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Calciphylaxis

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Synonyms and related keywords: necrotizing livedo reticularis, uremic gangrene syndrome, uremic necrosis, uremic small-artery disease with medial calcification and intimal hyperplasia, ischemic tissue necrosis, progressive ischemic gangrene, calcific uremic arteriopathy, obliterative calcific-thrombotic arteriopathy, calcifying panniculitis



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INTRODUCTION

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Background

Calciphylaxis is a poorly understood and highly morbid syndrome of vascular calcification and skin necrosis. Bryant and White first reported it in association with uremia in 1898. However, the significance of this relationship became uncertain when vascular calcification was subsequently shown to be prevalent in uremia, yet the syndrome of vascular calcification with cutaneous necrosis remained rare.

In 1962, Selye¹ constructed an experimental model and was able to precipitate systemic calcification, somewhat analogous to this syndrome, in nephrectomized rats. He was the first to coin the term calciphylaxis to characterize this enigma. Over the years, many other names have been suggested to characterize the pathogenic process, which has remained elusive.

Interestingly, the clinical importance of this syndrome was not recognized until a 1976 report by Gipstein et al.² Since then, a multitude of case reports of calciphylaxis have documented data outlining its morbidity and therapeutic dilemmas, as well as a quest to better understand its etiology and pathogenesis. Unfortunately, it remains a conundrum.

Pathophysiology

The pathogenesis of calciphylaxis remains obscure and is likely the result of a multiplicity of comorbid factors or events. Disorders that are most often implicated in the pathogenesis of calciphylaxis include chronic renal failure, obesity, diabetes mellitus, hypercalcemia, hyperphosphatemia, an elevated calcium-phosphate product, and secondary hyperparathyroidism. Yet, although these abnormalities are extremely common in patients with end-stage renal disease (ESRD), calciphylaxis is relatively rare.

Using a rat model, Selye¹ demonstrated that a series of events might be necessary for the formation of calciphylaxis. He defined calciphylaxis as a condition of hypersensitivity induced by a set of "sensitizing" agents, in which calcinosis occurred only in those subsequently subjected to a group of "challengers" and only after a critical lag time. Experimental sensitizing events and agents included nephrectomy and exposure to parathyroid hormone (PTH) and vitamin D. Substances used as challengers included egg albumin and metallic salts. Calciphylaxis was the end result.

Although extrapolation of animal data to humans is conjectural, it seems to be true that serial events, most consistently involving renal failure-induced abnormalities in calcium homeostasis, are required to occur over time for calciphylaxis to develop. The cause of calciphylaxis has been elusive, most likely because it is the common endpoint of a heterogeneous group of disorders.

Recently, molecular and cytochemical factors have been identified as crucial in bone metabolism. The receptor activator of nuclear factor- κ B (RANK), RANK ligand, and osteoprotegerin appear to regulate skeletal and extraskelatal mineralization. Uremia-induced defects in this system may predispose to calciphylaxis. Corticosteroids, aluminum, hyperparathyroidism, liver disease, and a variety of inflammatory processes all can alter this balance and promote vascular calcification. Chronic inflammatory conditions may predispose to calciphylaxis by reducing serum levels of fetuin-A, an important inhibitor of calcification produced in the liver.

Frequency

International

Calciphylaxis is an uncommon condition that affects 1-4% of the population with ESRD. A concern exists that the incidence has increased during the last decade because of a number of possible factors, including more widespread use of parenteral

vitamin D and iron dextran. No good data are available regarding the incidence of calciphylaxis in the general population without ESRD, but it is probably exceedingly rare.

Mortality/Morbidity

The mortality rate of calciphylaxis is reported to be as high as 60-80%. The leading cause of death is sepsis from infected, necrotic skin lesions, although death due to internal organ failure has been reported. The mortality rate is higher in patients with proximal disease than in those with only distal or acral disease. A 2-fold increase in mortality is seen in those with ulcerative disease. The overall 1- and 5-year survival rates have recently been reported to be 45% and 35%, respectively.

Race

Although the disease may affect persons of any race, it appears to be more prevalent in whites.

Sex

Females are affected more often than males, with a female-to-male ratio of approximately 3:1.

Age

Calciphylaxis has been reported in individuals ranging in age from 6 months to 83 years. From a large series of patients, a mean patient age of 48 years (± 16 y) has been calculated. Individuals seemingly more predisposed are younger patients who have had a longer duration of renal replacement therapy.

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History

- Most patients with calciphylaxis have a long-standing history of chronic renal failure and renal replacement therapy.
- On rare occasions, calciphylaxis may occur in a patient with chronic renal failure prior to the initiation of replacement therapy. Very rarely, it may occur in an individual without a history of chronic renal failure.
- Many persons who develop calciphylaxis have undergone renal allograft transplantation. The allograft may still be functional when calciphylaxis develops.
- Frequently, patients have been noncompliant with dietary, medical, and/or dialysis prescriptions prior to the onset of calciphylaxis.
- Lesions of calciphylaxis typically develop suddenly and progress rapidly. Lesions may be singular or numerous, and they generally occur on the lower extremities (see [Media File 1](#)); however, lesions also may develop on the hands and torso.
- Intense pain is a constant finding.
- The patient's history may reveal an event that is a suspected trigger or risk factor for the development of calciphylaxis. These triggers include the following:
 - Long-term obesity
 - Recent and sudden weight loss

- Malnutrition
 - Infusion of medications such as iron dextran
 - Remote and/or recent use of immunosuppressive agents, especially corticosteroids
 - Liver disease
 - Diabetes mellitus and insulin injections
 - Use of vitamin D and calcium-based phosphate binders
 - Concurrent use of warfarin anticoagulation: Current data suggest that warfarin therapy may lower protein C concentrations, leading to a procoagulant condition in the calcified vessel. Warfarin may also inhibit carboxylation of matrix Gla protein, an important inhibitor of calcification, thus promoting calcification
- Review of the patient's medical record usually reveals a history of hyperphosphatemia with hyperparathyroidism and hypoalbuminemia.

Physical

- Early lesions of calciphylaxis manifest as nonspecific violaceous mottling; as livedo reticularis; or as erythematous papules, plaques, or nodules.
- More developed lesions have a stellate purpuric configuration with central cutaneous necrosis (see [Media File 2](#)).
- Multiple lesions of variable age may be present, following the path of the vasculature.
- Less commonly, lesions may manifest as either bullae (see [Media File 3](#)) or distinct subcutaneous, erythematous nodules suggestive of erythema nodosum.
- Lesions are excruciatingly tender and extremely firm.
- The distribution of the lesions may be characterized as proximal or distal.
 - Ninety percent of lesions of calciphylaxis occur on the lower extremities.
 - Distal lesions are those that occur below the knee; proximal lesions occur on the thighs or the trunk.
 - Proximally distributed lesions occur in 44-68% of patients, with lesions developing predominantly on the thighs, the buttocks, and the lower part of the abdomen.
 - Distal and visceral involvement are not uncommon.
- An intact peripheral pulse helps to distinguish acral calciphylaxis from atherosclerotic peripheral vascular disease.

Causes

- Disorders associated with the development of calciphylaxis include the following:
 - Common associations include chronic renal failure, hypercalcemia, hyperphosphatemia, elevated calcium-phosphate product, hyperparathyroidism, and vascular calcification.
 - Speculative associations include aluminum toxicity, coagulation abnormalities, and iron dextran infusion.

- Associations suggested from clinical observations include renal transplantation, immunosuppressive agents, corticosteroid use, and obesity.
- The cause of calciphylaxis remains obscure. Most cases occur in the setting of chronic renal failure, abnormal calcium-phosphate homeostasis, and hyperparathyroidism. Both hypercalcemia and hyperphosphatemia may be present, and the calcium-phosphate product frequently exceeds $60\text{-}70\text{ mg}^2/\text{dL}^2$. However, calciphylaxis may occur in the setting of normal, or minimally elevated, calcium and phosphate levels.
- Case reports exist of calciphylaxis occurring in primary hyperparathyroidism, cirrhosis, and rheumatoid arthritis, without renal disease. The pathogenesis of calciphylaxis in these cases is uncertain. The exact role of PTH is uncertain because calciphylaxis may occur after total parathyroidectomy, in the absence of measurable PTH levels.
- Patients at an increased risk appear to be those who are obese and those who have been exposed to immunosuppressive agents, including glucocorticoids. Calciphylaxis occurs more frequently in areas where body fat is most abundant, such as the thighs, the buttocks, and the lower part of the abdomen. Fatty areas may be at higher risk for thrombosis, owing to lower blood flow or the increased potential for vascular kinking.
- Persons with diabetes mellitus may also be at an increased risk; insulin injections may be an independent risk due to trauma to the subcutis.
- The clinical appearance of the lesions of calciphylaxis (livedo reticularis and stellate purpura) suggests that the common endpoint of the process is small vessel occlusion. Indeed, microthrombi are found in most cases.
 - Hypercoagulable conditions, including protein C and protein S deficiencies, and the presence of a circulating anticoagulant have been described in a number of patients. However, conditions of hypercoagulability are not found uniformly. If they do exist, they could possibly precipitate or exacerbate calciphylaxis in a predisposed patient.
 - Vascular calcification is a constant finding in cases of calciphylaxis. Theoretically, various pathologic roles may be attributed to this vascular calcification. First, calcification of the vascular endothelium may alter the local interaction of procoagulant and anticoagulant factors, predisposing to a microenvironment of hypercoagulability. Alternatively, extensive endothelial calcification and intimal hyperplasia, which are known to compromise the luminal size of vessels in calciphylaxis, may result in vascular occlusion. Finally, recent data suggest that the uremic milieu may promote calcification through inhibition of various endogenous inhibitors of calcification such as alpha2-Heremans-Schmid glycoprotein/fetuin A (AHSG), osteopontin, and matrix Gla protein. These theories remain speculative.

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Other Problems to be Considered

Cryoglobulinemia
 Cryofibrinogenemia
 Coumarin necrosis
 Protein C deficiency
 Protein S deficiency
 Antiphospholipid syndrome

Polyarteritis nodosa
Atherosclerotic peripheral vascular disease
Pancreatic panniculitis
Cholesterol emboli
Subacute bacterial endocarditis
Disseminated intravascular necrosis

WORKUP

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Lab Studies

- Serum blood urea nitrogen and creatinine levels
- Serum calcium, phosphate, alkaline phosphatase, and albumin levels
- Serum PTH level
- Coagulation factors - Prothrombin time, activated partial thromboplastin time, protein C level, protein S level, anticardiolipin level, lupus anticoagulant level, factor V Leiden level, and homocysteine level
- Cryoglobulin and rheumatoid factor measurements
- Hepatitis C antibody level
- Cryofibrinogen level
- Serum amylase and lipase level
- Aluminum level
- Measures of inflammation - Erythrocyte sedimentation rate and C-reactive protein value

Imaging Studies

- Plain radiography uniformly demonstrates an arborization of vascular calcification within the dermis and the subcutaneous tissue (see [Media File 4](#)). However, this is common in persons with ESRD and is not specific for calciphylaxis.
- Bone scintigraphy may be used as a noninvasive diagnostic tool because the bone matrix protein osteopontin has recently been demonstrated in calciphylaxis lesions. Serial bone scanning can also possibly be used to monitor progression or regression of disease.

Procedures

- Punch biopsies may not be adequate because the quantity or depth of tissue obtained may not be enough for diagnosis.
- An incisional cutaneous biopsy is usually diagnostic. Ample subcutaneous tissue must be available for adequate evaluation.

- The decision to perform a biopsy on a nonulcerated lesion should not be made lightly because it could result in a nonhealing wound. Although lesions of calciphylaxis have a clinical appearance suggestive of avascular necrosis, the tissue often bleeds freely during surgery. Furthermore, lesional ulceration increases the mortality rate 2-fold.

Histologic Findings

Biopsy specimens typically demonstrate calcification within the media of small- and medium-sized arterioles with extensive intimal hyperplasia and fibrosis (see [Media Files 5-7](#)). A mixed inflammatory infiltrate frequently occurs. Subcutaneous calcium deposits with panniculitis and fat necrosis may sometimes be found. Vascular microthrombi are frequently evident.

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Medical Care

Medical care is mainly supportive. Aggravating conditions should be addressed, and trigger factors should be eliminated. This may mean the discontinuation of parenteral iron therapy, calcium supplementation, and vitamin D supplementation. Although implicated as a trigger in the past, recent studies suggest that some patients may benefit early on from systemic glucocorticoids, unless ulcerated lesions are present.

- Serum calcium and phosphate concentrations must be brought to low-normal levels as quickly and safely as possible.
 - Conservative therapy should be tried first, with dietary alteration, use of noncalcium, nonaluminum phosphate binders and low-calcium bath dialysis. Some benefit may be achieved with increasing the frequency or duration of dialysis sessions.
 - Calcimimetics such as cinacalcet hydrochloride may be beneficial in cases of hyperparathyroidism. These agents increase the sensitivity of the calcium receptors to available calcium, thereby decreasing PTH secretion. Studies have shown efficacy in decreasing PTH, calcium, and phosphate levels. Reports of successful treatment with these agents as adjunctive therapy for calciphylaxis are emerging.
 - Parathyroidectomy should be considered if conservative management fails, but only if hyperparathyroidism is present.
- Marked improvement of calciphylaxis has now been reported with the use of intravenous sodium thiosulfate. Sodium thiosulfate increases the solubility of calcium deposits.
 - Calciphylaxis therapy with sodium thiosulfate is off-label usage, but reports of success are mounting. Sodium thiosulfate has been administered both intravenously and intraperitoneally, and it has been used in both adults and children.
 - Intravenous doses have varied from 5-25 g after or during hemodialysis in adults.
 - Some have used weight-based dosing (especially in children) at using 12 g/1.7 m².
 - Infusion times vary from 30-60 minutes.
 - Although generally well tolerated, adverse effects have include nausea with emesis and the development of an anion gap metabolic acidosis that can be managed by altering the bicarbonate level of the dialysate.

- Symptomatic relief and clinical improvement may occur within 2 weeks.
- Judicious use of antibiotics may be advantageous.
- In some cases, hyperbaric oxygen may be beneficial.
- Conditions of hypercoagulability should be sought and addressed.
 - Patients with documented conditions of hypercoagulability may benefit from proper and adequate anticoagulation. Successful treatment of calciphylaxis with low-dose tissue plasminogen activator has been reported. Laboratory evaluation of the reported patient demonstrated low antithrombin III antigen and activity, as well as low protein C antigen and activity prior to intervention with tissue plasminogen activator therapy.
 - However, the role of anticoagulation in all cases of calciphylaxis is controversial. Random prophylactic use of warfarin or heparin is probably not indicated because precipitation of calciphylaxis has occurred with indiscriminate use.
 - In addition, most patients with ESRD have a prolonged bleeding time due to the uremic condition, and anticoagulation or tissue plasminogen activator therapy should be approached cautiously.
- Pain management is also crucially important. Consultation with pain-management specialists may be necessary.

Surgical Care

- Aggressive wound care and debridement may be necessary to avoid wound infection and sepsis. The decision to debride, and to what extent, depends on the patient's overall health and the clinical picture.
- Use of a vacuum-assisted closure device has been successful in several cases of calciphylaxis after extensive debridement and prior to skin grafting.
- Total or subtotal parathyroidectomy with autotransplantation has been shown to be of therapeutic benefit to many, but not all, individuals. Some investigators believe it is the single most effective treatment option, but this remains controversial. Only a few studies have been able to demonstrate a decrease in the mortality rate in patients who undergo parathyroidectomy. Hyperparathyroidism may recur after surgery.

Consultations

- Consult a surgeon regarding wound debridement and possible parathyroidectomy.
- Consult a dietitian regarding dietary alterations.
- Consider consulting a pain-management specialist.

Diet

- Patients with abnormalities in calcium and phosphate homeostasis need to be referred to a dietitian well versed in the dietary needs and restrictions of patients with ESRD.
- Special consideration should be given to phosphate restriction.

Activity

- The patient's activity may be greatly hampered by the pain and the ulceration of calciphylaxis lesions.

- Patients are generally hospitalized in intensive care units during the acute illness.

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MEDICATION

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Drug Category: *Calcimimetics*

Drug Name	Cinacalcet (Sensipar)
Description	Directly lowers PTH levels by increasing sensitivity of calcium-sensing receptor on chief cell of parathyroid gland to extracellular calcium. Also results in concomitant serum calcium decrease.
Adult Dose	30 mg PO qd initially; titrate q2-4wk prn to normalize calcium levels by sequential doses of 30 mg bid, 60 mg bid, 90 mg bid, and 90 mg tid/qid; take with meals or immediately pc; do not crush, chew, or cut tab
Pediatric Dose	Not established
Contraindications	Documented hypersensitivity
Interactions	Strong CYP450 2D6 inhibitor; may increase serum levels of CYP2D6 substrates (eg, flecainide, vinblastine, thioridazine, TCAs); coadministration with CYP450 3A4 inhibitors (eg, ketoconazole, erythromycin, itraconazole) may decrease clearance
Pregnancy	C - Fetal risk revealed in studies in animals but not established or not studies in humans; may use if benefits outweigh risk to fetus
	Serum calcium reduction may cause lowered seizure threshold, paresthesia, myalgia, cramping,

Precautions

and tetany; monitor calcium and phosphorus levels closely within 1 wk following initial dose or dose changes and then monthly (secondary hyperparathyroidism) and q2mo (parathyroid carcinoma); do not initiate treatment if serum calcium level <8.4 mg/dL; adynamic bone disease may occur if iPTH levels suppressed <100 pg/mL; caution with hepatic impairment; common adverse effects include nausea and vomiting

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Complications

- Complications of calciphylaxis range from moderate interference with activity to death.
- Lesions of calciphylaxis frequently result in nonhealing ulcers and cutaneous gangrene. Acral lesions may fail to heal with conservative therapy and lead to amputation.
- Sepsis may result from the nonhealing wounds.
- Patients with internal involvement may develop gastrointestinal hemorrhage, infarction, or organ failure.
- Patients treated with calcimimetics, sodium thiosulfate, and parathyroidectomy must be monitored for hypocalcemia.

Prognosis

- The prognosis is generally not good, with a mortality rate as high as 60-80% in patients with ulcerative disease. Patients who do not die of sepsis or organ failure frequently undergo amputation of an involved limb. Vascular calcification is theoretically reversible with aggressive management, but many patients have numerous comorbid diseases. Currently, the 1- and 5-year survival rates are estimated to be 45% and 35%, respectively.

Patient Education

- Emphasize compliance with the dialysis prescription.
- Educate patients regarding dietary restrictions and the need for phosphate binders.
- If anticoagulation is chosen, explain the risks and the benefits of this therapy.

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Media file 1: **Several lesions of calciphylaxis that occurred on the lower extremity of a patient undergoing dialysis. These lesions developed in areas of livedo reticularis and followed the path of the vasculature.**



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Media type: Photo

Media file 2: **An isolated lesion of calciphylaxis manifesting as an enlarging necrotic plaque on the lower extremity of a patient undergoing dialysis. The stellate purpuric morphology can be appreciated surrounding the area of necrosis.**



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Media type: Photo

Media file 3: **Calciphylaxis may manifest as rapidly progressive, diffuse and extensive, cutaneous necrosis, as is seen in this patient with chronic renal failure. Bullae may also be seen as a rare manifestation of calciphylaxis.**



 [View Full Size Image](#)

Media type: Photo

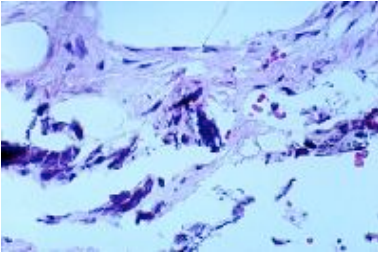
Media file 4: **Radiologic findings of a hand in a patient with calciphylaxis. Extensive calcification of the radial and ulnar arteries is readily visible.**



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Media type: X-RAY

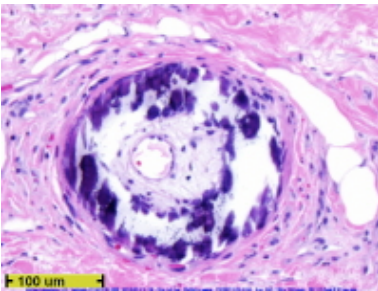
Media file 5: **Histologically, calcification of the blood vessels, as well as the subcutis, can be seen in calciphylaxis.**



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Media type: Photo

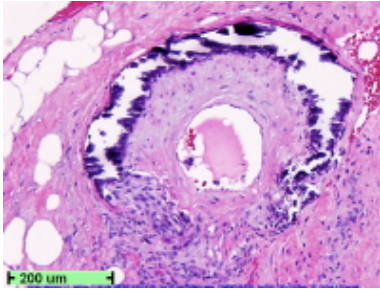
Media file 6: **Demonstrated here is the characteristic circumferential medial calcific deposit in an arteriole with subintimal edema. Histologic images courtesy of Steve A. McClain, MD, Department of Dermatology SUNY-Stony Brook.**



 [View Full Size Image](#)

Media type: Photo

Media file 7: **This image shows circumferential medial calcific deposits obliterating the external elastica of an arteriole. Histologic images courtesy of Steve A. McClain, MD, Department of Dermatology SUNY-Stony Brook.**


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Media type: Photo

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