekar SU, Brunelli SM, Meade D, Wang W, Hymes J, Lacson E Jr. Sodium thiosulfate therapy for calcific arteriolopathy. *Clin J Am Soc Nephrol* 2013;8:1162-70.

68. 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.

69. Strazzula L, Nigwekar SU, Steele D, et al. Intralesional sodium thiosulfate for the treatment of calciphylaxis. *JAMA Dermatol* 2013;149:946-9.

70. Ramjan KA, Roscioli T, Rutsch F, Silence D, Munns CF. Generalized arterial calcification of infancy: treatment with bisphosphonates. *Nat Clin Pract Endocrinol Metab* 2009;5:167-72.

71. Torregrosa JV, Sánchez-Escuredo A, Barros X, Blasco M, Campistol JM. Clinical management of calcific uremic arteriolopathy before and after therapeutic inclusion of bisphosphonates. *Clin Nephrol* 2015;83:231-4.

72. King BJ, El-Azhary RA, McEvoy MT, et al. Direct oral anticoagulant medications in calciphylaxis. *Int J Dermatol* 2017;56:1065-70.

73. Shea MK, O'Donnell CJ, Hoffmann U, et al. Vitamin K supplementation and progression of coronary artery calcium in older men and women. *Am J Clin Nutr* 2009;89:1799-807.

74. Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, Vermeer C. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women: a double-blind randomised clinical trial. *Thromb Haemost* 2015;113:1135-44.

75. Brandenburg VM, Reinartz S, Kaesler N, et al. Slower progress of aortic valve calcification with vitamin K supplementation: results from a prospective interventional proof-of-concept study. *Circulation* 2017;135:2081-3.

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